Neurology
Evaluation of a First Seizure

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Seizure is a common presentation in the emergency care setting, and new-onset epilepsy is the most common cause of unprovoked seizures. The patient history and physical examination should direct the type and timing of laboratory and imaging studies. No single sign, symptom, or test clearly differentiates a seizure from a nonseizure event (e.g., syncope, pseudoseizure). Electroencephalography is recommended for patients presenting with a first seizure, and neuroimaging is recommended for adults. Neuroimaging also should be performed in children with risk factors such as head trauma, focal neurologic deficits, or a history of malignancy. Magnetic resonance imaging is preferred over computed tomography except when acute intracranial bleeding is suspected. The most common laboratory findings associated with a seizure are abnormal sodium and glucose levels. Patients with a normal neurologic examination, normal test results, and no structural brain disease do not require hospitalization or antiepileptic medications. Treatment with antiepileptic medications reduces the one- to two-year risk of recurrent seizures but does not reduce the long-term risk of recurrence and does not affect remission rates. Regardless of etiology, a seizure diagnosis severely limits a patient's driving privileges, although laws vary by state. (Am Fam Physician 2007;75:1342-1347, 1348. Copyright © 2007 American Academy of Family Physicians.)

Patient Information:
A handout on seizures, written by the authors of this article, is provided on page 1348.

About 2 to 5 percent of Americans experience an afebrile seizure, and seizures account for approximately 1 to 2 percent of all emergency department visits. The self-reported prevalence of epilepsy is 1.1 to 2.2 percent in the United States. Most patients (57 percent) who present with a first seizure are younger than 25 years, and 71 percent of this subset is 15 years or younger; 58 percent of patients with a first seizure are men.

Seizure Types
Seizures are categorized based on presentation and etiology. A generalized seizure involves all areas of the brain (both hemispheres), whereas a partial (focal) seizure involves only one area of the brain. A first seizure is twice as likely to be a generalized seizure as a partial seizure. Most generalized seizures occur when the patient is awake, but one in four occurs during sleep. Partial seizures can be further classified as simple (i.e., no loss of consciousness) or complex (i.e., loss of consciousness).

Symptomatic seizures are those that have a recognizable cause (e.g., head injury, brain tumor), and idiopathic seizures are those for which no abnormality is found. Acute symptomatic seizures are caused by a recent or current event, whereas remote symptomatic seizures are caused by a chronic abnormality such as an old stroke. A provoked seizure is caused by an identifiable transient disturbance such as an electrolyte abnormality (e.g., hypocalcemia). In the year following an acute symptomatic seizure diagnosis, patients have a higher risk of death than those without this diagnosis. Idiopathic seizures are not associated with increased risk of death.

Etiology
There are multiple causes of seizure (Table 1), but new-onset epilepsy is the most common cause of a first seizure. One in six patients who present with a single seizure will have an identifiable potential cause such as pre- or perinatal brain injury (4.4 percent), cerebrovascular disease (3.9 percent), head injury (3.2 percent), brain tumor (1.7 percent), or alcohol use (0.3 percent).
Table 1. Selected Causes of Seizure

| Alcohol, drug and withdrawal | Meningitis |
| Brain injury or necrosis | Adverse drugs (e.g., local anesthetics) |
| Brain tumors | Nonspecific (e.g., tumor, trauma, brain) |
| Central nervous system infection | A reversible or beta blocker use |
| Central nervous system neoplasms | Scarring (e.g., radiation, quinacrine) |
| Endocrine and metabolic disorders | Some (e.g., hypothyroidism, Addison's disease) |
| Genetic disorder | Medications (e.g., anticoagulants) |
| Head trauma | Sodium channel antagonists (e.g., phenytoin) |
| Postoperative status | Thyroid disease |
| Central nervous system infection | Thyroid disease |
| Cysticercosis | Thyroid disease |
| Encephalitis | Thyroid disease |
| Meningitis | Thyroid disease |
| Contrast agents | Thyroid disease |
| Child abuse | Thyroid disease |
| Fever (children) | Thyroid disease |
| Illicit drug use and withdrawal | Thyroid disease |
| Information from references 5 |

The history should initially focus on determining whether a seizure actually occurred and evaluating the circumstances and characteristics of the event. The behaviors of the patient during the event and evidence of partial onset may be important in identifying a specific form of epilepsy. A history of trauma or symptoms of infection (e.g., stiff neck, fever, headache) also helps direct the evaluation. The patient should
Table 2. Risk Factors for Acute Intracranial Pathology in Adults with a First Unprovoked Seizure

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute head trauma</td>
<td>30%</td>
</tr>
<tr>
<td>Age older than 40 years</td>
<td>20%</td>
</tr>
<tr>
<td>Fever</td>
<td>15%</td>
</tr>
<tr>
<td>History of meningitis</td>
<td>10%</td>
</tr>
<tr>
<td>History of brain injury</td>
<td>5%</td>
</tr>
<tr>
<td>New focal neurologic deficit</td>
<td>2%</td>
</tr>
<tr>
<td>Persistent altered mental status</td>
<td>1%</td>
</tr>
<tr>
<td>Persistent headache</td>
<td>0.5%</td>
</tr>
<tr>
<td>Motor weakness</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Note: The table indicates the percentage of patients with each risk factor.

be asked about medication, illicit drug, and alcohol use. A history of neurologic or developmental disorders or a family history of epilepsy may help narrow the differential diagnosis. The physical examination should include a thorough neurologic and mental status evaluation.

Differential Diagnosis

No sign, symptom, or test clearly differentiates a seizure from a nonepileptic event (e.g., syncope, pseudoseizure).7 Up to 20 percent of patients diagnosed with epilepsy actually have pseudoseizures. Eye closure throughout the event is rare in true seizures but common in pseudoseizures, and a history of fibromyalgia or chronic pain syndrome is predictive of pseudoseizures.8

In older children and adults, a serum prolactin measurement, if obtained within 10 to 20 minutes of the event, is useful in differentiating a generalized tonic-clonic seizure or complex partial seizure from a pseudoseizure. The sensitivity of an elevated prolactin level is 60 percent for generalized tonic-clonic seizures and 46 percent for complex partial seizures.9

Syncope may be difficult to differentiate from seizures, particularly if the event was unwitnessed. Up to 90 percent of patients with syncope have myoclonic or other seizure-like movements while unconscious.10 Historic features suggestive of seizure include tongue biting, presence of an aura, sensation of epigastric fullness, postictal confusion, and focal neurologic signs. Tongue biting, especially lateral, is highly specific but not sensitive for generalized seizures.11 Events precipitated by an emotionally stressful event or preceded by light-headedness, sweating, prolonged standing, chest pain, palpitations, or slow heart rate are more likely to be syncopal.12

Diagnostic Testing

Adults who present to the emergency department after an unprovoked first seizure should receive immediate neuroimaging of the brain if feasible, although testing at a later date may be acceptable in certain patients if follow-up is reliable.1 Patients at an increased risk of acute intracranial pathology (Table 2) need immediate neuroimaging.1,7 Current practice guidelines allow a well-appearing child without risk factors to be discharged from the emergency department without emergent neuroimaging.7

A lumbar puncture is indicated for patients with a history or examination results suggestive of central nervous system infection in patients who are immunocompromised. New-onset seizures may be the only symptom of central nervous system infection in patients with human immunodeficiency virus.14 Lumbar puncture is not routinely recommended in afebrile children but should be considered in children younger than six months and in those who have persistently altered mental status or meningeal signs.7

Glucose abnormalities and hyponatremia are the most common laboratory findings associated with seizures.1 Practice guidelines recommend testing children based on individual clinical circumstances and routinely measuring serum glucose and sodium levels in adults. Pregnancy testing should be performed in premenopausal women, and toxicology testing should be performed when substance abuse is suspected.1,7 Infants with new-onset seizures should be tested for electrolyte abnormalities.
Electroencephalography (EEG) is recommended for all patients with new-onset seizures. Emergent EEG testing is indicated if there is concern about status epilepticus. Nonconvulsive or subtle convulsive status epilepticus may be difficult to diagnose clinically and may be mistaken for a prolonged postictal state. One fourth of patients with treated status epilepticus who appear to be seizure-free continue to have seizure activity that is only detectable with EEG. Patients who have had a seizure and are in a drug-induced coma or who have received a long-acting paralytic agent also should receive immediate EEG testing.

Most other patients with a first seizure can receive EEG testing at a scheduled follow-up visit. Although EEG within 24 to 48 hours of a seizure is more likely to show an abnormality, some early abnormalities, such as postictal slowing, may not be significant.

**Neuroimaging**
The recommendations for imaging after a first seizure depend on patient age, seizure type, and associated risk factors.

**Children**
There is insufficient evidence to recommend for or against routine neuroimaging in children who present only with a single unprovoked seizure, although unnecessary radiation exposure should be avoided. The estimated lifetime risk of death from radiation-induced malignancy caused by a single computed tomography (CT) scan of the head at one year of age is 0.07 percent.

Neuroimaging should be performed in children with a postictal focal neurologic deficit that does not resolve or in children who do not return to baseline neurologic function within several hours. Neuroimaging also should be performed in children with head trauma or a history of malignancy. Nonurgent magnetic resonance imaging (MRI) should be seriously considered in children younger than one year and in children with any of the following characteristics: significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic examination, partial onset of seizure with or without secondary generalization, or no evidence of benign partial epilepsy of childhood or primary generalized epilepsy on EEG. Seizures only provoked by the presence of fever (febrile seizures) do not require neuroimaging.

**Adults**
Neuroimaging scans reveal abnormalities in 3 to 38 percent of patients with a first seizure, depending on patient demographics. A joint consensus statement from the American College of Emergency Physicians (ACEP), the American Academy of Neurology (AAN), and others states that immediate neuroimaging is indicated when a serious structural brain lesion is suspected and also should be considered for patients with partial-onset seizures and for those who are older than 40 years. Neuroimaging at a later date is acceptable for patients who have completely recovered from their seizures and when there is no clear etiology, although immediate imaging should be performed if follow-up cannot be guaranteed.

MRI is the preferred imaging method because it has greater sensitivity for detecting abnormalities than CT. However, patients with acute seizures initially should undergo CT because it more accurately detects acute bleeding and is reasonably sensitive in detecting other abnormalities.

Intracranial disease is commonly detected on neuroimaging scans even if a nonbrain etiology for the seizure is apparent. A study of unselected patients presenting to an urban emergency department after a first seizure related to alcohol withdrawal showed brain abnormalities that required intervention or change in therapy in 10 out of 259 patients (3.9 percent). History of trauma and neurologic examination findings did not predict these abnormalities.

**Treatment**
When predicting future risk, all seizures occurring within 24 hours are considered a single seizure. Approximately one half of patients who have a first unprovoked seizure and three out of four who have multiple seizures will have another seizure within the next eight years. Risk factors for seizure
recurrence in children presenting with a first unprovoked seizure include abnormal EEG test results; a history of febrile seizures; remote, symptomatic etiology; seizure that occurs during sleep; and Todd’s paralysis.18

The decision to initiate treatment after a single unprovoked seizure is controversial. A randomized controlled trial showed that antiepileptic medications initiated at the occurrence of a first seizure reduced the incidence of additional seizures over the next one to two years but did not reduce the long-term recurrence risk or affect remission rates.19

An AAN practice guideline states that treatment with antiepileptic medications is not indicated in children for the purpose of preventing epilepsy, but treatment may be considered if the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial adverse effects.20 There is no guideline for adults.

ACEP policy states that patients evaluated in the emergency department for a seizure who have a normal neurologic examination, no known comorbidities, and no known structural brain abnormalities may be referred for outpatient follow-up without initiating an antiepileptic medication.1 Consultation with a subspecialist is indicated if uncertainty remains after evaluation.21 If an antiepileptic medication is initiated, acceptable choices include carbamazepine (Tegretol), phenytoin (Dilantin), valproic acid/divalproex (Depakene), phenobarbital, gabapentin (Neurontin), lamotrigine (Lamictal), oxcarbazepine (Trileptal), and topiramate (Topamax).22

Driving Limitations

Most states require a three- to 18-month seizure-free period before a patient may resume driving a private vehicle, although most states have an appeals process for driving restrictions.23 Some states require physicians to report patients who are diagnosed with epilepsy.24 State driving laws for patients with epilepsy are available at http://www.epilepsyfoundation.org; click the driving link under Quick Links.

Usually, patients with a history or current diagnosis of epilepsy may not hold a commercial driver’s license. If a seizure is caused by a medical condition (e.g., drug reaction, high fever, acute infectious disease, dehydration, acute metabolic disturbance), the patient may be allowed to hold a commercial driver’s license after full recovery from the condition.24 Drivers with a history of epilepsy or seizures who have not needed antiseizure medication and have been seizure-free for 10 years may reapply to operate a commercial vehicle in interstate commerce.24 Drivers with a history of a single unprovoked seizure may be qualified to drive a commercial vehicle if they have not needed antiseizure medication and have been seizure-free for at least five years.24

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REFERENCES


Seizure Disorders in the Elderly

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Seizure disorders become increasingly common after the age of 60 years and can have a significant impact on functional status. The goal of antiepileptic drug therapy is to control seizures but preserve quality of life. If possible, seizure control should be achieved with one agent given in the lowest effective dosage. Clinical response, rather than drug levels, should guide dosage changes. All antiepileptic drugs can cause dose-dependent sedation and cognitive impairment. Although the newer agents may have theoretical advantages over standard antiepileptic agents, higher cost may limit their use. Drugs for first-line monotherapy of seizures in elderly patients include carbamazepine, valproic acid, oxcarbazepine, gabapentin, and lamotrigine. (Am Fam Physician 2003;67:325-32. Copyright © 2003 American Academy of Family Physicians.)

Members of various medical faculties develop articles for "Practical Therapeutics." This article is one in a series coordinated by the Department of Family Medicine at the University of Michigan Medical School, Ann Arbor. Guest editor of the series is Barbara S. Apgar, M.D., M.S., who is also an associate editor of AFP.

The general perception is that seizures occur most often in infants but rarely in older adults. However, population-based studies indicate that seizure disorders increase in incidence and prevalence after the age of 60 years. Because people are living longer and becoming more likely to have concurrent medical illnesses requiring multiple medications, family physicians are increasingly challenged to provide appropriate management of seizures and monitoring of antiepileptic drug therapy in their older patients. This article reviews the epidemiology, etiology, and diagnosis of seizure disorders in the elderly. An approach to antiepileptic drug selection is suggested.

Epidemiology, Classification, and Etiology

Epidemiologic studies consistently document an increased incidence of seizure disorders in older adults and suggest that aging is a definite risk factor. In the United States, the annual incidence of seizures is approaching 100 seizures per 100,000 persons over 60 years of age. Epilepsy, a chronic condition characterized by recurrent and usually spontaneous seizures, affects 1.5 to 3 million people in the United States.

Epilepsies and epileptic syndromes are currently classified as localized (partial or focal) or generalized, based on clinical and electroencephalographic changes (Table 1). A generalized epilepsy or epileptic syndrome results in seizures that involve the cerebral hemispheres bilaterally and symmetrically at the time of onset. In contrast, a partial epilepsy produces seizures that originate in a specific region of the cerebral cortex. The seizures may be associated with signs or symptoms peculiar to their region of origin, and they may occur with or without mental status changes or loss of consciousness. Partial epilepsy, the most common type of epilepsy in the elderly, is often the result of localized cortical dysfunction.

In many older patients, an underlying cause of seizure activity is clearly identifiable. Epidemiologic studies have defined acute symptomatic seizures as those that happen in the context of an acute insult to the central nervous system (CNS) or during an acute metabolic disturbance. These seizures are associated with subdural hematoma, stroke, and CNS infection. They also can occur with systemic metabolic conditions such as uremia, hyperglycemia, hypoglycemia, hyponatremia, and alcohol withdrawal.

A five-year study of 151 patients with a first seizure after 60 years of age found that 32 percent of the seizures were caused by strokes and 14 percent by brain tumors, including meningiomas, malignant gliomas, and brain metastases; 25 percent had no identifiable cause. A community cohort study of 675 patients with a first stroke found that the risk of having a seizure was 2 percent at stroke onset and 11 percent in the first five years after the
Seizures in the elderly may be caused by stroke, systemic metabolic conditions, subdural hematoma, central nervous system infection, degenerative disorders, or malignancy. The seizures also can be idiopathic.

stroke. Seizure recurrence after a stroke can be immediate, or it may not happen for several years. Recurrences are more common after hemorrhagic or severe ischemic strokes with cortical (particularly occipital) involvement and late onset of the first seizure.

Of the degenerative disorders, Alzheimer’s dementia and amyloid angiopathy are known major causes of seizures. Advanced Alzheimer’s disease has been identified as a risk factor for new-onset generalized tonic-clonic seizures in older adults. It is associated with a 10 percent prevalence of seizures, particularly late in the illness. An increased prevalence of seizures also has been documented with other types of dementia.

Status epilepticus has been defined as a single generalized seizure lasting more than five minutes or a series of seizures lasting longer than 30 minutes without the patient regaining consciousness. The greatest increase in the

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**TABLE 1**

**Classification of Epilepsies and Epileptic Syndromes**

<table>
<thead>
<tr>
<th>Localized (partial or focal)</th>
<th>Generalized</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (with age-related onset)</td>
<td>Idiopathic (age-related onset; listed in order of age)</td>
<td>Situation-related seizures</td>
</tr>
<tr>
<td>Benign childhood epilepsy with centrotemporal spike</td>
<td>Benign neonatal familial convulsions</td>
<td>Febrile convolution</td>
</tr>
<tr>
<td>Childhood epilepsy with occipital paroxysms</td>
<td>Benign neonatal convulsions</td>
<td>Isolated seizures or isolated status epilepticus</td>
</tr>
<tr>
<td>Primary reading epilepsy</td>
<td>Benign myoclonic epilepsy in infancy</td>
<td>Seizures occurring only</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Childhood absence epilepsy</td>
<td>when there is an acute metabolic or toxic event</td>
</tr>
<tr>
<td>Chronic progressive epilepsy</td>
<td>Juvenile myoclonic epilepsy (impulsive petit mal epilepsy)</td>
<td>because of alcohol, drugs, eclampsia, nonketotic hyperglycemia, or other factors</td>
</tr>
<tr>
<td>partialis continua of childhood syndrome characterized by seizures with specific modes of presentation</td>
<td>Epilepsy with grand mal seizures on awakening</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe epilepsies</td>
<td>Other generalized idiopathic epilepsies not defined above</td>
<td></td>
</tr>
<tr>
<td>Frontal lobe epilepsies</td>
<td>Epilepsies with seizures precipitated by specific modes of activation</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe epilepsies</td>
<td>Cryptogenic or symptomatic (age-related onset; listed in order of age)</td>
<td></td>
</tr>
<tr>
<td>Occipital lobe epilepsies</td>
<td>West’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic (presumed to be symptomatic, with unknown etiology)</td>
<td>Lennox-Gastaut syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilepsy with myoclonic-astatic seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilepsy with myoclonic absences</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonspecific etiology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early myoclonic encephalopathy</td>
<td></td>
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<tr>
<td></td>
<td>Early infantile encephalopathy with suppression burst</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other symptomatic generalized epilepsies not defined above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific syndromes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diseases in which seizures are a presenting or predominant feature*</td>
<td></td>
</tr>
</tbody>
</table>

*—Epileptic seizures may complicate many disease states.

incidence of status epilepticus occurs after the age of 60 years. The most dramatic clinical presentation is generalized convulsive seizures. Nonconvulsive seizures may cause sudden changes in behavior and cognition.

A study of 342 patients with status epilepticus who had their first seizure after 60 years of age found that cerebrovascular disease was the leading cause, followed by head trauma. Status epilepticus also can occur because of hypoxia, hyperglycemia, intracranial infection, brain tumors, and drug intoxication or withdrawal.

In patients with status epilepticus, the immediate goals are to stop the seizure and support cardiopulmonary function. Once these goals are accomplished, treatment of possible causes and precipitants (e.g., intracranial infection, hyperglycemia) is indicated.

**Diagnostic Evaluation**

The first step in diagnosing the cause of a seizure is to obtain a moment-by-moment description of the event from a witness. When more than one event clearly recognizable as a seizure has occurred, the diagnosis of epilepsy is made.

If the diagnosis of epilepsy is established, a careful search for predisposing factors is indicated. A detailed medical history should be obtained from the patient and family members. It is important to inquire about the patient’s current habits (e.g., possible substance abuse), a history of seizures, and the presence of risk factors (e.g., head trauma, cerebrovascular disease). A systematic review of systems should include questions about possible sleep disorders. A careful review of current medications, including over-the-counter agents, is essential, because some drugs used to treat common geriatric problems may lower the seizure threshold. Finally, the physical examination should include a thorough neurologic assessment.

The initial laboratory evaluation of possible acute symptomatic seizures should include: a complete blood count; electrolyte, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, and glucose levels; an erythrocyte sedimentation rate; liver function tests; serologic tests; a chest radiograph; and an electrocardiogram. When appropriate, serum drug levels and a toxicology screen should be obtained.

A detailed cardiovascular evaluation is often required in the patient with suspected cardiogenic syncope, transient ischemic attack, or stroke. The work-up often might include an echocardiogram, Holter monitoring, and carotid Doppler ultrasonography. Acutely, computed tomographic scanning of the brain may exclude hemorrhage. When feasible, magnetic resonance imaging is the neurodiagnostic study of choice because of its sensitivity to infarcts and focal gliosis. Lumbar puncture is not routinely required unless the patient is febrile or has recently had a fever, meningitis is suspected, or the patient is immunocompromised.

Electroencephalography can help to establish the diagnosis of epilepsy and classify the seizure type. When possible, an electroencephalogram (EEG) should be obtained to assess prognosis and select appropriate drug therapy. Elderly patients can have episodes that mimic seizures but are actually the result of syncope, a sleep disorder, or a psychiatric illness. Older adults without epilepsy generally have no significant background changes on their EEG. A study comparing changes on EEGs in young patients (20 to 59 years) and older patients (over 60 years of age) who had epilepsy found decreased background rhythm, rhythmicity, and amplitude in the older group. Temporal lobe abnormalities were common in both groups, but frontal lobe discharges and slow waves were seen significantly more often in the older patients.

If the diagnosis is uncertain, inpatient monitoring may be indicated. A recent retrospective review of 18 older adults who were admitted to an epilepsy-monitoring unit at a university hospital found that three patients who were receiving antiepileptic drug therapy
### TABLE 2
Antiepileptic Drugs Recommended for Use in the Elderly

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose-related toxicities</th>
<th>Idiosyncratic side effects</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Partial seizures (simple and complex), generalized seizures</td>
<td>Ataxia, nystagmus, diplopia, confusion, sedation, lethargy, blurred vision</td>
<td>Blood dyscrasias, rash, hepatotoxicity, Stevens-Johnson syndrome, neuropathy, lymphadenopathy, pancreatitis, osteomalacia, osteoporosis, folate deficiency</td>
<td>Low cost</td>
</tr>
<tr>
<td>Valproic acid (Depakene)</td>
<td>Generalized seizures, absence seizures, myoclonic seizures, partial seizures (simple and complex), migraine prophylaxis, mania</td>
<td>Tremors, diarrhea, somnolence, sedation, lethargy, minor hepatic enzyme elevation, nausea, vomiting, ataxia</td>
<td>Pancreatitis, rash, thrombocytopenia, blood dyscrasia, Stevens-Johnson syndrome, weight gain, osteoporosis</td>
<td>Broad-spectrum efficacy</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Partial seizures (simple and complex), generalized seizures, trigeminal neuralgia</td>
<td>Diplopia, dizziness, ataxia, drowsiness, hyponatremia, nausea, headache</td>
<td>Hyponatremia, cardiac conduction problems, morbilliform rash, agranulocytosis, aplastic anemia, Stevens-Johnson syndrome, hepatic failure, serum sickness, osteomalacia, osteoporosis</td>
<td>Minimal sedation and cognitive adverse effects</td>
</tr>
<tr>
<td>Newer drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal)</td>
<td>Partial seizures (simple and complex), generalized seizures, trigeminal neuralgia</td>
<td>Dizziness, nausea, vomiting, ataxia, diplopia, sedation, lethargy, hyponatremia, tremor</td>
<td>Hyponatremia, cardiac conduction problems, rash</td>
<td>Few drug interactions</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>Partial seizures (simple and complex)</td>
<td>Somnolence, fatigue, ataxia, dizziness, blurred vision, diplopia, nystagmus, peripheral edema, tremor, nausea, weight gain</td>
<td>Leukopenia</td>
<td>No hepatic metabolism, drug interaction only with antacids</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>Partial seizures (simple and complex), generalized seizures</td>
<td>Dizziness, tremor, ataxia, diplopia, headache, somnolence, blurred or dimmed vision, nausea, vomiting, incoordination, insomnia</td>
<td>Stevens-Johnson syndrome, aplastic anemia, thrombocytopenia, rash, weight loss (occasional), neutropenia, pancytopenia</td>
<td>Interaction with antiepileptic drugs only (especially valproic acid derivatives)</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>Partial seizures (simple and complex), generalized seizures</td>
<td>Difficulty thinking or concentrating, impaired memory, confusion, dizziness, ataxia, nervoussness, tremor, fatigue, depression, anorexia, weight loss, dyspnea, diplopia, sedation, lethargy</td>
<td>Nephro lithiasis, paresthesias, narrow-angle glaucoma (blurred vision, periorbital pain)</td>
<td>Interaction with antiepileptic drugs only</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
<td>Partial seizures (simple and complex)</td>
<td>Dizziness, sedation, lethargy, tremor, nervousness, emotional changes, possible confusion</td>
<td>Rash, paresthesias, possible nonconvulsive status epilepticus</td>
<td>None</td>
</tr>
</tbody>
</table>

*—Estimated cost to the pharmacist for 30 days of treatment at the lowest given dosage, based on average wholesale prices (rounded to the nearest dollar) in Red book. Montvale, N.J.: Medical Economics Data, 2002. Cost to the patient will be higher, depending on prescription filling fee. Adapted with permission from Lackner TE. Strategies for optimizing antiepileptic drug therapy in elderly people. Pharmacotherapy 2002;22:332.

The table provides a list of antiepileptic drugs along with their indications, dose-related toxicities, idiosyncratic side effects, and advantages. The table is structured to compare different types of drugs, with older and newer options highlighted. Each entry includes specific information about the drug's effects and potential benefits.

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**Antiepileptic Drug Selection**

In general, all antiepileptic drugs have significant drug interactions, depend on gastrointestinal absorption, and may cause cog-
Seizures

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Representative</th>
<th>Cost of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>geriatric</td>
<td>brand name</td>
</tr>
<tr>
<td>maintenance</td>
<td>dosage</td>
<td>drug*</td>
</tr>
<tr>
<td>Many drug interactions and food/nutrient interactions</td>
<td>200 mg per day</td>
<td>$18</td>
</tr>
<tr>
<td>Extensive protein binding, multiple drug interactions (e.g., with phenytoin)</td>
<td>500 mg once to three times daily</td>
<td>113</td>
</tr>
<tr>
<td>Ataxia, diplopia, multiple drug interactions</td>
<td>400 mg twice daily</td>
<td>61</td>
</tr>
<tr>
<td>None</td>
<td>600 mg twice daily</td>
<td>194</td>
</tr>
<tr>
<td>Dosage modification in renal disease, three times daily dosing</td>
<td>300 mg three times daily</td>
<td>116</td>
</tr>
<tr>
<td>Dosage modification in liver disease (?)</td>
<td>150 mg twice daily</td>
<td>169</td>
</tr>
<tr>
<td>Weight loss; dosage modification if creatinine clearance is &lt;60 mL per minute (1 mL per second)</td>
<td>100 mg twice daily</td>
<td>195</td>
</tr>
<tr>
<td>Dosage modification in liver disease</td>
<td>32 mg per day</td>
<td>138</td>
</tr>
</tbody>
</table>

decide whether a first single seizure requires treatment: Is the episode an isolated event or one that will require lifelong treatment? The fact that a large percentage of older adults will not experience another seizure episode makes a strong argument against treatment of a first single seizure. Candidates for antiepileptic drug therapy include patients with recurrent seizures, onset of epilepsy presenting as status epilepticus, or a clear structural predisposition for seizures.

It is estimated that broad use of the newer antiepileptic drugs would increase the annual cost of antiepileptic drug therapy in the United States from $25 million to more than $1.2 billion. Few trials support the use of one antiepileptic medication over the others. Hence, the ideal antiepileptic drug is one with once-daily or twice-daily dosing, a low cost, minimal side effects, few or no drug interactions, low protein binding, little or no allergic or idiosyncratic reaction potential, and availability in a parenteral formulation.

In general, it is advisable to "start low and go slow" with one agent. Results from the Veterans Affairs Cooperative Study on the effects of age on epilepsy and its treatment indicate that compared with younger adults, older adults appear to be more responsive to antiepileptic drug therapy. However, they are also more likely to experience side effects at lower serum antiepileptic drug concentrations. Consequently, older adults usually require lower dosages and longer dosing intervals. With any antiepileptic drug therapy, patients should be monitored closely for adverse effects, drug interactions, poor seizure control, and toxicity. Determination of the unbound drug concentration may be helpful when the clinical response appears inappropriate or side effects are prominent.

Once the decision to treat is made, the next step is to determine whether to use a standard (older) antiepileptic drug or one of the newer agents (Table 2). The older antiepileptic drugs, which include phenytoin (Dilantin), valproic acid (Depakene), and carbamazepine
Few trials support the use of one antiepileptic drug over the others in elderly patients. Older agents are less expensive, newer agents sometimes have the benefit of fewer drug interactions or cognitive side effects.

(Tegretol), are less expensive than the newer agents and are considered appropriate selections for the initial treatment of seizures in older adults. In older adults, treatment with phenobarbital or primidone (Mysoline) is not widely recommended because of significant side effects, including sedation and drug-induced cognitive impairment.

Newer antiepileptic drugs that are appropriate as first-line treatment in the elderly include oxcarbazepine (Trileptal), gabapentin (Neurontin), and lamotrigine (Lamictal). These agents have fewer drug interactions and better side effect profiles than the standard antiepileptic drugs. Because of serious hematologic and hepatic side effects, felbamate (Felbatol) is no longer generally recommended for use in older adults.

PHENYTOIN

The absorption of phenytoin is altered by the physiologic changes of aging and by medications that affect gastrointestinal motility. For example, antacids and enteral feedings decrease the absorption and efficacy of the drug. Phenytoin is 90 percent protein bound; changes in protein binding caused by hepatic or renal disease result in a greater proportion of free or unbound drug, increasing the possibility of adverse events.

Because of the saturation kinetics of phenytoin, serum drug levels need to be monitored carefully. Small changes in the maintenance dosage lead to large changes in the total serum drug concentration.

The major advantages of phenytoin are low cost and the availability of an intravenous preparation for use in emergency situations. A liquid formulation is also available; however, the difficulty of maintaining phenytoin in suspension recommends against use of the suspension unless no other route or formulation is feasible. Drug interactions are common and are a major disadvantage to the use of phenytoin in older patients who are taking multiple medications.

VALPROIC ACID

Valproic acid is highly protein bound. This drug is metabolized by cytochrome P450, fatty acid oxidation, and conjugation to active and inactive metabolites. Valproic acid levels may be decreased and phenytoin levels may be increased in patients taking both medications.

CARBAMAZEPINE

Carbamazepine is 65 to 85 percent bound to a combination of albumin and α1-acid glycoprotein. The drug is metabolized in the liver, where it can induce its own metabolism and accelerate the oxidation and conjugation of other drugs. Because drug clearance is reduced in elderly people, carbamazepine levels should be monitored carefully, especially at the initiation of treatment.

The major advantages of carbamazepine include proven efficacy, twice-daily dosing in the elderly, and the availability of an extended-release preparation. However, hyponatremia and cardiac conduction problems may occur more often in older patients than in younger ones. Furthermore, carbamazepine interacts with a number of drugs.
OXCARBAZEPINE

Oxcarbazepine was recently labeled for use as monotherapy for partial-onset seizures in adults. Structurally related to carbamazepine and with a similar spectrum of activity, oxcarbazepine does not induce its own metabolism and has few drug interactions. Hepatic cytosolic enzymes metabolize the drug, with conversion to glucuronidase and subsequent renal excretion.

A recent multicenter, double-blind clinical trial showed that oxcarbazepine is well tolerated and can be rapidly titrated over 14 days without compromising safety. In this trial, dizziness, fatigue, headache, somnolence, nausea, and vomiting were the most common side effects of the drug. Hyponatremia and cardiac disturbances remain clinically important problems.

No significant data are available on the use of oxcarbazepine in older adults. Theoretically, however, the drug has significant advantages.

GABAPENTIN

Gabapentin is well absorbed and eliminated unchanged by the kidneys. The only known drug interaction is with aluminum-magnesium antacids, which decrease the absorption of gabapentin. Hence, gabapentin and these antacids should be administered at least two hours apart.

Of the newer antiepileptic drugs, gabapentin has the most favorable safety profile, although it can cause somnolence, dizziness, blurred vision, and leukopenia. Gabapentin may be recommended as initial monotherapy or add-on therapy for the treatment of seizure disorders in older patients who are taking multiple medications.[Evidence level B, lower quality randomized controlled trial]

LAMOTRIGINE

Lamotrigine is weakly bound to plasma proteins and extensively metabolized by the liver, which is a significant advantage in patients with severe renal disease. The drug is well tolerated by most patients.

The most common adverse effect of lamotrigine is a morbilliform rash that can develop during the first eight weeks of treatment. Slow titration minimizes the rash, which is usually mild and resolves when treatment is stopped. If lamotrigine needs to be discontinued, the dosage should be tapered over two weeks.

TOPIRAMATE AND TIAGABINE

Topiramate (Topamax) is weakly bound to proteins and not extensively metabolized. It is excreted primarily by the kidney. Tiagabine (Gabitril) is highly protein bound and extensively metabolized by the liver. Neither drug should be considered first-line therapy for seizure disorders in the elderly, because of the significant associated risk of personality changes or cognitive impairment.

FOSPHENYTOIN

Current recommendations for the treatment of status epilepticus in older adults are similar to those in younger adults. Treatment is started with a benzodiazepine, preferably lorazepam (Ativan) because of its relative rapid onset of action and long half-life. Next, fosphenytoin (Cerebyx) is given, and if the status epilepticus persists for more than 60 minutes, anesthesia is induced with pentobarbital, propofol (Diprivan), or midazolam (Versed).

Fosphenytoin is a safe and well-tolerated phenytoin prodrug that can be given intravenously with a lower risk of adverse effects (e.g., phlebitis, intravenous incompatibilities, hypotension, cardiac dysrhythmia) than parenterally administered phenytoin. Fosphenytoin also can be administered intramuscularly when intravenous access and cardiac monitoring are not available. Side effects are similar to those of phenytoin but occur less frequently. The prodrug is more expensive than phenytoin.

RECTAL DIAZEPAM

A recent randomized study demonstrated that the administration of a single dose of diazepam rectal gel (Diastat) was safe and effective in the treatment of homebound patients.
who had repetitive seizures.28 [Evidence level A, randomized controlled trial] Somnolence was the most frequent adverse effect. The drug appeared to have no observable depressive effect on respiratory rate.

Seizures and Motor Vehicle Operation

State driving laws must be reviewed carefully with the patient who has seizures and with the patient’s family. Information about these laws can be obtained from the Epilepsy Foundation (www.epa.org) but should be verified by contacting the state Department of Motor Vehicles. Revocation of driving privileges, along with loss of independence, can have significant psychosocial implications for an elderly patient, especially when adequate and secure public transportation is not available or the patient’s family cannot provide as-needed transportation.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

REFERENCES

Management of Alcohol Withdrawal Syndrome

JANET RICKS, DO, and WILLIAM H. REPLOGLE, PhD, Department of Family Medicine, University of Mississippi Medical Center, Jackson, Mississippi
NAKIA JOYE COOK, MSIS, AHIP, Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee

Clinical Question
What is the most effective detoxification regimen for persons with alcohol withdrawal syndrome (AWS)?

Evidence-Based Answer
AWS may be managed with outpatient therapy if the patient has mild to moderate symptoms. (Strength of Recommendation [SOR]: B, based on one randomized, prospective trial). The Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised (CIWA-Ar) may be used to assess symptom severity. (SOR: C, based on consistent reliability and validity from case series studies). The decision to prescribe medication is based on the severity of symptoms. High-quality randomized controlled trials and meta-analyses suggest that long-acting benzodiazepines are generally preferred for managing AWS in the inpatient setting. (SOR: A). However, there is also evidence that benzodiazepines are safe in the outpatient setting. (SOR: B, based on one randomized prospective trial).

Evidence Summary
The CIWA-Ar is a valid and reliable method of determining AWS severity based on 10 symptoms of withdrawal. This scale is easily incorporated into practice and can be used to monitor the success of therapy.¹

Patients with mild AWS symptoms (CIWA-Ar score of less than 8 to 10) can be monitored on an outpatient basis and may not require medication. Patients with moderate symptoms (CIWA-Ar score of 8 to 15) may require medication to alleviate withdrawal symptoms and may be monitored on an outpatient basis. Patients with a CIWA-Ar score of 15 or higher or a history of alcoholic withdrawal seizure, suicidal ideation, or other comorbid conditions are not eligible for outpatient treatment.²³ Patients may also require inpatient treatment if they develop seizures, delirium, or worsening of symptoms. Uncomplicated detoxification usually requires four to five days.⁴

Although there are data supporting the use of long-acting benzodiazepines for inpatient detoxification of patients with AWS,³ evidence for benzodiazepine use in the outpatient setting is limited. In a randomized prospective trial, 164 male veterans of low socioeconomic status were randomly assigned to inpatient (n = 77) or outpatient (n = 87) detoxification.³ Those in the outpatient group returned to the treatment facility each day, Monday through Friday, for evaluation. Patients in both groups usually received 30 mg of oxazepam. Those in the inpatient group were initially given four capsules per day, and dosages were adjusted daily based on patient progress. Persons in the outpatient group were instructed to take one capsule at bedtime and up to four capsules as needed during the day. There were no medical complications (i.e., seizures, delirium tremens, or death) in either cohort.

The mean treatment duration was significantly shorter for persons in the outpatient group than in the inpatient group (6.5 versus 9.2 days); however, significantly more persons in the inpatient group completed detoxification (95 versus 72 percent).³ Of the 24 persons in the outpatient group who did not complete detoxification, six were admitted to inpatient detoxification and 16 had stopped returning for daily evaluations by day 7 (eight patients did not return on day 2). The cost of inpatient therapy ranged from $3,319 to $3,665 per patient compared

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Table 1. Benzodiazepine Dosages for Fixed-Schedule Detoxification in Patients with Alcohol Withdrawal Syndrome

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting</td>
<td></td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>10 mg every six hours for four doses, followed by 5 mg every six hours for eight doses</td>
</tr>
<tr>
<td>Chloridiazepoxide (Librium)</td>
<td>50 mg every six hours for four doses, followed by 25 mg every six hours for eight doses</td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>2 mg every six hours for four doses, followed by 1 mg every six hours for eight doses</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30 mg every six hours for four doses, followed by 15 mg every six hours for eight doses</td>
</tr>
</tbody>
</table>

Information from references 2 and 4.

REFERENCES


Recommendations from Others

Recommendations from the Substance Abuse and Mental Health Services Administration consensus panel apply only to the management of acute intoxication and withdrawal, and are not appropriate for outpatient detoxification. However, according to the American Society of Addiction Medicine, patients with mild AWS, no history of seizures or delirium tremens, and no concurrent comorbidities may be eligible for outpatient detoxification. Patients must have a responsible person to monitor them, must be evaluated by medical personnel on a daily basis until they have stabilized, and must have access to transportation to emergency medical services.

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Author disclosure: Nothing to disclose.
Transient Ischemic Attacks: Part I. Diagnosis and Evaluation

NINA J. SOLENSKI, M.D., University of Virginia Health Sciences Center, Charlottesville, Virginia

Transient ischemic attack is no longer considered a benign event but, rather, a critical harbinger of impending stroke. Failure to quickly recognize and evaluate this warning sign could mean missing an opportunity to prevent permanent disability or death. The 90-day risk of stroke after a transient ischemic attack has been estimated to be approximately 10 percent, with one half of strokes occurring within the first two days of the attack. The 90-day stroke risk is even higher when a transient ischemic attack results from internal carotid artery stenosis. Most patients reporting symptoms of transient ischemic attack should be sent to an emergency department. Patients who arrive at the emergency department within 180 minutes of symptom onset should undergo an expedited history and physical examination, as well as selected laboratory tests, to determine if they are candidates for thrombolytic therapy. Initial testing should include complete blood count with platelet count, prothrombin time, International Normalized Ratio, partial thromboplastin time, and electrolyte and glucose levels. Computed tomographic scanning of the head should be performed immediately to ensure that there is no evidence of brain hemorrhage or mass. A transient ischemic attack can be misdiagnosed as migraine, seizure, peripheral neuropathy, or anxiety. (Am Fam Physician 2004;69:1665-74,1679-80. Copyright© 2004 American Academy of Family Physicians.)

This is part I of a two-part article on transient ischemic attacks. Part II, "Treatment," will appear in this issue on page 1681.

This article exemplifies the AAFP 2004 Annual Clinical Focus on caring for America's aging population.

See page 1591 for definitions of strength-of-recommendation labels.

Based on an increased understanding of brain ischemia and the introduction of new treatment options, a working group has proposed redefining transient ischemic attack (TIA) as "a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction." This definition underscores the urgency of recognizing TIA as an important warning of impending stroke and facilitating rapid evaluation and treatment of TIA to prevent permanent brain ischemia.

Epidemiology

An estimated 200,000 to 500,000 TIs occur annually in the United States. One study found that 25 percent of patients who presented to an emergency department with TIA had adverse events within 90 days; 10 percent of the events were strokes, and the vast majority of the strokes were fatal or disabling. More than 50 percent of all adverse events occurred within the first four days after the TIA. Notably, of the patients with TIA who returned to the emergency department with stroke (10.5 percent), approximately one half had the stroke within the first 48 hours after the initial TIA. In 2.6 percent of patients with TIA, hospitalization was required for cardiac events, including congestive heart failure, unstable angina, cardiac arrest, and ventricular arrhythmia.

Clinical Presentation

The more common clinical presentations of TIA are described in Table I. In general, a TIA presents as a syndrome rather than any one sign or symptom.

Pre-emergency Department Care

There is no reliable way to determine if the abrupt onset of neurologic deficits represents reversible ischemia without subsequent brain damage or if ischemia will result in permanent damage to the brain (e.g., stroke). Therefore, all patients...
### TABLE 1
Common Clinical Presentations of TIA

<table>
<thead>
<tr>
<th>Affected area</th>
<th>Signs and symptoms</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerves</td>
<td>Visual loss in one or both eyes</td>
<td>Bilateral loss may indicate more ominous onset of brainstem ischemia.</td>
</tr>
<tr>
<td></td>
<td>Double vision</td>
<td>If double vision is subtle, the patient may describe it as &quot;blurry&quot; vision.</td>
</tr>
<tr>
<td></td>
<td>Vestibular dysfunction</td>
<td>True vertigo is likely to be described as a spinning sensation rather than nonspecific lightheadedness.</td>
</tr>
<tr>
<td></td>
<td>Difficulty swallowing</td>
<td>Trouble swallowing may indicate brainstem involvement; if the swallowing problem is severe, there may be an increased risk of aspiration.</td>
</tr>
<tr>
<td>Motor function</td>
<td>Unilateral or bilateral weakness affecting the face, arm, or leg</td>
<td>Bilateral signs may indicate more ominous onset of brainstem ischemia.</td>
</tr>
<tr>
<td>Sensory function</td>
<td>Unilateral or bilateral; either decreased sensation (numbness) or increased sensation (tingling, pain) in the face, arm, leg, or trunk</td>
<td>If sensory dysfunction occurs without other signs or symptoms, the prognosis may be more benign, but recurrence is high.</td>
</tr>
<tr>
<td>Speech and language</td>
<td>Slurring of words or reduced verbal output; difficulty pronouncing, comprehending, or &quot;finding&quot; words</td>
<td>If speech is severely slurred or facial drooling is excessive, there is an increased risk of aspiration. Writing and reading also may be impaired.</td>
</tr>
<tr>
<td>Coordination</td>
<td>Clumsy arms, legs, or trunk; loss of balance or falling (particularly to one side) with standing or walking</td>
<td>Incoordination of limbs, trunk, or gait may indicate cerebellar or brainstem ischemia.</td>
</tr>
<tr>
<td>Psychiatric or cognitive</td>
<td>Apathy or inappropriate behavior</td>
<td>These symptoms can indicate frontal lobe involvement and frequently are misinterpreted as poor volitional cooperation.</td>
</tr>
<tr>
<td>function</td>
<td>Excessive somnolence</td>
<td>This symptom may indicate bilateral hemispheric or brainstem involvement.</td>
</tr>
<tr>
<td></td>
<td>Agitation or psychosis</td>
<td>Rarely, these symptoms may indicate brainstem ischemia, particularly if they occur in association with cranial nerve or motor dysfunction.</td>
</tr>
<tr>
<td></td>
<td>Confusion or memory changes</td>
<td>These rarely are isolated symptoms; more frequently, they are associated with language, motor, sensory, or visual changes.</td>
</tr>
<tr>
<td></td>
<td>Inattention to surrounding environment, particularly to one side; if severe, patient may deny deficit or even his or her own body parts</td>
<td>Depending on the severity of neglect, the physician may need to lift the patient's arm to check for strength, rather than rely on the patient to perform this task.</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack.
TABLE 2  
Relative Indications for Inpatient Evaluation of Possible TIA or Stroke*  

<table>
<thead>
<tr>
<th>Condition</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk cardioembolic source: acute myocardial infarction (especially if large and significant wall-motion abnormality is present), mural thrombi, new-onset atrial fibrillation</td>
<td>Consider anticoagulation.</td>
</tr>
<tr>
<td>TIA manifested by major symptoms such as dense paralysis or severe language disorder</td>
<td>Possible evolving large hemispheric stroke with increased risk of brain swelling</td>
</tr>
<tr>
<td>Increasing frequency or severity of TIA (crescendo pattern)</td>
<td>Possible evolving thromboembolic stroke</td>
</tr>
<tr>
<td>Evidence of high-grade carotid artery stenosis</td>
<td>Carotid artery evaluation for possible emergency intervention (surgery, stent, or angioplasty)</td>
</tr>
<tr>
<td>Drooling, imbalance, decreased alertness, difficulty swallowing</td>
<td>Increased risk of falling, or of aspiration and other pulmonary complications</td>
</tr>
<tr>
<td>Severe headache, photophobia, stiff neck, recent syncope</td>
<td>Possible subarachnoid hemorrhage: obtain emergency computed tomographic scan of the head; if the scan is negative but clinical suspicion remains high, cerebrospinal fluid evaluation or possible cerebral angiography is needed.</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack.  
*—May require more than 23 hours of observation in the emergency department, or hospitalization for observation.

for treatment with tissue-type plasminogen activator (tPA).5,6 If a patient is not a candidate for tPA treatment, antplatelet therapy should be initiated as soon as it can be determined that there are no contraindications.4-6 [Reference 6: SOR A, rating of benefits]

Inpatient or Outpatient Evaluation  
Guidelines issued by the National Stroke Association7 recommend evaluation within hours of the onset of TIA symptoms, preferably in an emergency department. If appropriate imaging studies are not immediately available in the emergency department or outpatient setting, the patient should be hospitalized for observation.7 [SOR C, expert opinion] Relative indications for more extended inpatient evaluation for TIA or stroke are listed in Table 2.  

Patients with symptoms of acute TIA for fewer than 24 to 48 hours should undergo diagnostic testing in the emergency department.8 [SOR C, expert opinion] Patients whose symptoms have resolved for more than 48 hours should receive urgent inpatient or outpatient evaluation.

Initial Work-Up for Suspected TIA  
The first step in evaluating a patient with symptoms of TIA is to confirm the diagnosis (Figure 1).  

Differential Diagnosis  
The most common imitators of TIA are glucose derangement, migraine, seizure, postictal states, and tumors (especially with acute hemorrhage).  
TIA typically has a rapid onset, and maximal intensity usually is reached within minutes. Fleeting episodes lasting one or two seconds or nonspecific symptoms such as fatigue, lightheadedness (in the absence of other cerebellar or brainstem symptoms), and bilateral rhythmic shaking of the limbs are less likely presentations of acute cerebral ischemia.

Distinguishing TIA from migraine aura can be difficult. Younger age, previous history of migraine (with or without aura), and associated headache, nausea, or photophobia are more suggestive of migraine than TIA. In general, migraine aura tends to have a marching quality, for example, symptoms such as tingling may progress from the fingers to the forearm to the face. Migraine aura also is

Neurologic symptoms that crescendo with increasing frequency, duration, or severity are particularly ominous signs of impending stroke.
**Initial Work-Up for Suspected TIA**

Confirm TIA history.

Acute (did transient symptoms occur < 24 to 48 hours ago)?

- **Yes**
  - Send patient to hospital emergency department for evaluation.
  - Is patient a candidate for thrombolytic therapy?
  - **No**
    - Urgent outpatient evaluation to identify cause of TIA; if imaging studies are not available in a timely fashion, admit patient. Identify and treat stroke risk factors. Begin medical therapy, including antiplatelet therapy, as soon as possible.
  - **Yes**
    - Initiate aspirin therapy within 24 to 48 hours (if no contraindications).
    - Perform certain tests (*) within 25 minutes of patient’s arrival in emergency department; screen for inclusion/exclusion criteria for IV tPA therapy.
      - Frequent vital signs, with attention to blood pressure* and heart rhythm
      - Head CT*
      - Cardiac monitoring: ECG
      - Medical and neurologic examination*
      - Initial laboratory tests: complete blood count with platelet count*; electrolyte, glucose,* and renal function measurements; PT,* aPTT,* and INR*.
      - Carotid artery evaluation
      - Head MRI and MRA of intracranial and neck vessels, if available and appropriate

Further testing in selected patients (see Table 3)

**FIGURE 1.** Initial work-up for the patient with possible transient ischemic attack (TIA). (*IV = intravenous; tPA = tissue-type plasminogen activator; CT = computed tomography; ECG = electrocardiography; PT = prothrombin time; aPTT = activated partial thromboplastin time; INR = International Normalized Ratio; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography)

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more likely to have a more gradual onset and resolution, with a longer duration of symptoms than in a typical TIA.

If a patient has explosive onset of a severe headache, with or without photophobia, stiff neck, or syncope, acute subarachnoid hemorrhage is a possibility. Rarely, TIA is mistaken for the first presentation of multiple sclerosis in young patients or for amyotrophic lateral sclerosis in older patients.

**HISTORY**

A general medical history should be obtained in all patients with suspected TIA. Special emphasis should be given to possible symptoms of TIA (Table 1), and stroke risk factors should be identified to determine the likelihood that the symptoms are caused by TIA. Modifiable risk factors for stroke include hypertension, diabetes, cardiac disease, elevated blood lipid levels, carotid artery stenosis, smoking, sickle cell anemia, excessive alcohol use, obesity, and physical inactivity.7

Whether hypercholesterolemia is an independent primary risk factor for stroke remains uncertain.9 However, hypercholesterolemia is a significant risk factor for coronary heart disease (CHD) and therefore can be considered
an important risk factor for ischemic stroke. There appears to be a stronger data relationship between total and low-density lipoprotein cholesterol levels, as well as a protective influence of high-density lipoprotein cholesterol levels, in cervical carotid artery atherosclerosis.10

Other important information includes a family history of stroke (including cerebral aneurysm or hypercoagulable state), the use of over-the-counter or illicit drugs, a history of migraine or "severe headaches," recent head trauma, previous systemic clots and, in a woman of childbearing age, a history of spontaneous abortion. Certain findings may indicate the need for special diagnostic tests (Table 3).

PHYSICAL EXAMINATION

Vital signs should be evaluated, including blood pressures in both arms, to rule out stenosis of the subclavian artery, which may manifest as grossly asymmetric pressures. Auscultation of the heart and neck also should be performed. Carotid bruits, when present, are neither highly specific nor highly sensitive for carotid artery stenosis.

All patients with possible TIA should receive a detailed, documented neurologic examination, with emphasis on cognitive and language function, cranial nerve function, facial and limb strength, sensory function, deep tendon reflex symmetry, and coordination. This examination can be helpful in determining whether a patient previously had an unrecognized stroke. It also can serve as a baseline examination if the patient's neurologic status worsens or neurologic symptoms recur. Occasionally, the neurologic examination may identify a nonspecific cause for an acute neurologic deficit (e.g., acute radial nerve palsy, isolated third-nerve palsy in a patient with diabetes mellitus).

DIAGNOSTIC TESTS

Brain Imaging. Computed tomographic (CT) scanning of the head without contrast medium should be performed to identify subarachnoid hemorrhage, intracranial hemorrhage, or subdural hematoma. Urgent identification of these conditions is critical because neurosurgical intervention or special management may be required.

If hemorrhage is present, treatment with tPA or anticoagulants that may worsen central nervous system bleeding should be avoided. Special measures may be needed to manage blood pressure if the patient is found to have hypertension-mediated intracranial hematoma, and further testing may be required if the patient is found to have subarachnoid hemorrhage (e.g., cerebral angiography to rule out aneurysm).

CT scanning also can identify conditions that mimic TIA, including tumors and other masses (especially if hemorrhage occurs acutely within a mass), as well as conditions that are associated with seizures or auras. A head CT scan can identify signs of early brain damage or evidence of old strokes.11,12

Finally, CT scanning of the head with contrast medium should be performed in the febrile patient to rule out an infectious cause or in the patient with a suspected mass (e.g., metastatic carcinoma, abscess).

Because of increased bony artifact in the posterior fossa, CT scanning is not sensitive for evaluating disease in the brainstem or cerebellum. In these instances, magnetic resonance imaging (MRI) is the preferred study.

Electrophysiologic Testing. All patients should have a baseline electrocardiogram (ECG) with rhythm strip.5,12,13 If the ECG is abnormal or the patient has a history of cardiac disease, echocardiography should be performed. Atrial fibrillation and left ventricular hypertrophy (suggesting unrecognized chronic hypertension) are important risk factors for stroke. Recent data suggest that the 90-day risk for a cardiac event
<table>
<thead>
<tr>
<th>History</th>
<th>Implications</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache in postpartum or dehydration setting</td>
<td>Venous thrombosis</td>
<td>MRI with venography or cerebral angiography</td>
</tr>
<tr>
<td>Fever</td>
<td>Subacute or acute bacterial endocarditis</td>
<td>Blood cultures, head CT scan with and without contrast medium; in selected patients with confirmed bacterial endocarditis, perform cerebral angiography to rule out a mycotic aneurysm.</td>
</tr>
<tr>
<td>Confusion, headache, seizure</td>
<td>CNS vasculitis</td>
<td>Cerebral angiography, ESR, lumbar puncture (to look for elevation of white blood cell counts in particular)</td>
</tr>
<tr>
<td>MRI.</td>
<td>Hypertensive encephalopathy</td>
<td>Careful blood pressure monitoring in intensive care setting; consider</td>
</tr>
<tr>
<td>Rheumatologic disease, sympathomimetic drug use</td>
<td>CNS vasculitis</td>
<td>Consider cerebral angiography, ESR, lumbar puncture (to look for elevation of white blood cell counts in particular).</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>Cardioembolic source</td>
<td>Transthoracic or esophageal echocardiography</td>
</tr>
<tr>
<td>Head, neck, jaw pain, especially after trauma</td>
<td>Carotid or vertebral dissection</td>
<td>Consider cerebral angiography or other neck neuroimaging studies (see text).</td>
</tr>
<tr>
<td>Abrupt onset of severe headache with photophobia, or recent syncope</td>
<td>Subarachnoid hemorrhage</td>
<td>Emergency head CT scan; if the scan is negative, evaluate cerebrospinal fluid for elevated red blood cell count or perform cerebral angiography to rule out aneurysm or arteriovenous malformation.</td>
</tr>
<tr>
<td>Confusion, stupor, coma, other brainstem symptoms (poor prognosis)</td>
<td>Vertebrobasilar ischemia</td>
<td>Consider intracranial magnetic resonance angiography or cerebral angiography; if basilar artery is significantly thrombosed, consider intra-arterial thrombolytic therapy (if available).</td>
</tr>
<tr>
<td></td>
<td>Brain swelling, impending herniation</td>
<td>Immediate head CT scan; if the scan is positive, emergency neurosurgical intervention may be required.</td>
</tr>
<tr>
<td>No obvious risk factors for stroke</td>
<td>“Cryptogenic stroke,” patent foramen ovale, intra-atrial septal aneurysm, valvular or aortic arch disease</td>
<td>Consider cerebral angiography, transesophageal echocardiography, and work-up for hypercoagulable state.</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack; MRI = magnetic resonance imaging; CT = computed tomography; CNS = central nervous system; ESR = erythrocyte sedimentation rate.

*—The initial work-up for the patient with possible TIA is outlined in Figure 1.

is seven times higher in patients with TIA and abnormal ECG findings than in those with a normal ECG (4.2 versus 0.6 percent).13

If the ECG is unrevealing, cardiac monitoring in selected patients could help diagnose paroxysmal atrial fibrillation (or other arrhythmias in patients with syncope or palpitations). In patients with untreated atrial fibrillation, echocardiography may identify a thromboembolic source or left ventricular systolic dysfunction, both of which are common predictors of ischemic stroke.14

Transesophageal echocardiography is superior to transthoracic echocardiography for evaluating possible dysfunction of the left atrium (including thrombus) or a patent foramen ovale (an etiology for paradoxical emboli), atrial septal defects (including aneurysm), and aortic plaque. Recent clinical trials15,16 suggest that transesophageal echocardiography should be considered in patients without an identifiable cause of TIA or known cardiac disease, because it may detect a condition requiring therapeutic intervention (e.g., anticoagulation for thrombus). Aortic plaque, which has been associated with stroke, can be visualized well on transesophageal echocardiography.

**Laboratory Tests.** A complete blood count with platelet count should be obtained to rule out polycythemia, thrombocytopenia, and thrombocytosis. It is helpful to know the prothrombin time (PT), activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR) before antiplatelet or anticoagulation therapy is administered; the PT, aPTT, and INR can be elevated in some hypercoagulable states.

The glucose level should be determined to
rule out hypoglycemia or hyperglycemia and to help diagnose occult diabetes. Blood urea nitrogen and creatinine levels are important, because poor renal status may prohibit the use of contrast media in imaging studies. An erythrocyte sedimentation rate (ESR) should be obtained to potentially rule out vasculitis. Finally, a drug of abuse screen, a pregnancy test, a homocystine level determination, or a blood alcohol level measurement should be performed in selected patients.

**Follow-Up Evaluation**

**LIPID PROFILE**

After the initial more abbreviated evaluation in the emergency department, risk factors for stroke can be reassessed thoroughly later in the evaluation. Recent data indicate that treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) reduces the risk of stroke by about 30 percent in patients with CHD.17,18 Therefore, a fasting lipid profile reflective of the patient’s normal eating habits should be obtained, and statin therapy should be initiated if indicated.

**HYPERCOAGULABLE STATES**

Patients with known risk factors for stroke and those with a history of migraine, spontaneous abortion, pulmonary emboli, or deep venous thrombosis, or a family history of any of these conditions, should be evaluated for hypercoagulable states. Initial tests include ESR, antinuclear antibody test, rapid plasma reagent test, and antiphospholipid antibody tests. Referral to a hematologist or neurologist can ensure cost-effective evaluation of the multiple coagulation-factor abnormalities and conditions that can cause embolic stroke.

**TESTING FOR ARTERIAL PATENCY AND BLOOD FLOW**

Carotid duplex ultrasonography should be performed in a reliable laboratory, preferably one with validation against the results of cerebral angiography. Alternatively, cerebral and cervical vessels can be evaluated by magnetic resonance angiography (MRA) with contrast medium or by CT angiography. If the workup demonstrates carotid or other large-vessel atherosclerotic disease in the patient with TIA and unrecognized CHD, coronary artery testing is recommended.19

**MRI.** Clear advantages of MRI of the brain over CT scanning of the head include better imaging of tissues (i.e., greater sensitivity for early edema), superior imaging within the posterior fossa (including the brainstem and cerebellum), additional planes of imaging (sagittal, coronal, and oblique), and no exposure to radiation.

A clear disadvantage of brain MRI is that it may or may not identify hemorrhage. For this reason, although MRI can be helpful, it should not replace urgent CT scanning of the head in the initial work-up of patients with possible TIA. When cerebrovascular malformation, aneurysm, cerebral venous thrombosis, or arteritis is suspected, MRI or MRA is preferred.

Diffusion-weighted imaging detects cellular edema as early as 10 to 15 minutes after symptom onset. However, this technique is not yet widely available.

**MRA.** This imaging modality is a noninvasive means of assessing intra- and extracranial vessels. Current MRA techniques use intravenously administered contrast medium (gadolinium) to visualize the vessels.

MRA with the administration of contrast medium also is effective in identifying vertebrobasilar stenosis, although recent data suggest that intracranial vertebral artery disease can be missed.20 Depending on the MRA acquisition technique, the percentage of intracranial vessel stenosis can be overestimated (sensitivity of approximately 85 percent compared with cerebral angiography).21 Therefore, if accuracy is therapeutically important, cerebral angiography is necessary.

When near occlusion of the carotid artery cannot be distinguished from complete occlusion on MRA or carotid Doppler ultrasound studies, cerebral angiography should be con-
sidered. Surgery generally cannot be performed on completely occluded vessels.

Special consideration should be given to patients who present with a history or symptoms that suggest arterial dissection. This condition can be diagnosed using neck MRI scans in certain sequences that can identify hemorrhage within the vessel wall (T₁-weighted images with fat suppression).

Patients with carotid artery dissection can present with acute or subacute unilateral neck, head, or jaw pain. These symptoms may be associated with visual or language deficits, or with sensorimotor deficits, particularly in the opposite arm. More typically, patients with carotid artery dissection present with only some of these features, such as temporal headache with lateral neck pain and, possibly, transient visual obscuration (amaurosis fugax) because of thromboemboli in the ophthalmic artery.

Both carotid and vertebral artery dissections have been described after trauma, although spontaneous dissection also is common. Patients should be evaluated for connective tissue disease because of the associated increased risk of dissection.

If the MRI or MRA study is inconclusive, cerebral angiography should be used to rule out arterial dissection or better define the percentage of vessel narrowing.

**CT Angiography.** This modality is another state-of-the-art technique for detecting blood flow to the brain. CT angiography also is becoming a useful imaging modality for identifying carotid or vertebral artery dissection. Because the technique requires venous injection of contrast dye, the patient's renal status should be considered before the test is performed.

Conventional CT scanning in combination with CT angiography currently is being evaluated as an addition to the diagnostic imaging tools for use in patients with TIA or stroke. This combination can provide useful information about vascular anatomy (in the form of three-dimensional reconstructions) and the extent and location of infarction. It may allow rapid evaluation of patients with TIA or stroke in hospitals or institutions that do not have MRI capability.

**Cerebral Angiography.** This technique continues to be the gold standard for complete evaluation of intracranial and extracranial vessels. With cerebral angiography, both arterial and venous phases of cerebral blood flow can be visualized (dynamic study). However, cerebral angiography is an invasive technique that can result in neurologic complications (total incidence rate: 1.3 to 4.6 percent),²³ including major stroke or death in 0.1 to 1.3 percent of patients, depending on the study.²⁴²⁵

Relative indications for cerebral angiography include suspected carotid dissection unconfirmed on a noninvasive neuroimaging study, subarachnoid hemorrhage (to identify bleeding source), intracerebral hemorrhage in the absence of hypertension, and vasculitis. If one of these conditions is suspected, referral to a neurologist can be helpful in obtaining and interpreting the angiogram.

**Special Considerations**

**VERTEBROBASILAR ISCHEMIA**

Typical signs and symptoms of ischemic syndromes involving the anterior and posterior circulations are listed in Table 4. The brainstem and cerebellum are confined within the posterior fossa, a bony cavity with poor tolerance of brain swelling or mass effects (e.g., from hemorrhage). Because brainstem structures are essential for preserving critical respiratory function and arousal states,
### TABLE 4
**Typical Characteristics of Ischemic Syndromes Involving the Anterior and Posterior Circulations**

<table>
<thead>
<tr>
<th>Ischemic syndrome: circulation involved</th>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior circulation*</td>
<td>Visual-field cut</td>
<td>Inability to see well (i.e., difficulty reading or driving</td>
</tr>
<tr>
<td></td>
<td>Language dysfunction (left hemisphere most often affected): aphasia</td>
<td>Difficulty finding or understanding words, inability to read, garbled or slurred speech</td>
</tr>
<tr>
<td></td>
<td>Motor dysfunction: contralateral face, arm, or leg weakness</td>
<td>Dropping objects; depending on severity, inability to lift or move a body part or objects</td>
</tr>
<tr>
<td></td>
<td>Sensory dysfunction: contralateral increased or decreased sensation to pain, heat, or cold</td>
<td>Tingling (paresthesias), numbness, or pain</td>
</tr>
<tr>
<td></td>
<td>Behavior dysfunction (right hemisphere): inattention to surrounding environment, particularly to one side; if severe, patient may deny deficits or even his or her own body parts</td>
<td>The patient usually reports no symptoms, but family members or others report that the patient has difficulty dressing, ignores half of food on a plate, or has poor attention to one side of the room or to someone speaking to the patient on one side versus the other (most often, the left side is ignored).</td>
</tr>
<tr>
<td>Posterior circulation†</td>
<td>Nystagmus</td>
<td>Vertigo (spinning sensation)</td>
</tr>
<tr>
<td></td>
<td>Disconjugate gaze</td>
<td>If subtle, blurry or double vision</td>
</tr>
<tr>
<td></td>
<td>Homonymous visual-field cut</td>
<td>Inability to see well, especially to one side</td>
</tr>
<tr>
<td></td>
<td>Contralateral weakness</td>
<td>Dropping objects, inability to fully lift or move the limb</td>
</tr>
<tr>
<td></td>
<td>Incoordination of trunk or limbs (ataxia)</td>
<td>Clumsiness, falling, inability to coordinate an action (e.g., drink from a cup without spilling contents)</td>
</tr>
<tr>
<td></td>
<td>Motor or sensory dysfunction on opposite side of cranial nerve deficits (crossed signs suggest brainstem involvement)</td>
<td>For example, the patient may report double vision, droopiness on the left side of the face, and dragging of the right leg (because of weakness)</td>
</tr>
<tr>
<td></td>
<td>Bilateral signs</td>
<td>Abrupt weakness of both legs, falling</td>
</tr>
<tr>
<td></td>
<td>Decreased mentation; stupor or coma</td>
<td>Family members or others report that the patient has poor responsiveness or that they are unable to arouse the patient</td>
</tr>
</tbody>
</table>

*—Includes the internal carotid artery, middle cerebral artery, and anterior cerebral artery, as well as the branches of these arteries.  †—Includes the vertebral arteries, basilar artery, and posterior cerebral artery, as well as the branches of these arteries.

Patients with vertebrobasilar ischemia should be monitored closely. It also is crucial to search for life-threatening cerebrovascular disease, such as basilar artery stenosis or thrombosis or disease affecting multiple large vessels (e.g., bilateral, vertebral, or carotid artery stenosis).

**TIA IN A YOUNG PATIENT**

When a TIA occurs in a patient younger than 45 years, particularly if there are no clear risk factors for stroke, it is advisable to refer the patient to a neurologist for consideration of specialized testing. For example, it may be necessary to determine the utility of cerebral angiography to rule out vasculitis, carotid artery dissection, and other forms of nonatherosclerotic vasculopathy, or lumbar spinal puncture with cerebrospinal fluid evaluation may be required to rule out chronic infection or inflammation.

Because cardiac abnormalities are among the most common causes of TIA in young patients, a baseline ECG with rhythm strip should be obtained, and transthoracic and transesophageal echocardiography should be considered. A toxicology screen for drugs of abuse (especially sympathomimetic compounds) usually is performed.

Several newly identified, genetically based metabolic and hematologic syndromes have been found to be associated with stroke. With some of these syndromes, initial symptoms occur in the younger years (late childhood, adolescence, or early adulthood). Diagnosis of these syndromes may require specialized tests. Such testing could be important to better define treatment options and prognosis, as well as to identify family members who may
be at risk for TIA or stroke. The author indicates that she does not have any conflicts of interest. Sources of funding: none reported.

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Transient Ischemic Attacks: Part II. Treatment

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Risk factors for stroke should be evaluated in patients who have had a transient ischemic attack. Blood pressure, lipid levels, and diabetes mellitus should be controlled. When applicable, smoking cessation and weight loss also are important. Angiotensin-converting enzyme inhibitor therapy may help prevent stroke. Aspirin is the treatment of choice for stroke prevention in patients who do not require anticoagulation. Clopidogrel is an alternative therapy in patients who do not tolerate aspirin. Atrial fibrillation, a known cardioembolic source (confirmed thrombus), or a highly suspected cardioembolic source (e.g., recent large myocardial infarction, dilated cardiomyopathy, mechanical valve, rheumatic mitral valve stenosis) are indications for anticoagulation. (Am Fam Physician 2004;69:1681-8. Copyright © 2004 American Academy of Family Physicians.)

This is part II of a two-part article on transient ischemic attacks. Part I, "Diagnosis and Evaluation," appears in this issue on page 1665.

New data suggest that long-term management of stroke risk factors after a transient ischemic attack (TIA) generally is inadequate. Part II of this two-part article reviews recent information on the management of the more important risk factors for stroke, the use of antiplatelet therapy, and special management issues in patients with TIAs.

Risk Factor Management

BLOOD PRESSURE

Elevated blood pressure (above 140/90 mm Hg) is the most important treatable risk factor for TIA and stroke. Antihypertensive drugs reduce the risk of strokes, regardless of whether patients have hypertension. Currently, however, the American Heart Association (AHA) does not have any recommendations for antihypertensive drug therapy in "nonhypertensive" patients after a TIA or stroke.

Hypertension occurs more frequently and more severely in blacks; therefore, this patient group merits special attention. Patients with diabetes mellitus or chronic renal disease also are at increased risk for hypertension and, thus, TIA or stroke. In patients with diabetes mellitus or chronic renal disease, the treatment goal is to keep blood pressure below 130/80 mm Hg.

Important new guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) require lifestyle modifications (weight reduction, sodium restriction, regular aerobic activity, limited alcohol intake) to prevent cardiovascular disease in prehypertensive patients with a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg. [SOR C, consensus opinion]

Starting Antihypertensive Drug Therapy After a TIA or Stroke. Typically, blood pressure lowering without treatment in the first two weeks after a stroke. Therefore, it is rational to wait two weeks before continuing or beginning antihypertensive drug therapy.

In the patient found to have high blood pressure after a stroke or TIA, evidence of end-organ damage should be sought, because such damage suggests a chronic disorder rather than an acute condition. In some patients with chronically elevated blood pressure, the brain may depend on abnormally higher perfusion pressures because of derangement of the normal cerebral autoregulation of intracranial blood vessels. In this setting, abrupt lowering of blood pressure could promote cerebral ischemia or even extend an evolving infarction. Rarely, TIA is a manifestation of hemodynamically significant critical stenosis of an extracranial or intracranial vessel. In this condition, the brain requires increased cerebral perfusion pressure, and overtreatment of blood pressure may promote cerebral ischemia. The physician may note that TIAs occur when the patient's blood pressure drops or when the patient stands up or sits up.
Patients with diabetes mellitus or chronic renal disease should maintain a blood pressure lower than 130/80 mm Hg.

In most patients, blood pressure should not be treated aggressively immediately (i.e., within the first 24 hours) after a stroke or TIA unless the systolic blood pressure is higher than 220 mm Hg or the diastolic blood pressure is above 120 mm Hg. Important exceptions include patients with acute myocardial infarction (especially with left ventricular failure), hypertensive crisis or hypertensive encephalopathy, renal failure, aortic dissection, or retinal hemorrhages. If, in the absence of the previously mentioned conditions, treatment is necessary, blood pressure should be reduced slowly over days to prevent worsening ischemia.

Angiotensin-Converting Enzyme (ACE) Inhibitors. Increased attention is being directed at ACE inhibitors because of the results of the recent Heart Outcomes Prevention Evaluation (HOPE) study. In this large, randomized trial, inpatients considered to be at "high cardiovascular risk" were treated with ramipril or placebo. Over four years, the relative reduction in the risk of stroke was 32 percent (within a composite outcome) in the patients who received ramipril. Debate currently centers on whether the HOPE study findings were unique to ACE inhibitors as a class or occurred because of a more general blood pressure–lowering effect that also could be obtained with other antihypertensive drug classes.

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS),7 patients with stroke or TIA within the previous five years were given placebo or combination therapy consisting of perindopril (an ACE inhibitor) and indapamide (a diuretic). In both hypertensive and "nonhypertensive" patients, the drug combination resulted in a 43 percent reduction in the relative risk of recurrent stroke (four-year follow-up). In PROGRESS, hypertension was defined as a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher. To date, however, no consensus statements indicate a preference for one antihypertensive drug or drug class over another for use in secondary (or primary) stroke prevention.8,9 In particular, the use of ACE inhibitors after acute stroke remains controversial.9 [Reference 2: SOR B, unknown effectiveness]

SMOKING

A meta-analysis10 of 32 studies found that the risk of stroke in persons of either sex and all ages was 50 percent higher in smokers than in nonsmokers. Therefore, the family physician should make a vigorous attempt, at every clinic visit, to implement a smoking cessation plan, particularly in the patient who has had a TIA. Smoking cessation may be more likely to be successful if the physician encourages all family members to quit smoking simultaneously.

HEART DISEASE

Cardiac disease (i.e., rheumatic heart disease, mitral valve stenosis, atrial fibrillation with or without valvular disease) is a predisposing factor for TIA and stroke. In addition, the electrocardiographic finding of left ventricular hypertrophy resulting from prolonged hypertension is associated with a fourfold increased risk of stroke. Patients with atrial fibrillation who also have other risk factors are at particularly high risk for TIA or stroke. These additional risk factors include a history of hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valves, previous stroke, systemic embolism, and age greater than 75 years. Patients with atrial fibrillation who have already had a TIA are considered to be at high risk for stroke. The results of one study11 of patients with atrial fibrillation and TIA or minor stroke indicate that anticoagulant therapy is significantly more effective than aspirin in preventing recurrent stroke.

In addition, short-term cardiac morbidity is substantial after a TIA. One recent study12 suggested that among patients who have a TIA, the 90-day risk for a cardiac event is higher in those who have any abnormal finding on an electrocardiogram (ECG). In this study, the ECG findings of left ventricular hypertrophy, atrial fibrillation, and atrio-ventricular conduction abnormalities in patients with TIA were independently associated with more than a doubling of the risk of a cardiac event.

BLOOD LIPID LEVELS

Convincing evidence from observational studies shows that elevated blood lipid levels are a risk factor for ischemic stroke.13 High cholesterol levels are a risk factor for coronary heart disease (CHD) and, thus, a substantial secondary risk factor for stroke. Recent data indicate that in patients with CHD, treatment with statins (3-hydroxy-3-methylglutaryl coenzyme
TABLE 1
Summary of Antiplatelet Therapy After TIA

| In most patients, aspirin in a dosage of 50 to 325 mg per day is the recommended initial agent for antiplatelet therapy.3,30 | TIA = transient ischemic attack. Information from references 3, 27, and 29 through 31. |

A reductase inhibitors) results in a 30 to 32 percent reduction of the stroke risk.2,14,15 [Reference 2; SOR A, beneficial] Because statins have multiple vascular effects, as well as cholesterol-lowering properties, the exact mechanism of stroke prophylaxis is unknown.

Current guidelines16,17 recommend consideration of statin therapy in patients with known CHD, many of whom could present with TIA or stroke. According to a recent Cochrane review,18 it is not clear whether statin therapy is as effective in the prevention of recurrent stroke or TIA as it is in the primary prevention of stroke in patients with CHD.

DIABETES MELLITUS

Diabetes mellitus, independent of its association with hypertension, increases the overall risk of stroke by approximately 25 to 50 percent.19 There is no conclusive evidence that "tight" glucose control results in a reduction of ischemic stroke or other macrovascular events.20,21

Recent data from the Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE (MICRO-HOPE) sub-study22,23 indicate that ramipril therapy reduces cardiovascular and cerebrovascular events in patients with diabetes mellitus and one cardiac risk factor. In MICRO-HOPE, stroke events were reduced by 33 percent, and stroke-related deaths were reduced by 37 percent.

Antiplatelet Therapy

Currently available antiplatelet agents for stroke prophylaxis include aspirin, clopidogrel (Plavix), ticlopidine (Ticlid), and aspirin-dipyridamole (Aggrenox). Except in patients with special conditions such as atrial fibrillation, anticoagulation has no advantages over antiplatelet therapy and is associated with an increased risk of bleeding.24,25 [Reference 2; SOR A, likely to be harmful or ineffective]

ASPIRIN

Aspirin is the most widely used and most economical antiplatelet agent. Aspirin therapy after a stroke or TIA reduces the long-term relative risk of stroke and increases the chance of a full recovery.26 The optimal aspirin dosage for use in the prevention of stroke or TIA remains controversial, but a range of 50 to 325 mg per day has been recommended.3

OTHER ANTIPLATELET AGENTS

Because of safety and tolerance issues associated with ticlopidine, clopidogrel is the more widely used second-line antiplatelet agent. Neutropenia, rash, diarrhea, and thrombotic thrombocytopenic purpura (TTP) occur less frequently with clopidogrel than with ticlopidine. The incidence of ticlopidine-related TTP is estimated to be one case per 1,600 to 5,000 patients treated.3 Although clopidogrel and aspirin have similar safety profiles, there have been rare reports of clopidogrel-related TTP, with the majority of cases occurring within two weeks of initiation of the drug.27

One large, randomized, double-blind clinical trial28 compared clopidogrel (75 mg per day) and aspirin (325 mg per day), with the composite outcome being the primary end points of stroke, myocardial infarction, and vascular death. There was a slight trend for clopidogrel to reduce annual outcome events compared with aspirin (5.3 percent versus 5.8 percent; P = .043). Based on this marginal difference and the fact that clopidogrel currently is more expensive than aspirin, many physicians favor the use of aspirin in a standard dosage (325 mg per day) for antiplatelet therapy but choose clopidogrel when patients cannot tolerate aspirin.

The U.S. Food and Drug Administration recently approved the use of combination aspirin-dipyridamole (Aggrenox) for stroke prevention. The combination drug contains 50 mg of aspirin (low dose) and 400 mg of extended-release dipyridamole. A single large, randomized study29 found that this specific aspirin-dipyridamole combination reduced stroke by 22 percent compared with low-dose aspirin therapy alone. However, the expected similar benefits for reducing myocardial infarction and vascular death were not observed with aspirin, dipyridamole, or combination therapy.

Debate continues about the value of combination therapy and the interpretation of study data. Table 1 summarizes key points about antiplatelet therapy in
patients who have had a TIA.

**Special Management Issues**

**TIA or Stroke Recurrence during Antiplatelet Therapy**

Although well-established evidence supports the role of antiplatelet therapy in the prevention of recurrent stroke, fewer data are available to guide therapeutic decisions in patients who are receiving antiplatelet therapy but have another TIA or stroke. In patients who are taking an antiplatelet agent (most often, aspirin), the annual rate of recurrent stroke is estimated to be about 8 percent (range: 4 to 14 percent).30,32

Patient compliance with antiplatelet therapy should be determined. When possible, the cause of the TIA or stroke should be identified. If there is evidence of new-onset atrial fibrillation or a cardioembolic source, anticoagulation (rather than antiplatelet therapy) may be required, depending on the patient’s age and other risk factors. All stroke risk factors should be immediately reevaluated and aggressively treated.

Many physicians question the therapeutic value of increasing the dosage of an antiplatelet agent, switching to a new agent, adding a second antiplatelet agent, or adding a low-dose anticoagulant drug.3

**Symptomatic Carotid Disease**

*Carotid Endarterectomy.* There is little controversy surrounding the use of carotid endarterectomy for secondary prevention of stroke in patients with symptomatic severe carotid stenosis, defined as 70 to 99 percent vessel occlusion, based on the results of the North American Symptomatic Endarterectomy Trial (NASCET).33 In the initial trial analysis (two-year follow-up), carotid endarterectomy reduced the relative risk of stroke by 65 percent compared with medical management.

The NASCET collaborators34 recently reported that carotid endarterectomy may result in only a modest reduction of the stroke rate in patients with symptomatic moderate stenosis, defined as 50 to 69 percent vessel occlusion. The incidence of ipsilateral stroke was 16 percent in surgically treated patients and 22 percent in medically managed patients ($P = .045$). Based on their results, the authors recommended restraint rather than promotion of carotid endarterectomy.

A substudy analysis of patients from NASCET35 who presented with bilateral carotid stenosis—one side that was symptomatic (noncardioembolic TIA or stroke) and the other side that was asymptomatic—revealed that the overall risk of stroke at five years was relatively low. Patients with 60 to 99 percent stenosis in the asymptomatic carotid artery had an overall 10 percent risk of a first stroke in the territory of the asymptomatic carotid, and a total 16 percent risk of stroke when lacunar and cardioembolic strokes were included (3.2 percent annual risk of stroke). High-risk patients included those with diabetes mellitus, silent brain infarction, or higher degree of stenosis. AHA guidelines for carotid endarterectomy recommend the use of aspirin (unless contraindicated) before surgery.36

*Vascular Angioplasty and Stenting.* The roles of vascular angioplasty and stenting procedures in stroke prevention remain controversial. The controversy has been fueled by the rapid development of new technologies and techniques, including distal cerebral protection devices.37 It has been argued that patients with symptomatic high-grade carotid stenosis (70 percent vessel stenosis or higher) who are not candidates for routine carotid endarterectomy may represent a small subpopulation of patients who can benefit from extracranial carotid stenting or angioplasty; to date, however, this view has not been supported by published data from any large clinical trial.

**Anticoagulation**

Unless contraindicated, anticoagulation therapy is appropriate in patients with high-risk cardioembolic conditions.3 These conditions include atrial fibrillation, a known cardioembolic source (confirmed thrombus), or a suspected cardioembolic source (recent large myocardial infarction, mechanical valve, dilated cardiomyopathy, rheumatic mitral valve stenosis).

Anticoagulation has a well-established role in the primary prevention of stroke in patients with atrial fibrillation, especially high-risk patients with hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valves, a previous stroke, a TIA, systemic embolism, or age greater than 75 years. There is also evidence that warfarin (Coumadin) is useful for secondary prevention of stroke, as well as primary prevention.38 It is unclear whether heparin should be started immediately after a TIA in patients with atrial fibrillation.

The rate of stroke recurrence after acute stroke in patients with atrial fibrillation currently is under debate. Reported recurrence rates for the initial weeks vary widely.
(2.5 to 20 percent).³⁹ The Cerebral Embolism Task Force⁴⁰ concluded that the risk of recurrent stroke was low during the first two weeks after a stroke in patients with nonvalvular atrial fibrillation. Whether the risk of recurrent TIA or the risk of stroke also is low in the patient with atrial fibrillation and TIA alone is unknown.

Patients who have atrial fibrillation also have noncardioembolic strokes. Therefore, even in the patient with atrial fibrillation, an evaluation for noncardioembolic risk factors should be performed. In the patient who previously has been diagnosed with TIA or stroke and is adequately anticoagulated, a second TIA or stroke could represent a noncardioembolic source.⁴¹

In patients with cardiogenic emboli, consensus is lacking on whether to start intravenous heparin therapy before chronic oral anticoagulation is initiated.²⁷,⁴²,⁴³

HORMONE THERAPY IN WOMEN AFTER A TIA

The Women’s Estrogen for Stroke Trial⁴⁴,⁴⁵ was a randomized, blinded, placebo-controlled study that evaluated the effects of estrogen alone in a large cohort of postmenopausal women who had a stroke or TIA. In this trial, estrogen therapy did not affect the incidence of nonfatal stroke during a mean follow-up period of 2.8 years.

New data indicate that certain menopausal hormone therapies increase the risk of CHD and ischemic stroke.⁴⁵,⁴⁶ Therefore, the benefits and risks of hormone therapy should be weighed carefully in women who have had a TIA.

A recent meta-analysis⁴⁷ found an increased risk of stroke in women who use oral contraceptive pills (OCPs), including those who use low-dose OCPs. However, because of the low incidence of stroke in this young population, the overall benefit of OCPs may outweigh the risk. In women with previous stroke or TIA, it may be prudent to withhold OCPs or hormone therapy.

VERTEBROBASILAR ISCHEMIA

Anticoagulation commonly is used in patients who have had a vertebrobasilar stroke. However, a joint committee

**TABLE 2**

**SUMMARY OF GUIDELINES FOR THE MANAGEMENT OF STROKE RISK FACTORS AFTER TIA**

<table>
<thead>
<tr>
<th>Stroke risk factor</th>
<th>Management goal</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Systolic blood pressure &lt;140 mm Hg and diastolic blood pressure &lt;90 mm Hg or Systolic blood pressure &lt;130 mm Hg and diastolic blood pressure &lt;80 mm Hg if the patient has end-organ damage, diabetes mellitus, or chronic renal disease</td>
<td>Consult JNC 7 recommendations,⁴ including new data on “prehypertension” (systolic blood pressure of 120 to 139 mm Hg and diastolic blood pressure of 80 to 89 mm Hg), which requires aggressive lifestyle modifications.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking cessation</td>
<td>Smoking cessation program, including nicotine replacement, drug therapy, and counseling as indicated Consult national guideline for specific treatment.⁵⁰</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Blood glucose level &lt;126 mg per dl (7.0 mmol per l)</td>
<td>Consult AAFP and ADA evidence-based policy statement.⁵¹</td>
</tr>
<tr>
<td>Lipid levels</td>
<td>Low-density lipoprotein cholesterol level &lt;100 mg per dl (2.60 mmol per l)</td>
<td>Dietary control, lipid-lowering agent (e.g., statin)¹⁶,¹⁷,⁵²</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack; JNC 7 = the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; AAFP = American Academy of Family Physicians; ADA = American Diabetes Association.

Information from references 4, 16, 17, 21, and 50 through 53.
TABLE 3
Summary of Guidelines for the Management of Specific Conditions After TIA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncardioembolic source</td>
<td>Aspirin in a dosage of 50 to 325 mg per day1,30,49 or Clopidogrel (Plavix), ticlopidine (Ticlid), or aspirin-dipyrindamole (Aggrenox)9</td>
<td>If aspirin therapy is not tolerated or is contraindicated, consider alternative antiplatelet agent.</td>
</tr>
<tr>
<td>Cardioembolic source</td>
<td></td>
<td>With ticlopidine therapy, monitor blood cell count; consider the same monitoring during initial treatment with clopidogrel. Clopidogrel has not been tested for TIA prophylaxis only.</td>
</tr>
<tr>
<td>Known thrombus</td>
<td>Oral anticoagulation, unless contraindicated2,40</td>
<td>AHA: recommended for high-risk patients who have had a TIA NSA: consider IV heparin therapy.</td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>Warfarin (Coumadin); INR of 3.0 to 4.0 (long term)30,54,55</td>
<td>Consult AHA and EUSI recommendations.2,30,55</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation</td>
<td>Warfarin: INR of 2.0 to 3.0 (long term)2,21,43,54,55</td>
<td>Consult AHA, ACC, and EAC combined recommendations for timing of treatment and role of cardioversion.</td>
</tr>
<tr>
<td>Recent myocardial infarction or left ventricular thrombus</td>
<td>Warfarin; INR of 2.0 to 3.0 (6 months)2,21,30,43,54,55</td>
<td>Monitor the INR frequently, particularly when there is coadministration of protein-bound medications, during major illness, or when there is a major change in diet.</td>
</tr>
<tr>
<td>Possible cardioembolic source</td>
<td>Antiplatelet agents2,30</td>
<td>In most patients, aspirin in a dosage of 50 to 325 mg per day (unless contraindicated)</td>
</tr>
<tr>
<td>Carotid artery stenosis (atherosclerosis)</td>
<td>Symptomatic (ipsilateral), severe (70% to 99% occlusion) carotid endarterectomy if patient is good surgical candidate2,21,33,36</td>
<td>Beneficial if surgical complication rate of less than 3%; life expectancy of 5 years or greater; continue to maximize treatment of other risk factors. Antiplatelet therapy is recommended before and after surgery.</td>
</tr>
<tr>
<td>Carotid artery stenosis (atherosclerosis)</td>
<td>Symptomatic (ipsilateral), moderate (50% to 69% occlusion) carotid endarterectomy in selected patients2,21,34,56</td>
<td>Consider the patient’s sex, comorbid conditions, and life expectancy in the decision-making process; continue to maximize treatment of other risk factors. Antiplatelet therapy is recommended before and after surgery.</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack; AHA = American Heart Association; NSA = National Stroke Association; IV = intravenous; INR = International Normalized Ratio; EUSI = European Stroke Initiative; ACC = American College of Cardiology; EAC = European Society of Cardiology.

Information from references 3, 21, 30, 33, 34, 36, 43, 49, and 54 through 56.

from the American Academy of Neurology and the American Stroke Association46 found no clear evidence addressing this specific clinical situation and therefore provided no specific recommendations for the use of anticoagulation in these patients during acute cerebral ischemia. There is no mention of the use of anticoagulation in patients who have had a TIA, or of the use of surgical or endovascular treatments in patients with significant vertebrobasilar stenosis.

In patients with recurrent vertebrobasilar symptoms, interventions such as angioplasty, stenting, surgical reconstruction, and decompression have unproven efficacy. In an acute life-threatening situation such as midbasilar thrombotic occlusion (a condition associated with high morbidity and mortality rates), intra-arterial thrombolysis (if available) is an extreme option. Patients with refractory vertebrobasilar TIA should be evaluated by a neurologist before invasive procedures are performed, because these procedures can be associated with significant morbidity and mortality.21,49

Guidelines for the management of patients with TIAS are summarized in Tables 2A,16,17,21,30,35 and 3,2,21,30,33,34,36,43,49,54-56.
The author indicates that she does not have any conflicts of interest. Sources of funding: none reported.

REFERENCES


Acute Stroke Diagnosis

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ERIC CHENG, MD, MS, University of California, Los Angeles, Department of Neurology, Los Angeles, California

Stroke can be categorized as ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Awakenings with or experiencing the abrupt onset of focal neurologic deficits is the hallmark of ischemic stroke diagnosis. The most common presenting symptoms for ischemic stroke are difficulty with speech and weakness on one half of the body. Many stroke mimics exist; two of the most common are a postictal seizure and hypoglycemia. Taking a detailed history and performing ancillary testing will usually exclude stroke mimics. Neuroimaging is required to differentiate ischemic stroke from intracerebral hemorrhage, as well as to diagnose entities other than stroke. The choice of neuroimaging depends on its availability, eligibility for acute stroke interventions, and the presence of patient contraindications. Subarachnoid hemorrhage presents most commonly with severe headache and may require analysis of cerebrospinal fluid when neuroimaging is not definitive. Public education of common presenting stroke symptoms is needed for patients to activate emergency medical services as soon as possible after the onset of stroke. (Am Fam Physician. 2009;80(1):33-40. Copyright © 2009 American Academy of Family Physicians.)

The symptoms of stroke can sometimes be misleading and misinterpreted by physicians and patients. Family physicians are on the front line in their communities to recognize and manage acute cerebrovascular diseases. Accurate and prompt evaluation of cerebrovascular disease will increase eligibility of patients to receive acute therapy for stroke.

Classifying Stroke
Stroke can be subclassified by pathologic process and the vascular distribution affected. Defining the overall pathologic process is critical for decisions regarding thrombolysis, inpatient therapy, and prognosis. In the United States, 87 percent of all strokes are ischemic secondary to large-artery atherosclerosis, cardioembolism, small-vessel occlusion, and other or undetermined causes. The remaining 13 percent of strokes are hemorrhagic in intracerebral or subarachnoid locations. A common means of subclassifying ischemic stroke is by vascular distribution. Clinical determination of the affected vascular territory may aid rational evaluation and individualization of therapy. However, this type of subclassification has only fair to good interobserver agreement among stroke experts. Table 1 lists stroke subtypes by vascular distribution. The cause of subarachnoid hemorrhage is attributed to an aneurysm in approximately 85 percent of cases, with rarer causes accounting for the rest.

Clinical Diagnosis

HISTORY AND PHYSICAL EXAMINATION

History and physical examination remain the pillars of diagnosing stroke. The most common historical feature of an ischemic stroke is its acute onset; the most common physical findings of ischemic stroke are focal weakness and speech disturbance. The most common and reliable symptoms and signs of ischemic stroke are listed in Table 2. Primary care physicians practicing in an emergency setting had a 92 percent sensitivity for diagnosis of stroke and transient ischemic attack (TIA) in a community-based study of
Table 1. Oxfordshire Ischemic Stroke Subtypes and Clinical Features

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total anterior circulation</td>
<td>Combination of new higher cerebral dysfunction (e.g., dysphasia, dyscalculia, visual-spatial disorder), homonymous visual field defect and ipsilateral</td>
</tr>
<tr>
<td>infarct (TACI)</td>
<td>motor and/or sensory defect involving two areas of the face, arm, or leg, or with the arm, leg, and/or sensory defects included.</td>
</tr>
<tr>
<td>Lacunar infarct (LACI)</td>
<td>Pure motor or pure sensory symptoms; sensorimotor stroke; or ataxic hemiparesis. Face, arm, and leg syndromes included.</td>
</tr>
<tr>
<td>Partial anterior circulation</td>
<td>Patients with only two of the three TACI components, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those classified as TACI (e.g., confined to one limb or to face and hand, but not the whole arm).</td>
</tr>
<tr>
<td>infarct (PACI)</td>
<td></td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>Any one of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; disordered conjugate gaze; cerebellar dysfunction without ataxic hemiparesis; isolated homonymous visual field defect.</td>
</tr>
</tbody>
</table>

Information from reference 6.

Table 2. Most Common Symptoms and Signs of Stroke and Their Reliability

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Prevalence (%)</th>
<th>Agreement among examiners (Kappa)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute onset</td>
<td>96</td>
<td>Good (0.63)*</td>
</tr>
<tr>
<td>Subjective arm weakness</td>
<td>63</td>
<td>Moderate (0.59)*</td>
</tr>
<tr>
<td>Subjective leg weakness</td>
<td>54</td>
<td>Moderate (0.59)*</td>
</tr>
<tr>
<td>Self-reported speech</td>
<td>53</td>
<td>Good (0.64)*</td>
</tr>
<tr>
<td>disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective facial weakness</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Arm paresthesia</td>
<td>20</td>
<td>Good (0.62)*</td>
</tr>
<tr>
<td>Leg paresthesia</td>
<td>17</td>
<td>Good (0.62)*</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>Good (0.65)*</td>
</tr>
<tr>
<td>Nonorthostatic dizziness</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm paresis</td>
<td>69</td>
<td>Moderate to excellent (0.42 to 1.00)*</td>
</tr>
<tr>
<td>Leg paresis</td>
<td>61</td>
<td>Fair to excellent (0.40 to 0.84)*</td>
</tr>
<tr>
<td>Dysphasia or dysarthria</td>
<td>57</td>
<td>Moderate to excellent (0.54 to 0.84)*</td>
</tr>
<tr>
<td>Hemiparetic or ataxic gait</td>
<td>53</td>
<td>Excellent (0.91)*</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>45</td>
<td>Poor to excellent (0.13 to 1.00)*</td>
</tr>
<tr>
<td>Eye movement abnormality</td>
<td>27</td>
<td>Fair to excellent (0.33 to 1.00)*</td>
</tr>
<tr>
<td>Visual field defect</td>
<td>24</td>
<td>Poor to excellent (0.16 to 0.81)*</td>
</tr>
</tbody>
</table>

*—Kappa statistic: 0 to 0.20 = poor agreement; 0.21 to 0.40 = fair agreement; 0.41 to 0.60 = moderate agreement; 0.61 to 0.80 = good agreement; 0.81 to 1.00 = excellent agreement.

**—Noted as “loss of power.”

††—Noted as “loss of sensation.”

Information from references 4, 6, and 9.

Diagnostic accuracy. The overall accuracy of a physician’s diagnosis of stroke is moderate to good, with lower reliability in less experienced or less confident examiners.

Physicians need to quickly assess persons with suspected acute ischemic stroke because acute therapies for stroke have a narrower time window of effectiveness than therapies for myocardial infarction. The National Institutes of Health Stroke Scale (NIHSS) is available at http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf was designed to be completed in five to eight minutes.

The exact time of symptom onset is critical for determining eligibility for thrombolysis. However, a community-based study found that examiners agreed to the minute less than 50 percent of the time, suggesting the need to corroborate time of symptom onset with a witness or known event.

Reliably distinguishing between intracerebral hemorrhage and ischemic stroke can only be done through neuroimaging. Both entities are characterized by acute onset of focal symptoms. Persons with intracerebral hemorrhage may have gradual worsening of symptoms after the abrupt onset, reflecting an increasing size of the hematoma. Persons with hemorrhage also may have a decreased level of consciousness.

Subarachnoid hemorrhage presents differently from intracerebral hemorrhage and ischemic stroke. The most common
### Table 3. Accuracy of Selected Stroke Screening Tools

<table>
<thead>
<tr>
<th>Name</th>
<th>Components</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cincinnati Prehospital Stroke Scale</td>
<td>Facial paralysis; arm drift; abnormal speech</td>
<td>≥ 1 item: 85% (80 to 90)°</td>
<td>≥ 1 item: 79% (73 to 85)°</td>
<td>0 items: 0.39 (0.25 to 0.61)°</td>
</tr>
<tr>
<td>Face, Arm, Speech Test</td>
<td>In patients with Glasgow Coma Scale &gt; 6 and presence of at least one of the following: facial paralysis; arm weakness; speech impairment</td>
<td>82 (76 to 88)°</td>
<td>83 (77 to 89)°</td>
<td>—</td>
</tr>
<tr>
<td>Los Angeles Prehospital Stroke Screen</td>
<td>Presence of all six items is positive for stroke: age &gt; 45 years; no seizure history; symptoms present &lt; 24 hours; ambulatory at baseline; serum glucose &gt; 60 mg per dl; 3.35 mmol per l; &lt; 400 mg per dl; 22.20 mmol per l; unilateral deficit of one of three items (facial paresis, arm drift, weak hand grip)</td>
<td>91 (76 to 98)°</td>
<td>97 (93 to 99)°</td>
<td>LR+: 31 (13 to 75)°</td>
</tr>
<tr>
<td>Melbourne Ambulance Stroke Screen</td>
<td>Presence of all six items is positive for stroke: age &gt; 45 years; no seizure history; symptoms present &lt; 24 hours; ambulatory at baseline; serum glucose &gt; 60 and &lt; 400 mg per dl; presence of ≥ one of four items (facial droop, arm drift, weak hand grip, speech impairment)</td>
<td>90 (81 to 96)°</td>
<td>74 (53 to 88)°</td>
<td>LR+: 3.49 (1.83 to 6.63)°</td>
</tr>
<tr>
<td>Recognition of Stroke in the Emergency Room scale</td>
<td>A score of 1 point or higher is positive for stroke: History of syncope or loss of consciousness (-1 pt)</td>
<td>93 (89 to 97)°</td>
<td>83 (77 to 89)°</td>
<td>LR+: 5.49 (3.11 to 9.68)°</td>
</tr>
<tr>
<td>von Arbin</td>
<td>All three positive for stroke: acute onset of focal neurologic deficit; onset &lt; seven days prior; no recent head trauma</td>
<td>86 (81 to 91)°</td>
<td>99 (98.5 to 99.4)°</td>
<td>LR+: 94 (59 to 152)°</td>
</tr>
</tbody>
</table>

° CI = confidence interval, LR = likelihood ratio; LR+ = positive likelihood ratio; LR− = negative likelihood ratio.

Assumption: All blood glucose checks and treatments with < 63 mg per dl (3.50 mmol per l).

*Information from references 8, 9, and 15 through 19.

symptom described by the patient is the "worst headache of my life." Symptoms may also include vomiting, seizures, meningismus, and a decreased level of consciousness. Persons with subarachnoid hemorrhage may not exhibit focal signs because the bleeding occurs outside the brain, except when an aneurysm bleeds into a focal location, such as a posterior communication artery aneurysm compressing the third cranial nerve.

**VALIDATED DECISION SUPPORT TOOLS**

The NIHSS is one of the most common classifications of early stroke severity; it provides a structured neurologic examination that has diagnostic and prognostic value. Current guidelines recommend the use of the NIHSS, but no trial data exist to show its use improves outcomes. In general, combinations of signs and symptoms are more useful than single findings. Table 3 describes operating characteristics for several validated stroke diagnostic tools. Common signs across stroke diagnostic tools include acute onset of unilateral weakness or numbness and speech disturbance. One of the validated instruments, the Recognition of Stroke in the Emergency Room (ROSIER) scale, adds a visual field defect on examination. Most of these tools were designed for prehospital care, but emergency department physicians using the ROSIER scale correctly classified 90 percent of all patients in a community-based validation study of consecutive patients seen in the United Kingdom. Physicians using ROSIER missed patients with ischemic posterior or lacunar lesions, which emphasizes the need.
Table 4. Stroke Mimics and Distinguishing Features

<table>
<thead>
<tr>
<th>Condition</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>History of loss of consciousness; seizure activity; postictal state^1,8</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>Chest most common source; acute illness exacerbating an old deficit^1</td>
</tr>
<tr>
<td>Syncope/presyncope or hypotension</td>
<td>Hypotension unusual in acute stroke; prevalence of blood pressure &lt; 120/80 mm Hg at initial stroke presentation = 7.1 percent^2; symptoms may be transient or respond to hydration.</td>
</tr>
<tr>
<td>Toxic-metabolic disturbances</td>
<td>Hypoglycemia most common^11</td>
</tr>
<tr>
<td>Tumor</td>
<td>Mass noted on neuroimaging</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td>May be related to alcohol intoxication, medication adverse effect, or other encephalopathy</td>
</tr>
<tr>
<td>Vertigo or dizziness</td>
<td>Imbalance, but not vertigo, increases the likelihood of stroke^20; prevalence of stroke or transient ischemic attack in adults older than 44 years with isolated dizziness symptoms in emergency setting = 0.7 percent^13</td>
</tr>
<tr>
<td>Migraine</td>
<td>History of similar events, preceding aura and headache^11</td>
</tr>
<tr>
<td>Functional or medically unexplained symptoms</td>
<td>Reported incidence is 0.2 to 4.3 percent of patients admitted for stroke^35; only history of headache or pre- or post-presentation functional syndrome was associated with unexplained symptoms in a United Kingdom case control study; dysarthria, vertigo, and/or ataxia were less likely to be unexplained; motor, sensory, and visual field symptoms; stroke risk factors, and history of pre- or post-presentation depression or anxiety equally likely in patients with stroke and unexplained symptoms^14</td>
</tr>
<tr>
<td>Dementia</td>
<td>Presence of known cognitive impairment was one of two factors that independently predicted a stroke mimic in an Australian prospective study of patients admitted with suspected stroke^14</td>
</tr>
</tbody>
</table>

Note: Conditions in approximate order of likelihood as a stroke mimic.
Information from references 8, 11, 14, and 20 through 24.

for an examination more thorough than a scale alone. No head-to-head trials have been performed to demonstrate improved patient outcomes using a validated stroke scale versus global clinical impression. In practice, because most of these tools demonstrate good clinical accuracy, a physician should become familiar with one of them to help confirm their overall clinical impression of stroke.

STROKE MIMICS AND DIFFERENTIAL DIAGNOSIS

Physicians need to consider a broad differential diagnosis when evaluating a patient presenting with a suspected stroke (Table 4).^1,11,14,20-24 The two most common stroke mimics are hypoglycemia and seizure.11,14,20,21

One potential area of confusion is among patients presenting with a symptom of dizziness. In a population-based study of adults older than 44 years presenting to the emergency department or directly admitted to the hospital with a principal symptom of dizziness, only 0.7 percent of patients with isolated dizziness symptoms had an ultimate diagnosis of stroke or TIA.15 Vertigo from a central cause such as stroke is normally associated with nystagmus or other cerebellar signs.

The rates of overdiagnosis of stroke in studies of consecutive patients vary from 19 to 31 percent.14,20,21 Known history of cognitive impairment,14 non-neurologic abnormal physical findings,14 and decreased level of consciousness14 are independent predictors of a stroke mimic in patients with suspected stroke. Patient factors such as confusion, aphasia, and presentation more than 48 hours after the event also make diagnostic information less reliable.14

Duration of symptoms distinguishes stroke from TIA, which has been traditionally defined as a focal ischemic neurologic event resolving within 24 hours. Subsequent observations have shown that a majority of TIA's resolve within one hour.25 The National Institute of Neurological Disorders and Stroke trial found that patients treated with placebo who did not have resolution in one hour or improvement in three hours had only a 2 percent chance of resolving in 24 hours.26

Diagnostic Tests and Imaging

Figure 1 presents an algorithm for the diagnosis of acute stroke.24,11 Table 5 lists initial diagnostic studies recommended by current guidelines for patients with suspected stroke.11 These studies help exclude stroke mimics, uncover critical comorbidities (e.g., myocardial ischemia), and establish the safety of thrombolytic therapy.

The primary purpose of neuroimaging in a patient with suspected ischemic stroke is to rule out the presence of other types of central nervous system lesions and to distinguish between ischemic and hemorrhagic stroke. Figure 2 shows examples of intracerebral and subarachnoid hemorrhages on computed tomography (CT) scans. CT scans are considered sufficiently sensitive for detecting mass lesions, such as a brain mass or abscess, as well as detecting acute hemorrhage. However, CT scans may not be sensitive enough to detect an ischemic stroke, especially if it is small, acute, or in the posterior fossa (i.e., brainstem and cerebellum areas).27 The purpose of a CT scan is to rule out certain stroke mimics and detect hemorrhage, not necessarily to rule in the diagnosis of
ischemic stroke. In other words, a normal CT scan does not rule out the diagnosis of ischemic stroke.

Multimodal magnetic resonance imaging (MRI) sequences, particularly diffusion-weighted imaging, have better resolution than CT; therefore, they have a greater sensitivity for detecting acute ischemic stroke and show ischemic lesions in about one half of all cases of TIA. Recent studies also indicate that MRI sequences (particularly gradient-recalled echo and diffusion-weighted imaging sequences) are as sensitive as CT scans for detecting intracerebral hemorrhagic stroke. Figure 3 shows the head CT and diffusion-weighted MRI images of a patient with a prior stroke and a new acute stroke. Figure 4 depicts the time course of resolution of ischemic changes on diffusion-weighted MRI.

Although MRI scans have better resolution than CT scans, MRI scanners are less available and more expensive than CT scanners. Also, MRI scans cannot be performed on persons with certain types of implanted devices (e.g., pacemakers) or in persons with claustrophobia. If a patient is within the time window of acute stroke intervention, guidelines recommend that an MRI scan can be ordered if it can be obtained as quickly as a CT scan; if not, then CT is the recommended test because acute stroke treatments should not wait for detailed imaging when the history and physical are consistent for acute stroke. Online Table A compares CT and MRI in the setting of acute stroke. Guidelines recommend that whichever imaging modality is performed, it should be interpreted by a physician with expertise in reading brain imaging studies.

Table 5. Immediate Diagnostic Studies: Evaluation of Suspected Acute Ischemic Stroke


***CT = computed tomography; MRI = magnetic resonance imaging. Although it is desirable to know the results of these tests before giving recombinant tissue plasminogen activator, thrombolytic therapy should not be delayed while awaiting the results unless there is clinical suspicion of a bleeding abnormality or thrombocytopenia, the patient has received heparin or warfarin (Coumadin), or the use of anticoagulants is not known. Adapted with permission from: Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the American Academy of Neurology. affirms the value of this guideline as an educational tool for neurologists (published corrections appear in Stroke, 2007;38(8):e38, and Stroke, 2007;38(9):e96). Stroke. 2007;38(9):1665. http://www.com.
Unlike ischemic stroke and intracerebral hemorrhage, diagnosing subarachnoid hemorrhage requires a different diagnostic algorithm. The frequency of misdiagnosis for subarachnoid hemorrhage can be as high as 50 percent on initial presentation. Although MRI can detect subarachnoid hemorrhage, CT is still considered the imaging test of choice for persons suspected to have subarachnoid hemorrhage. CT scans have a 95 to 100 percent sensitivity of detecting subarachnoid blood in the first 12 hours; however, unlike ischemic stroke, sensitivity greatly decreases over time as the subarachnoid blood is cleared. The sensitivity of subarachnoid hemorrhage detection by CT drops to about 50 percent after one week, and is not detectable by CT after a period of about two to three weeks.

Persons with suspected subarachnoid hemorrhage and a normal CT scan should undergo a lumbar puncture to detect bilirubin. Red blood cells can be found in a subarachnoid hemorrhage and a traumatic tap. Distinguishing between these two entities requires recognition that only within the human body do red blood cells break down into bilirubin. Red blood cells in cerebrospinal fluid collected from a traumatic tap will break down into oxyhemoglobin, but not into bilirubin. Because the breakdown of red blood cells can take up to 12 hours, guidelines recommend that the lumbar puncture should wait until 12 hours after the initial onset of symptoms. Bilirubin will turn fluid yellow (xanthochromia), but visual inspection alone is not considered sufficiently reliable. Therefore, all specimens should undergo spectrophotometry analysis to detect bilirubin, which can be detected as long as two weeks after the initial onset of symptoms. If subarachnoid hemorrhage is detected,
the patient should immediately undergo angiography (CT angiography, MRI angiography, or catheter angiography) to look for an aneurysm.

**Teaching Patients to Recognize Stroke Symptoms**

Guidelines recommend that persons having an acute stroke activate the emergency medical system by calling 9-1-1. However, patients often do not activate the emergency medical system, or do not activate it immediately. Such behavior accounts for up to two thirds of the delay to hospital admission. Therefore, patients commonly present outside the time window for thrombolytic therapy. Patient and family sense of urgency for stroke symptoms is associated with greater use of emergency medical systems, which results in shorter times to evaluation and admission.

Numerous surveys have shown that there is considerable room for improvement in knowledge of stroke in the general population. When persons are asked to answer "yes" or "no" as to whether a described symptom can be a sign of a stroke, they are correct about 60 to 80 percent of the time. However, when persons are asked open-ended questions to name stroke warning signs, most cannot name more than one warning sign.

To improve public awareness of stroke warning signs, numerous organizations have embarked on public education campaigns. Family physicians are well placed to emphasize these messages in their practices.

The authors thank Dr. Jack Tsao for providing Figure 2 and Dr. James Sminiotopoulos for his assistance with Figure 3.

The views expressed in this article are those of the authors and do not necessarily reflect the official position of the Department of the Navy, Department of Defense, Department of Veterans Affairs or the United States Government.

**REFERENCES**


**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an abrupt onset of a focal persistent neurologic deficit should be evaluated for stroke.</td>
<td>C</td>
<td>8, 9, 17, 19</td>
</tr>
<tr>
<td>Stroke mimics should be excluded by history and diagnostic testing.</td>
<td>C</td>
<td>8, 11, 14, 20, 21, 23</td>
</tr>
<tr>
<td>Diagnostic tools, such as the Recognition of Stroke in the Emergency Room scale, can aid in stroke diagnosis.</td>
<td>C</td>
<td>8, 9</td>
</tr>
<tr>
<td>All patients with stroke should have urgent neuroimaging with computed tomography or magnetic resonance imaging.</td>
<td>C</td>
<td>11</td>
</tr>
<tr>
<td>Patients and family members should be educated about stroke symptoms and the need for urgent evaluation.</td>
<td>C</td>
<td>11</td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/sort.xml.
Acute Stroke


Intravenous Thrombolytic Therapy for Acute Ischemic Stroke

Lawrence R. Wechsler, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

An 81-year-old man arrived at the emergency department at 9:15 a.m. with speech difficulty and weakness on the right side. He had awakened that morning without symptoms. During breakfast at 8 a.m. his wife saw him slump over and fall from the chair to the floor. He was unable to speak and could not move his right arm or leg. She called 911, and he was transported to the emergency department. He made a few attempts to speak, but his speech was unintelligible. He could move his right arm and leg but could not lift either limb off the bed. Computed tomography (CT) of the brain showed no hemorrhage and no early ischemic changes. Blood pressure was 160/90 mm Hg. His platelet count, glucose level, and prothrombin time were all normal. After the patient returned from imaging at 10 a.m., a neurologist was consulted, who confirmed the presumptive diagnosis of acute ischemic stroke and recommended immediate initiation of intravenous thrombolytic therapy.

The Clinical Problem

Stroke is the leading cause of disability among adults in the United States. Despite advances in preventive strategies and initial therapy for stroke, nearly 800,000 strokes occur per year in the United States, and 87% of all strokes worldwide are ischemic in origin (caused by in situ thrombosis, embolism, or systemic hypoperfusion). The risk of stroke is higher among men than among women, among blacks than among whites, and in older than in younger age groups.

In 2007, stroke accounted for 1 of every 18 deaths in the United States. According to one report, the 30-day mortality for ischemic stroke was 8% to 12% for people 45 to 64 years of age. In the Framingham Heart Study, among survivors of an ischemic stroke who were 65 years of age or older and were evaluated 6 months after the event, 50% had some evidence of hemiparesis, 30% were unable to walk without assistance, 19% had aphasia, and 26% were institutionalized. The estimated direct medical cost of stroke in the United States was $25 billion in 2007.

Pathophysiology and Effect of Therapy

Ischemic stroke results from vascular occlusion that reduces cerebral blood flow to the area of brain perfused by the occluded artery. In either thrombotic or embolic stroke, such occlusion is caused by obstruction of the artery by thrombus. If the reduction in blood flow is sufficiently severe, a series of events occurs at the cellular level that leads to infarction. The release of excitatory amino acid neurotransmitters, the influx of calcium, the generation of oxygen free radicals, membrane depolarization, and eventually, the loss of membrane integrity are all...
thought to contribute to the detrimental effects of ischemia. A newer concept of ischemic injury considers neurons, astrocytes, and vascular structures and their interactions to be a neurovascular unit. Disturbance of the complex signaling and interactions between components of the neurovascular unit probably plays an important role in ischemic brain injury. Matrix metalloproteinase 9 is up-regulated during ischemia and may contribute to the breakdown of the blood–brain barrier and hemorrhagic transformation. Similarly, oxidative stress and inflammation are triggered by ischemia and contribute to the process of cellular injury and infarction.

In experimental models of stroke, both the duration and the severity of ischemia determine the threshold for irreversible damage. Magnetic resonance imaging (MRI) and CT perfusion studies in patients with acute stroke suggest that the ischemic areas of the brain may in some cases remain viable for as long as 24 hours, with the potential for the restoration of normal function after reperfusion (Fig. 1). However, the benefit of extending the treatment window for patients selected on the basis of the results of perfusion imaging has not been validated by clinical studies.

Tissue plasminogen activator (t-PA) is a serine protease that acts by enhancing the conversion of inactive plasminogen to active plasin. Plasmin acts on fibrin clots, causing dissolution and lysis. The activity of t-PA is greatly enhanced in the presence of fibrin, increasing fibrinolysis specifically at the site of thrombosis. In vivo, t-PA is released by endothelial cells; in contrast, exogenously administered t-PA is derived from the application of recombinant DNA technology and is thus designated recombinant t-PA (rt-PA). Unlike first-generation plasminogen activators such as streptokinase and urokinase, rt-PA is fibrin-selective and preferentially activates fibrin-bound plasminogen. Although rt-PA is inhibited by plasminogen activator inhibitor type 1 (PAI-1) in plasma, the capacity of PAI-1 to bind rt-PA is rapidly exceeded when the drug is administered systemically, thus increasing the risk of bleeding. The half-life of rt-PA in the circulation is about 4 minutes, but the physiological effect may last longer as a consequence of fibrin binding.

In 1996, the Food and Drug Administration (FDA) approved the use of intravenous rt-PA for the treatment of acute ischemic stroke after the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study was completed. In part 1 of this study, 291 patients with acute ischemic stroke were randomly assigned, within 3 hours after the onset of the stroke, to either intravenous rt-PA or placebo. The primary end point was the rate at 24 hours of either complete neurologic recovery or neurologic improvement, as indicated by an improvement of at least 4 points above baseline values on the National Institutes of Health Stroke Scale (NIHSS) (a 42-point scale that quantifies neurologic deficits in 11 categories, with higher scores indicating more severe deficits).

In this part of the trial, no significant difference was seen in the primary end point between patients receiving rt-PA and those receiving placebo (51% and 46%, respectively; relative risk with rt-PA, 1.1; 95% confidence interval [CI], 0.8 to 1.6; P=0.56).

In part 2 of this study, an additional 333 patients were enrolled and randomly assigned to the same two groups. The primary end point was the rate of complete or nearly complete recovery at 90 days, as indicated by a combined assessment of four separate neurologic-outcome scales. In this part of the trial, the rate of a favorable outcome was significantly greater with intravenous rt-PA than with placebo (odds ratio, 1.7; 95% CI, 1.2 to 2.6; P=0.008). This benefit was sustained at 6 months and at 1 year.

Three additional randomized trials showed no benefit of intravenous rt-PA as compared with placebo. These trials included the European Cooperative Acute Stroke Study (ECASS), ECASS II, and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial. These trials differed from the NINDS study in several important respects. Most notably, patients could be enrolled up to 6 hours after the onset of stroke, and only 14% of patients were treated within 3 hours after the event. In contrast, in the NINDS trial, almost all patients were treated within 3 hours and 48% within 90 minutes after stroke onset.

In the subsequent ECASS III, 82% of patients who presented between 3 and 4.5 hours after the onset of stroke were randomly assigned to intravenous rt-PA or placebo. The primary outcome was disability at 90 days, dichotomized as either a favorable outcome (a score of 0 or 1) or an unfavorable outcome (a score of 2 to 6) according to the
Figure 1. CT Perfusion Imaging in a Patient with Stroke, before and after Thrombolysis with Recombinant Tissue Plasminogen Activator (rt-PA).

Standard CT images without contrast material (left two images) and CT perfusion images obtained during the first pass of an intravenous bolus of iohexolated contrast material (right six images) are shown. Images were obtained before (Panel A) and after (Panel B) thrombolysis with rt-PA. Mathematical algorithms are used to create, from the perfusion data, maps of the mean transit time (MTT) (the difference in time between arterial inflow and venous outflow), cerebral blood volume (CBV), and cerebral blood flow (CBF). The CT scan without contrast material that was obtained before thrombolysis shows hypodensity in the area of the left caudate nucleus (arrow), with loss of definition between gray matter and white matter. The scan obtained after thrombolysis shows a central area of hyperdensity in the area of the left caudate nucleus, which is consistent with hemorrhage within the infarct zone, surrounded by an area of hypodensity (arrow), which is consistent with infarction. The CT perfusion maps in Panel A, obtained before thrombolysis, show prolonged MTT (arrow), decreased CBV (arrow), and decreased CBF (arrow) in the left hemisphere. There is some degree of mismatch between the CBV map (which emphasizes irreversible injury, primarily in the area of the left caudate nucleus) and the CBF map (which shows an extensive area of abnormality throughout the left hemisphere, indicating tissue at risk). The CT perfusion maps in Panel B, obtained after thrombolysis, show some improvement in MTT, CBV, and CBF in most areas, although the focus of hypoperfusion in the area of the left caudate nucleus persists (arrows), which is consistent with the area of infarction shown on the CT scan obtained without contrast material. In these images, the color spectrum indicates the spectrum of values for each quantity. On the MTT map, the areas of fastest transit time appear red and those of slowest transit time appear blue. On the CBV and CBF maps, the area of greatest blood volume or blood flow appear red and those of least blood volume or blood flow appear blue. Although quantitative values can be assigned to these data, CT perfusion images are usually interpreted qualitatively by comparing areas of normal with areas of abnormal perfusion. Areas without detectable perfusion are black. A denotes anterior, and R right.

modified Rankin scale (which ranges from 0 to 6, with 0 indicating no symptoms and 6 indicating death). In ECASS III, patients were excluded if they were older than 80 years of age, had had a severe stroke (defined as an NIHSS score >25 or hypodensity of more than one third of the middle-cerebral-artery territory on CT scanning), had received prior treatment with anticoagulants, regardless of the international normalized ratio (INR), or had a history of both stroke and diabetes. At 90 days, significantly more patients treated with rt-PA had favorable outcomes, as com-
pared with those given placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% CI, 1.02 to 1.76; P=0.04).

CLINICAL USE

Intravenous administration of t-PA within 3 hours after the onset of stroke increases the probability of a favorable outcome. Recommended protocols for selecting patients for treatment with intravenous rt-PA are adapted from the inclusion and exclusion criteria from the NINDS rt-PA trial (Table 1). On the basis of results of BCASS III, some stroke centers now treat patients who present from 3 to 4.5 hours after stroke onset; however, at present, the FDA has approved only rt-PA treatment delivered within 3 hours after stroke onset.

The timing of the onset of stroke should be determined with as much certainty as possible by obtaining first-hand information. If the onset was not observed, the time when the patient was last seen to be neurologically normal should be considered the time of stroke onset. Although this recommendation may exclude some eligible patients, it ensures that those whose stroke occurred outside the time limit for a favorable risk-to-benefit ratio will not be treated.

A rapid examination with the use of the NIHSS will help to quantify the neurologic deficit. Many protocols exclude patients who have mild deficits, since their prognosis for recovery is good without thrombolytic therapy. However, treatment should be initiated on the basis of the assessment of a disabling deficit rather than on a defined lower limit for the NIHSS score. For example, isolated aphasia or hemianopia is a disabling deficit despite an NIHSS score of 2 or 3.

Rapidly resolving deficits may complicate decision making. If the residual deficit continues to be disabling, treatment should be undertaken despite the improvement. Occasionally, rapid recovery is later followed by clinical worsening. Patients should therefore be observed closely and reevaluated frequently during the first 24 hours after the onset of stroke.

Another common concern regarding eligibility for intravenous thrombolysis is poorly controlled blood pressure. In patients receiving intravenous rt-PA, markedly elevated blood pressure may increase the risk of hemorrhage. Current guidelines recommend treatment to achieve a systolic blood pressure of 185 mm Hg or lower and a diastolic blood pressure of 110 mm Hg or lower before intravenous rt-PA is administered. One or two doses of labetalol may be used to bring blood pressure below these limits, but if the response is not rapid, treatment with intravenous nicardipine or occasionally sodium nitroprusside may be started, with the dose rapidly adjusted to achieve blood-pressure control.

<table>
<thead>
<tr>
<th>Table 1. Inclusion and Exclusion Criteria for Intravenous t-PA Therapy in Patients with Acute Ischemic Stroke.</th>
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</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td>Diagnosis of ischemic stroke causing measurable neurologic deficit</td>
</tr>
<tr>
<td>Onset of symptoms &lt;3 hr before start of treatment (or, in selected cases, &lt;4.5 hr)*</td>
</tr>
<tr>
<td>Age ≥18 yr</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>Head trauma or prior stroke within the previous 3 mo</td>
</tr>
<tr>
<td>Symptoms suggestive of subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Arterial puncture at noncompressible site within the previous 7 days</td>
</tr>
<tr>
<td>History of intracranial hemorrhage</td>
</tr>
<tr>
<td>Elevated blood pressure (systolic, ≥185 mm Hg, or diastolic, ≥110 mm Hg) that has not responded to antihypertensive treatment</td>
</tr>
<tr>
<td>Evidence of active bleeding on examination</td>
</tr>
<tr>
<td>Acute bleeding diathesis, including but not limited to the following:</td>
</tr>
<tr>
<td>Platelet count ≤100,000/mm³</td>
</tr>
<tr>
<td>Heparin received within 48 hours, resulting in aPTT &gt; upper limit of normal</td>
</tr>
<tr>
<td>Current use of anticoagulant, with INR ≥1.7 or PT ≥15 sec</td>
</tr>
<tr>
<td>Blood glucose concentration ≤50 mg/dl (2.7 mmol/liter)</td>
</tr>
<tr>
<td>CT evidence of multilobar infarction (hypodensity &gt; one third of the cerebral hemisphere)</td>
</tr>
<tr>
<td><strong>Relative exclusion criteria, depending on risk:benefit ratio</strong></td>
</tr>
<tr>
<td>Only minor or rapidly improving stroke symptoms (clearing spontaneously)</td>
</tr>
<tr>
<td>Seizure at onset with postictal residual neurologic impairments</td>
</tr>
<tr>
<td>Major surgery or serious trauma within the previous 14 days</td>
</tr>
<tr>
<td>Gastrointestinal or urinary tract hemorrhage within the previous 21 days</td>
</tr>
<tr>
<td>Acute myocardial infarction within the previous 3 mo</td>
</tr>
</tbody>
</table>

* Adapted from Jauch et al.
+ The abbreviation aPTT denotes activated partialthromboplastin time, INR international normalized ratio, PT prothrombin time, and rt-PA recombinant tissue plasminogen activator.
† This criterion is based on the results of European Cooperative Acute Stroke Study III, in which the onset of symptoms was between 3 and 4.5 hours and which excluded patients older than 80 years of age, those with severe stroke (defined by a score ≥25 on the National Institutes of Health Stroke Scale), those receiving anticoagulant therapy regardless of the INR, and those with both diabetes and prior stroke.
‡ Recent experience suggests that under some circumstances, with careful consideration and weighing of the risks versus benefits of rt-PA administration, patients may receive fibrinolytic therapy despite one or more of the listed relative contraindications.
A CT scan of the brain should be obtained before the start of treatment and examined for hemorrhage or early ischemic changes. If a focal area of low density is seen that involves more than one third of the middle-cerebral-artery territory, most treatment protocols recommend withholding thrombolytic therapy, because in some studies this finding (which suggests irreversible injury) has been predictive of subsequent hemorrhagic transformation of the infarct. Laboratory studies that should be obtained before the initiation of thrombolytic therapy include, at a minimum, a platelet count, measurement of glucose levels, and assessment of the prothrombin time. The platelet count should be greater than 100,000 per cubic millimeter, the prothrombin time less than 15 seconds (or the INR <1.7), and the glucose level greater than 50 mg per deciliter (2.7 mmol per liter) before rt-PA is administered.

The patient and family members must be informed of the benefits and risks of intravenous rt-PA therapy before it is initiated. Specifically, they should be told that the benefits include an absolute increase in the odds of a good outcome of 11 to 15 percentage points and a 6% risk of intracerebral hemorrhage possibly causing neurologic worsening or death. Some hospitals choose to use a formal consent form, but at a minimum, the consent process should be documented in the medical record.

The FDA-approved dose of intravenous rt-PA is 0.9 mg per kilogram of body weight, with a maximum dose of 90 mg. A bolus of 10% of the dose is given over a period of 1 minute, with the remainder infused over a period of 60 minutes. Weight should be determined as reliably as is possible. Reports of treatment with a lower dose of rt-PA (0.6 mg per kilogram) in Japan suggest that it has similar efficacy but the lower dose has not yet been assessed in large, randomized trials.

Third-generation plasminogen activators, such as tenecteplase and desmoteplase, are more fibrin-specific than rt-PA and cause less activation of systemic lytic activity. These agents have been tested in early-phase trials, with mixed results. However, their clinical efficacy has not been established, and neither agent should be used in patients with acute ischemic stroke.

For the first 24 hours after treatment, patients receiving rt-PA should be closely monitored in a specialized stroke unit. If a stroke unit is not available, admission to an intensive care unit is warranted so that the patient can be evaluated frequently by the nursing staff. Blood pressure should be checked every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour for 16 hours. Antihypertensive therapy with labetalol or, if necessary, intravenous nicardipine should be administered to maintain blood pressure at a level below 180 mm Hg systolic and 105 mm Hg diastolic. Neurologic examination with the use of the NIHSS should be performed every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour for 16 hours. If a change in neurologic status is noted, the rt-PA infusion should be discontinued and a CT scan obtained. No anticoagulant or antiplatelet therapy should be given for the first 24 hours after treatment with intravenous rt-PA. If a CT scan at 24 hours shows no evidence of hemorrhage, antithrombotic therapy directed at secondary stroke prevention and tailored to the presumed cause of the stroke should be started.

In some stroke centers, a CT angiogram is obtained after intravenous rt-PA has been administered in order to examine the intracranial vasculature for persistent arterial occlusions. In patients with persistent arterial occlusion, one option is an intraarterial intervention: lytic therapy, mechanical clot disruption with the use of various endovascular devices, or both. Although this approach is not approved by the FDA in the treatment of acute stroke, a randomized, controlled trial has suggested a potential benefit from intraarterial lytic therapy. However, intraarterial interventions should be carried out only at experienced stroke centers.

In one U.S. study, the cost of rt-PA was estimated to be $2,750. In similar studies, the costs were £480 in the United Kingdom and $1,647 U.S. in Australia. Cost-effectiveness analyses in general suggest that rt-PA therapy is more expensive than standard care for ischemic stroke in the short term, owing to the cost of the drug and the need for additional resources, but it is associated with lower costs in the long term, since it reduces the risk of subsequent disability.

ADVERSE EFFECTS

The major complication of thrombolytic therapy for acute stroke is hemorrhage. Symptomatic intracranial hemorrhage occurs in 1.7 to 8.0% of treated patients. Patients with severe
stroke have a greater likelihood of hemorrhage, but there is no evidence that this subgroup does not benefit from intravenous rt-PA. Symptomatic hemorrhage is not increased in the elderly, but outcomes are worse and mortality is increased. In addition to age and NIHSS score, other independent risk factors for symptomatic intracranial hemorrhage include hypodensity on CT scanning, elevated serum glucose levels, and persistence of proximal arterial occlusion for more than 2 hours after administration of the rt-PA bolus. Hemorrhagic transformation of ischemic infarcts without clinical change (asymptomatic hemorrhage) occurs more frequently than symptomatic hemorrhage and may be associated with reperfusion and, in some cases, clinical improvement. Serious systemic (extracranial) hemorrhage has been reported in 0.4 to 1.5% of patients. Recommendations for the treatment of intracranial or serious systemic bleeding after thrombolytic therapy often include the administration of cryoprecipitate and platelets, although evidence-based guidelines for such an approach are lacking. Angioedema of the tongue, lips, face, or neck occurs in 1 to 5% of patients receiving intravenous rt-PA. In most cases, the symptoms are mild and resolve rapidly. Concomitant use of angiotensin-converting–enzyme inhibitors is strongly associated with this complication. Treatment includes glucocorticoids and antihistamines. In rare cases, edema of the pharynx is sufficiently severe to compromise breathing, and intubation may be necessary.

GUIDELINES

Guidelines for the management of acute stroke issued by the American Heart Association (AHA) and the European Stroke Organization recommend treatment with intravenous rt-PA for patients who meet the stated inclusion criteria, including presentation within 3 hours after the onset of stroke, and who do not meet any of the stated exclusion criteria. Both groups have recently updated their guidelines to extend the treatment window to 4.5 hours. The AHA Science Advisory and Coordinating Committee also recommends that treatment be started within 3 hours to 4.5-hour time window be limited to patients who do not meet any of the ECASS III exclusion criteria. An American Academy of Emergency Medicine (AAEM) position statement adopted in 2002 concluded that intravenous rt-PA should not be considered the standard of care, citing the lack of data from trials confirming the NINDS study findings as well as concerns raised about the study. Physicians were advised to use their discretion when deciding whether to use rt-PA. After the results of the ECASS III were published, an updated clinical practice statement from the AAEM stated that intravenous rt-PA is a reasonable...
treatment option when used in academic centers and primary stroke centers. A policy statement approved by the board of directors of the American College of Emergency Physicians in 2002 endorsed the use of intravenous rt-PA when it is administered according to the guidelines established by the NINDS study.

RECOMMENDATIONS

The patient described in the case vignette meets all the inclusion criteria for treatment with intravenous rt-PA. Assuming that further history taking reveals no pertinent findings, he also has no contraindications to treatment. Evidence from clinical trials does not suggest that persons older than 80 years of age do not benefit from intravenous rt-PA. He completed evaluation in the emergency department 2 hours after the onset of the stroke, which is within the FDA-approved 3-hour window, and the probability of recovery is greater the more rapidly treatment can be administered. Once consent has been obtained from his wife, I would elect to proceed with intravenous rt-PA therapy at the standard dose of 0.9 mg per kilogram, with 10% given as a bolus and the remainder infused over a 60-minute period. After the administration of intravenous rt-PA, the patient should be admitted to a specialized stroke unit for monitoring and additional workup to determine the cause of the stroke.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Treatment of Acute Migraine Headache

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MAGDALENA MICHAEL, MD, Mountain Area Health Education Center, Hendersonville, North Carolina

Migraine headache is a common and potentially debilitating disorder often treated by family physicians. Before diagnosing migraine, serious intracranial pathology must be ruled out. Treating acute migraine is challenging because of substantial rates of nonresponse to medications and difficulty in predicting individual response to a specific agent or dose. Data comparing different drug classes are relatively scarce. Abortive therapy should be used as early as possible after the onset of symptoms. Effective first-line therapies for mild to moderate migraine are nonprescription nonsteroidal anti-inflammatory drugs and combination analgescics containing acetaminophen, aspirin, and caffeine. Triptans are first-line therapies for moderate to severe migraine, or mild to moderate migraine that has not responded to adequate doses of simple analgescics. Triptans should be avoided in patients with vascular disease, uncontrolled hypertension, or hemiplegic migraine. Intravenous antiemetics, with or without intravenous dihydroergotamine, are effective therapies in an emergency department setting. Dexamethasone may be a useful adjunct to standard therapy in preventing short-term headache recurrence. Intranasal lidocaine may also have a role in relief of acute migraine. Isometheptene-containing compounds and intranasal dihydroergotamine are also reasonable therapeutic options. Medications containing opiates or barbiturates should be avoided for acute migraine. During pregnancy, migraine may be treated with acetaminophen or nonsteroidal anti-inflammatory drugs (prior to third trimester), or opiates in refractory cases. Acetaminophen, ibuprofen, intranasal sumatriptan, and intranasal zolmitriptan seem to be effective in children and adolescents, although data in these age groups are limited. (Am Fam Physician. 2011;83(3):271-280. Copyright © 2011 American Academy of Family Physicians.)

Patient information:

Migraine headache is one of the most common, yet potentially debilitating disorders encountered in primary care. Approximately 18 percent of women and 6 percent of men in the United States have migraine headaches, and 51 percent of these persons report reduced work or school productivity.1 Patients typically describe recurrent headaches with similar symptoms, and approximately one-third describe an aura preceding the headache.1 This article reviews treatment options for acute migraine headache.

Diagnosis
Table 1 lists International Headache Society diagnostic criteria for migraine with and without aura.2 A thorough history and physical examination can help confirm the diagnosis of migraine and rule out emergent conditions. The mnemonic POUND is an evidence-based aid for migraine diagnosis3:
- Pulsatile quality of headache
- One-day duration (four to 72 hours)
- Unilateral location
- Nausea or vomiting
- Disabling intensity

In a primary care setting, the probability of migraine is 92 percent in patients who report at least four of the five POUND symptoms.4 The probability decreases to 64 percent in patients with three of the symptoms, and 17 percent in patients with two or less symptoms.4

Table 2 outlines other serious causes of headache that must be considered in the differential diagnosis of migraine, such as temporal arteritis, cluster headache, and acute glaucoma.5 Fever, meningismus, or altered mental status should prompt investigation for meningitis or subarachnoid
Migraine Headache

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans are effective and safe for treatment of acute migraine.</td>
<td>A</td>
<td>8</td>
</tr>
<tr>
<td>Abortive therapy should be used as early as possible in the course of a migraine.</td>
<td>B</td>
<td>19</td>
</tr>
<tr>
<td>Combination analgesics containing aspirin, caffeine, and acetaminophen are an effective first-line abortive treatment for migraine.</td>
<td>A</td>
<td>7, 9</td>
</tr>
<tr>
<td>Ibuprofen at standard doses is effective for acute migraine treatment.</td>
<td>A</td>
<td>21</td>
</tr>
<tr>
<td>Intravenous metoclopramide (Reglan) is effective for acute migraine treatment.</td>
<td>B</td>
<td>11</td>
</tr>
<tr>
<td>Parenteral dexamethasone is useful as an adjunctive treatment in the emergency department to help prevent short-term headache recurrence.</td>
<td>A</td>
<td>12, 18</td>
</tr>
<tr>
<td>Opiates and barbiturate-containing compounds should not be routinely used for abortive treatment of migraine.</td>
<td>C</td>
<td>14, 34</td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

hemorrhage. The U.S. Headache Consortium recommends considering neuroimaging in patients with an unexplained abnormal finding on neurologic examination and in patients with atypical headache features or headaches that do not fulfill the strict definition of migraine or other primary headache disorder. The Consortium notes that neuroimaging generally is not indicated for patients with migraine and a normal neurologic examination.

In one study, age older than 50 years, sudden onset, and abnormal neurologic examination predicted serious intracranial pathology in adults presenting to an emergency department with nontraumatic headache; the presence of any one of these three features detected serious intracranial pathology with 98.6 percent sensitivity.

General Treatment Principles
Several medications from different classes are available to treat acute migraine (Table 3). Because relatively few trials have directly compared the different medication classes

<table>
<thead>
<tr>
<th>Migraine without aura</th>
<th>Migraine with aura</th>
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<tbody>
<tr>
<td><strong>Diagnostic criteria:</strong></td>
<td><strong>Diagnostic criteria:</strong></td>
</tr>
<tr>
<td>Headache lasts four to 72 hours (untreated or unsuccessfully treated)</td>
<td>Aura consisting of at least one of the following, but no motor weakness:</td>
</tr>
<tr>
<td>Headache has at least two of the following:</td>
<td>- Fully reversible dysphasic speech disturbance</td>
</tr>
<tr>
<td>Aggravation by or causing avoidance of routine physical activity (e.g., walking, climbing stairs)</td>
<td>- Sensory symptoms that are fully reversible, including positive features (pins and needles) and/or negative features (numbness)</td>
</tr>
<tr>
<td>Moderate or severe pain intensity</td>
<td>- Visual symptoms that are fully reversible, including positive features (flickering lights, spots, lines) and/or negative features (loss of vision)</td>
</tr>
<tr>
<td>Pulsiating quality</td>
<td>At least two of the following:</td>
</tr>
<tr>
<td>Unilateral location</td>
<td>- Homonymous visual symptoms and/or unilateral sensory symptoms</td>
</tr>
<tr>
<td>During headache, at least one of the following:</td>
<td>At least one aura symptom develops gradually over five minutes or different aura symptoms occur in succession over five minutes</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>Each symptom lasts at least five minutes, but no longer than 60 minutes</td>
</tr>
<tr>
<td>Photophobia and phonophobia</td>
<td>Headache fulfilling criteria for migraine without aura begins during the aura or follows aura within 60 minutes</td>
</tr>
<tr>
<td>Not attributed to another disorder</td>
<td>Not attributed to another disorder</td>
</tr>
<tr>
<td>History of at least five attacks fulfilling above criteria</td>
<td>History of at least two attacks fulfilling above criteria</td>
</tr>
</tbody>
</table>

Information from reference 2.
Table 2. Differential Diagnosis of Migraine Headache

<table>
<thead>
<tr>
<th>Condition</th>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Acute glaucoma</td>
<td>Associated with blurred vision, nausea, vomiting, and seeing halos around lights; ophthalmologic emergency</td>
</tr>
<tr>
<td>Acute or chronic subdural hematoa</td>
<td>Antecedent trauma; may have subacute onset; altered level of consciousness or neurologic deficit may be present</td>
</tr>
<tr>
<td>Acute severe hypertension</td>
<td>Marked blood pressure elevation (systolic &gt; 210 mm Hg or diastolic &gt; 120 mm Hg); may have confusion or irritability</td>
</tr>
<tr>
<td>Benign intracranial hypertension (pseudotumor cerebri)</td>
<td>Often abrupt onset; associated with nausea, vomiting, dizziness, blurred vision, and papilledema; may have cranial nerve V1 palsy, aggravated by coughing, straining, or changing position</td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
<td>May be insidious or associated with dyspnea; occurs more commonly in colder months</td>
</tr>
<tr>
<td>Carotid dissection</td>
<td>Cause of stroke; can be spontaneous or follow minor trauma or sudden neck movement; unilateral headache or face pain; ipsilateral Horner syndrome</td>
</tr>
<tr>
<td>Cervical spondylosis</td>
<td>Worse with neck movement; posterior distribution; pain is neuralgic in character and sometimes referred to vertex or forehead; more common in older patients</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>Uncommon; sudden onset; duration of minutes to hours; repeats over a course of weeks, then may disappear for months or years; unilateral lacrimation and nasal congestion; severe unilateral and periorbital pain; more common in men; patient is restless during episode</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Neurologic abnormalities, confusion, altered mental status or level of consciousness</td>
</tr>
<tr>
<td>Frontal sinusitis</td>
<td>Usually worse when lying down; nasal congestion; tenderness over affected sinus</td>
</tr>
<tr>
<td>Greater occipital neuralgia</td>
<td>Occipital location; tenderness at base of skull; pain is neuralgic in character and referred to vertex or forehead</td>
</tr>
<tr>
<td>Intracranial neoplasm</td>
<td>Worse on awakening; generally progressive; aggravated by coughing, straining, or changing position</td>
</tr>
<tr>
<td>Medication-induced headache</td>
<td>Chronic headache with few features of migraine; tends to occur daily; hormone therapy and hormonal contraceptives are frequent culprits; includes analgesic rebound</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Fever; meningeal signs</td>
</tr>
<tr>
<td>Postconcussion syndrome</td>
<td>Antecedent head trauma; vertigo, lightheadedness; poor concentration and memory; lack of energy; irritability and anxiety</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Explosive onset of severe headache; 10 percent preceded by sentinel headaches</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>Almost exclusively in patients older than 50 years; associated with tenderness of scalp or temporal artery and jaw claudication; visual changes</td>
</tr>
<tr>
<td>Temporomandibular joint dysfunction</td>
<td>Pain generally involves the temporomandibular joint and temporal areas; associated with symptoms when chewing</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>Common; duration of 30 minutes to seven hours; typically bilateral; nonpulsating; mild to moderate intensity without limiting activity; no nausea or vomiting</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>Brief episodes of sharp, stabbing pain and trigeminal face distribution</td>
</tr>
</tbody>
</table>


available to treat acute migraine, definitive treatment algorithms cannot be developed. More than one-half of persons treat their migraine headaches with nonprescription medications, and patients often present to physicians after unsuccessfully trying multiple nonprescription therapies. The U.S. Headache Consortium guidelines offer a general strategy based on expert consensus. Nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeine-containing combination analgesics may be first-line treatment for mild to moderate migraine, or severe migraine that has previously responded to these agents. Triptans are considered first-line abortive treatment of moderate to severe migraine, or mild attacks that have not responded to nonprescription medicines. Ergotamine-containing compounds may also be reasonable in this situation. Figure 1 provides a suggested algorithm for management of acute migraine headaches.

Predicting individual response to a specific medication is difficult. Complete pain relief is not always achievable. For example, studies report complete pain relief within
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Combination analgesics</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen, 250 mg/aspirin, 250 mg/caffeine, 65 mg (Excedrin Migraine)</td>
<td>1 or 2 tablets (or capsules) every 6 hours, not to exceed 8 tablets per day</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200 to 800 mg orally every 6 to 8 hours, not to exceed 2.4 g per day</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 to 500 mg orally every 12 hours, not to exceed 2 g per day</td>
</tr>
<tr>
<td>Triptans</td>
<td></td>
</tr>
<tr>
<td>Almotriptan (Axert)</td>
<td>6.25 to 12.5 mg orally, can be repeated in 2 hours, not to exceed 25 mg per day</td>
</tr>
<tr>
<td>Eletriptan (Relapax)</td>
<td>20 to 40 mg orally, can be repeated in &gt; 2 hours, not to exceed 80 mg per day</td>
</tr>
<tr>
<td>Frovatriptan (Frova)</td>
<td>2.5 mg orally, can be repeated in 2 hours, not to exceed 7.5 mg per day</td>
</tr>
<tr>
<td>Naratriptan (Amerge)</td>
<td>1 to 2.5 mg orally, can be repeated in 2 hours, not to exceed 5 mg per day</td>
</tr>
<tr>
<td>Rizatriptan (Maxalt)</td>
<td>5 to 10 mg orally, can be repeated in 2 hours, not to exceed 30 mg per day</td>
</tr>
</tbody>
</table>
| Sumatriptan (Imitrex)    | * Intranasal: 5 to 20 mg, can be repeated in 2 hours, not to exceed 40 mg per day  
|                          | Oral: 25 to 100 mg, can be repeated in 2 hours, not to exceed 200 mg per day |
|                          | Subcutaneous: 4 to 6 mg, may repeat in 1 hour, not to exceed 12 mg per day |
| Zolmitriptan (Zomig, Zomig-ZMTe) | * Intranasal: 5 mg, may repeat in 2 hours, not to exceed 10 mg per day  
|                          | Oral disintegrating tablets: 2.5 mg, can be repeated in 2 hours, not to exceed 10 mg per day |
|                          | Oral: 1.25 to 2.5 mg, can be repeated in 2 hours, not to exceed 10 mg per day |
| Combination triptans and NSAIDs |                                                       |
| Sumatriptan, 85 mg/naproxen, 500 mg (Trexima) | 1 tablet at onset, may repeat in 2 hours, not to exceed 2 tablets per day |
| **Other effective therapies** |                                                                       |
| Antiemetics             |                                                                       |
| Metoclopramide (Reglan) | 10 mg IV every 8 hours                                                |
| Prochlorperazine         | 10 mg IV every 8 hours, not to exceed 40 mg per day                   |
| Dexamethasone            | * IV: 4 to 10 mg, one-time dose                                        |
|                          | Oral: 8 to 24 mg, one-time dose                                         |
| Ergotamines              |                                                                       |
| Dihydroergotamine (DHE; Migranal§) | * Intranasal: 1 spray in each nostril, repeat once after 15 minutes; not to exceed 4 sprays per attack, 6 sprays per day, 8 sprays per week  
|                          | IV: 0.5 to 1 mg repeated every 8 hours, or continuous IV infusion totaling 3 mg per 24 hours; not to exceed 3 mg per attack |
|                          | Subcutaneous: 1 mg every hour; not to exceed 3 mg per day               |
| Isomethylenepine compounds |                                                          |
| Acetaminophen, 325 mg/dichloralphenazone, 100 mg/isomethylenepine, 65 mg (Midrin) | 1 to 2 capsules orally every 4 hours; not to exceed 8 capsules per day |
| Lidocaine (Xylocaine)    | Intranasal: 0.5 mL of topical lidocaine 4% solution dripped into the nostril on the affected side over 30 seconds; administered by a clinician while patient lies in the supine position with head hyperextended and tilted to 30 degrees |

*—Estimated retail price based on lowest dose provided. Information obtained at http://www.drugstore.com (accessed December 2, 2010). Generic price listed first; brand price listed in parentheses.
†—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data, 2010. Cost to the patient will be higher, depending on prescription filling fee.
‡—Zomig-ZMTe is brand name for oral disintegrating tablet form.
§—Migranal is brand name for intranasal form.
<table>
<thead>
<tr>
<th>Cost of generic (brand)*</th>
<th>Major adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varies</td>
<td>See individual medications</td>
<td>Available without a prescription</td>
</tr>
<tr>
<td>Varies</td>
<td>Heartburn, gastric bleeding, ulcers, rebound headache, renal toxicity; can exacerbate heart failure and hypertension</td>
<td>Available without a prescription; many patients have already tried nonprescription NSAIDs before seeking medical advice Cannot be used in the third trimester of pregnancy Generally well-tolerated</td>
</tr>
<tr>
<td>NA ($154) for 12 tablets</td>
<td>Hypertension, vasospasm, chest pain, malaise, fatigue, rebound headache</td>
<td>Should be avoided in patients with a history of myocardial infarction, cerebrovascular accident, Prinzmetal angina, uncontrolled hypertension, or other vascular diseases, and in pregnant women Do not use with monoamine oxidase inhibitors Case reports of serotonin syndrome when combined with selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>NA ($155) for 6 tablets</td>
<td>NA ($242) for 9 tablets</td>
<td>NA ($276) for 9 tablets</td>
</tr>
<tr>
<td>NA ($287) for 3 tablets</td>
<td>Intranasal: $391 ($55) Oral: $620 ($792) for 27 tablets Subcutaneous: $184 for 2 vials ($445 for 5 vials) Intranasal: NA ($38) Oral disintegrating tablets: NA ($154) for 9 tablets Oral: NA ($156) for 6 tablets (2.5 mg)</td>
<td></td>
</tr>
<tr>
<td>NA ($206 for 9 tablets)</td>
<td>See individual medications</td>
<td>—</td>
</tr>
<tr>
<td>$11 ($21) for 5-mg vial</td>
<td>Dystonic reaction; parkinsonism withmetoclopramide use</td>
<td>—</td>
</tr>
<tr>
<td>$31 for 5-mg vial</td>
<td>NA ($100) Nausea; rhinorhea with intranasal use; similar adverse effects as triptans</td>
<td>IV dosing can be used in combination with 10 mg metoclopramide every 8 hours as needed for nausea</td>
</tr>
<tr>
<td>Oral: $42 for 25 vials (4 mg) Oral: $66 for 120 tablets (6 mg)</td>
<td>Hyperglycemia, mood changes, insomnia; multiple adverse effects with long-term use</td>
<td>Use as adjunctive therapy only</td>
</tr>
<tr>
<td>Intranasal: NA ($100)</td>
<td>IV: $32 ($124)</td>
<td></td>
</tr>
<tr>
<td>IV: $43 ($221) for 30 capsules</td>
<td>Subcutaneous: $32</td>
<td>Use caution in patients with cardiovascular risk factors</td>
</tr>
<tr>
<td>NA ($221) for 50 mL</td>
<td>Rare cardiac adverse effects if systemically absorbed</td>
<td>Not all patients will benefit, and symptoms may recur</td>
</tr>
</tbody>
</table>

NOTE: None of the prescription medications are available at discounted prices ($10 or less per prescription) at national retail chains.

IV = intravenous; NA = not available in generic form; NSAIDs = nonsteroidal anti-inflammatory drugs.

Information from references 7 through 13.
Management of Acute Migraine Headache

Suspected migraine headache

- Fever, altered mental status, or meningismus?
  - Yes
  - Workup for meningitis or subarachnoid hemorrhage
    - Acute onset?
    - Occipitomastoid location?
    - Older than 55 years?
    - Abnormal neurologic examination?
    - Increasing headache frequency?
    - Lack of coordination?
    - Localized neurologic signs?
    - Headache causing awakening from sleep?
    - Atypical features?
    - Does not fulfill strict definition of migraine?

- No
  - Consider neuroimaging
    - More serious conditions ruled out and migraine diagnosed

Mild to moderate intensity

- Trial of combination acetaminophen/aspirin/caffeine (Excedrin Migraine) or nonsteroidal anti-inflammatory drugs; also consider isometheptene compounds

Moderate to severe intensity

- Triptans
  - In emergency department setting: consider intravenous antiemetics with or without intravenous dihydroergotamine (DHE); consider adjunctive dexamethasone
  - Poor response
    - Increase triptan dose or trial of a different triptan or consider sumatriptan/naproxen (Trexima) or consider dihydroergotamine nasal spray (Migranal)
    - Also consider isometheptene compounds or intranasal lidocaine (Xylocaine)
  - Poor response

NOTE: Abortive migraine therapy should be used as soon as possible after symptom development for maximum benefit; if abortive therapy is unsuccessful or used more than twice weekly, consider adding prophylactic therapy. Patients with nausea and vomiting may require nonoral medication. For all medications, consider patient comorbidities and contraindications.

Figure 1. Algorithm for management of suspected migraine headache.
Information from references 5, 6, 11, 12, and 14 through 18.

two hours in 45 to 77 percent of patients taking triptans.13 Potential adverse effects, contraindications, pharmacokinetics, and route of administration are often primary determinants of medication choice. Patients with severe nausea and vomiting often require nonoral medication.

Evidence suggests that abortive therapy works best if taken soon after the onset of migraine or during aura, before pain progresses. A trial using almotriptan (Axert) showed that early users (i.e., therapy initiated within one hour of headache onset) had greater relief and lower recurrence rates of pain than non-early users.19 Nonprescription analgesics have shown comparable effectiveness with triptans if used in adequate doses soon after headache onset.8

Prophylactic therapy may be appropriate for selected patients. The U.S. Headache Consortium's recommended indications for prophylactic therapy in patients with migraine headache are:20

- Contraindications or intolerance to abortive therapies
- Headache symptoms occurring more than two days per week
- Headaches that severely limit quality of life despite abortive therapy
- Presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction.

First-Line Therapies

COMBINATION ANALGESICS

The combination analgesic acetaminophen/aspirin/caffeine (Excedrin Migraine) is effective, inexpensive, available without prescription, and free from most vascular contraindications associated with triptans. Its use in migraine treatment has shown favorable results when compared with 50 mg of sumatriptan (Imitrex) in one trial and with placebo in previous trials.9 Patients with severe pain were included, but patients requiring bed rest or who were consistently vomiting during headaches were excluded.9 A study that included these more severe cases reported that acetaminophen/aspirin/caffeine is superior to 400 mg of ibuprofen.7
Migraine Headache

NSAIDS

NSAIDs are a convenient first-line therapy for mild to moderate migraine or historically responsive severe attacks. A 2007 meta-analysis of ibuprofen for moderate to severe migraine showed that 200-mg and 400-mg doses were effective for short-term pain relief, but had 24-hour pain-free rates similar to placebo. The 400-mg dose also helped relieve photophobia and phonophobia. A study comparing ketoprofen with zolmitriptan (Zomig) showed zolmitriptan to be modestly more effective (two-hour relief in 61.6 versus 66.8 percent of participants, respectively), but it was associated with more adverse events, such as tight throat and flushing. Keta
orlac, a parenteral NSAID commonly used in emergency departments, was found to be effective in reducing self-reported headache symptoms one hour after injection, including one study showing more effectiveness than intranasal sumatriptan.

TRIPTANS

Triptans are migraine-specific drugs that bind to serotonin receptors. They are considered first-line therapy for moderate to severe migraine, or mild to moderate attacks unresponsive to nonspecific analgesics. Seven triptans are currently available, but data guiding which to select for an individual patient is limited. A Cochrane review found that all triptans are similar in effectiveness and tolerability. A meta-analysis of 53 trials using oral triptans found that the three most effective agents for pain relief were 10 mg of rizatriptan (Maxalt), 80 mg of eletriptan (Relpax), and 12.5 mg of almotriptan. A Cochrane review found a dose of 100 mg of sumatriptan to be more effective than lower doses. It is sometimes necessary to increase the dose of an individual agent before judging response. Trials suggest that nonresponders to one triptan may respond to another; therefore, switching triptans is also reasonable.

Triptans differ from one another in pharmacokinetics. Rizatriptan has a quicker onset of action than sumatriptan; frovatriptan (Frovای), naratriptan (Amerge), and eletriptan have longer half-lives than sumatriptan. In practice, route of administration or pharmacokinetics often guide choice. Some triptans are available as nasal sprays, rapidly dissolving tablets (absorbed despite vomiting), or subcutaneous injections. Some physicians choose a triptan by matching pharmacokinetics to the temporal pattern of their patient’s migraine (e.g., rapid-onset medication for short course of migraine versus longer-acting medication with slower onset for longer lasting symptoms); however, there is no definitive evidence to support this approach.

The vasoconstrictive properties of triptans preclude their use in patients with ischemic heart disease, stroke, uncontrolled hypertension, or hemiplegic or basilar migraine. However, the chest pain occurring in 3 to 5 percent of oral triptan users has not been associated with electrocardiographic changes and is rarely ischemic. A post-marketing study of subcutaneous sumatriptan in 12,339 patients without ischemic heart disease revealed 36 cardiac events, only two of which occurred within 24 hours of sumatriptan use. Nonetheless, if patients taking triptans develop suspected cardiac symptoms, triptans should be discontinued pending further evaluation. Cardiac evaluation is reasonable before triptan initiation in patients with multiple vascular risk factors.

Triptans are contraindicated in patients taking mono
amine oxidase inhibitors. Combining triptans with selective serotonin reuptake inhibitors can lead to sero
tonin syndrome, a potentially life-threatening condition characterized by altered mentation, autonomic instability, diarrhea, neuromuscular hyperactivity, and fever. The true incidence of serotonin syn
drome in this setting is unknown. A 2006 U.S. Food and Drug Administration (FDA) alert cited 29 case reports over five years, although almost 700,000 patients per year are prescribed both selective serotonin reuptake inhibitors and triptans. Physicians treating patients who are taking triptans and selective serotonin reuptake inhibitors should be vigilant for serotonin syndrome, and should minimize drug dosages.

COMBINATION TRIPTANS AND NSAIDS

A fixed-dose combination of sumatriptan, 85 mg/naproxen, 500 mg (Trexima) is an option for acute treatment. One trial showed that the combination provided superior pain relief compared with either monotherapy. Another trial found similar results in previous nonresponders to triptans. Patients also may take triptans and NSAIDs concurrently.

Other Effective Therapies

ANTIEMETICS

Evidence supports a role for parenteral antiemetics in acute migraine, independent of their antinausea effects. A meta-analysis of 13 randomized controlled trials concluded that intravenous metoclopramide (Reglan)
Migraine Headache

should be considered a primary agent in the treatment of migraine in emergency departments. Given the potential for rebound and dependence associated with opiates, antiemetics offer a reasonable alternative in acute settings. No evidence supports migraine-specific effects of oral antiemetics, other than relieving nausea.

Dexamethasone

Intravenous dexamethasone has been used as adjunctive therapy for migraine in emergency departments. Two meta-analyses, each with seven randomized controlled trials in which dexamethasone was added to other standard therapies, showed that about 10 patients needed treatment to prevent headache recurrence within 24 to 72 hours, one of these trials showed that oral dexamethasone is similar in effectiveness to the parenteral form.

Ergotamines

Like triptans, ergotamines and dihydroergotamine (DHE) are migraine-specific drugs that bind to serotonergic receptors. Although their use has been largely supplanted by triptans, ergot alkaloids still have a role in selected patients. Little evidence supports the use of oral ergotamines. Poor absorption and high rates of adverse events preclude their use in most situations. Combination medications containing ergotamines (e.g., ergotamine/caffeine [Cafergot]) may have fewer adverse effects than pure ergotamines.

Nine placebo-controlled trials have demonstrated the effectiveness of dihydroergotamine nasal spray (Migranal), making it an option for nonoral medication. Comparison with subcutaneous sumatriptan showed lower effectiveness but fewer adverse effects. Intravenous dihydroergotamine, combined with antiemetics, may be a reasonable option in emergency departments. A meta-analysis showed comparable effectiveness to opiates and ketorolac when combined with an antiemetic, but inferiority to phenothiazines and triptans when used alone. Trials comparing subcutaneous dihydroergotamine with subcutaneous sumatriptan showed that dihydroergotamine had inferior effectiveness but fewer adverse events and headache recurrences.

Isometheptene Compounds

The combination drug acetaminophen/isometheptene/dichloralphenazone (Midrin) includes a sympathomimetic (isometheptene) and a muscle relaxant (dichloralphenazone). One trial showed similar effectiveness to low-dose sumatriptan when used early in mild to moderate migraine. Due to sympathomimetic effects, it should be used cautiously in patients with cardiac risk factors.

Lidocaine

Intranasal lidocaine (Xylocaine) has a rapid onset of action and may be useful as a temporizing measure until longer-acting treatment can take effect. Lidocaine 4% solution administered into the nostril, either by a clinician or self-administered by patients, resulted in rapid symptom reduction compared with control, although recurrences were common.

Non-Preferred Therapies

Acetaminophen alone is not effective therapy for acute migraine. There are no placebo-controlled trials documenting the effectiveness of barbiturate-containing analgesics (e.g., butalbital/aspirin/caffeine [Fiorinal]) for acute migraine. The U.S. Headache Consortium recommends limiting opiate use in migraine treatment because of its potential for abuse and rebound headache. Intranasal butorphanol is effective, but its use should be limited because of these concerns. One study linked opiate or barbiturate use with an increased risk of episodic migraine becoming chronic. Opiates or barbiturate-containing medications should be used only in patients with migraine headaches resistant to other therapies.

Experimental Therapies

Calcitonin gene-related peptide is a neuropeptide thought to be central to migraine pathogenesis. Intravenous infusion of a calcitonin gene-related peptide antagonist showed promising results in one small study. Transcranial magnetic stimulation, a modality where a magnetic field is generated on the scalp to create currents in the adjacent cortex, seems promising. A controlled trial of 200 patients who had migraine with aura showed that this therapy is superior to sham in two-hour pain relief and sustained responses over 24 to 48 hours. Further research is needed to evaluate its role in treating migraine without aura and in migraine prophylaxis.

Special Populations

Pregnancy

Acetaminophen, despite questionable effectiveness, is reasonable in the treatment of migraine in pregnant women because of its established safety. NSAIDs are effective and generally considered safe until the third trimester. The combination analgesic acetaminophen, 250 mg/aspirin, 250 mg/caffeine, 65 mg also must be used with caution; aspirin is FDA pregnancy category C, but is downgraded to category D for third trimester use, and consuming more than 100 mg of caffeine daily is associated with mild fetal growth restriction, although the clinical significance of this is
Migraine Headache

unclear. The American Congress of Obstetricians and Gynecologists recommends limiting daily caffeine consumption to 300 mg during pregnancy. Avoidance of triptans is recommended during pregnancy, although limited data on first-trimester exposures are reassuring. Metoclopramide is FDA pregnancy category B and may be used intravenously for migraine or orally for associated nausea. Opiates may be used for intractable cases, but pose risks of neonatal withdrawal and maternal dependence. The safety of isometheptene in pregnancy is unknown, so its use is not recommended. Ergotamines are abortifacients and are therefore absolutely contraindicated in pregnant women and women of childbearing age who are not using reliable contraception. Given scant data and cautions regarding medication safety, preventive approaches are key.

MENSTRUAL MIGRAINE

Many women report migraine or migraine exacerbations occurring exclusively near the time of menses. Long-acting triptans frovatriptan and naratriptan, taken perimenstrually around-the-clock for short-term prevention, have been found effective in reducing frequency and severity of menstrual migraine. For abortive therapy, the highest-quality evidence supports the use of sumatriptan, rizatriptan, and the NSAID mefenamic acid (Ponstel).

CHILDREN AND ADOLESCENTS

Limited evidence is available to guide pharmacologic treatment of acute migraine in children and adolescents. A systematic review found acetaminophen and ibuprofen safe and effective in children. Triptans are often prescribed, although this is not FDA-approved or recommended by drug manufacturers. Intranasal sumatriptan and nasal zolmitriptan, but not oral formulations, have shown effectiveness in children and adolescents, perhaps because of the quicker onset of nasal formulations and shorter duration of migraines in children. Given limited data, prevention is important.

REFERENCES


The Authors

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Migraine Headache


Evaluation of Syncope

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Though relatively common, syncope is a complex presenting symptom defined by a transient loss of consciousness, usually accompanied by falling, and with spontaneous recovery. Syncope must be carefully differentiated from other conditions that may cause a loss of consciousness or falling. Syncope can be classified into four categories: reflex mediated, cardiac, orthostatic, and cerebrovascular. A cardiac cause of syncope is associated with significantly higher rates of morbidity and mortality than other causes. The evaluation of syncope begins with a careful history, physical examination, and electrocardiography. Additional testing should be based on the initial clinical evaluation. Older patients and those with underlying organic heart disease or abnormal electrocardiograms generally will need additional cardiac evaluation, which may include prolonged electrocardiographic monitoring, echocardiography, and exercise stress testing. When structural heart disease is excluded, tests for neurogenic reflex-mediated syncope, such as head-up tiltable testing and carotid sinus massage, should be performed. The use of tests such as head computed tomography, magnetic resonance imaging, carotid and transcranial ultrasonography, and electroencephalography to detect cerebrovascular causes of syncope should be reserved for those few patients with syncope whose history suggests a neurologic event or who have focal neurologic signs or symptoms. (Am Fam Physician 2005;72:1492-500. Copyright © 2005 American Academy of Family Physicians.)

Approximately 1 to 3 percent of emergency department visits and 6 percent of hospital admissions involve syncope, and 20 to 50 percent of adults experience one or more episodes during their lives.¹ More than 75 percent of persons older than 70 years will experience syncope at least once, 20 percent will have two episodes, and a small subset will have three or more episodes.²⁻⁵

The defining characteristics of syncope include rapid onset with transient loss of consciousness usually accompanied by falling, followed by spontaneous, complete, and usually prompt recovery without intervention.²⁻⁵ Because some patients use the term dizziness to describe syncopal events, it is important to ask patients exactly what they mean by dizziness and whether loss of consciousness occurred.

Syncope must be differentiated from vertigo, coma, drop attacks, dizziness, sudden cardiac death, and seizures. Vertigo (i.e., sensation of movement) does not include loss of consciousness. Coma involves loss of consciousness without spontaneous recovery. Drop attacks involve sudden falls without loss of consciousness or warning and with immediate recovery. Drop attacks may be idiopathic but also have several specific causes (e.g., underlying cardiovascular disease, spondylotic osteophytes or colloidal cysts that transiently block the vertebral arteries or cerebral aqueduct, verteobasilar stroke). The typical signs of epileptic seizures include déjà vu, tongue lacerations, limb jerking, and postictal confusion but not common signs of syncope, such as prodromal diaphoresis, palpitations, or provocation by prolonged sitting or standing.⁶ Although limb jerking is noted in 15 percent of syncopal patients, the other typical signs of seizures are absent.⁶

Decreased cerebral perfusion is common to all causes of syncope. Positional change from supine to erect causes a 300- to 800-mL shift in blood volume from the thoracic cavity to the lower extremities.
Cerebrovascular autoregulation ensures that cerebral blood flow remains within a narrow range independent of systemic blood pressure. Healthy adults tolerate a drop in systolic blood pressure to 70 mm Hg without incident; however, older patients and those with chronic hypertension are susceptible to syncpe when a relatively small decrease in systemic blood pressure occurs.

**Differential Diagnosis**

The underlying cause of syncope remains unidentified in 13 to 31 percent of patients even after a thorough evaluation.2,6,9–11 Although underlying causes are reported in various ways, this review uses four causal categories: reflex mediated (36 to 62 percent), cardiac (10 to 30 percent), orthostatic (2 to 24 percent), and cerebrovascular (about 1 percent).3,5 The major underlying causes for syncope are listed in Table 1.5,12

**REFLEX-MEDIATED CAUSES**

Reflex-mediated syncope has three common variations: vasovagal (i.e., common faint), carotid sinus, and situational. There is no increased risk for cardiovascular morbidity or mortality associated with reflex-mediated syncope.2

Upon positional change, a series of complex neurohormonal events maintain cerebral perfusion in healthy persons. Normally, decreased venous return and subsequent decreased left ventricular filling result in increased sympathetic tone and a hypercontractile left ventricle. However, overly sensitive left ventricular receptors may misinterpret hypercontractility as volume overload and falsely inhibit sympathetic stimulation while promoting parasympathetic drive,6 resulting in hypotension, bradycardia, and syncope.

Vasovagal syncope has three distinct phases: a prodrome, loss of consciousness, and a postsyncopal phase. A precipitating event or situation (e.g., emotional stress, trauma, pain, sight of blood, prolonged standing) usually is identifiable. The prodrome, characterized by diaphoresis, epigastric discomfort, extreme fatigue, weakness, yawning, nausea, dizziness, and vertigo, results from increased parasympathetic tone and may last seconds to several minutes. Lying down or removing the stimulus may abort the syncopal episode. The postsyncopal phase may last hours or, rarely, days and may include protracted confusion, disorientation, nausea, dizziness, and a general sense of poor health.3,13 A prolonged postsyncopal phase may be associated with causes more serious than vasovagal stimulation and should prompt a more extensive evaluation.

Carotid sinus syncope is suggested by a history of syncope after head turning, shaving, or wearing a tight collar, particularly in older patients. Carotid sinus massage should be considered in older patients with unexplained presyncope, syncope, or falls when
TABLE 1
Underlying Causes of Syncope

<table>
<thead>
<tr>
<th>Causal Subcategory</th>
<th>Indicated Disease Entities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasovagal Syncope</td>
<td>Common faint</td>
</tr>
<tr>
<td>Carotid Sinus</td>
<td>Carotid sinus type syncope</td>
</tr>
<tr>
<td>Situational (coughing, sneezing, defecation, microuria, postural)</td>
<td>Situational syncope</td>
</tr>
<tr>
<td>Glossoptymgeal and vagus nerve syncope</td>
<td></td>
</tr>
<tr>
<td>Cardiac: Mechanical or structural</td>
<td>Vascular disease, particularly acute myocardial infarction, valve heart syndrome, pericardial tamponade, intraventricular conduction disturbances, supraventricular tachycardia, supraventricular tachycardia with trigemiinal neuralgia</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Sinus node dysfunction, second or third degree heart block, ventricular tachycardia, atrial tachycardia, atrial flutter, atrial fibrillation</td>
</tr>
<tr>
<td>Catheter or device</td>
<td>Medical implant, pacemaker, implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>Hypoxic VA</td>
<td>Hypoxic events</td>
</tr>
</tbody>
</table>

Information from references 8 and 12.

TABLE 2
Carotid Sinus Massage

**Indications**
History of syncope after head turning, shaving, or while wearing a tight collar; syncopal episodes with unexplained presyncope of falls, negative cardiovascular and neurologic investigation.

**Contraindications**
Recent within last three months myocardial infarction, recent ischemic attack, or stroke, presence of ventricular fibrillation, ventricular arrhythmia, or carotid bruits.

**Monitoring equipment**
Intravenous access, pulse oximeter, electrocardiograph.

**Required personnel**
Nurse of technician to monitor blood pressure and pulse, physician to perform the procedure.

**Procedure**
Patient in the upright position, by convention, begin with the right carotid artery, massage to the superior border of the thyroid cartilage at the base of the mandible, use firm longitudinal massage with increasing pressure, massage is continued for five seconds, at no time should both arteries be massaged at once.

**Positive results**
Paroxysmal atrioventricular block or asystole of at least three seconds' duration, or blood pressure decrease from baseline of 50 mm Hg systolic or 30 mm Hg diastolic, and occurrence of syncope or presyncope symptoms.

Information from references 9 and 14.

Cardiovascular or neurologic investigations are nondiagnostic. The procedure and diagnostic criteria for carotid sinus massage are found in Table 2.9,14

Situational syncope is related to micturition, defecation, coughing, or gastrointestinal stimulation. The history is diagnostic. The mechanism involves a similar vagal stimulation in addition to the decreased venous return associated with the Valsalva maneuver.7

Glossopharyngeal neuralgia is an uncommon pain syndrome that can cause syncope. Swallowing, talking, sneezing, and touching trigger points in the tonsils, ear, pharynx, and larynx produce painful stimuli interpreted as increased pressure in the carotid sinus. This leads to parasympathetic stimulation and can cause syncope.15 Trigeminal neuralgia is uncommonly accompanied by syncope, and the pathophysiological mechanism of syncope in this condition is unclear.16

**CARDIAC CAUSES**
Coronary artery disease, congestive heart failure, ventricular tachycardia, and myocarditis may be precursors to arrhythmia and syncope.
Patients with underlying cardiac disease are at greater risk for recurrent syncopal events than are other patients with syncope.\textsuperscript{2,3,11} Patients with syncope are more likely to have coronary artery or cerebrovascular disease and to take cardiac or antihypertensive medications than patients without syncope.\textsuperscript{1} Medications that affect cardiac conduction are a potential cause of syncope, and arrhythmias may be induced despite nontoxic blood levels. Compared with all other patients with syncope, patients with cardiac-induced syncope have almost double the risk of all-cause mortality and an increased risk of fatal and nonfatal cardiovascular events.\textsuperscript{2,11} Patients with underlying cardiac disease, particularly older patients, are also more likely to require hospital admission.\textsuperscript{17} Indications for hospitalization of patients with syncope are shown in Table 3.\textsuperscript{4} A cardiac cause is found in only 3 percent of patients with syncope who have no previous diagnosis of heart disease.\textsuperscript{9}

**CEREBROVASCULAR CAUSES**

In patients without focal neurologic symptoms and signs, syncope from cerebrovascular disease is extremely rare. Transient ischemia may result from vertebrobasilar insufficiency and may cause syncope. Concurrent neurologic symptoms including vertigo, ataxia, or sensory disturbance often will be found.\textsuperscript{7} Headache, vertigo, dysarthria, and diplopia also are suggestive of syncope resulting from neurologic causes. Neurologic causes should be suspected if headache or dizziness occurs during recovery from syncopal episodes.

**Initial Assessment**

The cause of syncope can be identified by history and physical examination alone in more than 60 percent of patients.\textsuperscript{3,10} Assessment should focus on verification of a syncopal event, presence of heart disease, presence of other life-threatening causes, and clinical features of the history that suggest a diagnosis. An algorithm for the evaluation of patients with syncope is shown in Figure 1.\textsuperscript{6}

**HISTORY**

Syncope may be a symptom of a life-threatening condition such as aortic dissection, pulmonary embolism, acute myocardial infarction, or outflow tract obstruction, all of which require immediate identification and treatment.\textsuperscript{4}

The history should focus on circumstances immediately before the attack, its onset, the attack, the end of the attack, and the patient’s background (Table 4\textsuperscript{14}).

Prior awareness of syncopal events or...
Diagnosing the Cause of Syncope Following a Verified Syncopal Event

History, physical examination, electrocardiography.

Diagnostic
Such as polymorphic ventricular tachycardia, vasovagal syncope, situational syncope, and orthostatic hypotension

Suggestive
Such as aortic stenosis, pulmonary embolism, neurologic symptoms, or family history of syncope or sudden death

Obtain specific testing,
such as echocardiography, long-term electrocardiographic monitoring, echocardiography, or electrophysiology

Positive
No unexpected disease

Negative
Unexplained syncope

Positive

Negative

No unexpected disease

Positive

Negative

Normal sinus rhythm

Arrhythmia with syncope

No diagnosis for arrhythmia

Stop work-up for arrhythmia

Stop work-up

Treat or refer

Recurrent syncope

First syncope episode

Positive

Negative

Frequent syncope

Infrequent syncope

Stop work-up

Figure 1. Algorithm for the diagnosis of syncope.

<table>
<thead>
<tr>
<th>Time relative to attack</th>
<th>Diagnosis</th>
<th>Possible diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Just before Activity</td>
<td>Must have been upright or standing</td>
<td>Reflex-mediated syncope, vasovagal syncope, orthostatic hypotension, pulmonary hypertensive, diabetic, Leriche's disease</td>
</tr>
<tr>
<td>Just before Position</td>
<td>Must have been standing or sitting</td>
<td>Reflex-mediated syncope, vasovagal syncope, orthostatic hypotension, idiopathic, autonomic dysfunction, vasovagal syncope, situational syncope</td>
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<tr>
<td>During Activity</td>
<td>Must have been upright or standing</td>
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</tr>
</tbody>
</table>

Information from references 2, 4, and 6.
Syncope

The Authors

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cytochrome P450 enzyme inhibitors such as itraconazole (Sporanox), resulting in hypotension and syncope. Syncope also may result from the interaction of antihypertensive agents and many other classes of medications.

PHYSICAL EXAMINATION

The physical examination should focus on vital signs, including measures of orthostatic and bilateral blood pressure and the cardiovascular and neurologic systems. The cardiac examination should assess volume status, valvular heart disease, and rhythm disturbance. The neurologic examination should seek signs of focal neurologic deficit. Signs of occult blood loss should be assessed.

ADDITIONAL TESTING

Cerebrovascular causes of syncope are rare, and tests to detect cerebrovascular disease, such as head computed tomography (CT), magnetic resonance imaging (MRI), electroencephalography (EEG), and carotid ultrasonography are overused and they tend to displace the higher yield cardiovascular tests, which are not used enough. Head CT, MRI, EEG, and carotid ultrasonography should be ordered only when history or physical examination suggests a neurologic cause or after testing for cardiac or neurally mediated causes of syncope has been completed.

An electrocardiogram (ECG) should be ordered for all patients with syncope. Although the cost-effectiveness of ECG has been questioned, it is risk free and inexpensive. Abnormal ECG findings are common in patients with syncope. Abnormal ECG findings occur in about 90 percent of patients with cardiac-induced syncope but in only 6 percent of patients with neurally mediated syncope. ECG findings suggestive of cardiac-induced syncope are shown in Table 5. A normal ECG in a patient with syncope also is important. In one study, none of the 67 patients with syncope who had a negative cardiac history and a normal ECG had an abnormal echocardiogram.

Twenty-four hour (Holter) electrocardiographic monitoring is indicated when there is an increased probability of identifying an
arrhythmic cause for syncope. This includes syncope with the electrocardiographic abnormalities listed in Table 5, patients with known or suspected heart disease, patients with syncope preceded by palpitations, syncope when supine or during exertion, and patients with a family history of sudden death.4 Holter monitoring may document syncopal symptoms without arrhythmia, thus discounting arrhythmic causes, or may document instances of arrhythmia without syncope. Uncommonly, asymptomatic arrhythmias such as prolonged sinus pauses, Mobitz type II block, and nonsustained ventricular tachycardia suggest the need for further treatment. If no arrhythmias are found and no syncope occurs during monitoring, prolonged electrocardiographic monitoring (i.e., event monitor) is indicated.23,24

Echocardiography is unlikely to be helpful in the absence of known cardiac disease, a history suggestive of cardiac disease, or an abnormal ECG.5,22 However, in patients with syncpe who have a history of heart disease or an abnormal ECG, echocardiography is useful.23 Patients presenting with exercise-associated syncope, particularly those with a heart murmur, should have an echocardiogram to exclude hypertrophic or valvular causes of cardiac disease.23 Finally, for patients with syncope unexplained by history, physical examination, or ECG, the diagnosis of arrhythmia is twice as likely in patients with systolic dysfunction compared with those who have normal systolic function.22

Exercise testing can diagnose ischemia and exercise-induced tachyarrhythmias or reproduce exercise-associated and exertional syncope. Postexertional syncope, as distinct from exertional syncope, results from autonomic failure and reflex-mediated mechanisms.4

Intracardiac electrophysiologic studies (EPS) use electric stimulation and monitoring to discover conduction abnormalities that predispose patients to ventricular or supraventricular tachyarrhythmias. The diagnostic yield of EPS is significantly greater in patients with heart disease; it is only rarely indicated in patients with clinically normal hearts and normal ECGs. Patients with underlying organic heart disease and non-diagnostic prolonged electrocardiographic monitoring, and older patients with conduction disease or those at high risk for injury-causing accidents are candidates for EPS testing.25 Recently, subcutaneous recorders have been investigated for the diagnosis of recurrent unexplained syncope or presyncope following inconclusive EPS results.23,24

Head-up tilt-table (HUTT) testing (Table 6) is used widely for the evaluation of patients with unexplained syncope and is particularly important in those with structurally normal hearts.5 HUTT testing uses changes in position to reproduce the symptoms of the syncopal event by inducing bradycardia or hypotension suggestive of reflex-mediated syncope. After arrhythmias have been excluded as the cause of syncope, the specificity of a positive HUTT test is such that it is considered diagnostic for reflex-mediated vasovagal syncope.11 For patients in whom HUTT testing provokes loss of consciousness despite no change in blood pressure or heart rate, psychiatric disorders should be considered.27

Tests for cerebrovascular disease such as EEG, CT, MRI, and carotid or transcranial...
Doppler and ultrasound studies are indicated only when the history and physical examination suggest a cerebrovascular cause. This includes a history of seizure activity, prolonged loss of consciousness, disturbance in vision (e.g., diplopia), headache and postictal symptoms; or focal neurologic signs or bruise upon physical examination.

Although hemocrit and the serum level of glucose may be useful when initially evaluating syncope, other blood tests rarely yield useful information. Syncope caused by bleeding usually can be clinically diagnosed.

Abnormal serotonin metabolism may play a role in neurally mediated syncope, and generalized anxiety disorder, panic disorder, major depression, and alcohol dependence have been reported more commonly in patients with syncope. Patients with psychiatric illness generally do not have underlying heart disease, have more frequent syncope, and have a higher frequency of recurrent syncope than those with other disorders.

Author disclosure: Nothing to disclose.

Members of various family medicine departments develop articles for "Problem-Oriented Diagnosis." This is one in a series from the Department of Family and Community Medicine at Southern Illinois University School of Medicine, Springfield. Coordinator of the series is Robert M. Wesley, M.D.

REFERENCES


Cardiology
Diagnosing the Cause of Chest Pain

WILLIAM E. CAYLEY, JR., M.D., Eau Claire Family Medicine Residency, Eau Claire, Wisconsin

Chest pain presents a diagnostic challenge in outpatient family medicine. Noncardiac causes are common, but it is important not to overlook serious conditions such as an acute coronary syndrome, pulmonary embolism, or pneumonia. In addition to a thorough history and physical examination, most patients should have a chest radiograph and an electrocardiogram. Patients with chest pain that is predictably exertional, with electrocardiogram abnormalities, or with cardiac risk factors should be evaluated further with measurement of troponin levels and cardiac stress testing. Risk of pulmonary embolism can be determined with a simple prediction rule, and a D-dimer assay can help determine whether further evaluation with helical computed tomography or venous ultrasound is needed. Fever, egophony, and dullness to percussion suggest pneumonia, which can be confirmed with chest radiograph. Although some patients with chest pain have heart failure, this is unlikely in the absence of dyspnea; a brain natriuretic peptide level measurement can clarify the diagnosis. Pain reproducible by palpation is more likely to be musculoskeletal than ischemic. Chest pain also may be associated with panic disorder, for which patients can be screened with a two-item questionnaire. Clinical prediction rules can help clarify many of these diagnoses. (Am Fam Physician 2005;72:2012-21. Copyright © 2005 American Academy of Family Physicians.)

Chest pain is the chief complaint in about 1 to 2 percent of outpatient visits, and although the cause is often noncardiac, heart disease remains the leading cause of death in the United States. Thus, distinguishing between serious and benign causes of chest pain is imperative, and diagnostic and prognostic questions are important in making this determination.

The epidemiology of chest pain differs markedly between outpatient and emergency settings. Cardiovascular conditions such as myocardial infarction (MI), angina, pulmonary embolism (PE), and heart failure are found in more than 50 percent of patients presenting to the emergency department with chest pain, but the most common causes of chest pain seen in outpatient primary care are musculoskeletal conditions, gastrointestinal disease, stable coronary artery disease (CAD), panic disorder or other psychiatric conditions, and pulmonary disease (Table 1). Unstable CAD rarely is the cause of chest pain in primary care, and around 15 percent of chest pain episodes never reach a definitive diagnosis. Despite these figures, when evaluating chest pain in primary care it is important to consider serious conditions such as stable or unstable CAD, PE, and pneumonia, in addition to more common (but less serious) conditions such as chest wall pain, peptic ulcer disease, gastroesophageal reflux disease (GERD), and panic disorder.

Clinical Diagnosis

Chest pressure with dyspnea commonly leads physicians and other health care professionals to consider an acute coronary syndrome such as unstable angina or MI, but these symptoms also may represent chest wall pain or PE. Dyspnea is common in patients with heart failure, whereas dyspnea with fever is characteristic of pneumonia and bronchitis. The usual descriptions of peptic ulcer disease and GERD include epigastric discomfort and retrosternal burning, but often it is difficult to distinguish clearly between classic “heartburn” and classic “chest pressure.” Although it often is thought that symptoms of anxiety can help distinguish pulmonary diseases from other causes of chest pain, this is not a
### SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determining whether chest pain is anginal, atypical anginal, or non-anginal is recommended to help determine a patient’s cardiac risk.</td>
<td>C</td>
<td>16</td>
</tr>
<tr>
<td>The Rouan decision rule is recommended to help predict which patients are at higher risk of MI.</td>
<td>C</td>
<td>17</td>
</tr>
<tr>
<td>A Wells score of less than 2 plus a normal d-Dimer assay should rule out PE.</td>
<td>A</td>
<td>20, 32, 33</td>
</tr>
<tr>
<td>In patients with an abnormal d-Dimer assay or a Wells score indicating moderate to high risk, helical CT and lower extremity venous ultrasound examination should be used to rule in or rule out PE.</td>
<td>A</td>
<td>33, 35</td>
</tr>
<tr>
<td>The Diehr diagnostic rule is recommended to predict the likelihood of pneumonia based on clinical findings.</td>
<td>A</td>
<td>11</td>
</tr>
<tr>
<td>Patients should be screened for panic disorder using two set questions.</td>
<td>C</td>
<td>14</td>
</tr>
<tr>
<td>Patients presenting with chest pain should have an ECG evaluation for ST segment elevation, Q waves, and conduction defects. Results should be compared with previous tracings.</td>
<td>C</td>
<td>7, 9</td>
</tr>
<tr>
<td>Serum troponin-level testing is recommended to aid in the diagnosis of MI and help predict the likelihood of death or recurrent MI within 30 days.</td>
<td>C</td>
<td>25, 28, 29</td>
</tr>
<tr>
<td>Patients with chest pain and a negative initial cardiac evaluation should have further testing with stress ECG, perfusion scanning, or angiography depending on their level of risk.</td>
<td>C</td>
<td>16</td>
</tr>
<tr>
<td>The Duke treadmill score is recommended to help predict long-term prognosis for patients undergoing stress ECG testing.</td>
<td>A</td>
<td>31</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; PE = pulmonary embolism; CT = computed tomography; ECG = electrocardiography.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1949 or http://www.aafp.org/afpsort.xml.

### TABLE 1

**Epidemiology of Chest Pain in Primary Care and Emergency Department Settings**

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>Primary care United States</th>
<th>Primary care Europe</th>
<th>Emergency department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal condition</td>
<td>36</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>19</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Serious cardiovascular disease</td>
<td>16</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td>Stable coronary artery disease</td>
<td>10</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Unstable coronary artery disease</td>
<td>1.5</td>
<td>--</td>
<td>13</td>
</tr>
<tr>
<td>Psychosocial or psychiatric disease</td>
<td>8</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>5</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Nonspecific chest pain</td>
<td>16</td>
<td>11</td>
<td>15</td>
</tr>
</tbody>
</table>

* -- Diagnoses are listed in order of prevalence in United States.
1 -- Including infection, unstable angina, pulmonary embolism, and heart failure.
2 -- Including pneumonia, pneumothorax, and lung cancer.

Adapted with permission from Klothman M, Stevens D, Gorenflo DW. Episodes of care for chest pain: a preliminary report from MIRNET. Fam Pract 1994;11:149, with additional information from reference 3.
TABLE 2

Accuracy of Chest Pain Diagnosis Using the History and Physical Examination

<table>
<thead>
<tr>
<th>Diagnosis* (Overall outpatient probability)</th>
<th>Clinical finding</th>
<th>LL</th>
<th>LR</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction (2%)†</td>
<td>Chest pain radiates to both arms*</td>
<td>7.10</td>
<td>0.67</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Hypotension†</td>
<td></td>
<td>3.80</td>
<td>0.56</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>S. gallop‡</td>
<td></td>
<td>3.20</td>
<td>0.88</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Diaphoresis†</td>
<td></td>
<td>2.00</td>
<td>0.64</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pleuritic chest pain†</td>
<td></td>
<td>0.17</td>
<td>1.20</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Palpation of tender area reproduces chest pain</td>
<td></td>
<td>0.16</td>
<td>1.20</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia (5%)†</td>
<td>Dyspnea*</td>
<td>8.60</td>
<td>0.56</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Dullness to percussion*</td>
<td></td>
<td>4.35</td>
<td>0.75</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Fever*</td>
<td></td>
<td>2.10</td>
<td>0.71</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Heart failure (2%)‡</td>
<td>Cardiac oedema‡</td>
<td>1.20</td>
<td>0.71</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Displaced apical impulse‡</td>
<td>17.00</td>
<td>0.35</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>Panic disorder (3%)‡</td>
<td>&quot;Yes&quot; on at least one item of Autonomic Nervous System Questionnaire‡†</td>
<td>1.30</td>
<td>0.60</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Chest wall pain (36%)‡</td>
<td>Palpation of tender area reproduces chest pain</td>
<td>12.00</td>
<td>0.28</td>
<td>87</td>
<td>3</td>
</tr>
</tbody>
</table>

* = positive likelihood ratio; † = negative likelihood ratio.

1. Diagnoses are listed in order of Clinical Importance.
2. Screening questions. (†) "In the past three months, did you ever have a spell or an attack when all of a sudden your heart started to race, you felt faint, or you could not catch your breath?" 3. Information from references 4 through 15.

The Author

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consistent finding and should not be relied upon. There is enough overlap among the clinical manifestations of different causes of chest pain to make "classic" symptoms unhelpful in differentiating among diagnoses and ruling out serious causes. However, there are several validated clinical decision rules that combine key groups of symptoms.

HISTORY AND PHYSICAL EXAMINATION

It is important to obtain a clear history of the onset and evolution of chest pain, with particular attention to details such as location, quality, duration, and aggravating or alleviating factors. Certain key symptoms and clinical findings can help rule in or out specific diagnoses (Table 2).4-15

Determining whether pain is (1) substernal, (2) provoked by exertion, or (3) relieved by rest or nitroglycerin helps to clarify whether it is typical anginal pain (has all three characteristics), atypical anginal pain (has two characteristics), or nonanginal
Chest Pain Dx

TABLE 3
Rouan Decision Rule for Myocardial Infarction

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
<th>Risk of MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age greater than 60 yrs</td>
<td>0</td>
<td>Up to 0.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>Up to 3.4</td>
</tr>
<tr>
<td>History of MI or angina</td>
<td>2</td>
<td>Up to 5.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>3</td>
<td>Up to 12.0</td>
</tr>
<tr>
<td>Pain described as severe</td>
<td>4</td>
<td>Up to 27.0</td>
</tr>
</tbody>
</table>

MI = myocardial infarction

- One point for each clinical characteristic.
- Note: At no level of risk can one be completely ruled out.
- Information from reference 17.

Pain (has one characteristic). Anginal chest pain has a high risk for CAD in all age groups; atypical anginal chest pain carries intermediate risk for CAD in women older than 50 years and in all men; and nonanginal chest pain carries intermediate risk for CAD in women older than 60 years and men older than 40 years.16

The likelihood of MI is higher if there is pain radiating to both arms,5 hypotension,6 an S3 gallop on physical examination,7 or diaphoresis.8,9 Other factors predicting MI include age greater than 60 years, male sex, and prior MI.17 MI is less likely if pain is sharp or pleuritic.7 If the pain is reproducible by palpation of a specific tender area, the likelihood of MI decreases8 but the likelihood of chest wall pain increases.15 A history of rheumatoid arthritis or osteoarthritis also increases the likelihood of chest wall pain.18

The Rouan decision rule reliably predicts which patients with chest pain and a normal or nonspecific electrocardiogram (ECG) are at higher risk for MI (Table 3).17 However, because up to 3 percent of patients initially diagnosed with a noncardiac cause of chest pain suffer death or MI within 30 days of presentation, patients with cardiac risk factors such as male sex, greater age, diabetes, hyperlipidemia, prior CAD, or heart failure warrant close follow-up.19

There are no individual signs or symptoms that reliably diagnose PE, but the simplified Wells scoring system20 (Table 4)21 is well validated for determining whether patients have low, moderate, or high likelihood of PE,20,22 and this guides further evaluation.

Findings that suggest pneumonia include fever, egophony, and dullness to percussion, but their absence does not rule out the diagnosis.10 Although chest pain in patients with chronic obstructive pulmonary disease and at least four previous acute exacerbations of chronic bronchitis is more likely to be caused by a recurrent exacerbation of bronchitis or pneumonia,23 these patients are also at greater risk for CAD or acute coronary syndrome. The Diehr diagnostic rule, developed in a large study11 from 1984, uses seven clinical findings to predict the likelihood of pneumonia (Table 5).12

Although heart failure alone is an uncommon cause of chest pain, it may accompany acute coronary syndrome, valvular disease, or MI. A displaced apical impulse and a history of MI also support this diagnosis. Almost all patients with heart failure have exertional dyspnea, so the absence of exertional dyspnea is helpful in ruling out this diagnosis.13

Two simple questions14 are a highly sensitive screen for panic disorder:

- "In the past six months, did you ever have a spell or an attack when all of a sudden you felt frightened, anxious, or very uneasy?"
- "In the past six months, did you ever have a spell or an attack when for no reason your heart suddenly began to race, you felt faint, or you couldn't catch your breath?"14

A "yes" on either item is a positive screen,
TABLE 4
Wells Model for Clinical Diagnosis of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Clinical finding*</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (i.e., objectively measured leg swelling or pain with palpation of deep leg veins)</td>
<td>3.0</td>
</tr>
<tr>
<td>PE as likely or more likely than an alternative diagnosis</td>
<td>1.0</td>
</tr>
<tr>
<td>Heart rate more than 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobility (i.e., bedridden, recent for bathroom access)</td>
<td>1.5</td>
</tr>
<tr>
<td>For at least three consecutive days or surgery in the past four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous objectively diagnosed DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (treatment for cancer that is ongoing, within the past six months, or palliative)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total points</th>
<th>Risk of PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 points</td>
<td>Low</td>
</tr>
<tr>
<td>2 to 6 points</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;6 points</td>
<td>High</td>
</tr>
</tbody>
</table>

Adapted with permission from Wells PS, Anderson DR, Rodger M, Gruberg A, Kirtan G, Grant AE, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the model’s specificity with the simplified D-dimer. Thromb Haemost 2000;83:428, with additional information from reference 21

TABLE 5
Dierks Rule for Diagnosing Pneumonia in Adults with Acute Cough

<table>
<thead>
<tr>
<th>Finding</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>-3</td>
</tr>
<tr>
<td>Sore throat</td>
<td>-2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>-1</td>
</tr>
<tr>
<td>Night sweats</td>
<td>-1</td>
</tr>
<tr>
<td>Sputum all day</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory rate more than 15 breaths per minute</td>
<td>2</td>
</tr>
<tr>
<td>Temperature more than 100°F (37.8°C)</td>
<td>2</td>
</tr>
</tbody>
</table>

Probability of pneumonia

<table>
<thead>
<tr>
<th>Total points</th>
<th>(%; overall probability = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>0</td>
<td>2.2</td>
</tr>
<tr>
<td>1</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>10.3</td>
</tr>
<tr>
<td>3</td>
<td>25.0</td>
</tr>
<tr>
<td>&gt;25</td>
<td>29.6</td>
</tr>
</tbody>
</table>


and a “no” on both items makes panic disorder unlikely. However, neither these questions nor a general clinical impression are specific enough to allow a definite diagnosis of anxiety-related noncardiac chest pain, and a positive screen should not preclude further cardiac testing in patients with cardiac risk factors.19

Gastrointestinal disease can cause chest pain, but the history and physical examination are relatively inaccurate for ruling in or ruling out serious gastrointestinal pathology,24 and it is important first to rule out immediately life-threatening cardiovascular and pulmonary causes of chest pain.

Diagnostic Testing

Once the clinical examination has narrowed the differential diagnosis, diagnostic testing helps determine whether the patient has a serious condition (Table 6).4,7,12,25,26 Most adults with chest pain should have at least an ECG and a chest radiograph, unless the history and physical examination suggest an obviously nonthreatening cause of chest discomfort.

ACUTE CORONARY SYNDROME AND CAD

Important diagnostic tests when evaluating for acute coronary syndrome include the 12-lead ECG, serum markers of myocardial damage, and cardiac testing with stress testing or nuclear imaging. ECG findings that most strongly suggest MI are ST segment elevation, Q waves, and a conduction defect, especially if such findings are new compared with a previous ECG. New T-wave inversion also increases the likelihood of MI.7,9 However, none of these findings is sensitive enough that its absence can exclude MI.

The most common markers of myocardial damage are creatine kinase, the MB isoenzyme of creatine kinase (CK-MB), troponin T, and troponin I. A CK-MB level greater than 6.0 ng per mL (6.0 mcg per L) within nine hours of presentation for emergency care modestly increases the likelihood of MI or death in the next 30 days.27 Elevated
<table>
<thead>
<tr>
<th>Diagnosis (overall outpatient probability)</th>
<th>Clinical finding</th>
<th>L.R+</th>
<th>L.R-</th>
<th>Present (%)</th>
<th>Absent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction (2%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>New ST elevation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.0</td>
<td>0.52</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>New Q wave&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.4</td>
<td>0.68</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>New conduction defect?</td>
<td>6.3</td>
<td>0.88</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Any ST segment elevation&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11.0</td>
<td>0.45</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any Q wave&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.9</td>
<td>0.60</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any conduction defect?</td>
<td>2.7</td>
<td>0.89</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>New T wave inversion&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.5</td>
<td>0.72</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Troponin T &gt; 2 ng per ml (2 mcg per L) at least eight hours from presentation&lt;sup&gt;g&lt;/sup&gt;</td>
<td>5.2</td>
<td>0.05</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Troponin T &gt; 1 ng per ml (1 mcg per L) at least six hours from presentation&lt;sup&gt;h&lt;/sup&gt;</td>
<td>18.0</td>
<td>0.01</td>
<td>27</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Heart failure (2%)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Abnormal electrocardiogram&lt;sup&gt;g&lt;/sup&gt;</td>
<td>38.0</td>
<td>0.36</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Abnormal BNP level (cutoff)</td>
<td>3.5</td>
<td>0.10</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>80 ng per ml (1 ng per L)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>0.36</td>
<td>0.10</td>
<td>7</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

L.R+ = positive likelihood ratio; L.R- = negative likelihood ratio; BNP = brain natriuretic peptide.

* Diagnoses are listed in order of clinical importance.

Information from references 4, 7, 12, 25, and 26.

Levels of either troponin T (i.e., higher than 2 ng per mL [2 mcg per L]) at least eight hours from presentation or troponin I (i.e., higher than 1 ng per mL [1 mcg per L]) at least six hours from presentation support the diagnosis of MI or acute coronary syndrome and increase the likelihood of death or recurrent MI within 30 days. A normal level of troponin T or troponin I between six and 72 hours after the onset of chest pain is strong evidence against MI and acute coronary syndrome, particularly if the ECG is normal or near normal. In one study of 773 patients who each presented to an emergency department with chest pain and had a normal ECG, researchers found that only 0.3 percent of those with a normal troponin I at six hours and 1.1 percent of those with a normal troponin T at six hours experienced acute MI or death in the 30 days following presentation. Thus, individuals with chest pain who have a history that indicates low risk of cardiovascular disease, a normal or near-normal ECG, and normal troponin levels can safely be evaluated as outpatients.

Patients at low risk usually do not need further testing unless there are other risk factors in their family or medical history that markedly increase their likelihood of CAD. Patients at intermediate risk for CAD who can exercise and have no left bundle branch block, preexcitation, or significant resting ST depression on their ECG can be evaluated with an exercise stress ECG. Patients with baseline ECG abnormalities should have perfusion imaging performed along with a stress ECG, and patients who cannot exercise may be evaluated with a pharmacologic stress or vasodilator test (e.g., dobutamine [Dobutrex], adenosine [Adenocard]). Patients at high risk for CAD generally should proceed directly to angiography, which allows definitive assessment of coronary artery anatomy for patients in whom other testing is nondiagnostic and for patients who could benefit from revascularization.

For patients undergoing stress ECG testing, the Duke treadmill score (Table 7<sup>i</sup>) provides helpful prognostic information. Among 1,466 patients with a normal resting ECG, and 939 patients with ST-T abnormalities on a resting ECG, low-, intermediate-, and high-risk Duke treadmill scores accurately predicted seven-year survival rates for all-cause mortality.<sup>31</sup>
PULMONARY EMBOLISM

D-dimer testing has become an important part of the evaluation for PE and deep venous thrombosis (DVT). Quantitative enzyme-linked immunosorbent antibody assay (ELISA) D-dimer assays are more sensitive and have been more thoroughly tested in clinical settings than whole-blood agglutination assays. A low clinical suspicion for PE (e.g., Wells score less than 2) plus a normal quantitative ELISA D-dimer assay safely rules out PE, with a negative predictive value greater than 99.5 percent. If further testing is needed, helical computed tomography (CT), combined with clinical suspicion and other testing such as lower extremity venous ultrasound, can be used to rule in or rule out PE. A number of different sequential testing protocols have been proposed, all of which involve the same basic elements: (1) for patients with low clinical suspicion and a normal D-dimer, no further evaluation or treatment is needed unless symptoms change or progress; (2) for patients with low clinical suspicion and an abnormal D-dimer, or moderate to high clinical suspicion, helical CT and lower extremity venous ultrasound examination should be ordered; (3) for patients with moderate or high clinical suspicion and an abnormal CT scan or venous ultrasound result, treatment should be given for PE or DVT regardless of D-dimer; and (4) for patients with an abnormal D-dimer plus a normal CT scan and a normal venous ultrasound result, serial ultrasound should be considered if clinical suspicion is low to moderate, and pulmonary angiography should be considered if clinical suspicion is high. Patients in whom PE initially is ruled out by such an approach and who do not receive treatment have a less than 1 percent risk for PE occurring over the subsequent three months. An encounter form that takes this approach appears in the February 1, 2004, issue of American Family Physician and can be accessed online at http://www.aafp.org/afp/20040201/pocform.html.

PNEUMONIA AND HEART FAILURE

Chest radiograph generally is considered the reference standard for patients suspected of having pneumonia, and it is the standard against which clinical evaluations for pneumonia are compared. An abnormal ECG and cardiomegaly on chest radiograph increase the likelihood of heart failure among patients with chest pain, and brain natriuretic peptide (also known as B-type natriuretic peptide) level has been found to be reliable for detecting heart failure in patients presenting with acute dyspnea. Brain natriuretic peptide level is particularly helpful for ruling in heart failure if it is more than 500 pg per mL (500 ng per L), and for ruling out heart failure if it is less than 100 pg per mL (100 ng per L).

CHEST WALL PAIN

Chest wall pain usually can be diagnosed by history and physical examination if other etiologies have been excluded. Measurement of the sedimentation rate generally is not helpful in making the diagnosis; in unusual situations, radiography may be helpful.

Recommended Diagnostic Strategy

An algorithm illustrating the considered diagnostic strategy is provided in Figure 1. When a patient presents with new chest pain, a typical or atypical
Outpatient Diagnosis of Chest Pain

Patient presents with chest pain.

Does the patient have a typical or atypical anginal pattern, pain radiation or diaphoresis, or cardiac risk factors?  

No  

Is there a clinical suspicion for pulmonary embolism?  

No  

Does the patient have fever, egophony, or dulness to percussion?  

No  

Has the patient had spontaneous fright, anxiety, palpitations, dyspnea, or faintness in the past six months?  

No  

Is the pain reproducible by palpation?  

No  

Consider heart failure or gastrointestinal pathology  

Yes  

Consider panic disorder  

Perform chest radiography to evaluate for pneumonia  

No  

Yes  

Wells score 2 or greater  

Wells score less than 2  

Measure D-dimer  

Is the D-dimer normal?  

No  

Perform CT and venous ultrasound  

No further testing  

Yes  

CT scan and venous ultrasound result normal (and the D-dimer abnormal)  

Wells score 2 to 6  

Perform serial ultrasound  

Wells score greater than 6  

Perform pulmonary angiography  

Yes  

Vena cava ultrasound result positive  

Treat for deep venous thrombosis  

CT scan positive  

Treat for pulmonary embolism  

Yes  

Measure troponin levels  

8 to 72 hours after the onset of chest pain  

Are troponin levels normal?  

No  

Evaluate as an inpatient  

Yes  

Consider outpatient evaluation for patients with low cardiac risk, perform stress ECG  

For patients with moderate risk or abnormal ECG, perform stress test with perfusion scan  

For patients with high risk, perform angiography.

Note: This algorithm combines and simplifies diagnostic recommendations from multiple sources to provide an overview, and does not represent a validated decision rule.

Figure 1. Algorithm for the outpatient diagnosis of causes of chest pain. (ECG = electrocardiography; CT = computed tomography.)

Information from references 4, 5, 7 through 12, 14 through 17, 20 through 22, 25, 26, 28, 29, and 32 through 35.
anginal pattern, pain radiation or diaphoresis, cardiac risk factors, or ischemic ECG changes, serial measurement of troponins should be considered to determine whether hospitalization or outpatient evaluation with stress testing is warranted. If the probability of PE is low, based on the Wells score, a negative D-dimer result eliminates the need for further testing; an abnormal D-dimer or moderate to high probability of PE should prompt helical CT and venous ultrasound examination to guide further management. Fever, egophony, or dullness to percussion should prompt evaluation for pneumonia with chest radiograph. If life-threatening causes of chest pain are ruled out, then a history of spontaneous anxiety, palpitations, faintness, or dyspnea suggests panic disorder. A history of exertional dyspnea and a displaced apical impulse should prompt investigation for heart failure. Gastrointestinal symptoms should prompt further evaluation.

Data Sources: The PubMed database was searched using the following terms: chest pain, angina, acute myocardial infarction, coronary artery disease, heart failure, pulmonary embolism, chest wall pain, bronchitis, pneumonia, and peptic ulcer disease. Titles were reviewed to identify literature relevant to the outpatient diagnosis of chest pain. Additional searches were performed using the following databases: InfOPOEMS (http://www.infopoeems.com), Agency for Healthcare Research and Quality (http://www.ahrq.gov), Cochrane Collaboration (http://www.cochrane.org), Database of Abstracts of Reviews of Effects (http://www.york.ac.uk/inst/cedr/darehp.htm), and Institute for Clinical Systems Improvement (http://www.isci.org).

Author disclosure: Nothing to disclose.

REFERENCES


Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction: Part I. Initial Evaluation and Management, and Hospital Care

STEPHEN D. WIVIOTT, M.D., and EUGENE BRAUNWALD, M.D., Thrombolysis in Myocardial Infarction Study Group, Brigham and Women’s Hospital, and Harvard Medical School, Boston, Massachusetts

Each year, more than 1 million patients are admitted to U.S. hospitals because of unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI). To help standardize the assessment and treatment of these patients, the American College of Cardiology and the American Heart Association convened a task force to formulate a management guideline. This guideline, which was published in 2000 and updated in 2002, highlights recent medical advances and is a practical tool to help physicians provide medical care for patients with UA/NSTEMI. Management of suspected UA/NSTEMI has four components: initial evaluation and management; hospital care; coronary revascularization; and hospital discharge and post-hospital care. Part I of this two-part article discusses the first two components of management. During the initial evaluation, the history, physical examination, electrocardiogram, and cardiac biomarkers are used to determine the likelihood that the patient has UA/NSTEMI and to aid in risk assessment when the diagnosis is established. Hospital care consists of appropriate initial triage and monitoring. Medical treatment includes anti-ischemic therapy (oxygen, nitroglycerin, beta blocker), antiplatelet therapy (aspirin, clopidogrel, platelet glycoprotein IIb/IIIa inhibitor), and antithrombotic therapy (heparin, low-molecular-weight heparin). (Am Fam Physician 2004;70:525-32 Copyright © 2004 American Academy of Family Physicians.)

This is part I of a two-part article on unstable angina and non–ST-segment elevation myocardial infarction. Part II, “Coronary Revascularization, Hospital Discharge, and Post-Hospital Care,” appears on page 535 in this issue.

This article exemplifies the AAFP 2004 Annual Clinical Focus on caring for America’s aging population.

See page 425 for definitions of strength-of-recommendation labels.

The term “acute coronary syndrome” encompasses unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI) and ST-segment elevation myocardial infarction (STEMI). UA/NSTEMI is the combination of two closely related clinical entities (i.e., a syndrome), whereas STEMI is a distinct clinical entity. UA/NSTEMI is characterized by an imbalance between myocardial oxygen supply and demand. Most often, the syndrome develops because of decreased myocardial perfusion resulting from coronary narrowing caused by nonocclusive thrombus formation subsequent to disruption of an atherosclerotic plaque. In contrast, STEMI results from an occlusive thrombus.

Each year, more than 5 million patients present to U.S. emergency departments with chest pain and related symptoms. Approximately 1.4 million of these patients are admitted for management of UA/NSTEMI. Because of the scope of the problem, it is important for family physicians to understand the diagnosis, risk assessment, and treatment of this syndrome.

To help standardize the assessment and treatment of patients with UA/NSTEMI, the American College of Cardiology (ACC) and the American Heart Association (AHA) convened a task force to produce a management guideline. The ACC/AHA guideline, which was published in 2000 and updated in 2002, divides the management of suspected UA/NSTEMI into four components: initial evaluation and management; hospital care; coronary revascularization; and hospital discharge and post-hospital care. This two-part article focuses on the major management recommendations in the guideline, using the ACC/AHA classification of recommendations (Table 1). Recent advances in management are highlighted. Part I reviews the first two components of management, and part II reviews the other two components.
### TABLE 1
ACC/AHA Classification of Evidence Used in the UA/NSTEMI Guideline

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective</td>
</tr>
<tr>
<td>IIa</td>
<td>Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence or opinion favors usefulness or efficacy</td>
</tr>
<tr>
<td>IIc</td>
<td>Usefulness or efficacy is less well established by evidence or opinion</td>
</tr>
<tr>
<td>III</td>
<td>Conditions for which there is evidence or general agreement that a given procedure or treatment is not useful or effective, and in some cases may be harmful</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association. UA/NSTEMI = unstable angina and non-ST-segment elevation myocardial infarction. Information from Reference 3.

### Initial Evaluation and Management

Two important issues arise in the initial evaluation of the patient with a suspected acute coronary syndrome: the likelihood that the clinical presentation represents an acute coronary syndrome (Table 2)\(^2\) and the risk of adverse outcomes (Table 3).\(^3\) The initial clinical evaluation to address both issues should include a history, a physical examination, an electrocardiogram, and a cardiac biomarker measurement (a cardiac-specific troponin level [preferred in the ACC/AHA guideline\(^2\)] or an MB isoenzyme of creatine kinase level). Data from this evaluation aid in the assessment of risk and in decisions about the required intensity of monitoring (intensive care unit versus "step-down" unit), choice of therapeutic agents, and use of cardiac catheterization and revascularization.

### RISK PREDICTION RULE

The 2002 ACC/AHA guideline\(^2\) includes the use of a risk prediction rule for early assessment. Multiple risk scores have been developed to predict the likelihood of adverse outcomes in patients presenting with UA/NSTEMI.\(^6\) One example is the seven-point Thrombolysis in Myo-

### TABLE 2
Likelihood of Acute Coronary Syndrome Secondary to Coronary Artery Disease Based on Clinical Features

<table>
<thead>
<tr>
<th>Area of assessment</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Chest or left arm pain or discomfort reproducing previously documented angina</td>
<td>Chest or left arm pain or discomfort</td>
<td>Symptoms with features other than those indicating intermediate or high likelihood</td>
</tr>
<tr>
<td>History</td>
<td>Known history of coronary artery disease or myocardial infarction</td>
<td>Patient age &gt; 70 years, male sex, diabetes mellitus</td>
<td>Recent cocaine use</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Transient mital regurgitation, hypotension, diaphoresis, tachycardia</td>
<td>Manifestations of extracardiac vascular disease</td>
<td>Chest pain reproduced by palpation</td>
</tr>
<tr>
<td>ECG</td>
<td>New transient ST-segment deviation or T-wave inversions with symptoms</td>
<td>Q waves; abnormal ST segments or T waves not documented to be new</td>
<td>Normal ECG</td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td>Elevated cardiac-specific troponin level or elevated MB isoenzyme of creatine kinase level</td>
<td>Cardiac biomarker levels not elevated</td>
<td>Cardiac biomarker levels not elevated</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram.

TABLE 3
Clinical Features Associated with Risk of Death or Nonfatal Myocardial Infarction in Patients with Unstable Angina

<table>
<thead>
<tr>
<th>Risk of death or nonfatal myocardial infarction based on clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of assessment</td>
</tr>
<tr>
<td>History</td>
</tr>
<tr>
<td>Character of pain</td>
</tr>
<tr>
<td>Clinical findings</td>
</tr>
<tr>
<td>ECG</td>
</tr>
<tr>
<td>Cardiac biomarker</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram.

1 Risk is high if at least one clinical feature is present.
2 Risk is intermediate if at least one clinical feature in the column is present and no high-risk clinical features are present.


cardial Infarction (TIMI) risk score for UA/NSTEMI (Figure 1).6

The TIMI risk score integrates historical factors, frequency of symptoms, electrocardiographic findings, and cardiac biomarker levels.6 Higher scores are associated with an increased risk of adverse outcomes such as death, (re)infarction, or recurrent ischemia requiring revascularization. The risk of these outcomes ranges from approximately 5 percent with a TIMI risk score of zero or one point to approximately 41 percent with a risk score of six or seven points. The risk score may be used to help guide therapeutic decisions. Patients with higher risk scores have been shown to derive greater benefit from specific pharmacologic therapies (enoxaparin [Lovenox],6 platelet glycoprotein IIb/IIIa inhibitor9) and an early cardiac catheterization (invasive) strategy.10

BIOMARKERS

Recent studies have examined the role of nontraditional biomarkers in the risk stratification of patients with acute coronary syndrome. High-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, has been shown to provide prognostic information in patients with acute coronary syndromes, independent of clinical factors and

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traditional markers of necrosis.\textsuperscript{11-13} B-type natriuretic peptide (BNP) has been associated with heart failure, as well as adverse clinical outcomes (predominantly mortality), in patients with acute coronary syndromes.\textsuperscript{14} The study findings\textsuperscript{15-18} suggest that future risk stratification in patients with acute coronary syndrome may involve a panel of biomarkers.

One investigative team\textsuperscript{15} has proposed a simplified method of combining the information provided by biomarkers. From zero to three points are assigned, depending on the number of elevated biomarkers (cardiac-specific troponin, hs-CRP, BNP). The risk of death, recurrent myocardial infarction, or congestive heart failure has been found to be 4.5 times higher when all three biomarkers are elevated than when no biomarker is elevated.\textsuperscript{15} However, more data are needed before use of hs-CRP and BNP can be recommended for risk stratification in UA/NSTEMI.

**Hospital Care**

Patients with UA/NSTEMI should be admitted to an inpatient unit, where they should undergo continuous monitoring for arrhythmias and recurrent ischemia. Patients with high-risk indicators, such as recurrent pain or hemodynamic disturbance (Table 4),\textsuperscript{3} should be admitted to a coronary care or intensive care unit capable of more extensive monitoring. Therapy should include anti-ischemic, antiplatelet, and antithrombotic agents, as well as a care plan that includes consideration of an early invasive strategy (Figure 2).\textsuperscript{3}

**ANTI-ISCHEMIC THERAPY**

ACC/AHA class I anti-ischemic interventions include supplemental oxygen, sublingually or intravenously administered nitroglycerin for relief of recurrent ischemia and associated symptoms and, in the absence of contraindications, an intravenously administered beta blocker for management of ongoing chest pain followed by an orally administered beta blocker.\textsuperscript{2,3} Beta blockers should be used cautiously in patients with marked first-degree atrioventricular block, second- and third-degree atrioventricular block without a pacemaker, asthma, severe left ventricular dysfunction with congestive heart failure, significant chronic obstructive pulmonary disease, and significant sinus bradycardia or hypotension.\textsuperscript{2,3}
Figure 2. Evaluation and management of the patient with a high likelihood of having an acute coronary syndrome (ACS).

(ACC = American College of Cardiology; AHA = American Heart Association)


ANTIPLATELET THERAPY

Three classes of antiplatelet agents have important roles in the management of UA/NSTEMI: aspirin, thienopyridines, and platelet glycoprotein IIb/IIIa inhibitors.

Aspirin. A cornerstone of management in acute coronary syndromes, aspirin has been shown to reduce cardiovascular events by 50 to 70 percent. In the absence of known contraindications, aspirin therapy should be used in all patients with suspected, probable, or definite acute coronary syndrome.

Clotidogrel. The updated ACC/AHA guideline recommends use of the thienopyridine clotidogrel (Plavix) in patients who cannot tolerate aspirin (ACC/AHA class I). Because of its safety profile (compared with ticlopidine [Ticlid]), clotidogrel currently is the preferred thienopyridine. Clotidogrel is a potent antiplatelet agent that acts by irreversibly blocking the P2Y12 adenosine diphosphate receptor on the platelet surface, thereby interrupting platelet activation and aggregation.

One of the major changes in the care of patients with
UA/NSTEMI has been the ACC/AHA class I indication for use of clopidogrel in addition to aspirin in patients with acute coronary syndromes.\textsuperscript{1,2} This change occurred because of the findings of recent major clinical trials. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial\textsuperscript{10} randomized more than 12,000 patients with UA/NSTEMI to receive clopidogrel or placebo in addition to aspirin. Patients were followed for three to 12 months. In the CURE trial, death, myocardial infarction, or stroke occurred in 9.3 percent of the patients treated with clopidogrel, compared with 11.5 percent of those who received placebo. The improvement occurred at the cost of a small, but significant increase in bleeding (relative risk: 27 percent), especially in patients who underwent coronary artery bypass grafting within five days of discontinuing clopidogrel therapy.

In an analysis of patients undergoing percutaneous coronary intervention (PCI-CURE study),\textsuperscript{19} patients were treated with clopidogrel or placebo for a median of 10 days before the intervention (all patients also received aspirin). After the intervention, patients in the PCI-CURE study received open-label clopidogrel or ticlopidine for four weeks, followed by the initial study drug (clopidogrel or placebo) for an average of eight months. The clopidogrel-treated patients had fewer early (30-day) and long-term cardiovascular events.

As a result of the study findings, the 2002 ACC/AHA guideline\textsuperscript{2,3} considers the use of clopidogrel in addition to aspirin to have a class I indication in patients with UA/NSTEMI who are undergoing an early noninterventional or interventional approach and are not at high risk for bleeding. Clopidogrel therapy is recommended for at least one month and may be continued for up to nine months. Aspirin, unless contraindicated, should be continued for life. When elective coronary artery bypass grafting is planned, clopidogrel should be withheld for five to seven days.

**Platelet Glycoprotein IIb/IIIa Inhibitors.** These agents constitute a third class of antiplatelet agents that may be used in patients hospitalized with UA/NSTEMI. Three agents in this class currently are available for clinical use: abciximab (ReoPro), which is a monoclonal antibody; and eptifibatide (Integrilin) and tirofiban (Aggrastat), which are “small molecule” glycoprotein IIb/IIIa inhibitors. These potent inhibitors of platelet aggregation are administered intravenously.

Clinical trials have shown that platelet glycoprotein IIb/IIIa inhibitor therapy is beneficial in selected patients with UA/NSTEMI.\textsuperscript{20} However, benefit appears to be greater in patients for whom an early invasive strategy is planned (i.e., cardiac catheterization and percutaneous coronary intervention)\textsuperscript{20,21} and patients who have elevated cardiac-specific troponin levels\textsuperscript{22} or other high-risk indicators such as an elevated TIMI risk score\textsuperscript{6} or diabetes mellitus.\textsuperscript{23} In patients for whom an early invasive strategy is not planned, the Global Utilization of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndromes (GUSTO IV-ACS) randomized trial\textsuperscript{24} showed no benefit for abciximab compared with placebo. As a result of the GUSTO IV-ACS study findings, use of abciximab is contraindicated in patients for whom an early invasive strategy is not planned (ACC/AHA class III).

Based on the combined study findings,\textsuperscript{20-23,25} platelet glycoprotein IIb/IIIa inhibitors have an ACC/AHA class I indication in patients for whom catheterization and percutaneous coronary intervention are planned. These agents should be administered in addition to aspirin and heparin. An ACC/AHA class IIa recommendation is given to the use of eptifibatide or tirofiban in addition to aspirin and heparin in patients with continuing ischemia, elevated cardiac-specific troponin levels, or other high-risk features for whom an invasive strategy is not planned.

**ANTITHROMBOTIC THERAPY**

The final component of medical therapy to consider in patients with UA/NSTEMI is antithrombotic/anticoagulant therapy. Unfractionated heparin results in anticoagulation by facilitating the action of antithrombin which, in turn, inactivates factor IIa (thrombin), factor
Strength of Recommendations

<table>
<thead>
<tr>
<th>Key clinical recommendation</th>
<th>SOR labels</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>The updated ACC/AHA guideline recommends use of the thienopyridine clopidogrel (Plavix) in patients who cannot tolerate aspirin (ACC/AHA class I).</td>
<td>A</td>
<td>2, 3, 17</td>
</tr>
<tr>
<td>The updated ACC/AHA guideline considers the use of clopidogrel in addition to aspirin to have a class I indication in patients with UA/NSTEMI who are undergoing an early noninterventional or interventional approach and are not at high risk for bleeding.</td>
<td>A</td>
<td>2, 3, 18,19</td>
</tr>
<tr>
<td>When elective coronary artery bypass grafting is planned, clopidogrel should be withheld for five to seven days.</td>
<td>C</td>
<td>2, 3</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa inhibitors have an ACC/AHA class I indication in patients for whom catheterization and percutaneous coronary intervention are planned. These agents should be administered in addition to aspirin and heparin.</td>
<td>A</td>
<td>20-23, 25</td>
</tr>
<tr>
<td>Anticoagulation with unfractionated heparin or low-molecular-weight heparin for patients with UA/NSTEMI has an ACC/AHA class I indication. The heparin is to be used in addition to aspirin or clopidogrel.</td>
<td>A</td>
<td>27</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; UA/NSTEMI = unstable angina and non-ST-segment elevation myocardial infarction.

IXa, and factor Xa. Treatment with unfractionated heparin has been shown to be superior to aspirin therapy alone in patients with UA/NSTEMI. Low-molecular-weight (LMW) heparin (e.g., enoxaparin) is obtained through cleavage of heparin to provide chains with different molecular weights. Compared with unfractionated heparin, the LMW heparins are relatively more potent inhibitors of factor Xa. LMW heparins also have a more predictable pharmacology, which means that laboratory monitoring of anticoagulation status is not needed. Anticoagulation with unfractionated heparin or LMW heparin has an ACC/AHA class I indication. One of these agents is to be used in addition to aspirin or clopidogrel.

Recent trial data have shown superior results with the use of enoxaparin compared with unfractionated heparin in patients with UA/NSTEMI. Consequently, the guideline indicates a ACC/AHA class IIa recommendation for the use of enoxaparin, rather than unfractionated heparin, in patients with UA/NSTEMI. Although data are not conclusive, recent trials have shown that LMW heparin is safe to use in combination with glycoprotein IIb/IIIa inhibitors and in percutaneous coronary intervention.

Despite the role of thrombosis in UA/NSTEMI, thrombolytic agents have not been shown to provide benefit in patients with UA/NSTEMI; in fact, there is a trend toward worse outcomes. Consequently, thrombolytic agents are contraindicated for use in the treatment of patients who have UA/NSTEMI.

REFERENCES


Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction: Part II. Coronary Revascularization, Hospital Discharge, and Post-Hospital Care

STEPHEN D. WIVIOTT, M.D., and EUGENE BRAUNWALD, M.D., *Thrombolysis in Myocardial Infarction Study Group, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts*

In the guideline developed by the American College of Cardiology and the American Heart Association, the management of suspected unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI) has four components: initial evaluation and management; hospital care; coronary revascularization; and hospital discharge and post-hospital care. Part II of this two-part article discusses coronary revascularization, hospital discharge, and post-hospital care. Decisions must be made about the use of coronary angiography and coronary revascularization in patients hospitalized with UA/NSTEMI. With an early conservative strategy, medical management is employed. Coronary angiography and revascularization are reserved for use in patients with evidence of ischemia at rest (or with minimal activity) and patients with a strongly positive stress test. With an early invasive strategy, coronary angiography and revascularization are recommended within 48 hours in patients without contraindications. Hospital discharge planning involves coordination of medical care, preparation of the patient for resumption of normal activities, and evaluation of the need for long-term risk factor reduction. Discharge medications should be continued to control ongoing symptoms (anti-ischemic agents) and prevent recurrent events (aspirin, dipyridamole, beta blocker, and an angiotensin-converting enzyme inhibitor or statins in selected patients). (Am Fam Physician 2004;70:535-8 Copyright © 2004 American Academy of Family Physicians.)

The updated guideline from the American College of Cardiology and the American Heart Association (ACC/AHA) divides the assessment and treatment of patients with unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI) into four components. Part I of this two-part article discusses initial evaluation, management, and hospital care for these patients. Part II reviews issues related to coronary revascularization, hospital discharge, and post-hospital care, using the ACC/AHA classification of strength of recommendations (see Table 1 in part I).

**Coronary Revascularization**

In patients hospitalized with UA/NSTEMI, one of the most important decisions is the early strategy of care regarding coronary angiography and revascularization. The goals of coronary angiography are to provide information about prognosis based on the location and extent of coronary atherosclerosis and to identify the patients who will benefit from percutaneous or surgical revascularization.

The term "early conservative strategy" refers to medical management, with the use of coronary angiography and revascularization reserved for patients who have evidence of recurrent ischemia at rest (or with minimal activity) or who have a strongly positive predischarge stress test. The term "early invasive strategy" refers to the routine use of coronary angiography and revascularization (within 12 to 48 hours of presentation) in patients without contraindications.

Recent trials employing modern antiplatelet and antithrombotic therapies and catheterization techniques have included the FRagmin and Fast Revascularization during InStability in Coronary artery disease II (FRISC II) study and the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS II) study.
in Myocardial Infarction 18 (TACTICS-TIMI 18) trial.3 These trials have demonstrated significant benefit from pursuing an early invasive strategy, especially in patients who have high-risk indicators, with the strongest benefit occurring in patients who have ST-segment deviation or an elevated cardiac-specific troponin level.

Based on the results of the FRISC II4 and TACTICSTIMI 185 studies, the 2002 ACC/AHA guideline6-7 recommends an early invasive strategy in patients with UA/NSTEMI and any high-risk indicators (ACC/AHA class I recommendation; see Table 4 in part I). In the absence of high-risk indicators, an equal recommendation is given for an early conservative strategy or an early invasive strategy. However, it should be noted that patients who initially are treated conservatively should be managed invasively if they develop high-risk indicators or have a strongly positive stress test before hospital discharge. In addition, the ACC/AHA recommendations apply only to patients with a strong likelihood of acute coronary syndrome.12 Angiography is contraindicated in patients with acute chest pain and a low likelihood of acute coronary syndrome.12

When an invasive strategy is undertaken, the decision for revascularization follows from the results of coronary angiography, and indications are similar to those for revascularization in patients with chronic stable angina.6 The decision and mode of revascularization (percutaneous coronary intervention or coronary artery bypass grafting) are influenced not only by coronary anatomy but also by anticipated life expectancy, ventricular function, comorbidity, functional capacity, severity of symptoms, and quantity of viable myocardium at risk.12

Specific recommendations for mode of revascularization are as follows.12 Coronary artery bypass grafting (CABG) is recommended for patients with left main coronary artery disease (ACC/AHA class I). CABG is also recommended for patients with three-vessel coronary artery disease or with two-vessel disease, including proximal left anterior descending coronary involvement with either decreased left ventricular function or diabetes mellitus (ACC/AHA class I). Percutaneous coronary intervention is recommended for other patients with multivessel coronary artery disease who have suitable anatomy for this technique and do not have depressed ventricular function or diabetes mellitus (ACC/AHA class I). Either percutaneous coronary intervention or coronary artery bypass grafting is considered suitable in patients with one- or two-vessel disease and none of the features mentioned above. As surgical procedures (e.g., minimally invasive surgery) and interventional procedures (e.g., drug-coated stents) improve, recommendations are likely to evolve.

**Hospital Discharge and Post-Hospital Care**

**DISCHARGE PLANNING**

After receiving initial care in the hospital, most patients with UA/NSTEMI but no complications can be discharged on the day after percutaneous coronary intervention or four to seven days after coronary artery bypass grafting. Low-risk patients who are treated conservatively can be discharged on the day of noninvasive stress testing or the day after such testing.

Goals during the discharge process include preparing the patient to resume usual activities, evaluating long-term medical therapy and risk factor reduction to prevent recurrent coronary events, and confirming or establishing long-term medical follow-up care. A multidisciplinary approach involving physicians, nurses, pharmacists, and rehabilitation specialists can help to achieve these goals.

A mnemonic for remembering issues to consider at the time of discharge is “ABCD” (aspirin and antianginals, beta blockers and blood pressure, cholesterol and cigarettes, diet and diabetes, education and exercise).6 Because of current pressures for shorter hospitalizations, critical pathways and discharge planning protocols can help to avoid omission of important medications and instructions.

**DISCHARGE MEDICATIONS AND RISK FACTOR MODIFICATION**

Anti-ischemic medications (e.g., nitroglycerin, beta blocker) should be continued to control symptoms in patients with incomplete revascularization. The ACC/AHA guideline lists five medications as class I recommendations for long-term treatment of patients after UA/NSTEMI (Table 1).1

The benefits of aspirin, clopidogrel (Plavix), and beta blockers were discussed in part 1 of this article. Clinical trials have demonstrated benefit from the use of angiotensin-converting enzyme (ACE) inhibitors in patients with congestive heart failure; in addition, the Heart Outcomes Prevention and Evaluation study7 has shown favorable effects from long-term use of ACE inhibitors in
Recommended Discharge Medications for Patients with UA/NSTEMI

Aspirin, 75 to 325 mg per day.
Cholesterol lowering agents and diet therapy in patients with an LDL cholesterol level above 100 mg per dl, or patients with an LDL cholesterol level higher than 100 mg per dl (2.60 mmol per L) after diet therapy.
Angiotensin converting enzyme inhibitors in patients with congestive heart failure, left ventricular dysfunction (ejection fraction below 40%), hypertension, or diabetes.

UA/NSTEMI = Unstable angina or non-ST-elevation myocardial infarction, LDL = Low-density lipoprotein.

Table 1

A recent trial also suggested benefit of lipid lowering in patients with LDL levels above 100 mg per dl. Some experts have emphasized an LDL goal of 130 mg per dl (3.40 mmol per L).

Another controversy has been the benefit of intensive therapy compared with moderate therapy. The recently published Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT—TIMI 22) study11 compared intensive (atorvastatin, 80 mg per day) and moderate (pravastatin, 40 mg per day) statin therapy in patients stabilized from acute coronary syndromes. The median low-density lipoprotein cholesterol level achieved was 95 mg per dl (2.45 mmol per L) with pravastatin and 62 mg per dl (1.60 mmol per L) with atorvastatin. A highly statistically significant 16 percent reduction in deaths, myocardial infarctions, and readmissions for acute coronary syndromes or revascularization was observed in the patients who received intensive treatment. The findings of the PROVE-IT—TIMI 22 study suggest that intensive therapy is preferable in patients stabilized from acute coronary syndromes.

As a result of the publication of recent trials of cholesterol lowering, such as PROVE-IT—TIMI 2211 and the Heart Protection Study (HPS),12 cholesterol experts have reevaluated treatment goals in high-risk patients, including those who have had UA/NSTEMI. HPS showed a benefit from simvastatin compared with placebo in patients at high risk of coronary events (including those with established CAD) regardless of baseline cholesterol values. A position statement by the coordinating committee for the National Cholesterol Education Program (NCEP)13 endorsed a lower goal (LDL levels less than 70 mg per dl [1.80 mmol per L]) and supported the initiation of cholesterol-lowering therapy in patients with LDL levels less than 100 mg per dl in high-risk and very-high-risk patients. It is likely that future versions of the UA/NSTEMI guidelines will reflect treatment goals and strategies similar to those of the NCEP.

Secondary prevention through the control or elimination of known risk factors for coronary artery disease (e.g., hyperglycemia in patients with diabetes mellitus, tobacco use, physical inactivity) also should be part of discharge planning.

Long-term anticoagulation with warfarin (Coumadin), a vitamin K antagonist, has been evaluated in recent studies14-17 of patients with myocardial infarction or unstable angina. Results have been mixed, with some trials14-15 showing benefit from the use of warfarin, when compared with aspirin alone in the prevention of recurrent cardiovascular events, and other trials16,17 (predominantly involving low-intensity warfarin therapy) showing no significant benefit.

The routine use of warfarin in patients with acute coronary syndromes has been limited by the occurrence of bleeding and the need for frequent monitoring. The ACC/AHA guideline1-2 does not recommend routine use of warfarin after hospitalization in patients with UA/NSTEMI. Warfarin therapy is recommended after acute coronary syndromes in patients with an additional indication for long-term anticoagulation, such as atrial fibrillation or a mechanical prosthetic heart valve.1,2

CONTINUING CARE AND FOLLOW-UP

At the time of hospital discharge, patients should have a clear plan for follow-up with a physician to assess recovery and symptoms and to reinforce secondary preventive measures. Low-risk medically treated patients and revascularized patients usually should be seen within two to six weeks, whereas higher-risk patients should be seen within one to two weeks.
Despite the efforts of hospital staff to adhere to guidelines and evidence-based treatment, or because of temporary contraindications, important therapies may be omitted. Family physicians can provide an invaluable “safety net” to ensure that patients with UA/NSTEMI receive optimal medical care. Therefore, even though all family physicians may not provide acute care for patients with UA/NSTEMI, familiarity with the ACC/AHA guideline will facilitate optimal treatment of patients with UA/NSTEMI and those with a history of this syndrome.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

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4. Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC II prospective randomised multicentre study. FRAGmin and Fast Revascularisation during InStability in Coronary artery disease II; TACTICS-TIMI 18: Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy. Thrombolysis in Myocardial Infarction 18; ACC/AHA = American College of Cardiology; AHA = American Heart Association; UA/NSTEMI = unstable angina and non-ST-segment elevation myocardial infarction.

HE CLINICAL SYNDROME OF HEART FAILURE IS THE FINAL PATHWAY for myriad diseases that affect the heart. Since the mid-1990s, when the last review of heart failure appeared in the Journal,1 discoveries from basic research and findings from key clinical trials have resulted in considerable change in the scope of therapies available and the continuing advancement of our understanding of the pathophysiologic mechanisms of heart failure. In this article, we highlight these new developments.

A COSTLY AND DEADLY DISORDER

Nearly 5 million Americans have heart failure today, with an incidence approaching 10 per 1000 population among persons older than 65 years of age. Heart failure is the reason for at least 20 percent of all hospital admissions among persons older than 65. Over the past decade, the rate of hospitalizations for heart failure has increased by 159 percent.2 In 1997, an estimated $5,501 was spent for every hospital-discharge diagnosis of heart failure, and another $1,742 per month was required to cover for each patient after discharge. Accordingly, substantial efforts have been made to identify and treat the factors that predict recurrent hospitalization. End points of large randomized trials now include the effect of the studied intervention on the rate of hospital admissions. For example, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor antagonists, beta-blockers, spironolactone, biventricular pacing, coronary bypass surgery, and the use of multidisciplinary teams to treat heart failure have all been shown to reduce the rate of hospitalizations substantially, as well as to reduce mortality or improve functional status.3–5 Considerable debate has focused on the mechanisms that reduce the rate of admissions and on the type of physician who should care for patients with heart failure. In the United States, more than two thirds of patients with heart failure are cared for exclusively by primary care practitioners.

Multiple clinical trials completed during the past 15 years have unequivocally shown a substantial reduction in mortality for patients with systolic heart failure. Simultaneously, however, large epidemiologic surveys, such as the ongoing Framingham Study, have not documented any meaningful change in overall death rates. (Death seems to have been delayed, however, and occurs a longer time after major cardiac events such as a myocardial infarction.) Symptomatic heart failure continues to confer a worse prognosis than the majority of cancers in this country, with one-year mortality of approximately 45 percent.6,7

Why have the newer and successful therapies failed to result in a meaningful reduction in mortality due to heart failure? It is important to recognize that heart failure is a clinical syndrome arising from diverse causes. Not all patients with the condition have poorly contracting ventricles and a low ejection fraction. Many have uncorrected valvular disease, such as aortic stenosis or mitral regurgitation, or abnormal filling, resulting in diastolic heart failure. A large majority of patients with heart failure are elderly, and 75

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percent of patients have a history of hypertension. Many patients have at least one serious coexisting condition, in addition to advanced age. Such patients have not usually been subjects in investigational trials. Moreover, until recently, the majority of patients entered into trials of investigational drugs were middle-aged white men with heart failure due to ischemic cardiomyopathy. Fewer women and members of racial minorities have taken part in trials, and very few trials have included persons older than 75 years of age. Thus, despite the acknowledged successes of the therapies outlined below, there is much to be done in the prevention and management of heart failure in the large subgroups of patients who are not well represented in trials. Certainly, successful treatments have not been systematically applied to the majority of patients with heart failure, and for the reasons stated above, those that have been applied may not be efficacious.

Although heart failure is a major public health problem, there are no national screening efforts to detect the disease at its earlier stages, as there are for breast and prostate cancer or even osteoporosis. Heart failure is largely preventable, primarily through the control of blood pressure and other vascular risk factors. Yet, until recently, the factors that render a patient at high risk for heart failure had not been clearly defined or publicized. The guidelines for the evaluation and management of chronic heart failure that were published recently by the American College of Cardiology and the American Heart Association have corrected this deficit. The writing committee developed a new approach to the classification of heart failure that emphasizes its evolution and progression and defined four stages of heart failure. Patients with stage A heart failure are at high risk for the development of heart failure but have no apparent structural abnormality of the heart. Patients with stage B heart failure have a structural abnormality of the heart but have never had symptoms of heart failure. Patients with stage C heart failure have a structural abnormality of the heart and current or previous symptoms of heart failure. Patients with stage D heart failure have end-stage symptoms of heart failure that are refractory to standard treatment.

This staged classification underscores the fact that established risk factors and structural abnormalities are necessary for the development of heart failure, recognizes its progressive nature, and superimposes treatment strategies on the fundamentals of preventive efforts. The classification is a departure from the traditional New York Heart Association (NYHA) classification, which has primarily been used as shorthand to describe functional limitations. Heart failure may progress from stage A to stage D in a given patient but cannot follow the path in reverse. In contrast, a patient with NYHA class IV symptoms might have quick improvement to class III with diuretic therapy alone. This staged heart-failure classification promotes a way of thinking about heart failure that is similar to our way of thinking about cancer — that is, the identification and screening of patients who are at risk, patients with in situ disease, and patients with established or widespread disease. The ensuing discussion about the treatment of heart failure is keyed toward this new staging classification.

THE SYNDROME OF HEART FAILURE

The traditional view that heart failure is a constellation of signs and symptoms caused by inadequate performance of the heart focuses on only one aspect of the pathophysiology involved in the syndrome. Currently, a complex blend of structural, functional, and biologic alterations are evoked to account for the progressive nature of heart failure and to explain the efficacy or failure of therapies used in clinical trials. For example, the rationale for the use of beta-blockers in a patient with a poorly contracting heart is based on a conceptual framework broader than that which suggests the treatment of congestion with diuretics or digoxin. The rationale for using beta-blockers is predicated on an understanding of the role of the sympathetic nervous system in promoting the release of renin and other vasoactive substances that trigger vasoconstriction, tachycardia, and changes in myocytes that lead to disadvantageous ventricular dilatation.

Indeed, recent reviews have combined several models that had been used previously to understand heart failure in order to illustrate more fully the cascade of mechanisms, as well as the opportunities for intervention. Thus, the hemodynamic model of heart failure emphasized the effect of an altered load on the failing ventricle and ushered in the era of vasodilators and inotropic agents. The neurohumoral model recognized the importance of activation of the renin–angiotensin–aldosterone axis and the sympathetic nervous system in the progression of cardiac dysfunction. More recently, efforts to antagonize the effects of circulating norepinephrine and angiotensin II have shifted with the
recognition that these and other vasoactive substances are also synthesized within the myocardium and therefore act in an autocrine and paracrine manner, in addition to their actions in the circulation. For example, brain natriuretic peptide is produced by the ventricular myocardium in response to stretch; its vasodilatory and natriuretic effects counteract the opposing actions of angiotensin II and aldosterone. Other studies have scrutinized myocytes from failing hearts in an attempt to detect abnormal signaling, gene expression, or contractile protein structure. Table 1 details many of the factors that contribute to the heart-failure syndrome as it is currently understood. Because no single pathophysiological model can account for the host of clinical expressions of heart failure, current therapy often targets more than one organ system, as outlined in Figure 1. Additional pathophysiological concepts that have become clinically meaningful areas for investigation or treatment are described below.

**Remodeling**

Increased levels of circulating neurohormones are only part of the response seen after an initial insult to the myocardium. Left ventricular remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Remodeling occurs in several clinical conditions, including myocardial infarction, cardiomyopathy, hypertension, and valvular heart disease; its hallmarks include hypertrophy, loss of myocytes, and increased interstitial fibrosis.\(^{12,13}\)

For example, after a myocardial infarction, the acute loss of myocardial cells results in abnormal loading conditions that involve not only the border zone of the infarction, but also remote myocardium. These abnormal loading conditions induce dilatation and change the shape of the ventricle, rendering it more spherical, as well as causing hypertrophy. Remodeling continues for months after the initial insult, and the eventual change in the shape of the ventricle becomes deleterious to the overall function of the heart as a pump (Fig. 2A).\(^{14}\) In cardiomyopathy, the process of progressive ventricular dilatation or hypertrophy occurs without the initial apparent myocardial injury observed after myocardial infarction (Fig. 2B).

Several trials involving patients who were studied after a myocardial infarction or who had dilated cardiomyopathy found a benefit from ACE inhibitors, beta-adrenergic antagonists, or cardiac resynchronization.\(^{15-18}\) Such beneficial effects were associated with so-called reverse remodeling, in which the therapy promoted a return to a more normal ventricular size and shape.\(^{15-18}\) The reverse-remodeling process is a mechanism through which a variety of treatments palliate the heart-failure syndrome.

**MitrAL REgURGITATION**

Another potential deleterious outcome of remodeling is the development of mitral regurgitation. As

<table>
<thead>
<tr>
<th>Table 1. Pathophysiological Mechanisms Important in the Syndrome of Heart Failure.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac abnormalities</strong></td>
</tr>
<tr>
<td><strong>Structural abnormalities</strong></td>
</tr>
<tr>
<td>Myocardium or myocyte</td>
</tr>
<tr>
<td>Abnormal excitation-contraction coupling</td>
</tr>
<tr>
<td>beta-Adrenergic desensitization</td>
</tr>
<tr>
<td>Hypertrophy</td>
</tr>
<tr>
<td>Necrosis</td>
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<tr>
<td>Fibrosis</td>
</tr>
<tr>
<td>Apoptosis</td>
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<tr>
<td>Left ventricular chamber</td>
</tr>
<tr>
<td>Remodeling</td>
</tr>
<tr>
<td>Dilatation</td>
</tr>
<tr>
<td>Increased sphericity</td>
</tr>
<tr>
<td>Aneurysmal dilatation or wall thinning</td>
</tr>
<tr>
<td>Coronary arteries</td>
</tr>
<tr>
<td>Obstruction</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td><strong>Functional abnormalities</strong></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>Intermittent ischemia or hibernating myocardium</td>
</tr>
<tr>
<td>Induced atrial and ventricular arrhythmias</td>
</tr>
<tr>
<td>Altered ventricular interaction</td>
</tr>
<tr>
<td><strong>Biologically active tissue and circulating substances</strong></td>
</tr>
<tr>
<td>Renin–angiotensin–aldosterone system</td>
</tr>
<tr>
<td>Sympathetic nervous system (norepinephrine)</td>
</tr>
<tr>
<td>Vasodilators (bradykinin, nitric oxide, and prostaglandins)</td>
</tr>
<tr>
<td>Natriuretic peptides</td>
</tr>
<tr>
<td>Cytokines (endothelin, tumor necrosis factor, and interleukins)</td>
</tr>
<tr>
<td>Vasopressin</td>
</tr>
<tr>
<td>Matrix metalloproteinases</td>
</tr>
<tr>
<td><strong>Other factors</strong></td>
</tr>
<tr>
<td>Genetic background, including effects of sex</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Environmental factors, including use of alcohol, tobacco, and toxic drugs</td>
</tr>
<tr>
<td>Coexisting conditions</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Renal disease</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Sleep apnea</td>
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<tr>
<td>Depression</td>
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</tbody>
</table>
the left ventricle dilates and the heart assumes a more globular shape, the geometric relation between the papillary muscles and the mitral leaflets changes, causing restricted opening and increased tethering of the leaflets and distortion of the mitral apparatus. Dilatation of the annulus occurs as a result of increasing left ventricular or atrial size or as a result of regional abnormalities caused by myocardial infarction. The presence of mitral regurgitation results in an increasing volume overload on the overburdened left ventricle that further contributes to remodeling, the progression of disease, and symptoms. Correction of mitral regurgitation has been an appropriate focus of therapy.

**ARRHYTHMIAS AND BUNDLE-BRANCH BLOCK**

The myocardial conduction system is vulnerable to the same pathophysiological processes that occur in the myocytes and interstitium, with altered conduction properties observed in response to ischemia, inflammation, fibrosis, and aging. Supraventricular arrhythmias, particularly atrial fibrillation, are often the precipitating events that herald the onset of either systolic or diastolic heart failure. Elevated ventricular end-diastolic pressure in a patient with hypertension or abnormal myocardial function leads to atrial stretch, which in turn incites electrical instability. Recognition of the presence of atrial fibrillation in a patient is critical, since several studies have now demonstrated the effectiveness of oral anticoagulant therapy for the prevention of stroke.

Abnormal myocardial conduction can also lead to delays in ventricular conduction and bundle-branch block. Left bundle-branch block is a significant predictor of sudden death and a common finding in patients with myocardial failure. Its presence also affects the mechanical events of the cardiac cycle by causing abnormal ventricular activation and contraction, ventricular dyssynchrony, delayed opening and closure of the mitral and aortic valves, and abnormal diastolic function. Hemodynamic sequelae include a reduced ejection fraction, decreased cardiac output and arterial pressure, paradoxical septal motion, increased left ventricular volume, and mitral regurgitation. Ventricular arrhythmias are thought to be secondary to a dispersion of normal conduction through nonhomogeneous myocardial tissue, which promotes repetitive ventricular arrhythmias.

The rate of sudden cardiac death among persons with heart failure is six to nine times that seen in the...
Figure 2. Ventricular Remodeling after Infarction (Panel A) and in Diastolic and Systolic Heart Failure (Panel B).
At the time of an acute myocardial infarction — in this case, an apical infarction — there is no clinically significant change in overall ventricular geometry (Panel A). Within hours to days, the area of myocardium affected by the infarction begins to expand and become thinner. Within days to months, global remodeling can occur, resulting in overall ventricular dilatation, decreased systolic function, mitral-valve dysfunction, and the formation of an aneurysm. The classic ventricular remodeling that occurs with hypertensive heart disease (middle of Panel B) results in a normal-sized left ventricular cavity with thickened ventricular walls (concentric left ventricular hypertrophy) and preserved systolic function. There may be some thickening of the mitral-valve apparatus. In contrast, the classic remodeling that occurs with dilated cardiomyopathy (right side of Panel B) results in a globular shape of the heart, a thinning of the left ventricular walls, an overall decrease in systolic function, and distortion of the mitral-valve apparatus, leading to mitral regurgitation.

general population. Major innovations in medical and device-based therapy for the primary and secondary prevention of lethal ventricular arrhythmias have occurred during the past decade but are beyond the scope of this article. Increasing use of implantable cardioverter–defibrillators has unequivocally reduced mortality in a subgroup of patients with heart failure.

DIASTOLIC HEART FAILURE
It is estimated that 20 to 50 percent of patients with heart failure have preserved systolic function or a normal left ventricular ejection fraction. Although such hearts contract normally, relaxation (diastole) is abnormal. Cardiac output, especially during exercise, is limited by the abnormal filling characteristics of the ventricles. For a given ventricular volume,
Ventricular pressures are elevated, leading to pulmonary congestion, dyspnea, and edema identical to those seen in patients with a dilated, poorly contracting heart.\textsuperscript{32} \textsuperscript{33} Characteristics of patients with systolic heart failure and those with diastolic heart failure are compared in Table 2. Patients with diastolic heart failure are typically elderly, often female, and usually obese and frequently have hypertension and diabetes. Mortality among these patients may be as high as that among patients with systolic heart failure, and the rates of hospitalization in the two groups are equal.\textsuperscript{36} The diagnosis of diastolic heart failure is usually made by a clinician who recognizes the typical signs and symptoms of heart failure and who is not deterred by the finding of normal systolic function (i.e., a normal ejection fraction) on echocardiography. Echocardiography may be useful in the detection of diastolic filling abnormalities.

Unfortunately, unlike heart failure due to systolic dysfunction, diastolic heart failure has been studied in few clinical trials, so there is little evidence to guide the care of patients with this condition. Physiological principles used in the treatment of such patients include the control of blood pressure, heart rate, myocardial ischemia, and blood volume.

**MANAGEMENT OF HEART FAILURE**

**CLINICAL ASSESSMENT**

Breathlessness, fatigue, and even edema may be due to a host of noncardiac conditions and do not necessarily indicate the presence of heart failure. Nevertheless, the clinician must have a high index of suspicion that the source of a patient’s problems may be cardiac and must become adept at assessing patients for fluid overload and cardiac abnormalities. Measurement of serum brain natriuretic peptide may aid in the diagnosis of heart failure.\textsuperscript{37} Serial measurements of weight at office visits, combined with instructions for daily weighing at home, help to alert the clinician and the patient to the possibility of fluid retention. The patient should be evaluated regularly in an appropriate position (45-degree elevation), with notation of the jugular venous pressure. Hepatolabial reflex, presence of a gallop rhythm, and peripheral edema are key findings on physical examination that may indicate a need for additional diuretic therapy and may be prognostically important.\textsuperscript{38}

**TREATMENT OF PATIENTS WITH STAGE A HEART FAILURE**

Control of risk factors in stage A (e.g., hypertension, coronary artery disease, and diabetes mellitus) has a favorable effect on the incidence of later cardiovascular events (Fig. 3). Results from trials have shown that the effective treatment of hypertension decreases the occurrence of left ventricular hypertrophy and cardiovascular mortality, as well as reducing the incidence of heart failure by 30 to 50 percent.\textsuperscript{39,40} Guidelines have recommended that the target for diastolic blood pressure in patients considered to be at high risk, particularly those with diabetes, be below 80 mm Hg, with the goal of further reducing morbidity and mortality.\textsuperscript{41} Patients with diabetes have a high incidence of heart disease, with multiple

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diastolic Heart Failure</th>
<th>Systolic Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Frequently elderly</td>
<td>All ages, typically 50–70 yr</td>
</tr>
<tr>
<td>Sex</td>
<td>Frequently female</td>
<td>More often male</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>Preserved or normal, approximately 40% or higher</td>
<td>Depressed, approximately 40% or lower</td>
</tr>
<tr>
<td>Left ventricular cavity size</td>
<td>Usually normal, often with concentric left ventricular hypertrophy</td>
<td>Usually dilated</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on electrocardiography</td>
<td>Usually present</td>
<td>Sometimes present</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Congestion with or without cardiomegaly</td>
<td>Congestion and cardiomegaly</td>
</tr>
<tr>
<td>Gallop rhythm present</td>
<td>Fourth heart sound</td>
<td>Third heart sound</td>
</tr>
</tbody>
</table>

\textsuperscript{4} A single plus sign denotes "occasionally associated with," two plus signs "often associated with," three plus signs "usually associated with," and a zero "not associated with."
adaptive and maladaptive biochemical and functional cardiac abnormalities.\textsuperscript{42} ACE-inhibitor treatment of asymptomatic high-risk patients with diabetes or vascular disease and no history of heart failure has yielded significant reductions in the rates of death, myocardial infarction, and stroke.\textsuperscript{43-45} The use of the angiotensin-receptor blocker losartan has been shown to delay the first hospitalization for heart failure in patients with diabetes mellitus and nephropathy.\textsuperscript{46} In short, the goal of treatment in stage A is to prevent remodeling.

TREATMENT OF STAGE B, C, OR D HEART FAILURE WITH OR WITHOUT SYMPTOMS

The goals of therapy for patients with heart failure and a low ejection fraction are to improve survival, slow the progression of disease, alleviate symptoms, and minimize risk factors. Modifications of lifestyle can be helpful in controlling the symptoms of heart failure. For example, basic habits of moderate sodium restriction, weight monitoring, and adherence to medication schedules may aid in avoiding fluid retention or alerting the patient to its presence. Moderation of alcohol intake is advised; avoidance of nonsteroidal antiinflammatory drugs (NSAIDs) is also important.\textsuperscript{47} NSAIDs have been associated with an increase in the incidence of new heart failure, decompensated chronic heart failure, and hospitalizations for heart failure. For selected patients, a regularly scheduled exercise program may have beneficial effects on symptoms.\textsuperscript{48,49} ACE inhibitors decrease the conversion of angiotensin I to angiotensin II, thereby minimizing the multiple pathophysiological effects of angiotensin II, and decrease the degradation of bradykinin. Bradykinin promotes vasodilatation in the vascular endothelium and...
causes natriuresis in the kidney. The beneficial effects of ACE inhibitors in heart failure and after a myocardial infarction include improvements in survival, the rate of hospitalization, symptoms, cardiac performance, neurohormonal levels, and reverse remodeling. 50–52

ACE inhibitors have not been unequivocally shown to reduce the incidence of sudden death. They are recommended for many patients with stage A heart failure and all patients with stage B, stage C, or stage D heart failure. But unresolved issues persist. First, underuse of ACE inhibitors by physicians for fear of potential side effects has been a concern. Yet side effects are fairly predictable and reversible and can usually be successfully managed. Second, the optimal dose of an ACE inhibitor is uncertain. Most randomized trials have shown no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors. 53–56 Finally, it is uncertain whether there are any meaningful differences among the many ACE inhibitors available today. Table 3 details some common clinical problems with recommended approaches.

Beta-blockers have long been used for the treatment of hypertension, angina, and arrhythmias and for prophylaxis in patients who have had a myocardial infarction. This class of medication has had a

<table>
<thead>
<tr>
<th>Clinical Problem</th>
<th>Recommended Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient has classic symptoms of heart failure with a normal left ventricular ejection fraction.</td>
<td>Consider diastolic heart failure, valvular heart disease, hypertensive heart disease, and ischemia.</td>
</tr>
<tr>
<td>The patient has hypotension: when is the systolic blood pressure too low?</td>
<td>Asymptomatic patients with dilated cardiomyopathy often tolerate a systolic blood pressure of 90 mm Hg. If the patient has no lightheadedness or undue fatigue, peripheral perfusion is adequate, and blood urea nitrogen and creatinine are unchanged, continue the same doses of medications.</td>
</tr>
<tr>
<td></td>
<td>In symptomatic patients, decrease the dose of diuretic. If symptoms persist, adjustment of the timing of concomitant medications may be helpful. Decreasing the dose of the ACE inhibitor, beta-blocker, ARB, or vasodilator is indicated.</td>
</tr>
<tr>
<td>The patient has hyperkalemia.</td>
<td>Ensure that the patient is taking no exogenous potassium supplement or potassium-containing salt substitute. Avoid hypokalemia. Consider decreasing the dose of a potassium-sparing diuretic. Concomitant use of an ACE inhibitor or ARB and spironolactone may increase the risk of hyperkalemia. Avoid high doses of ACE inhibitors and ARBs in patients receiving spironolactone. Avoid use of spironolactone in patients with renal failure, and use low doses of ACE inhibitors and ARBs.</td>
</tr>
<tr>
<td>The patient has increasing azotemia while taking ACE inhibitors.</td>
<td>Decrease the dose of diuretic. Consider renal-artery stenosis if azotemia persists.</td>
</tr>
<tr>
<td>The patient has a cough while taking ACE inhibitors.</td>
<td>Rule out worsening congestive heart failure. Change to ARB if severe cough persists.</td>
</tr>
<tr>
<td>Should the dose of the ACE inhibitor be increased or should beta-blocker therapy be initiated in a symptomatic patient?</td>
<td>Start beta-blocker therapy if there are no contraindications.</td>
</tr>
<tr>
<td>Should an ARB be added to ACE-inhibitor therapy or should a beta-blocker be added in a symptomatic patient?</td>
<td>Start beta-blocker therapy if there are no contraindications.</td>
</tr>
<tr>
<td>The patient has worsening symptoms of congestive heart failure after starting beta-blocker therapy.</td>
<td>Increase the dose of diuretic and slow the titration of the beta-blocker.</td>
</tr>
<tr>
<td>The patient has worsening bronchospasm after starting beta-blocker therapy.</td>
<td>Decrease the dose of the beta-blocker. Consider a beta-selective agent. Discontinue treatment with the drug if the problem persists.</td>
</tr>
<tr>
<td>Persistent paroxysmal nocturnal dyspnea or obstructive sleep apnea or daytime fatigue despite absence of fluid retention on physical examination.</td>
<td>Evaluate the patient for central or obstructive sleep apnea.</td>
</tr>
<tr>
<td>The patient requires repeated hospitalizations.</td>
<td>A multidisciplinary approach should be initiated, with a visiting nurse in the home. Referral for heart failure is indicated.</td>
</tr>
</tbody>
</table>

* ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.
remarkable effect on chronic heart failure. The primary action of beta-blockers is to counteract the harmful effects of the sympathetic nervous system that are activated during heart failure. The beneficial effects of these drugs have been demonstrated in trials involving patients with heart failure from various causes and of all stages. These effects include improvements in survival, morbidity, ejection fraction, remodeling, quality of life, the rate of hospitalization, and the incidence of sudden death.\textsuperscript{3,57} Beta-blockers should be used in all patients in stable condition without substantial fluid retention and without recent exacerbations of heart failure requiring inotropic therapy. There are a few populations of patients in whom beta-blockers should not be used or should be used only with extreme caution. Such patients include those with reactive airway disease, those with diabetes in association with frequent episodes of hypoglycemia, and those with bradycardia or heart block who do not have a pacemaker.

Although the short-term effects of beta-blockers may result in a temporary exacerbation of symptoms, their long-term effects are uniformly beneficial. Placebo-controlled trials involving long-term treatment have shown improved systolic function after three months of treatment and reverse remodeling after four months.\textsuperscript{18,58,59} In the United States, two beta-blockers are specifically approved for the treatment of heart failure: carvedilol and long-acting metoprolol. Currently, neither drug has proved to be consistently superior; both have shown significant clinical efficacy. Carvedilol is a nonselective \(\beta\)-adrenergic antagonist with alpha-blocking effects; metoprolol is a selective \(\beta\)-adrenergic antagonist with no alpha-blocking effects. A large trial comparing these drugs is nearing completion. However, the most frequently prescribed beta-blocker in the United States is atenolol; there have been no studies to date on the use of atenolol in patients with heart failure. Drugs that antagonize the sympathetic nervous system through alternative pathways, such as clonidine or mexitol, have been less clinically useful in patients with heart failure.

Available angiotensin-receptor antagonists block the effects of angiotensin II at the angiotensin II subtype 1 receptor. The recently published guidelines recommend that these drugs should not be used as first-line therapy for heart failure of any stage but should be used only in patients who cannot tolerate ACE inhibitors because of severe cough or angioedema.\textsuperscript{8} Several trials involving patients with heart failure have shown that angiotensin-receptor antagonists have efficacy similar to that of ACE inhibitors but are not superior.\textsuperscript{60-62} On the other hand, in a randomized trial of patients with symptomatic left ventricular systolic dysfunction, the addition of valsartan to ACE-inhibitor treatment reduced the rate of the combined end point of death or cardiovascular events and improved clinical signs and symptoms of heart failure.\textsuperscript{63} However, patients who were receiving beta-blockers, an ACE inhibitor, and the angiotensin-receptor blocker valsartan had more adverse events and increased mortality. More recently, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial was completed in patients with stage B heart failure — specifically, asymptomatic patients with hypertension and left ventricular hypertrophy on electrocardiography. Treatment with the angiotensin-receptor blocker losartan yielded improvements in cardiovascular morbidity and survival, as well as a decrease in the incidence of new-onset diabetes, as compared with treatment with the beta-blocker atenolol.\textsuperscript{64} Thus, accumulating data lend support to the contention that angiotensin-receptor antagonists are a reasonable alternative to ACE inhibitors.

**ADDITIONAL THERAPY FOR SYMPOMATIC PATIENTS WITH STAGE C OR STAGE D HEART FAILURE**

There is evidence to support the use of spironolactone, an aldosterone antagonist, in patients with advanced symptoms of heart failure — specifically, NYHA class III or IV symptoms.\textsuperscript{65} In patients with advanced heart failure, circulating levels of aldosterone become elevated in response to stimulation by angiotensin II, and there is a decrease in the hepatic clearance of aldosterone due to hepatic congestion. Aldosterone stimulates the retention of salt, myocardial hypertrophy, and potassium excretion; spironolactone counters these responses.\textsuperscript{66} The beneficial effects of spironolactone in heart failure may also include a decrease in collagen synthesis that promotes organ fibrosis.

Since heart failure is a salt-avid syndrome resulting in intravascular volume overload, diuretics are a mainstay for controlling symptoms of congestion. Thiazide or loop diuretics are often prescribed, and combination therapy may be used to promote effective diuresis in advanced cases.\textsuperscript{67,68} It is only within the past five years that a large, randomized, placebo-controlled study of digoxin for symptomatic patients with a low ejection frac-
tion has been completed. There was no difference in mortality between patients receiving digoxin and patients receiving placebo, but there were decreases in the digoxin group in the rates of worsening heart failure and hospitalization.69 Recent data suggest that the maintenance of a low serum digoxin concentration (=0.09 ng per milliliter) is as effective in reducing the rate of cardiovascular events as the maintenance of a higher concentration and is associated with a lower rate of toxic effects.70 Elderly patients and those with renal insufficiency are more prone to toxic effects. There is a commonly observed and clinically important interaction between digoxin and amiodarone: digoxin levels can become markedly elevated after the introduction of amiodarone.

There are some patients who cannot tolerate either ACE inhibitors or angiotensin-receptor blockers, usually because of hyperkalemia or renal insufficiency. In such patients who remain symptomatic despite diuretic and beta-blocker therapy, treatment with the vasodilator combination of hydralazine and isosorbide dinitrate may be an option.71

NONPHARMACOLOGIC THERAPY
Cardiac resynchronization therapy is an innovative, pacemaker-based approach to the treatment of patients with heart failure who have a wide QRS complex on 12-lead electrocardiography. The purpose of resynchronization is to provide electromechanical coordination and improved ventricular synchrony in symptomatic patients who have severe systolic dysfunction and clinically significant intraventricular conduction defects, particularly left bundle-branch block.

A percutaneous, three-lead, biventricular pacemaker system is used; one lead is placed in the right atrium, one is placed in the right ventricle, and a third is passed through the right atrium, through the coronary sinus, and into a cardiac vein on the lateral wall of the left ventricle. This left ventricular lead constitutes the key difference between resynchronization therapy and standard dual-chamber pacing. Beneficial effects include reverse remodeling, resulting in decreased heart size and ventricular volumes, improved ejection fraction, and decreased mitral regurgitation. Clinical improvements in exercise tolerance, quality of life, and the rate of hospitalization have been documented.72-78 To date, however, resynchronization therapy has not been shown to enhance survival.

REvascularization and surgical therapy
Patients with heart failure of any stage who are at risk for coronary artery disease should be screened for myocardial ischemia. Revascularization, through either a catheter-based or a surgical approach, often improves ischemic symptoms, improves cardiac performance, and reduces the risk of sudden death.79,80 Patients with stage C or stage D heart failure, who have heretofore been considered unacceptable candidates for surgery, may in fact derive substantial benefit from bypass surgery and additional techniques designed to reduce myocardial wall stress. Procedures to eliminate or exclude areas of infarction, repair mitral regurgitation, or support the failing myocardium are undergoing clinical trials.81-83 Similarly, the role of mechanical devices that serve to support patients who are awaiting heart transplantation or are definitive therapy for end-stage (stage D) heart failure continues to evolve, and such devices offer great hope to many patients who are not eligible for cardiac transplantation.84

The Future
Many common clinical problems encountered in patients with heart failure remain unresolved. The role of anticoagulant therapy in patients with systolic dysfunction and sinus rhythm is unclear; neither the type of therapy needed nor the appropriate duration of treatment is known. There may be an important adverse interaction between aspirin and ACE inhibitors that will be clarified in upcoming trials.85 The optimal care for patients with heart failure and preserved systolic function (diastolic heart failure) awaits further research. The value of revascularization in patients with symptoms of heart failure but without angina will be explored in an important trial that is slated to begin soon.86 How will we identify patients with familial cardiomyopathy at an earlier stage?87-89 How do we identify patients with the greatest risk of sudden death? What is the best way to prevent sudden death in a cost-effective manner? Who will be best served by mechanical cardiac-support devices? Can we afford optimal care for the growing number of patients with heart failure? These questions and many others will undoubtedly be answered in the years to come. Perhaps our most intensive investigations, however, should be reserved for efforts that have been shown to prevent this cardiac plague — the control of hypertension and vascular risk factors.
MEDICAL PROGRESS

Dr. Jessup reports having received consulting fees from Acorn, Medtronic, Guidant, and GlaxoSmithKline, lecture fees from GlaxoSmithKline, AstraZeneca, Scios, Guidant, and Medtronic, and grant support from Guidant. Dr. Benza reports having received grant support from Abbott, Icon, and Medtronic and lecture fees from Merck and GlaxoSmithKline.

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The Role of BNP Testing in Heart Failure

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Brain natriuretic peptide (BNP) levels are simple and objective measures of cardiac function. These measurements can be used to diagnose heart failure, including diastolic dysfunction, and using them has been shown to save money in the emergency department setting. The high negative predictive value of BNP tests is particularly helpful for ruling out heart failure. Treatment with angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, spironolactone, and diuretics reduces BNP levels, suggesting that BNP testing may have a role in monitoring patients with heart failure. However, patients with treated chronic stable heart failure may have levels in the normal range (i.e., BNP less than 100 pg per mL and N-terminal proBNP less than 125 pg per mL in patients younger than 75 years). Increases in BNP levels may be caused by intrinsic cardiac dysfunction or may be secondary to other causes such as pulmonary or renal diseases (e.g., chronic hypoxia). BNP tests are correlated with other measures of cardiac status such as New York Heart Association classification. BNP level is a strong predictor of risk of death and cardiovascular events in patients previously diagnosed with heart failure or cardiac dysfunction. (Am Fam Physician 2006;74:1893-8. Copyright © 2006 American Academy of Family Physicians.)

Until recently, no simple blood test could detect heart failure or monitor its progression or guide its treatment. With the increasing availability of assays for the measurement of brain natriuretic peptide (BNP), a cardiac hormone, this test may have a role in detecting, monitoring, and perhaps preventing chronic heart failure.

Pathophysiology

The heart secretes natriuretic peptides as a homeostatic signal to maintain stable blood pressure and plasma volume and to prevent excess salt and water retention. Atrial natriuretic peptide (ANP) initially was identified in the atrial myocardium of rats. BNP subsequently was isolated in porcine brains. Natriuretic peptides have several actions: (1) down-regulating the sympathetic nervous system and the renin-angiotensin-aldosterone system, (2) facilitating natriuresis and diuresis through the afferent and efferent hemodynamic mechanisms of the kidney and distal tubules, (3) decreasing peripheral vascular resistance, and (4) increasing smooth muscle relaxation. Natriuretic peptides also may inhibit cardiac growth and hypertrophy, countering the mitogenesis that causes ventricular remodeling.

BNP primarily is secreted by the ventricles in the heart as a response to left ventricular stretching or wall tension. It may be a backup hormone that is activated only after a prolonged period of volume overload. Cardiac myocytes secrete a BNP precursor that is synthesized into proBNP, which consists of 108 amino acids. After it is secreted into the ventricles, proBNP is cleaved into the biologically active C-terminal portion and the biologically inactive N-terminal (NT-proBNP) portion.

Influences on BNP Levels

Many medications used to treat heart failure (e.g., diuretics such as spironolactone [Aldactone], angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers) reduce natriuretic peptide concentrations. Therefore, many patients with chronic stable heart failure will have BNP levels in the normal diagnostic range (i.e., BNP level less than 100 pg per mL [100 ng per L]). However, digoxin and some beta blockers appear to increase natriuretic peptide concentrations. Exercise causes a short-term increase in BNP levels, although only small changes (i.e., increase of 0.9 percent in patients without heart failure, 3.8 percent in patients with New York Heart Association [NYHA] class I or II heart failure, and...
SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP testing is recommended to detect or rule out heart failure, including</td>
<td>C</td>
<td>24</td>
</tr>
<tr>
<td>diastolic heart failure. The test has a high negative predictive value—a negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>result rules out disease more effectively than a positive result rules in disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP testing is a useful tool in predicting prognosis in patients with heart failure</td>
<td>C</td>
<td>33</td>
</tr>
<tr>
<td>and appears to be a stronger predictor than some traditional indicators (e.g., left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ventricular ejection fraction, ischemic etiology, serum levels, New York Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association classification).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP is a predictor of death and cardiovascular events in persons without a previous</td>
<td>C</td>
<td>33</td>
</tr>
<tr>
<td>cardiac dysfunction diagnosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is premature to use BNP for treatment monitoring in patients with heart failure</td>
<td>C</td>
<td>32</td>
</tr>
<tr>
<td>until further randomized controlled trials are completed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BNP = brain natriuretic peptide.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1821 or http://www.aafp.org/afpsort.xml.

15 percent in patients with NYHA class III to IV heart failure) are detectable one hour after exercise. No circadian variation has been reported when BNP is measured every three hours for 24 hours, and there is less hourly variation with BNP than with ANP.

**BNP to Diagnose Heart Failure**

There is no agreed-upon first-line test for the diagnosis of heart failure and no simple method of measuring the adequacy of cardiac output in relation to normal levels of activity. Heart failure usually is diagnosed in persons with known heart disease who present with nonspecific symptoms (e.g., breathlessness, ankle swelling) and signs (e.g., basal lung crackles). To confirm clinically suspected heart failure, physicians rely on surrogate measures of cardiac function such as left ventricular ejection fraction. However, it is clear that a large proportion of patients with heart failure, particularly older patients and women, have preserved systolic function (i.e., diastolic heart failure). The best way to diagnose and treat these patients is unclear. BNP increases when cardiac myocytes are strained; therefore, BNP is an effective method for detecting heart failure with or without systolic dysfunction.

Elevated BNP levels also have been associated with renal failure (because of reduced clearance), pulmonary embolism, pulmonary hypertension, and chronic hypoxia. A systematic review included 20 studies evaluating BNP testing in the diagnosis of heart failure. The eight studies that measured BNP against a reference standard of reduced left ventricular ejection fraction (i.e., 40 percent or lower or the equivalent) had a pooled diagnostic odds ratio of 12 (95% confidence interval [CI], 8 to 16). This result is consistent with a moderately accurate diagnostic test. The seven studies that measured BNP against clinical criteria (i.e., a consensus view using all other clinical information and often using a panel of two or three cardiologists) had a pooled diagnostic odds ratio of 31 (95% CI, 27 to 35). The two studies that measured BNP against echocardiographic criteria for systolic and diastolic heart failure had a pooled diagnostic odds ratio of 38 (95% CI, 6 to 237). Therefore, the review showed a greater agreement with a heart failure measure that included diastolic heart failure than one that included systolic heart failure alone (assuming there were no other differences between the studies).

Results from significant studies of the diagnostic accuracy of BNP and NT-proBNP measurements are shown in Table 1. The largest of these studies enrolled 1,586 patients presenting with dyspnea to seven emergency departments. Using a cutoff BNP level of 50 pg per mL (50 ng per L), the positive likelihood ratio was 2.6 (95% CI, 2.3 to 2.8), and the negative likelihood ratio was 0.05 (95% CI, 0.03 to 0.07). This indicates that a low BNP value is highly effective at ruling out...
heart failure, whereas a value more than 50 pg per mL is only a fair indicator of disease.

The number of studies conducted in the primary care setting is approximately equal to the number set in hospitals, and little difference in diagnostic odds ratio has been shown between the two settings. Although the sensitivity and specificity of BNP testing in primary care and hospital settings are similar, interpretation of the test varies between asymptomatic and symptomatic patients and between primary and acute care settings (Table 2).25,27,28

The optimal cutoff value for a heart failure diagnosis and whether reference levels should vary with age and sex remain unclear. There is a trade-off, because lowering the cutoff decreases the false-negative rate (i.e., increased sensitivity and fewer missed diagnoses) but increases the false-positive rate (i.e., decreased specificity and more incorrect diagnoses). In addition, the average levels of BNP and NT-proBNP are greater in women than in men and increase with age.19,30 However, these higher levels in women may reflect an increasing prevalence of undetected and possibly asymptomatic cardiac dysfunction in this group.

A trial that included patients presenting with dyspnea to a Swiss emergency department assessed health outcomes and cost of treatment associated with BNP-assisted diagnoses.31 The trial showed that, compared with no BNP test, the test reduced the median length of hospitalization (eight versus 11 days) and the mean total cost of

<table>
<thead>
<tr>
<th>Study setting</th>
<th>Number of patients</th>
<th>Cutoff value</th>
<th>Reference test</th>
<th>Overall probability of heart failure (%)</th>
<th>LR+ (95% CI)*</th>
<th>LR− (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BNP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with suspected heart failure in general practice (United Kingdom)27</td>
<td>106</td>
<td>77 pg per mL (77 ng per L)</td>
<td>Consensus of three cardiologists using ESC criteria</td>
<td>27</td>
<td>6.2 (3.8 to 10.6)</td>
<td>0.04 (0.01 to 0.20)</td>
</tr>
<tr>
<td>Patients presenting with dyspnea to emergency departments (United States, France, Norway)25</td>
<td>1,586</td>
<td>50 pg per mL (50 ng per L)</td>
<td>Consensus of two cardiologists</td>
<td>47</td>
<td>2.6 (2.34 to 2.79)</td>
<td>0.05 (0.03 to 0.07)</td>
</tr>
<tr>
<td>Patients without a previous heart failure diagnosis randomly selected from 21 general practices (United Kingdom)26</td>
<td>1,331</td>
<td>66 pg per mL (66 ng per L)</td>
<td>LVEF of 40 percent or lower</td>
<td>1</td>
<td>1.8 (1.8 to 1.9)</td>
<td>0.0 (0.0 to 0.4)</td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients selected from general practices (Denmark)28</td>
<td>672</td>
<td>366 pg per mL (366 ng per L)</td>
<td>LVEF of 40 percent or lower</td>
<td>6</td>
<td>2.3 (1.8 to 2.8)</td>
<td>0.35 (0.19 to 0.59)</td>
</tr>
<tr>
<td>General population older than 45 years (United Kingdom)29</td>
<td>307</td>
<td>304 pg per mL (304 ng per L)</td>
<td>Consensus of three cardiologists using ESC criteria</td>
<td>2</td>
<td>3.3 (3.2 to 4.0)</td>
<td>0.0 (0.0 to 0.5)</td>
</tr>
</tbody>
</table>

BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; LR+ = positive likelihood ratio; CI = confidence interval; LR− = negative likelihood ratio; LVEF = left ventricular ejection fraction; ESC = European Society of Cardiologists.

*—Values from 2 to 5 weakly to moderately increase the likelihood of heart failure.
†—Values of 0.1 or less greatly decrease the likelihood of heart failure.

Information from references 25 through 29.
treatment ($5,410 versus $7,264). These results are attributable to the test’s ability to rule out heart failure, allowing the physician to initiate treatment for an alternative diagnosis such as chronic obstructive pulmonary disease or pneumonia. According to an updated guideline from the American College of Cardiology (ACC) and the American Heart Association (AHA), BNP measurements can be useful in patients presenting in the urgent care setting when the clinical diagnosis of heart failure is uncertain.

Determining Prognoses

Nineteen studies showed that elevated BNP levels in patients with heart failure are associated with an increased risk of death or cardiovascular events. Pooled results from five studies showed that a BNP increase of 100 pg per mL caused a 35 percent increase in risk of death. BNP was the only statistically significant independent predictor of mortality in nine studies, indicating that BNP tests potentially are more useful than traditional predictors of mortality (e.g., age, ischemic etiology, left ventricular ejection fraction, NYHA classification, serum creatinine levels).

Screening and Prevention

Because BNP tests can predict death and cardiovascular events in patients without a previous heart disease diagnosis, they are being studied as a possible tool for heart failure screening. Although BNP tests may help detect patients at high risk of overt heart failure and may prevent its progression, randomized controlled trials are needed to determine who should be tested and whether or not treating asymptomatic patients is beneficial.

Several studies (some of which excluded persons previously diagnosed with heart failure) have measured the prognostic value of BNP in asymptomatic populations. In the two largest studies, the relative risk of death during the four to five years of follow-up approximately doubled in patients with a BNP value higher than relatively low cutoff levels (17.9 to 23.3 pg per mL [17.9 to 23.3 pg per mL]).

Monitoring Patients with Heart Failure

BNP measurement is a potential tool for monitoring treatment response in patients with heart failure because of the test’s ability to diagnose heart failure, predict prognosis, and correlate with more invasive clinical

| TABLE 2 |
| Interpreting BNP Measurements for Heart Failure in Different Clinical Settings |

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Pretest probability of heart failure (%)</th>
<th>Posttest probability of heart failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients presenting in the primary care setting (screening)</strong></td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Patients presenting in the primary care setting who have at least one risk factor for heart failure (e.g., history of myocardial infarction, angina, hypertension, or diabetes)</strong></td>
<td>7</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Patients with suspected heart failure in the primary care setting</strong></td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td><strong>Patients presenting with dyspnea to the emergency department</strong></td>
<td>50</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>BNP 50 pg per mL (50 ng per L)</strong></th>
<th><strong>BNP 50 to 150 pg per mL (150 ng per L)</strong></th>
<th><strong>BNP &gt; 150 pg per mL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>17</td>
<td>36</td>
<td>83</td>
</tr>
</tbody>
</table>

**BNP** = brain natriuretic peptide; **LR+** = positive likelihood ratio; **LR-** = negative likelihood ratio.

**—Based on an assumed LR+ of 5.0 for > 150 pg per mL, LR+ of 0.57 for 50 to 150 pg per mL, and LR- of 0.08 for < 50 pg per mL.**

**Information from references 25, 27, and 29.**

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measures (e.g., pulmonary capillary wedge pressure). Prognostic studies have shown that BNP levels measured after treatment took effect were more predictive of the risk of death or further cardiovascular events than those initiated at first presentation.

Ideally, randomized trials would offer definitive evidence; however, only two small trials (including 69 and 21 patients) have evaluated BNP-guided treatment. The first trial showed a nearly twofold decrease in cardiovascular events, and the second trial showed a decrease in BNP levels with BNP-guided treatment. However, according to the ACC/AHA guideline on the management of heart failure, the value of serial BNP measurements in guiding therapy for patients with heart failure is not well established. Larger randomized controlled trials are needed before routine BNP monitoring of heart failure can be recommended.

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Practice Guidelines

ACC and AHA Update on Chronic Heart Failure Guidelines

LIZ HORSLEY


Guideline source: American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines

Literature search described? Yes

Evidence rating system used? Yes

Published source: Circulation, April 14, 2009

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In 2009, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a focused update of the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult. The guidelines writing committee reviewed recent trial data and other clinical information in the revision process for the 2009 update.

The 2005 guidelines described four stages (i.e., stages A, B, C, and D) in the development of heart failure (Figure 1). Patients in stages A and B do not have heart failure, but have risk factors that predispose them toward the development of heart failure. Patients in stage C comprise the majority of patients with heart failure—those who have current or past symptoms of heart failure associated with underlying structural heart disease. Patients in stage D have refractory heart failure and may be eligible for specialized, advanced treatments (e.g., mechanical circulatory support, fluid removal procedures, continuous inotropic infusions, cardiac transplantation) or end-of-life care, such as hospice.

Management of Patients Who Have or Are at Risk of Heart Failure
Figure 1.
Algorithm of the stages in the development of heart failure, with recommended therapy for patients by stage. (ACE = angiotensin-converting enzyme; ARB = angiotensin-II receptor blocker.)


Updated Recommendations

Updates to the 2005 guidelines are included in sections about the evaluation of patients presenting with heart failure; patients with reduced left ventricular ejection fraction (LVEF); patients with refractory end-stage heart failure; and the treatment of special population groups (e.g., blacks). The updated guidelines also contain a new section with recommendations about heart failure in the hospitalized patient.
EVALUATION OF HEART FAILURE

Updates to the section on the evaluation of patients presenting with heart failure were made to clarify the role of functional assessment beyond the New York Heart Association (NYHA) classification, and to expand on the use of brain natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) testing for patient evaluation. According to the update, patients with left ventricular dysfunction or heart failure generally present in one of three ways: with a syndrome of decreased exercise tolerance; with a syndrome of fluid retention; or with no symptoms, or symptoms of another cardiac or noncardiac disorder.

2009 updated recommendation: Measurement of natriuretic peptides (i.e., BNP and NT-proBNP) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of heart failure is uncertain. Measurement of natriuretic peptides can be useful in risk stratification. (Level of Evidence: A) The 2005 guidelines also recommended measurement of BNP for evaluating patients who present in the urgent care setting with possible heart failure; the 2009 update expanded this recommendation to include the measurement of NT-proBNP. The level of evidence remained the same for this recommendation. The 2009 update warns that, although elevated natriuretic peptide levels may help confirm a suspected diagnosis of heart failure, the results of this testing alone should not be used to confirm or exclude a heart failure diagnosis.

REDUCED LVEF

The section of the guidelines on patients with reduced LVEF included minor updates on recommendations about the use of angiotensin-II receptor blockers (ARBs) and exercise testing.

2009 updated recommendation: Use of ARBs is recommended in patients with current or previous symptoms of heart failure and reduced LVEF who have an intolerance to angiotensin-converting enzyme (ACE) inhibitors. (Level of Evidence: A) For this recommendation, the 2009 update modified the text in the 2005 guidelines by eliminating mention of specific agents tested.

2009 updated recommendation: Maximal exercise testing with or without measurement of respiratory gas exchange is reasonable to facilitate prescription of an appropriate exercise program for patients presenting with heart failure. (Level of Evidence: C) The 2009 update changed the class of recommendation from class I (i.e., treatment should be performed) to class IIa (i.e., treatment is reasonable to perform).

The section on patients with reduced LVEF also included several changes to recommendations concerning implantable cardioverter-defibrillator therapy and cardiac resynchronization therapy.

2009 updated recommendation: Implantable cardioverter-defibrillator therapy is recommended for the primary prevention of sudden cardiac death to reduce total mortality in patients with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days after myocardial infarction (MI); an LVEF of 35 percent or less; and NYHA functional class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for longer than one year. (Level of Evidence: A) This recommendation was modified in the 2009 update to be consistent with the 2008 Device-Based Therapy guidelines from the ACC, AHA, and Heart Rhythm Society (HRS). It replaces recommendations from the 2005 guidelines on implantable cardioverter-defibrillator therapy for patients with ischemic heart disease at least 40 days after MI (2005 Level of Evidence: A) or nonischemic cardiomyopathy (2005 Level of Evidence: B) with an LVEF of 30 percent or less, and for patients with an LVEF of 30 to 35 percent of any origin (2005 Level of Evidence: B).

In two of the major trials reviewed by the guidelines committee, no survival benefit was observed from implantable cardioverter-defibrillator therapy until after the first year of recovery from an acute coronary event. Patients with heart failure and low ejection fraction are typically older than 70 years, although this patient population was not well represented in the trials. Physicians should consider common comorbidities in older adults (e.g., previous stroke, chronic pulmonary disease, arthritic conditions) when discussing this type of therapy with patients.
Medication may substantially improve LVEF; therefore, consideration of implantable cardioverter-defibrillator therapy should follow documentation of sustained reduction of LVEF despite a course of beta blockers and ACE inhibitors or ARBs. Implantable cardioverter-defibrillator therapy is not warranted in patients with refractory heart failure (stage D) or in those with concomitant diseases that would shorten their life expectancy independent of heart failure. Before implantation, physicians should inform patients of the effectiveness, safety, and mortality risks of implantable cardioverter-defibrillator therapy; of the morbidity associated with an implantable cardioverter-defibrillator shock; and that the therapy does not improve clinical function or delay progression of heart failure.

2009 updated recommendation: Patients with LVEF of 35 percent or less, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony (i.e., a QRS duration of 0.12 seconds or more) should receive cardiac resynchronization therapy, with or without an implantable cardioverter-defibrillator, unless contraindicated. (Level of Evidence: A) The 2009 recommendation was updated to clarify that cardiac resynchronization therapy may be indicated for patients with or without an implantable cardioverter-defibrillator. Evidence shows that cardiac resynchronization therapy can improve symptoms, exercise capacity, quality of life, LVEF, and survival; it can also decrease hospitalizations in patients with persistently symptomatic heart failure receiving optimal medical therapy who have cardiac dyssynchrony. The use of an implantable cardioverter-defibrillator in addition to cardiac resynchronization therapy should be based on the indications for implantable cardioverter-defibrillator therapy.

END-STAGE HEART FAILURE
The section of the guidelines on patients with refractory end-stage heart failure (stage D) included a modified recommendation on intermittent infusions.

2009 updated recommendation: Routine intermittent infusions of vasoactive and positive inotropic agents are not recommended for patients with refractory end-stage heart failure. (Level of Evidence: A) The 2009 update changed the level of evidence from B to A for this recommendation, based on evidence from an additional multicenter trial. Intermittent outpatient infusions of vasoactive medications (e.g., nesiritide [Natrecor]) or positive inotropic medications have not been shown to improve symptoms or survival in patients with advanced heart failure.

New Recommendations

HYDRAZINE/NITRATES
New recommendation to 2009 update: The combination of hydralazine and nitrates is recommended to improve outcomes for patients with reduced LVEF whose ethnicity is self-described as African American and who have moderate to severe symptoms on optimal therapy with ACE inhibitors, beta blockers, and diuretics. (Level of Evidence: B) Analysis of vasodilator trials showed effectiveness of treatment with isosorbide dinitrate and hydralazine in black participants. Adding these medications to standard therapy with an ACE inhibitor, a beta blocker, or both proved to be beneficial in a subsequent trial. Accordingly, this combination is recommended for black patients who remain symptomatic despite optimal medical therapy. However, patient compliance with this combination may be low because of the large number of tablets required and the high incidence of adverse reactions. The combination treatment should not be prescribed in patients who have not previously used an ACE inhibitor, nor should it be substituted for ACE inhibitors in those who are tolerating them without difficulty. It is unclear if this combination is beneficial in non-black patients.

ATRIAL FIBRILLATION AND SINUS RHYTHM
New recommendation to 2009 update: It is reasonable to treat patients who have atrial fibrillation and heart failure with strategies to maintain sinus rhythm or to control ventricular rate alone. (Level of Evidence: A) Four trials evaluated the effectiveness and safety of restoring and maintaining sinus rhythm in patients with atrial fibrillation. There were equivalent outcomes for restoring and maintaining sinus rhythm by electrical or pharmacologic conversion compared with controlling ventricular rate in patients with atrial fibrillation. Most patients quickly relapse to atrial fibrillation unless they are treated with a class I or III antiarrhythmic medication, but patients with heart failure are not likely to respond favorably to class I medications. Class III antiarrhythmic medications (e.g., sotalol [Betapace], dofetilide [Tikosyn], amiodarone [Cordarone])
can maintain sinus rhythm in some patients, although treatment is associated with an increased risk of organ toxicity (amiodarone) and proarrhythmia (dofetilide).

CARDIAC RESYNCHRONIZATION THERAPY

New recommendations to 2009 update: For patients who have LVEF of 35 percent or less, a QRS duration of 0.12 seconds or more, and atrial fibrillation, cardiac resynchronization therapy, with or without an implantable cardioverter-defibrillator, is reasonable for the treatment of NYHA functional class III or ambulatory class IV heart failure symptoms on optimal recommended medical therapy. (Level of Evidence: B) Cardiac resynchronization therapy is reasonable for patients with LVEF of 35 percent or less with NYHA functional class III or ambulatory class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing. (Level of Evidence: C) Cardiac resynchronization therapy recommendations were added to be consistent with the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities.

New Section: The Hospitalized Patient

The 2009 update includes a new section on the evaluation and treatment of heart failure in patients who are hospitalized. Patients may require hospitalization if they develop acute or progressive symptoms of heart failure. Generally there are three clinical profiles for these patients: those who have volume overload (manifested by pulmonary and/or systemic congestion and often precipitated by an acute increase in chronic hypertension); those with profound depression of cardiac output (manifested by hypotension, renal insufficiency, and/or a shock syndrome); and those with signs and symptoms of fluid overload and shock. Patients with heart failure and preserved LVEF are just as likely to be admitted to the hospital as those with heart failure and low LVEF.

Patients are usually admitted to the hospital following a concomitant cardiovascular or cerebrovascular event, and admission often is related to medical or dietary noncompliance. Other common factors that precipitate hospitalization for heart failure include acute myocardial ischemia; uncorrected high blood pressure; atrial fibrillation and other arrhythmias; recent addition of negative inotropic medications; pulmonary embolus; use of nonsteroidal anti-inflammatory drugs; excessive alcohol or illicit drug use; endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism); and concurrent infections (e.g., pneumonia, viral illnesses).

INPATIENT EVALUATION AND DIAGNOSIS

The diagnosis of heart failure in hospitalized patients should be based primarily on signs and symptoms, including volume status, the adequacy of circulatory support or perfusion, and consideration of precipitating factors or comorbidities. Many of the evaluation steps are identical to those used in the initial evaluation of heart failure. For an uncertain diagnosis of heart failure, plasma BNP or NT-proBNP concentrations should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with heart failure. In patients who have already been diagnosed with heart failure, it is important to understand what has caused the clinical symptoms to worsen.

Acute MI is an important cause of worsening or new-onset heart failure, and criteria for an acute coronary event that might indicate the need for further intervention may be present in up to 20 percent of patients hospitalized for heart failure. However, several other patients may have low levels of detectable troponins that do not meet criteria for an acute ischemic event, but that are typical of chronic heart failure with an acute exacerbation. For patients with newly discovered heart failure, physicians should keep in mind the causative role of coronary artery disease in heart failure and be certain that coronary structure and function are well delineated. Therefore, coronary visualization may be an important step in the evaluation of patients hospitalized with heart failure.

INPATIENT TREATMENT

A careful review of each patient's maintenance medications for heart failure is important, and medication adjustments may be necessary as a result of the hospitalization. The majority of patients should continue taking their medications during hospitalization, and most are able to tolerate the continuation of beta blockers, which results in better outcomes.

Patients with substantial fluid overload on hospital admission should be treated with loop diuretics, initiated upon arrival to the emergency department. After admission, careful and frequent evaluation and monitoring are important and include
assessing volume status and circulatory support; monitoring daily weight and vital signs; managing daily fluid input and output; and assessing daily electrolyte levels and renal function, which should be performed while intravenous diuretics or active heart failure medication titration is being done. Optimal dosing of diuretics should produce a rate of diuresis that will benefit volume status and relieve signs and symptoms of congestion without inducing an excessively rapid reduction in intravascular volume, possibly resulting in hypotension, renal dysfunction, or both. Limiting sodium intake and dosing the diuretic multiple times daily can enhance diuresis effectiveness. Patients who present with congestion and moderate to severe renal dysfunction may have a blunted response to diuretics, requiring higher initial doses. If all diuretic strategies are unsuccessful, ultrafiltration or another renal replacement strategy may be considered, as well as consultation with a kidney subspecialist.

Intravenous vasodilators may be added to the treatment regimen in patients who have adequate blood pressure and ongoing congestion that does not adequately respond to diuretics and standard oral therapy. The goals of vasodilator therapy include a more rapid resolution of congestive symptoms; relief of anginal symptoms while awaiting coronary intervention; control of hypertension; and improvement of hemodynamic abnormalities before beginning oral medications for heart failure.

Patients presenting with predominantly low output syndrome or combined congestion and low output may be considered for intravenous inotropes (e.g., dopamine, dobutamine, milrinone), which may help relieve symptoms caused by poor perfusion and preserve end-organ function in those with severe systolic dysfunction and dilated cardiomyopathy. These medications are most beneficial in patients with relative hypotension and who have intolerance or no response to vasodilators and diuretics. However, the use of inotropes indicates a poor prognosis, and a thorough hemodynamic assessment is necessary. There is no evidence of benefit for routine use of these agents in patients with acute heart failure caused by congestion only; therefore, inotropes should be limited to carefully selected patients with low blood pressure and reduced cardiac output, who will require close monitoring of blood pressure and heart rhythm.

Routine invasive hemodynamic monitoring is not indicated for most patients hospitalized with symptoms of worsening heart failure, but should be considered in those whose volume and filling pressures are uncertain or who are refractory to initial therapy, particularly when filling pressures and cardiac output are unclear. Routine invasive hemodynamic monitoring also may be beneficial in patients with clinically significant hypotension (i.e., systolic blood pressure typically less than 90 mm Hg or symptomatic low systolic blood pressure) or worsening renal function during initial therapy. Invasive hemodynamic monitoring should be performed in patients with presumed cardiogenic shock that requires escalating pressor therapy and consideration of mechanical support; those with severe clinical decompensation in whom therapy is limited by uncertainty regarding relative contributions of elevated filling pressures, hypoperfusion, and vascular tone; those with apparent dependence on intravenous inotropic infusions after initial clinical improvement; or those with persistent, severe symptoms despite adjustment of recommended treatments.

As patients stabilize and volume status normalizes, oral therapy for heart failure should be initiated or resumed. Caution should be used when starting beta blockers in patients who were treated with inotropes while hospitalized, or when initiating ACE inhibitors in patients who had marked azotemia. Before discharge, patients should be fully transitioned off all intravenous therapy, and oral therapy should be adjusted and maximized. Patients should be given written discharge instructions or educational materials that address activity level, diet, discharge medications, follow-up appointments, weight monitoring, and what to do if symptoms worsen.

Coverage of guidelines from other organizations does not imply endorsement by AFP or the AAFP.
Review Articles

Systolic and Diastolic Heart Failure: Differences and Similarities

KANU CHATTERJEE, MB, FRCP, FCCP, FACC, FAHA, MACP, AND BARRY MASSIE, MD, FACC

San Francisco, California

ABSTRACT

Background: Diastolic heart failure (DHF) and systolic heart failure (SHF) are 2 clinical subsets of the syndrome of chronic heart failure that are most commonly encountered in clinical practice.

Methods and Results: The clinically overt DHF and SHF appear to be 2 separate syndromes with distinctive morphologic and functional changes although signs, symptoms, and prognosis are very similar. In DHF, the left ventricle is not dilated and the ejection fraction is preserved. In contrast in SHF, it is dilated and the ejection fraction is reduced. The neurohormonal abnormalities in DHF and SHF appear to be similar. The stimuli and the signals that ultimately produce these 2 different phenotypes of chronic heart failure remain, presently, largely unknown.

Conclusions: Although there has been considerable progress in the management of SHF, the management of DHF remains mostly empirical because of lack of knowledge of the molecular and biochemical mechanisms which produce myocardial structural and functional changes in this syndrome. Further research and investigations are urgently required. (J Cardiac Fail 2007;13:569–576)

Key Words: Systolic heart failure, diastolic heart failure, remodeling, function.

Diastolic heart failure (DHF) and systolic heart failure (SHF) are 2 clinical subsets of the syndrome of heart failure that are most frequently encountered in clinical practice. That these 2 forms of heart failure exist was recognized by Dr. Fishberg almost 70 years ago, as reported by Katz and Zile in a recent editorial. Dr. Fishberg wrote “those forms of cardiac insufficiency which are due to inadequate diastolic filling of the heart (hypodiastolic failure) [and] the far more common ones in which the heart fills adequately but does not empty to the normal extent (hypovasculitis heart failure).” However, confusions and controversies regarding the definitions, pathophysiology, prognosis and management of DHF and SHF continue.

Definitions and Diagnosis

In the Webster Dictionary diastole is defined as “the dilatation of the heart with blood: opposed to systole, or contraction.” Conventionally, the closure of the aortic valve is regarded to indicate the onset of diastole as it indicates the onset of ventricular relaxation phase. Because left ventricular ejection influences relaxation and the rapid filling, it has been suggested that these phases should be considered phases of systole. The most commonly accepted view, however, is that the rapid filling phase is part of diastole.

Several definitions of DHF have been proposed. One definition is “a condition resulting from an increased resistance to filling of one or both ventricles leading to symptoms of congestion due to an inappropriate upward shift of the diastolic pressure-volume relation (that is, during the terminal phase of the cardiac cycle).” Another proposed definition is that diastolic heart failure is a condition in which the “ventricular chamber is unable to accept an adequate volume of blood during diastole at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume.” These definitions describe the functional abnormalities, but cannot be applied in clinical practice. Many clinical definitions of diastolic heart failure have been suggested. Zile and Brutsaert proposed a definition, which is “a clinical syndrome characterized
by the symptoms and signs of heart failure, a preserved ejection fraction (EF), and abnormal diastolic function. Other definitions such as "heart failure with preserved systolic function" or "heart failure with normal or near normal ejection fraction" have also been used.

Several definitions of systolic heart failure also exist. In 1933, Sir Thomas Lewis defined heart failure as "a condition in which the heart fails to discharge its contents adequately." In 1980, Dr. Braunwald described heart failure as "a pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues." Although these definitions describe the pathologic mechanisms, it is difficult to employ in clinical practice. Thus it is preferable to use the terms "diastolic" and "systolic" heart failure as these definitions describe the principal mechanisms.

Systolic and Diastolic Dysfunction and Clinical Heart Failure

Systolic dysfunction from impaired contractile or pump function and diastolic dysfunction from impaired ventricular relaxation, compliance or filling are not always associated with clinical heart failure characterized by signs and symptoms of low cardiac output or of congestion. Furthermore, in SHF, diastolic dysfunction as assessed by changes in the ventricular filling features is common, particularly in advanced heart failure. In diastolic heart failure, left ventricular systolic performance, function and contractility in general, remain normal. In some studies, long-axis systolic dysfunction has been observed.

Diagnosis

Based on the proposed definitions, it appears that for establishing the diagnosis of DHF or SHF, it is only necessary to measure left ventricular ejection fraction after confirming the presence of heart failure. If ejection fraction is preserved it is DHF, and if reduced it is SHF. It is highly desirable to establish the normal range of ejection fraction for any technique employed, preferably under similar loading conditions. It should be appreciated that signs and symptoms, radiologic and electrocardiographic findings and neurohormonal profile cannot distinguish between DHF and SHF.

Is Cardiac Catheterization Necessary?

Coronary angiography is occasionally indicated when myocardial ischemia is strongly suspected, irrespective of type of heart failure. Similarly, endomyocardial biopsy is rarely necessary to establish the etiology of heart failure. Cardiac catheterization is not necessary to assess ejection fraction, contractile function, or diastolic functions.

Incidence, Prevalence, and Prognosis

The incidence and prevalence of both SHF and DHF is considerable and increasing. The recent epidemic increase in heart failure in older population appears to be related both to increase in the incidence and improved survival. The incidence of systolic and diastolic heart failure has been reported to be 61% to 68% and 16% to 39%, respectively. The cross-sectional population echocardiographic studies have reported that of patients diagnosed with heart failure, 40% to 71% have DHF.

Natural History of Asymptomatic Systolic and Diastolic Dysfunction

Asymptomatic left ventricular systolic dysfunction constitutes Stage B systolic heart failure. The prevalence of Stage B systolic heart failure in the community is between 3% and 6%. The risk of development of symptomatic heart failure is reported to be between 5.1% and 10.5%.

The echo-Doppler studies have reported that patients with asymptomatic left ventricular diastolic dysfunction have a higher incidence of all-case mortality adjusted for age, sex, and ejection fraction. Mild diastolic dysfunction was associated with 8.3-fold, and moderate-to-severe dysfunction with 10.2-fold increased risk of mortality.

Natural History in Symptomatic Patients

The overall mortality of symptomatic patients with DHF or SHF is very similar and is related to the functional class. In patients with New York Heart Association Class II and III DHF, an annual mortality rate of 3.8% was observed. In patients who required hospital admissions for treatment, 1-year all cause death was 27% in DHF and 36% in SHF (Fig. 1).

Mode of Death

In systolic heart failure approximately 50% of deaths are sudden and the rate of sudden death in systolic heart failure is 6 to 9 times higher compared with that in the general population. Interestingly, with the increased severity of systolic heart failure (New York Heart Association IV), incidence of sudden cardiac death decreases. The absolute rates of pump failure death and sudden cardiac death increases with decreasing left ventricular ejection fraction. However, it has been reported that the risk of sudden cardiac death is better correlated to left ventricular mass than to the ejection fraction. The left ventricular mass is increased considerably in both DHF and SHF; thus, the risk assessment for sudden cardiac death based on ejection fraction alone may not be appropriate. In a recent report, the risk of sudden cardiac death was found to be only 7% among 2314 patients, compared with death from other causes, which was 93%.
Risk Factors

Older age, hypertension, diabetes, obesity, and coronary artery disease are risk factors for both DHF and SHF. Although DHF is more common in elderly females, diastolic dysfunction is more common in elderly males. In DHF, hypertension is a more common risk factor. However, a substantial proportion of patients with SHF have a history of hypertension. In SHF, ischemic heart disease is the most common etiology, but many patients with DHF have coronary artery disease. In decompensated heart failure, 63% of patients with systolic and 54% of patients with diastolic heart failure have coronary artery disease. Thus, for prevention, modification of the same risk factors should be employed in both DHF and SHF.

Remodeling

The distinctive features of remodeling in DHF and SHF are summarized in Table 1 and illustrated in Fig. 2. In SHF, the left ventricular cavity size is increased with an increase in both end-diastolic and end-systolic volumes, decreased or unchanged wall thickness, increased wall stress, and reduced ejection fraction. The mass is increased, but the mass/cavity ratio remains unchanged or is decreased. In SHF, there is an alteration in ventricular shape and geometry with a greater increase in transverse than in long axis, and mechanical dyssynchrony with or without electrical dyssynchrony occur in a substantial number of patients. In DHF, the cavity size remains unchanged or may even decrease, and the end-diastolic and end-systolic volumes remain normal or decrease. In DHF, there is usually an increase in wall thickness and mass; however, mass/cavity ratio is substantially increased. In DHF, end-diastolic wall stress is increased and systolic wall stress remains normal and ejection fraction remains normal or may even be higher than normal. In DHF, significant alteration in ventricular shape and geometry is uncommon; however, mechanical dyssynchrony may occur even without electrical dyssynchrony. The left ventricular morphologic and functional changes in DHF and SHF compared to controls as evaluated by echocardiographic studies are summarized in Table 2.

The differences in the structural changes in systolic and diastolic heart failure are summarized in Table 3 and illustrated in Fig. 3. In SHF there is myocyte lengthening and an increase in myocyte length/width ratio. The sarcomeres are replicated in parallel. In DHF there is an increase in the myocyte cross-sectional area with little or no change in its length/width ratio. The sarcomeres are replicated in parallel. The abnormality in calcium regulation occurs in both types of heart failure. Increased collagen volume and fibrosis occur in both but the character and degree of fibrosis appear to be different. In animal models, in SHF, there is degradation and disruption of fibrillar collagen; in contrast, in the pressure-overloaded hypertrophy which is associated with diastolic failure, there is an increase in collagen with increased width and continuity of the fibrillar collagen. The collagen cross links are decreased in SHF and increased in DHF. In general the matrix metalloproteinases
are increased in SHF and decreased in DHF. In contrast, their endogenous tissue inhibitors tend to decrease in SHF and increase in DHF.37,38 Other biochemical evidences for abnormal collagen metabolism such as increased circulating levels of amino-terminal propeptide of Type III pro-collagen have been reported in systolic heart failure.39 The titin isoforms N2BA/N2B ratio is decreased in systolic failure and it is increased in diastolic failure.40 Left ventricular endomyocardial biopsy studies have reported an increase in myocyte diameter and less decrease in myocyte volume in DHF compared with SHF, whereas collagen volume fractions increased in both types.40

The initiating stimuli for remodeling in SHF and DHF have not been clearly delineated. In SHF, after acute myocardial infarction, the extent of myocardial injury and the magnitude of left ventricular systolic dysfunction appear to be the major determinants. A small infarct and relatively preserved ejection fraction is not usually associated with ventricular remodeling.41,42 Abnormal neurohormonal activation has also been implicated as a major mechanism for progressive remodeling in systolic heart failure.43

In DHF, the stimuli for ventricular remodeling remain unclear. The pressure overload resulting from hypertension

<table>
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<tr>
<th>Table 2. Echocardiographic Left Ventricular Morphologic and Functional Characteristics in Primary Systolic and Diastolic Heart Failure Compared With Controls</th>
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<tr>
<td>Controls</td>
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<tr>
<td>LVEDV (mL)</td>
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<td>LVESV (mL)</td>
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<td>LVEF %</td>
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<tr>
<td>LV mass (g)</td>
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<tr>
<td>LV mass/volume</td>
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<tr>
<td>NÈ g/mL</td>
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<tr>
<td>BNP pg/mL</td>
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</tbody>
</table>

Adapted from Kitzman DW, et al. JAMA 2002;288:2144–50.31
LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LV, left ventricle; NÈ, norepinephrine; BNP, B-type natriuretic peptide.

*Systolic heart failure vs. controls, P < .001.
Diastolic heart failure vs. controls, P < .001.
Diastolic heart failure vs. controls, P < .002.

<table>
<thead>
<tr>
<th>Table 3. Diastolic and Systolic Heart Failure Remodeling: Myocyte and Matrix Changes</th>
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<tr>
<td>Systolic Heart Failure</td>
</tr>
<tr>
<td>Myocyte</td>
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</tbody>
</table>
Hypertrophy | + |
Apoptosis | + |
Necrosis | + |
Myocardial fibrosis | + |
Calcium regulation | - |
MMPs/TIMPs | + |
Collagen cross-links | - |
Titin isoforms N2BA/N2B | - |

+; increased; −, decreased or impaired; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases. 
Fig. 3. Changes in myocytes (left) and in extracellular matrix (right) in systolic heart failure resulting from dilated cardiomyopathy, and diastolic heart failure resulting from pressure over load compared with normals in animal models. In systolic heart failure, the myocyte length is increased without any change in the cross-sectional area; in diastolic heart failure, the cross-sectional area of the myocyte is increased without a significant change in its length. In systolic heart failure, collagen degradation and disruption occur; in diastolic heart failure, there is increased width and continuity of fibrillar collagen. (Reprinted with permission.11)

and obesity associated with concentric hypertrophy is likely to be an important contributing factor. Neurohormonal abnormalities, similar to those observed in systolic heart failure, occur in DHF.11 Thus neurohormonal abnormalities do not explain differences in ventricular remodeling in DHF and SHF. It is possible that neurohormonal abnormalities produce different substrate response in DHF and SHF.

Functional Changes

In SHF, impaired contractile function is the principal functional derangement and is the major mechanism for reduced ejection fraction (Fig. 3).34,44 The other mechanism for reduced ejection fraction in SHF is increased wall stress. Diastolic function, as assessed by echo-Doppler studies, is frequently abnormal in patients with overt SHF. Impaired left ventricular relaxation and increased passive stiffness is the principal functional derangement in DHF.34 The pressure-volume relation during diastole shifts upward and to the left (Fig. 4); as a result there is a disproportionately greater increase in diastolic pressure for any increase in volume.45

The hemodynamic profile may be similar in SHF and DHF. In SHF, reduced ejection fraction results in a decrease in stroke volume and cardiac output. Increased left ventricular end-diastolic volumes and often associated abnormal

Fig. 4. Schematic diagram of pressure-volume relations in normals, systolic and diastolic heart failure. In systolic heart failure, a downward and rightward shift of the end-systolic pressure-volume line indicates decreased contractile function, which is the principal cause of reduced ejection fraction and forward stroke volume. In primary diastolic heart failure, diastolic pressure-volume relation (dashed line) shifts upward and to the left, indicating a disproportionate and a greater increase in diastolic pressure for any increase in diastolic volumes. If there is also a decrease in end-diastolic volume, then a decrease in stroke volume also occurs. (Reprinted with permission.44)
diastolic filling result in increased left ventricular diastolic pressure, a passive increase in left atrial and pulmonary venous pressure, and postcapillary pulmonary arterial hypertension. Right ventricular failure and systemic venous hypertension and its hemodynamic and clinical consequences occur.

In DHF, because of the disproportionate increase in left ventricular diastolic pressure, there is an increase in left atrial and pulmonary venous pressure that is associated with symptoms and signs of pulmonary venous congestion (Fig. 5). Postcapillary pulmonary hypertension resulting from increased pulmonary venous pressure may precipitate right heart failure. Left ventricular stroke volume and cardiac output may also decline because of decreased end-diastolic volume (preload dependent). Chronic elevation of pulmonary venous pressure may be associated with increased pulmonary vascular resistance from secondary pulmonary vasoconstriction, which may occur in both SHF and DHF.

**Does Left Ventricle Dilate in Diastolic Heart Failure?**

Left ventricular dilation always occurs in SHF. In DHF, however, left ventricular dilation does not appear to occur without an additional insult such as myocardial infarction. In some patients with DHF without coronary artery disease, serial assessment of ventricular volumes and pressures and stiffness have been performed; end-diastolic volumes and ejection fraction remain unchanged, but end-diastolic pressure and stiffness index increase, suggesting that in DHF ventricular dilatation does not occur and worsening diastolic function is the mechanism for development and progression of heart failure (Table 4). Thus left ventricle size remains unchanged and it does not dilate without an ischemic insult.

**Differences in Therapeutic Options**

Although there have been considerable advances in the treatment of SHF, very little progress has been made in the management of DHF. The improvement in prognosis in SHF is most likely related to the therapeutic discoveries that have been observed to attenuate adverse remodeling and improve hemodynamic abnormalities. The neurohormonal modulators such as renin-angiotensin-aldosterone and adrenergic antagonists clearly improve symptoms and quality of life and decrease mortality. So far no such therapies have been discovered for improving prognosis in patients with DHF. Angiotensin receptor blocking agents have the potential for decreasing morbidity but not mortality. It has been reported that statin therapy has the potential to decrease mortality of patients with DHF. Statin therapy is also associated with lower mortality in SHF.

Chronic resynchronization therapy with or without implantable cardioverter defibrillator improves prognosis of patients with SHF. However, chronic resynchronization therapy has not been shown to produce beneficial effects in DHF. Cardiac transplantation is likely to benefit selected patients either with SHF or DHF.

**Conclusion**

Established clinical systolic and diastolic heart failure appear to be 2 distinct syndromes of chronic heart failure. The myocardial structural and primary functional derangements are distinctive in these 2 syndromes, although hemodynamic consequences, clinical presentations, signs and symptoms, and prognosis are similar. The neurohormonal abnormalities are also similar in both of these syndromes. Although there have been considerable advances in the
management of systolic heart failure, the management of DHF remains primarily to relieve symptoms. Because of inadequate knowledge of the molecular and biochemical mechanisms of the structural remodelling and principal functional derangement in diastolic heart failure, treatments to improve prognosis have not evolved. Thus further basic science and clinical research is urgently required. However, potential exists for discovery of therapeutic agents to improve fundamental abnormalities of the cytoskeleton and myocardial architecture and thereby decrease myocardial stiffness—the principal functional derangement in diastolic heart failure. Until then the treatment of diastolic heart failure will remain empirical.

Acknowledgment

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Newly Diagnosed Atrial Fibrillation

Richard L. Page, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

A 77-year-old woman with a history of hypertension treated with metoprolol presents for her annual examination. She reports no new symptoms. The examination is remarkable only for the finding of an irregular heart rate. Electrocardiographic testing reveals atrial fibrillation at an average rate of 75 beats per minute. She has no history of arrhythmia, coronary disease, valvular disease, diabetes, alcohol abuse, transient ischemic attack, or stroke. For the past several months, she has exercised on a treadmill without difficulty, although she notes that the machine does not always measure her heart rate. What should her physician advise?

THE CLINICAL PROBLEM

Atrial fibrillation is the most common arrhythmia that requires treatment, with an estimated prevalence in the United States of 2.3 million patients in 2001. The prevalence increases with age — atrial fibrillation occurs in 3.8 percent of people 60 years of age and older and in 9.0 percent of those 80 years of age and older.

RISK OF STROKE AND DEATH

The most devastating consequence of atrial fibrillation is stroke as a result of thromboembolism typically emanating from the left atrial appendage. The rate of stroke varies but may range from 5.0 percent to 9.6 percent per year among patients at high risk who are taking aspirin (but not warfarin). Patients with paroxysmal (i.e., self-terminating) and persistent atrial fibrillation (i.e., that lasts more than seven days or requires cardioversion) appear to have a risk of stroke that is similar to that of patients with permanent atrial fibrillation. In the Stroke Prevention in Atrial Fibrillation studies of patients with atrial fibrillation, the risk of stroke among those with sinus rhythm that had been documented within the 12 months before enrollment (3.2 percent per year) was similar to that among those with permanent atrial fibrillation (3.3 percent per year). The duration of episodes of atrial fibrillation and the overall time spent in atrial fibrillation (i.e., burden) have not been established as determining the risk of stroke. Atrial fibrillation is associated with an increase in the relative risk of death ranging from 1.3 to twice that value, independent of other risk factors. This risk may be greater for women than for men.

ASSOCIATED DISEASES AND PREDISPOISING CONDITIONS

In most cases, atrial fibrillation is associated with cardiovascular disease, in particular hypertension, coronary artery disease, cardiomyopathy, and valvular disease (primarily mitral); it also occurs after cardiac surgery and in the presence of myocarditis or pericarditis. When atrial fibrillation complicates severe mitral regurgitation, valve repair or replacement is indicated. In some cases, atrial fibrillation results from another supraventricular tachycardia. When it is associated with the Wolff–Parkinson–White syn-
drome, rapid conduction down the accessory pathway may result in hemodynamic collapse.9

Other predisposing conditions include excessive alcohol intake, hyperthyroidism, and pulmonary disorders, including pulmonary embolism. Obstructive sleep apnea may also be related, in which case the provision of continuous positive airway pressure reduces the risk of the recurrence of atrial fibrillation.10 Both vagal and sympathetic mechanisms of paroxysmal atrial fibrillation have been described (neurogenic atrial fibrillation),11 as have familial forms of the condition.12 “Lone” atrial fibrillation (i.e., that occurring in the absence of a cardiac or other explanation) is common, particularly in patients with paroxysmal atrial fibrillation — up to 45 percent of such patients have no underlying cardiac disease.13

EVALUATION
The patient’s history and the physical examination should focus on these potential causes of atrial fibrillation. The “minimum evaluation” recommended at diagnosis should include 12-lead electrocardiography, chest radiography, transthoracic echocardiography, and serologic tests of thyroid function.11 Echocardiographic testing is used to assess valve function, chamber size, and the peak right ventricular pressure and to detect hypertrophy and pericardial disease. Additional tests may be warranted, including exercise testing to determine whether the patient has symptoms and to assess the heart rate with exercise, 24-hour ambulatory monitoring to evaluate heart-rate control, transesophageal echocardiography to screen for a left atrial thrombus and to guide cardioversion, and, rarely, an electrophysiological study to detect predisposing arrhythmias.11

SYMPTOMS AND HEMODYNAMIC CONSEQUENCES
Patients with atrial fibrillation may have palpitations, dyspnea, fatigue, light-headedness, and syncope. These symptoms are usually related to the elevated heart rate and, in most patients, can be mitigated with the use of drugs to control the heart rate. Exceptions are due, presumably, to an irregural ventricular response or a reduction of cardiac output.

The hemodynamic consequences of atrial fibrillation are related to the loss of atrial mechanical function, irregularity of ventricular response, and high heart rate. These consequences are magnified in the presence of impaired diastolic ventricular filling, hypertension, mitral stenosis, left ventricular hypertrophy, and restrictive cardiomyopathy.11 Irregularity of the cardiac cycle, especially when accompanied by short coupling intervals, and rapid heart rates in atrial fibrillation lead to a reduction in diastolic filling, stroke volume, and cardiac output. In a study of patients who were evaluated while in atrial fibrillation and again during ventricular pacing at the same overall heart rate, the irregular rhythm was associated with a lower cardiac output (4.4 vs. 5.2 liters per minute) and higher pulmonary-capillary wedge pressure (17 vs. 14 mm Hg).14

A chronically elevated heart rate of 130 beats per minute or more may result in secondary cardiomyopathy,15 a type of left ventricular dysfunction that may largely be reversed when control of the ventricular rate is achieved.15,16 A report in this issue of the Journal17 indicates that, in patients with atrial fibrillation, heart-rate control and rhythm control with the use of radiofrequency catheter ablation improve left ventricular function in both those with and those without congestive heart failure.

ASYMPTOMATIC ATRIAL FIBRILLATION
Asymptomatic, or “silent,” atrial fibrillation occurs frequently.18 Among patients in the Canadian Registry of Atrial Fibrillation, 21 percent in whom the condition was newly diagnosed were asymptomatic.19 The first presentation of asymptomatic atrial fibrillation may be catastrophic; in the Framingham Study, among patients with stroke that was associated with atrial fibrillation, the arrhythmia was newly diagnosed in 24 percent.20 Even among patients with documented symptomatic atrial fibrillation, asymptomatic recurrences are common. In one study of patients with symptomatic paroxysmal atrial fibrillation, asymptomatic episodes were 12 times more common than symptomatic episodes.21 In a recent trial,22 among untreated patients, 17 percent had asymptomatic episodes before they noted symptoms, and the percentage was probably an underestimation, because the monitoring of these patients was intermittent. Some antiarrhythmic agents, by reducing conduction in the atrioventricular node, may increase the likelihood of the occurrence of asymptomatic atrial fibrillation. Both propafenone and propranolol have been associated with frequent asymptomatic atrial fibrillation,23 and the risk may be similar with other agents that block atrioventricular nodal conduction.24 Among patients with a pacemaker and a history of atrial fibrillation, one in six had silent recurrences lasting 48 hours or longer.25
STRATEGIES AND EVIDENCE

ANTICOAGULANT THERAPY

The need for anticoagulation to reduce the risk of stroke among patients with atrial fibrillation due to mitral stenosis is well recognized. Several randomized, prospective trials involving patients with nonvalvular atrial fibrillation have confirmed a significant reduction in the risk of stroke with warfarin. These studies defined the patients at greatest risk as the elderly, variably defined as those older than 60, 65, and 75 years of age, and those with a history of thromboembolism, diabetes mellitus, coronary artery disease, hypertension, heart failure, and thyrotoxicosis. These trials have provided a basis for two important guidelines for the use of warfarin in such patients (Table 1). Recently, an index based on the assignment of points for five risk factors (i.e., congestive heart failure, hypertension, age, diabetes, and transient ischemic attack or stroke) was reported to be accurate in predicting stroke when it was used to evaluate the risk among patients in the Medicare database; it is the basis for the other guideline for antithrombotic therapy in atrial fibrillation (Table 1). In addition, complex aortic plaques detected by transesophageal echocardiography that are associated with an increased risk of stroke in patients with atrial fibrillation also warrant the institution of anticoagulant therapy.

An international normalized ratio (INR) value in the range of 2.0 to 3.0 is recommended. The risk of stroke doubles when the INR falls to 1.7, although values up to 3.5 do not convey an increased risk of bleeding complications. INR values of 2.0 or greater are associated with a reduced severity of stroke and, if stroke occurs, a lower likelihood that it will result in death.

Certain patients are at relatively low risk for a thromboembolic event and do not require intensive anticoagulant therapy (Table 1). Aspirin is often recommended for these patients, although their risk is so low that even aspirin may not be necessary. Alternative antiplatelet agents, such as clopidogrel, have not been tested adequately in this clinical situation.

The duration of atrial fibrillation becomes important when cardioversion (with the use of electric or pharmacologic means) is being considered. It is generally accepted that patients who have had an episode of atrial fibrillation lasting less than 48 hours may safely undergo cardioversion without anticoagulant therapy, although the data supporting this practice are scant. For episodes lasting longer than 48 hours, adequate anticoagulant therapy is warranted, both before cardioversion and for four weeks afterward. A recent report concluded that a strategy of initiating anticoagulant therapy and ruling out left atrial thrombus with the use of transesophageal echocardiography was a possible alternative to the usual strategy of anticoagulant therapy for three weeks before cardioversion.

RATE CONTROL

Current guidelines recommend a ventricular rate during atrial fibrillation of 60 to 80 beats per minute at rest and 90 to 115 beats per minute during exercise. A number of pharmacologic agents are available to control the heart rate and rhythm (Tables 2 and 3). Digoxin has been replaced as first-line therapy for rate control by β-adrenergic blockers and calcium-channel blockers, largely owing to improved rate control during exercise with the use of these alternative agents. In one study, during peak exercise, the mean heart rate was 175 beats per minute in patients receiving digoxin, as compared with 130 in those receiving a β-adrenergic blocker and 151 in those receiving a calcium-channel blocker. Digoxin is useful in combination with other agents or when β-adrenergic–blocking agents and calcium-channel blockers are not tolerated. In some patients, particularly the elderly, the ventricular rate during atrial fibrillation may be intrinsically controlled, so that no atrioventricular nodal–blocking agent is required. Among patients with a pause that causes symptoms after the spontaneous conversion of atrial fibrillation, or those whose symptoms are due to low heart rates in spite of their having high heart rates at other times, a pacemaker may be necessary to permit therapy with atrioventricular nodal–blocking agents (as in the “tachy-brady” or the sick sinus syndrome).

RHYTHM CONTROL

A number of agents may maintain sinus rhythm (Tables 2 and 3). The use of β-adrenergic agents may be effective in adrenergically mediated and paroxysmal atrial fibrillation (although the effects may be related to the conversion of symptomatic atrial fibrillation into asymptomatic atrial fibrillation). With the exception of the β-adrenergic–blocking agents, most antiarrhythmic drugs carry a risk of serious adverse effects. Antiarrhythmic therapy should be chosen on the basis of the patient’s underlying
Table 1. Guidelines for Antithrombotic Therapy in Atrial Fibrillation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Therapy Recommended by the ACC–AHA and ESC</th>
<th>Differences in ACCP Guidelines</th>
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<tr>
<td>Age</td>
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<tr>
<td>&lt;60 yr, no heart disease</td>
<td>Aspirin at a dose of 325 mg per day, or no therapy</td>
<td>Aspirin at a dose of 325 mg for patients &lt;65 yr of age with no risk factor†</td>
</tr>
<tr>
<td>&lt;60 yr, with heart disease but no risk factors*</td>
<td>Aspirin at a dose of 325 mg per day</td>
<td>No divergence</td>
</tr>
<tr>
<td>≥60–75 yr, no risk factors*</td>
<td>Aspirin at a dose of 325 mg per day</td>
<td>Option of aspirin at a dose of 325 mg per day or warfarin (INR, 2.0–3.0) for patients 65–75 yr of age</td>
</tr>
<tr>
<td>≥60 yr, with diabetes mellitus or coronary artery disease</td>
<td>Warfarin (INR, 2.0–3.0), aspirin optional in addition (at a dose of 81–162 mg per day)</td>
<td>Option of aspirin at a dose of 325 mg per day or warfarin (INR, 2.0–3.0) for patients with diabetes alone or coronary artery disease alone who are &lt;65 yr of age</td>
</tr>
<tr>
<td>&gt;75 yr, especially among women</td>
<td>Warfarin (INR, approximately 2.0; target INR, 1.6–2.5)</td>
<td>Warfarin (INR, 2.0–3.0), but no recommendation for INR value &lt;2.0</td>
</tr>
<tr>
<td>Heart failure, left ventricular ejection fraction ≤0.35, thyrotoxicosis, and hypertension</td>
<td>Warfarin (INR, 2.0–3.0)</td>
<td>No divergence</td>
</tr>
<tr>
<td>Rheumatic heart disease (mitral stenosis)</td>
<td>Warfarin (INR, 2.5–3.5 or higher) may be appropriate</td>
<td>Other than for patients with mechanical valves, no INR recommended above target, 2.5 (range, 2.0–3.0)</td>
</tr>
<tr>
<td>Previous thromboembolism</td>
<td>Warfarin (INR, 2.5–3.5 or higher) may be appropriate</td>
<td>Other than for patients with mechanical valves, no INR recommended above target, 2.5 (range, 2.0–3.0)</td>
</tr>
<tr>
<td>Persistent atrial thrombus on transesophageal echocardiography</td>
<td>Warfarin (INR, 2.5–3.5 or higher) may be appropriate</td>
<td>Other than for patients with mechanical valves, no INR recommended above target, 2.5 (range, 2.0–3.0)</td>
</tr>
<tr>
<td>Prosthetic heart valves</td>
<td>Warfarin (INR, 2.5–3.5 or higher) may be appropriate</td>
<td>Depending on the type of prosthetic valve, warfarin (INR, 2.5 [range, 2.0–3.0] or INR, 3.0 [range, 2.5 to 3.5]) with or without additional aspirin, at a dose of 80 to 100 mg††</td>
</tr>
<tr>
<td>Warfarin recommended but contraindicated or refused</td>
<td>Aspirin at a dose of 325 mg per day</td>
<td>No divergence</td>
</tr>
</tbody>
</table>

* According to the guidelines of the American College of Cardiology and American Heart Association (ACC–AHA) Task Force on Practice and the European Society of Cardiology (ESC) Committee for Practice, the risk factors for thromboembolism include heart failure, a left ventricular ejection fraction of less than 35 percent, and a history of hypertension.††† INR denotes international normalized ratio.
† According to the American College of Chest Physicians (ACCP), moderate risk factors include an age of 65 to 75 years, diabetes mellitus, and coronary artery disease with preserved left ventricular function; high risk factors include previous stroke, transient ischemic attack, or systemic embolus; a history of hypertension; poor left ventricular systolic function; an age of 75 years or older; rheumatic mitral-valve disease; and the presence of a prosthetic heart valve.\textsuperscript{33}

Cardiac condition (Table 3).\textsuperscript{12} Antiarrhythmic agents classified according to the Vaughn Williams system as class IC are reserved to treat patients without a structural cardiac abnormality, and as described elsewhere in this issue of the Journal,\textsuperscript{42} may be prescribed for outpatients with acute conversion of paroxysmal atrial fibrillation (i.e., the so-called pill-in-the-pocket approach). Agents in classes IA and III should be avoided by patients with prolongation of the QT interval or left ventricular hypertrophy because of the potential for torsades de pointes. On the one hand, amiodarone, which has a low risk of proarrhythmia (less than 1 percent per year),\textsuperscript{43} causes substantial noncardiac toxic effects and is therefore generally reserved for second-line therapy except in the treatment of patients with severe cardiomyopathy. On the other hand, it is the most effective antiarrhythmic agent; in one trial, 65 percent of patients treated with amiodarone were free from recurrence after 16 months of therapy (as compared with 37
<table>
<thead>
<tr>
<th>Drug (Class)†</th>
<th>Purpose</th>
<th>Usual Maintenance Dose</th>
<th>Adverse Effects</th>
<th>Cautions and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol (II)</td>
<td>Rate control (rhythm in some cases)</td>
<td>50–200 mg daily, divided doses or sustained-release formulation</td>
<td>Hypotension, heart block, bradycardia, asthma, congestive heart failure</td>
<td>—</td>
</tr>
<tr>
<td>Propranolol (II)</td>
<td>Rate control (rhythm in some cases)</td>
<td>80–240 mg daily, divided doses or sustained-release formulation</td>
<td>Hypotension, heart block, bradycardia, asthma, congestive heart failure</td>
<td>—</td>
</tr>
<tr>
<td>Diltiazem (IV)</td>
<td>Rate control</td>
<td>120–360 mg daily, divided doses or sustained-release formulation</td>
<td>Hypotension, heart block, congestive heart failure</td>
<td>—</td>
</tr>
<tr>
<td>Verapamil (IV)</td>
<td>Rate control</td>
<td>120–360 mg daily, divided doses or sustained-release formulation</td>
<td>Hypotension, heart block, congestive heart failure, interaction with digoxin</td>
<td>—</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Rate control</td>
<td>0.125–0.375 mg daily</td>
<td>Toxic effects of digitalis, heart block, bradycardia</td>
<td>—</td>
</tr>
<tr>
<td>Amiodarone (III)</td>
<td>Rhythm control (rate in some cases)</td>
<td>100–400 mg daily</td>
<td>Pulmonary toxic effects, skin discoloration, hypothyroidism, gastrointestinal upset, hepatic toxic effects, corneal deposits, optic neuropathy, interaction with warfarin, torsades de pointes (rare)</td>
<td>—</td>
</tr>
<tr>
<td>Quinidine (IA)</td>
<td>Rhythm control</td>
<td>600–1500 mg daily, divided doses</td>
<td>Torsades de pointes, gastrointestinal upset, enhanced atrioventricular nodal conduction</td>
<td>Prolongs QT interval; avoid with left ventricular wall thickness ≥1.4 cm</td>
</tr>
<tr>
<td>Procaainamide (IA)</td>
<td>Rhythm control</td>
<td>1000–4000 mg daily, divided doses</td>
<td>Torsades de pointes, lupus-like syndrome, gastrointestinal symptoms</td>
<td>Prolongs QT interval; avoid with left ventricular wall thickness ≥1.4 cm</td>
</tr>
<tr>
<td>Disopyramide (IA)</td>
<td>Rhythm control</td>
<td>400–750 mg daily, divided doses</td>
<td>Torsades de pointes, congestive heart failure, glaucoma, urinary retention, dry mouth</td>
<td>Prolongs QT interval; avoid with left ventricular wall thickness ≥1.4 cm</td>
</tr>
<tr>
<td>Flecainide (IC)</td>
<td>Rhythm control</td>
<td>200–300 mg daily, divided doses</td>
<td>Ventricular tachycardia, congestive heart failure, enhanced atrioventricular nodal conduction (conversion to atrial flutter)</td>
<td>Contraindicated in patients with ischemic and structural heart disease</td>
</tr>
<tr>
<td>Propafenone (IC)</td>
<td>Rhythm control</td>
<td>450–900 mg daily, divided doses</td>
<td>Ventricular tachycardia, congestive heart failure, enhanced atrioventricular nodal conduction (conversion to atrial flutter)</td>
<td>Contraindicated in patients with ischemic and structural heart disease</td>
</tr>
<tr>
<td>Sotalol (III)</td>
<td>Rhythm control</td>
<td>240–320 mg daily, divided doses</td>
<td>Torsades de pointes, congestive heart failure, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease</td>
<td>Prolongs QT interval; avoid with left ventricular wall thickness ≥1.4 cm</td>
</tr>
<tr>
<td>Dofetilide (III)</td>
<td>Rhythm control</td>
<td>500–1000 μg daily, divided doses</td>
<td>Torsades de pointes</td>
<td>Prolongs QT interval; avoid with left ventricular wall thickness ≥1.4 cm</td>
</tr>
</tbody>
</table>

* The information in the table is adapted from Fuster et al.11
† The Vaughn Williams class of antiarrhythmic drugs is given for those classified. Digoxin is not classified in this system.
<table>
<thead>
<tr>
<th>Underlying Disorder</th>
<th>Rate Control†</th>
<th>Rhythm Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal or no heart disease</td>
<td>β-adrenergic blocker or calcium-channel blocker</td>
<td>First Choice: Flecainide, propafenone, sotalol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second Choice: Amiodarone, dofetilide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third Choice: Disopyramide, procainamide, quinidine (or nonpharmacologic options)</td>
</tr>
<tr>
<td>Adrenergic atrial fibrillation with minimal or no heart disease</td>
<td>β-adrenergic blocker</td>
<td>First Choice: Amiodarone, dofetilide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second Choice: —</td>
</tr>
<tr>
<td>Heart failure</td>
<td>β-adrenergic blocker, if tolerated; digoxin</td>
<td>—</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>β-adrenergic blocker</td>
<td>Sotalol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amiodarone, dofetilide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disopyramide, procainamide, quinidine</td>
</tr>
<tr>
<td>Hypertension with LVH but wall thickness &lt;1.4 cm</td>
<td>β-adrenergic blocker or calcium-channel blocker</td>
<td>First Choice: Flecainide, propafenone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second Choice: Amiodarone, dofetilide, sotalol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third Choice: Disopyramide, procainamide, quinidine</td>
</tr>
<tr>
<td>Hypertension with LVH and wall thickness ≥1.4 cm</td>
<td>β-adrenergic blocker or calcium-channel blocker</td>
<td>Amiodarone</td>
</tr>
</tbody>
</table>

* LVH denotes left ventricular hypertrophy. The information in this table is adapted from Fuster et al.11† β-adrenergic blockers include metoprolol and propranolol; calcium-channel blockers includes diltiazem and verapamil.

percent of those who were treated with propafenone or sotalol).44

RATE CONTROL VERSUS RHYTHM CONTROL

In three recent randomized studies, rate control was compared with rhythm control in patients with persistent atrial fibrillation.45-47 The Pharmacological Intervention in Atrial Fibrillation trial found no difference between the treatment groups in the primary end point of the quality of life, although a secondary analysis showed improvement in the distance walked in six minutes among patients in the rhythm-control group.45 The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial found that rate control was not inferior to rhythm control in the effects on a composite end point (consisting of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and serious adverse effects of drugs) over a period of 2.3 years (rate control, 17.2 percent, vs. rhythm control, 22.6 percent).46 The largest of these trials, the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial, which was designed to assess mortality, found no significant difference in this end point between the groups at five years (rhythm control, 23.8 percent, vs. rate control, 21.3 percent).47 Thus, the evidence suggests that the strategy used to treat atrial fibrillation — rate control versus rhythm control — does not have a substantial effect on the quality of life or on cardiovascular end points, including death.

Nonetheless, some questions remain. All three of these trials compared strategies with the use of an intention-to-treat analysis. The success rate for maintaining sinus rhythm was as low as 39 percent after 2.3 years of treatment46 and as high as 73 percent at 3 years.47 A secondary analysis of the data from the RACE trial showed that for patients with symptoms related to atrial fibrillation and those who were in sinus mechanism at the end of the follow-up period, regardless of the treatment randomly assigned, the quality of life had improved.48 All three studies enrolled only patients for whom rhythm control was considered to be an option by both the patient and the physician; in highly symptomatic patients, rhythm control may still be preferable. For patients who have minimal symptoms or when sinus rhythm cannot be maintained, however, a strategy of rate control is safe and appropriate. Anticoagulant therapy should be continued, irrespective of the strategy used.
ABALATION

In the past decade, ablation for atrial fibrillation has become a therapeutic option. The initial efforts involved the creation of radiofrequency lines of conduction block, rather than surgical incisions. The subsequent discovery that paroxysmal atrial fibrillation primarily emanates from the pulmonary veins led to the use of focal-vein ablation and then to techniques to isolate the firing foci with the use of circumferential or segmental ablation near the ostia of the pulmonary veins.

Recently, the use of anatomical ablation with lesions placed circumferentially around the right and left veins, with or without additional left atrial linear lesions, has been successful in patients with paroxysmal atrial fibrillation and those with persistent atrial fibrillation. In an observational study of 1171 patients, those who underwent ablation had significantly lower rates of recurrence after one year (16 percent) than those receiving antiarrhythmic drugs (39 percent); among the patients who underwent ablation, mortality and morbidity also were lower and the quality of life was better.

However, data are needed from a randomized trial to establish whether these differences are attributable to the therapy or to other factors. Early series primarily enrolled patients with normal left ventricular function, but in a recent study of 377 patients, one quarter had an ejection fraction below 40 percent, and 73 percent of this group had no recurrence during a follow-up period of 14 months (as compared with 87 percent of the patients with a left ventricular ejection fraction of 40 percent or greater).

Although new techniques and increased experience are associated with lower complication rates, concern persists about potential stroke and tamponade (events that are estimated to occur in 1 percent of cases among experienced physicians). Furthermore, pulmonary-vein stenosis may occur in 5 to 6 percent of patients, even when techniques to minimize the risk are used. When a pulmonary-vein stenosis occurs, conservative management may be appropriate, but dilation with or without stenting may be necessary.

AREAS OF UNCERTAINTY

Approaches to prevent the development of atrial fibrillation warrant further attention. Recent randomized trials involving patients with left ventricular dysfunction suggest that angiotensin-converting-enzyme inhibitors reduce the risk of atrial fibrillation. These data emphasize the importance of treatment for hypertension and cardiovascular disease in such patients.

The role of ablation, as compared with antiarrhythmic therapy, remains uncertain; its use may increase as tools and techniques are improved. The role of new oral anticoagulant agents that are currently in development, which might obviate the need for dose adjustment and the measurement of INR values, needs to be determined. The direct thrombin inhibitor ximelagatran appears to be as effective as warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation. However, clinical use of ximelagatran may be limited by its hepatic toxicity; the elevation of levels of alanine aminotransferase to more than three times the upper limit of normal occurred in 6 percent of the patients taking ximelagatran, as compared with 1 percent of those taking warfarin, and hepatic failure leading to death has been reported with the use of ximelagatran.

GUIDELINES

The American College of Cardiology and American Heart Association (ACC-AHA) Task Force on Practice and the European Society of Cardiology (ESC) Committee for Practice have published guidelines for the management of atrial fibrillation that recommend the "minimum evaluation" of newly discovered atrial fibrillation, mentioned earlier, and advise on the use of antiarrhythmic agents (Tables 2 and 3). These guidelines suggest that there is "no clear advantage" to a strategy of rate control as compared with rhythm control. Their recommendations for antithrombotic therapy are similar to, but not identical with, those published by the American College of Chest Physicians (ACCP) and the American College of Physicians (ACP), recommend less aggressive anticoagulant therapy with warfarin. This set of guidelines defines patients who have no history of stroke or transient ischemic attack and have only a single risk factor for stroke (e.g., an age of 75 years or older, congestive heart failure, hypertension, or diabetes) as at low risk (i.e., not in need of warfarin therapy).

RECOMMENDATIONS

The patient described in the vignette presented with atrial fibrillation that was asymptomatic and
may have been present for months (as suggested by the failure of the treadmill monitor to measure her heart rate). The evaluation should include testing with electrocardiography, echocardiography, and chest radiography and measurement of the serum thyroid hormone levels. On the basis of data from randomized trials, her survival would not be improved by the use of strategies aimed at conversion and the maintenance of sinus rhythm, and no strategy could improve her symptoms since she has none. Thus, I would continue heart-rate–control therapy with the use of her current β-adrenergic–blocking agent.

Her age and hypertension place her at elevated risk for thromboembolism, and anticoagulant therapy with warfarin is indicated, with a target INR of 2.0 to 3.0. Because atrial fibrillation represents a marker of risk for atherosclerotic disease and stroke,62 I would also assess the patient for and aggressively treat other risk factors for cardiovascular disease, including her hypertension.

Dr. Page reports having received honoraria from Berlex and AstraZeneca.

REFERENCES


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Atrial Fibrillation: Diagnosis and Treatment

CECILIA GUTIERREZ, MD, and DANIEL G. BLANCHARD, MD, University of California, San Diego, La Jolla, California

Atrial fibrillation is the most common cardiac arrhythmia. It impairs cardiac function and increases the risk of stroke. The incidence of atrial fibrillation increases with age. Key treatment issues include deciding when to restore normal sinus rhythm, when to control rate only, and how to prevent thromboembolism. Rate control is the preferred management option in most patients. Rhythm control is an option for patients in whom rate control cannot be achieved or who have persistent symptoms despite rate control. The current recommendation for strict rate control is a resting heart rate of less than 80 beats per minute. However, one study has shown that more lenient rate control of less than 110 beats per minute while at rest was not inferior to strict rate control in preventing cardiac death, heart failure, stroke, and life-threatening arrhythmias. Anticoagulation therapy is needed with rate control and rhythm control to prevent stroke. Warfarin is superior to aspirin and clopidogrel in preventing stroke despite its narrow therapeutic range and increased risk of bleeding. Tools that predict the risk of stroke (e.g., CHADS₂) and the risk of bleeding (e.g., Outpatient Bleeding Risk Index) are helpful in making decisions about anticoagulation therapy. Surgical options for atrial fibrillation include disruption of abnormal conduction pathways in the atria, and obliteration of the left atrial appendage. Catheter ablation is an option for restoring normal sinus rhythm in patients with paroxysmal atrial fibrillation and normal left atrial size. Referral to a cardiologist is warranted in patients who have complex cardiac disease; who are symptomatic on or unable to tolerate pharmacologic rate control; or who may be candidates for ablation or surgical interventions. (Am Fam Physician. 2011;83(1):61-68. Copyright © 2011 American Academy of Family Physicians.)

Atrial fibrillation is the most common cardiac arrhythmia, and its incidence increases with age. It affects about 1 percent of patients younger than 60 years and about 8 percent of patients older than 80 years. Atrial fibrillation is defined as a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical atrial function. Electrocardiographic findings include the replacement of the normal consistent P waves (which represent synchronous atrial activation) with oscillatory or fibrillatory waves of different sizes, amplitudes, and timing (Figure 1). The QRS complex remains narrow unless other conduction abnormalities exist (e.g., bundle branch block, accessory pathways). The ventricular response is often rapid, between 90 and 170 beats per minute.

Atrial fibrillation is a source of significant morbidity and mortality because it impairs cardiac function and increases the risk of stroke. Its most important clinical implications are shown in Figure 2. The cost of caring for patients with atrial fibrillation is about five times greater than caring for patients without it. Atrial fibrillation is an independent risk factor for mortality; it can also lead to or worsen heart failure and increase mortality rates in patients who have had myocardial infarction.

**Pathophysiology**

Two mechanisms have been identified in triggering and maintaining atrial fibrillation: enhanced automaticity in one or more depolarizing foci, and reentry involving one or more aberrant circuits. If it persists, atrial fibrillation can cause atrial remodeling, which is characterized by patchy fibrosis; abnormal and excessive deposition of collagen; fatty infiltration of the sinoatrial node; molecular changes in ion channels; changes in depolarization pattern and cellular energy use; and apoptosis. Chronic remodeling leads to irreversible atrial enlargement. The longer the heart remains in atrial fibrillation, the more difficult it is to restore normal sinus rhythm. After a critical point is reached, paroxysmal atrial fibrillation self-perpetuates and becomes persistent.

**Definitions**

Different types of atrial fibrillation have different prognoses, morbidity rates, mortality rates, and treatment options (Table 1).
For example, valvular atrial fibrillation, which is caused by structural changes in the mitral valve or congenital heart disease, carries the highest risk of stroke (i.e., 17 times that of the general population and five times the risk of stroke with nonvalvular atrial fibrillation).^4 Secondary atrial fibrillation is caused by an underlying condition and is reversible if the condition is treated. The most common underlying conditions are listed in Table 2. Atrial fibrillation may occur immediately after cardiac and thoracic surgery. It is usually self-limited, but should be treated aggressively if it persists because of the increased risk of stroke. Lone atrial fibrillation occurs in patients younger than 60 years who have no underlying cardiac disease and no identifiable cause. The prognosis is very good in patients with lone atrial fibrillation. Paroxysmal atrial fibrillation refers to episodes of intermittent atrial fibrillation that terminate spontaneously. Chronic atrial fibrillation is continuous and either cannot be converted back to normal sinus rhythm or a decision has been made not to attempt cardioversion. Persistent atrial fibrillation does not self-terminate, but may be terminated by electrical or pharmacologic cardioversion.

**Clinical Presentation**

Atrial fibrillation has a wide spectrum of clinical presentations. Some patients may be asymptomatic. Others may present with stroke, overt heart failure, or cardiovascular collapse. Patients most commonly report palpitations, dyspnea, fatigue, lightheadedness, and chest pain. Because symptoms are nonspecific, they cannot be used to diagnose and determine the onset of atrial fibrillation. If electrocardiography does not demonstrate atrial fibrillation and a strong suspicion persists, a Holter or cardiac event monitor may be needed to document the arrhythmia.
Table 1. Classification of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Type of atrial fibrillation</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic/permanent</td>
<td>Continuous atrial fibrillation that is unresponsive to cardioversion; cardioversion will not be reattempted</td>
</tr>
<tr>
<td>Lone</td>
<td>Occurs in persons younger than 60 years and in whom no clinical or echocardiographic causes are found</td>
</tr>
<tr>
<td>Nonvalvular</td>
<td>Not caused by valvular disease, prosthetic heart valves, or valve repair</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>Episodes that terminate spontaneously</td>
</tr>
<tr>
<td>Persistent</td>
<td>Paroxysmal atrial fibrillation sustained for more than seven days, or atrial fibrillation that terminates only with cardioversion</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Two or more episodes of atrial fibrillation</td>
</tr>
<tr>
<td>Secondary</td>
<td>Caused by a separate underlying condition or event (e.g., myocardial infarction, cardiac surgery, pulmonary disease, hyperthyroidism)</td>
</tr>
</tbody>
</table>

Information from reference 4.

Table 2. Secondary Causes of Atrial Fibrillation

- **Cardiac**
  - Cardiothoracic surgery
  - Congenital heart disease
  - Heart failure
  - Infiltrative disease (e.g., amyloid heart disease)
  - Longstanding hypertension
  - Myocardial infarction
  - Myocarditis
  - Pericarditis
  - Valvular disease
  - Wolff-Parkinson-White syndrome

- **Noncardiac**
  - Alcoholism
  - Cor pulmonale
  - Drug abuse
  - Hyperthyroidism
  - Pneumonia
  - Pulmonary embolism
  - Sleep apnea

Table 3. Initial Evaluation of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td>Identify possible pulmonary disease (e.g., pneumonia, vascular congestion, chronic obstructive pulmonary disease)</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Identify comorbid conditions (e.g., anemia, infection)</td>
</tr>
<tr>
<td>Complete metabolic profile</td>
<td>Identify electrolyte abnormalities that may cause or exacerbate atrial fibrillation</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Assess kidney and liver function and blood glucose level</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Assess heart size and shape, chamber sizes and pressures, valve structure and function; presence of pericardial effusion; wall motion abnormalities; systolic and diastolic function</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Diagnose atrial fibrillation and identify other arrhythmia (e.g., atrial flutter, atrial tachycardia)</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Identify other cardiac conditions (e.g., left ventricular hypertrophy, ischemia, strain, injury)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>Identify hyperthyroidism</td>
</tr>
<tr>
<td>measurement</td>
<td></td>
</tr>
</tbody>
</table>

The first goal is to determine the patient's cardiac stability and provide emergency stabilization if needed. If the patient is unstable because of hypotension, ongoing ischemia, severe heart failure, or cerebrovascular events, emergency electrical cardioversion is warranted. If the patient is clinically stable, the history, physical examination, and diagnostic testing should focus on potential causes, triggers, and comorbid conditions. Standard tests used to evaluate cardiac function and identify common comorbid conditions include electrocardiography, complete blood count, complete metabolic profile, thyroid-stimulating hormone measurement, chest radiography, and echocardiography (Table 3). Echocardiography provides information about heart size, chamber sizes, valvular anatomy and function, wall motion abnormalities, systolic and diastolic function, and pericardial disease. If there is clinical suspicion of myocardial ischemia, creatine kinase isoenzyme and troponin levels should be obtained. Select patients may need additional tests, such as stress testing and electrophysiology studies.

**Management**

Two main strategies have been compared in the treatment of atrial fibrillation: rhythm control and rate control. Data show that patients assigned to rhythm control have more hospitalizations from adverse cardiovascular events, more serious adverse effects from medications, and the same rate of thromboembolic events compared with patients assigned to rate control.12-15 Therefore, rate control is recommended in most patients. Rhythm control remains an option when rate control is unsuccessful or when symptoms persist despite rate control.16 Both strategies require anticoagulation therapy to prevent stroke.
Atrial Fibrillation

RHYTHM CONTROL
Cardioversion to restore normal sinus rhythm can be achieved electrically or pharmacologically. Anticoagulation therapy, before and after cardioversion, is recommended with either strategy to prevent thromboembolism. Guidelines recommend initiating anticoagulation therapy three weeks before and four weeks after cardioversion, because thrombi may form as soon as 48 hours after the onset of atrial fibrillation (Figure 3), and atrial function does not return to normal immediately after cardioversion to normal sinus rhythm. The atria are often “stunned,” and the risk of stroke is high for several weeks if warfarin (Coumadin) is not used.\textsuperscript{15,18}

Pharmacologic cardioversion and maintenance of normal sinus rhythm are difficult to achieve because of the limited long-term effectiveness of medications, the risk of triggering ventricular arrhythmias, and the risk of long-term adverse effects from medication use. Medications commonly used for cardioversion include ibutilide (Corvert), flecainide (Tambocor), dofetilide (Tikosyn), sotalol (Betapace), propafenone (Rythmol), and amiodarone (Cordarone).\textsuperscript{4} Older agents such as quinidine, procainamide, and disopyramide (Norpace) are rarely used because of adverse effects. Dronedarone (Multaq), which is a noniodinated derivative of amiodarone, has been shown to reduce atrial fibrillation without the long-term serious adverse effects of amiodarone, but there are concerns about safety in patients with severe heart failure.\textsuperscript{15,20}

The choice of medication depends on the patient’s cardiac history. For example, flecainide and propafenone are preferred in patients with minimal or no heart disease and preserved left ventricular systolic function, whereas amiodarone and dofetilide are preferred in patients with heart failure.\textsuperscript{4} Patients with paroxysmal atrial fibrillation may use the “pill-in-the-pocket” approach with flecainide or propafenone, which involves taking a pill when an episode begins. This method is often effective in converting the rhythm to normal, and obviates the need to take antiarrhythmic medications long term. Table 4 lists the most commonly used antiarrhythmic medications, potential adverse effects, and costs.

RATE CONTROL
Decreasing the ventricular response rate, known as rate control, improves diastolic filling and coronary perfusion, decreases myocardial energy demand, and prevents tachycardia-mediated cardiomyopathy. Current guidelines recommend aiming for a ventricular response of less than 80 beats per minute at rest and less than 110 beats per minute during exercise.\textsuperscript{4} However, a recent randomized controlled trial showed that lenient rate control, defined as a ventricular rate of less than 110 beats per minute at rest, was not inferior to strict rate control in preventing cardiac death, heart failure, stroke, and life-threatening arrhythmias.\textsuperscript{21}

Beta blockers (e.g., metoprolol, esmolol [Brevibloc], propranolol [Inderal]) and nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) are often used for rate control. Beta blockers are generally first-line agents.

Digoxin is no longer considered a first-line agent for atrial fibrillation, because studies have shown that it has little effect during exercise.\textsuperscript{4} However, it may be used in conjunction with beta blockers or calcium channel blockers. Digoxin slows the ventricular rate mostly via enhancing vagal tone.

ANTICOAGULATION
In patients with atrial fibrillation, the estimated risk of stroke without anticoagulation therapy is 5 percent per year.\textsuperscript{22} Paroxysmal and chronic atrial fibrillation, treated by rate or rhythm control, require long-term anticoagulation therapy unless the risks of anticoagulation use exceed the benefits.\textsuperscript{4,16}

Warfarin, aspirin, and clopidogrel (Plavix) are the most commonly used oral agents for anticoagulation. Several trials and a Cochrane review have demonstrated
Table 4. Antiarrhythmic Medications for the Treatment of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Suggested dosage</th>
<th>Cost of generic (brand)*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (Cordarone)</td>
<td>600 to 1,200 mg per day for one to two weeks, then taper to lowest possible dosage 200 mg per day for maintenance dosage</td>
<td>$29† ($136) for maintenance dosage</td>
<td>Potential adverse effects include abnormal cardiac conduction, anaphylaxis, heart failure, pulmonary toxicity, ocular toxicity, thyroid abnormalities, hypersensitivity reaction, liver failure, lupus, thrombocytopenia, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Disopyramide (Norpace)</td>
<td>400 to 800 mg per day in divided doses</td>
<td>$63 ($198)</td>
<td>Potential adverse effects include torsades de pointes, drug-induced lupus, hepatotoxicity, hypoglycemia, heart failure</td>
</tr>
<tr>
<td>Dofetilide (Tikosyn)</td>
<td>500 mcg orally every 12 hours at initiation of therapy, titrate downward based on QT response</td>
<td>NA ($234)</td>
<td>Potential adverse effects include prolonged QT interval and various proarrhythmias Use is restricted to trained prescribers and facilities In-hospital electrocardiographic monitoring required for at least three days</td>
</tr>
<tr>
<td>Flecainide (Tambocor)</td>
<td>100 to 150 mg taken at onset of atrial fibrillation May also be taken twice per day for prevention of atrial fibrillation</td>
<td>$58 ($146)</td>
<td>Potential adverse effects include various proarrhythmias, torsades de pointes</td>
</tr>
<tr>
<td>Ibutilide (Corvert)</td>
<td>A one-time 1 mg intravenous dosage, may repeat once after 10 minutes if no response</td>
<td>$336 ($452) for 1 mg per 10 mL vial†</td>
<td>Potential adverse effects include polymorphic ventricular tachycardia, hypotension, headache Caution is needed in patients with QT prolongation, hypokalemia, hypomagnesemia, bradycardia Continuous electrocardiographic monitoring required for four hours after last dosage</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Up to 50 mg per kg per day in divided dosages</td>
<td>$37 (NA) for 500 mg every six hours‡</td>
<td>Potential adverse effects include agranulocytosis, aplastic anemia, coagulation disorder, arrhythmia, hepatotoxicity, drug-induced lupus</td>
</tr>
<tr>
<td>Propafenone (Rythmol)</td>
<td>225 to 425 mg orally every 12 hours</td>
<td>$80 ($340)</td>
<td>Potential adverse effects include granulocytosis, angina, chest pain, heart failure, atrioventricular block, bradyarrhythmias, hypotension, palpitations, sinus arrest, drug-induced lupus, bronchospasm</td>
</tr>
<tr>
<td>Quinidine</td>
<td>324 to 648 mg; one to two tablets every eight hours to 12 hours</td>
<td>$60 (NA)</td>
<td>Potential adverse effects include various proarrhythmias, torsades de pointes, hepatotoxicity, kidney disease, myelosuppression, drug-induced lupus</td>
</tr>
<tr>
<td>Sotalol (Betapace)</td>
<td>80 to 160 mg twice per day</td>
<td>$21† ($249)</td>
<td>Potential adverse effects include torsades de pointes, various proarrhythmias, heart failure, bradycardia, heart block, asthma Continuous electrocardiographic monitoring required for three days after initiation of therapy Avoid in patients with renal insufficiency</td>
</tr>
</tbody>
</table>

NA = not available in designated form.

*—Estimated retail price of one month’s treatment based on information obtained at http://www.drugstore.com (accessed September 8, 2010), except where noted. Generic price listed first; brand price listed in parentheses. Prices based on lowest suggested dosage.
†—May be available at discounted prices ($10 or less for one month’s treatment) at one or more national retail chains.
‡—Estimated cost to the pharmacist based on average wholesale prices in Red Book. Montvale, N.J.: Medical Economics Data, 2010. Cost to the patient will be higher, depending on prescription filling fee.

that warfarin is more effective than aspirin but confers a higher risk of bleeding; that warfarin is superior to aspirin plus clopidogrel, with the same risk of bleeding; and that adding full-dose aspirin to warfarin should be avoided because of an increased risk of bleeding. Pooled data from five randomized controlled trials demonstrated that warfarin use reduces the risk of stroke by about 68 percent, whereas data from three randomized controlled trials showed that aspirin reduces the risk of stroke by about 21 percent.
Atrial Fibrillation

Warfarin poses significant challenges because of its narrow therapeutic range, the need for frequent monitoring, multiple drug and food interactions, and the risk of bleeding. The warfarin dosage should be adjusted to achieve a target International Normalized Ratio (INR) of 2 to 3. An INR less than 1.8 doubles the risk of stroke, whereas an INR greater than 3.5 does not further benefit patients and increases the risk of bleeding.4 Contraindications to warfarin therapy include hypersensitivity to warfarin, severe liver disease, recent trauma or surgery, and active bleeding.

As patients age, the risk of experiencing a thromboembolic event increases, as does the risk of experiencing adverse effects from anticoagulation therapy. Balancing these risks is key to optimizing outcomes.26,28 The stroke risk prediction tool known by the acronym CHADS2, has been validated in several trials.29,30 CHADS2 uses the following risk factors: congestive heart failure; hypertension; age 75 years or older; diabetes mellitus; stroke or transient ischemic attack. Each risk factor counts as one point, except for the stroke and transient ischemic attack risk factor, which counts as two points. Risk is stratified into high (score of 4 or greater), moderate (score of 2 or 3), and low (score of 0 or 1). Table 5 shows the corresponding stroke rates.16 The CHADS2 tool has limitations; it does not include coronary artery disease and sex as risk factors, although women are at a higher risk of thromboembolic events than men.20

The American College of Physicians, the American Academy of Family Physicians, and the American College of Cardiology/American Heart Association/European Society of Cardiology recommend that patients with nonvalvular atrial fibrillation who are at low risk of stroke be treated with 81 to 325 mg of aspirin per day, whereas patients at higher risk should be treated with warfarin (at a dosage necessary to achieve a target INR of 2 to 3).4,16 There is general agreement that warfarin should be recommended in patients with atrial fibrillation and a CHADS2 score of 2 or greater.

Decisions about the use of warfarin versus aspirin can be challenging in older patients and in those at risk of bleeding. The Outpatient Bleeding Risk Index is a validated tool used to predict the risk of bleeding in patients taking warfarin.20,21 The Outpatient Bleeding Risk Index includes four risk factors, each counting as one point: (1) age older than 65 years; (2) history of stroke; (3) history of gastrointestinal bleeding; and (4) one or more of the following: recent myocardial infarction, severe anemia (hematocrit level less than 30 percent), diabetes, or renal impairment (serum creatinine level greater than 1.5 mg per dl [132.6 μmol per l]).32 A score of 0 is considered low risk, a score of 1 or 2 is intermediate risk, and a score of 3 or 4 is high risk.31 One study evaluating the Outpatient Bleeding Risk Index found that the risk of major bleeding after one year in low-, intermediate-, and high-risk patients was 3, 12, and 48 percent, respectively.33 Point-of-care guides from the American Academy of Family Physicians are useful tools to assess the risk of stroke and bleeding using CHADS2, the American College of Chest Physicians risk assessment, and the Outpatient Bleeding Risk Index. These guides are available at http://www.aafp.org/afp/2005/0615/p2348.html and http://www.aafp.org/afp/2010/0315/p780.html.

The anticoagulation agent dabigatran (Pradaxa), a direct thrombin inhibitor, was recently approved by the U.S. Food and Drug Administration for the prevention of stroke and systemic embolism with atrial fibrillation. In a randomized trial, 150 mg of dabigatran twice per day was shown to be superior to warfarin in decreasing the incidence of ischemic and hemorrhagic strokes. Patients assigned to dabigatran had a higher incidence of myocardial infarction than those assigned to warfarin, but the difference was not statistically significant.34,35

SURGICAL THERAPIES

There are two surgical therapies for atrial fibrillation: disruption of abnormal conduction pathways in the atria, and obliteration of the left atrial appendage. The maze procedure disrupts the initiation and

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**Table 5. Risk of Stroke Stratified by CHADS2 Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Adjusted stroke rate* (95% confidence interval)</th>
<th>Risk level</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2 to 3.0)</td>
<td>Low</td>
<td>Aspirin; 81 to 325 mg per day</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0 to 3.8)</td>
<td>Low</td>
<td>Warfarin (Coumadin); target INR of 2 to 3</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1 to 5.1)</td>
<td>Moderate</td>
<td>Warfarin; target INR of 2 to 3</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6 to 7.3)</td>
<td>Moderate</td>
<td>Warfarin; target INR of 2 to 3</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3 to 11.1)</td>
<td>High</td>
<td>Warfarin; target INR of 2 to 3</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2 to 17.5)</td>
<td>High</td>
<td>Warfarin; target INR of 2 to 3</td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5 to 27.4)</td>
<td>High</td>
<td>Warfarin; target INR of 2 to 3</td>
</tr>
</tbody>
</table>

*Expected stroke rate per 100 person-years.

---

Note: CHADS2 = congestive heart failure; hypertension; age 75 years or older; diabetes mellitus; stroke or transient ischemic attack. To assess risk, add one point for each risk factor, except the stroke and transient ischemic attack risk factor, which counts as two points.

INR = International Normalized Ratio.
conduction of electrical activity of the arrhythmogenic foci. Incisions are made in both atria to isolate and interrupt the multiple reentry circuits while maintaining the physiologic activation of the atria.36,37

The rationale for left atrial appendage obliteration is that more than 90 percent of thrombi form in the left atrial appendage (Figure 3). If successful, obliteration decreases the patient’s risk of stroke and potentially avoids the need for long-term anticoagulation therapy. Preliminary data on percutaneous left atrial appendage obliteration show promise, but little long-term follow-up data are available.38,39 Direct left atrial appendage obliteration is an option in patients who will undergo valve surgery, particularly involving the mitral valve.

CATHETER ABLATION

The discovery of specific foci that trigger atrial fibrillation (e.g., at or near the pulmonary veins, at the isthmus of the mitral valve) has stimulated research and development of ablation approaches. In 2009, a systematic review of six trials showed that catheter ablation is effective for up to 12 months as second-line therapy in patients with minimal cardiac disease (mean age of 55 years).40 A later study found that ablation was significantly more effective than medical treatment for preventing recurrences in patients with intermittent atrial fibrillation.41 Currently, ablation therapy is a good option in patients with paroxysmal atrial fibrillation and normal left atrial size.

REFERRAL

Cardiology referral is warranted in the following situations: (1) when patients have complex cardiac disease; (2) when they remain symptomatic on pharmacologic rate control or cannot tolerate pharmacologic rate control; (3) when they are potential candidates for ablation or other surgical treatment; or (4) when they require a pacemaker or defibrillator.

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Acute Management of Atrial Fibrillation: 
Part I. Rate and Rhythm Control

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Atrial fibrillation is the arrhythmia most commonly encountered in family practice. Serious complications can include congestive heart failure, myocardial infarction, and thromboembolism. Initial treatment is directed at controlling the ventricular rate, most often with a calcium channel blocker, a beta blocker, or digoxin. Medical or electrical cardioversion to restore sinus rhythm is the next step in patients who remain in atrial fibrillation. Heparin should be administered to hospitalized patients undergoing medical or electrical cardioversion. Anticoagulation with warfarin should be used for three weeks before elective cardioversion and continued for four weeks after cardioversion. The recommendations provided in this two-part article are consistent with guidelines published by the American Heart Association and the Agency for Healthcare Research and Quality. (Am Fam Physician 2002;66:249-56. Copyright © 2002 American Academy of Family Physicians.)

In recent years, management strategies for atrial fibrillation have expanded significantly, and new drugs for ventricular rate control and rhythm conversion have been introduced.1-3 Family physicians have the challenge of keeping current with recommendations on heart rate control, antiarrhythmic drug therapy, cardioversion, and antithrombotic therapy.

Atrial fibrillation is the most common sustained arrhythmia encountered in the primary care setting. Approximately 4 percent of persons in the general U.S. population have permanent or intermittent atrial fibrillation, and the prevalence of the arrhythmia increases to 9 percent in persons older than 60 years.2 Atrial fibrillation can result in serious complications, including congestive heart failure, myocardial infarction, and thromboembolism. Recognition and acute management of atrial fibrillation in the physician’s office or emergency department are important in preventing adverse consequences.

Diagnosis

The diagnosis of atrial fibrillation should be considered in elderly patients who present with complaints of shortness of breath, dizziness, or palpitations. The arrhythmia should also be suspected in patients with acute fatigue or exacerbation of congestive heart failure.3 In some patients, atrial fibrillation may be identified on the basis of an irregularly irregular pulse or an electrocardiogram (ECG) obtained for the evaluation of another condition.

Cardiac conditions commonly associated with the development of atrial fibrillation include rheumatic mitral valve disease, coronary artery disease, congestive heart failure, and hypertension. Noncardiac conditions that can predispose patients to develop atrial fibrillation include hyperthyroidism, hypoxia, alcohol intoxication, and surgery.4

The ECG is the mainstay for diagnosis of atrial fibrillation (Figure 1). An irregularly irregular rhythm, inconsistent R-R interval, and absence of P waves are usually noted on the cardiac monitor or ECG. Atrial fibrillation waves (f waves), which are small, irregular waves seen as a rapid-cycle baseline fluctuation, indicate rapid atrial activity (usually between 150 and 300 beats per minute) and are the hallmark of the arrhythmia.

When the fibrillation waves reach 300
beats per minute, they may be difficult to see (fine versus coarse fibrillation). These waves may be even harder to detect on a cardiac monitor in a busy emergency department because of interference from other electrical equipment. The f waves may be easier to identify on a printed rhythm strip. In addition, when the ventricular response to atrial fibrillation is very rapid (more than 200 beats per minute), variability of the R-R interval can frequently be seen more easily using calipers on a paper tracing.

Atrial flutter is included in the spectrum of supraventricular arrhythmia. This rhythm disturbance is usually distinguishable by its more prominent saw-tooth wave configuration and slower atrial rates (Figure 2). Atrial fibrillation should also be distinguished from atrial tachycardia with variable atrioventricular block, which usually presents with an atrial rate of approximately 150 beats per minute. In this condition, the atrial rate is regular (unlike the irregular disorganized f waves of atrial fibrillation), but conduction to the ventricles is not regular. The resultant irregularly irregular rhythm may be difficult to differentiate from atrial fibrillation.

**Initial Management**

Recent advances in treatment and the introduction of new drugs have not changed initial management goals in patients with atrial fibrillation. These goals are hemodynamic stabilization, ventricular rate control, and prevention of embolic complications. When atrial fibrillation does not terminate spontaneously, the ventricular rate should be treated to slow ventricular response and, if appropriate, efforts should be made to terminate atrial fibrillation and restore sinus rhythm (Figure 3).
Initial Management of Atrial Fibrillation

Patient with diagnosis of atrial fibrillation

Hemodynamically stable (no angina, no hypotension, etc.)?

Yes

Control ventricular rate (goal = <100 beats per minute): administer diltiazem (Cardizem), 15 mg IV over 2 minutes, then 5 to 15 mg per hour by continuous IV infusion or administer other rate-control drug (see Table 1).

No

Electrical cardioversion: sedate, then shock (100 J, 200 J, 300 J, 360 J) until sinus rhythm returns.

Spontaneous conversion to sinus rhythm?

Yes

Assess cause of atrial fibrillation; hospital discharge, follow-up

No

Contraindications to cardioversion?

Yes

Consider long-term anticoagulation.

No

Consider cardioversion, if indicated (see text):
- Start heparin IV; then choose—
  - Atrial fibrillation < 48 hours: immediate medical or electrical cardioversion
  - Atrial fibrillation > 48 hours or unknown duration:
    - Later elective cardioversion (electrical cardioversion with or without medical cardioversion) after 3 weeks of warfarin (Coumadin)
    - Early TEE-guided cardioversion (electrical cardioversion with or without medical cardioversion)

Atrial fibrillation persists?

Yes

Consider long-term anticoagulation.

No

Assess cause of atrial fibrillation; hospital discharge, follow-up

FIGURE 3. Initial approach to the patient with acute atrial fibrillation. (IV = intravenous; J = joule; TEE = transesophageal echocardiography)

In patients with atrial fibrillation, the initial management goals are hemodynamic stabilization, ventricular rate control, and prevention of embolic complications.

VENTRICULAR RATE CONTROL

Ventricular rate control to achieve a rate of less than 100 beats per minute is generally the first step in managing atrial fibrillation. Beta blockers, calcium channel blockers, and digoxin (Lanoxin) are the drugs most commonly used for rate control.24,47 (Table 1). These agents do not have proven efficacy in converting atrial fibrillation to sinus rhythm and should not be used for that purpose.4,5,10,11

Beta blockers and calcium channel blockers are the drugs of choice because they provide rapid rate control.4,7,12 These drugs are effective in reducing the heart rate at rest and during exercise in patients with atrial fibrillation.4,7,12 Factors that should guide drug selection include the patient’s medical condition, the presence of concomitant heart failure, the characteristics of the medication, and the physician’s experience with specific drugs.

Compared with beta blockers and calcium channel blockers, digoxin is less effective for ventricular rate control, particularly during exercise. Digoxin is most often used as adjunctive therapy because of its slower onset of action (usually 60 minutes or more) and its weak potency as an atrioventricular node-blocking agent.5,13 It can be used when rate control during exercise is of less concern.4,7,12 Digoxin is a positive inotropic agent, which makes it especially useful in patients with systolic heart failure.7

The calcium channel blockers diltiazem (Cardizem) and verapamil (Calan, Isoptin) are effective for initial ventricular rate control in patients with atrial fibrillation. These agents are given intravenously in bolus doses until the ventricular rate becomes slower.7 Dihydropyridine calcium channel blockers (e.g., nifedipine [Procardia], amlodipine [Norvasc], felodipine [Plendil], isradipine [DynaCirc], nisoldipine [Sular]), are not effective for ventricular rate control.

Physicians can use the “rule of 15” in administering diltiazem to patients weighing 70 kg (154 lb): first, give 15 mg intravenously over two minutes, repeat the dose in 15 minutes if necessary, and then start an intravenous infusion of 15 mg per hour; titrate the dose to control the ventricular rate (5 to 15 mg per hour). Verapamil, in a dose of 5 to 10 mg administered intravenously over two minutes and repeated in 30 minutes if needed, can also be used for initial rate control. Although all calcium channel blockers can cause hypotension, verapamil should be used with particular caution because of the possibility of prolonged hypotension as a result of the drug’s relatively long duration of action.

Beta blockers such as propranolol (Inderal) and esmolol (Brevibloc) may be preferable to calcium channel blockers in patients with myocardial infarction or angina, but they should not be used in patients with asthma. As initial treatment, 1 mg of propranolol is given intravenously over two minutes; this dose can be repeated every five minutes up to a max-

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Atrial Fibrillation

um of 5 mg. Maintenance dosing of propranolol is 1 to 3 mg given intravenously every four hours. Esmolol has an extremely short half-life and may be given as a continuous intravenous infusion to maintain rate control (Table 1).3

Despite depressive effects on contractility (unless the ejection fraction is below 0.20), calcium channel blockers and beta blockers can be used for initial ventricular rate control in patients with heart failure. Oxygen delivery to the heart is usually much improved once the ventricular rate is controlled (less than 100 beats per minute). A slower ventricular response rate also allows more filling time for the heart and, thus, improved cardiac output.14 However, the benefits of long-term treatment with calcium channel blockers or beta blockers should be carefully weighed against the negative inotropic effects. Drugs for rate control can generally be stopped once sinus rhythm is restored.3

Limited data suggest that combination regimens provide better rate control than any agent alone.15

RESTORATION OF SINUS RHYTHM

Medical (Pharmacologic) Cardioversion. After patients with atrial fibrillation have been stabilized and the ventricular rate has been controlled, conversion to sinus rhythm is the next consideration. The decision to restore sinus rhythm should be individualized.

The many reasons for not attempting pharmacologic cardioversion include duration of atrial fibrillation for more than 48 hours, recurrence of atrial fibrillation despite multiple treatment attempts, poor tolerance of antiarrhythmic agents, advanced patient age and concomitant structural disease, large size of left atrium (greater than 6 cm), and the presence of sick sinus syndrome.2 However, continued atrial fibrillation is associated with

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dosing</th>
<th>Maintenance dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem (Cardizem)</td>
<td>15 to 20 mg IV over 2 minutes; may repeat in 15 minutes</td>
<td>5 to 15 mg per hour by continuous IV infusion</td>
<td>Convenient; easy to titrate to heart rate goal</td>
</tr>
<tr>
<td>Verapamil (Calan, Isoptin)</td>
<td>5 to 10 mg IV over 2 minutes; may repeat in 30 minutes</td>
<td>Not standardized</td>
<td>More myocardial depression and hypotension than with diltiazem</td>
</tr>
<tr>
<td>Beta blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol (Brevidloc)</td>
<td>Bolus of 500 mcg per kg IV over 1 minute; may repeat in 5 minutes</td>
<td>50 to 300 mcg per kg per minute by continuous IV infusion</td>
<td>Very short-acting; easy to titrate to heart rate goal</td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>1 mg IV over 2 minutes; may repeat every 5 minutes to maximum of 5 mg</td>
<td>1 to 3 mg IV every 4 hours</td>
<td>Short duration of action; hence, need for repeat dosing</td>
</tr>
<tr>
<td>Digoxin (Lanoxin)</td>
<td>0.25 to 0.5 mg IV, then 0.25 mg IV every 4 to 6 hours to maximum of 1 mg</td>
<td>0.125 to 0.25 mg per day IV or orally</td>
<td>Adjunctive therapy, less effective for rate control than beta blockers or calcium channel blockers</td>
</tr>
</tbody>
</table>

*IV = intravenous.*

long-term complications that can best be avoided by prompt return to sustained normal sinus rhythm and correction of underlying ischemic or structural abnormality. Early successful cardioversion may also reduce the incidence of recurrent atrial fibrillation.5

Medical cardioversion may be appropriate in certain situations, especially when adequate facilities and support for electrical cardioversion are not available or when patients have never been in atrial fibrillation before. Pharmacologic agents are effective in converting atrial fibrillation to sinus rhythm in about 40 percent of treated patients.2,5

Physicians should use medical cardioversion only after careful consideration of the possibility of proarrhythmic complications, particularly in patients with structural heart disease or congestive heart failure.7 Because cardioversion can lead to systemic emboli, heparin should be given before medical cardioversion is attempted7 (see part II for more information on this subject). Anticoagulation with warfarin (Coumadin) should be continued for four weeks after cardioversion.

After anticoagulation is initiated, quinidine sulfate (Quiniodex), flecainide (Tambocor), or propafenone (Rythmol) may be used to attempt pharmacologic conversion. The following intravenously administered drugs may also be used: dofetilide (Tikosyn), ibutilide (Corvert), procainamide, or amiodarone (Cordarone).8,16

A recent review4 and a meta-analysis17 concluded that flecainide, ibutilide, and dofetilide were the most efficacious agents for medical conversion of atrial fibrillation, but that propafenone and quinidine were also effective. In the presence of Wolff-Parkinson-White syndrome, procainamide is the drug of choice for converting atrial fibrillation.7 Less evidence supports the use of disopyramide (Norpace) and amiodarone, and evidence supports a negative effect for sotalol (Betapace).4,17 However, some investigators consider amiodarone to be the most effective agent for converting to sinus rhythm in patients who do not respond to other agents.7

Quinidine, disopyramide, propafenone, and sotalol have been found to be effective in maintaining sinus rhythm. One study comparing amiodarone and disopyramide found moderate evidence of efficacy for amiodarone in the maintenance of sinus rhythm.17

Overall, antiarrhythmic drug selection should be individualized based on the patient’s renal and hepatic function, concomitant illnesses, use of interacting medications, and underlying cardiovascular function. Because of intravenous formulation availability and effectiveness, one drug may be used for conversion and another for maintenance therapy. Amiodarone is the recommended agent in patients with a low ejection fraction (below 0.35) or structural heart disease. Patients should be monitored closely because quinidine, propafenone, and amiodarone may increase the International Normalized Ratio when they are used with warfarin. These same drugs and verapamil raise digoxin levels, which may necessitate a decrease in the digoxin dosage.7

The question of whether rate control or rhythm control should take precedence is currently being investigated in a randomized trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management).18 A recent small study19 examined rate control (using diltiazem) versus rhythm control (using amiodarone) plus anticoagulation. Overall, rate control was as good as rhythm control in reducing or eliminating symptoms and in reducing hospitalization rates, but the comparative effect on stroke risk was not studied.

Electrical Cardioversion. When patients with atrial fibrillation are hemodynamically unstable (e.g., angina, hypotension) and not responding to resuscitative measures, emergency electrical cardioversion is indicated. In stable patients, elective cardioversion is performed after three weeks of warfarin therapy.20 To prevent thrombus formation, warfarin is continued for four weeks after cardioversion. Although the success rate for electrical cardioversion is high (90 percent), proper equipment and expertise are necessary for safe performance.5
If there is time and patients are conscious, sedation should be achieved before cardioversion is attempted. Synchronized external direct-current cardioversion is performed with the pads placed anteriorly and posteriorly (over the sternum and between the scapulae) at 100 joules (J). If no response occurs, the current is applied again at 200 J; if there is still no response, the current is increased to 300 J, and then to a maximum of 360 J. If patients cannot be moved, the pads can be applied over the right sternal border and left lateral chest wall.³

Patients with atrial fibrillation at a ventricular rate of less than 150 beats per minute who are hemodynamically stable can be initially treated with drugs for ventricular rate control and intravenously administered heparin for anticoagulation (see part II for more information). Medical cardioversion or elective electrical cardioversion can then be considered as appropriate. Patients are usually monitored in the hospital while cardioversion is being attempted. However, one study⁹ documented positive results for emergency-department performance of cardioversion followed by direct discharge of hemodynamically stable patients without congestive heart failure.

An alternative approach for achieving earlier return to sinus rhythm is early electrical cardioversion and the use of transesophageal echocardiography according to American Heart Association guidelines.⁷ Transesophageal echocardiography is used to detect thrombi in the right atrium. If no thrombi are present, electrical cardioversion can be performed immediately; if thrombi are detected, cardioversion can be delayed until patients have undergone three weeks of oral anticoagulation using warfarin.²¹ One recent comparative study²² found no differences in thromboembolic complications between conventional treatment and early cardioversion following transesophageal echocardiography.

Because of the risk of complications such as heart failure and embolic stroke, restoration of sinus rhythm is thought to be preferable to allowing atrial fibrillation to continue. However, restoration of sinus rhythm is not always possible. In elderly patients with longstanding atrial fibrillation, repeated attempts at cardioversion may be counterproductive. The chances of reverting to and maintaining sinus rhythm are lower with longer duration of atrial fibrillation and decrease to particularly low levels when atrial fibrillation has been present for more than one year. When cardioversion is inappropriate or unsuccessful, medication should be used for ventricular rate control, and anticoagulation therapy should be considered.

General recommendations for the initial management of atrial fibrillation are summarized in Table 2.²,³,⁷,⁸,²²

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>General Recommendations for Initial Management of Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute control of the ventricular rate is best achieved with an intravenously administered calcium channel blocker (e.g., diltiazem [Cardizem]) or beta blocker (e.g., esmolol [Brevibloc]).</td>
<td></td>
</tr>
<tr>
<td>Immediate electrical cardioversion should be considered in hemodynamically unstable patients with atrial fibrillation.</td>
<td></td>
</tr>
<tr>
<td>Medical (pharmacologic) or electrical cardioversion following anticoagulation should be considered in hemodynamically stable patients with atrial fibrillation.</td>
<td></td>
</tr>
<tr>
<td>Elective electrical cardioversion should be used in patients with persistent or recurrent atrial fibrillation. The success rate for electrical cardioversion is 90%.</td>
<td></td>
</tr>
<tr>
<td>Medical cardioversion is a convenient and reasonable alternative in some patients, but it does not always terminate atrial fibrillation. The success rate for medical cardioversion is about 40%.</td>
<td></td>
</tr>
<tr>
<td>Early cardioversion after transesophageal echocardiography with intravenous anticoagulation is an increasingly used alternative strategy.</td>
<td></td>
</tr>
</tbody>
</table>

Information from references 2, 3, 7, 8, and 22.
REFERENCES


Acute Management of Atrial Fibrillation: Part II. Prevention of Thromboembolic Complications

DANA E. KING, M.D., LORI M. DICKERSON, PHARM.D., and JONATHAN I. SACK, M.D.
Medical University of South Carolina, Charleston, South Carolina

Family physicians should be familiar with the acute management of atrial fibrillation and the initiation of chronic therapy for this common arrhythmia. Initial management should include hemodynamic stabilization, rate control, restoration of sinus rhythm, and initiation of antithrombotic therapy. Part II of this two-part article focuses on the prevention of thromboembolic complications using anticoagulation. Heparin is routinely administered before medical or electrical cardioversion. Warfarin is used in patients with persistent atrial fibrillation who are at higher risk for thromboembolic complications because of advanced age, history of coronary artery disease or stroke, or presence of left-sided heart failure. Aspirin is preferred in patients at low risk for thromboembolic complications and patients with a high risk for falls, a history of non-compliance, active bleeding, or poorly controlled hypertension. The recommendations provided in this article are consistent with guidelines published by the American Heart Association and the Agency for Healthcare Research and Quality. (Am Fam Physician 2002;66:261-4,271-2. Copyright © 2002 American Academy of Family Physicians.)

Atrial fibrillation is the underlying cause of 30,000 to 40,000 embolic strokes per year in the United States.¹ The incidence of these strokes increases with age, rising from 1.5 percent in patients aged 50 to 59 years to 23.5 percent in patients aged 80 to 89 years.²

Although comorbid conditions such as hypertension and vascular disease are factors, the predominant cause of strokes in patients with atrial fibrillation is embolization of a clot from the left atrium. When evaluated using transesophageal echocardiography, up to 30 percent of patients with atrial fibrillation and embolic stroke are found to have atrial thrombi within 72 hours of the stroke.³,⁴ Risk factors for stroke in patients with atrial fibrillation include a history of transient ischemic attack or stroke, age greater than 65 years, a history of hypertension, the presence of a prosthetic heart valve (mechanical or tissue), rheumatic heart disease, left ventricular systolic dysfunction, or diabetes.

Most atrial fibrillation–derived strokes occur within the first 72 hours after medical (pharmacologic) or electrical cardioversion. The risk of stroke is significant for both rhythm conversion methods and is presumed to be due to the presence of left atrial thrombi at the time of cardioversion, rather than to the method used.² These data offer compelling support for the use of antithrombotic therapy with heparin, warfarin (Coumadin), or aspirin in patients with atrial fibrillation, unless specific contraindications exist.

Anticoagulant Drugs

**HEPARIN**

Heparin is the preferred agent for initial anticoagulation because it provides almost immediate effects and can be discontinued rapidly if bleeding complications arise.⁵ The drug should be given as a continuous intravenous infusion, with the dose titrated to achieve an activated partial thromboplastin time of 1.5 to 2.5 times the baseline value.

Heparin should not be used in patients with signs of active bleeding. In addition, its use in patients with acute embolic stroke is contro-
versial and should be guided by the results of transesophageal echocardiography to detect atrial thrombi.6

In patients with atrial fibrillation that has persisted for more than 48 hours, heparin can be used to reduce the risk of thrombus formation and embolization until the warfarin level is therapeutic or cardioversion is performed. Prevention of deep venous thrombosis and pulmonary embolism are potential added benefits of initial anticoagulation with heparin.

Low-molecular-weight heparins such as enoxaparin (Lovenox) and dalteparin (Fragmin) have not been studied extensively in patients with atrial fibrillation. However, low-molecular-weight heparin are easier to use than standard unfractionated heparin, and anticoagulation with these agents may facilitate early hospital discharge. Studies are currently being performed to evaluate anticoagulation with low-molecular-weight heparins before and after cardioversion in patients with atrial fibrillation.7

WARFARIN

Chronic warfarin therapy is commonly used to prevent thromboembolic complications in patients with atrial fibrillation. Warfarin acts by inhibiting the production of vitamin K-dependent clotting factors, thereby prolonging the prothrombin time.8

Warfarin therapy is monitored using the International Normalized Ratio (INR), which is derived from the prothrombin time. Treatment is challenging because of the narrow therapeutic window for efficacy and the risk of major bleeding (e.g., intracranial hemorrhage). Therefore, it is important to consider risk versus benefit before warfarin is prescribed. Risk factors for major bleeding include poorly controlled hypertension, propensity for falling, dietary factors, interactions with concomitant medications, and difficulty controlling the degree of anticoagulation because of patient noncompliance.9,10 To ensure efficacy and minimize harm, the INR should be kept between 2.0 and 3.0.

ASPIRIN

If bleeding risk prohibits the use of warfarin, aspirin is an appropriate alternative. Aspirin acts to inhibit platelet aggregation and thrombus formation by irreversibly inhibiting the production of cyclooxygenase and thromboxane.11 Compared with warfarin, aspirin is slightly less effective in preventing stroke in patients with atrial fibrillation, but it is safer in patients at high risk for bleeding.12

### TABLE 1

<table>
<thead>
<tr>
<th>Timing of cardioversion</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early cardioversion* in patients with atrial fibrillation for less than 48 hours</td>
<td>Heparin during cardioversion period to achieve PT of 1.5 to 2.5 times the baseline value</td>
</tr>
<tr>
<td>Early cardioversion* in patients with atrial fibrillation for more than 48 hours or an unknown duration, but without documented atrial thrombi</td>
<td>Heparin during cardioversion period to achieve PT of 1.5 to 2.5 times the baseline value</td>
</tr>
<tr>
<td>Elective cardioversion in patients with atrial fibrillation for more than 48 hours or an unknown duration</td>
<td>Warfarin (Coumadin) for 4 weeks after cardioversion to achieve target INR of 2.5 (range: 2.0 to 3.0)</td>
</tr>
<tr>
<td>Warfarin for 3 weeks before and 4 weeks after cardioversion to achieve target INR of 2.5 (range: 2.0 to 3.0)</td>
<td></td>
</tr>
</tbody>
</table>

PTT = partial thromboplastin time; INR = International Normalized Ratio.

*—Electrical or medical (pharmacologic) cardioversion.

Information from references 2, 9, and 10.

### OTHER ANTIPLATELET AGENTS

Other antiplatelet agents, such as ticlopidine (Ticlid), clopidogrel (Plavix), and the combination of aspirin and extended-release dipyridamole (Aggrenox), have not been studied in the prevention of embolic strokes in patients with atrial fibrillation. Hence, they are not recommended for use in these patients.

### Anticoagulation During Cardioversion

#### EARLY CARDIOVERSION

Early medical or electrical cardioversion may be instituted without prior anticoagulation therapy when atrial fibrillation has been present for less than 48 hours. No specific data suggest significant benefit for heparin therapy in the first 48 hours of atrial fibrillation; however, heparin is routinely used.6

If the duration of atrial fibrillation exceeds 48 hours or is unknown, transesophageal echocardiography (to rule
out atrial thrombi) followed by early cardioversion is a clinically effective strategy. Heparin therapy should be instituted during transesophageal echocardiography. If no atrial thrombi are observed, cardioversion can be performed. If atrial thrombi are detected, cardioversion should be delayed and anticoagulation continued. To decrease the risk of thrombus extension, heparin should be continued, and warfarin therapy should be initiated. Once the INR is above 2.0, heparin can be discontinued, but warfarin should be continued for four weeks (Table 1).

If cardioversion is unsuccessful and patients remain in atrial fibrillation, warfarin or aspirin may be considered for long-term prevention of stroke.

**ELECTIVE CARDIOVERSION**

Warfarin should be given for three weeks before elective electrical cardioversion is performed. After successful cardioversion, warfarin should be continued for four weeks to decrease the risk of new thrombus formation. Alternative approaches using low-molecular-weight heparins are under investigation.

If atrial fibrillation recurs or patients are at high risk for recurrent atrial fibrillation, warfarin may be continued indefinitely, or aspirin therapy may be considered. Factors that increase the risk of recurrent atrial fibrillation include an enlarged left atrium and left ventricular dysfunction.

**Long-Term Anticoagulation**

Long-term anticoagulation therapy should be considered in patients with persistent atrial fibrillation who have failed cardioversion and in patients who are not candidates for medical or electrical cardioversion. Patients with a significant risk of falling, a history of noncompliance, active bleeding, or poorly controlled hypertension should not receive long-term anticoagulation therapy because of the high risk of bleeding complications.

Several studies have evaluated the effects of aspirin, warfarin, and the combination of aspirin and warfarin for stroke prevention in patients with atrial fibrillation. Current recommendations for anticoagulant drug selection are based on the risk factors for stroke. Guidelines from the American College of Chest Physicians, the American Heart Association, and the Agency for Healthcare Research and Quality suggest that patients at highest risk for future stroke should receive warfarin and that patients at lowest risk should receive aspirin (Table 2).

Factors that significantly increase the risk for stroke include previous stroke, previous transient ischemic attack or systemic embolus, hypertension, poor left ventricular systolic function, age greater than 75 years, prosthetic heart valve, and history of rheumatic mitral valve disease. With persistent atrial fibrillation, patients older than 65 years and those with diabetes are also at increased risk. The lowest risk for stroke is in patients with atrial fibrillation who are less than 65 years of age and have no history of cardiovascular disease, diabetes, or hypertension.

Overall, warfarin therapy has been shown to reduce the absolute risk of stroke by 0.8 percent per year, compared with aspirin. In patients with a history of stroke, warfarin

<table>
<thead>
<tr>
<th>Stroke risk</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Warfarin (Coumadin) to achieve target INR of 2.5 (range: 2.0 to 3.0)</td>
</tr>
<tr>
<td>Previous stroke, transient ischemic attack, or systemic embolus</td>
<td>History of hypertension</td>
</tr>
<tr>
<td>Poor left ventricular systolic function</td>
<td>Patient age &gt; 75 years</td>
</tr>
<tr>
<td>Rheumatic mitral valve disease</td>
<td>Prosthetic heart valve</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>One risk factor: warfarin to achieve target INR of 2.5 (range: 2.0 to 3.0), or aspirin (325 mg per day)</td>
</tr>
<tr>
<td>Patient age 65 to 75 years</td>
<td>Coronary artery disease with preserved left ventricular systolic function</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Prosthetic heart valve</td>
</tr>
<tr>
<td>Coronary artery disease with preserved left ventricular systolic function</td>
<td>More than one risk factor: warfarin</td>
</tr>
<tr>
<td>Low risk</td>
<td>Aspirin (325 mg per day)</td>
</tr>
<tr>
<td>Patient age &lt; 65 years</td>
<td>Absence of cardiovascular disease</td>
</tr>
</tbody>
</table>

INR = International Normalized Ratio.

Information from references 2, 9, and 10.
Atrial Fibrillation

TABLE 3
General Recommendations for Anticoagulation in Atrial Fibrillation

Heparin therapy should be considered in hospitalized patients with atrial fibrillation persisting beyond 48 hours and in patients undergoing medical (pharmacologic) or electrical cardioversion.

Antithrombotic therapy using warfarin (Coumadin) should be given for 3 weeks before cardioversion and 4 weeks after successful cardioversion.

Patients with persistent or recurrent atrial fibrillation after attempted cardioversion should be given chronic warfarin or aspirin therapy for stroke prevention.

Warfarin is the preferred agent in patients at high risk for stroke because of previous stroke, age over 75 years, and/or poor left ventricular function.

Aspirin is the preferred agent in patients at low risk for stroke and in patients with a risk of falling, history of noncompliance, active bleeding, and/or poorly controlled hypertension.

Information from references 2, 9, and 10.

reduces the absolute risk of stroke by 7 percent per year. In recent meta-analyses, all-cause mortality was similar in patients receiving warfarin and aspirin. A meta-analysis of studies involving patients with atrial fibrillation but no history of stroke found that warfarin would prevent 30 strokes at the expense of six additional major bleeding episodes. Aspirin would prevent 17 strokes without increasing the incidence of major hemorrhage. No difference in mortality was found for anticoagulation with aspirin or warfarin.

Evidence on stroke prevention using combined low-dose warfarin and aspirin or using low-molecular-weight heparin has been inconclusive. Combination therapy is not currently recommended.

The price of stroke prevention is an added risk of major bleeding and intracranial hemorrhage. Compared with aspirin, warfarin is associated with a 0.3 percent increase in the risk of major bleeding and a 0.9 percent increase in the risk of intracranial hemorrhage. The risk of major bleeding increases dramatically with age over 75 years and when the INR is above 4.0. Blood pressure control (i.e., maintaining systolic pressure below 160 mm Hg) is imperative to reducing the risk of intracranial hemorrhage in patients taking warfarin. The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

REFERENCES

Pulmonology
Management of COPD Exacerbations

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Exacerbations of chronic obstructive pulmonary disease contribute to the high mortality rate associated with the disease. Randomized controlled trials have demonstrated the effectiveness of multiple interventions. The first step in outpatient management should be to increase the dosage of inhaled short-acting bronchodilators. Combining ipratropium and albuterol is beneficial in relieving dyspnea. Oral corticosteroids are likely beneficial, especially for patients with purulent sputum. The use of antibiotics reduces the risk of treatment failure and mortality in moderately or severely ill patients. Physicians should consider antibiotics for patients with purulent sputum and for patients who have inadequate symptom relief with bronchodilators and corticosteroids. The choice of antibiotic should be guided by local resistance patterns and the patient's recent history of antibiotic use. Hospitalized patients with exacerbations should receive regular doses of short-acting bronchodilators, continuous supplemental oxygen, antibiotics, and systemic corticosteroids. Noninvasive positive pressure ventilation or invasive mechanical ventilation is indicated in patients with worsening acidosis or hypoxemia. (Am Fam Physician. 2010;81(5):607-613, 616. Copyright © 2010 American Academy of Family Physicians.)

In patients with known chronic obstructive pulmonary disease (COPD), exacerbations occur an average of 1.3 times per year. Exacerbations range in severity from transient declines in functional status to fatal events. In the United States, exacerbations have contributed to a 102 percent increase in COPD-related mortality from 1970 to 2002 (21.4 to 43.3 deaths per 100,000 persons). Effective management of a COPD exacerbation combines relieving acute symptoms and lowering the risk of subsequent exacerbations.

Definition and Classification
Criteria for the diagnosis of COPD have been established. However, there is no validated diagnostic test or biomarker of COPD exacerbations. The American Thoracic Society (ATS) and European Respiratory Society (ERS) define an exacerbation as an acute change in a patient's baseline dyspnea, cough, or sputum that is beyond normal variability, and that is sufficient to warrant a change in therapy. The ATS and ERS classify COPD exacerbations as mild, moderate, or severe, based on the intensity of the medical intervention required to control the patient's symptoms (Table 1). In addition to the hallmark symptoms of a COPD exacerbation (cough, dyspnea, and increased sputum), systemic inflammation also causes extrapulmonary symptoms (Table 2). Factors that increase the risk of a severe exacerbation are listed in Table 3.

<table>
<thead>
<tr>
<th>Severity of exacerbation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Can be controlled with an increase in dosage of regular medications</td>
</tr>
<tr>
<td>Moderate</td>
<td>Requires treatment with systemic corticosteroids or antibiotics</td>
</tr>
<tr>
<td>Severe</td>
<td>Requires hospitalization or evaluation in the emergency department</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease.
Information from references 4 and 5.
COPD Exacerbations

Etiology
Infection of the tracheobronchial tree and air pollution (e.g., tobacco smoke, occupational exposures, ozone) are the most common identifiable causes of COPD exacerbations. One third of exacerbations have no identifiable cause. Other medical problems, such as congestive heart failure, nonpulmonary infections, pulmonary embolism, and pneumothorax, can also prompt a COPD exacerbation.²

Initial Evaluation
The initial evaluation of patients with a suspected COPD exacerbation should include a history of baseline and current symptoms, such as limitations in activities of daily living. If available, previous chest radiographs, arterial blood gas measurements, and spirometry results can help establish the baseline lung function and illustrate a typical exacerbation. Because increasing confusion is a hallmark of respiratory compromise, the physical examination should include a mental status evaluation, as well as heart and lung examinations.

Recommended diagnostic evaluation of an exacerbation depends on its severity (Table 4).⁵⁻⁶,⁸⁻¹³ Pulse oximetry should be performed in all patients. Chest

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Table 2. Symptoms of COPD Exacerbation

<table>
<thead>
<tr>
<th>Body system</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Chest tightness, Tachycardia</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Decreased exercise tolerance</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Confusion, Depression, Insomnia, Sleepiness</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Change in volume, color, or tenacity of sputum</td>
</tr>
<tr>
<td></td>
<td>Cough, Dyspnea, Tachypnea, Wheezing</td>
</tr>
<tr>
<td>Systemic</td>
<td>Fatigue, Fever, Malaise</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease.
Information from references 6 through 8.

---

Table 3. Factors that Increase Risk of Severe COPD Exacerbations

- Altered mental status
- At least three exacerbations in the previous 12 months
- Body mass index of 20 kg per m² or less
- Marked increase in symptoms or change in vital signs
- Medical comorbidities (especially cardiac ischemia, congestive heart failure, pneumonia, diabetes mellitus, or renal or hepatic failure)
- Poor physical activity levels
- Poor social support
- Severe baseline COPD (FEV₁/FVC ratio less than 0.70 and FEV₁ less than 50 percent of predicted)
- Underutilization of home oxygen therapy

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity.
Information from references 5 through 7, and 9 through 11.

---

Table 4. Diagnostic Evaluation of Patients with Suspected COPD Exacerbation

<table>
<thead>
<tr>
<th>Test</th>
<th>Potential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perform routinely</strong></td>
<td></td>
</tr>
<tr>
<td>Pulse oximetry</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td><strong>Perform if hospitalized</strong></td>
<td></td>
</tr>
<tr>
<td>Arterial blood gas measurement</td>
<td>Hypercarbia</td>
</tr>
<tr>
<td></td>
<td>Hypoxemia</td>
</tr>
<tr>
<td></td>
<td>Respiratory acidosis</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Alternate sources of dyspnea</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis</td>
</tr>
<tr>
<td></td>
<td>Polycythemia</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Cardiac ischemia</td>
</tr>
<tr>
<td>Metabolic panel</td>
<td>Electrolyte disturbances</td>
</tr>
<tr>
<td></td>
<td>Hypo- or hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Metabolic acid-base changes</td>
</tr>
<tr>
<td><strong>Consider performing, especially if patient is not responding to conventional exacerbation treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Brain natriuretic peptide measurement</td>
<td>CHF (one third of dyspnea in chronic lung disease may be attributable to CHF)</td>
</tr>
<tr>
<td>Cardiac enzyme measurement</td>
<td>Cardiac ischemia (myocardial infarction is underdiagnosed in patients with COPD)</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.
Information from references 5, 8, 9, 12, and 13.
COPD Exacerbations

radiography is appropriate in hospitalized patients and can guide treatment by revealing comorbid conditions such as congestive heart failure, pneumonia, and pleural effusion. A room air arterial blood gas (ABG) measurement should be obtained at the time of hospital admission to quantify hypercarbia and hypoxemia. Measurement of brain natriuretic peptide and serial cardiac enzyme levels should be considered in hospitalized patients, because cardiac ischemia and congestive heart failure are common comorbidities in patients with COPD.\textsuperscript{5,12,13}

Other physical examination maneuvers, laboratory tests, and assessments of cardiac function have not been proven beneficial in the treatment of COPD exacerbations.\textsuperscript{9}

**Indications for Hospitalization**

About 50 percent of COPD exacerbations are not reported to physicians, suggesting that many exacerbations are mild.\textsuperscript{14} The risk of death from an exacerbation increases with the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support.\textsuperscript{3} Patients with symptoms of respiratory distress and those at risk of distress should be admitted to the hospital to provide access to critical care personnel and mechanical ventilation. Inpatient mortality for COPD exacerbations is 3 to 4 percent.\textsuperscript{3} Patients admitted to the intensive care unit have a 43 to 46 percent risk of death within one year after hospitalization.\textsuperscript{9}

Nonambulatory patients should receive routine prophylaxis for deep venous thrombosis. Because COPD is a progressive and often fatal illness, physicians should consider discussing and documenting the patient's wishes concerning end-of-life care.

**Oxygenation and Ventilation**

Oxygen supplementation should be titrated to an oxygen saturation level of at least 90 percent. High-flow oxygen devices deliver oxygen more reliably than nasal prongs, but nasal prongs may be better tolerated. Noninvasive positive pressure ventilation (NIPPV) is indicated if adequate oxygenation or ventilation cannot be achieved using a high-flow mask.\textsuperscript{15} Patients requiring NIPPV should be monitored continuously for decompensation.

If the patient cannot be adequately oxygenated, complications, such as pulmonary embolism or edema, should be considered.\textsuperscript{8} Carbon dioxide retention is possible in moderately and severely ill patients; therefore, ABG should be measured 30 to 60 minutes after initiating oxygen supplementation.

Invasive mechanical ventilation is needed if the patient cannot tolerate NIPPV; has worsening hypoxemia, acidosis, confusion, or hypercapnia despite NIPPV; or has severe comorbid conditions, such as myocardial infarction or sepsis.\textsuperscript{5} Worsening hypercarbia and acidosis herald respiratory failure. A pH of less than 7.36 and an arterial partial pressure of carbon dioxide of more than 45 mm Hg indicate the need for mechanical ventilation.

**Therapeutic Options**

**SHORT-ACTING BRONCHODILATORS**

Inhaled short-acting bronchodilators include beta agonists (e.g., albuterol, levalbuterol [Xopenex]) and anticholinergics (e.g., ipratropium [Atrovent]). These agents improve dyspnea and exercise tolerance.\textsuperscript{6,8} The first step in treating a COPD exacerbation is increasing the dosage of albuterol delivered via metered dose inhaler or nebulizer.\textsuperscript{7} Levalbuterol is more expensive than albuterol but has similar benefits and adverse effects.\textsuperscript{16} If the patient is not already taking ipratropium, it can be added to the treatment regimen.\textsuperscript{5} Fixed-dose albuterol/ipratropium (Combivent) is available.

**CORTICOSTEROIDS**

Short courses of systemic corticosteroids increase the time to subsequent exacerbation, decrease the rate of treatment failure, shorten hospital stays, and improve hypoxemia and forced expiratory volume in one second (FEV\textsubscript{1}).\textsuperscript{1,6,9,17-20} Administration of oral corticosteroids early in an exacerbation decreases the need for hospitalization.\textsuperscript{21} A randomized controlled trial (RCT) of patients with COPD compared eight weeks of corticosteroids, two weeks of corticosteroids, and placebo; participants in the treatment groups had fewer treatment failures than those in the control group.\textsuperscript{17} Treatment failure rates were the same for long and short courses of corticosteroids.

High-dosage corticosteroid regimens (methylprednisolone [Solu-Medrol], 125 mg intravenously every six hours) and low-dosage regimens (prednisolone, 30 mg orally daily) decrease the length of hospitalization and improve FEV\textsubscript{1}, compared with placebo.\textsuperscript{17,19} An RCT comparing oral and intravenous prednisolone in equivalent dosages (60 mg daily) showed no difference in lengths of hospitalization and rates of early treatment failure.\textsuperscript{22}

Because oral corticosteroids are bioavailable, inexpensive, and convenient, parenteral corticosteroids should be reserved for patients with poor intestinal absorption or comorbid conditions that prevent safe oral intake (e.g., decreased mental status, vomiting).\textsuperscript{5,6} Inhaled corticosteroids have no role in the management of an acute exacerbation.\textsuperscript{8}
COPD Exacerbations

ANTIBIOTICS
One half of patients with COPD exacerbations have high concentrations of bacteria in their lower airways.\(^6,13\) Cultures often show multiple infectious agents, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and viruses.\(^6,25\) The use of antibiotics in moderately or severely ill

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Outpatient management</th>
<th>Inpatient management</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic, broad spectrum (e.g., amoxicillin/clavulanate [Augmentin], macrolides, second- or third-generation cephalosporins, quinolones)</td>
<td>Consider if sputum is purulent or after treatment failure</td>
<td>Use if local microbial patterns show resistance to narrow-spectrum agents</td>
<td>Decreases risk of treatment failure and mortality compared with narrow-spectrum agents</td>
</tr>
<tr>
<td>Antibiotic, narrow spectrum (e.g., amoxicillin, ampicillin, trimethoprim/sulfamethoxazole [Bactrim, Septra], doxycycline, tetracycline)</td>
<td>Consider if sputum is purulent or after treatment failure</td>
<td>Use if local microbial patterns show minimal resistance to these agents and if patient has not taken antibiotics recently</td>
<td>Believed to decrease mortality risk, but has not been tested in placebo-controlled trials</td>
</tr>
<tr>
<td>Anticholinergic, short acting (e.g., ipratropium [Atrovent])</td>
<td>May add to beta agonist; if patient is already taking an anticholinergic, increase dosage</td>
<td>May add to beta agonist; if patient is already taking an anticholinergic, increase dosage</td>
<td>Improves dyspnea and exercise tolerance</td>
</tr>
<tr>
<td>Beta agonist, short acting (e.g., albuterol, levalbuterol [Xopenex])</td>
<td>Increase dosage</td>
<td>Increase dosage</td>
<td>Improves dyspnea and exercise tolerance</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Consider using oral corticosteroids in moderately ill patients, especially those with purulent sputum</td>
<td>Use oral corticosteroids if patient can tolerate; if not suitable for oral therapy, administer intravenously</td>
<td>Decreases risk of subsequent exacerbation, rate of treatment failures, and length of hospital stay</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>NA</td>
<td>Use if patient cannot tolerate NIPPV; has worsening hypoxemia, acidosis, confusion, or hypercapnia despite NIPPV; or has comorbid conditions such as myocardial infarction or sepsis</td>
<td>Improves FEV, and hypoxemia</td>
</tr>
<tr>
<td>NIPPV</td>
<td>NA</td>
<td>Use in patients with worsening respiratory acidosis and hypoxemia when oxygenation via high-flow mask is inadequate</td>
<td>Improves respiratory acidosis and decreases respiratory rate, breathlessness, need for intubation, mortality, and length of hospital stay</td>
</tr>
<tr>
<td>Oxygen supplementation</td>
<td>NA</td>
<td>Use in patients with hypoxemia (PaO(_2), less than 60 mm Hg)</td>
<td>Decreases mortality risk</td>
</tr>
</tbody>
</table>

*COPD = chronic obstructive pulmonary disease; FEV\(_1\) = forced expiratory volume in one second; MDI = metered dose inhaler; NA = not applicable; NIPPV = noninvasive positive pressure ventilation; PaO\(_2\) = arterial partial pressure of oxygen.

*Spacer can be used with MDI to improve delivery.

Information from references 5, 6, 8, 9, 18, and 25.
patients with COPD exacerbations reduces the risk of treatment failure and death.24 Antibiotics may also benefit patients with mild exacerbations and purulent sputum.3 The optimal choice of antibiotic and length of use are unclear. Increasing microbial resistance has prompted some physicians to treat exacerbations with broad-spectrum agents, such as second- or third-generation cephalosporins, macrolides, or quinolones. One meta-analysis showed a lower risk of treatment failure with broad-spectrum antibiotics compared with narrow-spectrum antibiotics (odds ratio = 0.51; 95% confidence interval, 0.34 to 0.75), but no change in mortality rates.25 Another meta-analysis showed no difference in clinical cure rates when broad-spectrum antibiotics were administered for at least five days versus less than five days.26 There is no comparable study of narrow-spectrum antibiotics. The decision to use antibiotics and the choice of antibiotic should be guided by the patient’s symptoms (e.g., presence of purulent sputum), recent antibiotic use, and local microbial resistance patterns.18,23,25 Prophylactic, continuous use of antibiotics does not improve outcomes in patients with COPD.4

<table>
<thead>
<tr>
<th>Disadvantages/common adverse effects</th>
<th>Typical dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic resistance, diarrhea, yeast vaginitis; side effects specific to the antibiotic prescribed</td>
<td>Amoxicillin/clavulanate: 875 mg orally twice daily or 500 mg orally three times daily for 5 days. Levofoxacin (Levaquin): 500 mg daily for 5 days.</td>
</tr>
<tr>
<td>Antibiotic resistance, diarrhea, yeast vaginitis; side effects specific to the antibiotic prescribed</td>
<td>Amoxicillin: 500 mg orally three times daily for 3 to 14 days. Doxycycline: 100 mg orally twice daily for 3 to 14 days.</td>
</tr>
<tr>
<td>Dry mouth, tremor, urinary retention</td>
<td>Ipratropium: 500 mcg by nebulizer every 4 hours as needed; alternatively, 2 puffs (18 mcg per puff) by MDI every 4 hours as needed*</td>
</tr>
<tr>
<td>Headache, nausea, palpitations, tremor, vomiting</td>
<td>Albuterol: 2.5 mg by nebulizer every 1 to 4 hours as needed, or 4 to 8 puffs (90 mcg per puff) by MDI every 1 to 4 hours as needed*</td>
</tr>
<tr>
<td>Gastrointestinal bleeding, heartburn, hyperglycemia, infection, psychomotor disturbance, steroid myopathy</td>
<td>Oral prednisone: 30 to 60 mg once daily. Intravenous methylprednisolone (Solu-Medrol): 60 to 125 mg 2 to 4 times daily.</td>
</tr>
<tr>
<td>Aspiration, cardiovascular complications, need for sedation, pneumonia</td>
<td>Titrated to correct hypercarbia and hypoxemia</td>
</tr>
<tr>
<td>Expensive, poorly tolerated by some patients</td>
<td>Titrated to correct hypercarbia and hypoxemia</td>
</tr>
<tr>
<td>Hypercarbia</td>
<td>Titrated to PaO₂ &gt; 60 mm Hg or oxygen saturation ≥ 90 percent</td>
</tr>
</tbody>
</table>

OTHER TREATMENT OPTIONS

Parenteral methylxanthines, such as theophylline, are not routinely recommended for the treatment of COPD exacerbations.27 These agents are less effective and have more potentially adverse effects than inhaled bronchodilators.

Several therapies lack adequate evidence for routine use in the treatment of COPD exacerbations, including mucolytics (e.g., acetylcysteine [formerly Mucomyst]), nitric oxide, chest physiotherapy, antitussives, morphine, nedocromil, leukotriene modifiers, phosphodiesterase IV inhibitors (drug class not available in the United States), and immunomodulators (e.g., OM-85 BV, AM3 [neither drug available in the United States]).6,7 Table 5 summarizes the treatment options for acute COPD exacerbations.5,6,8,9,18,25

Preparation for Hospital Discharge

To qualify for discharge, a patient should have stable clinical symptoms and a stable or improving arterial partial pressure of oxygen of more than 60 mm Hg for at least 12 hours. The patient should not require albuterol more often than every four hours. If the patient is stable and can use a metered dose inhaler, there is no benefit to using nebulized bronchodilators.28 Patient education may improve the response to future exacerbations29; suggested topics include a general overview of COPD, available medical treatments, nutrition, advance directives, and advice about when to seek medical help. In-home support, such as an oxygen concentrator, nebulizer, and home health nurse services, should be arranged before discharge.

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**SORT: Key Recommendations for Practice**

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive positive pressure ventilation improves respiratory acidosis and decreases respiratory rate, breathlessness, need for intubation, mortality, and length of hospital stay.</td>
<td>A</td>
<td>6, 9, 15, 18</td>
<td>—</td>
</tr>
<tr>
<td>Inhaled bronchodilators (beta agonists, with or without anticholinergics) relieve dyspnea and improve exercise tolerance in patients with COPD.</td>
<td>A</td>
<td>6, 9</td>
<td>—</td>
</tr>
<tr>
<td>Short courses of systemic corticosteroids in patients with COPD increase the time to subsequent exacerbation, decrease the rate of treatment failure, shorten hospital stays, and improve FEV, and hypoxemia.</td>
<td>A</td>
<td>1, 6, 7, 9, 17-20</td>
<td>—</td>
</tr>
<tr>
<td>Low-dosage corticosteroid regimens are not inferior to high-dosage regimens in decreasing the risk of treatment failure in patients with COPD.</td>
<td>B</td>
<td>17, 19</td>
<td>—</td>
</tr>
<tr>
<td>Oral prednisolone is equivalent to intravenous prednisolone in decreasing the risk of treatment failure in patients with COPD.</td>
<td>B</td>
<td>22</td>
<td>Because they are bioavailable, inexpensive, and convenient, oral corticosteroids are recommended in patients who can safely swallow and absorb them.</td>
</tr>
<tr>
<td>Antibiotics should be used in patients with moderate or severe COPD exacerbations, especially if there is increased sputum purulence or the need for hospitalization.</td>
<td>B</td>
<td>6, 9, 18, 24</td>
<td>—</td>
</tr>
<tr>
<td>The choice of antibiotic in patients with COPD should be guided by symptoms (e.g., presence of purulent sputum), recent antibiotic use, and local microbial resistance patterns.</td>
<td>C</td>
<td>18, 23, 25</td>
<td>There is limited evidence that broad-spectrum antibiotics are more effective than narrow-spectrum antibiotics.</td>
</tr>
<tr>
<td>Smoking cessation reduces mortality and future exacerbations in patients with COPD.</td>
<td>A</td>
<td>6, 7, 30</td>
<td>—</td>
</tr>
<tr>
<td>Long-term oxygen therapy decreases the risk of hospitalization and shortens hospital stays in severely ill patients with COPD.</td>
<td>B</td>
<td>7, 32</td>
<td>—</td>
</tr>
</tbody>
</table>

*COPD = chronic obstructive pulmonary disease; FEV, = forced expiratory volume in one second.*

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.*

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**Preventing Future Exacerbations**

Smoking cessation, immunization against influenza and pneumonia, and pulmonary rehabilitation have been shown to improve function and reduce subsequent COPD exacerbations. Long-term oxygen therapy decreases the risk of hospitalization and shortens hospital stays in severely ill patients with COPD. The indications for long-acting inhaled bronchodilators and inhaled corticosteroids to improve symptoms and reduce the risk of exacerbations in patients with stable COPD are reviewed elsewhere.

The author thanks Brian Earley, DO, for assistance in the preparation of the manuscript.

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**The Author**

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Address correspondence to Ann E. Evensen, MD, FAAFP, University of Wisconsin School of Medicine and Public Health, 100 N. Nine Mound Rd., Verona, WI 53593 (e-mail: ann.evensen@uwmf.wisc.edu). Reprints are not available from the author.

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COPD Exacerbations


COPD: Management of Acute Exacerbations and Chronic Stable Disease

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Medical University of South Carolina College of Medicine, Charleston, South Carolina

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are treated with oxygen (in hypoxemic patients), inhaled beta2 agonists, inhaled anticholinergics, antibiotics and systemic corticosteroids. Methylxanthine therapy may be considered in patients who do not respond to other bronchodilators. Antibiotic therapy is directed at the most common pathogens, including Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. Mild to moderate exacerbations of COPD are usually treated with older broad-spectrum antibiotics such as doxycycline, trimethoprim-sulfamethoxazole and amoxicillin-clavulanate potassium. Treatment with augmented penicillins, fluoroquinolones, third-generation cephalosporins or aminoglycosides may be considered in patients with more severe exacerbations. The management of chronic stable COPD always includes smoking cessation and oxygen therapy. Inhaled beta2 agonists, inhaled anticholinergics and systemic corticosteroids provide short-term benefits in patients with chronic stable disease. Inhaled corticosteroids decrease airway reactivity and reduce the use of health care services for management of respiratory symptoms. Preventing acute exacerbations helps to reduce long-term complications. Long-term oxygen therapy, regular monitoring of pulmonary function and referral for pulmonary rehabilitation are often indicated. Influenza and pneumococcal vaccines should be given. Patients who do not respond to standard therapies may benefit from surgery. (Am Fam Physic 2001;64:603-12,621-2.)

Despite public education about the dangers of smoking, chronic obstructive pulmonary disease (COPD) continues to be a major medical problem and is now the fourth leading cause of death in the United States. Approximately 20 percent of adult Americans have COPD. Acute bronchitis and acute exacerbations of COPD are among the most common illnesses encountered by family physicians and account for more than 14 million physician visits annually.

To date, widespread agreement on the precise definition of COPD is lacking. The American Thoracic Society (ATS) defines COPD as a disease process involving progressive chronic airflow obstruction because of chronic bronchitis, emphysema, or both. Chronic bronchitis is defined clinically as excessive cough and sputum production on most days for at least three months during at least two consecutive years. Emphysema is characterized by chronic dyspnea resulting from the destruction of lung tissue and the enlargement of air spaces. Asthma, which also features airflow obstruction, airway inflammation and increased airway responsiveness to various stimuli, may be distinguished from COPD by reversibility of pulmonary function deficits.

Outpatient management of patients with stable COPD should be directed at improving quality of life by preventing acute exacerbations, relieving symptoms and slowing the progressive deterioration of lung function. The clinical course of COPD is characterized by chronic disability, with intermittent acute exacerbations that occur more often during the winter months. When exacerbations occur, they typically manifest as increased sputum production, more purulent sputum and worsening of dyspnea. Although infectious etiologies account for most exacerbations, exposure to allergens, pollutants...
Exacerbations of COPD typically manifest as increased sputum production, more purulent sputum and worsening of dyspnea.

or inhaled irritants may also play a role. This article reviews the management of acute exacerbations and stable COPD.

Epidemiology
COPD is one of the most serious and disabling conditions in middle-aged and elderly Americans. Cigarette smoking is implicated in 90 percent of cases and, along with coronary artery disease, is a leading cause of disability. Two thirds of patients with COPD have serious chronic dyspnea, and nearly 25 percent have profound total body pain.

COPD has a major impact on the families of affected patients. Caring for these patients at home can be difficult because of their functional limitations and anxieties about air hunger. Furthermore, patients with COPD can have frequent exacerbations that often require medical intervention. Ultimately, caregivers may have the burden of considering end-of-life decisions.

Pathophysiology
COPD is a subset of obstructive lung diseases that also includes cystic fibrosis, bronchiectasis and asthma. COPD is characterized by degeneration and destruction of the lung and supporting tissue, processes that result in emphysema, chronic bronchitis, or both. Emphysema begins with small airway disease and progresses to alveolar destruction, with a predominance of small airway narrowing and mucous gland hyperplasia.

The pathophysiology of COPD is not completely understood. Chronic inflammation of the cells lining the bronchial tree plays a prominent role. Smoking and, occasionally, other inhaled irritants, perpetuates an ongoing inflammatory response that leads to airway narrowing and hyperactivity. As a result, airways become edematous, excess mucus production occurs and cilia function poorly. With disease progression, patients have increasing difficulty clearing secretions. Consequently, they develop a chronic productive cough, wheezing and dyspnea. Bacterial colonization of the airways leads to further inflammation and the formation of diverticula in the bronchial tree.

Exacerbations of COPD can be caused by many factors, including environmental irritants, heart failure or noncompliance with medication use. Most often, however, exacerbations are the result of bacterial or viral infection (Table 1). Bacterial infection is a factor in 70 to 75 percent of exacerbations, with up to 60 percent caused by Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis. Atypical organisms such as Chlamydia pneumoniae have been implicated in about 10 percent of exacerbations. The remaining 25 to 30 percent of cases are usually caused by viruses. More serious exacerbations requiring mechanical ventilation have been associated with Pseudomonas

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**TABLE 1**

**Most Common Infectious Causes of COPD Exacerbations**

<table>
<thead>
<tr>
<th>Mild to moderate exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumonia</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>Viruses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas species</td>
</tr>
<tr>
<td>Other gram-negative enteric bacilli</td>
</tr>
</tbody>
</table>

**COPD = chronic obstructive pulmonary disease.**

species. These exacerbations are more common in patients with severe disease and a history of frequent exacerbations.13

Prognostic Indicators

Over the past 40 years, numerous studies have attempted to determine which factors influence survival in patients with COPD. Most of these studies have examined survival in stable outpatients. The long-term prognosis for patients with symptomatic chronic bronchitis is not promising. Data from the past decade indicate that 60-year-old smokers with chronic bronchitis have a 10-year mortality rate of 60 percent, which is four times higher than the mortality rate for age-matched nonsmoking asthmatics.15

Several studies have shown that the strongest predictors of mortality are older age and a decreased forced expiratory volume per second (FEV1)16,17 (Table 2).18 Younger patients with COPD generally have a lower mortality rate unless they also have α1-antitrypsin deficiency, a rare genetic abnormality that causes panlobular emphysema in younger adults. α1-antitrypsin deficiency should be suspected when COPD develops in a patient younger than 45 years who does not have a history of chronic bronchitis or tobacco use, or when multiple family members develop obstructive lung disease at an early age. Reversible changes after bronchodilator administration are a sign of less advanced disease and improved survival.

Decreases in FEV1 on serial testing are associated with increased mortality (i.e., patients with a faster decline of FEV1 have a higher rate of death). Cigarette smoking is the major risk factor associated with an accelerated decline of FEV1. Smoking cessation in patients with early COPD improves lung function initially and slows the annual decline of FEV1.19-21 Other factors found to relate positively to survival include a higher partial pressure of arterial oxygen (PaO2), a history of atopy and higher diffusion and exercise capacity.16,22-24 Factors found to decrease survival include malnutrition and weight loss, dyspnea, hypoxemia (PaO2 less than 55 mm Hg), right-sided heart failure, tachycardia at rest and increased partial pressure of arterial carbon dioxide (PaCO2 higher than 45 mm Hg).16,25-28

Recommendations for the clinical monitoring of patients with COPD include serial FEV1 measurements, pulse oximetry and timed walking of predetermined distances, although a decline in the FEV1 has the most predictive value.27 An FEV1 of less than 1 L signifies severe disease, and an FEV1 of less than 750 mL or less than 50 percent predicted on spirometric testing is associated with a poorer prognosis.

<p>| TABLE 2 |</p>
<table>
<thead>
<tr>
<th>Factors Influencing Survival in Patients with COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
</tr>
<tr>
<td>Postbronchodilator FEV1</td>
</tr>
<tr>
<td>Rate of FEV1 decline</td>
</tr>
<tr>
<td>History of atopy</td>
</tr>
<tr>
<td>Higher diffusion capacity</td>
</tr>
<tr>
<td>PaO2 level</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Hypercapnia (PaCO2 &gt; 45 mm Hg)</td>
</tr>
<tr>
<td>Right-sided heart failure</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Resting tachycardia</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume per second; PaO2 = partial pressure of arterial oxygen; PaCO2 = partial pressure of arterial carbon dioxide.

Adapted with permission from Hughes JR, Goldstein MG, Hurt RD, Schiffman S. Recent advances in the pharmacotherapy of smoking. JAMA 1998;281:72-6.
Compared with β₂ agonists, inhaled anticholinergics such as ipratropium provide the same or greater bronchodilation.

Pharmacologic Management of Exacerbations

Because no curative therapy is available, management of severe exacerbations of COPD should be directed at relieving symptoms and restoring functional capacity (Figure 1). Patients with COPD often have poor baseline functional status with few respiratory reserves. Infections can worsen their condition and lead to a quick decline in pulmonary function.

The ATS has recommended strategies for managing acute exacerbations of chronic bronchitis and emphysema. These strategies include β₂ agonists, the addition of anticholinergics (or an increase in their dosage), the intravenous administration of corticosteroids, antibiotic therapy when indicated, and the intravenous administration of methylnaloxone such as aminophylline.

Hospitalization of patients with COPD may be necessary to provide antibiotic therapy, appropriate supportive care and monitoring of oxygen status. Oxygen supplementation via external devices or mechanical ventilation may be indicated to maintain oxygen delivery to vital tissues.

OXYGENATION

Initial therapy should focus on maintaining oxygen saturation at 90 percent or higher. Oxygen status can be monitored clinically, as well as by pulse oximetry. Oxygen supplementation by nasal cannula or face mask is frequently required. With more severe exacerbations, intubation or a positive-pressure mask ventilation method (e.g., continuous positive airway pressure [CPAP]) is often necessary to provide adequate oxygenation. Such interventions are more likely to be needed when hypercapnia is present, exacerbations are frequent or altered mental status is evident.

BRONCHODILATORS

Inhaled β₂ agonists should be administered as soon as possible during an acute exacerbation of COPD. Use of a nebulizer to provide albuterol (Ventolin) or a similar agent with saline and oxygen enhances delivery of the medication to the airways.

Beta₂ agonists can be delivered effectively by metered-dose inhaler if patients are able to use proper technique, which may be difficult during an exacerbation. Salmeterol (Seretide), a long-acting β₂ agonist, has been shown to relieve symptoms in patients with COPD.

Twice-daily dosing is an added benefit and may be convenient for many patients.

Orally administered β₂ agonists have more side effects than inhaled forms. Hence, oral agents generally are not used to treat exacerbations of COPD.

ANTICHOLINERGICS

Compared with β₂ agonists, inhaled anticholinergics such as ipratropium (Atrovent) provide the same or greater bronchodilation. These agents have been shown to be beneficial in patients with COPD. Anticholinergics can be delivered by nebulizer or metered-dose inhaler. In inhaled forms, anticholinergics have few adverse effects because of minimal sys-

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Management of COPD

Establish diagnosis of COPD and assess patient's symptoms.

Treat obstruction.

Assess patient for hypoxemia.

Encourage nonpharmacologic measures: patient education, exercise, smoking cessation, nutrition, and influenza and pneumococcal vaccines.

Variable to mild symptoms

Beta₂ agonist by MDI as needed

Mild to moderate continual symptoms

Anticholinergic by MDI, or beta₂ agonist

Severe exacerbations

Increase beta₂ agonist by MDI to up to 6 to 8 puffs every 1 to 2 hours; consider nebulizer for delivery.

Increase anticholinergic by MDI to up to 6 to 8 puffs every 3 to 4 hours.

Intravenously or orally administered corticosteroid

Consider supplemental oxygen therapy if Pao₂ is < 55 mg Hg or nocturnal oxygen saturation is < 88%.

Suboptimal response

Add long-acting beta₂ agonist.

Suboptimal response

Consider methylxanthine.

Suboptimal response

Consider orally administered corticosteroid.

Improvement

No improvement

Wean patient to lowest dosage or consider inhaled corticosteroid.

Stop corticosteroid.

Assess patient's response to treatment.

Severe symptoms or impaired functional capacity

Yes

Refer patient for multidisciplinary pulmonary rehabilitation.

No

Provide patient with periodic monitoring (i.e., pulmonary function tests) and continuing care.

FIGURE 1. Algorithm for the management of chronic obstructive pulmonary disease (COPD). (MDI = metered-dose inhaler; Pao₂ = partial pressure of arterial oxygen)

temic absorption. Use of a combination product such as Ipratropium-albuterol (Combivent) may simplify the medication regimen, thereby improving compliance.

**ANTIBIOTICS**

Antibiotic therapy has been shown to have a small but important effect on clinical recovery and outcome in patients with acute exacerbations of chronic bronchitis and emphysema. Therefore, antibiotic administration should be considered at the beginning of treatment for exacerbations of COPD.

A recent meta-analysis of nine clinical trials demonstrated the benefit of antibiotic therapy in the management of COPD. Therapy for moderate acute exacerbations of chronic bronchitis and emphysema should be directed at *C. pneumoniae*, *H. influenzae* and *M. catarrhalis*, which are the most common pathogens, with *C. pneumoniae* and *Mycoplasma pneumoniae* occurring less often.

Initial outpatient management may include orally administered doxycycline (Vibramycin), trimethoprim-sulfamethoxazole (Bactrim DS, Septra DS) or amoxicillin-clavulanate potassium (Augmentin). Patients who are older than 65 years of age or have more frequent exacerbations (four or more episodes per year) may need an augmented penicillin or a fluoroquinolone.

Hospitalized patients should receive intravenous treatment with an antipseudomonal penicillin, a third-generation cephalosporin, a newer macrolide or a fluoroquinolone, as determined by local bacterial resistance patterns. In more severe exacerbations, infections with gram-negative bacteria (especially Klebsiella and Pseudomonas species) are more common. Thus, treatment should include a

**TABLE 3**

Antibiotics Commonly Used in Patients with COPD Exacerbations

<table>
<thead>
<tr>
<th>Mild to moderate exacerbations*</th>
<th>Moderate to severe exacerbations†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Doxycycline (Vibramycin), 100 mg twice daily</td>
<td>Ceftriaxone (Rocephin), 1 to 2 g IV daily</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (Bactrim DS, Septra DS), one tablet twice daily</td>
<td>Cefotaxime (Claforan), 1 g IV every 8 to 12 hours</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate potassium (Augmentin), one 500 mg/125 mg tablet three times daily</td>
<td>Cefazolin (Tizan), 1 to 2 g IV every 8 to 12 hours</td>
</tr>
<tr>
<td>or one 875 mg/125 mg tablet twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin (Biaxin), 500 mg twice daily</td>
<td>Antipseudomonal penicillins</td>
</tr>
<tr>
<td>Azithromycin (Zithromax), 500 mg initially, then 250 mg daily</td>
<td>Piperacillin-tazobactam (Zosyn), 3.375 g IV every 6 hours</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>Ticarcillin-clavulanate potassium (Timentin), 3.1 g IV every 4 to 6 hours</td>
</tr>
<tr>
<td>Levofloxacin (Levaquin), 500 mg daily</td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin (Tequin), 400 mg daily</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Moxifloxacin (Avelox), 400 mg daily</td>
<td>Levofoxacin, 500 mg IV daily</td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin, 400 mg IV daily</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside</td>
</tr>
<tr>
<td></td>
<td>Tobramycin (Tobrex), 1 mg per kg IV every 8 to 12 hours, or 5 mg per kg IV daily</td>
</tr>
</tbody>
</table>

*IV = intravenous.

*—For orally administered antibiotics, the usual duration of therapy is five to 10 days.
†—Drugs are often used in combination for synergy; IV therapy is usually employed.

Information from references 12, 28 and 29.
third-generation cephalosporin or an augmented penicillin, plus a fluoroquinolone or an aminoglycoside for synergy.

Some of the antibiotics most commonly used to treat acute exacerbations of chronic bronchitis and emphysema are listed in Table 3.\textsuperscript{12,28,29} Antibiotic resistance poses an increasing problem, especially in infections caused by \textit{S. pneumoniae}, beta-lactamase–producing \textit{H. influenzae} and \textit{M. catarrhalis}. Consequently, physicians often are forced to use broader spectrum antibiotics for empiric therapy.\textsuperscript{31} Cultures of respiratory samples are useful for guiding antibiotic therapy in patients who require mechanical ventilation.\textsuperscript{13}

**CORTICOSTEROIDS**

Short courses of systemic corticosteroids may provide important benefits in patients with exacerbations of COPD. A recent clinical trial\textsuperscript{32} involving 271 patients in Veterans Affairs hospitals showed that steroid therapy resulted in moderate improvement of clinical outcomes, with shorter hospital stays and increases in FEV\textsubscript{1}. The fact that there were no significant differences between patients treated for two weeks and those treated for eight weeks justifies the use of a shorter course of corticosteroids to reduce the occurrence of adverse effects. Adverse effects can include hyperglycemia, secondary infection and behavioral changes.\textsuperscript{33}

For severe exacerbations of COPD requiring inpatient therapy, methylprednisolone sodium succinate (Solu-Medrol) is commonly used initially. The steroid is administered intravenously in a dosage of 1 to 2 mg per kg every six to 12 hours. After two to three days of intravenous therapy, the patient can be switched to orally administered prednisone in a starting dosage of 60 mg daily for a total of two weeks of therapy. Tapering doses of prednisone should then be given over a two-week period to avoid adverse effects from sudden withdrawal.

Currently, no criteria have been established for deciding which patients benefit most from corticosteroid therapy. Thus, all patients without serious contraindications should receive systemic corticosteroids for severe exacerbations of COPD.

**METHYXANTHINES**

The use of methylxanthines such as aminophylline and theophylline is controversial in patients with exacerbations of COPD. Although methylxanthines can be of some help in improving diaphragmatic function, they are potentially toxic and are associated with serious drug effects.\textsuperscript{34}

Nevertheless, with close monitoring and attention to potential adverse effects, methylxanthines may have a place in the treatment of patients who do not respond to other bronchodilators. They may also have a role in the management of patients with chronic stable disease who cannot operate metered-dose inhalers or use other medications because of adverse drug effects.

Dosages of aminophylline ranging from 10 to 15 mg per kg daily are required to achieve therapeutic levels of 10 to 20 mg per mL. Increased serum levels can be expected with concomitant use of cimetidine (Tagamet), ciprofloxacin (Cipro) or erythromycin.\textsuperscript{35} Smoking promotes methylxanthine metabolism and decreases serum drug levels.\textsuperscript{9}

**Management of Chronic Stable Disease**

**NONPHARMACOLOGIC INTERVENTIONS**

Patients with COPD should be encouraged to adopt and maintain a healthy lifestyle. Regular exercise should be promoted, and nutritional management should be provided. Patients who smoke should stop smoking. Weight loss should be encouraged in obese patients labeled as “blue bloaters,” and nutritional supplementation should be considered in thin patients labeled as “pink puffers.” Comprehensive pulmonary rehabilitation also should be considered.

Home health care services are key to successful management in outpatient settings. Hospice care may be appropriate for selected patients.
Smoking cessation is the most important factor in the prevention or treatment of COPD.

Smoking cessation is the most important, and probably the most difficult, factor in preventing or treating COPD. Interventions available to help patients stop smoking include behavioral modification programs and pharmacologic agents such as nicotine replacement products and antidepressants (e.g., bupropion [Zyban]). A combination of pharmacologic and behavioral approaches appears to yield the best quit rates. The effectiveness of nicotine patches is improved in patients who also receive even minimal counseling from a health care provider.26

PHARMACOLOGIC INTERVENTIONS

Pharmacologic interventions used in the treatment of stable COPD include essentially the same medications for the management of acute exacerbations of chronic bronchitis and emphysema (Figure 1).28 Based on clinical evidence, at least short-term benefits result from treatment that includes inhaled beta2 agonists, inhaled anticholinergics and orally administered corticosteroids.

Anticholinergics such as ipratropium seem to provide some short-term improvement in airway obstruction but have no significant effect on the rate of decline of FEV1.29 Both short-acting and long-acting beta2 agonists produce short-term bronchodilation, relieve symptoms and improve quality of life in patients with COPD.28 The use of combined beta2 agonists and anticholinergic agents has been found to provide small additional bronchodilation compared with the use of either medication alone.29

Treatment with orally administered corticosteroids for two to four weeks has been correlated with a 20 percent or greater improvement of the baseline FEV1 in patients with COPD.30 However, no current evidence is available on the long-term effects of steroid therapy on lung function.

The effectiveness of inhaled corticosteroids remains controversial. Recent investigations in the Lung Health Study41 have shown no slowing of the rate of decline of FEV1. However, inhaled steroids seem to improve airway reactivity and respiratory symptoms, and they also have been found to decrease the use of health care services for treatment of respiratory problems.

If long-term corticosteroid therapy is contemplated, it is important to consider possible adverse effects. These include potential effects on bone mineral density, weight gain and the development of glucose intolerance.

Antibiotics are generally reserved for use in episodes of acute exacerbations of chronic bronchitis and emphysema. Theophylline may induce short-term improvement of the FEV1, but the benefits of methyloxanthine therapy should be weighed against potential side effects and possible toxicity.

HYPOXEMIA

Apart from smoking cessation, supplemental oxygen therapy is the only measure that has been shown to reduce mortality in patients with COPD.42 Supplemental oxygen should be given to patients who are hypoxicemic with a PaO2 of 55 mm Hg or less, or an oxygen saturation of 88 percent or less while sleeping.

Oxygen therapy, with delivery by nasal cannula or CPAP, may be provided in the home. Continuous long-term oxygen therapy (LTOT) should be considered in patients with a PaO2 below 55 mm Hg while at rest and awake, and in patients with accompanying polycythemia, pulmonary hypertension, right-sided heart failure or hypercapnia (Paco2 above 45 mm Hg). CPAP is generally reserved for patients with chronic hypercapnia.

One set of investigators43 found significant decreases in hospital admissions and length of hospital stays for acute exacerbations of COPD in patients treated with CPAP and LTOT. Home health care services and nursing
care are essential to assist patients in the proper use of these measures.

PULMONARY REHABILITATION

Pulmonary rehabilitation and exercise may be beneficial as adjunct treatment in patients whose symptoms are not adequately addressed with pharmacologic therapy. The goals of pulmonary rehabilitation are to enhance standard medical therapy and maximize functional capacity. Rehabilitation exercises can also improve exercise tolerance. Pulmonary rehabilitation may be most useful in patients who have limited activity and decreased quality of life.

Rehabilitation programs should include the following: patient and family education; smoking cessation; physical, nutritional and occupational therapy; and, in selected patients, LIOT or CPAP.

Long-term management and monitoring should include periodic spirometry and measurement of arterial blood gases to assess the need for supplemental LIOT or CPAP once the PaO₂ is below 55 mm Hg or the PaCO₂ is above 45 mm Hg. The use of sedatives and hypnotics should be avoided.

Annual influenza immunization is recommended for patients with COPD. Pneumococcal vaccine should be given at least once, with consideration of re-vaccination every five to 10 years.

SURGERY

Surgical interventions in COPD include lung transplantation and lung volume reduction procedures. Recent advances in immune suppression and an improved understanding of the timing of Interventions and the selection of appropriate recipients have made transplantation a realistic option.

The goal of lung volume reduction surgery is to reduce hyperinflation of one or both lungs by surgical and/or laser resection. The results of one study showed a one-year 45 percent increase in FEV₁, a 25 percent decrease in total lung capacity and an improvement of exercise performance in patients who underwent the procedure. Preliminary findings in other studies have shown improvement in dyspnea, quality of life and lung function. However, the perioperative mortality rate can be as high as 10 percent, and cost-effectiveness should be considered before lung volume reduction surgery becomes widely used.

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REFERENCES

COPD


Practice Guidelines

ACP Guideline Recommends Diagnosis and Management Strategies for COPD

LIZ HORSLEY

Am Fam Physician. 2008 Aug 1;78(3):401-402.

Guideline source: American College of Physicians
Literture search described? Yes
Evidence rating system used? Yes
Published source: Annals of Internal Medicine, November 6, 2007
Available at: http://annals.org/cgi/content/full/147/9/633

The American College of Physicians (ACP) released a guideline providing recommendations on the diagnosis and treatment of chronic obstructive pulmonary disease (COPD). The evidence and recommendations in this guideline were graded with the ACP’s clinical practice guidelines grading system and were based on a systematic evidence review published in Annals of Internal Medicine and on a Minnesota Evidence-based Practice Center evidence report sponsored by the Agency for Healthcare Research and Quality. According to the ACP, the objective of the guideline was to analyze the evidence for the following questions: What is the value of clinical examination for prediction of airflow obstruction? What is the incremental value of spirometry for case finding and diagnosis of adults who are candidates for COPD treatment? What management strategies are effective for COPD treatment?

Symptoms of COPD include chronic cough, sputum production, wheezing, dyspnea, poor exercise tolerance, and signs and symptoms of right-sided heart failure. Cigarette smoking is the most common cause of COPD. A patient with any combination of two findings (i.e., at least a 70-pack-year history of smoking, a history of COPD, or decreased breath sounds) is considered likely to have airflow obstruction. The ACP defined airflow obstruction as a forced expiratory volume in one second (FEV₁) of less than 60 percent predicted or FEV₁/forced vital capacity ratio of less than 0.60. The ACP found that the combination of factors that best excluded COPD were having never smoked, no reported wheezing, and no wheezing on examination.

Recommendations

Recommendation 1: In patients with respiratory symptoms (particularly dyspnea), spirometry should be performed to diagnose airflow obstruction. Spirometry should not be used to screen for airflow obstruction in asymptomatic persons. (Strong recommendation, moderate-quality evidence). Spirometry may help identify patients who might benefit from initiating therapy (Table 1). However, no high-quality evidence has shown that obtaining and providing spirometry results will help improve smoking cessation rates.

Recommendation 2: Treatment for stable COPD should be reserved for patients who have respiratory symptoms and FEV₁ of less than 60 percent predicted, as documented by spirometry. (Strong recommendation, moderate-quality evidence). Most likely to benefit from therapy are patients with respiratory symptoms and clinically significant airflow obstruction. Evidence does not support treating asymptomatic patients, nor does it support periodic spirometry for monitoring disease status or modifying treatment after therapy is initiated. This recommendation does not address the occasional use of bronchodilators for acute symptomatic relief.

Recommendation 3: Physicians should prescribe one of the following maintenance mono-therapies for symptomatic patients with
COPD and FEV\textsubscript{1} of less than 60 percent predicted: long-acting inhaled beta agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids. (Strong recommendation, high-quality evidence). Although there is similar effectiveness with inhaled corticosteroids and long-acting inhaled bronchodilators, these therapies differ in their adverse effects, reductions in deaths, and hospitalizations. There is not enough evidence to recommend one monotherapy over another.

Recommendation 4: Physicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV\textsubscript{1} of less than 60 percent predicted. (Weak recommendation, moderate-quality evidence). It has not been clearly established when it is better to use combination therapy over monotherapy, and studies have not consistently shown that combination therapy is better.

### TABLE 1

**Spirometric Classification of Chronic Obstructive Pulmonary Disease**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATS/ERS</strong></td>
<td></td>
</tr>
<tr>
<td>At risk*</td>
<td>FEV\textsubscript{1}/FVC ratio &gt; 0.7; FEV\textsubscript{1} ≥ 80% predicted</td>
</tr>
<tr>
<td>Mild</td>
<td>FEV\textsubscript{1}/FVC ratio ≤ 0.7; FEV\textsubscript{1} ≥ 80% predicted</td>
</tr>
<tr>
<td>Moderate</td>
<td>FEV\textsubscript{1}/FVC ratio ≤ 0.7; FEV\textsubscript{1} of 50% to 80% predicted</td>
</tr>
<tr>
<td>Severe</td>
<td>FEV\textsubscript{1}/FVC ratio ≤ 0.7; FEV\textsubscript{1} = 30% to 50% predicted</td>
</tr>
<tr>
<td>Very severe</td>
<td>FEV\textsubscript{1}/FVC ratio ≤ 0.7; FEV\textsubscript{1} &lt; 30% predicted</td>
</tr>
<tr>
<td><strong>GOLD</strong></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>FEV\textsubscript{1}/FVC ratio &lt; 0.7; FEV\textsubscript{1} ≥ 80% predicted</td>
</tr>
<tr>
<td>Moderate</td>
<td>FEV\textsubscript{1}/FVC ratio &lt; 0.7; ≤ 50% FEV\textsubscript{1} &lt; 80% predicted</td>
</tr>
<tr>
<td>Severe</td>
<td>FEV\textsubscript{1}/FVC ratio &lt; 0.7; ≤ 30% FEV\textsubscript{1} &lt; 50% predicted</td>
</tr>
<tr>
<td>Very severe</td>
<td>FEV\textsubscript{1}/FVC ratio &lt; 0.7; FEV\textsubscript{1} ≤ 30% predicted, or FEV\textsubscript{1} &lt; 50% predicted plus chronic respiratory failure</td>
</tr>
</tbody>
</table>

ATS/ERS = American Thoracic Society/European Respiratory Society; FEV\textsubscript{1} = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

*— At-risk patients are those who smoke or have exposure to pollutants; have cough, sputum, or dyspnea; or have a family history of respiratory disease.


Recommendation 5: Physicians should prescribe oxygen therapy in patients with COPD and resting hypoxemia (arterial partial pressure of oxygen [PaO\textsubscript{2}] of 55 mm Hg or less). (Strong recommendation, moderate-quality evidence). For patients with resting hypoxemia and severe airflow obstruction (i.e., FEV\textsubscript{1} of less than 30 percent predicted), use of supplemental oxygen for 15 hours or longer per day can help improve survival.

Recommendation 6: Physicians should consider prescribing pulmonary rehabilitation in symptomatic patients with COPD who have FEV\textsubscript{1} of less than 50 percent predicted. (Weak recommendation, moderate-quality evidence). Evidence shows that pulmonary rehabilitation programs reduce hospitalization rates and improve health status and exercise capacity in patients with severe airflow obstruction; however, the evidence is not clear concerning the benefits for patients with FEV\textsubscript{1} of greater than 50 percent predicted.
An Approach to Interpreting Spirometry

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University of Rochester School of Medicine and Dentistry, Rochester, New York

Spirometry is a powerful tool that can be used to detect, follow, and manage patients with lung disorders. Technology advancements have made spirometry much more reliable and relatively simple to incorporate into a routine office visit. However, interpreting spirometry results can be challenging because the quality of the test is largely dependent on patient effort and cooperation, and the interpreter’s knowledge of appropriate reference values. A simplified and stepwise method is key to interpreting spirometry. The first step is determining the validity of the test. Next, the determination of an obstructive or restrictive ventilatory pattern is made. If a ventilatory pattern is identified, its severity is graded. In some patients, additional tests such as static lung volumes, diffusing capacity of the lung for carbon monoxide, and bronchodilator challenge testing are needed. These tests can further define lung processes but require more sophisticated equipment and expertise available only in a pulmonary function laboratory. (Am Fam Physician 2004;69:1107-14. Copyright © 2004 American Academy of Family Physicians.)

Chronic obstructive pulmonary disease (COPD) is the most common respiratory disease and the fourth leading cause of death in the United States. Despite preventive efforts, the number of new patients with COPD has doubled in the past decade, and this trend is likely to continue. Evidence indicates that a patient’s history and physical examination are inadequate for diagnosing mild and moderate obstructive ventilatory impairments. Although a complete pulmonary function test provides the most accurate objective assessment of lung impairment, spirometry is the preferred test for the diagnosis of COPD because it can obtain adequate information in a cost-effective manner.

A great deal of information can be obtained from a spirometry test; however, the results must be correlated carefully with clinical and roentgenographic data for optimal clinical application. This article reviews the indications for use of spirometry, provides a stepwise approach to its interpretation, and indicates when additional tests are warranted.

Background

The National Health Survey of 1988 to 1994 found high rates of undiagnosed and untreated COPD in current and former smokers. Population-based studies have identified vital capacity (VC) as a powerful prognostic indicator in patients with COPD. The Framingham study identified a low forced vital capacity (FVC) as a risk factor for premature death. The Third National Health and Nutritional Examination Survey and the multicenter Lung Health Study showed potential benefits for patients with early identification, intervention, and treatment of COPD. The Lung Health Study was the first study to show that early identification and intervention in smokers could affect the natural history of COPD. These surveys also showed that simple spirometry could detect mild airflow obstruction, even in asymptomatic patients.

Increased public awareness of COPD led to the formation of the National Lung Health Education Program (NLHEP) as part of a national strategy to combat chronic lung disease. The World Health Organization and the U.S. National Heart, Lung, and Blood Institute recently published the Global Initiative for Chronic Obstructive Lung Disease to increase awareness of the global burden of COPD.
Normal lungs can empty more than 80 percent of their volume in six seconds or less.

and to provide comprehensive treatment guidelines aimed at decreasing COPD-related morbidity and mortality.\textsuperscript{10}

**Spirometry Measurements and Terminology**

Spirometry measures the rate at which the lung changes volume during forced breathing maneuvers. Spirometry begins with a full inhalation, followed by a forced expiration that rapidly empties the lungs.Expiration is continued for as long as possible or until a plateau in exhaled volume is reached. These efforts are recorded and graphed. (A glossary of terms used in this article can be found in Table 1.)

Lung function is physiologically divided into four volumes: expiratory reserve volume, inspiratory reserve volume, residual volume, and tidal volume. Together, the four lung volumes equal the total lung capacity (TLC). Lung volumes and their combinations measure various lung capacities such as functional residual capacity (FRC), inspiratory capacity, and VC. Figure 1\textsuperscript{11} shows the different volumes and capacities of the lung.

The most important spirometric maneuver is the FVC. To measure FVC, the patient inhales maximally, then exhales as rapidly and as completely as possible. Normal lungs generally can empty more than 80 percent of their volume in six seconds or less. The forced expiratory volume in one second (FEV\textsubscript{1}) is the volume of air exhaled in the first second of the FVC maneuver. The FEV\textsubscript{1}/FVC ratio is expressed as a percentage (e.g., FEV\textsubscript{1} of 0.5 L divided by FVC of 2.0 L gives a FEV\textsubscript{1}/FVC ratio).

**TABLE 1**

**Glossary**

<table>
<thead>
<tr>
<th>Spirometric values</th>
<th>Lung volumes</th>
<th>Lung capacities</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC—Forced vital capacity; the total volume of air that can be exhaled during a maximal forced expiration effort.</td>
<td>ERV—Expiratory reserve volume; the maximal volume of air exhaled from end-expiration.</td>
<td>FRC—Functional residual capacity; the volume of air in the lungs at resting end-expiration.</td>
</tr>
<tr>
<td>FEV\textsubscript{1}—Forced expiratory volume in one second; the volume of air exhaled in the first second after a maximal inhalation.</td>
<td>IRV—Inspiratory reserve volume; the maximal volume of air inhaled from end-inspiration.</td>
<td>IC—Inspiratory capacity; the maximal volume of air that can be inhaled from the resting expiratory level.</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC ratio—The percentage of the FVC expired in one second.</td>
<td>RV—Residual volume; the volume of air remaining in the lungs after a maximal exhalation.</td>
<td>TLC—Total lung capacity; the volume of air in the lungs at maximal inflation.</td>
</tr>
<tr>
<td>FEV\textsubscript{2}/FVC—Forced expiratory volume in two seconds.</td>
<td>V\textsubscript{T}—Tidal volume; the volume of air inhaled or exhaled during each respiratory cycle.</td>
<td>VC—Vital capacity; the largest volume measured on complete exhalation after full inspiration.</td>
</tr>
</tbody>
</table>

**Lung Volumes and Capacities**

| Maximal inspiratory level | Maximal expiratory level |

![Figure 1. Lung volumes and capacities.](image)

of 25 percent). The absolute ratio is the value used in interpretation, not the percent predicted.

Some portable office spirometers replace the 
FVC with the FEV for greater patient and technician ease. The parameter is based on a 
six-second maneuver, which incorporates a standard time frame to decrease patient variability 
and the risk of complications. One of the pitfalls of using this type of spirometer is that it 
must be calibrated for temperature and water vapor. It should be used with caution in patients 
with advanced COPD because of its inability to detect very low volumes or flows. However, the 
FEV/FEV ratio provides accurate surrogate measure for the FEV/FVC ratio. The reported 
FEV and FEV values should be rounded to the nearest 0.1 L and the percent predicted and the 
FEV/FEV ratio to the nearest integer.

Different spirometric and flow volume curves are shown in Figure 2. It is important to 
understand that the amount exhaled during the first second is a constant fraction of the FVC, 
regardless of lung size. The significance of the FEV/FVC ratio is twofold. It quickly identifies 
patients with airway obstruction in whom the FVC is reduced, and it identifies the cause of a 
low FEV.

Normal spirometric parameters are shown in Table 2.

**Indications for Office Spirometry**

Spirometry is designed to identify and quantify functional abnormalities of the respiratory system. The NLHEP recommends that primary care physicians perform spirometry in patients 45 years of age or older who are

<table>
<thead>
<tr>
<th>Pulmonary function test</th>
<th>Normal value (95 percent confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>80% to 120%</td>
</tr>
<tr>
<td>FVC</td>
<td>80% to 120%</td>
</tr>
<tr>
<td>Absolute FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ratio</td>
<td>Within 5% of the predicted ratio</td>
</tr>
<tr>
<td>TLC</td>
<td>80% to 120%</td>
</tr>
<tr>
<td>FRC</td>
<td>75% to 120%</td>
</tr>
<tr>
<td>RV</td>
<td>75% to 120%</td>
</tr>
<tr>
<td>DLCO</td>
<td>&gt; 60% to &lt; 120%</td>
</tr>
</tbody>
</table>

_DLCO = diffusing capacity of lung for carbon monoxide._

Adapted with permission from Salzman SH. Pulmonary function testing: tips on how to interpret the results. _J Resp Dis_ 1989;20:812.

### TABLE 3
**Indications for Spirometry**

<table>
<thead>
<tr>
<th>Detecting pulmonary disease</th>
<th>Contraindications to Use of Spirometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of pulmonary symptoms</td>
<td>Acute disorders affecting test performance (e.g., vomiting, nausea, vertigo)</td>
</tr>
<tr>
<td>Chest pain or orthopnea</td>
<td>Hemoptysis of unknown origin (FVC maneuver may aggravate underlying condition)</td>
</tr>
<tr>
<td>Cough or phlegm production</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Dyspnea or wheezing</td>
<td>Recent abdominal or thoracic surgery</td>
</tr>
<tr>
<td>Physical findings</td>
<td>Recent eye surgery (increases in intraocular pressure during spirometry)</td>
</tr>
<tr>
<td>Chest wall abnormalities</td>
<td>Recent myocardial infarction or unstable angina</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Thoracic aneurysms (risk of rupture because of increased thoracic pressure)</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td></td>
</tr>
<tr>
<td>Finger clubbing</td>
<td></td>
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<tr>
<td>Abnormal laboratory findings</td>
<td></td>
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<tr>
<td>Blood gases</td>
<td></td>
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<tr>
<td>Chest radiograph</td>
<td></td>
</tr>
</tbody>
</table>

### Assessing severity or progression of disease
- Pulmonary diseases
  - Chronic obstructive pulmonary disease
  - Cystic fibrosis
  - Interstitial lung diseases
  - Sarcoidosis
- Cardiac diseases
  - Congestive heart failure
  - Congenital heart disease
  - Pulmonary hypertension
- Neurovascular diseases
  - Amyotrophic lateral sclerosis
  - Guillain-Baré syndrome
  - Multiple sclerosis
  - Myasthenia gravis

### Risk stratification of patients for surgery
- Thoracic surgeries
  - Lobectomy
  - Pneumonectomy
- Cardiac surgeries
  - Coronary bypass
  - Correction of congenital abnormalities
  - Valvular surgery
- Organ transplantation
- General surgical procedures
  - Cholecystectomy
  - Gastric bypass

### Evaluating disability or impairment
- Social Security or other compensation programs
- Legal or insurance evaluations

Current or former smokers; in patients who have a prolonged or progressive cough or sputum production; or in patients who have a history of exposure to lung irritants. Other indications for spirometry are to determine the strength and function of the chest, follow disease progression, and obtain baseline measurements before prescribing drugs that are potentially toxic to the lungs, such as amiodarone (Cordarone) and bleomycin (Blenoxane). Spirometry also is helpful in preoperative risk assessment for many surgeries and often is used in workers’ compensation and disability claims to assess occupational exposure to inhalation hazards. Tables 3 and 4 list indications and contraindications for spirometry.

### Interpreting Spirometry Results
Spirometry requires considerable patient effort and cooperation. Therefore, results must be assessed for validity before they can be interpreted. Inadequate patient effort can lead to misdiagnosis and inappropriate treatment. An algorithm for interpreting spirometry results is given in Figure 3.

The clinical context of the test is important because parameters in patients with mild disease can overlap with values in healthy persons. Normal spirometry values may vary, and interpr-
tation of results relies on the parameters used. The normal ranges for spirometry values vary depending on the patient's height, weight, age, sex, and racial or ethnic background. Predicted values for lung volumes may be inaccurate in very tall patients or patients with missing lower extremities. FEV₁ and FVC are greater in whites compared with blacks and Asians. FVC and VC values vary with the position of the patient. These variables can be 7 to 8 percent greater in patients

**Interpreting Spirometry Results**

*Determine if the test is interpretable.*

**Assess FVC, FEV₁, and absolute FEV₁/FVC ratio.**

- **FVC decreased, FEV₁ decreased or normal, absolute FEV₁/FVC > 0.7**
  - **Restrictive ventilatory impairment**
    - **Referral to pulmonary laboratory for static lung volumes**
      - **Dlco, DlcoVA, ERV**
    - **Check MVV.**
      - **MVV < 40 × FEV₁**
        - **Consider poor patient effort, neuromuscular disease, possible airway lesion.**
      - **MVV > 40 × FEV₁**
        - **Referral to pulmonary laboratory for static lung volumes.**
          - **Determine severity.**

- **FVC normal or decreased, FEV₁ decreased, absolute FEV₁/FVC < 0.7**
  - **Obstructive ventilatory impairment**
    - **Perform bronchodilator challenge test.**
      - **More than 12 percent increase in FEV₁ and 200 mL increase in FVC or FEV₁, or 15 to 25 percent increase in FEF₂₅₋₇₅%**
        - **Yes**
          - **Reversible airway disease**
            - **Determine severity.**
        - **No**
          - **Obstructive ventilatory impairment**
            - **Determine severity.**

**FIGURE 3. Algorithm for interpreting results of spirometry. (Dlco = diffusing capacity of lung for carbon monoxide; VA = alveolar volume.)**
The absolute FEV₁/FVC ratio distinguishes obstructive from restrictive spirometry patterns.

who are sitting during the test compared with patients who are supine. FVC is about 2 percent greater in patients who are standing compared with patients who are supine.

To determine the validity of spirometric results, at least three acceptable spiograms must be obtained. In each test, patients should exhale for at least six seconds and stop when there is no volume change for one second. The test session is finished when the difference between the two largest FVC measurements and between the two largest FEV₁ measurements is within 0.2L. If both criteria are not met after three maneuvers, the test should not be interpreted. Repeat testing should continue until the criteria are met or until eight tests have been performed.²⁶

Figure 4 shows normal flow-volume and time-volume curves. Notice that the lines of the flow-volume curve are free of glitches and irregularities. The volume-time curve extends longer than six seconds, and there are no signs of early termination or cutoff.

If the test is valid, the second step is to determine whether an obstructive or restrictive ventilatory pattern is present. When the FVC and FEV₁ are decreased, the distinction between an obstructive and restrictive ventilatory pattern depends on the absolute FEV₁/FVC ratio. If the absolute FEV₁/FVC ratio is normal or increased, a restrictive ventilatory impairment may be present. However, to make a definitive diagnosis of restrictive lung disease, the patient should be referred to a pulmonary laboratory for static lung volumes. If the TLC is less than 80 percent, the pattern is restrictive, and diseases such as pleural effusion, pneumonia, pulmonary fibrosis, and congestive heart failure should be considered.

A reduced FEV₁ and absolute FEV₁/FVC ratio indicates an obstructive ventilatory pattern, and bronchodilator challenge testing is recommended to detect patients with reversible airway obstruction (e.g., asthma). A bronchodilator is given, and spirometry is repeated after several minutes. The test is positive if the FEV₁ increases by at least 12 percent and the FVC increases by at least 200 mL. The patient should not use any bronchodilator for at least 48 hours before the test. A negative bronchodilator response does not completely exclude the diagnosis of asthma.

The mid-expiratory flow rate (FEF25-75%) is the average forced expiratory flow rate over the middle 50 percent of the FVC. It can help in the diagnosis of an obstructive ventilatory pattern. Because it is dependent on FVC, the FEF25-75% is highly variable. In the correct clinical situation, a reduction in FEF25-75% of less than 60 percent of that predicted and an FEV₁/FVC ratio in the low to normal range may confirm airway obstruction.²⁹

The maximal voluntary ventilation (MVV) maneuver is another test that can be used to confirm obstructive and restrictive conditions. The patient is instructed to breathe as hard and fast as possible for 12 seconds. The result is extrapolated to 60 seconds and reported in liters per minute. MVV generally is approximately equal to the FEV₁ × 40. A low MVV can occur in obstructive disease but is more common in restrictive conditions. If the MVV is low but FEV₁ and FVC are normal, poor patient

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The final step in interpreting spirometry is to determine if additional testing is needed to further define the abnormality detected by spirometry. Measurement of static lung volumes, including FRC, is required to make a definitive diagnosis of restrictive lung disease.

Final Comment

Basic spirometry can be performed in the family physician's office with relative ease and inexpensive equipment. In most cases, office spirometry provides an adequate assessment of pulmonary function. In addition, spirometry may be used to address major issues in clinical management and health screening.

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REFERENCES

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Spirometry


Diagnostic Approach to Pleural Effusion in Adults

JOSE M. PORCEL, M.D., Arnau de Vilanova University Hospital, Lleida, Spain
RICHARD W. LIGHT, M.D., Saint Thomas Hospital, Nashville, Tennessee

The first step in the evaluation of patients with pleural effusion is to determine whether the effusion is a transudate or an exudate. An exudative effusion is diagnosed if the patient meets Light’s criteria. The serum to pleural fluid protein or albumin gradients may help better categorize the occasional transudate misidentified as an exudate by these criteria. If the patient has a transudative effusion, therapy should be directed toward the underlying heart failure or cirrhosis. If the patient has an exudative effusion, attempts should be made to define the etiology. Pneumonia, cancer, tuberculosis, and pulmonary embolism account for most exudative effusions. Many pleural fluid tests are useful in the differential diagnosis of exudative effusions. Other tests helpful for diagnosis include helical computed tomography and thoracoscopy. (Am Fam Physician 2006;73:1211-20. Copyright © 2006 American Academy of Family Physicians.)

Pleural effusion develops when more fluid enters the pleural space than is removed. Potential mechanisms of pleural fluid accumulation include: increased interstitial fluid in the lungs secondary to increased pulmonary capillary pressure (i.e., heart failure) or permeability (i.e., pneumonia); decreased intrapleural pressure (i.e., atelectasis); decreased plasma oncotic pressure (i.e., hypoalbuminemia); increased pleural membrane permeability and obstructed lymphatic flow (e.g., pleural malignancy or infection); diaphragmatic defects (i.e., hepatic hydrothorax); and thoracic duct rupture (i.e., chylothorax). Although many different diseases may cause pleural effusion, the most common causes in adults are heart failure, malignancy, pneumonia, tuberculosis, and pulmonary embolism, whereas pneumonia is the leading etiology in children.1,2

Initial Evaluation of Pleural Effusion

The history and physical examination are critical in guiding the evaluation of pleural effusion (Table 1). Signs and symptoms of an effusion vary depending on the underlying disease, but dyspnea, cough, and pleuritic chest pain are common. Chest examination of a patient with pleural effusion is notable for dullness to percussion, decreased or absent tactile fremitus, decreased breath sounds, and no voice transmission. Posteroanterior and lateral chest radiographs usually confirm the presence of a pleural effusion, but if doubt exists, ultrasound or computed tomography (CT) scans are definitive for detecting small effusions and for differentiating pleural fluid from pleural thickening.3 Small amounts of pleural fluid not readily seen on the standard frontal view may be recognized in a lateral decubitus view (Figures 1a and 1b). On a posteroanterior radiograph, free pleural fluid may blunt the costophrenic angle; form a meniscus laterally; or hide in a subpulmonic location, simulating an elevated hemidiaphragm.

Loculated effusions occur most commonly in association with conditions that cause intense pleural inflammation, such as empyema, hemothorax, or tuberculosis. Occasionally, a focal intrathoracic fluid collection may look like a lung mass. This situation most commonly is seen in patients with heart failure. The disappearance of the apparent mass when the heart failure is treated definitively establishes the diagnosis of pseudotumor (i.e., vanishing tumor). Heart failure is by far the most common cause of bilateral pleural effusion, but if cardiomegaly is not present, other causes such as malignancy should be investigated.

Large effusions may opacify the entire hemithorax and displace mediastinal structures toward the opposite side. More than
SORT KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendations</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracentesis should be performed in all patients with more than a minimal pleural effusion unless clinically evident heart failure is present.</td>
<td>C</td>
<td>5, 33</td>
</tr>
<tr>
<td>An effusion is exudative if it meets any of the following three criteria: (1) the ratio of pleural fluid protein to serum protein is greater than 0.5, (2) the pleural fluid lactate dehydrogenase (LDH) to serum LDH ratio is greater than 0.6, (3) pleural fluid LDH is greater than two thirds of the upper limit of normal for serum LDH.</td>
<td>C</td>
<td>1, 5, 8</td>
</tr>
<tr>
<td>The serum-effusion protein or albumin gradients can be used to diagnose the presence of a transudate after diuresis.</td>
<td>C</td>
<td>1, 9, 10</td>
</tr>
<tr>
<td>In a lymphocyte-predominant exudate, a pleural fluid adenosine deaminase greater than 40 U per L (667 nkat per L) indicates that the most likely diagnosis is tuberculosis.</td>
<td>C</td>
<td>26-28</td>
</tr>
<tr>
<td>If malignancy is a concern and cytologic examination is nondiagnostic, thoracoscopy should be considered.</td>
<td>C</td>
<td>5, 39, 40</td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1135 or http://www.aafp.org/afpsort.xml.

TABLE 1
Causes of Pleural Effusions: History, Signs, and Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Potential causes of the pleural effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
</tr>
<tr>
<td>Abdominal surgical procedures</td>
<td>Postoperative pleural effusion, subphrenic abscess, pulmonary embolism</td>
</tr>
<tr>
<td>Alcohol abuse or pancreatic disease</td>
<td>Pancreatic effusion</td>
</tr>
<tr>
<td>Artificial pneumothorax therapy</td>
<td>Tuberculous empyema, pyothorax-associated lymphoma, trapped lung</td>
</tr>
<tr>
<td>Asbestos exposure</td>
<td>Mesothelioma, benign asbestos pleural effusion</td>
</tr>
<tr>
<td>Cancer</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Cardiac surgery or myocardial injury</td>
<td>Pleural effusion secondary to coronary artery bypass graft surgery or Dressler’s syndrome</td>
</tr>
<tr>
<td>Chronic hemodialysis</td>
<td>Heart failure, uremic pleuritis</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Hepatic hydrothorax, spontaneous bacterial empyema</td>
</tr>
<tr>
<td>Childbirth</td>
<td>Postpartum pleural effusion</td>
</tr>
<tr>
<td>Esophageal dilatation or endoscopy</td>
<td>Pleural effusion secondary to esophageal perforation</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>Pneumonia, tuberculosis, primary effusion lymphoma, Kaposi sarcoma</td>
</tr>
<tr>
<td>Medication use</td>
<td>Medication-induced pleural disease</td>
</tr>
<tr>
<td>Remote inflammatory pleural process</td>
<td>Trapped lung</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid pleuritis, pseudochylopleural</td>
</tr>
<tr>
<td>Superovulation with gonadotrophins</td>
<td>Pleural effusion secondary to ovarian hyperstimulation syndrome</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Lupus pleuritis, pneumonia, pulmonary embolism</td>
</tr>
<tr>
<td>Trauma</td>
<td>Hemothorax, chylothorax, duropleural fistula</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>Hepatic hydrothorax, ovarian cancer, Meigs’ syndrome</td>
</tr>
<tr>
<td>Dyspnea on exertion, orthopnea, peripheral edema, elevated jugular venous pressure</td>
<td>Heart failure, constrictive pericarditis</td>
</tr>
<tr>
<td>Pericardial friction rub</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Unilateral lower extremity swelling</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Yellowish nails, lymphedema</td>
<td>Pleural effusion secondary to yellow nail syndrome*</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Pneumonia, empyema, tuberculosis</td>
</tr>
<tr>
<td>Hemoptyisis</td>
<td>Lung cancer, pulmonary embolism, tuberculosis</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Malignancy, tuberculosis, anaerobic bacterial pneumonia</td>
</tr>
</tbody>
</table>

*—Yellow nail syndrome results from an abnormality of lymphatics and consists of the triad of yellow nails, lymphedema, and pleural effusion.
Pleural Effusion

Thoracentesis

Except for patients with obvious heart failure, thoracentesis should be performed in all patients with more than a minimal pleural effusion (i.e., larger than 1 cm height on lateral decubitus radiograph, ultrasound, or CT) of unknown origin. In the context of heart failure, diagnostic thoracentesis is only indicated if any of the following atypical circumstances is present: (1) the patient is febrile or has pleuritic chest pain; (2) the patient has a unilateral effusion or effusions of markedly disparate size; (3) the effusion is not associated with cardiomegaly, or (4) the effusion fails to respond to management of the heart failure.

Thoracentesis is urgent when it is suspected that blood (i.e., hemothorax) or pus (i.e., empyema) is in the pleural space, because immediate tube thoracostomy is indicated in these situations. If difficulty in obtaining pleural fluid is encountered because the effusion is small or loculated, ultrasound-guided thoracentesis minimizes the risk for iatrogenic pneumothorax. In most instances, analysis of the pleural fluid yields valuable diagnostic information or definitively establishes the cause of the pleural effusion. This is the case when malignant cells, microorganisms, or chyle are found, or when a transudative effusion is found in the setting of heart failure or cirrhosis.

Observing the gross appearance of the pleural fluid may suggest a particular cause. For example, turbidity of the pleural fluid can be caused either by cells and debris (i.e., empyema) or by a high lipid level (i.e., chylothorax). A uniformly blood-stained fluid (i.e., hematocrit greater than 1 percent) narrows the differential diagnosis of the pleural effusion to malignancy, trauma (including recent cardiac surgery), pulmonary embolism, and pneumonia. If the hematocrit of the pleural fluid exceeds half the simultaneous peripheral blood hematocrit, the patient has hemothorax.

Although common, chest radiography is not necessary after thoracentesis unless air is obtained during the procedure; the patient develops symptoms such as dyspnea, cough, or chest pain; or tactile fremitus is lost over the upper part of the aspirated hemothorax.
Pleural Effusion

Analysis of Pleural Fluid

Pleural effusions are either transudates or exudates based on the biochemical characteristics of the fluid, which usually reflect the physiologic mechanism of its formation.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Leading Causes of Pleural Effusion in the United States*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Annual Incidence</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>500,000</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>300,000</td>
</tr>
<tr>
<td>Cancer</td>
<td>200,000</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>150,000</td>
</tr>
<tr>
<td>Viral disease</td>
<td>100,000</td>
</tr>
<tr>
<td>Coronary-artery bypass surgery</td>
<td>60,000</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>50,000</td>
</tr>
</tbody>
</table>

*—based on analysis of patients subjected to thoracentesis


TRANSUDATIVE EFFUSIONS

Transudates result from imbalances in hydrostatic and oncotic forces and are caused by a limited number of recognized clinical conditions such as heart failure and cirrhosis. Less common causes include nephrotic syndrome, atelectasis, peritoneal dialysis, constrictive pericarditis, superior vena caval obstruction, and urinotherax. Transudative effusions usually respond to treatment of the underlying condition (e.g., diuretic therapy).

EXUDATIVE EFFUSIONS

In contrast, exudates occur when the local factors influencing the accumulation of pleural fluid are altered. Exudates present more of a diagnostic dilemma. Pneumonia, malignancy, and thromboembolism account for most exudative effusions in the United States (Table 2).1

In clinical practice, exudative effusions can be separated effectively from transudative effusions using Light’s criteria. These criteria classify an effusion as exudate if one or more of the following are present: (1) the ratio of pleural fluid protein to serum protein is greater than 0.5, (2) the ratio of pleural fluid lactate dehydrogenase (LDH) to serum LDH is greater than 0.6, or (3) the pleural fluid LDH level is greater than two thirds of the upper limit of normal for serum LDH.

Light’s criteria are nearly 100 percent sensitive at identifying exudates, but approximately 20 percent of patients with pleural effusion caused by heart failure may fulfill the criteria for an exudative effusion after receiving diuretics.6 In these circumstances, if the difference between protein levels in the serum and the pleural fluid is greater than 3.1 g per dL, the patient should be classified as having a transudative effusion.9 A serum-effusion albumin gradient greater than 1.2 g per dL also can indicate that the pleural effusion is most likely a true transudative effusion.10 However, neither protein nor albumin gradients alone should be the primary test used to distinguish transudative effusions from exudative effusions because they result in the incorrect classification of a significant number of exudates. This lower sensitivity may be caused by the fact that a single test is employed as opposed to

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Likelihood of Exudates Using the Pleural Fluid to Serum Protein Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid to serum protein ratio</td>
<td>Likelihood ratio*</td>
</tr>
<tr>
<td>≥ 0.71</td>
<td>93.03</td>
</tr>
<tr>
<td>0.66 to 0.70</td>
<td>31.81</td>
</tr>
<tr>
<td>0.61 to 0.65</td>
<td>4.24</td>
</tr>
<tr>
<td>0.56 to 0.60</td>
<td>3.58</td>
</tr>
<tr>
<td>0.51 to 0.55</td>
<td>1.50</td>
</tr>
<tr>
<td>0.46 to 0.50</td>
<td>0.48</td>
</tr>
<tr>
<td>0.41 to 0.45</td>
<td>0.27</td>
</tr>
<tr>
<td>0.36 to 0.40</td>
<td>0.15</td>
</tr>
<tr>
<td>0.31 to 0.35</td>
<td>0.07</td>
</tr>
<tr>
<td>≤0.30</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* A likelihood ratio of 1 does not change the likelihood of disease. Likelihood ratios above 1 increase the risk of disease and likelihood ratios below 1 reduce the risk of disease (see http://www.aafp.org/afppapers.xml)

the three-test combination of the standard criteria described above. Another approach to the classification of pleural effusions is to apply continuous or multilevel likelihood ratios (Table 311).

FURTHER TESTING FOR EXUDATES

In patients with exudative effusion, the following pleural fluid tests should be performed on fluid obtained during the initial thoracentesis: cell counts and differential, glucose, adenosine deaminase (ADA), and cytologic analysis. Bacterial cultures and pH should be tested if infection is a concern12 (Tables 4,5,13,12 and 5,13-24).

Pleural fluid for total white blood cell (WBC) count and differential cell count should be sent in an anticoagulated tube.

**Table 4**

<table>
<thead>
<tr>
<th>Test</th>
<th>Test value</th>
<th>Suggested diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine deaminase (ADA)</td>
<td>&gt; 40 U per L</td>
<td>Tuberculosis (&gt; 90 percent), empyema (60 percent), complicated parapneumonic effusion (30 percent), malignancy (5 percent), rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(667 nkat per L)</td>
<td></td>
<td>in the United States, ADA is not routinely requested because of the low prevalence of tuberculous pleurisy.</td>
</tr>
<tr>
<td>Cytology</td>
<td>Present</td>
<td>Malignancy</td>
<td>Actively dividing mesothelial cells can mimic an adenocarcinoma.</td>
</tr>
<tr>
<td>Glucose</td>
<td>&lt; 60 mg per dl</td>
<td>Complicated parapneumonic effusion or empyema, tuberculosis</td>
<td>in general, pleural fluids with a low glucose level also have low pH and high LDH levels.</td>
</tr>
<tr>
<td></td>
<td>(3.3 mmol per L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>&gt; Two thirds of upper limits of normal for serum LDH</td>
<td>Any condition causing an exudate</td>
<td>Very high levels of pleural fluid LDH (&gt; 1,000 U per L) typically are found in patients with complicated parapneumonic pleural effusion and in about 40 percent of those with tuberculous pleurisy.</td>
</tr>
<tr>
<td>LDH fluid to serum ratio</td>
<td>&gt; 0.6</td>
<td>Any condition causing an exudate</td>
<td>Most patients who meet the criteria for an exudative effusion with LDH but not with protein levels have either parapneumonic effusions or malignancy.</td>
</tr>
<tr>
<td>Protein fluid to serum ratio</td>
<td>&gt; 0.5</td>
<td>Any condition causing an exudate</td>
<td>A pleural fluid protein level &gt; 3 mg per dl suggests an exudate, but when taken alone this parameter misclassifies more than 10 percent of exudates and 15 percent of transudates.</td>
</tr>
<tr>
<td>Red blood cell count</td>
<td>&gt; 100,000 per mm³</td>
<td>Malignancy, trauma, parapneumonic effusion, pulmonary embolism</td>
<td>A fluid hematocrit &lt; 1 percent is nonsignificant.13</td>
</tr>
<tr>
<td></td>
<td>(100 × 10⁶ per L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count and differential</td>
<td>&gt; 10,000 per mm³</td>
<td>Emphyema, other exudates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10 × 10³ per L)</td>
<td>(uncommon)</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>&gt; 10 percent</td>
<td>Not diagnostic</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&gt; 50 percent</td>
<td>Malignancy, tuberculosis, pulmonary embolism, coronary artery bypass surgery</td>
<td>Pleural fluid lymphocytosis &gt; 90 percent suggests tuberculosis or lymphoma</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>&gt; 50 percent</td>
<td>Parapneumonic effusion, pulmonary embolism, abdominal diseases</td>
<td>In about 7 percent of acute tuberculous pleurisy and 20 percent of malignant pleural effusions, a neutrophilic fluid predominance can be seen.</td>
</tr>
</tbody>
</table>

*Information from references 3, 5, and 13.*
Pleural Effusion

If the fluid is sent in a plastic or glass tube without anticoagulation, the fluid may clot, resulting in an inaccurate count. The predominant WBC population is determined by the mechanism of pleural injury and the timing of the thoracentesis in relation to the onset of the injury. Thus, the finding of neutrophil-rich fluid heightens suspicion for parapneumonic pleural effusion (an acute process), whereas a lymphocyte-predominant fluid profile suggests cancer or tuberculosis (a chronic process).

Pleural fluid for pH testing should be collected anaerobically in a heparinized syringe and measured in a blood-gas machine. Frank pus should not be sent for pH determination because thick, purulent fluid may clog the blood-gas machine. A low pleural fluid pH

---

**TABLE 5**

**Optional Pleural Fluid Tests for Pleural Effusion**

<table>
<thead>
<tr>
<th>Test</th>
<th>Test value</th>
<th>Suggested diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase</td>
<td>&gt; Upper limit of normal</td>
<td>Malignancy (&lt;20 percent), pancreatic disease, esophageal rupture.</td>
<td>Obtain when esophageal rupture or pancreatic disease is suspected. The amylase in malignancy and esophageal rupture is of the salivary type</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&gt; 45 to 60 mg per dl (1.16 to 1.55 mmol per L)</td>
<td>Any condition causing an exudate</td>
<td>Measure if chylothorax or pseudochylothorax is suspected. This parameter taken alone misclassifies 10 percent of exudates and 20 percent of transudates.</td>
</tr>
<tr>
<td>Culture</td>
<td>Positive</td>
<td>Infection</td>
<td>Obtain in all parapneumonic pleural effusions because a positive Gram stain or culture should lead to prompt chest tube drainage.</td>
</tr>
<tr>
<td>Hematocrit fluid to blood ratio</td>
<td>≥0.5</td>
<td>Hemothorax</td>
<td>Obtain when pleural fluid is bloody. Hemothorax most often originates from blunt or penetrating chest trauma.</td>
</tr>
<tr>
<td>Interferon*</td>
<td>Different cutoff points</td>
<td>Tuberculosis</td>
<td>Consider when ADA is unavailable or nondiagnostic and tuberculosis is suspected.</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>&gt; 1,500 pg per ml</td>
<td>Heart failure</td>
<td>If available, consider testing when heart failure is suspected and exudate criteria are met.</td>
</tr>
<tr>
<td>pH</td>
<td>&lt; 7.20</td>
<td>Complicated parapneumonic effusion or empyema, malignancy (&lt;10 percent), tuberculosis (&lt;10 percent), esophageal rupture</td>
<td>Obtain in all nonpurulent effusions if infection is suspected. A low pleural fluid pH indicates the need for tube drainage only for parapneumonic pleural effusions.</td>
</tr>
</tbody>
</table>

Polymerase chain reaction† Positive Infection\[15,21\]

Triglycerides > 110 mg per dl (1.24 mmol per L) Chylothorax

Tumor markers‡ Different cutoff points Malignancy

ADA = adenosine deaminase; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

*—ADA measurement is cheaper, easier, and quicker to perform than interferon for diagnosing tuberculosis.
†—For example, Streptococcus pneumoniae and Mycobacterium tuberculosis.
‡—For example, carcinoembryonic antigen (CEA), CA 15.3 and CA 549 (markers for breast carcinoma), CYFRA 21-1 (marker for lung carcinoma), CA 125 (marker for ovarian and endometrial carcinoma), human epidermal growth factor receptor (HER-2/neu) gene amplification, telomerase.

Information from references 5 and 13 through 24.
value has prognostic and therapeutic implications for patients with parapneumonic and malignant pleural effusions. A pH value less than 7.20 in a patient with a parapneumonic effusion indicates the need to drain the fluid.\textsuperscript{14,15} In a patient with malignant pleural effusion, a pleural fluid pH value less than 7.30 is associated with a shorter survival and poorer response to chemotherapies.\textsuperscript{1} When a pleural fluid pH value is not available, a pleural fluid glucose concentration less than 60 mg per dL can be used to identify complicated parapneumonic effusions.\textsuperscript{14}

ADA is an enzyme that plays an important role in lymphoid cell differentiation. A pleural fluid ADA level greater than 40 U per L (667 nkat per L) has a sensitivity of 90 to 100 percent and a specificity of 85 to 95 percent for the diagnosis of tuberculous pleurisy.\textsuperscript{5,26-28} The specificity rises above 95 percent if only lymphocytic exudates are considered.\textsuperscript{29,30} In areas where the prevalence of tuberculosis is low, the positive predictive value of pleural ADA declines but the negative predictive value remains high.

Cultures for both aerobic and anaerobic bacteria will identify the responsible microorganism in about 40 percent of parapneumonic effusions (70 percent if fluid is grossly purulent).\textsuperscript{5} The yield with culture is increased if blood-culture bottles are inoculated at the bedside with the pleural fluid. In addition, both pleural fluid and sputum should be cultured for mycobacteria when tuberculous pleuritis is suspected. The yield of sputum cultures in tuberculous pleural effusion varies from 10 to 60 percent, largely dependent on the extent of associated pulmonary involvement.\textsuperscript{31} Because delayed hypersensitivity plays a major role in the pathogenesis of tuberculous pleuritis, it is not possible to isolate Mycobacterium tuberculosis from pleural fluid samples in more than 60 to 70 percent of patients.\textsuperscript{2,26} The use of broth medium (e.g., BACTEC radiometric system) with bedside inoculation provides higher yields and faster results (one to two weeks) than conventional methods.\textsuperscript{32} Smears of the pleural fluid for mycobacteria are rarely positive (5 percent)\textsuperscript{5} unless the patient has a tuberculous empyema. About one third of patients with tuberculous pleuritis have a negative tuberculin skin test.\textsuperscript{26}

Cytology is positive in approximately 60 percent of malignant pleural effusions.\textsuperscript{31} Negative test results are related to factors such as the type of tumor (e.g., commonly negative with mesothelioma, sarcoma, and lymphoma); the tumor burden in the pleural space; and the expertise of the cytopathologist. The diagnostic yield may be somewhat improved by additional pleural taps. Submission of 10 mL of pleural fluid appears adequate for cytologic processing.\textsuperscript{24}

A second thoracentesis should be considered in the following situations: (1) suspected malignant effusion and the initial pleural fluid cytocologic examination is negative; (2) a parapneumonic effusion with borderline biochemical characteristics of the pleural fluid for indicating chest tube drainage; and (3) suspected acute tuberculous pleurisy with initial nondiagnostic pleural ADA levels.

Other diagnostic procedures

**IMAGING TECHNIQUES**

Helical CT has become the first-line modality for imaging of pulmonary circulation in a patient suspected of having pulmonary embolism, supplanting ventilation-perfusion scintigraphy. Helical CT also can identify alternative explanations for the pleural effusion, can diagnose deep venous thrombosis when combined with CT venography of the pelvis and lower extremities, and can distinguish malignant from benign pleural disease. CT findings suggestive of malignant disease are the presence of pleural nodules or nodular pleural thickening (Figure 2), circumferential or mediastinal pleural thickening, or infiltration of the chest wall or diaphragm. However, a recent study\textsuperscript{35} found that this was true in less than 20 percent of patients with malignant pleural effusion. Positron emission tomography seems promising for differentiating between benign and malignant pleural diseases (sensitivity 97 percent and specificity 88.5 percent in one study).\textsuperscript{35}

**BRONCHOSCOPY**

Bronchoscopy is useful whenever an endobronchial malignancy is likely, as suggested
by one or more of the following characteristics: a pulmonary infiltrate or a mass on the chest radiograph or CT scan, hemothysis, a massive pleural effusion, or shift of the mediastinum toward the side of the effusion.

PERCUTANEOUS PLEURAL BIOPSY

Closed-needle biopsy of the pleura for histologic examination classically has been recommended for undiagnosed exudative effusions when tuberculosis or malignancy is suspected. The combination of histology (80 percent sensitivity) and culture (56 percent sensitivity) of pleural biopsy tissue establishes the diagnosis of tuberculosis in up to 90 percent of patients.35 However, this diagnosis is strongly suggested by a high ADA level in the pleural fluid, as detailed above, thus avoiding the need for a confirmatory biopsy in most patients.

Cytology is superior to blind pleural biopsy for the diagnosis of pleural malignancy. In one case series,37 needle biopsy of the pleura was positive in only 17 percent (20 of 119) of patients with malignancy involving the pleura but a negative pleural fluid cytology. The diagnostic yield from pleural biopsy is higher when it is used with some form of image guidance to identify areas of particular thickening or nodularity.38

THORACOSCOPY

Because thoracoscopy is diagnostic in more than 90 percent of patients with pleural malignancy and negative cytology, it is the preferred diagnostic procedure in patients with cytology-negative pleural effusion who are suspected of having pleural malignancy.39 Moreover, thoracoscopy offers the possibility of effective pleurodesis during the procedure.

Criteria for Referral

No diagnosis is ever established for approximately 15 percent of patients.1 Observation is probably the best option if the patient is improving and there are no parenchymal infiltrates or pleural nodules, because most pleural effusions that are undiagnosed after a thorough initial evaluation are benign.40,41 Figure 3 is a suggested algorithm for the investigation of pleural effusions.

Pulmonary consultation should be obtained when thoracentesis is technically difficult; the etiology is uncertain after initial thoracentesis; or drainage of the pleural space is advised (e.g., symptomatic large or massive pleural effusion, hemothorax, empyema, or complicated parapneumonic effusion).

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Evaluation of Patients with Pleural Effusion

Pleural effusion (>1 cm height on decubitus radiograph, ultrasound or CT) without clinically evident heart failure

- Perform thoracentesis; measure pleural fluid protein and LDH.

Are any of the following met?
- Pleural to serum protein ratio > 0.5
- Pleural to serum LDH ratio > 0.6
- Pleural LDH > two thirds upper limit of normal serum LDH

No
- Transudate.
  - Treat heart failure, cirrhosis, or nephrosis.

Yes
- Exudate.
  - Further diagnostic procedures:
    - Obtain pleural fluid glucose; ADA; total and differential cell counts; cytologic analysis; and, if suspected infection, pH and cultures.

ADA > 40 U per L (657 nkat per L) and lymphocytic effusion
- No diagnosis
- Suspected pancreatic pleural effusion or esophageal rupture
- Perform helical chest CT.
- Pleural fluid amylase

Positive helical CT: pulmonary embolism confirmed
- No diagnosis

Consider bronchoscopy if hemoptysis, atelectasis, or pulmonary infiltrates are present.

Symptoms improving?
- No
  - Consider pleural biopsy (blind, image-guided, or by thoracoscopy).
- Yes
  - Observe

Potential diagnosis (e.g., empyema, hemothorax, chylothorax)
Additional pleural fluid testing (cultures, hematocrit, triglycerides)

Figure 3. Algorithm for the evaluation of patients with pleural effusion. (CT = computed tomography; LDH = lactate dehydrogenase; ADA = adenosine deaminase.)

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opathic pleuritis" exist? Natural history of non-specific
pleuritis diagnosed after thoracoscopy. Respiration
DVT and Pulmonary Embolism: Part I. Diagnosis

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The incidence of venous thromboembolic diseases is increasing as the U.S. population ages. At least one established risk factor is present in approximately 75 percent of patients who develop these diseases. Hospitalized patients and nursing home residents account for one half of all cases of deep venous thrombosis. A well-validated clinical prediction rule can be used for risk stratification of patients with suspected deep venous thrombosis. Used in combination with D-dimer or Doppler ultrasound tests, the prediction rule can reduce the need for contrast venography, as well as the likelihood of false-positive or false-negative test results. The inclusion of helical computed tomographic venography (i.e., a below-the-pelvis component) in pulmonary embolism protocols remains under evaluation. Specific combinations of a clinical prediction rule, ventilation-perfusion scanning, and D-dimer testing can rule out pulmonary embolism without an invasive or expensive investigation. A clinical prediction rule for pulmonary embolism is most helpful when it is used with subsequent evaluations such as ventilation-perfusion scanning, D-dimer testing, or computed tomography. Technologic advances are improving the resolution of helical computed tomography to allow detection of smaller emboli; however, further study is needed to provide definitive evidence supporting the role of this imaging technique in the diagnosis of pulmonary embolism. D-dimer testing is helpful clinically only when the result is negative. A negative D-dimer test can be used in combination with a clinical decision rule, ventilation-perfusion scanning, and/or helical computed tomography to lower the probability of pulmonary embolism to the point that aggressive treatment is not required. Evidence-based algorithms help guide the diagnosis of deep venous thrombosis and pulmonary embolism. (Am Fam Physician 2004;69:2829-36. Copyright © 2004 American Academy of Family Physicians.)

This is part I of a two-part article on DVT and PE. Part II, "Treatment and Prevention," appears in this issue on page 2841.

Members of various medical faculties develop articles for "Practical Therapeutics." This article is one in a series coordinated by the Department of Family and Preventive Medicine at Emory University School of Medicine, Atlanta. Guest editor of the series is Timothy Clenney, M.D.

See page 2745 for definitions of strength-of-recommendation labels.

Venous thromboembolic disease represents a spectrum of conditions that includes deep venous thrombosis (DVT) and pulmonary embolism (PE). The estimated annual incidence of venous thromboembolism is 117 cases per 100,000 persons. The incidence rises markedly in persons 60 years and older and may be as high as 900 cases per 100,000 by the age of 85 years.1

Most clinically important PEs originate from proximal DVT of the leg (popliteal, femoral, or iliac veins).2 Upper extremity DVT is less common but also may lead to PE, especially in the presence of a venous catheter. A much less common cause of upper extremity DVT is Paget-Schroetter syndrome (idiopathic upper extremity DVT in young athletes).3

As the U.S. population ages, the medical and economic impact of venous thromboembolic disease is expected to increase. Part I of this two-part article reviews the diagnosis of DVT and PE. Part II4 reviews treatment and prevention.

Risk Factors for Venous Thromboembolism

Risk factors for venous thromboembolic disease include increasing age, prolonged immobility, surgery, trauma, malignancy, pregnancy, estrogenic medications (e.g., oral contraceptive pills, hormone therapy, tamoxifen [Nolvadex]), congestive heart failure, hyperhomocysteinemia, diseases that alter blood viscosity (e.g., polycythemia, sickle cell disease, multiple myeloma), and inherited thrombophilias.

About 75 percent of patients with venous thromboembolic disease have at least one established risk factor, and one half of all cases of DVT occur in hospitalized patients or nursing home residents.5 Inherited thrombophilias can be identified in 24 to 37 percent of patients with DVT and in the majority of patients with familial thrombosis6-7 (Table 1).
One study found that the combination of a low-risk assessment by a validated clinical prediction rule and a negative second-generation latex agglutination d-dimer test effectively rules out deep venous thrombosis.

**TABLE 1**

**Thrombophilias Identified in Patients Presenting with DVT or PE**

<table>
<thead>
<tr>
<th>Thrombophilias</th>
<th>Anticoagulant protein deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein S</td>
<td></td>
</tr>
<tr>
<td>Protein C</td>
<td></td>
</tr>
<tr>
<td>Antithrombin</td>
<td></td>
</tr>
<tr>
<td>Plasminogen</td>
<td></td>
</tr>
<tr>
<td>Heparin cofactor II</td>
<td></td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td></td>
</tr>
<tr>
<td>Combination deficiencies</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden mutation (heterozygous)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin G20210A mutation (heterozygous)</td>
<td></td>
</tr>
</tbody>
</table>

*DVT = deep venous thrombosis; PE = pulmonary embolism.*

**Diagnosis of DVT**

When considered alone, the individual clinical features of DVT and PE have low predictive value (about 15 percent). 8 Classic symptoms of DVT include swelling, pain, and discoloration in the affected extremity. Physical examination may reveal the palpable cord of a thrombosed vein, unilateral edema, warmth, and superficial venous dilation. 8 Classic signs of DVT, including Homans sign (pain on passive dorsiflexion of the foot), edema, tenderness, and warmth, are difficult to ignore, but they are of low predictive value and can occur in other conditions such as musculoskeletal injury, cellulitis, and venous insufficiency. However, combinations of clinical features in the form of clinical prediction rules can be useful for stratifying patients into risk categories.

An algorithm developed by the Institute for Clinical Systems Improvement (ICSI), an independent nonprofit collaboration of health care providers and insurance companies, incorporates evidence-based recommendations for the use of pretest clinical probability with prediction rules, d-dimer testing, and imaging in the diagnosis of DVT (Figure 1). 10

**CLINICAL PREDICTION RULE**

A well-validated clinical prediction rule provides a reliable estimate of the pretest probability of DVT (Table 2), 9 which should, in turn, guide the interpretation of subsequent diagnostic tests. The value of various diagnostic tests and imaging studies in predicting the presence of DVT depends on the likelihood of disease in each risk group. 5, 11-14 For example, the same test may rule out disease when it is negative in a low-probability patient but not when it is negative in a high-probability patient. Because many patients have an intermediate probability of venous thromboembolism, clinical judgment continues to be an important factor in making the decision to treat.

**D-DIMER TESTS**

Available d-dimer tests vary widely in sensitivity and specificity. Therefore, caution must be exercised in interpreting the results of these tests. 15 However, one recent study 16 found that the combination of a low-risk assessment by a validated clinical prediction rule and a negative second-generation latex agglutination d-dimer assay effectively rules out DVT. In another recent study, 14 patients with a Wells clinical prediction rule score of less than 2 points and a negative d-dimer test were less likely to have venous thromboembolism during follow-up than were patients with a negative ultrasound examination (0.4 percent versus 1.4 percent). Note that a positive d-dimer assay does not raise the likelihood of DVT appreciably and therefore has limited clinical value.

**DOPPLER ULTRASONOGRAPHY**

Doppler ultrasonography is the most widely used modality for evaluating patients with suspected DVT. When used in combination with a clinical prediction rule, ultrasound examination is accurate in predicting the need for anticoagulation. However, a normal ultrasound study in a high-probability patient requires additional investigation before DVT can be ruled out.

Ultrasound assessment has several limitations: its accuracy depends on the operator; it cannot distinguish between an old clot and a new clot; and it is not accurate in
detecting DVT in the pelvis or the small vessels of the calf, or in detecting DVT in the presence of obesity or significant edema. Causes of false-positive examinations include superficial phlebitis, popliteal cysts, and abscess.

**HELICAL COMPUTED TOMOGRAPHY**

With the advent of helical (spiral) computed tomographic (CT) scanning, protocols have emerged that combine CT pulmonary angiography with simultaneous below-the-pelvis CT venography. These "PE protocols" make it convenient to examine the chest and lower extremities simultaneously, without added contrast medium. One of the secondary objectives of the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II)\(^2\) is to evaluate the diagnostic accuracy of helical CT scanning in patients with DVT.

Helical CT scanning of the legs costs about 50 percent more than compression ultrasonography. In addition, the risk of adverse reactions to contrast agents must be weighed. Currently, insufficient evidence supports the use of CT venography over Doppler ultrasonography for the diagnosis of lower extremity DVT.\(^1\)

**CONTRAST VENOGRAPHY**

Although contrast venography is not performed often, it remains the gold standard against which noninvasive studies for DVT are compared. The use of contrast venography is limited by the risk of pain, phlebitis, and hypersensitiv-

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**Deep Venous Thrombosis**

Leg symptoms and clinical suspicion for DVT

Determine pretest probability of DVT.

- Low probability
  - D-dimer test
    - Negative
      - Venous ultrasound examination
        - Negative
          - DVT excluded
        - Positive
          - Venous ultrasound examination
            - Negative
              - DVT excluded
            - Positive
              - DVT confirmed
  - Positive or not available
    - Venous ultrasound examination
      - Negative
        - DVT excluded
      - Positive
        - DVT confirmed

- Moderate or high probability
  - Venous ultrasound examination
    - Negative
      - D-dimer test
        - Negative
          - DVT excluded
        - Positive
          - DVT confirmed
    - Positive
      - DVT confirmed
      - Treat.

---

**FIGURE 1.** Diagnosis of deep venous thrombosis (DVT).

TABLE 2
Wells Clinical Prediction Rule for DVT

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment within 6 months, or palliation)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or immobilization of lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Bedridden for more than 3 days because of surgery (within 4 weeks)</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along distribution of deep veins</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral calf swelling of greater than 3 cm (below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral pitting edema</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely or more likely than DVT</td>
<td>22</td>
</tr>
</tbody>
</table>

Total points: 22

DVT = deep venous thrombosis.
Risk score interpretation (probability of DVT): ≥3 points: high risk (75%); 1 to 2 points: moderate risk (17%); <1 point: low risk (3%).

... or toxic reactions to contrast agents. Furthermore, DVT develops in a small number of patients who undergo the procedure. Conditions such as edema or obesity, which impair venous access, may make the test difficult or impossible to perform in approximately 10 percent of patients.17

IMPEDEANCE PLETHYSMOGRAPHY

Impedance plethysmography (IPG) is a noninvasive and highly portable modality that has proved useful in the evaluation of patients with suspected DVT. Serial IPG is less sensitive than previously thought, and it may not detect proximal DVT.18 Failure to detect this condition is important, because proximal thrombi pose the greatest risk of embolization. Although IPG is popular in some countries, it is highly operator-dependent and relatively unavailable in the United States.

EMERGING TECHNOLOGIES

Magnetic resonance imaging (MRI) appears to be at least as sensitive as ultrasonography in detecting calf and pelvic DVTs.13 These thromboses are difficult to compress with ultrasonography and difficult to visualize with venography. However, MRI is highly operator-dependent, relatively unavailable, and generally more than twice as expensive as ultrasound examination.

Diagnosis of PE

The assessment for PE begins with a careful clinical examination and a determination of risk factors. The chest radiograph, arterial blood gas measurements, and electrocardiogram (ECG) also can be used to establish a high, intermediate, or low risk of PE.10

The ICSI algorithm for the diagnosis of PE is presented in Figure 2.10 This algorithm, like the one for DVT (Figure 1),10 incorporates the use of a clinical prediction rule to determine the pretest probability of disease and options for imaging (Table 3).19 The value of a laboratory test or imaging study in predicting the presence of PE depends on the likelihood of disease in each risk group.19-21 The clinical prediction rule is most useful when a patient’s ventilation-perfusion scan is reported as showing intermediate or high probability.

The presence of DVT can alter the probability of PE. This is especially useful when the helical CT scan is negative or the ventilation-perfusion scan is not diagnostic. The ICSI algorithm10 describes one rational approach to a complex and confusing area.

CLINICAL PREDICTION RULES

Wells clinical prediction rule for PE produces a point score based on clinical features and the likelihood of diagnoses other than PE.19 However, Wells rule has been criticized for the subjectivity of the judgment about other diagnoses, a problem that could affect the ability of physicians to apply the rule outside the research setting.

Other clinical prediction rules include the Geneva rule22 and the rule developed in the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED).23-24 However, the Geneva rule requires an arterial blood gas measurement and a chest radiograph, while the PISA-PED rule requires an ECG. One investigative team has developed rules for explicit use with D-dimer tests,25 and Wells rule has been simplified for use with D-dimer tests.19

No consensus has emerged on the best clinical prediction rule for PE or the criteria that should be used to judge the performance of the various rules. This article presents...
DVT and PE

Pulmonary Embolism

Clinical signs and symptoms of PE

Estimate clinical pretest probability of PE.

Choose lung imaging study.

CT pulmonary angiography

Positive

Diagnosis: PE

Treat.

Negative

Compression ultrasound examination of lower extremities

Low- or intermediate-probability scan (nondiagnostic)

Ventilation-perfusion lung scan

High-probability scan

Clinical pretest probability

Follow-up for other diagnosis

Normal scan

Intermediate or high

Angiography

Diagnosis: PE

Treat.

Low

Follow-up for other diagnosis

Intermediate

P-dimer test or serial ultrasound examination

Angiography

Positive

Diagnosis: VTE

Treat.

Negative

Clinical pretest probability

Intermediate

Diagnosis: PE

Treat.

High

Follow-up for other diagnosis

FIGURE 2. Diagnosis of pulmonary embolism (PE). (CT = computed tomographic; VTE = venous thromboembolism)

the original Wells clinical prediction rule\textsuperscript{\textordmasculine 19} to help guide physicians when D-dimer testing is not available. This prediction rule is one of the oldest and most frequently used decision rules. A low probability based on the combination of a prediction rule and a negative D-dimer test significantly reduces the probability of PE; however, the development of PE protocols awaits empiric validation.\textsuperscript{\textordmasculine 26}

In the landmark PIOPED study,\textsuperscript{\textordmasculine 21} physicians were asked to use clinical judgment alone to categorize their clinical suspicion of PE as high, intermediate, or low. Despite the absence of standard or objective criteria, the PIOPED categorization has been validated, and even the most objective clinical prediction rules perform only marginally better than the physician's subjective assessment.\textsuperscript{\textordmasculine 27} Therefore, subjective impression remains a good alternative to the use of a clinical prediction rule.

**VENTILATION-PERFUSION SCANNING**

For several decades, the ventilation-perfusion scan has been the first-line study in patients with suspected PE. Defects in radioactive tracer uptake from ventilated and perfused areas of the lungs are reported as normal, nearly normal, or indicating a low, intermediate, or high probability of embolus.

A high-probability ventilation-perfusion scan provides sufficient evidence for the initiation of treatment for PE. Likewise, a normal scan should be considered sufficient to exclude PE. Unfortunately, 50 to 70 percent of scans are indeterminate (low or intermediate probability). In the PIOPED study,\textsuperscript{\textordmasculine 21} 40 percent of patients with confirmed PE had a high-probability ventilation-perfusion scan, 40 percent had an intermediate-probability scan, and 14 percent had a low-probability scan. Note that a low-probability scan does not rule out PE.\textsuperscript{\textordmasculine 21}

**HELICAL COMPUTED TOMOGRAPHY**

Studies indicate that helical CT scanning detects large PEs, with a sensitivity and specificity of nearly 90 percent for the identification of main and lobar emboli. However, this imaging modality generally is unable to detect smaller PEs.\textsuperscript{\textordmasculine 28}

One potential advantage of helical CT scanning is its ability to identify an alternative diagnosis in about two thirds of cases in which PE is not present.\textsuperscript{\textordmasculine 29,\textordmasculine 30} A potential disadvantage is the identification of suspicious-appearing abnormalities that require further evaluation or even biopsy but actually are benign. Current use of helical CT scanning is determined by its availability. This imaging modality often is used to supplement other diagnostic tests (e.g., ventilation-perfusion scanning) when such tests are nondiagnostic.

At this time, helical CT scanning does not have suffi-
DVT and PE

<table>
<thead>
<tr>
<th>Strength of Recommendations</th>
<th>Strength of recommendation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>A well-validated clinical prediction rule provides a reliable estimate of the pretest probability of DVT.</td>
<td>A</td>
<td>8, 14</td>
</tr>
<tr>
<td>A well-validated clinical prediction rule provides a reliable estimate of the pretest probability of PE.</td>
<td>A</td>
<td>19, 22, 25, 27</td>
</tr>
<tr>
<td>Compression ultrasonography should be the initial test in patients with acute symptomatic DVT.</td>
<td>A</td>
<td>10, 17</td>
</tr>
<tr>
<td>A d-dimer assay can be used as a negative prediction tool to reduce the need for further studies to rule out DVT.</td>
<td>B</td>
<td>17</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis; PE = pulmonary embolism.

icient resolution to justify its widespread adoption. Moreover, use of the imaging technique has not been unequivocally demonstrated to improve patient outcomes. As thin-collimation CT technology advances and resolution increases to the point that reliable evaluation of subsegmental vessels is possible, helical CT scanning may replace pulmonary angiography as the gold standard in the diagnosis of PE.

One analysis suggests that in patients with suspected PE, helical CT scanning is as cost-effective as ventilation-perfusion scanning and Doppler ultrasound examination of the lower extremity, but only when combined with d-dimer testing. Two recent multicenter trials suggest that helical CT scanning is safe to use for ruling out PE, at least in patients with a low or intermediate clinical probability of embolism. PIOPED II should yield important information about the diagnostic role of helical CT scanning.

D-DIMMER TESTS

Use of the new generation of d-dimer tests in combination with the Wells clinical prediction rule is effective in ruling out PE in patients who present to the emergency department. A negative d-dimer test may rule out PE in patients with a low to moderate pretest probability of thrombus and a nondiagnostic ventilation-perfusion scan.

As with DVT, it is prudent for physicians to know the specific type of d-dimer test for PE that is offered at their institution and to understand the properties of that test. However, in a general office population, where the pretest probability of PE is lower than it is in an emergency department, the usefulness of the clinical prediction rule in ruling out PE in the low-risk patients declines proportionately.

CHEST RADIOGRAPH AND ECG

In PIOPED, the ECGs were abnormal in 70 percent of patients with PE and no preexisting cardiovascular disease, but none of the electrocardiographic findings were specific or sensitive. In addition, only 12 percent of patients with PE had a normal chest radiograph. Again, the radiographic abnormalities (atelectasis, pulmonary parenchymal abnormality, pleural effusion, cardiomegaly) were neither specific nor sensitive for PE.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

The online version of this article contains two tables that summarize risk-stratified performance of tests in DVT and PE and are available online at: http://www.aafp.org/afp/20040615/2829.html.

REFERENCES

DVT and PE


DVT and Pulmonary Embolism: Part II. Treatment and Prevention

DINO W. RAMZI, M.D., C.M., and KENNETH V. LEEPER, M.D.
Emory University School of Medicine, Atlanta, Georgia

Treatment goals for deep venous thrombosis include stopping clot propagation and preventing the recurrence of thrombus, the occurrence of pulmonary embolism, and the development of pulmonary hypertension, which can be a complication of multiple recurrent pulmonary emboli. About 30 percent of patients with deep venous thrombosis or pulmonary embolism have a thrombophilia. An extensive evaluation is suggested in patients younger than 50 years with an idopathic episode of deep venous thrombosis, patients with recurrent thrombosis, and patients with a family history of thromboembolism. Infusion of unfractionated heparin followed by oral administration of warfarin remains the mainstay of treatment for deep venous thrombosis. Subcutaneously administered low-molecular-weight (LMW) heparin is at least as effective as unfractionated heparin given in a continuous infusion. LMW heparin is the agent of choice for treating deep venous thrombosis in pregnant women and patients with cancer. Based on validated protocols, warfarin can be started at a dosage of 5 or 10 mg per day. The intensity and duration of warfarin therapy depends on the individual patient, but treatment of at least three months usually is required. Some patients with thrombophilias require lifetime anticoagulation. Treatment for pulmonary embolism is similar to that for deep venous thrombosis. Because of the risk of hypoxemia and hemodynamic instability, in-hospital management is advised. Unfractionated heparin commonly is used, although LMW heparin is safe and effective. Thrombolysis is used in patients with massive pulmonary embolism. Subcutaneous heparin, LMW heparin, and warfarin have been approved for use in surgical prophylaxis. Elastic compression stockings are useful in patients at lowest risk for thromboembolism. Intermittent pneumatic leg compression is a useful adjunct to anticoagulation and an alternative when anticoagulation is contraindicated. (Am Fam Physician 2004;69:2841-8. Copyright © 2004 American Academy of Family Physicians.)

This is part II of a two-part article on DVT and PE. Part I, "Diagnosis," appears in this issue on page 2829.

Mortality from venous thromboembolic disease has decreased significantly in the past 10 to 20 years. Increased survival may be due to better diagnostic strategies, improved recognition of risk factors, and better treatment guidelines. In the past decade, a great deal has been learned about the role of inherited and acquired thrombophilias as risk factors for venous thromboembolic disease. Although treatment of venous thromboembolism remains primarily supportive, there have been refinements in the intensity and duration of anticoagulation regimens for various therapeutic and preventive clinical situations.

Part I of this two-part article addressed the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism (PE). Part II discusses the evaluation for thrombophilias and other secondary causes of venous thromboembolic disease, presents an evidence-based approach to the treatment of DVT and PE, and reviews current recommendations for prevention of venous thromboembolism.

Evaluation for Thrombophilias and Other Secondary Causes

The evaluation for apparent venous thromboembolism begins with a careful history and physical examination. Attention should be given to important risk factors, including previous venous thromboembolism, recent trauma or immobilization, malignancy, use of estrogenic medications, and pregnancy. Multiple spontaneous miscarriages also may indicate underlying thrombogenic conditions.

The basic laboratory evaluation includes a complete blood count, platelet count, prothrombin time, activated partial thromboplastin time (APTT), and comprehensive metabolic panel to look for electrolyte, renal, or hepatic abnormalities. If an evaluation for thrombo-
philias is being considered, blood should be set aside for screening tests before treatment with heparin and warfarin is initiated.

With the discovery that common thrombophilias are risk factors for venous thromboembolism, the question of when to launch an investigation has been raised. The combined prevalence of inherited thrombophilias and hyperhomocysteinemia is about 50 percent in all patients with DVT and PE. Unfortunately, not all studies included a control group; therefore, it is difficult to establish a reliable estimate of the prevalence of thrombophilias in asymptomatic persons. Because of the lack of prospective studies, there is no clear evidence to guide the decision about when to evaluate patients for thrombophilias. The cost-effectiveness of the evaluation is a concern.

Based on a review of the literature, one investigator proposed the following strategy: patients older than 50 years with an idiopathic first episode of venous thromboembolism and no family history should be considered "weakly thrombophilic" and should undergo a limited investigation (Table 1). Patients with an idiopathic episode of venous thromboembolism who are younger than 50 years, patients with recurrent thrombosis, and patients with a family history of venous thromboembolism should be considered "strongly thrombophilic" and should undergo a more extensive evaluation for thrombophilias. Patients with a first episode of thromboembolism, a clear risk factor for a first episode of venous thromboembolism, (e.g., trauma, immobilization), and no family history of thromboembolism require no work-up for thrombophilias. Most patients with venous thromboembolic disease and a genetic or unchangeable thrombophilia should receive lifetime anticoagulation.

There is no clear evidence that screening all or even selected patients for thrombophilias improves long-term outcomes. Until such evidence becomes available, the above guidelines, the physician's clinical judgment, and consultation with appropriate subspecialists should guide

### TABLE 1

**Risk-Specific Investigations for Thrombophilias**

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Risk of having a thrombophilia</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of venous thromboembolic disease with known risk factors for thromboembolism and no family history of thromboembolism*</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Age older than 50 years, idiopathic first episode of venous thromboembolic disease, and no family history of thromboembolism*</td>
<td>Moderate</td>
<td>Resistance to activated protein C with a clotting assay that dilutes patient plasma in factor V-deficient plasma, or genetic test for factor V Leiden mutation Genetic test for prothrombin G20210A mutation Clotting assay for lupus anticoagulant ELISA for antiphospholipid antibodies Plasma homocysteine level</td>
</tr>
<tr>
<td>Idiopathic venous thromboembolic disease before age 50 years or Recurrent thrombosis or Family history of thromboembolism*</td>
<td>High</td>
<td>All of the above and— Antithrombin assay (heparin cofactor assay) Protein C assay Protein S assay</td>
</tr>
</tbody>
</table>

ELISA = enzyme-linked immunosorbent assay.

*—Family history is defined as venous thromboembolic disease occurring in a first-degree relative before the age of 50 years.

### TABLE 2

**Weight-Based Heparin Therapy with Adjustments Based on the APTT**

<table>
<thead>
<tr>
<th>Initial dosage</th>
<th>Bolus of 80 units per kg, then 18 units per kg per hour by infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT &lt; 35 seconds (≤ 1.2 times control)</td>
<td>Bolus of 80 units per kg, then 4 units per kg per hour by infusion</td>
</tr>
<tr>
<td>APTT = 35 to 45 seconds (1.2 to 1.5 times control)</td>
<td>Bolus of 40 units per kg, then 2 units per kg per hour by infusion</td>
</tr>
<tr>
<td>APTT = 46 to 70 seconds (1.5 to 2.3 times control)</td>
<td>No change</td>
</tr>
<tr>
<td>APTT = 71 to 90 seconds (2.3 to 3.0 times control)</td>
<td>Decrease infusion rate by 2 units per kg per hour</td>
</tr>
<tr>
<td>APTT &gt; 90 seconds (&gt; 3.0 times control)</td>
<td>Hold infusion for 1 hour, then decrease infusion rate by 3 units per kg per hour</td>
</tr>
</tbody>
</table>

*APTT = activated partial thromboplastin time.*


---

management.

Physicians should be aware that antithrombin III, protein C, and S protein assays are inaccurate once a patient has begun anticoagulation therapy. Therefore, an investigation for thrombophilies should not be conducted until at least two weeks after warfarin therapy has been discontinued. Anticoagulation does not affect tests for other common thrombophilies, such as factor V Leiden mutation, hyperhomocysteinemia, and antiphospholipid antibody.

### Treatment of DVT

The goals of treatment for DVT are to stop clot propagation and prevent clot recurrence, PE, and pulmonary hypertension (a potential complication of multiple recurrent PEs). These goals usually are achieved with anticoagulation using heparin followed by warfarin (Coumadin). Despite some controversy about the need to treat isolated calf–vein DVT, a recent evidence-based guideline on antithrombotic therapy recommends at least six to 12 weeks of anticoagulation.

There are few evidence-based recommendations for the use of nonpharmacologic measures in patients with DVT. Usual advice for local care includes limb elevation and local application of heat. Activity should be minimal for several days (i.e., the patient’s activity should be limited to walking to the bathroom and kitchen). Graded elastic compression stockings have been associated with a 50 percent reduction in the incidence of postphlebitic syndrome.

**UNFRACTIONATED HEPARIN**

Treatment with unfractionated heparin is based on body weight, and the dosage is titrated based on the APTT. An APTT of 1.5 to 2.3 times control is desirable. Weight-based heparin dosing and adjustments based on the APTT are provided in *Table 2.* This approach to heparin therapy has been shown to achieve adequate anticoagulation quickly and safely.

Adverse reactions associated with heparin therapy include bleeding and thrombocytopenia. The risk of adverse reactions is highest in patients with any of the following: age greater than 65 years, recent surgery, or conditions such as peptic ulcer disease, liver disease, occult neoplasia, and bleeding diathesis. Transient thrombocytopenia may occur in 10 to 20 percent of patients, but major hemorrhagic complications occur in fewer than 2 percent of patients.

Heparin can be stopped after four or five days of combined therapy with warfarin if the International Normalized Ratio (INR) of prothrombin clotting time exceeds 2.0.

**LOW-MOLECULAR-WEIGHT HEPARIN**

Compared with unfractionated heparin, low-molecular-weight (LMW) heparin offers distinct advantages: it has a longer biologic half-life, it can be administered subcutaneously once or twice daily, dosing is fixed, and laboratory monitoring is not required. In addition, some adverse effects of unfractionated heparin, such as thrombocytopenia, appear to be less likely. In patients with DVT, subcutaneous administration of heparin is at least as effective as continuous infusion of unfractionated heparin in preventing complications and reducing the risk of recurrence.

Outpatient management of DVT using LMW heparin for short-term anticoagulation until warfarin is at a therapeutic level is safe and cost-effective, despite the higher cost of the heparin. Candidates for outpatient therapy must be hemodynamically stable, without renal failure, and not at high risk for bleeding. Furthermore, they must have a stable and supportive home environment, as well as access to daily monitoring until the INR is therapeutic. Like unfractionated heparin, LMW heparin is given in combination with warfarin for four to five days. Simultaneous initiation of warfarin and unfrac-
### TABLE 3

Initiation of Warfarin Therapy at 5 mg per Day

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
<th>Warfarin dosage (mg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&lt; 1.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1.5 to 1.9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2.0 to 2.9</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>&lt; 1.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1.5 to 1.9</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>2.0 to 2.9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 2.0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2.0 to 2.9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>&lt; 1.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1.5 to 1.9</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>2.0 to 2.9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0</td>
</tr>
</tbody>
</table>

INR = International Normalized Ratio.

Adapted with permission from Crowther MA, Harrison L, Hirsh J. Reply. Warfarin: less may be better. Ann Intern Med 1997;127:333.

...tionated heparin or LMW heparin has not been associated with any clinically important adverse outcomes.4

Enoxaparin (Lovenox) was the first LMW heparin approved by the U.S. Food and Drug Administration (FDA) for the treatment of DVT in a dosage of 1 mg per kg twice daily or 1.5 mg once daily. Dalteparin (Fragmin), another LMW heparin, is approved only for prophylaxis of DVT. In clinical trials of DVT treatment,11,12 dalteparin has been given in a dosage of 200 IU per kg per day (single dose or two divided doses). The FDA has approved the use of tinzaparin (Innohep), in a dosage of 175 anti-Xa IU per kg per day, for the treatment of DVT.

### WARFARIN

Once acute anticoagulation is achieved, warfarin is the drug of choice for long-term therapy to prevent clot recurrence. A standard warfarin protocol includes starting treatment at 5 mg per day and titrating the dosage every three to seven days to achieve an INR between 2.0 and 3.0 (Table 3).13 Attempts have been made to maintain patients at an even lower INR (between 1.5 and 2.0), but results have been contradictory.14,15 Unless further data show otherwise, anticoagulation with a standard INR goal of 2.0 to 3.0 should be used.

Promising results have been shown for a protocol in which warfarin is initiated in a dosage of 10 mg per day (Table 4).16 In one study,16 consecutive outpatients being treated with LMW heparin for DVT or PE were randomized to a 5-mg or 10-mg warfarin protocol. An INR higher than 1.9 was achieved an average of 1.4 days sooner in the patients who received warfarin according to the 10-mg protocol. Clot recurrence, bleeding events, and morbidity did not differ in the two treatment groups.

### DURATION OF ANTICOAGULATION

The duration of anticoagulation depends on whether the patient has a first episode of DVT, ongoing risk factors for venous thromboembolic disease, and known thrombophilia. The most recent evidence-based recommendations from the American College of Chest Physicians are based on the risk of clot recurrence (Table 5).4,17

### SPECIAL SITUATIONS

Warfarin therapy is contraindicated during pregnancy. Therefore, long-term treatment with LMW heparin is used when DVT occurs in a pregnant woman.4

The incidence of recurrent venous thromboembolism is increased in patients with cancer. These patients also are more likely to have complications from long-term warfarin therapy. A large multicenter trial18 in patients with cancer and venous thromboembolism found that the likelihood of recurrent clots was lower in the patients who received long-term prophylaxis with LMW heparin than in those who received warfarin. In this trial, 13 patients needed to be treated with LMW heparin instead of warfarin to avoid one episode of recurrent DVT. An interpretation of the study results must consider the fact that a significant proportion of patients in both groups died of cancer, and none died of PE.

Except in patients who are pregnant or have cancer, there is no advantage to using LMW heparin rather than warfarin for long-term anticoagulation.

### OTHER THERAPIES

Most patients do well with unfractionated heparin or LMW heparin. Therefore, thrombolytic therapy is not recommended for the treatment of DVT, except in selected patients with massive iliofemoral thrombi or as part of a research protocol.7 No evidence from adequately powered, randomized controlled trials indicates that thrombolytic
TABLE 4
Initiation of Warfarin Therapy at 10 mg per Day*

<table>
<thead>
<tr>
<th>Warfarin dosage (mg per day)</th>
<th>Day 3 INR</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5 INR</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 to 1.4</td>
<td>10</td>
<td>10</td>
<td>2.0 to 3.0</td>
<td>7.5</td>
<td>5</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>0</td>
<td>0</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 to 1.6</td>
<td>10</td>
<td>5</td>
<td>&lt;2.0</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>1.7 to 1.9</td>
<td>5</td>
<td>5</td>
<td>2.0 to 3.0</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>0</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0 to 2.2</td>
<td>2.5</td>
<td>&lt;2.0</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 to 3.0</td>
<td>0</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 to 3.5</td>
<td>0</td>
<td>2.5</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>0</td>
<td>0</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INR = International Normalized Ratio.

*—On days 1 and 2, all patients receive 10 mg per day.


TABLE 5
ACCP Recommendations for Long-Term Anticoagulation in Patients with DVT or PE (INR goal: 2.0 to 3.0)

<table>
<thead>
<tr>
<th>Thromboembolism</th>
<th>Duration of anticoagulation</th>
<th>Strength of recommendation*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>First event with a reversible or time-limited risk factor for venous thromboembolic disease (e.g., trauma, surgery)</td>
<td>At least 3 months</td>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>First episode of idiopathic venous thromboembolic disease</td>
<td>At least 6 months</td>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>Recurrent idiopathic venous thromboembolic disease or continuing risk factor (e.g., thrombophilia)</td>
<td>At least 12 months</td>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td>Symptomatic isolated calf-vein thrombosis</td>
<td>6 to 12 weeks†</td>
<td>A</td>
<td>17</td>
</tr>
</tbody>
</table>

ACCP = American College of Chest Physicians; DVT = deep venous thrombosis; PE = pulmonary embolism; INR = International Normalized Ratio.

*—ACCP ratings have been converted to American Family Physician’s strength-of-recommendation taxonomy.

†—Serial noninvasive studies of the lower extremities to assess for extension are an option.

therapy reduces all-cause mortality (even in patients with massive iliopelvic thrombi). Furthermore, the risk of intracranial hemorrhage is greater with thrombolytic therapy than with unfractionated heparin therapy.

**Treatment of PE**

Anticoagulation is the mainstay of treatment for PE. Because of the risks of hypoxemia and hemodynamic instability associated with PE, close monitoring and supportive therapy are necessary. Therefore, outpatient treatment of PE is not advised.

Unfractionated heparin most commonly is used to treat patients with PE, although LMW heparin also is safe and effective. Only enoxaparin and tinzaparin have received formal FDA approval for use in the treatment of PE.

Thrombolysis clearly is indicated in patients with massive PE and associated hemodynamic instability. However, the role of thrombolysis in patients with submassive PE remains controversial. In the largest study to date, improved survival was observed in patients treated with alteplase plus heparin compared with heparin alone. Using death and major complications as the end point, the number needed to treat was 7.3. One fewer death was observed for every 82 patients treated with the combination therapy.

In patients with PE, the usual dose of alteplase (Activase) is 100 mg given by intravenous infusion over a period of two hours. Streptokinase (Streptase) is given in a 250,000-IU loading dose, followed by 100,000 IU per hour for 24 hours. Delivery of thrombolytics directly into the thrombus by catheter has been described but has not been shown to be superior to peripheral infusion.

---

**TABLE 6**

**Prevention of Venous Thromboembolism in Patients Undergoing Surgery**

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Options for prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>LMW heparin</td>
</tr>
<tr>
<td></td>
<td>Warfarin (Coumadin)</td>
</tr>
<tr>
<td></td>
<td>Low-dose unfractionated heparin or LMW heparin, and</td>
</tr>
<tr>
<td></td>
<td>graduated compression stockings or pneumatic compression stockings</td>
</tr>
<tr>
<td></td>
<td>Intravenous unfractionated heparin</td>
</tr>
<tr>
<td>High</td>
<td>Low-dose unfractionated heparin administered every 8 hours</td>
</tr>
<tr>
<td></td>
<td>LMW heparin</td>
</tr>
<tr>
<td></td>
<td>Pneumatic compression stockings</td>
</tr>
<tr>
<td>Moderate</td>
<td>Low-dose unfractionated heparin administered every 12 hours</td>
</tr>
<tr>
<td></td>
<td>LMW heparin</td>
</tr>
<tr>
<td></td>
<td>Graduated compression stockings</td>
</tr>
<tr>
<td></td>
<td>Pneumatic compression stockings</td>
</tr>
<tr>
<td>Low</td>
<td>Aggressive mobilization</td>
</tr>
</tbody>
</table>

LMW = low-molecular-weight.

Anticoagulation with warfarin should follow heparin therapy. The same regimens are used for DVT and PE (Tables 3 and 4). Use of an inferior vena cava filter occasionally is indicated when PE recurs despite anticoagulation or there are contraindications to such treatment. Evidence from a single clinical trial showed added benefit from the use of a filter in patients who were receiving anticoagulation. The filter was associated with a lower 12-day rate of PE, but a higher rate of DVT recurrence and no difference in survival at two years of follow-up. At this time, the inferior vena cava filter cannot be considered standard first-line therapy.

Finally, acute pulmonary embolism may be beneficial in the unstable patient who has not responded to conventional treatments.

Prevention of Thromboembolic Disease

The need for preventive measures depends on a patient’s risk factors for venous thromboembolism. Prolonged immobilization, such as may occur with hospitalization, trauma, or general debility, is one risk factor. Surgical patients, especially the elderly and patients undergoing orthopedic procedures, are at particularly high risk for thromboembolic disease. The risk of venous thromboembolism in critically ill patients generally is under-recognized; many of these patients have at least one significant risk factor.

Healthy younger patients undergoing minor surgery are at low risk for venous thromboembolism, and aggressive postoperative mobilization usually is sufficient. The highest risk category is reserved for patients with acute spinal cord injury or other major trauma, as well as patients undergoing lower-extremity orthopedic surgery and patients with risk factors for venous thromboembolism (Table 6).

The simplest approach to prophylaxis for venous thromboembolism is low-dose unfractionated heparin, 5,000 units administered subcutaneously every eight or 12 hours. However, LMW heparin has been shown to be as effective as unfractionated heparin for surgical prophylaxis of DVT over periods of seven to 10 days (with a possible dose-dependent advantage on bleeding complications) and appears to be at least as effective as warfarin in most postoperative settings. In hip replacement surgery, LMW heparin or warfarin may be used for a minimum of seven to 10 days, and some studies have extended the period to over a month. Regimens for LMW heparin in different

<table>
<thead>
<tr>
<th>TABLE 7</th>
<th>LMW Heparin: Regimens for Prevention of Venous Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery in high-risk patient</td>
<td>Dalteparin (fragmin): 5,000 units SC 8 to 12 hours before surgery and once daily after surgery</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)*: 40 mg SC 1 to 2 hours before surgery and once daily after surgery; or 30 mg SC every 12 hours starting 8 to 12 hours after surgery</td>
<td></td>
</tr>
<tr>
<td>General surgery in moderate-risk patient</td>
<td>Dalteparin: 2,500 units SC 1 to 2 hours before surgery and once daily after surgery</td>
</tr>
<tr>
<td>Enoxaparin: 20 mg SC 1 to 2 hours before surgery and once daily after surgery</td>
<td></td>
</tr>
<tr>
<td>Nadroparin: 2,850 units SC 2 to 4 hours before surgery and once daily after surgery</td>
<td></td>
</tr>
<tr>
<td>Tinzaparin (Innohep): 3,500 units SC 2 hours before surgery and once daily after surgery</td>
<td></td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Dalteparin: 5,000 units SC 8 to 12 hours before surgery, then once daily starting 12 to 24 hours after surgery; or 2,500 units SC 6 to 8 hours after surgery, then 5,000 units SC once daily</td>
</tr>
<tr>
<td>Enoxaparin: 30 mg SC every 12 hours starting 12 to 24 hours after surgery; or 40 mg SC once daily starting 10 to 12 hours after surgery</td>
<td></td>
</tr>
<tr>
<td>Nadoparin: 38 units per kg SC 12 hours before surgery, 12 hours after surgery, and once daily on postoperative days 1, 2, and 3, then increase to 57 units per kg SC once daily</td>
<td></td>
</tr>
<tr>
<td>Tinzaparin: 75 units per kg SC once daily starting 12 to 24 hours after surgery; or 4,500 units SC 12 hours before surgery and once daily after surgery</td>
<td></td>
</tr>
<tr>
<td>Major trauma</td>
<td>Enoxaparin: 30 mg SC every 12 hours starting 12 to 36 hours after injury if the patient is hemostatically stable</td>
</tr>
<tr>
<td>For acute spinal cord injury, enoxaparin: 30 mg SC every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Medical conditions</td>
<td>Dalteparin: 2,500 units SC once daily</td>
</tr>
<tr>
<td>Enoxaparin: 40 mg SC once daily</td>
<td></td>
</tr>
<tr>
<td>Nadoparin: 2,850 units SC once daily</td>
<td></td>
</tr>
</tbody>
</table>

LMW = low-molecular-weight; SC = subcutaneous.
*—Dosage for enoxaparin is expressed in anti-Xa units: 1 mg = 100 anti-Xa units.
†—Available in Canada.

prophylactic scenarios are provided in Table 7.22

Intermittent pneumatic leg compression devices are useful adjuncts to anticoagulation, as well as alternatives in patients with significant contraindications to the use of anticoagulants. Elastic compression stockings also are useful, but only in low-risk patients. Aspirin is not recommended for surgical prophylaxis.23 Measures shown to be effective in the prevention of DVT in surgical patients, depending on level of risk, are listed in Table 6.22

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REFERENCES

Recurrent Venous Thromboembolism

NICHOLAS J. GALIOTO, MD; DANA L. DANLEY, MD; and RYAN J. VAN MAANEN, DO
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A previous venous thromboembolism is the most important risk factor for predicting recurrence of the condition. Several studies have shown that routine testing for inherited thrombophilias is not helpful in predicting the risk of recurrence or altering treatment decisions, and therefore is not cost-effective. Updated practice guidelines from the American College of Chest Physicians shift the focus away from laboratory testing and place stronger emphasis on identifying clinical factors when making treatment decisions. The major determinants for treatment duration are whether the deep venous thrombosis was located in a distal or proximal vein, whether the thrombotic episode was an initial or recurrent event, and whether recurrent risk factors were present. Persistent elevations on the D-dimer test or the presence of residual thrombosis may provide further information to predict recurrence risk and determine treatment duration. Screening for antiphospholipid syndrome and/or malignancy should be considered in patients presenting with arterial thrombosis, thrombosis at an unusual site, or recurrent pregnancy loss. Patients with venous thromboembolism and a known malignancy should be treated with low-molecular-weight heparin rather than oral anticoagulation as long as the cancer is active. All patients with recurrent, unprovoked venous thromboembolism should be considered for long-term treatment. (Am Fam Physician. 2011;83(3):293-300. Copyright © 2011 American Academy of Family Physicians.)

The annual incidence of venous thromboembolism (VTE), which includes deep venous thrombosis and pulmonary embolism, is one or two per 1,000 persons.1-3 Recurrent thrombosis is relatively common, particularly in patients with idiopathic VTE; a previous VTE is the main risk factor for a second VTE.1-3 Following treatment of an initial thrombotic event, it is important to determine whether the VTE was provoked (acquired risk factor) or unprovoked (idiopathic) to guide duration of anticoagulant therapy.5 If a patient has a recurrent or idiopathic VTE, a careful evaluation for intrinsic risk factors should be performed.

Assessing Risk of Recurrent VTE

A thorough history in a patient with thrombosis should include age at the first thrombotic event, location of the thrombosis, and presence of any precipitating or provoking conditions. Risk factors for venous thromboembolism are listed in Table 1.1-3-8 and Table 2 includes the relative risk of recurrent VTE based on risk factors.8,10 A VTE is considered provoked if transient risk factors are present. These transient risk factors are divided into major and minor categories.1-3,4 The more significant the provoking risk factor (e.g., surgery, trauma), the lower the expected risk of recurrence after anticoagulant therapy is discontinued.1-3,11 Patients with a transient provoking risk factor but no persistent risk factors do not require further testing,1,11 because these patients do not have a higher risk of recurrence than the general population.1,3 Conversely, patients with idiopathic VTE are at high risk of recurrence. One study found the cumulative

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**Table 1. Risk Factors for VTE**

<table>
<thead>
<tr>
<th>Major transient risk factors</th>
<th>Potential acquired or persistent risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>Collagen vascular diseases</td>
</tr>
<tr>
<td>Plaster cast immobilization</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Surgery</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Trauma</td>
<td>Medications</td>
</tr>
<tr>
<td>Minor transient risk factors</td>
<td>Myeloproliferative disorders</td>
</tr>
<tr>
<td>Oral contraceptives or hormone therapy</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Presence of major risk factor 1 to 3 months before VTE</td>
<td></td>
</tr>
<tr>
<td>Prolonged travel (≥ 2 hours)*</td>
<td></td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism.

*—Every two hours spent traveling increases VTE risk by 18 percent.

Information from references 1, and 3 through 8.
SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a transient provoking risk factor, but no persistent risk factors, for VTE do not require further testing.</td>
<td>C</td>
<td>3, 11-13</td>
</tr>
<tr>
<td>Routine testing for hereditary thrombophilies in patients with a first VTE is not helpful in predicting risk of recurrence or altering initial therapy.</td>
<td>C</td>
<td>3, 4, 11, 12, 19</td>
</tr>
<tr>
<td>Extensive screening for occult malignancy in patients with VTE has not been proven to be cost-effective, to reduce mortality, or to improve survival.</td>
<td>B</td>
<td>33, 36, 38</td>
</tr>
<tr>
<td>Clinical factors, such as whether the deep venous thrombosis was confined to a distal or proximal vein, whether the thrombotic episode was an initial or recurrent event, or whether transient risk factors were present, should determine duration of anticoagulant therapy in patients with VTE.</td>
<td>B</td>
<td>1, 4</td>
</tr>
<tr>
<td>Patients with a VTE and cancer should be treated with low-molecular-weight heparin for at least the first three to six months of long-term anticoagulation therapy. Subsequent treatment with low-molecular-weight heparin or vitamin K antagonist should be continued for as long as the cancer is active.</td>
<td>B</td>
<td>4, 39</td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Table 2. Relative Risk of Recurrent VTE After Stopping Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Persistent risk factors</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Transient risk factors</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
</tr>
<tr>
<td>Metastatic versus nonmetastatic</td>
<td>6 to 9</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
</tr>
<tr>
<td>D-dimer elevation</td>
<td>2.2</td>
</tr>
<tr>
<td>Unprovoked (idiopathic) VTE</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Second versus first episode of VTE</td>
<td>1.5</td>
</tr>
<tr>
<td>Distal DVT versus proximal DVT or PE</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Thrombophilies</strong></td>
<td></td>
</tr>
<tr>
<td>Factor VIII level &gt; 200 IU per dl. (&gt; 90th percentile)</td>
<td>6</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>2.5</td>
</tr>
<tr>
<td>Protein C, protein S, and antithrombin deficiencies</td>
<td>1.8</td>
</tr>
<tr>
<td>Heterozygous for prothrombin G20210A mutation</td>
<td>1.7</td>
</tr>
<tr>
<td>Heterozygous for factor V Leiden and prothrombin G20210A mutation</td>
<td>1.6</td>
</tr>
<tr>
<td>Homozygous for factor V Leiden</td>
<td>1.6</td>
</tr>
<tr>
<td>Mild hyperhomocysteinemia</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**NOTE:** Age, sex, and family history were not important predictors.

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Adapted with permission from Kearon C. Long-term management of patients after venous thromboembolism. Circulation. 2004;110(9 suppl 1):111, with additional information from reference 10.

risk of recurrence at one, five, and 10 years to be 15, 41, and 53 percent, respectively, in patients with an idiopathic VTE, compared with 7, 16, and 23 percent in patients with a provoked event. Another study found the risk of recurrence to be 4.8 percent at two years in patients with transient risk factors versus 12.1 percent in those with an unprovoked event.

An idiopathic VTE can be caused by an acquired or inherited thrombophilia. Table 3 includes risk factors that suggest an underlying thrombophilia. Antiphospholipid syndrome is the most common cause of acquired thrombophilia. This syndrome is usually secondary to autoimmune disease and may cause venous or arterial thrombosis, thrombocytopenia, acute ischemic encephalopathy, or recurrent pregnancy loss. Antiphospholipid syndrome may also be induced by the use of certain medications, such as hydralazine, phenothiazines, or procainamide. Other thrombophilies include factor V Leiden deficiency, prothrombin G20210A mutation, antithrombin deficiency, and protein C and protein S deficiency. Elevated levels of homocysteine, factor VIII, factor IX, and factor XI may also increase the risk of VTE.

There is no consensus regarding who should be tested for inherited thrombophilies, and several studies have called
### Table 3. Factors Suggesting an Underlying Thrombophilia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age younger than 50 years at onset of first thrombosis</td>
<td></td>
</tr>
<tr>
<td>Atypical site of thrombosis (e.g., hepatic, mesenteric, or cerebral veins)</td>
<td></td>
</tr>
<tr>
<td>History of thrombosis</td>
<td></td>
</tr>
<tr>
<td>No identifiable provoking risk factors</td>
<td></td>
</tr>
<tr>
<td>Positive family history for venous thromboembolism</td>
<td></td>
</tr>
<tr>
<td>Recurrent pregnancy loss</td>
<td></td>
</tr>
<tr>
<td>Repeated pregnancies with evidence of intrauterine growth retardation</td>
<td></td>
</tr>
</tbody>
</table>

* — Risk association between intrauterine growth retardation and thrombophilia is controversial.

Information from references 1, 7, 15, and 17.

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into question the cost-effectiveness of routinely testing patients with an initial idiopathic VTE. Routine testing has not been shown to be helpful in predicting risk of recurrence, deciding the duration of initial treatment, or determining the need for long-term prophylactic anticoagulation. A systematic review examining the risk of recurrence in persons with an initial idiopathic VTE found only a modest increase in risk in persons who were heterozygous for factor V Leiden or who had a prothrombin gene mutation. The difference between those with and those without either of these conditions was not significant, and patients did not benefit significantly from an extended period of anticoagulant therapy. An evidence report prepared for the Agency for Healthcare Research and Quality (AHRQ) on genetic testing in patients with a history of VTE found only low-grade evidence (derived from models) that testing for factor V Leiden, prothrombin G20210A mutation, or both is cost-effective when caring for patients with VTE or their family members. The AHRQ report also found low-grade evidence that these test results altered patient management decisions, and no direct evidence that testing leads to improved clinical outcomes, such as reduced incidence of recurrent VTE.

Updated guidelines from the American College of Chest Physicians (ACCP) shift the focus away from testing for the presence of a thrombophilia to assessing the risk of recurrent VTE based on location of the thrombus, whether it was idiopathic, and whether it was recurrent when considering treatment duration. Thrombophilia testing should be considered only if it is clear that the results would influence management decisions. For patients who have had a VTE, the knowledge of thrombophilia does not seem to have any specific impact on future management decisions, with the possible exception of antiphospholipid syndrome in pregnancy.

Table 4 summarizes guidelines for prevention of recurrent VTE in pregnancy.

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### Laboratory and Other Testing

Before the initiation of anticoagulant therapy, certain baseline laboratory studies should be ordered to confirm that anticoagulation would be safe for the patient (Table 3). Impaired liver or renal function may require adjustments to anticoagulant dosing. Laboratory testing may also identify potential persistent risk factors for recurrent thrombosis. For example, elevations in the hematocrit or platelet count, especially if splenomegaly is present, can suggest a myeloproliferative disorder; polycythemia or thrombocytosis may suggest an underlying occult malignancy; prolongation of the partial thromboplastin time that is not corrected using a 1:1 dilution with normal plasma may suggest lupus anticoagulant syndrome; and high levels of urine protein may suggest nephrotic syndrome.

Patients with venous thrombosis at atypical sites, such as the hepatic, mesenteric, or cerebral veins, and those with arterial thromboli should be evaluated for hematologic disorders and malignancy (see Evaluation for Malignancy section).

Recent studies have also identified other laboratory and imaging tests that can help predict recurrence or decide treatment duration. A persistently elevated D-dimer value one month after stopping anticoagulation has been associated with an increased risk of recurrent VTE. A recent systematic review found that patients with a negative D-dimer result after at least three months of anticoagulation had an annual recurrence rate of 3.5 percent, compared with 8.9 percent in those with a persistently elevated D-dimer.
result. In another study, the presence of residual thrombosis on ultrasonography after anticoagulation was associated with a significant risk of recurrence. However, the PROLONG study found that the presence of residual venous occlusion was not a risk factor for VTE recurrence, but confirmed that an elevated \( \text{d-dimer} \) result one month after anticoagulation withdrawal was a risk factor for VTE recurrence. Although \( \text{d-dimer} \)

### Table 4. ACCP Recommendations for Prevention of Recurrent VTE in Pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment*</th>
<th>Recommendation grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE secondary to transient risk factors</td>
<td>Antepartum clinical surveillance and postpartum anticoagulant prophylaxis</td>
<td>1C</td>
</tr>
<tr>
<td>Previous VTE related to pregnancy or estrogen therapy</td>
<td>Antepartum clinical surveillance or prophylactic or intermediate-dose LMWH/unfractionated heparin plus postpartum anticoagulant prophylaxis</td>
<td>2C</td>
</tr>
<tr>
<td>Previous single unprovoked (idiopathic) VTE without thrombophilia or with laboratory-confirmed thrombophilia but patient not on long-term anticoagulants</td>
<td>Prophylactic or intermediate-dose LMWH/unfractionated heparin or clinical surveillance throughout pregnancy plus postpartum anticoagulants</td>
<td>1C</td>
</tr>
<tr>
<td>Higher risk thrombophilias (i.e., antithrombin deficiency, antiphospholipid syndrome, compound heterozygous for prothrombin G20210A mutation and factor V Leiden, or homozygous for either condition) with a single previous VTE and patient not on long-term anticoagulants</td>
<td>Antepartum prophylactic or intermediate-dose LMWH/unfractionated heparin plus postpartum anticoagulants</td>
<td>2C</td>
</tr>
<tr>
<td>At least two episodes of VTE and patient not on long-term anticoagulants</td>
<td>Antepartum prophylactic, intermediate-dose, or adjusted-dose LMWH/unfractionated heparin plus postpartum anticoagulants</td>
<td>2C</td>
</tr>
<tr>
<td>Patient receiving long-term anticoagulants for previous VTE</td>
<td>Adjusted-dose or intermediate-dose LMWH/unfractionated heparin throughout pregnancy followed by resumption of long-term anticoagulants postpartum</td>
<td>1C</td>
</tr>
</tbody>
</table>

ACCP = American College of Chest Physicians; INR = International Normalized Ratio; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; SQ = subcutaneously; VTE = venous thromboembolism.

*—Prophylactic unfractionated heparin: 5,000 units SQ every 12 hours; intermediate-dose unfractionated heparin: administered SQ every 12 hours in doses adjusted to target an anti-Xa level of 0.1 to 0.3 units per ml; adjusted-dose unfractionated heparin: administered SQ every 12 hours in doses adjusted to target a midinterval activated partial thromboplastin time in the therapeutic range; prophylactic LMWH: for example, dalteparin (Fragmin) 5,000 units SQ every 24 hours, tinzaparin 4,500 units SQ every 24 hours, or enoxaparin (Lovenox) 40 mg SQ every 24 hours (with extremes of body weight, dosage modification may be required); intermediate-dose LMWH: for example, dalteparin 5,000 units SQ every 12 hours or enoxaparin 40 mg SQ every 12 hours; adjusted-dose LMWH: weight-adjusted, full-treatment doses of LMWH given once or twice daily (e.g., dalteparin 200 units per kg or tinzaparin 175 units per kg daily, dalteparin 100 units per kg or enoxaparin 1 mg per kg every 12 hours); postpartum anticoagulants: warfarin (Coumadin) for 4 to 6 weeks for a target INR of 2.0 to 3.0, with initial unfractionated heparin or LMWH overlap until the INR is at least 2.0, or prophylactic LMWH for 4 to 6 weeks.

†—ACCP grading scale: 1A = strong recommendation, high-quality evidence, consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; 1B = strong recommendation, moderate-quality evidence, evidence from RCTs with important limitations or very strong evidence from observational studies; 1C = strong recommendation, low- or very low-quality evidence, evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence; 2A = weak recommendation, high-quality evidence, consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; 2B = weak recommendation, moderate-quality evidence, evidence from RCTs with important limitations, or very strong evidence from observational studies; 2C = weak recommendation, low- or very low-quality evidence, evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence.

Information from references 7 and 22.
Table 5. Suggested Baseline Laboratory Studies for Patients with Venous Thromboembolism

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
<th>Associated condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>Increased hematocrit or platelet count, plus splenomegaly Polycythemia or thrombocytosis</td>
<td>Myeloproliferative disorder Occult malignancy</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>Elevated result that does not correct using 1:1 dilution with normal plasma</td>
<td>Lupus anticoagulant syndrome</td>
</tr>
<tr>
<td>Serum chemistries*</td>
<td>Elevated result</td>
<td>Impaired liver or renal function (dosage adjustments may be required to prevent bleeding complications)</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>Proteinuria</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Hematuria</td>
<td>Occult malignancy</td>
</tr>
</tbody>
</table>

*—Blood urea nitrogen, creatinine, alanine transaminase, aspartate transaminase.

Information from references 5, and 23 through 26.

measurement after the cessation of anticoagulation is a promising tool, it has not yet been incorporated into practice guidelines.

Timing of Testing
The thrombotic event itself or treatment with heparin or warfarin (Coumadin) can influence the results of assays for thrombophilias and d-dimer testing to assess the risk of recurrence. Systemic conditions, such as acute inflammatory response processes, liver failure, nephrotic syndrome, and disseminated intravascular coagulation, can also affect these tests. Therefore, measurement of these functional assays should be postponed until the thrombotic event is resolved and anticoagulant therapy has been discontinued for three to four weeks. Because antiphospholipid antibodies are acquired and may be transient, these laboratory tests should be repeated at least once 12 weeks after an initial positive result to confirm the diagnosis. The notable exception is genetic testing for factor V Leiden and prothrombin G20210A mutation, which can be ordered at any time.

Evaluation for Malignancy
VTE may be the first manifestation of an underlying occult malignancy or may indicate recurrence of a previously treated cancer. A systematic review found that approximately 10 percent of patients who presented with an unprovoked or idiopathic VTE received a cancer diagnosis within one year of the thrombotic event. An unprovoked VTE is most commonly associated with pancreatic, lung, and gastrointestinal cancers. Other associated malignancies include prostate, ovarian, and brain cancers, lymphoma, and acute leukemia. Therefore, patients should be asked about history of cancer or constitutional symptoms that may suggest an underlying malignancy (e.g., loss of appetite, weight loss, fatigue, pain, hematochezia, hemoptysis, hematuria). In addition to a thorough history, a complete physical examination should be performed, including colorectal cancer screening and a pelvic examination in women. However, detection of an occult malignancy is clinically important only if it leads to improved survival, which often is not the case if the malignancy has metastasized and is causing constitutional symptoms.

Data from the Computerized Registry of Patients with Venous Thromboembolism (RIETE registry) found that occult malignancy was more common in patients 60 to 75 years of age and in those with idiopathic VTE, bilateral deep venous thrombosis, or anemia. Other recent reviews have compared the benefits of limited versus extensive cancer screening protocols. In most of the studies, limited screening involved a history, physical examination, laboratory blood testing (i.e., complete blood count, electrolyte levels, creatinine level, calcium level, liver function tests), urinalysis, and chest radiography. Extensive screening included limited screening plus ultrasonography or computed tomography of the abdomen and pelvis,
Table 6. ACCP Recommendations for Duration of Anticoagulation Therapy in Patients with VTE

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration of therapy</th>
<th>Recommendation grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First VTE provoked by transient risk factor (see Table 1)</td>
<td>3 months</td>
<td>1A</td>
</tr>
<tr>
<td>First unprovoked (idiopathic), distal DVT</td>
<td>At least 3 months†‡</td>
<td>1A</td>
</tr>
<tr>
<td>First unprovoked, proximal DVT</td>
<td>Long-term therapy§</td>
<td>1A</td>
</tr>
<tr>
<td>Second unprovoked VTE</td>
<td>Long-term therapy§</td>
<td>1A</td>
</tr>
<tr>
<td>Unprovoked pulmonary embolism</td>
<td>At least 3 months†‡</td>
<td>1A</td>
</tr>
<tr>
<td>VTE and cancer</td>
<td>3 to 6 months of LMWH or Continued treatment with LMWH or vitamin K antagonist for as long as the cancer is active</td>
<td>1A 1C</td>
</tr>
</tbody>
</table>

ACCP = American College of Chest Physicians; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; VTE = venous thromboembolism.

*—ACCP grading scale: 1A = strong recommendation, high-quality evidence, consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; 1B = strong recommendation, moderate-quality evidence, evidence from RCTs with important limitations or very strong evidence from observational studies; 1C = strong recommendation, low- or very low-quality evidence, evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence; 2A = weak recommendation, high-quality evidence, consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; 2B = weak recommendation, moderate-quality evidence, evidence from RCTs with important limitations, or very strong evidence from observational studies; 2C = weak recommendation, low- or very low-quality evidence, evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence.

†—After 3 months, all patients should be evaluated for risk-to-benefit ratio of long-term therapy (grade 1C recommendation).

‡—Three months of anticoagulant therapy is sufficient rather than indefinite therapy, which is continued without a scheduled stop date until the risk of bleeding increases or patient preference changes (grade 2B recommendation).

§—Long-term therapy is recommended only for those who do not have risk factors for bleeding (i.e., older age, particularly > 75 years; previous gastrointestinal bleeding if not associated with reversible cause; previous noncardioembolic stroke; chronic renal or hepatic disease; concomitant antiplatelet therapy; severe chronic illness; poor anticoagulant control; and suboptimal monitoring of anticoagulation) and if good monitoring of anticoagulation is achievable. Long-term therapy refers to continued treatment after the initial therapy (heparin or thrombolytics). Early phase of long-term therapy (first 3 months) treats acute episode, and late phase of long-term therapy (after 3 months) focuses on preventing new VTE episodes.

Information from references 4 and 22.

and measurement of tumor markers (e.g., prostate-specific antigen, carcinoembryonic antigen, cancer antigen 125). Of the 10 percent of patients with cancer, approximately one-half could be identified with limited screening. The extensive screening protocol increased this detection rate to 67 percent. However, these studies did not determine whether increased detection through extensive screening is cost-effective, reduces morbidity, or improves survival. Because the clinical usefulness of extensive screening has not been established, only limited screening for malignancy can be recommended in patients with idiopathic VTE.

Duration of Therapy
The ACCP guidelines on antithrombotic and thrombolytic therapy do not recommend testing for the presence of a hereditary thrombophilia to guide decisions on the duration of anticoagulant therapy. This is based on data from several prospective studies that suggest that results of this testing are not major determinants in predicting the risk of recurrence. Instead, the guidelines recommend using clinical factors, such as whether the deep venous thrombosis was confined to a distal or proximal vein, whether the thrombotic episode was an initial or recurrent episode, and whether transient risk factors were present. Table 6 summarizes the ACCP
guidelines on duration of anticoagulant therapy. Patients with known malignancy should be treated with low-molecular-weight heparin, as long as the cancer is active. All other patients, regardless of clinical factors, should receive at least three months of anticoagulant therapy. However, the optimal duration of therapy depends on balancing the risk of recurrence, the risk of major hemorrhage (approximately 1 percent per year in low-risk patients), and the cost and inconvenience of anticoagulation. The D-dimer test shows promise in guiding treatment duration, but further refinements are needed before such testing is routine.

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Author disclosure: Nothing to disclose.

REFERENCES

Recurrent VTE


Chronic Thromboembolic Pulmonary Hypertension

Gregory Piazza, M.D., and Samuel Z. Goldhaber, M.D.

Chronic thromboembolic pulmonary hypertension is defined as mean pulmonary-artery pressure greater than 25 mm Hg that persists 6 months after pulmonary embolism is diagnosed. The 2008 World Symposium on Pulmonary Hypertension emphasized the importance of chronic thromboembolic pulmonary hypertension, which occurs in 2 to 4% of patients after acute pulmonary embolism. The frequency of this condition among patients with pulmonary hypertension is unknown. Patients with chronic thromboembolic pulmonary hypertension generally present in their 40s, although this condition has been reported in patients in other age groups. The diagnosis is often overlooked because many patients do not have a history of clinically overt pulmonary embolism.

The natural history of chronic thromboembolic pulmonary hypertension has been difficult to determine because a subgroup of patients have had occult pulmonary embolism, with subtle clues to the diagnosis that became apparent only in retrospect. Patients with chronic thromboembolic pulmonary hypertension typically have a honeymoon period after acute pulmonary embolism, during which symptoms are absent despite the onset of pulmonary hypertension. Long-term follow-up of patients with chronic thromboembolic pulmonary hypertension, including those with mild symptoms and those who are asymptomatic, is needed to elucidate the natural history of this disease.

Although symptomatic disease develops in a substantial proportion of patients, the clinical importance of asymptomatic chronic thromboembolic pulmonary hypertension remains controversial. This condition is usually detected when pulmonary hypertension worsens and causes dyspnea, hypoxemia, and right ventricular dysfunction. Death is usually due to progressive pulmonary hypertension culminating in right ventricular failure. The risk of the development of chronic thromboembolic pulmonary hypertension is increased by factors associated with pulmonary embolism, certain chronic medical conditions, thrombophilia, and a genetic predisposition (Table 1). Thyroid disease is a risk factor for both chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension.

Currently, no pharmacologic regimen helps prevent chronic thromboembolic pulmonary hypertension, except anticoagulation with or without fibrinolysis. When administered in hemodynamically stable patients with right ventricular dysfunction due to acute pulmonary embolism (submassive pulmonary embolism), fibrinolytic therapy has been shown to reduce the frequency of chronic thromboembolic pulmonary hypertension. Such therapy, which is most effective if administered within 2 weeks after acute pulmonary embolism is detected, is considered a lifesaving intervention in patients with massive pulmonary embolism but remains
humoral factors, including endothelin-1, play a central role in chronic thromboembolic pulmonary hypertension as potent vasoconstrictors and as triggers of microvascular changes.\textsuperscript{17} Reductions in the cross-sectional area of the pulmonary arteries due to thrombosis and vasoconstriction cause further abnormal vascular remodeling. In situ thrombosis may also accompany secondary small-vessel arteriopathy. The combination of persistent macrovascular obstruction, small-vessel arteriopathy, and vasoconstriction results in pulmonary hypertension and right ventricular pressure overload that exceeds the level expected from macrovascular obstruction alone. Persistent increases in pulmonary vascular resistance due to continued vascular remodeling and vasoconstriction in chronic thromboembolic pulmonary hypertension result in pulmonary-artery systolic pressures that are typically greater than those in acute pulmonary embolism.

### Clinical Presentation

Exercise intolerance, fatigue, and dyspnea are the most commonly reported symptoms. Subsequently, patients may report chest discomfort, syncope, hemoptysis, light-headedness, or peripheral leg edema. Diagnostic delays are common because many patients do not provide a history of pulmonary embolism. In patients without a history of pulmonary embolism, we recommend that clinicians take the history again to identify any clinical events that might be consistent with venous thromboembolism. If no event suggestive of pulmonary embolism is identified, clinicians should consider diagnoses other than chronic thromboembolic pulmonary hypertension.

Initial findings of pulmonary hypertension, including chronic thromboembolic pulmonary hypertension, may include a reduction in the splitting of the second heart sound (S\textsubscript{2}), accentuation of the sound of pulmonary closure (P\textsubscript{2}), and a palpable right ventricular heave. Subsequent findings correspond to decreasing right ventricular function; jugular venous distention, fixed splitting of S\textsubscript{2}, a right-sided third heart sound (S\textsubscript{3}), tricuspid regurgitation, hepatomegaly, ascites, and peripheral edema. Subtle bruits may be heard on auscultation over the peripheral lung fields; they arise from turbulent flow through partially obstructed pulmonary arteries. The 6-minute walk test may be a useful component of the evaluation because it

### Table 1. Risk Factors for Chronic Thromboembolic Pulmonary Hypertension.

<table>
<thead>
<tr>
<th>Factors specific to pulmonary embolism</th>
<th>Chronic medical conditions</th>
<th>Thrombotic factors</th>
<th>Genetic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent or unprovoked pulmonary embolism</td>
<td>Infected surgical cardiac shunts or pacemaker or defibrillator leads</td>
<td>Lupus anticoagulant or antiphospholipid antibodies</td>
<td>ABO blood groups other than O</td>
</tr>
<tr>
<td>Large perfusion defects when pulmonary embolism detected</td>
<td>Postpneumonectomy</td>
<td>Increased levels of factor VIII</td>
<td>HLA polymorphisms</td>
</tr>
<tr>
<td>Young or old age when pulmonary embolism detected</td>
<td>Chronic inflammatory disorders</td>
<td>Dysfibrinogenemia</td>
<td>Abnormal endogenous fibrinolysis</td>
</tr>
<tr>
<td>Pulmonary-artery systolic pressure &gt;50 mm Hg at initial manifestation of pulmonary embolism</td>
<td>Thyroid-replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent pulmonary hypertension on echocardiography performed 6 mo after acute pulmonary embolism detected</td>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

controversial in the treatment of patients with submassive pulmonary embolism.\textsuperscript{12}

### Pathophysiology

In 1973, Moser and Braunwald\textsuperscript{13} discovered a paradox when they examined the histopathological features of specimens obtained from patients who had undergone pulmonary thromboendarterectomy. They detected marked small-vessel abnormalities that appeared similar to idiopathic pulmonary arterial hypertension distal to patent pulmonary arterial segments, whereas tissue distal to occluded segments appeared to be normal (Fig. 1). The small-vessel arteriopathy is characterized by medial hypertrophy and intimal proliferation, microvascular thrombosis, and plexiform-lesion formation (Fig. 2).

Chronic thromboembolic pulmonary hypertension results in persistent macrovascular obstruction and vasoconstriction. Chronic staphylococcal infection,\textsuperscript{14} abnormal sialylation of fibrinogen \(\gamma\)-chains,\textsuperscript{15} and abnormal fragmentation of fibrinogen\textsuperscript{16} have been proposed as mechanisms for ineffective fibrinolysis. Neuro-
Figure 1. Pathophysiological Features of the Pulmonary Vasculature in Chronic Thromboembolic Pulmonary Hypertension.
Chronic thromboembolic pulmonary hypertension results from persistent macrovascular obstruction and a vasoconstrictor response that lead to a secondary small-vessel arteriopathy. Reductions in the pulmonary-artery diameter due to thrombosis and vasoconstriction result in adverse vascular remodeling.
reflects the clinical and hemodynamic severity of disease. Specific levels for distance walked or desaturation have not been standardized. At specialized centers, the 6-minute walk distance is used to assess the prognosis and gauge the patient’s response to therapy.

DIAGNOSIS

After a thorough history taking and physical examination, patients with symptoms and signs of pulmonary hypertension and a clinical history compatible with pulmonary embolism or pulmonary hypertension of unexplained cause should be evaluated for chronic thromboembolic pulmonary hypertension with the use of imaging tests (Fig. 3). A broad workup for causes of pulmonary hypertension, including a rheumatologic panel, polysomnography, and thrombophilia testing, is unnecessary if there is a reasonable suspicion of chronic thromboembolic pulmonary hypertension. Referral to specialized centers for additional invasive testing, such as right heart catheterization and pulmonary angiography, may be advisable to define the anatomical location and extent of obstruction and to quantify the degree of pulmonary hypertension. Although not required for the diagnosis, invasive coronary angiography, pulmonary-function tests, and cardiopulmonary exercise testing may occasionally be useful to evaluate certain patients with established chronic thromboembolic pulmonary hypertension or to rule out alternative or concomitant diagnoses. Among patients with this condition, coronary angiography is typically unremarkable, whereas pulmonary-function tests and cardiopulmonary exercise testing are frequently abnormal.

Routine echocardiographic evaluation to detect persistent pulmonary hypertension within 6 months after acute pulmonary embolism may help to identify patients who are at increased risk for chronic thromboembolic pulmonary hypertension. Such testing may lead to early diagnosis of this disease and therefore may improve management and outcomes. However, this hypothesis remains to be proved.

Differentiating chronic thromboembolic pulmonary hypertension from recurrent pulmonary embolism can be challenging because there is an overlap among risk factors for the two conditions. Clues that suggest chronic thromboembolic pulmonary hypertension (as opposed to recurrent pulmonary embolism) include a gradual progression of symptoms and signs of pulmonary hypertension and right ventricular failure (rather than profound episodic exacerbations) and lack of a response to fibrinolytic therapy or at least 6 months of antithrombotic therapy. Differentiating persistent elevation of pulmonary-artery
pressures from preexisting pulmonary-artery hypertension with acute pulmonary-artery embolism and subsequently elevated pulmonary-artery pressures is a common problem. Clinicians should look for stepwise increases in pulmonary-artery pressures and episodic changes in symptoms as indicators of an intercurrent pulmonary embolism.

**IMAGING**

In the majority of patients with chronic thromboembolic pulmonary hypertension, echocardiography provides the first clues to the diagnosis by detecting the presence of pulmonary hypertension. Pulmonary hypertension with or without right ventricular dysfunction should raise concern about chronic thromboembolic pulmonary hypertension in a patient with a compatible history. Transthoracic echocardiography with Doppler imaging is sensitive for the detection of pulmonary hypertension and right ventricular dysfunction, but it is not specific for the diagnosis of chronic thromboembolic pulmonary hypertension. Common echocardiographic findings include right ventricular dilatation, hypertrophy, and hypokinesis; right atrial enlargement; right ventricular pressure overload as suggested by interventricular septal deviation toward the left ventricle during systole; and tricuspid regurgitation. The tricuspid regurgitant jet gradient provides an estimate of the pulmonary-artery systolic pressure. In rare cases, transthoracic echocardiography shows proximal pulmonary-artery thrombus. However, echocardiography cannot be used to reliably differentiate among acute, subacute, and chronic pulmonary embolism.

Ventilation–perfusion lung scanning may be used to differentiate chronic thromboembolic pulmonary hypertension from other causes of pulmonary hypertension. Normal findings on ventilation–perfusion lung scanning practically rule out the diagnosis, whereas multiple bilateral perfusion defects suggest chronic thromboembolic pulmonary hypertension as a likely diagnosis. Ventilation–perfusion lung scanning does not anatomically localize the extent of disease and cannot be used to determine surgical accessibility.

Chest computed tomographic angiography (CTA) may show eccentric thromboembolic material, subpleural densities, right ventricular enlargement, and a mosaic parenchymal pattern. CTA may complement the information obtained from ventilation–perfusion lung scanning by providing additional data regarding anatomical localization and surgical accessibility. The accuracy of CTA for detecting abnormalities is greatest in the main and lobar pulmonary arteries and subsequently decreases in the segmental and subsegmental vessels. Magnetic resonance angiography is an alternative form of imaging that remains unproven for the diagnosis of chronic thromboembolic pulmonary hypertension, but it has shown limited sensitivity (78%) for the diagnosis of acute pulmonary embolism.

We prefer CTA as the initial imaging test because expertise in the interpretation of ventilation–perfusion lung scanning is waning. If either CTA or ventilation–perfusion lung scanning is inconclusive for chronic thromboembolic pulmonary hypertension or if surgery is being considered, right heart catheterization and pulmonary angiography are typically performed to...
confirm the diagnosis and further define the physiological and anatomical characteristics. Invasive pulmonary angiography is not used as the initial test of choice because noninvasive forms of imaging, in particular CTA, provide information regarding alternative diagnoses and show baseline abnormalities that may be compared in serial follow-up studies. Right heart catheterization with pulmonary angiography continues to be the standard for establishing the diagnosis and assessing operability. Specific angiographic patterns that correlate with operative findings include pulmonary-artery webs or bands, intimal irregularities, abrupt stenoses of major pulmonary arteries, and obstruction of lobar or segmental arteries at their origins.25,26

HEMODYNAMIC EVALUATION
Right heart catheterization performed in conjunction with invasive pulmonary angiography quantifies the degree of pulmonary hypertension and can be used to assess responsiveness to vasodilator therapy. A reduction in pulmonary-artery pressure after administration of a vasodilator, inhaled nitric oxide, may be indicative of increased long-term survival among patients with chronic thromboembolic pulmonary hypertension who undergo pulmonary thromboendarterectomy.27

ROLE OF SPECIALIZED CENTERS IN DIAGNOSIS
Patients with pulmonary hypertension and findings of pulmonary embolism on CTA or ventilation-perfusion lung scanning and those with unexplained elevations in pulmonary-artery systolic pressure should be referred to specialized centers. Additional testing, such as right heart catheterization with vasodilator challenge and pulmonary angiography to establish the diagnosis of chronic thromboembolic pulmonary hypertension and to determine suitability for pulmonary thromboendarterectomy, is best performed at centers that are experienced in such procedures. Furthermore, specialized centers can offer advanced therapy such as pulmonary thromboendarterectomy as well as enrollment in clinical trials of medical therapy for patients who are ineligible for surgery.

TREATMENT
The most effective therapy for chronic thromboembolic pulmonary hypertension is pulmonary thromboendarterectomy.28 Advanced medical therapy, which includes any medical intervention in addition to anticoagulation, is considered in patients with inoperable disease or those with persistent or recurrent pulmonary hypertension after pulmonary thromboendarterectomy.

PULMONARY THROMBOENDARTERECTOMY
Successful pulmonary thromboendarterectomy removes obstructive, whitish, hardened thromboembolic material and markedly improves the hemodynamic measures of mean pulmonary-artery pressure, pulmonary vascular resistance, and cardiac output (Fig. 4).29,30 Improvement in hemodynamics causes reverse right ventricular remodeling, with reductions in tricuspid regurgitation and the return of right ventricular systolic and diastolic function toward normal levels.31-33 Hemodynamics and measures of functional capacity, such as the 6-minute walk distance and New York Heart Association (NYHA) class, markedly improve after successful pulmonary thromboendarterectomy, and the beneficial effect usually persists,30,34 unless small-vessel arteriopathy or recurrent pulmonary embolism develops. Data are lacking from clinical trials comparing survival among patients with chronic thromboembolic pulmonary hypertension treated with pulmonary thromboendarterectomy with survival among those treated nonsurgically.

When successful, pulmonary thromboendarterectomy improves hemodynamics, symptoms, and functional status. Data are lacking to provide support for the use of advanced medical therapy preoperatively.35 Pulmonary thromboendarterectomy is performed with the use of cardiopulmonary bypass with intermittent circulatory arrest to permit dissection from the main pulmonary arteries to the subsegmental branches. Patients with symptomatic chronic thromboembolic pulmonary hypertension, surgically accessible disease, and an acceptable perioperative risk should be referred for pulmonary thromboendarterectomy. Preoperative predictors of favorable outcomes include a pulmonary vascular resistance of less than 1200 dyn·sec·cm⁻² and the absence of major coexisting conditions.35 Patients in whom the postoperative pulmonary vascular resistance decreases by at least 50%, to a value of less than 500 dyn·sec·cm⁻², have a more favorable prognosis after surgery than those who do not.28 In contrast to the short-term response to inhaled nitric oxide, the response to the long-term use of pulmonary vasodilators, such as bosentan, sil-
denafil, or prostacyclin analogues, does not appear to predict hemodynamics or outcomes after pulmonary thromboendarterectomy.35

Contraindications to pulmonary thromboendarterectomy include small-vessel disease as suggested by a pulmonary vascular resistance that is out of proportion to the degree of obstruction noted on imaging, an expected postoperative reduction in pulmonary vascular resistance of less than 50%, and a prohibitive perioperative risk. The perioperative risk is assessed as it is for any intrathoracic procedure requiring cardiopulmonary bypass, and it incorporates center-specific morbidity and mortality associated with pulmonary thromboendarterectomy. The 30-day mortality ranges from less than 5% in the most experienced centers to 10% elsewhere.39,30,34

The two most common anticipated postoperative sequelae are the pulmonary-artery steal syndrome, which occurs when blood flow is redistributed from previously well-perfused segments to newly opened ones, and reperfusion pulmonary edema. Late adverse events include residual elevation in pulmonary-artery pressure and recurrent pulmonary hypertension in patients who initially had hemodynamic improvement after surgery. Residual pulmonary hypertension, which may result from incomplete endarterectomy, inaccessible chronic thromboemboli, or small-vessel arteriopathy, is itself an important predictor of late postoperative adverse events.30 Postoperative NYHA class III or IV symptoms, unsuccessful pulmonary thromboendarterectomy, high pulmonary vascular resistance, and persistent abnormalities of gas exchange are also associated with an increased risk of late adverse events.30 Inferior vena cava filters are usually implanted perioperatively, but their necessity has been challenged at some centers.

BALLOON PULMONARY-ARTERY ANGIOPLASTY
Balloon pulmonary-artery angioplasty is an alternative therapy in selected patients who have
inoperable disease due to distal surgically inaccessible disease or persistent or recurrent pulmonary hypertension after thromboendarterectomy. Successful balloon pulmonary angioplasty may reduce pulmonary-artery pressure in patients with chronic thromboembolic pulmonary hypertension. Improvement in the NYHA functional class and the 6-minute walk distance has also been observed after successful balloon pulmonary angioplasty. However, experience with this procedure is very limited, and it is rarely performed.

**MEDICAL THERAPY**

Anticoagulation is prescribed in most patients with chronic thromboembolic pulmonary hypertension, although data are lacking from randomized clinical trials to support this widespread practice. The rationale is to prevent in situ pulmonary-artery thrombosis and recurrent venous thromboembolism. Among patients with unprovoked or idiopathic pulmonary embolism, an indefinite duration of anticoagulation has reduced the risk of recurrent venous thromboembolism.

Prescription of advanced medical therapy with pulmonary vasodilators may contribute to increased survival among patients with inoperable disease. The underlying principle for this practice is that the morphologic characteristics of vessels in chronic thromboembolic pulmonary hypertension closely resemble those in idiopathic pulmonary arterial hypertension. Patients with chronic thromboembolic pulmonary hypertension may have acute vasoreactivity to inhaled pulmonary vasodilators, suggesting at least some shared pathophysiological features. Advanced medical therapies include the endothelin-receptor antagonist sitaxsentan and ambrisentan and the phosphodiesterase inhibitor tadalafil. Evaluation of these agents in the medical treatment of patients with chronic thromboembolic pulmonary hypertension is an important area for further research. A new soluble guanylate cyclase stimulator, riociguat, has been evaluated in chronic thromboembolic pulmonary hypertension and has shown promise.

**THERAPEUTIC ALGORITHM**

The pivotal decision is to identify patients with surgically accessible chronic thromboemboli in whom pulmonary thromboendarterectomy is expected to result in a substantial reduction in pulmonary vascular resistance. Advanced medical therapy should be reserved for patients with inoperable disease and those with persistent or recur-
rent pulmonary hypertension after pulmonary thromboendarterectomy. Patients with chronic thromboembolic pulmonary hypertension for whom pulmonary thromboendarterectomy or vasodilator therapy is being considered should be referred to centers that have experience in the management of this complex disorder and can offer an array of treatment protocols and enrollment in clinical trials. Online resources such as the Pulmonary Hypertension Association Web site (www.phassociation.org), which provide information regarding centers of excellence in the management of chronic thromboembolic pulmonary hypertension, are available to patients and providers.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES


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Management of Acute Asthma Exacerbations

SUSAN M. POLLART, MD, MS; REBEKAH M. COMPTON, MSN, FNP-C; and KURTIS S. ELWARD, MD, MPH
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Asthma exacerbations can be classified as mild, moderate, severe, or life threatening. Criteria for exacerbation severity are based on symptoms and physical examination parameters, as well as lung function and oxygen saturation. In patients with a peak expiratory flow of 50 to 79 percent of their personal best, up to two treatments of two to six inhalations of short-acting beta, agonists 20 minutes apart followed by a reassessment of peak expiratory flow and symptoms may be safely employed at home. Administration using a hand-held metered-dose inhaler with a spacer device is at least equivalent to nebulized beta, agonist therapy in children and adults. In the ambulatory and emergency department settings, the goals of treatment are correction of severe hypoxemia, rapid reversal of airflow obstruction, and reduction of the risk of relapse. Multiple doses of inhaled anticholinergic medication combined with beta, agonists improve lung function and decrease hospitalization in school-age children with severe asthma exacerbations. Intravenous magnesium sulfate has been shown to significantly increase lung function and decrease the necessity of hospitalization in children. The administration of systemic corticosteroids within one hour of emergency department presentation decreases the need for hospitalization, with the most pronounced effect in patients with severe exacerbations. Airway inflammation can persist for days to weeks after an acute attack; therefore, more intensive treatment should be continued after discharge until symptoms and peak expiratory flow return to baseline. (Am Fam Physician. 2011;84(1):40-47. Copyright © 2011 American Academy of Family Physicians.)

In 2005, the prevalence of asthma in the United States was nearly 8 percent (close to 9 percent in children younger than 18 years), and approximately 4 percent of Americans (5 percent of children) experienced an asthma attack.1,2 There have been many advances in medical therapy to prevent the worsening of asthma symptoms, including an improved understanding of asthma etiology, identification of risk factors for asthma exacerbations, and evidence supporting the benefits of written asthma action plans.

One study of children up to 18 years of age presenting to the emergency department with acute asthma symptoms identified multiple risk factors for a subsequent emergency department visit: age younger than two years, black race or Hispanic ethnicity, persistent asthma, public health insurance, lower asthma quality-of-life scores, and increased use of the health care system during the previous 12 months.3 In adults, variables associated with relapse within eight weeks of an asthma exacerbation include three or more visits for emergent care in the preceding six months, difficulty performing daily activities because of physical health in the preceding four weeks, and patient self-discharge from care within 24 hours of hospital admission without achieving 50 percent predicted peak expiratory flow (PEF).4 However, regular monitoring of PEF does not help predict an asthma exacerbation.5 Other risk factors for developing an asthma exacerbation include allergen triggers (e.g., pets, seasonal allergens, smoke exposure) and improper use of medications (e.g., not using a spacer, improper use of an inhaler or other delivery device).6

In persons older than two years with asthma, neither the injectable nor the intranasal influenza vaccine increases the likelihood of an asthma exacerbation in the period immediately following vaccination. However, one study of infants found an increase in wheezing and hospital admissions...
### Sort: Key Recommendations for Practice

<table>
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<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
<th>Comments</th>
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<tr>
<td>Inhaled short-acting beta₂ agonists are the cornerstones of treatment for acute asthma.</td>
<td>C</td>
<td>14-16</td>
<td>—</td>
</tr>
<tr>
<td>An inhaler with a spacer is equivalent to nebulized short-acting beta₂ agonist therapy in children and adults.</td>
<td>A</td>
<td>17, 18</td>
<td>—</td>
</tr>
<tr>
<td>Continuous beta₂ agonist administration reduces hospital admissions in patients with severe acute asthma.</td>
<td>A</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>Inhaled anticholinergic medication improves lung function and decreases hospitalization in school-age children with severe asthma exacerbations.</td>
<td>A</td>
<td>24, 25</td>
<td>When multiple doses are used in combination with short-acting beta₂ agonists</td>
</tr>
<tr>
<td>Intravenous magnesium sulfate increases lung function and decreases hospitalizations in children with an acute asthma exacerbation.</td>
<td>A</td>
<td>29</td>
<td>—</td>
</tr>
<tr>
<td>The administration of systemic corticosteroids within one hour of emergency department presentation decreases the need for hospitalization.</td>
<td>A</td>
<td>30</td>
<td>Largest effect noted in patients with severe asthma</td>
</tr>
<tr>
<td>Oral and parenteral corticosteroids are equally effective in preventing hospital admission in children.</td>
<td>B</td>
<td>31</td>
<td>—</td>
</tr>
</tbody>
</table>

* A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afp/sort.xml.

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**Table 1. Classifications of Severity of an Asthma Exacerbation**

<table>
<thead>
<tr>
<th>Degree of severity</th>
<th>Symptoms and signs</th>
<th>Initial PEF (or FEV₁)</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Dyspnea only with activity (assess tachypnea in young children)</td>
<td>PEF ≥ 70 percent of predicted or personal best</td>
<td>Usually treated at home; Prompt relief with inhaled short-acting beta₂ agonist; Possible short course of oral systemic corticosteroids</td>
</tr>
<tr>
<td>Moderate</td>
<td>Dyspnea interferes with or limits usual activity</td>
<td>PEF 40 to 69 percent of predicted or personal best</td>
<td>Usually requires office or emergency department visit; Relief from frequent inhaled short-acting beta₂ agonist; Oral systemic corticosteroids; some symptoms last for one to two days after treatment begins</td>
</tr>
<tr>
<td>Severe</td>
<td>Dyspnea at rest; interferes with conversation</td>
<td>PEF &lt; 40 percent of predicted or personal best</td>
<td>Usually requires emergency department visit and likely hospitalization; Partial relief from frequent inhaled short-acting beta₂ agonist; Oral systemic corticosteroids; some symptoms last for more than three days after treatment begins; Adjunctive therapies are helpful</td>
</tr>
<tr>
<td>Subset: life threatening</td>
<td>Too dyspneic to speak; perspiration</td>
<td>PEF &lt; 25 percent of predicted or personal best</td>
<td>Requires emergency department visit/hospitalization; possible intensive care unit; Minimal or no relief from frequent inhaled short-acting beta₂ agonist; Intravenous corticosteroids; Adjunctive therapies are helpful</td>
</tr>
</tbody>
</table>

*FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow.*


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After intranasal influenza vaccination, seasonal influenza vaccine does not reduce the risk of developing an asthma exacerbation. Influenza vaccination appears to improve asthma-related quality-of-life in children during influenza season.

**Diagnosis**

Asthma exacerbations can be classified as mild, moderate, severe, or life threatening (Table 1). Criteria for severity are based on symptoms and physical examination parameters, as well as lung function and oxygen...
Management of Asthma Exacerbations: Home Treatment

Assess severity
Patients at high risk of a fatal asthma attack require immediate medical attention after initial treatment.
Symptoms and signs suggestive of a more serious exacerbation (e.g., marked breathlessness, inability to speak more than short phrases, use of accessory muscles, drowsiness) require immediate and immediate consultation with a physician. Less severe signs and symptoms can be treated initially with assessment of response to therapy and further steps, as listed below.
If available, measure PEF; persons at 50 to 79 percent of predicted or personal best need quick-relief medication. Depending on the response to treatment, consultation with a physician also may be needed. Persons with PEF below 50 percent need immediate medical care.

Initial treatment
Inhaled short-acting beta, agonist: up to two treatments, 20 minutes apart, of two to six puffs by metered-dose inhaler with spacer or nebulizer treatments.
NOTE: Medication delivery is highly variable; children and persons who have exacerbations of lesser severity may need fewer puffs.

Good response
No wheezing or dyspnea (assess tachypnea in young children).
PEF ≥ 80 percent of predicted or personal best
• Contact physician for follow-up instructions and further management.
• May continue inhaled short-acting beta, agonist every three to four hours for 24 to 48 hours.
• Consider short course of oral systemic corticosteroid.

Incomplete response
Persistent wheezing and dyspnea (tachypnea).
PEF of 50 to 79 percent of predicted or personal best
• Add oral systemic corticosteroid.
• Continue inhaled short-acting beta, agonist.
• Contact physician immediately for further instructions.

Poor response
Marked wheezing and dyspnea.
PEF < 50 percent of predicted or personal best
• Add oral systemic corticosteroid.
• Repeat inhaled short-acting beta, agonist immediately.
• If distress is severe and nonresponsive to initial treatment: call physician and proceed to the emergency department; consider calling 911.

Figure 1. Algorithm for home management of acute asthma exacerbations. (PEF = peak expiratory flow.)

saturation. Although no single parameter has been identified to assess exacerbation severity, lung function is a useful method of assessment, with a PEF of 40 percent or less of predicted function indicating a severe attack in patients five years or older.6 The most useful signs for determining the severity of an asthma exacerbation in children younger than five years, or any child unable to perform a PEF, include the use of accessory muscles of respiration, chest wall retractions, tachypnea greater than 60 breaths per minute, cyanosis, and the presence of inspiratory and expiratory wheezing.8 For all patients, pulse oximetry on room air is a useful initial assessment. An oxygen saturation of less than 92 to 94 percent one hour after beginning standard treatment is a strong predictor of the need for hospitalization.9

Laboratory data are not required for most patients with acute exacerbations. Some tests that may be useful include complete blood count, serum theophylline, and basic chemistries. Chest radiography is not routinely recommended because it has not been shown to alter the care of patients with an uncomplicated asthma exacerbation.9 Measurement of arterial blood gases may be considered if hypoventilation is suspected. Electrocardiography is rarely helpful, unless there is a history or suspicion of cardiac disease.6

Management
HOME TREATMENT
Early treatment is the most effective strategy for managing asthma exacerbations. It is essential to teach patients how to monitor signs and symptoms, and take appropriate action. Patients who have a written asthma action plan and appropriate medication can often manage mild exacerbations at home (Figure 1). Key components of an asthma action plan that have reduced emergency department visits and hospitalization include standard written instructions; criteria based on symptoms or PEF (compared with personal best) to trigger action; two to three action points; and individualized, written instructions on the use of inhaled or oral corticosteroids.10 Patients at risk of asthma-related death may need more intensive treatment in a monitored setting at the first sign of an
Asthma Exacerbations

Exacerbation (Table 2). These patients should have an asthma action plan that emphasizes early communication with their physician.

In children five to 12 years of age with frequent acute exacerbations, a short course of oral prednisolone at the onset of worsening symptoms produced a modest benefit in terms of decreased symptoms, health resource use, and absence from school. Patient- or parent-initiated increases in the dosage of inhaled corticosteroids have been proposed to help with deteriorating asthma symptoms. The data are insufficient to make a recommendation for children; however, a meta-analysis of data from more than 1,200 adults confirms that increasing the dosage does not reduce the risk of a subsequent asthma exacerbation requiring oral corticosteroids.

A randomized controlled trial examined the use of parent-initiated montelukast (Singular; 4 mg for children two to five years of age and 5 mg for children six to 14 years of age) in children with intermittent asthma, defined as three to six episodes of asthma requiring acute hospital- or office-based care with symptom- and medication-free periods between episodes. When given at the onset of asthma or upper respiratory tract infection symptoms, montelukast therapy resulted in a reduction in unscheduled health care visits and time lost from work and school or childcare.

Inhaled short-acting beta, agonists are the cornerstones of treatment for patients with acute asthma. In patients with a PEF of 50 to 79 percent of their personal best, up to two treatments of two to six inhalations of a short-acting beta, agonist may be safely employed at home. Treatments should be 20 minutes apart followed by a reassessment of PEF and symptoms. Patients who do not achieve a PEF of at least 80 percent of their personal best after two treatments should contact their physician for further instructions. Patients whose PEF declines after treatment should contact their physician and seek emergent care.

Multiple studies have shown that administration using a hand-held metered-dose inhaler with a spacer device is at least equivalent to nebulized short-acting beta, agonist therapy in children older than one year (four puffs per dose) and adults (six puffs per dose). Homemade spacers, such as plastic bottles, foam or paper cups, cardboard tubes, and paper spacers, can be as effective as commercial spacers for the treatment of acute asthma exacerbations. There is no demonstrable difference in terms of safety or effectiveness between levalbuterol (Xopenex) and albuterol.

EMERGENCY DEPARTMENT TREATMENT

In the ambulatory and emergency department settings, the goals of treatment are correction of severe hypoxemia, rapid reversal of airflow obstruction, and reduction of the risk of relapse by intensifying therapy and carefully monitoring response (Figure 2). Correction of hypoxemia and rapid reversal of airflow obstruction are best achieved by oxygen administration and repetitive treatment with short-acting beta, agonists. Early use of systemic corticosteroids can reduce the risk of relapse.

The administration of oxygen to maintain saturation of at least 94 percent is recommended in all patients presenting with a moderate to severe asthma exacerbation. Oxygen should be administered as soon as possible, preferably in the prehospital phase in an office setting or in transport by emergency medical services. It has been proposed that the helium and oxygen mixture (heliox), which has a lower density than oxygen, flows more easily through constricted airways and, as a result, improves outcomes in asthma exacerbations. However, there are insufficient data to support the use of heliox in the treatment of acute asthma exacerbations.

Inhaled short-acting beta, agonist treatment is the mainstay of office or emergency department treatment of moderate to severe asthma exacerbations. If the patient can tolerate a measurement of PEF or forced expiratory volume in one second (FEV1), an initial value should be

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**Table 2. Risk Factors for Asthma-Related Death**

| Comorbidities (i.e., cardiovascular disease or other chronic lung disease) |
| Difficulty perceiving airway obstruction or severity of exacerbation |
| Illicit drug use |
| Low socioeconomic status or inner-city residence |
| Major psychosocial problems or psychiatric disorders |
| Previous severe exacerbation (e.g., intubation or admission to intensive care unit for asthma) |
| Two or more hospitalizations or three or more emergency department visits in the past year |
| Two or more refills of short-acting beta, agonist per month |

Management of Asthma Exacerbations: Emergency Department and Hospital-Based Treatment

**Initial assessment**
Brief history, physical examination (e.g., auscultation, use of accessory muscles, heart rate, respiratory rate), PEF or FEV₁, oxygen saturation, and other tests as indicated

- FEV₁ or PEF ≥ 40 percent (mild to moderate)
  - Oxygen to achieve saturation ≥ 90 percent
  - Inhaled short-acting β₂ agonist by nebulizer or metered-dose inhaler with valved holding chamber, up to three doses in first hour
  - Oral systemic corticosteroid if no immediate response or if patient recently took oral systemic corticosteroid

- FEV₁ or PEF < 40 percent (severe)
  - Oxygen to achieve saturation ≥ 90 percent
  - High-dose inhaled short-acting β₂ agonist plus ipratropium by nebulizer or metered-dose inhaler plus valved holding chamber, every 20 minutes or continuously for one hour
  - Oral systemic corticosteroid

**Impending or actual respiratory arrest**
- Intubation and mechanical ventilation with 100 percent oxygen
- Nebulized short-acting β₂ agonist and ipratropium
- Intravenous corticosteroid
- Consider adjunct therapies

**Repeat assessment:** Symptoms, physical examination, PEF, oxygen saturation, other tests as needed

- Moderate exacerbation
  - FEV₁ or PEF of 40 to 69 percent of predicted or personal best
  - Physical examination: moderate symptoms
    - Inhaled short-acting β₂ agonist every 60 minutes
    - Oral systemic corticosteroid
    - Continue treatment for one to three hours if there is improvement; make admit decision within four hours

- Severe exacerbation
  - FEV₁ or PEF < 40 percent of predicted or personal best
  - Physical examination: severe symptoms at rest, accessory muscle use, chest retraction
  - History: high-risk patient
  - No improvement after initial treatment
    - Oxygen
    - Nebulized short-acting β₂ agonist plus ipratropium, hourly or continuous
    - Oral systemic corticosteroid
    - Consider adjunct therapies

Admit to intensive care
Go to 

Figure 2. Algorithm for emergency department and inpatient management of acute asthma exacerbations. (FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow.)

obtained and repeated to monitor treatment response. In patients with severe exacerbations, continuous β₂ agonist administration has been shown to improve pulmonary function measurements and reduce hospital admission with no notable differences in pulse, blood pressure, or tremor. The use of high-dose albuterol (7.5 mg via nebulizer every 20 minutes for three doses) and intravenous β₂ agonists does not appear to be beneficial and is not recommended.

A meta-analysis of randomized controlled trials compared the combination of inhaled anticholinergics and β₂ agonists with β₂ agonists alone in children one to 18 years of age with mild, moderate, or severe exacerbations of asthma. The results showed that adding multiple doses of inhaled anticholinergic medication improves lung function and decreases hospitalizations in school-aged children with severe asthma exacerbations. The usefulness of inhaled ipratropium for the treatment of asthma exacerbations in adults is less clear, but it does appear to benefit those with a severe exacerbation.

The addition of intravenous magnesium sulfate to standard therapy has been studied in adults and children with divergent results. In adults with severe exacerbations of asthma (PEF of 25 to 30 percent or less of predicted function), intravenous magnesium sulfate therapy resulted in slightly better lung function but no change in rates of hospitalization. In children one to 18 years of age, intravenous magnesium sulfate (25 to 100 mg per kg) has been demonstrated to significantly increase lung function and to decrease hospitalizations. Nebulized magnesium sulfate has a weak effect on respiratory function and hospital admission rates in adults, and no effect on either outcome in children.
Management of Asthma Exacerbations: Emergency Department and Hospital-Based Treatment (continued)

**Moderate exacerbation**

- **Good response**
  - FEV₁ or PEF ≥ 70 percent
  - Responses sustained 60 minutes after last treatment
  - No distress
  - Physical examination: normal

- **Incomplete response**
  - FEV₁ or PEF of 40 to 80 percent
  - Mild-to-moderate symptoms
  - Individualized decision about hospitalization: consider social supports, access to care, ability to obtain medications and follow discharge plan

- **Poor response**
  - FEV₁ or PEF < 40 percent
  - Partial pressure carbon dioxide ≥ 42 mm Hg
  - Physical examination: severe symptoms, drowsiness, confusion

**Discharge home**
- Continue treatment with inhaled short-acting beta₂ agonist
- Continue course of oral systemic corticosteroid
- Consider initiation ofinhaled corticosteroid
- Patient education
  - Review medications, including inhaler technique
  - Review/initiate action plan
  - Recommend close medical follow-up

**Admit to hospital ward**
- Oxygen
- Inhaled short-acting beta₂ agonist
- Systemic (oral or intravenous) corticosteroid
- Consider adjunct therapies
- Monitor vital signs, FEV₁, or PEF, oxygen saturation

**Admit to hospital intensive care**
- Oxygen
- Inhaled short-acting beta₂ agonist, hourly or continuously
- Intravenous corticosteroid
- Consider adjunct therapies
- Possible intubation and mechanical ventilation

**Discharge**
- Continue treatment with inhaled short-acting beta₂ agonist
- Continue course of oral systemic corticosteroid
- Continue inhaled corticosteroid for patients not on long-term control therapy, consider initiation of an inhaled corticosteroid

**Patient education (e.g., review medications, including inhaler technique; review or initiate action plan; recommend close medical follow-up; provide immunizations)**
- Before discharge, schedule follow-up appointment with primary care physician and/or asthma subspecialist in one to four weeks

**Figure 2.** Algorithm for emergency department and inpatient management of acute asthma exacerbations. (FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow.) Adapted from the National Heart Lung and Blood Institute. National Asthma Education and Prevention Program. Expert panel report 3: Guidelines for the diagnosis and management of asthma, 2007:388. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdn.htm.

The administration of systemic corticosteroids (500 mg hydrocortisone sodium succinate injection [Solu-Cortef] or 125 mg methylprednisolone sodium succinate injection [Solu-Medrol] in adults, or 1 to 2 mg per kg of prednisone or prednisolone in children one to 18 years of age) within one hour of emergency department presentation decreases the need for hospitalization. In a Cochrane review, the most pronounced effect occurred in patients with severe exacerbations. Oral and parenteral corticosteroids are equally effective in preventing hospital admission in children, but only parenteral corticosteroids have been studied in adults. There is insufficient evidence to recommend the use of inhaled corticosteroids in place of or in conjunction with systemic corticosteroids at the time of discharge from the emergency department. Inhaled corticosteroids do not prevent relapse of symptoms requiring admission or improve quality of life or symptom scores.
Asthma Exacerbations

In adults and in hospitalized children one to 16 years of age, corticosteroid use resulted in earlier discharge and fewer symptomatic relapses.35-37 The optimal dosage in children is unknown,34 but in adults, lower dosages (80 mg or less per day of methylprednisolone [Depo-Medrol] or 400 mg or less per day of hydrocortisone) are equal to higher dosages in the improvement of lung function, adverse effects, and rates of respiratory failure.35

The addition of intravenous aminophylline to conventional therapy in children and adults has no additional benefit in reducing hospital admissions. It does significantly increase the risk of adverse effects, including vomiting, palpitations, and arrhythmias.36,37 There are insufficient data to recommend for or against the use of antibiotics in the treatment of acute exacerbations.38 In a Cochrane review, one randomized controlled trial of 30 adults examined the use of noninvasive positive pressure ventilation in the treatment of severe acute exacerbations of asthma as an adjunct to usual care. The intervention showed promising results in objective measure of lung function and reduced rates of hospitalization, but the data are insufficient to make broad recommendations for the use of noninvasive positive pressure ventilation.39 Drinking large amounts of water, high-dose mucolytics, antihistamines, chest physiotherapy, and sedation are all unproven treatments.6

POSTDISCHARGE CARE

Patients sent home from the emergency department with systemic corticosteroids (a five- to 10-day nontapering course of 50- to 100-mg prednisone per day in adults) have decreased relapse of asthma symptoms, future hospitalizations, and use of short-acting beta, agonists.40,41 Although seven to 10 days is the usual treatment duration for oral corticosteroids, three days of therapy (1 mg per kg of prednisone) has been shown to be as effective as five days for the complete resolution of symptoms within one week in children two to 15 years of age.42

There is insufficient data to recommend the initiation of montelukast in place of oral corticosteroids or the use of inhaled corticosteroids in combination with oral corticosteroids at the time of discharge to prevent a relapse of asthma symptoms.43,44

Allergen avoidance is routinely recommended after emergency department discharge to decrease further acute exacerbations of asthma. Despite multiple trials of allergen control, there are no data showing that pet allergen or dust mite allergen avoidance techniques successfully reduce allergens in the home to levels that improve asthma symptoms.45-46

Regardless of the therapy chosen in the acute care setting, step-up therapy should be continued for several days to weeks after discharge. Because exacerbations vary in severity, close communication between patients and physicians is required. Symptoms may be controlled quickly, but airway inflammation may persist for two to three weeks.47 Scheduled dosing with inhaled beta, agonists should be continued until symptoms and PEF return to baseline.

Data Sources: The National Guidelines Clearinghouse was searched for guidelines on asthma care. The National Asthma Education and Prevention Program's "Expert Panel 3 Report: Guidelines for the Diagnosis and Management of Asthma" section on management of asthma exacerbations was reviewed. Ovid Medline was searched for new information related to the major recommendations of both. PubMed was searched using the key terms asthma + acute + exacerbation. The Cochrane database and Essential Evidence Plus were searched for information pertaining to asthma exacerbations. Search dates: March 2010 and April 2010. Searches on select topics were performed weekly in May and June 2010, with a repeat search in November 2010.

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REFERENCES


Asthma Exacerbations


The ‘Crashing Asthmatic’

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Asthma is a common chronic disorder, with a prevalence of 8 to 10 percent in the U.S. population. From 5 to 10 percent of patients have severe disease that does not respond to typical therapeutic interventions. To prevent life-threatening sequelae, it is important to identify patients with severe asthma who will require aggressive management of exacerbations. Objective monitoring of pulmonary status using a peak flow meter is essential in patients with persistent asthma. Patients who have a history of fragmented health care, intubation, or hospitalization for asthma and those with mental illness or psychosocial stressors are at increased risk for severe asthma. Oxygen, beta, agonists, and systemic corticosteroids are the mainstays of acute asthma therapy. Inhaled anticholinergic medications provide additional bronchodilation. In patients who deteriorate despite usual therapeutic efforts, evidence supports individualized use of parenteral beta, agonists, magnesium sulfate, aminophylline, leukotriene inhibitors, or positive pressure mask ventilation before intubation. (Am Fam Physician 2003;67:997-1004. Copyright © 2003 American Academy of Family Physicians.)

Asthma is one of the most common chronic disorders managed by family physicians. A “crashing asthmatic” is a patient with asthma who is clinically deteriorating into respiratory failure or arrest despite initial treatment. Managing such a patient can be a major challenge. Crucial tasks include rapid assessment of the severity of the asthma attack, objective determination of the response to therapy, and identification of the risk of respiratory failure.

Background

Over the past decade, the mortality rate for asthma in the United States has increased.¹ Prevalence, morbidity rates, and treatment costs also have risen. These increases have occurred despite the reversible nature of asthma, a heightened awareness of the disease, and an expanding formulary of therapeutic agents for the management of asthma. To reverse these upward trends, national and global guidelines and strategies for the prevention and management of asthma have been developed.²

The prevalence of asthma is estimated to be has high as 8 percent in adults and 10 percent in children.¹³ From 5 to 10 percent of these patients have severe disease that does not respond to typical asthma medications.⁴ The mechanisms that differentiate between easily managed and unresponsive asthma are still being investigated.⁵

Status Asthmaticus

Status asthmaticus is a condition in which severe airway obstruction and asthmatic symptoms persist despite the administration of standard acute asthma therapy.⁶ It can present with little warning and progress rapidly to asphyxiation. Death can occur when asthma is severe, uncontrolled, and poorly responsive to treatment, with steady deterioration of respiratory status occurring over a period of days.¹⁴ Data indicate that in nearly 85 percent of asthma deaths, the final episode lasted longer than 12 hours.¹ This length of time should have allowed ample opportunity for treatment if the patients had presented promptly for care and their respiratory distress had been quickly recognized.¹ Fortunately, only one in 2,000 patients die of asthma; the vast majority survive.¹
TABLE 1
Risk Factors for Death from Severe Asthma

Previous asthma attacks with respiratory failure, seizure, loss of consciousness, or intubation
History of hypercapnia, metabolic acidosis, or pneumothorax with previous asthma attacks
Severe asthma attacks despite long-term oral corticosteroid therapy
Psychosocial factors, including mental illness, decreased perception of severity of dyspnea or disease, noncompliance with asthma therapy, substance abuse, or inner-city residence

Information from references 1, 3, and 4.

Pathology
Status asthmaticus can lead to several forms of sudden death. The most common scenario is severe bronchospasm, with mucus plugging leading to asphyxia.

Other reasons for sudden death include cardiac dysrhythmias related to hypoxia, hyperinflation leading to air trapping, and tension pneumothorax. In patients with asthma, deaths also have occurred subsequent to the use of sedatives (respiratory depression), beta blockers (bronchospasm) and, occasionally, nonsteroidal anti-inflammatory drugs (anaphylaxis).1,6

Pathologic findings in fatal asthma include bronchial lumen occlusion by mucus, hyperplasia of submucosal glands, basement membrane thickening, and tissue eosinophilia.

Risk Factors for Severe Asthma
Risk factors for death from asthma are listed in Table 1.1,3,4 Additional markers include frequent emergency department visits, wide variations in lung function, and use of multiple medications.

Studies1,6,9 have shown that patients with severe asthma are 10 times more likely to present to emergency departments during nighttime hours, and that the highest fatality rates are in inner-city young adults. The risk of death is greatest in patients who have severe, unstable disease that is not being objectively monitored. The National Heart, Lung, and Blood Institute (Expert Panel report 2)9 addresses these problems in a discussion of key preventive issues, including patient education, objective measurements, environmental considerations, and home action plans.

Evidence indicates that patients with a history of nearly fatal asthma attack may have a blunted perception of increasing airway resistance and worsening bronchospasm.4,10 Thus, these patients may be unable to sense critical worsening of airflow obstruction. Inadequate allergen control, insufficient use of inhaled corticosteroids, lack of objective monitoring criteria (e.g., home monitoring of peak flow), psychosocial or economic problems, and underuse of emergency ambulance services are well-documented risk factors for severe asthma exacerbations.11,12

Viral upper respiratory tract infection is the most common precipitant of an asthma attack. In addition to the usual common cold viruses, chlamydial pneumonia and herpes simplex virus infections may play a role in exacerbations of bronchospasm in patients with and without asthma. In some patients, allergic reactions to foods (e.g., peanuts) can result in life-threatening asthma attacks.6

TABLE 2
Guidelines for Assessing Severity of Asthma Exacerbation

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathlessness while at rest</td>
</tr>
<tr>
<td>Talking in words, not full sentences</td>
</tr>
<tr>
<td>Agitation (usually)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate &gt;30 per minute in adults</td>
</tr>
<tr>
<td>Use of accessory muscles for breathing</td>
</tr>
<tr>
<td>Wheezing during inhalation and exhalation</td>
</tr>
<tr>
<td>Pulse rate &gt;120 per minute</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF rate &lt;150 to 200 mL in adults, or &lt;50% of predicted or personal best effort</td>
</tr>
<tr>
<td>Oxygen saturation &lt;91% on room air</td>
</tr>
<tr>
<td>Pao₂ &lt;60 mm Hg on room air or Pco₂ &gt;42 mm Hg</td>
</tr>
</tbody>
</table>

PEF = peak expiratory flow; Pao₂ = partial pressure of oxygen; Pco₂ = partial pressure of carbon dioxide.

Adapted with permission from Expert Panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Institutes of Health, National Heart, Lung, and Blood Institute, 1997; NIH publication no. 97-4051.
Recognition of the "Crashing Asthmatic"

CLINICAL FINDINGS AND PEF VALUES

Asthma is a clinical diagnosis. While episodic and reversible symptoms of airflow obstruction are the primary clinical features, presentations can vary widely. However, the diagnosis of asthma is secure when key clinical elements are present and alternative diagnoses have been excluded. The physician must rapidly assess the severity of an asthma attack, objectively determine the response to therapy, and identify the risk of respiratory failure.

Criteria for diagnosing a severe asthma attack, including peak expiratory flow (PEF) rates, are listed in Table 2. Predicted average PEF rates for normal children, adolescents, and adults are provided in Tables 3 and 4. Although predicted PEF values are useful in patients with asthma who do not have a known "personal best" peak flow, they should be interpreted with caution. Predicted normal PEF rates can vary substantially according to different formulas, and patients with chronically impaired lung function typically cannot attain these values.

All patients who wheeze do not necessarily have asthma. Therefore, the physician must question the diagnosis of asthma, particularly when initial interventions fail. In children, wheezing can be associated with bronchiolitis, foreign-body aspiration, tracheomalacia, and congenital heart or lung abnormalities. Wheezing in adults may be caused by chronic obstructive pulmonary disease, respiratory infection, congestive heart failure, pulmonary embolism, aspiration, and vocal cord dysfunction. It is also important to look for comorbid conditions (e.g., coronary artery disease) that may complicate management.

ADDITIONAL FINDINGS

Hyperinflation is the most common finding on chest radiographs in patients hospitalized for treatment of asthma. Possible abnormalities include pneumonia, con-
Continuous nebulization of beta₂ agonists may be useful in the treatment of severe asthma.

gestive heart failure, atelectasis, pneumothorax, and pneumomediastinum.

Arterial blood gas (ABG) parameters are often used to guide treatment in patients with severe asthma. However, the decision to intubate should be based on clinical grounds, rather than on ABG determinations alone. Close observations of respiratory effort, level of consciousness, and pulse oximetry serve as clinical correlates of pulmonary gas exchange. ABG measurements may aid in decision-making by providing quantitative information on pulmonary gas exchange. Initial findings during an asthma exacerbation typically include hypoxemia and hypocapnia. Hypercapnia is usually a later finding that reflects increasing airflow obstruction and fatigue because of the increased work of breathing it may indicate impending respiratory failure. However, mechanical ventilation is required in fewer than 10 percent of patients who present with hypercapnia.

Eosinophilia is a common finding in patients with asthma or allergy. Hypokalemia and hypermagnesemia may occur with heavy use of beta₂ agonists. Serum creatine kinase MM isoenzyme levels may be elevated because of extreme exertion of the ventilatory muscles.

Patients who regularly measure peak flows at home usually document at least several days of depressed values and greater morning-to-evening variability in PEF rates before an exacerbation. During a severe asthma attack, patients may be unable to check their PEF because of marked dyspnea.

Conventional Management

The goals of acute asthma management are to relieve bronchospasm, improve gas exchange, treat the underlying cause, and prevent complications. Before an in-depth history is obtained, treatment of patients with acute dyspnea should be initiated to prevent further deterioration.

Close monitoring and objective reevaluation for response to therapy are essential. The PEF rate is a key quantitative measure for assessing airflow; however, marked dyspnea initially may prevent proper use of the peak flow meter in patients who are experiencing severe asthma flares.

Beta₂ Agonists

Inhaled beta₂-adrenergic agonists are the mainstays of bronchodilator therapy. These agents provide the most rapid relief of bronchospasm with the fewest side effects. [Reference 17—Evidence level B, uncontrolled trial] If patients can coordinate hand motion and breathing, albuterol (Ventolin) delivered by metered-dose inhaler (MDI) with a spacer (four to eight puffs every 20 to 30 minutes for three doses) compares favorably with nebulization (2.5 to 5 mg every 20 minutes). In patients with more severe asthma, MDI dosing can be increased to one puff every 30 to 60 seconds, or continuous nebulization can be instituted (10 to 15 mg per hour) to improve symptoms.

Anticholinergic Medications

Anticholinergic drugs, especially when given in combination with inhaled beta₂ agonists, are associated with significantly improved pulmonary function and decreased hospitalization rates in patients with acute asthma. [Reference 19—Evidence level A, meta-analysis] Ipratropium bromide (Atrovent) initially can be given by MDI (four to eight puffs) or nebulized solution (three doses of 250 mcg each). The recommended follow-up dosing of 250 to 500 mcg at six-hour intervals is well tolerated. Atropine solution should not be nebulized because atropine crosses the blood-brain barrier, leading to sedation and worsening of asthma.

Corticosteroids

Corticosteroids are potent anti-inflammatory drugs that are highly effective in the treatment of severe asthma. Sys-
temic corticosteroid therapy should be administered promptly to all patients with signs of severe asthma.11 [Evidence level A, systematic review of randomized controlled trials]

In patients who can tolerate oral medications, oral corticosteroid therapy is as effective as intravenous therapy.12 Typically, prednisone is given orally in a dosage of 1 to 2 mg per kg once daily (usual maximum: 60 to 80 mg per day) for five to seven days. For intravenous treatment, methylprednisolone sodium succinate (Solu-Medrol) is administered in a dosage of 0.5 to 2 mg per kg every six hours (usual maximum: 125 mg per day), or hydrocortisone is given in a dosage of 2 to 4 mg per kg every four to six hours.3

OXYGEN

Patients with severe asthma have a ventilation-perfusion mismatch and, thus, benefit from supplemental oxygen therapy. High-flow supplemental oxygen is best delivered using a partial or complete nonrebreather mask. The objective is to maintain the partial pressure of oxygen at a minimum of 92 mm Hg (oxygen saturation greater than 95 percent).8,16 [References 8 and 16—Evidence level C, expert guidelines] There is no evidence that oxygen suppresses the respiratory drive in the absence of preexisting chronic pulmonary disease.3

CRITERIA FOR HOSPITALIZATION

Factors to consider in determining the need for hospitalization include disease severity, socioeconomic factors, clinical features, pulmonary function, and response to treatment.18 Hospitalization is indicated in patients with a pretreatment arterial oxygen saturation of less than 90 percent, persistent respiratory acidosis, or severe obstruction that does not improve (or worsens) with the administration of sympathomimetic agents (i.e., the PEF rate remains at less than 70 percent of the predicted value).1

TREATMENT OF NONRESPONDING PATIENTS

Patients with severe asthma who do not respond to initial therapy require aggressive treatment to prevent cardiopulmonary arrest. In general, cardiorespiratory monitoring is necessary in patients who have status asthmaticus. A comfortable and supportive environment should be provided.

Pulse oximetry, blood pressure, and cardiac rhythm should be monitored continuously when initial acute asthma therapy fails. Intravenous access should be secured in patients with severe asthma. Although hypoxemia and anxiety may cause agitation and restlessness, anxiolytic medications should be administered only when the physician is prepared to intubate.

The key concern is to actively manage the airway by being prepared for the next intervention if the patient fails to respond. An overview of the management of acute severe asthma is provided in Figure 1.20

PARENTERAL BETA2 AGONISTS

Delivery of beta2 agonists by inhalation is the most effective treatment for asthma exacerbations. Unfortunately, some patients with severe exacerbations may not respond to this treatment. Inhaled beta2 agonists may be less effective in patients who have a strong inflammatory response or a history of long-term heavy use of beta2 agonists. Subcutaneous or intravenous administration of beta2 agonists may be indicated in patients who are coughing excessively, too weak to inspire adequately, or moribund.5,13

Terbutaline (Brethine) is given subcutaneously (0.1 to 0.25 mg) or intravenously (0.1 to 0.5 mcg per kg per minute).3 In one study4 of patients with “brittle asthma” (defined by wide diurnal variations in PEF rates), twice-daily subcutaneous administration of terbutaline improved symptoms, medication use, and PEF rates.4 The findings of this study suggest that some beta receptors may not be accessible by the aerosolized route.

Intravenously or subcutaneously administered epinephrine may help avoid the need for mechanical ventilation in patients with status asthmaticus.7 However, cardiovascular effects limit the use of epinephrine to patients less than 40 to 50 years of age. The subcutaneous dose of epinephrine is 0.1 to 0.5 mg in adults (0.01 mg per kg in children), usually given as 0.1 to 0.5 mL of a 1:1,000 solution every 20 minutes or longer. For convenience, adult patients may be given three 0.3-mg doses at 20-minute...
Acute Severe Asthma

Perform an initial rapid assessment:
Brief history (to exclude diagnoses other than asthma)
Focused physical examination—vital signs, lung sounds,
accessory muscle use, alertness, color
Objective testing—oxygen saturation, PEF or FEV₁ rate

Improve airflow:
Inhaled β₂ agonist
Inhaled anticholinergic drug
Intravenously administered magnesium sulfate (if patient's condition is severe)
Consider use of leukotriene inhibitor.

Decrease airway inflammation:
Systemic corticosteroid
Consider low-dose aminophylline therapy.
Consider use of leukotriene inhibitor.

Provide supportive care:
Ensure that oxygen saturation is above 95%.
Consider hydration.
Monitor vital signs and cardiac rhythm.
Consider use of heliox or noninvasive ventilation in cooperative patient.
Plan for intubation if patient has impending respiratory arrest.

Reassess patient:
Physical examination
PEF or FEV₁ rate
Oxygen saturation or ABG measurement
Ancillary studies (chest radiograph, laboratory tests)

Good response:
FEV₁ or PEF rate is ≥70% of predicted or personal best effort.
Response is sustained for >60 minutes.
Symptoms resolve.
Physical examination is normal.

Incomplete response:
FEV₁ or PEF rate is ≥50% but <70% of predicted or personal best effort.
Symptoms continue or improve slowly.

Hospitalize patient:
Monitor oxygen saturation and PEF rate.
Maintain oxygen saturation at >90%.
Continue inhaled β₂ agonist therapy.
Consider continued administration of inhaled anticholinergic drug therapy for 24 to 36 hours.
Administer systemic corticosteroid therapy.
Continue or initiate inhaled corticosteroid therapy.

Hospitalize patient for intensive care:
Monitor oxygen saturation and cardiac rhythms.
Obtain vital signs frequently.
Maintain oxygen saturation at >95%.
Administer inhaled β₂ agonist by continuous rehumidization.
Administer intravenous corticosteroid therapy.
Continue inhaled anticholinergic drug therapy for 24 to 36 hours.
Consider use of heliox, ketamine, noninvasive ventilation, or intubation.

Poor response:
FEV₁ or PEF rate is <50% of predicted or personal best effort.
Arterial carbon dioxide level is >42 mm Hg.
Patient has signs of fatigue (e.g., confusion, obtundation).

Discharge patient:
Prescribe inhaled β₂ agonist to be taken as needed.
Prescribe systemic corticosteroid to be taken as needed.
Continue or initiate inhaled corticosteroid therapy.
Provide patient education.
Create or update home action plan.
Provide close follow-up.

Improved

FIGURE 1. Overview of the initial management and disposition of patients with acute severe asthma. (PEF = peak expiratory flow; FEV₁ = forced expiratory volume in one second; ABG = arterial blood gas)

Adapted with permission from Hallstrand TS, Fahy JV. Practical management of acute asthma in adults. Respir Care 2002;47:178.
intervals (total dose: up to 1 mg). Incremental doses of 1 to 5 mL of a 1:10,000 epinephrine solution can be given intravenously over five to 10 minutes. Rarely, epinephrine is infused at a rate of 1 to 4 mcg per minute.

**MAGNESIUM SULFATE**

Magnesium sulfate is a calcium antagonist that induces smooth muscle relaxation. In three randomized controlled trials, magnesium sulfate improved symptoms in patients with severe asthma who had not responded to other treatments. A dose of 30 to 70 mg per kg (1 to 3 g) is given intravenously over 20 to 30 minutes. The safety and potential benefits of magnesium sulfate justify its use in nonresponding patients. This agent may be particularly beneficial in patients who are prone to hypomagnesemia because of prolonged, heavy use of inhaled beta2 agonists.

**METHYLXANTHINES**

At one time, aminophylline and theophylline were the mainstays of asthma treatment. Currently, these agents are second-line bronchodilators because they are only about one third as effective as beta2 agonists. Treatment with aminophylline has been shown to improve oxygenation and reduce the incidence of intubation in children with severe status asthmaticus. Unfortunately, the therapeutic level of this agent (approximately 10 mg per L) is close to the toxic level. Signs of toxicity include cardiac dysrhythmias, nausea, tremor, and headache. A prudent aminophylline regimen is a loading dose of 5 to 6 mg per kg administered intravenously over 30 minutes, then 0.5 mg per kg per hour.

**LEUKOTRIENE INHIBITORS**

Some patients with severe asthma seem to respond to leukotriene inhibitors, which are anti-inflammatory drugs. In the acute setting, zafirlukast (Accolate) may be given orally twice daily; the dose for adults is 20 mg, and the dose for children up to 12 years of age is 10 mg. Zileuton (Zyflo), in a dosage of 600 mg four times daily, may be given to patients older than 12 years.

**NONINVASIVE VENTILATION**

Continuous positive airway pressure or bi-level positive airway pressure machines use tight-fitting face masks to assist ventilation and reduce the work of breathing without intubation. Noninvasive ventilation is indicated in cooperative patients who may have impending respiratory failure but do not need immediate intubation. Noninvasive ventilation may avoid the possible complications of sedation, paralysis, and intubation, but it should only be used in alert patients who have an intact airway.

**HELIox**

Heliox is a helium-oxygen mixture that decreases turbulent airflow. Benefits include decreases in the work of breathing, muscle fatigue, and carbon dioxide production. No significant adverse effects have been reported; however, this treatment is not available in most hospitals.

**Intubation and Mechanical Ventilation**

When possible, intubation should be avoided. Tracheal intubation may aggravate bronchospasm, induce laryngospasm, increase barotrauma, and depress circulatory function. In addition, intubation is associated with a mortality rate of 10 to 13 percent. Indications for intubation include cardiac or respiratory arrest, severe hypoxia, exhaustion, or deterioration of mental status. To prevent complications, it is recommended that rapid normalization of the carbon dioxide level be avoided, and that mild hypercapnia be tolerated until lung function improves. In particular, high per-minute ventilation rates should not be used, because they lead to air trapping and decreased venous return, which may impair cardiopulmonary function.

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The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the U.S. Naval Medical Department or the U.S. Naval Service at large.

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Nephrology
Management of Acute Renal Failure

EDDIE NEEDHAM, M.D., Emory University School of Medicine, Atlanta, Georgia

Acute renal failure is present in 1 to 5 percent of patients at hospital admission and affects up to 20 percent of patients in intensive care units. The condition has prerenal, intrarenal, and postrenal causes, with prerenal conditions accounting for 60 to 70 percent of cases. The cause of acute renal failure usually can be identified through an appropriate history, a physical examination, and selected laboratory tests. The initial laboratory evaluation should include urinalysis, a determination of the fractional excretion of sodium, a blood urea nitrogen to creatinine ratio, and a basic metabolic panel. Management includes correction of fluid and electrolyte levels; avoidance of nephrotoxins; and kidney replacement therapy, when appropriate. Several recent studies support the use of acetylcysteine for the prevention of acute renal failure in patients undergoing various procedures. The relative risk of serum creatinine elevation was 0.11 in patients undergoing radiocontrast-media procedures (absolute risk reduction: 19 percent) and 0.33 in patients undergoing coronary angiography (absolute risk reduction: 8 percent). In patients pretreated with sodium bicarbonate before radiocontrast-media procedures, the relative risk of serum creatinine elevation was 0.13 and the absolute risk reduction was 11.9 percent. Dopamine and diuretics have been shown to be ineffective in ameliorating the course of acute renal failure. (Am Fam Physician 2005;72:1739-46. Copyright © 2005 American Academy of Family Physicians.)

Acute renal failure is an acute loss of kidney function that occurs over days to weeks and results in an inability to appropriately excrete nitrogenous wastes and creatinine. Electrolyte disturbances and loss of fluid homeostasis may occur. In spite of this rapid decline in kidney function, patients with acute renal failure often have few symptoms.

A strict definition of acute renal failure is lacking. Accepted diagnostic criteria include an increase in the serum creatinine level of 0.5 mg per dL (44.2 μmol per L) or a 50 percent increase in the creatinine level above the baseline value, a 50 percent decrease in the baseline-calculated glomerular filtration rate (GFR), or the need for acute kidney replacement therapy. Oliguria is defined as a urine output of less than 400 mL in 24 hours, and anuria is defined as a urine output of less than 100 mL in 24 hours.

Oliguria is defined as a urine output of less than 400 mL in 24 hours, and anuria is defined as a urine output of less than 100 mL in 24 hours.

Infection and cardiorespiratory complications are the most common causes of death in patients with acute renal failure.

Pathophysiology
Creatinine is a metabolic waste product excreted by the kidneys. When the GFR is normal, creatinine is filtered through the glomerulus into the tubules and then excreted. Creatinine also is secreted by tubular cells.

Medications such as trimethoprim (Proloprim; with sulfamethoxazole [Bactrim, Septra]) and cimetidine (Tagamet) can inhibit tubular secretion and falsely elevate the serum creatinine level. Formulas to estimate the GFR in patients with acute renal failure should not be used to adjust medication dosages because the serum creatinine level is not in a steady state and continues to fluctuate.

Causes of Acute Renal Failure
Traditionally, the causes of acute renal failure are classified as prerenal, intrarenal, or postrenal (Table 1). PRERENAL CAUSES

Prerenal causes of acute renal failure are common, with intravascular volume depletion being the most common cause. Fever,
TABLE 1
Causes of Acute Renal

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vomiting, and diarrhea can lead to decreased kidney perfusion. Dehydration from any cause, including diuretics, can precipitate acute renal failure.

Prerenal azotemia occurs in diseases that lead to a decrease in the effective arterial blood volume. These diseases include heart failure, liver failure, and nephrotic syndrome.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors are known to cause prerenal azotemia. NSAIDs affect the kidney by blocking cyclooxygenase, leading to an increase in thromboxane A2, which is a potent vasoconstrictor of the preglomerular arterioles. Because these afferent vessels supply blood to the kidney, vasoconstriction causes decreased glomerular perfusion.5

ACE inhibitors block the production of angiotensin II, causing vasodilation of the postglomerular efferent arterioles. The vasodilation results in a decrease in the glomerular pressure, which may cause azotemia.6

Large-vessel diseases, such as thrombosis, embolus, and dissection, also can reduce renal perfusion.

INTRARENAL CAUSES

Intrarenal causes of acute renal failure are classified as tubular, glomerular, interstitial, and vascular.

Injury to the tubules most often is caused by ischemia or nephrotoxins. If prerenal azotemia and poor perfusion continue without treatment, tubular cells begin to die. This condition is termed “acute tubular necrosis.” Acute tubular necrosis is not a separate entity; rather, it is a marker of a more severe ischemic insult to the kidneys. Therefore, prerenal azotemia and tubular ischemia represent stages in the continuum of tubular injury.7

Acute tubular necrosis has three phases: initiation, maintenance, and recovery. After the initial insult to the kidneys, the maintenance phase typically lasts one to two weeks. During the recovery phase, there may be marked diuresis and a slow return of kidney function. To date, no therapy has been shown to hasten recovery from acute tubular necrosis.
Acute Renal Failure

Efforts should be made to prevent the development of acute tubular necrosis in high-risk patients. Conditions that place patients at risk for this condition include untreated prerenal azotemia and the use of nephrotoxic drugs or exposure to other nephrotoxins (Table 2).

Glomerulonephritis, an uncommon cause of acute renal failure, has systemic manifestations such as fever, rash, and arthritis. Urine findings include red blood cell casts, hematuria, and proteinuria. It is important to evaluate all patients with glomerulonephritis for diseases such as systemic lupus erythematosus. Consultation with a nephrologist may be required; renal biopsy may be necessary.

Acute interstitial nephritis is an interstitial disturbance that leads to acute renal failure. (The diagnosis and management of this condition have been reviewed in American Family Physician.) Acute interstitial nephritis often results from an allergic reaction to a drug (Table 3). Symptoms include fever and rash. Serum and urine eosinophil counts may be elevated. Autoimmune diseases, infection, and infiltrative diseases also can lead to interstitial nephritis. If a drug is suspected as the causative agent, immediate withdrawal of the drug and supportive care are essential. Corticosteroids may be beneficial.

Vascular disease can occur on the microvascular and macrovascular levels. Depending on the location of the lesion(s), vascular causes can be prerenal or intrarenal. Microvascular processes commonly present as microangiopathic hemolytic anemia and acute renal failure secondary to small-vessel thrombosis or occlusion. Macrovascular causes of acute renal failure should be suspected in older patients. These causes include renal artery stenosis or thrombosis, atheroembolism secondary to atrial fibrillation, and aortic disease or acute dissection.

POSTRENAL CAUSES

Postrenal causes of acute renal failure result in obstruction of the outflow tracts of the kidneys. Causes include prostatic hypertrophy, catheters, tumors, strictures, and crystals. Neurogenic bladder also can cause an obstruction.

Because postrenal causes are readily reversible, it is imperative to exclude them. Recovery of renal function is directly proportional to the duration of the obstruction. Renal ultrasonography can be used to assess patients for hydronephrosis. Because no contrast dye is used, renal function is not further compromised.

Identification of Probable Causes

Probable causes of acute renal failure, based on the findings of the history, are listed in Table 4. Probable causes based on the physical findings are listed in Table 5. Urine test values and serum creatinine levels in prerenal and intrarenal acute renal failure are compared in Table 6. Selected diagnostic test results and their interpretations are given in Table 7.

Urine collected before the initiation of intravenous fluid or diuretic treatment can be used to calculate the

---

TABLE 2
Selected Nephrotoxins

<table>
<thead>
<tr>
<th>Acyclovir (Zovirax)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides*</td>
</tr>
<tr>
<td>Amphotericin B (Fungizone)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors*</td>
</tr>
<tr>
<td>Cancer drugs: cisplatin (Platinol AQ), ifosfamide (Ifex)</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Cyclosporine (Sandimmune)</td>
</tr>
<tr>
<td>Foscarnet (Foscavir)</td>
</tr>
<tr>
<td>Heavy metals</td>
</tr>
<tr>
<td>Myeloma light chains</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs*</td>
</tr>
<tr>
<td>Oxalic acid</td>
</tr>
<tr>
<td>Pentamidine (NebuPent, Pentam 300, Pneumopent)</td>
</tr>
<tr>
<td>Pigment: hemoglobin, myoglobin</td>
</tr>
<tr>
<td>Radiocontrast media*</td>
</tr>
<tr>
<td>Uric acid</td>
</tr>
</tbody>
</table>

*=Most common toxins.

TABLE 3
Common Drugs That Can Cause Allergic Interstitial Nephritis

<table>
<thead>
<tr>
<th>Allopurinol (Zyloprim)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Cimetidine (Tagamet)</td>
</tr>
<tr>
<td>Ciprofloxacin (Cipro)</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Penicillins</td>
</tr>
<tr>
<td>Phenyltoin (Dilanit)</td>
</tr>
<tr>
<td>Rifampin (Rifadin)</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Trimethoprim (Proloprim; with sulfamethoxazole [Bactrim, Septra])</td>
</tr>
</tbody>
</table>
Acute Renal Failure

### TABLE 4
**Probable Causes of Acute Renal Failure Based on the Findings of the History**

<table>
<thead>
<tr>
<th>History</th>
<th>Probable causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review of systems</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary system</td>
<td></td>
</tr>
<tr>
<td>Sinus, upper respiratory, or pulmonary symptoms</td>
<td>Pulmonary-renal syndrome, vasculitis</td>
</tr>
<tr>
<td>Cardiac system</td>
<td></td>
</tr>
<tr>
<td>Symptoms of heart failure</td>
<td>Decreased renal perfusion</td>
</tr>
<tr>
<td>Intravenous drug abuse, prosthetic valve or valvular disease</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td></td>
</tr>
<tr>
<td>Diarrhea, vomiting, poor intake</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td>Colicky abdominal pain radiating from flank to groin</td>
<td>Urolithias</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td></td>
</tr>
<tr>
<td>Symptoms of benign prostatic hypertrophy</td>
<td>Obstruction</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td></td>
</tr>
<tr>
<td>Bone pain in older patient</td>
<td>Multiple myeloma, prostate cancer</td>
</tr>
<tr>
<td>Trauma, prolonged immobilization</td>
<td>Rhabdomyolysis (pigment nephropathy)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Allergic interstitial nephritis, atheroemboli, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, vasculitis</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
</tr>
<tr>
<td>Anorexia, fatigue, fever, weight loss</td>
<td>Malignancy, vasculitis</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, multiple sclerosis, stroke</td>
<td>Neurogenic bladder</td>
</tr>
<tr>
<td><strong>Surgical history</strong></td>
<td></td>
</tr>
<tr>
<td>Recent surgery or procedure</td>
<td></td>
</tr>
<tr>
<td><strong>Medication history</strong></td>
<td></td>
</tr>
<tr>
<td>Acyclovir (Zovirax), angiotensin-converting enzyme inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs</td>
<td>Acute tubular necrosis, allergic interstitial nephritis, decreased renal perfusion</td>
</tr>
</tbody>
</table>


Fractional excretion of sodium (FENa). The first urine sample obtained from the patient in the emergency department is the most useful. In a patient with acute renal failure, a FENa below 1 percent reflects preservation of the kidneys' ability to avidly reabsorb sodium and water. A FENa higher than 1 percent suggests the presence of acute tubular necrosis and loss of the kidneys' ability to concentrate urine.

**Management**

Acute renal failure often is preventable. Risk factors for this condition include diabetes mellitus, chronic renal insufficiency, heart failure, and advanced age.

Many medications can injure the kidneys. Dosing schedules can help prevent acute renal failure. For example, acute renal failure is less likely to develop with a once-daily dose of an aminoglycoside than with multiple daily doses.

When acute renal failure is diagnosed, the cause(s) must be identified and treated (Figure 1). Critical measures include maintaining adequate intravascular volume and mean arterial pressure, discontinuing all nephrotoxic drugs, and eliminating exposure to any other nephrotoxins (Table 2). Electrolyte abnormalities must be corrected, and urine output should be monitored closely. Pigment or uric acid exposure can be treated with alkaline diuresis. Ethylene glycol or methanol poisoning should be treated with an alcohol drip or with fomepizole (Antizol).

Hyperkalemia is a common complication of acute renal failure. Potassium levels below 6 mEq per L (6 mmol per L) usually can be managed with dietary restriction and resin binders. Caloric intake should come primarily from carbohydrates. Protein intake should be balanced to minimize nitrogenous waste production while limiting starvation ketosis and subsequent production of ketoacids. This balance is achieved best with a protein intake of 0.6 g per kg per day.

Sodium bicarbonate therapy should be reserved for the treatment of severe metabolic acidosis (i.e., pH below 7.2 or a bicarbonate level below 10 to 15 mEq per dL [10 to 15 mmol per L]) with or without associated hyperkalemia. It is important to note that sodium bicarbonate and sodium polystyrene sulfonate have a large sodium load and may worsen fluid status in patients with acute renal failure.

When hyperkalemia is severe and unresponsive to treatment, kidney replacement therapy may be indicated (Table 8). The use of intermittent or continuous hemodialysis (multiple techniques)
continues to be debated. Both approaches are effective, and studies have not demonstrated either approach to be superior to the other. Intermittent hemodialysis requires less anticoagulation than does continuous hemodialysis; however continuous hemodialysis can be performed in patients with less hemodynamic stability.

Although renal biopsy rarely is performed, it may be indicated for patients with acute renal failure who do not respond to therapy or for assistance in the diagnosis of glomerulonephritis.

**Future Directions**

**ACETYLCYSTEINE**

Evidence exists that the prophylactic use of acetylcysteine (Mucomyst) before radiocontrast-media procedures decreases the incidence of acute renal failure.

In one randomized trial of 83 patients with chronic renal insufficiency, patients were assigned to receive 0.45 percent saline plus oral acetylcysteine (600 mg twice daily) or 0.45 percent saline alone before undergoing computed tomographic scanning. Within 48 hours after the imaging test, creatinine levels increased by 0.5 mg per dL or more in nine of the 42 patients in the saline-only group but increased in just one of the 41 patients in the acetylcysteine group (P = .01, relative risk = 0.11, absolute risk reduction = 19%, number needed to treat = 5).

A second randomized controlled trial evaluated acetylcysteine pretreatment in patients scheduled to undergo coronary angiography and angioplasty. All patients had stable, moderate renal insufficiency and a GFR of less than 60 mL per minute. Patients randomly received acetylcysteine (600 mg twice daily) the day before the coronary procedure and the day of the procedure. All patients received an infusion of 0.9 percent normal saline. Within 48 hours of the procedure, serum creatinine levels increased by more than 25 percent in 12 of 98 patients in the saline-only group and in four of 102 patients in the acetylcysteine group (P = 0.03, relative risk = 0.33, absolute risk reduction = 8%, number needed to treat = 12).

---

**TABLE 5**

**Probable Causes of Acute Renal Failure Based on the Physical Findings**

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Probable causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs</td>
<td></td>
</tr>
<tr>
<td>Elevated temperature</td>
<td>Possible infection</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Hypertension: nephrotic syndrome, malignant hypertension</td>
</tr>
<tr>
<td></td>
<td>Hypotension: volume depletion, sepsis</td>
</tr>
<tr>
<td>Weight loss or gain</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td>Mouth</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Jugular veins and axillae (perspiration)</td>
<td>Hypovolemia, hypervolemia</td>
</tr>
<tr>
<td>Pulmonary system</td>
<td>Signs of heart failure</td>
</tr>
<tr>
<td>Heart</td>
<td>New murmur of endocarditis, signs of heart failure</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Bladder distention suggesting urethral obstruction</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Pelvic mass</td>
</tr>
<tr>
<td>Rectum</td>
<td>Enlarged prostate</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash of interstitial nephritis, purpura of microvascular disease, livedo reticularis suggestive of atheroembolic disease, splinter hemorrhages or Osler's nodes of endocarditis</td>
</tr>
</tbody>
</table>


---

**TABLE 6**

**Laboratory Values in Acute Renal Failure**

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Values if prerenal cause of acute renal failure</th>
<th>Values if intrarenal cause of acute renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENa, percent*</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>BUN to creatinine ratio</td>
<td>&gt;20:1</td>
<td>10 to 20:1</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>&gt;1.020</td>
<td>1.010 to 1.020</td>
</tr>
<tr>
<td>Urine osmolality, mOsm per kg</td>
<td>&gt;500</td>
<td>300 to 500</td>
</tr>
<tr>
<td>Urine sodium concentration, mEq per L (mmol per L)</td>
<td>&lt;10 (10)</td>
<td>&gt;20 (20)</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Hyaline casts</td>
<td>Granular casts</td>
</tr>
</tbody>
</table>

FENa = fractional excretion of sodium; BUN = blood urea nitrogen.

*—FENa is calculated as follows:

\[
FENa = \frac{\text{Urine sodium} + \text{plasma sodium}}{\text{Urine creatinine} + \text{plasma creatinine}} \times 100
\]

Note: A prerenal FENa of greater than 1 percent can occur in patients receiving chronic diuretic therapy or in patients with acute renal failure superimposed on chronic renal failure. Conversely, an intrarenal FENa of less than 1 percent can occur with radiocontrast nephropathy and rhabdomyolysis.

Information from references 2, 3, 7, and 13.
TABLE 7
Selected Diagnostic Test Results and Corresponding Diseases in Patients with Acute Renal Failure

<table>
<thead>
<tr>
<th>Diagnostic test results</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated creatine kinase level, elevated myoglobin level</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Elevated uric acid level</td>
<td>Gouty nephropathy, malignancy, tumor lysis syndrome</td>
</tr>
<tr>
<td>Elevated calcium level</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Monoclonal spike on serum protein electrophoresis</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Hemoglobin SS on hemoglobin electrophoresis</td>
<td>Sickle cell nephropathy</td>
</tr>
<tr>
<td>Positive HIV test</td>
<td>HIV nephropathy</td>
</tr>
<tr>
<td>Elevated antistreptolysin-O titer</td>
<td>Poststreptococcal glomerulonephritis</td>
</tr>
<tr>
<td>Evidence of hemolysis (schistocytes on peripheral smear, decreased haptoglobin level, increased lactate dehydrogenase level; thrombocytopenia</td>
<td>Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, other autoimmune diseases</td>
</tr>
<tr>
<td>Positive antinuclear antibody</td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>Positive double-stranded DNA antibody</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Low complement level</td>
<td>Systemic lupus erythematosus, endocarditis, postinfectious glomerulonephritis</td>
</tr>
<tr>
<td>Positive antibasement membrane antibody</td>
<td>Goodpasture's syndrome</td>
</tr>
<tr>
<td>Positive cytoplasmic antineutrophil cytoplasmic antibody</td>
<td>Wegener's granulomatosis</td>
</tr>
<tr>
<td>Increased anion gap with Increased osmolar gap</td>
<td>Ethylene glycol or methanol poisoning</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Allergic interstitial nephritis</td>
</tr>
<tr>
<td>Positive blood cultures, with a new cardiac murmur</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Elevated prostate-specific antigen level</td>
<td>Prostate hypertrophy, prostate cancer</td>
</tr>
<tr>
<td>Calcifications on abdominal plain-film radiograph</td>
<td>Neprholithiasis, ureterolithiasis</td>
</tr>
<tr>
<td>Mass or calcifications on abdominal or pelvic computed tomographic scan, hydronephrosis on renal ultrasonography</td>
<td>Malignancy, prostate hypertrophy, uterine fibroids, nephrolithiasis, ureterolithiasis</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; Na⁺ = sodium ion; Cl⁻ = chloride ion; HCO₃⁻ = bicarbonate ion; BUN = blood urea nitrogen.

*—Calculations are as follows:

Anion gap = Na⁺ - (Cl⁻ + HCO₃⁻)

Serum osmolality = 2(Na⁺ [in mEq per L]) + (BUN [in mg per dl] x 2.8) + (glucose [in mg per dl] / 18)

Osmolar gap = measured serum osmolality - calculated serum osmolality


A third study23 showed that preprocedural acetylcysteine was neither helpful nor harmful.

**DOPAMINE**

Dopamine traditionally has been used to promote renal perfusion. However, systematic reviews23-25 of dopamine treatment in critically ill patients and in patients with sepsis do not support the use of dopamine to prevent renal insufficiency, morbidity, or mortality.

A multicenter, randomized, double-blind, placebo-controlled trial23 of low-dose dopamine therapy was conducted in patients with clinical evidence of early renal dysfunction who met two criteria for systemic inflammatory response syndrome (sepsis). In this study, 328 patients from 23 ICUs were assigned to receive dopamine (2 mcg per kg per minute) or placebo. The primary endpoint was elevation of the serum creatinine level during the infusion. No statistical differences were found between the two groups in elevation of creatinine levels, need for dialysis, duration of ICU stay, or length of hospital stay. There were 69 deaths in the dopamine group and 66 deaths in the placebo group. The study showed no benefit for dopamine.

A recent meta-analysis24 was conducted on the use of

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The Author

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Address correspondence to Eddie Needham, M.D., Emory University School of Medicine, 4575 N. Shallowford Rd., Atlanta, GA 30338. Reprints are not available from the author.
Initial Evaluation of Acute Renal Failure

Laboratory test results consistent with acute renal failure (rise of 0.5 mg per dl, or a 50 percent increase in creatinine above the baseline or a 50 percent decrease in the baseline calculated GFR)

Medical history, current medications; review of systems to include systemic symptoms (fever, weight loss); and physical examination to include vital signs, heart, lung, abdominal, pelvic, rectal, and skin examinations

Likely cause of acute renal failure apparent?

Yes
Confirm diagnosis with appropriate tests. Diagnosis confirmed?

Yes
Treat cause.

Electrolytes (plasma and urine)
Urinalysis with microscopic examination
FENa
Renal ultrasound

Intrarenal
BUN to creatinine ratio 10:1 to 20:1
FENa >1
Urinary specific gravity 1.010 to 1.020
Tubular or granular casts in urine
Ultrasound showing medical kidney disease or normal, no obstruction

CBC, ESR
Consider nephrology consult/ kidney biopsy
Eliminate toxins.
Treat causes.

Postrenal
Ultrasound shows hydronephrosis.
Serum and urine tests have similar results to intrarenal causes.

Order CT (without contrast) if cause of obstruction is not evident
Relieve obstruction.
Consider urology consult.

Pretrenal
BUN to creatinine ratio >20:1
FENa <1 percent
Urine specific gravity >1.020
Hyaline casts in urine sediment
No evidence of obstruction
No evidence of intrarenal causes of acute renal failure

Hydrate.
Eliminate toxins.
Treat causes.

Figure 1. Algorithm for the initial evaluation of acute renal failure. (GFR = glomerular filtration rate; FENa = fractional excretion of sodium; BUN = blood urea nitrogen; CBC = complete blood count; ESR = erythrocyte sedimentation rate; CT = computed tomography.)

dopamine to reduce the incidence or severity of acute renal failure, the need for dialysis, or mortality in critically ill patients. Of the 58 studies that were identified, 17 were randomized clinical trials. Dopamine did not prevent mortality, onset of acute renal failure, or need for dialysis. A literature review25 reached a similar conclusion.

OLIGURIC VS. NONOLIGURIC ACUTE RENAL FAILURE

Historically, nonoliguric renal failure has been assumed to have a better outcome than oliguric renal failure. As a result, diuretics commonly have been given in an attempt to convert the oliguric state to a nonoliguric state. However, diuretics have not been shown to be beneficial, and they may worsen outcomes.26

An observational study27 of 552 patients with acute renal failure in four ICUs found that 326 of the patients were given diuretics at the time of nephrology consultation. The patients initially given diuretics were older; were more likely to have a lower serum blood urea nitrogen concentration; and were more likely to have a history of heart failure, nephrotoxic renal failure, or acute respiratory failure. The main outcome measures were all-cause hospital mortality, nonrecovery of renal function, or both. Diuretic use in these higher risk patients was
associated with a significant risk of death or nonrecovery of renal function (odds ratio [OR] = 1.79; 95% confidence interval [CI] = 1.14 to 2.76). In the patients who survived one week past the initial nephrology consultation, the risk of death and nonrecovery of renal function was significantly increased (OR = 3.12; 95% CI = 1.73 to 5.62).

**SODIUM BICARBONATE**

A recent placebo-controlled trial involving 119 patients found an absolute risk reduction of 11.9 percent and a relative risk of 0.13 for elevated serum creatinine levels (from contrast-induced nephropathy) in patients who were given a sodium bicarbonate infusion before a radiocontrast-media procedure compared with those who were given only saline. This single-center study was stopped early because of the degree of benefit demonstrated for sodium bicarbonate infusion.

Author disclosure: Nothing to disclose.

**REFERENCES**

Clinical Practice Guidelines for Chronic Kidney Disease in Adults: Part I. Definition, Disease Stages, Evaluation, Treatment, and Risk Factors

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In February 2002, the Kidney Disease Outcome Quality Initiative of the National Kidney Foundation published clinical practice guidelines on chronic kidney disease. The first six of the 15 guidelines are of the greatest relevance to family physicians. Part I of this two-part article reviews guidelines 1, 2, and 3. Chronic kidney disease is defined by the presence of a marker of kidney damage, such as proteinuria (ratio of greater than 30 mg of albumin to 1 g of creatinine on untimed [spot] urine testing), or a decreased glomerular filtration rate for three or more months. Disease staging is based on the glomerular filtration rate. Evaluation should be directed at determining the type and severity of chronic kidney disease. Treatment goals include preventing disease progression and complications. The guidelines place special emphasis on the prevention and treatment of cardiovascular disease in patients with chronic kidney disease. Risk factors for chronic kidney disease include diabetes mellitus, hypertension, family history of chronic kidney disease, age older than 60 years, and U.S. racial or ethnic minority status. The guidelines recommend testing for proteinuria and estimating the glomerular filtration rate in patients at risk for chronic kidney disease. Family physicians should weigh the value of the National Kidney Foundation guidelines for their clinical practice based on the strength of evidence and perceived cost-effectiveness until additional evidence becomes available on the usefulness of the recommended quality indicators. (Am Fam Physician 2004;70:869-76. Copyright © 2004 American Academy of Family Physicians.)

Chronic kidney disease is a major public health problem throughout the world. In the United States, kidney failure is becoming increasingly common and is associated with poor health outcomes and high medical expenditures. In this country, the number of patients treated with dialysis or transplantation is projected to increase from 340,000 in 1999 to 651,000 in 2010.1

The major outcomes of chronic kidney disease, regardless of the specific diagnosis (i.e., type of kidney disease), include progression to kidney failure, complications from decreased kidney function, and development of cardiovascular disease. Increasing evidence shows that early detection and treatment often can prevent or delay some of these adverse outcomes.2 However, opportunities for prevention may be lost because chronic kidney disease is not diagnosed or is treated insufficiently.3-6 One reason is lack of agreement about the definition of chronic kidney disease, as well as the classification of its stages. Another reason is lack of uniform application of simple tests for the detection and evaluation of the disease.

In February 2002, the Kidney Disease
Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) published clinical practice guidelines on chronic kidney disease. The goals of the Work Group that developed the guidelines were as follows: to define chronic kidney disease and classify its stages, regardless of the underlying cause; to evaluate laboratory measurements for clinical assessment of kidney disease; to associate the level of kidney function with the complications of chronic kidney disease; and to stratify risk for the loss of kidney function and the development of cardiovascular disease.

The leaders of the NKF recognized the role of family physicians in providing medical care for patients with chronic kidney disease (particularly during the early stages when interventions might slow disease progression) and therefore wanted the guidelines to be practical and accessible to primary care physicians. To these ends, a family physician was invited to be an active participant in the guidelines Work Group and a member of the K/DOQI Advisory Board, which oversees all guidelines developed under its auspices. At present, there are only about 5,000 nephrologists in the United States. With the projected increase in the number of patients diagnosed with chronic kidney disease (especially as defined by the NKF guidelines), a strong partnership with family physicians and general internists will be necessary.

The first purpose of this article is to disseminate the simple definition and the five-stage classification system of chronic kidney disease that were developed through an evidence-based process and justified with existing literature. The second purpose is to describe the six guidelines with the most immediate relevance to family physicians. Guidelines on evaluation, treatment, and risk factors are reviewed in part 1 of this two-part article. Part II reviews guidelines on estimation of glomerular filtration rate, assessment of proteinuria, and use of markers of chronic kidney disease other than proteinuria.

Background

The NKF Work Group defined two principal outcomes of chronic kidney disease: progressive loss of kidney function and development of complications, particularly cardiovascular disease.

Progressive loss of kidney function over time in most patients with chronic kidney disease is a well-known outcome. Because of the older age at onset for many forms of kidney disease and the slow rate of decline in kidney function, decreased kidney function...
is far more common than kidney failure, for which replacement therapy (dialysis or transplantation) becomes necessary.

Decreased kidney function is associated with complications in virtually all organ systems. Therapeutic interventions in the earlier stages may prevent or ameliorate some of these complications, as well as slow progression to kidney failure. Cardiovascular disease is considered an outcome of chronic kidney disease for several reasons. First, cardiovascular events are more common than kidney failure in patients with chronic kidney disease. In addition, chronic kidney disease appears to be a risk factor for cardiovascular disease.

Cardiovascular disease in patients with chronic kidney disease is treatable, as well as potentially preventable. A 1998 report from the NKF Task Force on Cardiovascular Disease\textsuperscript{9,10} recommended that patients with chronic kidney disease be considered in the “highest risk” group for subsequent cardiovascular events, and that most interventions that are effective in the general population should be applied to patients with chronic kidney disease.\textsuperscript{11,12}

The NKF guidelines\textsuperscript{2,8} are based on a systematic literature review using an approach adapted from the one used by the Agency for Healthcare Research and Quality. A uniform format for summarizing strength of evidence was developed based on an evaluation of study size, applicability, results, and methodologic quality. Guideline statements were prepared from the analysis of this review. Each rationale statement was graded according to the supporting level of evidence (Table 1).\textsuperscript{7} Note that the evidence grading system differs from the system used in American Family Physician: only AFP’s evidence level C (consensus/expert opinion) compares with the NKF grade O (opinion).

In preparing the guidelines, 18,153 abstracts were screened, 1,045 articles were reviewed, and results were extracted from 367 articles. Many rationale statements are based on a structured review of evidence specifically for the guidelines (NKF grade S or C); however, most guidelines are based in part on unstructured review or opinion.

### Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Analysis of individual patient data from a single, large, generalizable study of high methodologic quality (e.g., NHANES III)</td>
</tr>
<tr>
<td>C</td>
<td>Compilation of original articles (using evidence tables)</td>
</tr>
<tr>
<td>R</td>
<td>Review of reviews and selected original articles</td>
</tr>
<tr>
<td>O</td>
<td>Opinion</td>
</tr>
</tbody>
</table>

NKF = National Kidney Foundation; NHANES III = Third National Health and Nutrition Examination Survey.


### Guideline 1: Definition and Stages of Chronic Kidney Disease

Early detection and treatment often can prevent or delay adverse outcomes in patients with chronic kidney disease. Routine laboratory tests can detect the disease in its earlier stages (NKF grades R and O).\textsuperscript{7}

A definition of chronic kidney disease is provided in Table 2.\textsuperscript{7} The presence of the disease should be established based on the occurrence of kidney damage and the level of kidney function (i.e., glomerular filtration rate [GFR]), regardless of the specific diagnosis. Disease stage should be assigned based on the level of kidney

### Table 2

**NKF Definition of Chronic Kidney Disease**

Kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests

GFR < 60 mL per minute per 1.73 m\(^2\) for three months or more, with or without kidney damage

NKF = National Kidney Foundation; GFR = glomerular filtration rate.

function, also regardless of the specific diagnosis.\(^7\)

Kidney damage usually is ascertained by the presence or absence of certain markers, rather than by kidney biopsy. The KNF guidelines\(^8\) emphasize persistent proteinuria as a marker of kidney damage, because proteinuria has been studied most thoroughly\(^9\) and is identified readily using a simple office procedure. A ratio of greater than 30 mg of albumin to 1 g of creatinine in an untimed (spot) urine sample usually is considered abnormal. Other markers of kidney damage include abnormalities in urine sediment, blood, and urine chemistries, and abnormal findings on imaging studies. Patients who have normal kidney function but have markers of kidney damage are at increased risk for adverse outcomes of chronic kidney disease.

The GFR is considered the best measure of overall kidney function.\(^14\) Normal GFR varies according to patient age, sex, and body size. In young adults, the normal GFR is approximately 120 to 130 mL per minute per 1.73 m\(^2\) and declines with age.\(^14\)-\(^17\) A GFR level below 60 mL per minute per 1.73 m\(^2\) represents loss of one half or more of the adult level of normal kidney function. Traditionally, an age-related decline in GFR has been considered "normal." However, a decreased GFR in an elderly patient requires adjustment of drug dosages\(^18\) and appears to be an independent predictor of adverse outcomes such as mortality and cardiovascular disease.\(^19\)-\(^21\)

The definition of chronic kidney disease is not modified based on patient age. The situation is analogous to the situation with blood pressure levels and the definition and prevalence of hypertension. Blood pressure rises with age, but hypertension in elderly persons is associated with adverse outcomes; however, the definition of hypertension is not age dependent, and the majority of elderly persons are classified as having hypertension.\(^22\) Similarly, because of the age-related decline in GFR, the prevalence of chronic kidney disease increases with age; approximately 17 percent of persons older than 60 years have an estimated GFR of less than 60 mL per minute per 1.73 m\(^2\).\(^5\)

Kidney failure is defined as a GFR below 15 mL per minute per 1.73 m\(^2\), usually accompanied by signs and symptoms of uremia, or as the need for initiation of kidney replacement therapy for management of the complications of a decreased GFR. In the United States, approximately 98 percent of patients begin dialysis when their GFR falls below 15 mL per minute per 1.73 m\(^2\).\(^23\)

Kidney failure is not synonymous with end-stage renal disease (ESRD). In the United States, "end-stage renal disease" is an administrative term based on the conditions for health care payment by the Medicare ESRD Program for patients treated with dialysis or transplantation. However, the term does not include patients with kidney failure who are not treated with dialysis or transplantation. Thus, although the term "end-stage renal disease" is in widespread use and provides a simple operational classification of patients according to treatment, it does not precisely define a stage of severity in kidney disease.

As demonstrated in Table 3,\(^6,7,24-26\) more than 20 million adults in the United States have chronic kidney disease, and millions more are at risk of developing the disease. Patients who have diabetes mellitus and hypertension are at highest risk. As the number of patients with diabetes and hypertension continues to increase, the number of patients with chronic kidney disease also will increase. Consequently, clear definition and classification of the stages of disease severity are needed to assess patients for the development and progression of chronic kidney disease.

The NKF classification of the stages of chronic kidney disease supports communication between physicians. The classification system helps clear up the ambiguities caused by vague terms such as "chronic renal insufficiency" and "chronic renal failure." Using the NKF system, family physicians can ask nephrologist consultants more precise questions and can expect more precise
answers. For example, at what stage does the nephrologist want to see a potential kidney transplant recipient? What interventions should be used at each stage to give a patient the best chance of preserving kidney function?

Staging of chronic kidney disease also allows physicians to talk more clearly with patients. For example, use of the word "kidney" rather than "renal" facilitates communication. In addition, patients are becoming accustomed to dealing with numbers (cholesterol levels, blood pressure measurements, blood sugar levels). Knowing their GFR and the type of personal interventions that may slow the decline in GFR allows patients to take greater control of their disease.

**Guideline 2: Evaluation and Treatment of Chronic Kidney Disease**

Patients with chronic kidney disease should be evaluated to determine the following: specific diagnosis (type of kidney disease), comorbid conditions, disease severity (assessed by the level of kidney function), complications (related to the level of kidney function), risk for loss of kidney function, and risk for development of cardiovascular disease (NKF grades R and O).7

Treatment of patients with chronic kidney disease includes the following: therapy based on the specific diagnosis, evaluation, and management of comorbid conditions; measures to slow loss of kidney function; measures to prevent and treat cardiovascu-

### TABLE 3

**NKF Classification of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml per minute per 1.73 m²)</th>
<th>U.S. prevalence, number of affected patients (%)</th>
<th>Action plan$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At increased risk for chronic kidney disease</td>
<td>&gt; 60 (with risk factors for chronic kidney disease)</td>
<td></td>
<td>Screening, reduction of risk factors for chronic kidney disease</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage with normal or elevated GFR</td>
<td>≥ 90</td>
<td>5.9 million (3.3)</td>
<td>Diagnosis and treatment, treatment of comorbid conditions, interventions to slow disease progression, reduction of risk factors for cardiovascular disease</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60 to 89</td>
<td>5.3 million (3.0)</td>
<td>Estimation of disease progression</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30 to 59</td>
<td>7.6 million (4.3)</td>
<td>Evaluation and treatment of disease complications</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15 to 29</td>
<td>400,000 (0.2)</td>
<td>Preparation for kidney replacement therapy (dialysis, transplantation)</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
<td>300,000 (0.1)</td>
<td>Kidney replacement therapy if uremia is present</td>
</tr>
</tbody>
</table>

NKF = National Kidney Foundation; GFR = glomerular filtration rate.

*—Chronic kidney disease is defined as either kidney damage or a GFR below 60 ml per minute per 1.73 m² for three months or more. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

1—For stages 1 and 2, kidney damage was estimated by a ratio of greater than 17 mg of albumin to 1 g of creatinine in men or greater than 25 mg of albumin to 1 g of creatinine in women on two timed (spot) urine tests.

2—Prevalence for stage 3, from the United States Renal Data System (1998-1999).26 Includes approximately 230,000 patients treated with dialysis and assumes 70,000 other patients who were not on dialysis. Prevalences for stages 1 through 4 are based on data obtained from the Third National Health and Nutrition Examination Survey (1988-1994).25 Population of 177 million adults 20 years of age and older. GFR was estimated from serum creatinine using an equation based on age, sex, race, and calibration for the serum creatinine level.25

3—Includes actions from preceding stages.

4—Prevalence of persons at increased risk for chronic kidney disease has not been estimated accurately.

lar disease; measures to prevent and treat complications of decreased kidney function; preparation for kidney failure and kidney replacement therapy; and replacement of kidney function by dialysis or transplantation if signs and symptoms of uremia are present.

Medications should be reviewed at all visits. Dosage adjustments should be based on the level of kidney function. It is important to detect drug interactions, as well as potentially adverse effects of medications on kidney function or complications of chronic kidney disease. If possible, therapeutic drug monitoring should be performed.

A clinical action plan should be developed for each patient, with the plan based on the disease stage (Table 3).5,24-26 Self-management behaviors should be incorporated into the treatment plan at all stages of the disease. Patients with chronic kidney disease should be referred to a nephrologist for consultation and co-management if a clinical action plan cannot be prepared, the appropriate evaluation cannot be performed, or the recommended treatment cannot be implemented. In most cases, patients with a GFR below 30 mL per minute per 1.73 m² should be referred to a nephrologist (NKF grade O).7

Diagnosis of chronic kidney disease traditionally is based on pathology and etiology. A simplified classification emphasizes diseases in the native kidneys (broadly divided into those that are diabetic or nondiabetic in origin) and kidney disease in the transplant patient. In the United States, diabetic kidney disease is the most common cause of kidney failure; its earliest manifestation is microalbuminuria with a normal or elevated GFR. Of note, the NKF guidelines7 classify patients who have diabetes and microalbuminuria with a normal GFR as having stage 1 chronic kidney disease. Nondiabetic kidney disease includes glomerular, vascular, tubulointerstitial, and cystic kidney diseases.

Specific treatment depends on the diagnosis, and a thorough search for "reversible causes" of kidney disease should be conducted. The remainder of the action plan is based on the stage of chronic kidney disease, irrespective of the diagnosis (Table 3).6,7,24-26

Guideline 3: Risk Factors for Chronic Kidney Disease

The risk of developing chronic kidney disease is increased in some patients without kidney damage and with a normal or elevated GFR (NKF grade R).7 During the routine health care visit, all patients should be assessed for increased risk based on clinical and sociodemographic factors (Table 4).7

 Patients determined to be at increased risk for kidney disease should undergo testing for markers of kidney damage and an estimation of their GFR. Patients found to have chronic kidney disease should be evaluated and treated as specified in NKF guideline 2. Patients at increased risk who are found not to have chronic kidney disease should be advised to follow a program

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**TABLE 4**

**Risk Factors for Chronic Kidney Disease and Its Outcomes**

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Factors that increase susceptibility to kidney damage</td>
<td>Older age, family history of chronic kidney disease, reduction in kidney mass, low birth weight, U.S. racial or ethnic minority status, low income or educational level</td>
</tr>
<tr>
<td>factors</td>
<td></td>
<td>Diabetes mellitus, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, obstruction of lower urinary tract, drug toxicity</td>
</tr>
<tr>
<td>Initiation factors</td>
<td>Factors that directly initiate kidney damage</td>
<td>Diabetes mellitus, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, obstruction of lower urinary tract, drug toxicity</td>
</tr>
<tr>
<td>Progression factors</td>
<td>Factors that cause worsening kidney damage and faster decline in kidney function after kidney damage has started</td>
<td>Higher level of proteinuria, higher blood pressure level, poor glycemic control in diabetes, smoking</td>
</tr>
<tr>
<td>End-stage factors</td>
<td>Factors that increase morbidity and mortality in kidney failure</td>
<td>Lower dialysis dose (Kt/V)*, temporary vascular access, anemia, low serum albumin level, late referral for dialysis</td>
</tr>
</tbody>
</table>

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*—In Kt/V (accepted nomenclature for dialysis dose), “K” represents urea clearance, “T” represents time, and “V” represents volume of distribution for urea.

**Strength of Recommendations**

<table>
<thead>
<tr>
<th>Key clinical recommendations</th>
<th>Label</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>The definition of chronic kidney disease is kidney damage or a GFR below 60 mL per minute per 1.73 m² for three months or more.</td>
<td>C</td>
<td>7,8</td>
</tr>
<tr>
<td>A clinical action plan should be developed for each patient, based on the stage of disease as defined by the classification system developed by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative.</td>
<td>C</td>
<td>7,8</td>
</tr>
<tr>
<td>In general, patients with a GFR below 30 mL per minute per 1.73 m² should be referred to a nephrologist.</td>
<td>C</td>
<td>7,8</td>
</tr>
<tr>
<td>A ratio of greater than 30 mg of albumin to 1 g of creatinine on untimed (spot) urine testing is abnormal and merits further evaluation.</td>
<td>C</td>
<td>7,8</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate.

of risk factor reduction (if appropriate) and should be reevaluated periodically.

During the routine health care visit, patients should be asked specifically about clinical and sociodemographic factors that have been implicated as susceptibility or initiation factors for chronic kidney disease. If any of these factors are present, patients should be assessed for albuminuria, and GFR should be estimated. The prevalence of persons at increased risk for chronic kidney disease has not been determined. However, the number of these persons is likely to far exceed the number of patients with the disease. Particular emphasis should be given to patients with diabetes mellitus, hypertension, family history of chronic kidney disease, age older than 60 years, and U.S. racial or ethnic minority status.

Guideline 3 is problematic for family physicians who have the task of identifying patients at risk for kidney disease. In preparing the NKF guideline, the Work Group evaluated evidence for the definition, classification, and prevalence of risk factors (NKF grade R). However, the issue of universal testing for kidney disease or testing of patients at increased risk for kidney disease has not been studied systematically. In the United States, testing currently is not recommended, except in patients with hypertension, diabetes, or known kidney disease.

Based on personal opinion and experience, the Work Group members recommend testing of patients who are at increased risk for kidney disease. In fact, a focus of the public awareness campaign stemming from the NKF guidelines is to encourage patients who think they may be at increased risk to tell their physician, and for the physician to test at-risk patients for albuminuria and GFR. Nonetheless, more research is needed to clearly identify the risks and benefits (both clinical and economic) of testing large segments of the U.S. population.

The authors indicate that they do not have any conflicts of interest. Sources of funding: AstraZeneca Pharmaceuticals LP is the primary sponsor of the NKF K/DOQI guidelines, Merck & Co., Inc. is the implementation sponsor, and Amgen Inc. is the founding and principal sponsor of K/DOQI.

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Chronic Kidney Disease


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Clinical Practice Guidelines for Chronic Kidney Disease in Adults: Part II. Glomerular Filtration Rate, Proteinuria, and Other Markers

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The Kidney Disease Outcome Quality Initiative of the National Kidney Foundation published clinical practice guidelines on chronic kidney disease in February 2002. Of the 15 guidelines, the first six are of greatest relevance to family physicians. Part II of this two-part review covers guidelines 4, 5, and 6. Glomerular filtration rate is the best overall indicator of kidney function. It is superior to the serum creatinine level, which varies with age, sex, and race and often does not reflect kidney function accurately. The glomerular filtration rate can be estimated using prediction equations that take into account the serum creatinine level and some or all of specific variables (age, sex, race, body size). In many patients, estimates of the glomerular filtration rate can replace 24-hour urine collections for creatinine clearance measurements. Urine dipsticks generally are acceptable for detecting proteinuria. To quantify proteinuria, the ratio of protein or albumin to creatinine in an untimed (spot) urine sample is an accurate alternative to measurement of protein excretion in a 24-hour urine collection. Patients with persistent proteinuria have chronic kidney disease. Other techniques for evaluating patients with chronic kidney disease include examination of urinary sediment, urine dipstick testing for red and white blood cells, and imaging studies of the kidneys (especially ultrasonography). These techniques also can help determine the underlying cause of chronic kidney disease. Family physicians should weigh the value of the National Kidney Foundation guidelines for their clinical practice based on the strength of evidence and perceived cost-effectiveness until additional evidence becomes available on the usefulness of the recommended quality indicators. (Am Fam Physician 2004;70:1091-7. Copyright© 2004 American Academy of Family Physicians.)


See page 1011 for definitions of strength-of-recommendation labels.

This article exemplifies the AAFP Annual Clinical Focus on caring for America's aging population.

In February 2002, the Kidney Disease Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) published clinical practice guidelines for chronic kidney disease\(^1\) that were based on a systematic literature review. A uniform format for summarizing strength of evidence was developed based on an evaluation of study size, applicability, results, and methodologic quality. Guideline statements were prepared from the analysis of the review, with each rationale statement graded according to the supporting level of evidence (Table 1).\(^1\) The evidence grading system differs from the system used in American Family Physician (AFP): only AFP's evidence level C (consensus/expert opinion) compares with the NKF grade O (opinion). Part I\(^2\) of this two-part article reviewed the guidelines on definition and stages of chronic kidney disease, evaluation and treatment, and risk factor identification. Chronic kidney disease is defined by kidney damage (often manifested by proteinuria) or a decreased glomerular filtration rate (GFR) for three or more months. The degree of decrease in the GFR provides the basis for straightforward classification of chronic kidney disease by stages (see Table 3 in part I\(^3\)). Treatment should focus on slowing disease progression and preventing complications, especially the development of cardiovascular disease. To identify chronic kidney disease and intervene early in its course, physicians should test for proteinuria and estimate GFR at-risk...
patients. Part II summarizes guidelines for using tests to evaluate patients with suspected or known chronic kidney disease.

**Guideline 4: Estimation of GFR**

The GFR is the best overall indicator of the level of kidney function. (NKF grades S, C, and R). The GFR should be estimated using a prediction equation that takes into account the serum creatinine level and some or all of these variables: age, sex, race, and body size. The Modification of Diet in Renal Disease (MDRD) study equation and the Cockcroft-Gault equation provide useful estimates of the GFR in adult patients. The NKF guidelines notes that the serum creatinine concentration alone is not optimal for assessing the level of kidney function.

In addition to reporting the serum creatinine measurement, clinical laboratories should report the estimated GFR as determined by a prediction equation. The NKF guidelines also recommend that autoanalyzers should be calibrated using an international standard.

In most cases, measurement of creatinine clearance using a timed (e.g., 24-hour) urine collection for assessment of the glomerular filtration rate is not more reliable than estimation using a prediction equation. However, a 24-hour urine sample provides information that is useful for estimating GFR in patients with exceptional dietary intake (vegetarian diet, creatine supplementation) or muscle mass (amputation, malnutrition, muscle wasting), assessing diet and nutritional status, and determining the need to start dialysis.

In clinical practice, GFR usually is estimated from the creatinine clearance or the serum creatinine concentration. Measurement of creatinine clearance requires the collection of a timed urine sample, which is inconvenient for the patient as well as frequently inaccurate. The serum creatinine concentration is affected by factors other than the GFR, including creatinine secretion, generation, and extrarenal excretion. Thus, there is a relatively wide range for serum creatinine levels in normal persons, and the GFR must decline to about one half of the normal level before the serum creatinine concentration rises above the upper limit of normal. This situation regarding a declining GFR with "normal" creatinine is especially important in elderly patients, in whom the age-related decline in GFR is not reflected by an increase in the serum creatinine level because of a concomitant age-related decline in creatinine production.

Table 3 shows the range of serum creatinine values corresponding with an estimated GFR of 60 mL per minute per 1.73 m², depending on age, sex, and race. Note that the NKF definition of chronic kidney disease includes a GFR level below 60 mL per minute per 1.73 m² for three months or more (see Table 2 in part I). The data in Table 3 demonstrate that minor elevations of the serum creatinine concentration may represent a substantial reduction in the GFR. Thus, with use of only the serum creatinine as the measure of kidney function, it is difficult to estimate the level of kidney function and detect earlier stages of chronic kidney disease.

The estimate of GFR from the serum cre-
Chronic Kidney Disease

Creatinine concentration can be improved by using a prediction equation that also takes into account the patient’s age, sex, race, and body size (e.g., the equations shown in Table 2). In patients with a GFR below about 90 mL per minute per 1.73 m², the abbreviated MDRD study equation appears to be more accurate and precise than the Cockcroft-Gault equation, but is more complicated to compute.

GFR calculators for use of the abbreviated MDRD study equation and the Cockcroft-Gault equation are available on the NKF Web site (http://www.kidney.org/kf/professionals/gfr_calculator.cfm). These equations can be programmed or imported into laboratory systems, personal computers, and hand-held calculators. As part of the implementation of the NKF guidelines and in cooperation with the National Institutes of Health (NIH), efforts are underway to have clinical laboratories report GFR in conjunction with the serum creatinine measurement.

Guideline 4 provides useful information for family physicians. Evidence is convincing that 24-hour urine collections for creatinine are not superior to prediction equations that are based on the serum creatinine level and other patient characteristics. Thus, it is possible to perform a straightforward serum collection, rather than subject a patient to the inconvenience of a 24-hour urine collection that then must be returned to the laboratory. Furthermore, a urine collection performed over 24 hours may be incomplete, even if the volume appears to be reasonable, leading to incorrect values for calculated creatinine clearance and possibly to inappropriate deci-

### TABLE 2
Equations for Predicting GFR in Adults Based on Serum Creatinine Concentration*

<table>
<thead>
<tr>
<th>Abbreviated MDRD study equation:</th>
<th>[ \text{GFR} = \frac{186 \times (\text{age})^{1.154} \times (\text{Age})^{0.203}}{(\text{Creatinine})^{1.209} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})} ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault equation:</td>
<td>[ \text{C_G} = \frac{140 \times \text{weight}}{72 \times \text{Age}} \times (0.85, \text{ if female}) ]</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; \( S_C \) = serum creatinine concentration; \( C_G \) = creatinine clearance.

*—For each equation, \( S_C \) is in milligrams per deciliter, age is in years, and weight is in kilograms.

Information from references 4, 5, and 6.

### TABLE 3
Serum Creatinine Levels Corresponding with an Estimated GFR of 60 mL per minute per 1.73 m² Using Two Prediction Equations*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Whites</th>
<th>Blacks</th>
<th>Whites</th>
<th>Blacks</th>
<th>Whites</th>
<th>Blacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30</td>
<td>1.47 (130)</td>
<td>1.13 (100)</td>
<td>1.73 (153)</td>
<td>1.34 (118)</td>
<td>1.83 (162)</td>
<td>1.56 (138)</td>
</tr>
<tr>
<td>40</td>
<td>1.39 (123)</td>
<td>1.08 (95)</td>
<td>1.65 (146)</td>
<td>1.27 (112)</td>
<td>1.67 (148)</td>
<td>1.42 (126)</td>
</tr>
<tr>
<td>50</td>
<td>1.34 (118)</td>
<td>1.03 (91)</td>
<td>1.58 (140)</td>
<td>1.22 (108)</td>
<td>1.50 (133)</td>
<td>1.28 (113)</td>
</tr>
<tr>
<td>60</td>
<td>1.30 (115)</td>
<td>1.00 (88)</td>
<td>1.53 (135)</td>
<td>1.18 (104)</td>
<td>1.33 (118)</td>
<td>1.13 (100)</td>
</tr>
<tr>
<td>70</td>
<td>1.26 (111)</td>
<td>0.97 (86)</td>
<td>1.49 (132)</td>
<td>1.15 (102)</td>
<td>1.17 (103)</td>
<td>0.99 (88)</td>
</tr>
<tr>
<td>80</td>
<td>1.23 (109)</td>
<td>0.95 (84)</td>
<td>1.46 (129)</td>
<td>1.12 (99)</td>
<td>1.00 (88)</td>
<td>0.85 (75)</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

*—The calculations in this table assume a patient weight of 72 kg (158 lb, 6 oz) and body surface area of 1.73 m².

†—The abbreviated MDRD study equation and the Cockcroft-Gault equation are shown in Table 2.

sions about patient care. On the other hand, if the volume of urine collected over 24 hours obviously is smaller than reasonable, the laboratory value will be dismissed, resulting in wasted time and effort.

It is unlikely that the GFR will become the standard measure used by physicians until clinical laboratories begin reporting estimated GFR values. If GFR values are to be computed and reported, the laboratory request will require patient information that not always is reported (e.g., weight, race); however, if these additional data become an expected part of the laboratory request, physicians will not have to calculate GFRs. Patients can be given their GFR “number” more dependably, and the GFR value will become a permanent part of the laboratory record.

Cooperation with the local clinical laboratory is important in another way. Differences among clinical laboratories in the calibration of serum creatinine assays can result in an error rate as high as 20 percent in GFR estimates. Consideration of differences in the calibration of creatinine assays is especially important in patients with nearly normal serum creatinine concentrations. Estimation of GFR using a prediction equation should take into account differences in creatinine calibration between the local laboratory and the laboratory where the prediction equation was developed. The National Kidney Disease Education Program, operating under the NIH, is working with clinical laboratories and autoanalyzer manufacturers to calibrate serum creatinine assays using an international standard and to build GFR reporting into the systems.

The practical implication of having the GFR readily available goes beyond the issue of classification of chronic disease: it allows adjustment of drug doses to the level of kidney function.

Guideline 5: Assessment of Proteinuria

Urine normally contains small amounts of protein. However, a persistent increase in protein excretion usually is a sign of kidney damage. The type of protein, such as low-molecular-weight globulins or albumin, depends on the type of kidney disease. Increased excretion of low-molecular-weight globulins is a sensitive marker of some types of tubulointerstitial disease. Increased excretion of albumin is a sensitive marker of chronic kidney disease resulting from diabetes mellitus, glomerular disease, or hypertension.

In the NKF guidelines, the term “proteinuria” refers to increased urinary excretion of albumin, other specific proteins, or total protein. The term “albuminuria” refers exclusively to the increased urinary excretion of albumin. The term “microalbuminuria” refers to albumin excretion that is above the normal range but below the level of detection by tests for total protein excretion in urine.

Evaluation of proteinuria or microalbuminuria generally does not require a timed (overnight or 24-hour) urine collection (NKF grades R and C). In most circumstances, untimed (spot) urine samples should be used to detect and monitor proteinuria (NKF grades R and C). First-morning urine specimens are preferred; if these specimens are not available, use of random urine specimens is acceptable (NKF grades R and O).

In most patients, urine dipstick tests are acceptable for detecting proteinuria (NKF grades R and O). Standard urine dipsticks may be used to detect increased total urine protein excretion, and albumin-specific dipsticks may be used to detect albuminuria.

If a urine dipstick test is positive (1+ or greater), proteinuria should be confirmed by a quantitative measurement (protein-to-creatinine ratio or albumin-to-creatinine ratio) within three montias. If two or more quantitative tests performed one to two weeks apart are positive, persistent proteinuria should be diagnosed, and the patient should undergo further evaluation for chronic kidney disease (see guideline 2 in part 1). In adults with chronic kidney disease, proteinuria should be monitored with the albumin-to-creatinine ratio (NKF grade O). Use of the total protein-to-creatinine ratio is acceptable if the albumin-to-cre-
Evaluation of Proteinuria

Patient not known to have kidney disease

- Not at risk for kidney disease
  - Standard urine dipstick test
    - \( \geq 1^+ \)
      - Total protein-to-creatinine ratio
        - \( > 200 \text{ mg to 1g} \)
        - Recheck at periodic health evaluation.
    - \( \leq 200 \text{ mg to 1g} \)
      - Diagnostic evaluation

- At risk for kidney disease
  - Albumin-specific dipstick test
    - Negative or trace amount of protein
      - Albumin-to-creatinine ratio
        - \( \leq 30 \text{ mg to 1g} \)
        - Consultation
    - Positive
      - Treatment

Figure 1. Evaluation of proteinuria in a patient not known to have kidney disease.


The serum creatinine concentration alone is not optimal for assessing the level of kidney function.
test should be repeated using a quantitative measurement. Only patients with persistent proteinuria are diagnosed with chronic kidney disease.

This guideline is useful to family physicians because it eliminates the need for patients to provide a 24-hour urine sample for quantification of proteinuria. The suggestion to measure albumin excretion, rather than total protein excretion, is a departure from current clinical practice. Note, however, that albumin assays may not be available at all clinical laboratories.

**Guideline 6: Other Markers of Chronic Kidney Disease**

In addition to proteinuria, markers of damage to the kidneys include abnormalities in the urinary sediment and abnormal findings on imaging studies. Some types of chronic kidney disease are defined by constellations of markers. For other types of chronic kidney disease, new markers are needed to identify kidney damage that occurs before a reduction in the GFR.

Examination of urinary sediment or dipstick testing for red and white blood cells should be performed in patients with chronic kidney disease and in patients who are at risk for the disease. Imaging studies of the kidneys also should be obtained in these patients.

Several new urinary markers, including tubular and low-molecular-weight proteins and specific mononuclear cells, show promise. At present, however, they should not be used for clinical decision-making (NKF grade C).1,2

As discussed in guideline 5, abnormal urinary albumin or total protein excretion is a highly sensitive marker of glomerular diseases, including diabetic kidney disease. Urinary sediment examination, kidney imaging studies, and specific clinical presentations also can suggest the type of chronic kidney disease.

A urinary sediment examination, especially when performed in conjunction with an assessment for proteinuria, is useful in detecting chronic kidney disease and identifying its type. Urine dipsticks include reagent pads that are sensitive for detecting red blood cells (hemoglobin), white blood cells (leukocyte esterase), and bacteria (nitrites). The dipsticks cannot detect tubular epithelial cells, fat, or casts, crystals, fungi, or parasites. The decision to perform a urinary sediment examination or urine dipstick test depends on the type of kidney disease that is being considered.

Abnormal imaging studies can suggest the cause of chronic kidney disease, such as arterial disease or a urologic condition. Imaging studies are recommended in all patients with chronic kidney disease, and in patients who are at risk for chronic kidney disease because of renal artery stenosis, serious systemic and complicated urinary tract infections, urinary tract stones or obstruction, vesicoureteral reflux, or polycystic kidney disease. Ultrasonography is particularly useful for detecting several of these conditions, and it does not involve exposure to radiation or contrast media.

The detailed text of the NKF K/DOQI guidelines1,2 describes guideline 6 as a "review." Only the material on new markers underwent evidence-based review before the guideline was developed. The recommendations for evaluation of at-risk patients may be problematic for family physicians. At this time, it is not clear which at-risk patients might be evaluated, and the risk-benefit ratio and cost of evaluation also are uncertain.

**Guidelines 7 Through 15**

The remainder of the NKF guidelines fall into two categories: association of the GFR level with the complications of chronic kidney disease in adults and stratification of risk for the progression of kidney disease and the development of cardiovascular disease. After chronic kidney disease has been diagnosed, several of these guidelines can be useful in outpatient follow-up and treatment.

**Final Comment**

Guidelines 1 through 6 of the NKF K/DOQI guidelines1,2 help family physicians appreciate the magnitude of the problem of chronic kidney disease. The new definition and staging system facilitate better identification and classification of kidney damage and chronic kidney disease, and also help guide evalu-
Chronic Kidney Disease

**Strength of Recommendation**

<table>
<thead>
<tr>
<th>Key clinical recommendations</th>
<th>Label</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR should be estimated using prediction equations that take into account the serum creatinine concentration and some or all of these variables: age, sex, race, and body size. In most circumstances, un timed (spot) urine samples, rather than 24-hour urine collections, should be used to detect and monitor proteinuria. If a urine dipstick test is positive (1+ or greater), proteinuria should be confirmed by a quantitative measurement (protein-to-creatinine ratio or albumin-to-creatinine ratio) within three months.</td>
<td>C</td>
<td>1,2</td>
</tr>
</tbody>
</table>

*GFR = glomerular filtration rate.*

...tion and treatment. Patients can be evaluated more effectively and efficiently using the serum creatinine concentration and prediction equations to estimate GFR, and protein or albumin-specific dipsticks and total protein-to-creatinine or albumin-to-creatinine ratios conducted on spot urine samples to determine the level of proteinuria. With these approaches, a 24-hour urine collection is not required.

On the other hand, concerns remain about areas of the guideline[2] that could have a significant impact on clinical practice but are not evidence based. These areas include the testing of patients at risk for chronic kidney (guideline 3), as well as the use of urinary sediment examination and kidney imaging in selected at-risk patients (guideline 6). Research is needed to demonstrate the utility of testing patients who are at increased risk for chronic kidney disease.

In future guidelines, the NKF K/DOQI will use a system for grading both the level of evidence and the strength of recommendation. Although this new system is specific to the needs of the NKF K/DOQI, it mirrors the systems currently used by AFP and the U.S. Preventive Services Task Force.

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The authors acknowledge the contributions of other members of the NKF K/DOQI Work Group and Evidence Review Team, the K/DOQI Support Group and Advisory Board, and the National Kidney Foundation.

**REFERENCES**

Chronic Kidney Disease: Prevention and Treatment of Common Complications

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University of California, San Diego, School of Medicine, La Jolla, California

Chronic kidney disease is a progressive condition that results in significant morbidity and mortality. Because of the important role the kidneys play in maintaining homeostasis, chronic kidney disease can affect almost every body system. Early recognition and intervention are essential to slowing disease progression, maintaining quality of life, and improving outcomes. Family physicians have the opportunity to screen at-risk patients, identify affected patients, and ameliorate the impact of chronic kidney disease by initiating early therapy and monitoring disease progression. Aggressive blood pressure control, with a goal of 130/80 mm Hg or less, is recommended in patients with chronic kidney disease. Angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists are most effective because of their unique ability to decrease proteinuria. Hyperglycemia should be treated; the goal is an A1C concentration below 7 percent. In patients with dyslipidemia, statin therapy is appropriate to reduce the risk of cardiovascular disease. Anemia should be treated, with a target hemoglobin concentration of 11 to 12 g per dL (110 to 120 g per L). Hyperparathyroid disease requires dietary phosphate restrictions, antacid use, and vitamin D supplementation; if medical therapy fails, referral for surgery is necessary. Counseling on adequate nutrition should be provided, and smoking cessation must be encouraged at each office visit. (Am Fam Physician 2004;70:1921-8,1929-30. Copyright © 2004 American Academy of Family Physicians.)

The National Kidney Foundation (NKF) defines chronic kidney disease as kidney damage or a glomerular filtration rate (GFR) of less than 60 mL per minute per 1.73 m² (body surface area) for three months or more. This GFR rate corresponds with a serum creatinine concentration higher than 1.5 mg per dL (132.6 μmol per L) in men and higher than 1.3 mg per dL (114.9 μmol per L) in women. Chronic kidney disease also can be defined by the presence of urinary albumin in an excretion rate higher than 300 mg per 24 hours or in a ratio of more than 200 mg of albumin to 1 g of creatinine (Table 1).

Chronic kidney disease currently affects as many as 20 million Americans. The incidence and prevalence of the disease have doubled in the past decade, most likely because improved treatments for hypertension, diabetes mellitus, and coronary disease have increased longevity in affected patients and, therefore, their likelihood of developing chronic kidney disease. Estimated medical and other economic costs of chronic kidney disease are expected to approach $28 billion annually by 2010, with an additional $90 billion in annual costs related to associated increased cardiovascular disease, infections, and hospitalizations.

Causes of chronic kidney disease include diabetes mellitus, hypertension, ischemia, infection, obstruction, toxins, and autoimmune and infiltrative diseases. Although it is important to identify the cause(s) of chronic kidney disease so that specific therapy can be instituted, the disease often progresses despite appropriate treatment. As kidney function deteriorates, patients develop complications related to fluid overload, electrolyte and acid-base imbalances, and the build-up of nitrogenous waste. To survive, some patients eventually need hemodialysis or kidney transplantation.

This article reviews the current recommendations and therapeutic strategies for preventing or delaying the progression of chronic kidney disease and the development of complications such as hypertension, hyperglycemia, hyperlipidemia, anemia, and...
TABLE 1
Definitions of Proteinuria and Albuminuria

<table>
<thead>
<tr>
<th>Concentration measured</th>
<th>Urine collection method</th>
<th>Normal value</th>
<th>Microalbuminuria</th>
<th>Albuminuria or clinical proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>24-hour excretion (varies with method)</td>
<td>&lt; 300 mg per 24 hours</td>
<td>—</td>
<td>&gt; 300 mg per 24 hours</td>
</tr>
<tr>
<td></td>
<td>Spot urine dipstick</td>
<td>&lt; 30 mg per dL</td>
<td>—</td>
<td>&gt; 30 mg per dL</td>
</tr>
<tr>
<td></td>
<td>Spot urine protein-to-creatinine ratio (varies with method)</td>
<td>&lt; 200 mg of protein to 1 g of creatinine</td>
<td>—</td>
<td>&gt; 200 mg of protein to 1 g of creatinine</td>
</tr>
<tr>
<td>Albumin</td>
<td>24-hour urinary excretion</td>
<td>&lt; 30 mg per 24 hours</td>
<td>30 to 300 mg per 24 hours</td>
<td>&gt; 300 mg per 24 hours</td>
</tr>
<tr>
<td></td>
<td>Spot urine albumin-specific dipstick</td>
<td>&lt; 3 mg per dL</td>
<td>&gt; 3 mg per dL</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Spot urine albumin-to-creatinine ratio (varies by sex†)</td>
<td>Men: &lt; 17 mg of albumin to 1 g of creatinine</td>
<td>Men: 17 to 250 mg of albumin to 1 g of creatinine</td>
<td>Men: &gt; 250 mg of albumin to 1 g of creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women: &lt; 25 mg of albumin to 1 g of creatinine</td>
<td>Women: 25 to 355 mg of albumin to 1 g of creatinine</td>
<td>Women: &gt; 355 mg of albumin to 1 g of creatinine</td>
</tr>
</tbody>
</table>

†—Sex-specific cutoff values are from a single study. Use of the same cutoff value for men and women leads to higher prevalence rates in women than in men. Current recommendations from the American Diabetes Association define cutoff values for the spot urine albumin-to-creatinine ratio for microalbuminuria as 30 mg of albumin to 1 g of creatinine and the spot urine albumin-to-creatinine ratio for albuminuria as 300 mg of albumin to 1 g of creatinine without regard to sex.


renal osteodystrophy. Recommendations for nutrition and smoking cessation also are discussed.

CLASSIFICATION OF SEVERITY AND MONITORING OF DISEASE PROGRESSION

The GFR is used to assess the degree of kidney-function impairment and to monitor disease progression and treatment response.

Table 2
Equations for Predicting GFR in Patients with Stable Chronic Kidney Disease†

| GFR (mL per minute per 1.73 m²) = 186 × (SCR)⁻¹.ο4 × (age)⁻².ο³ × (0.742 if female) × (1.210 if black) |
|——Cockcroft-Gault equation: Cₖₒ₉ (mL per minute) = \((\frac{140 \times \text{age} \times \text{weight}}{72 \times \text{SCR}})\) × (0.85 if female) |

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; SCR = serum creatinine concentration; Cₖₒ₉ = creatinine clearance.

†—For each equation, SCR is in mg per dL, age is in years, and weight is in kg. The MDRD study equation is available in computer programs that calculate the result when patient data are entered.

Information from references 6 through 8.

GFR is a measure of the overall filtration rate of all nephrons. In persons 30 years or younger, the normal GFR is approximately 125 mL per minute per 1.73 m²; after the age of 30 years, GFR declines by 1 mL per minute per 1.73 m² per year.

Estimation of the GFR no longer requires a 24-hour urine collection for creatinine clearance but can be accomplished with similar accuracy using a mathematical formula. The most commonly used formulas for estimating GFR in patients with stable chronic kidney disease are the Modification of Diet in Renal Disease (MDRD) equation and the Cockcroft-Gault equation (Table 2). The MDRD study equation is available in computer programs that calculate the result when patient data are entered.

Proteinuria is another marker of kidney injury. It is measured in a timed (overnight or 24-hour) urine collection or in an untimed (spot) urine sample by calculating the ratio of protein or albumin to creatinine (Table 1). The National Kidney Disease Outcome Quality Initiative (K/DOQI) stratifies chronic kidney disease into five stages based on the GFR and metabolic consequences (Table 3). The NKF suggests actions to slow disease progression.
HYPERTENSION

Hypertension is a frequent cause of chronic kidney disease. Systemic hypertension causes direct damage to small blood vessels in the nephron. The kidneys lose their ability to autoregulate glomerular filtration flow and pressure, with resultant hyperfiltration manifesting as albuminuria and proteinuria. When the proximal convoluted tubule reabsorbs the excess protein, secretion of vasoactive substances further damages the glomerular-tubular apparatus. Nephron damage activates the renin-angiotensin-aldosterone system, resulting in increased sympathetic tone and fluid overload, which compound the progression of hypertension and nephron loss.

Several trials have demonstrated the benefit of strict blood pressure control in slowing the progression of kidney disease. Thus, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target blood pressure of less than 130/80 mm Hg in patients with chronic kidney disease.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists preferentially lower intraglomerular pressure and reduce proteinuria. Ample evidence shows that these agents are more effective than other antihypertensive drugs in preventing the progression of kidney disease.

The JNC-7 guidelines recommend a target blood pressure of less than 130/80 mm Hg in patients with chronic kidney disease.

The Ramipril Efficacy in Nephropathy study found a significantly higher GFR and a lower rate of GFR decline in patients without diabetes who received the ACE inhibitor ramipril than in similar patients who were given placebo.

Angiotensin-II receptor antagonists have been shown to reduce the occurrence of kidney failure. Efficacy may be increased when

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### TABLE 3

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml per minute per 1.73 m²)</th>
<th>Metabolic consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>At increased risk</td>
<td>Higher than 60 (with risk factors for chronic kidney disease)</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage (early) with normal or elevated GFR</td>
<td>90 or higher</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR (early renal insufficiency)</td>
<td>60 to 89*</td>
<td>Parathyroid hormone level begins to rise (GFR of 60 to 80)</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR (moderate kidney failure)</td>
<td>30 to 59</td>
<td>Calcium absorption decreases (GFR below 50). Lipoprotein activity declines. Malnutrition develops. There is onset of left ventricular hypertrophy and/or anemia (erythropoietin deficiency).</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR (pre-end-stage kidney disease)</td>
<td>15 to 29</td>
<td>Triglyceride concentration begins to rise. Hyperphosphatemia or metabolic acidosis develops. There is a tendency toward hyperkalemia.</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (end-stage kidney disease [uremic])</td>
<td>&lt; 15 (or dialysis)</td>
<td>Azotemia develops.</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate

*—May be normal for age.

these agents are given in combination with ACE inhibitors. In one study,\textsuperscript{20} combination therapy with candesartan (angiotensin-II receptor antagonist) and lisinopril (ACE inhibitor) was more effective than treatment with either drug alone in reducing blood pressure and microalbuminuria in patients with type 2 diabetes, hypertension, and microalbuminuria.

When ACE-inhibitor therapy is started, some patients with chronic kidney disease may have an initial decrease in GFR (usually less than 10 mL per minute per 1.73 m\textsuperscript{2}), a mild increase in the serum creatinine concentration (less than 20 percent of the baseline value), and a mild increase in the potassium level (usually less than 0.5 mmol per L).\textsuperscript{21} Therefore, serum creatinine and potassium levels should be monitored one to two weeks after the initiation of therapy with an ACE inhibitor.

**DIABETES MELLITUS**

Diabetes mellitus is the most common cause of chronic kidney disease.\textsuperscript{22} Hyperglycemia is an independent risk factor for nephropathy.\textsuperscript{23} The pathophysiology of diabetic nephropathy is complex and most likely involves both hemodynamic and glucose-dependent factors, including the accumulation of advanced glycated products, endothelial dysfunction, and loss of intraglomerular blood pressure regulation.\textsuperscript{24} Studies have shown that the A1C level correlates with loss of renal function and that glycemic control reduces the progression of kidney disease.\textsuperscript{25,26}

To prevent progression of nephropathy in patients with diabetes mellitus, the American Diabetes Association (ADA)\textsuperscript{27} recommends glycemic control, with the goal being an A1C concentration below 7 percent. The ADA also recommends yearly screening for microalbuminuria and blood pressure control with an ACE inhibitor or angiotensin-II receptor antagonist.

**DYSLIPIDEMIA**

Dyslipidemia is a primary risk factor for cardiovascular disease and a common complication of progressive kidney disease. Most patients with chronic kidney disease have an abnormal lipid panel that increases their risk for atherogenesis. Dyslipidemia contributes to cardiovascular mortality, which is 10 to 20 times higher in dialysis patients than in the normal population even after adjustments are made for age, sex, and diabetes mellitus.\textsuperscript{28,29}

The most noticeable lipid abnormality in chronic kidney disease is an elevated triglyceride level, possibly because of defective clearance.\textsuperscript{30,31} Patients with chronic kidney disease also have an elevated ratio of low-density lipoprotein (LDL) cholesterol to high-density lipoprotein (HDL) cholesterol. LDL cholesterol, including lipoprotein(a), are pro-atherogenic, and levels are slightly elevated in patients with chronic kidney disease. Levels of oxidized LDL cholesterol also are elevated; these cholesterols activate pro-inflammatory pathways, thereby promoting atherogenesis and endothelial dysfunction. HDL cholesterol levels are decreased, indicating loss of anti-atherogenic effect.

Although no large randomized controlled trials have studied the effects of lipid reduction on the progression of kidney disease, animal models suggest that dyslipidemia worsens kidney function. A recent meta-analysis\textsuperscript{32} of 13 small studies showed that lipid reduction preserves GFR and reduces proteinuria. The most recent guidelines from the NKF K/DOQI\textsuperscript{33} recommend treating dyslipidemia.
aggressively in patients with chronic kidney disease. The goals are an LDL cholesterol level below 100 mg per dL (2.60 mmol per L) and a triglyceride level below 200 mg per dL (2.26 mmol per L). Fibrates are known to decrease triglyceride levels, but they may increase the risk for rhabdomyolysis in patients with chronic kidney disease. Statins can lower cholesterol levels safely and effectively in these patients, although research has not yet shown that treatment decreases cardiovascular mortality.\textsuperscript{33}

ANEMIA

The anemia of chronic renal disease is normocytic and normochromic. It occurs primarily because of lower production of erythropoietin by the decreased mass of functioning renal tubular cells.

Anemia results in fatigue, reduced exercise capacity, decreased cognition, and impaired immunity. Thus, it decreases quality of life. In addition, increased workload on the heart as a result of anemia can lead to left ventricular hypertrophy and maladaptive cardiomyopathy. These conditions increase the risk of death from heart failure or ischemic heart disease.\textsuperscript{35}

Study results\textsuperscript{36,37} have shown that correction of anemia can limit the progression of chronic kidney disease and possibly decrease mortality. The NKF K/DOQI guidelines\textsuperscript{1} recommend a target hemoglobin concentration of 11 to 12 g per dL (110 to 120 g per L) in patients with chronic kidney disease. Patients with plasma ferritin concentrations below 100 ng per mL (100 mcg per L) should be given iron supplements.

Erythropoietin should be administered to predialysis patients who have anemia-dependent angina or severe anemia with a hemoglobin concentration below 10 g per dL (100 g per L).\textsuperscript{38} Hypertension and an increased risk for thrombotic events are potential adverse effects of treatment. Therefore, patients receiving erythropoietin must be monitored closely.

RENA L OSTEODYSTROPHY

Changes in mineral metabolism and bone structure begin early in chronic kidney disease. These changes include osteitis fibrosa cystica (because of secondary hyperparathyroidism); less commonly, osteomalacia (defective mineralization); and adynamic bone disease (absence of cellular activity).\textsuperscript{39} Osteitis fibrosa cystica, the predominant bone defect, is characterized by an increase in bone turnover that leads to decreased cortical bone and impaired bone strength. Bone disease can result in pain and an increased risk of fracture.

Parathyroid hormone levels begin to rise when creatinine clearance falls below 60 mL per minute (1 mL per second).\textsuperscript{1} The development of hyperparathyroidism may be prevented by restricting dietary phosphate intake (e.g., colas, nuts, peas, beans, dairy products), using a calcium-based phosphate binder (antacid) with meals, and administering vitamin D (Rocaltril) to suppress parathyroid hormone secretion.\textsuperscript{39} Vitamin D supplementation is safe and effective for lowering parathyroid hormone secretion in patients with elevated parathyroid hormone levels or hypocalcemia despite adequate correction of hyperphosphatemia.\textsuperscript{40}

Even with appropriate medical therapy, some patients continue to have refractory hyperparathyroidism because of parathyroid gland hyperplasia. These patients should be referred for surgical treatment.

NUTRITION

Patients with chronic kidney disease are at risk for malnutrition and hypalbuminemia. Both of these conditions are associated with poor outcomes in patients who are beginning dialysis.\textsuperscript{41}

The effect of dietary protein restriction on kidney disease is the subject of debate. Some studies suggest that dietary protein restriction slows the progression of kidney disease, particularly in patients with diabetes mellitus.\textsuperscript{41} However, these studies were confounded by the benefits of ACE-inhibitor therapy on the rate of disease progression.

The MDRD study\textsuperscript{42} attempted to determine a level of protein intake that might reduce the risk of kidney disease progression and also minimize the risk of malnutrition. The study evaluated three levels of dietary
Strength of Recommendation

<table>
<thead>
<tr>
<th>Key clinical recommendations</th>
<th>Label</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target blood pressure of less than 130/80 mm Hg in patients with chronic kidney disease.</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>According to the evidence, ACE inhibitors are more effective than other antihypertensive drugs in preventing the progression of kidney disease in diabetic and nondiabetic patients.</td>
<td>A</td>
<td>12-15</td>
</tr>
<tr>
<td>Angiotensin-II receptor antagonists have been shown to reduce proteinuria and the occurrence of kidney failure.</td>
<td>A</td>
<td>17-21</td>
</tr>
<tr>
<td>To prevent progression of nephropathy in patients with diabetes mellitus, the American Diabetes Association recommends glycemic control, with the goal being an A1C concentration below 7 percent.</td>
<td>C</td>
<td>27</td>
</tr>
<tr>
<td>The most recent guidelines from the NKF K/DOQI recommend treating dyslipidemia aggressively in patients with chronic kidney disease. The goals are an LDL cholesterol level below 100 mg per dl (2.60 mmol per L) and a triglyceride level below 200 mg per dl (2.26 mmol per L).</td>
<td>C</td>
<td>33</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; NKF K/DOQI = National Kidney Foundation Kidney Disease Outcome Quality Initiative; LDL = low-density lipoprotein.

protein intake and found that a very-low-protein diet (0.28 g per kg per day) slightly decreased the rate of progression of proteinuria compared with diets with higher protein intake (0.56 g per kg per day and 1.3 g per kg per day). The very-low-protein diet did not result in malnutrition, but it also did not decrease progression to kidney failure or death.

Current recommendations from the NKF K/DOQI based on evidence from animal studies suggest a protein intake of 0.8 to 1.0 g per kg per day and a daily caloric intake of 30 to 35 kcal per kg per day in patients with chronic kidney disease. Patients with chronic kidney disease, particularly those requiring dialysis, need to be monitored closely every one to three months for serum albumin concentration and body weight so that appropriate interventions can be instituted to prevent malnutrition. Early referral to a nutritionist can help maintain optimal protein and caloric intake in these patients.

SMOKING CESSION

Smoking is a strong risk factor for cardiovascular mortality in patients at risk for chronic kidney disease. It also is strongly associated with the progression of nephropathy. The results of one small study showed that smoking cessation reduced the progression of kidney disease by 30 percent in patients with type 1 diabetes.

Smoking cessation should be strongly encouraged at each office visit. Patients should be offered nicotine-replacement therapies (e.g., patch, gum) and the antidepressant bupropion (Zyban).

UREMIA

Despite optimal treatment, kidney function may continue to deteriorate. Ultimately, patients may develop uremia and kidney failure. Symptoms of uremia include anorexia, nausea, vomiting, malaise, asterixis, muscle weakness, platelet dysfunction, pericarditis, mental status changes, seizures and, possibly, coma. These symptoms result from the accumulation of several toxins in addition to urea; thus, no strict correlation exists between clinical presentation and plasma blood urea nitrogen and creatinine levels.

Acute uremia or uremia resulting from progressive disease is an indication for immediate dialysis. Patients with kidney failure should be evaluated for kidney transplantation.
Members of various family practice departments develop articles for “Practical Therapeutics.” This article is one in a series from the Department of Family and Preventive Medicine at the University of California, San Diego, Family Medicine Residency Program. Coordinator of the series is Tyson Ikeda, M.D.

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Kidney Disease


Rhabdomyolysis is a potentially life-threatening syndrome resulting from the breakdown of skeletal muscle fibers with leakage of muscle contents into the circulation. The most common causes are crush injury, overexertion, alcohol abuse and certain medicines and toxic substances. Several inherited genetic disorders, such as McArdle’s disease and Duchenne’s muscular dystrophy, are predisposing factors for the syndrome. Clinical features are often nonspecific, and tea-colored urine is usually the first clue to the presence of rhabdomyolysis. Screening may be performed with a urine dipstick in combination with urine microscopy. A positive urine myoglobin test provides supportive evidence. Multiple complications can occur and are classified as early or late. Early complications include severe hyperkalemia that causes cardiac arrhythmia and arrest. The most serious late complication is acute renal failure, which occurs in approximately 15 percent of patients with the syndrome. Early recognition of rhabdomyolysis and prompt management of complications are crucial to a successful outcome. (Am Fam Physician 2002;65:907-12. Copyright © 2002 American Academy of Family Physicians.)

Rhabdomyolysis, which literally means striated muscle dissolution or disintegration, is a potentially lethal clinical and biochemical syndrome. Approximately 26,000 cases of rhabdomyolysis are reported annually in the United States. Prompt recognition and early intervention are vital. Full recovery can be expected with early diagnosis and treatment of the many complications that can develop in patients with this syndrome.

Clinical features of rhabdomyolysis may be absent initially, and its most serious complication, acute renal failure, is common. Many patients develop dialysis-dependent acute renal failure associated with the misuse of alcohol or other drugs. The nephrotoxicity of myoglobin is decreased by forced alkaline diuresis. Critically ill patients with acute renal failure are also likely to develop multiorgan failure syndrome, with a resultant increase in mortality.

**Pathophysiology**

Muscle injury, regardless of mechanism, results in a cascade of events that leads to leakage of extracellular calcium ions into the intracellular space. The excess calcium causes a pathologic interaction of actin and myosin that ends in muscle destruction and fiber necrosis (Figure 1).

With muscle injury, large quantities of potassium, phosphate, myoglobin, creatine kinase (CK) and urate leak into the circulation. Under

**FIGURE 1.** Fiber necrosis in rhabdomyolysis (hematoxylin and eosin).
The most common causes of rhabdomyolysis are alcohol abuse, muscle overexertion, muscle compression and the use of certain medications or illicit drugs.

### TABLE 1

**Medications and Toxic Substances That Increase the Risk of Rhabdomyolysis**

<table>
<thead>
<tr>
<th>Direct myotoxicity</th>
<th>Indirect muscle damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors, especially in combination with fibrate-derived lipid-lowering agents such as niacin (nicotinic acid; Nicolar) Cyclosporine (Sandimmune) Itraconazole (Sporanox) Erythromycin Colchicine Zidovudine (Retrovir) Corticosteroids</td>
<td>Alcohol Central nervous system depressants Cocaine Amphetamine Ecstasy (MDMA) LSD Neuromuscular blocking agents</td>
</tr>
</tbody>
</table>

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LSD = lysergic acid diethylamide; MDMA = 3,4-methylene dioxymethamphetamine.

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Physiologic circumstances, the plasma concentration of myoglobin is very low (0 to 0.003 mg per dL). If more than 100 g of skeletal muscle is damaged, serum haptoglobin binding capacity becomes saturated. The circulating myoglobin becomes “free” and is filtered by the kidneys. Myoglobin in the renal glomerular filtrate can precipitate and cause renal tubular obstruction, leading to renal damage.

### Etiology and Risk Factors

Several investigators have attempted to categorize the many diverse causes and risk factors for rhabdomyolysis. The most common causes are alcohol abuse, muscle overexertion, muscle compression, and the use of certain medications or illicit drugs. Medications and toxic substances that increase the risk of rhabdomyolysis are listed in Table 1.

Other significant causes of rhabdomyolysis include electrical shock injury and crush injury. In crush injury, rhabdomyolysis occurs because of the release of necrotic muscle material into the circulation after compression is relieved, for example, persons trapped in crashed cars or collapsed buildings. Heatstroke and sporting activities, especially in previously untrained persons, are also common causes of the syndrome. Heat dissipation impairment from wearing heavy sports equipment or exercising in humid, warm weather increases the risk of rhabdomyolysis. Traumatic, heat-related, ischemic and exertional causes of rhabdomyolysis are listed in Table 2.

Numerous infectious and inflammatory processes can lead to rhabdomyolysis. Certain metabolic and endocrinologic disorders can also increase the risk of developing the syndrome. These processes and disorders are listed in Table 3.

The cause of rhabdomyolysis can be obscure. In this situation, genetic etiologies should be considered (Table 4). A genetic disorder should be suspected in patients who have recurrent rhabdomyolysis after minimal moderate exertion or after viral infections starting in childhood.
TABLE 2
Traumatic, Heat-Related, Ischemic and Exertional Causes of Rhabdomyolysis

<table>
<thead>
<tr>
<th>Traumatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightning strike</td>
</tr>
<tr>
<td>Immobilization</td>
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<tr>
<td>Extensive third-degree burn</td>
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<tr>
<td>Crush injury</td>
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<tr>
<td>Heat-related causes</td>
</tr>
<tr>
<td>Heatstroke</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Ischemic causes</td>
</tr>
<tr>
<td>Ischemic limb injury</td>
</tr>
<tr>
<td>Exertional causes</td>
</tr>
<tr>
<td>Marathon running</td>
</tr>
<tr>
<td>Physical overexertion in untrained athletes</td>
</tr>
<tr>
<td>Pathologic muscle exertion</td>
</tr>
<tr>
<td>Heat dissipation impairment</td>
</tr>
<tr>
<td>Physical overexertion in persons</td>
</tr>
<tr>
<td>with sickle cell disease</td>
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</tbody>
</table>

TABLE 3
Infectious, Inflammatory, Metabolic and Endocrinologic Causes of Rhabdomyolysis

<table>
<thead>
<tr>
<th>Infectious causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses: influenza virus B, parainfluenza virus, adenovirus, coxsackievirus, echovirus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus</td>
</tr>
<tr>
<td>Bacteria: Streptococcus, Salmonella, Legionella, Staphylococcus and Listeria species</td>
</tr>
<tr>
<td>Inflammatory causes</td>
</tr>
<tr>
<td>Polymyositis</td>
</tr>
<tr>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Capillary leak syndrome</td>
</tr>
<tr>
<td>Snake bites (mostly in South America, Asia and Africa)</td>
</tr>
<tr>
<td>Metabolic and endocrinologic causes</td>
</tr>
<tr>
<td>Electrolyte imbalances: hypotension, hypernatremia, hypokalemia, hypophosphatemia, hypercalcemia</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Nonketotic hyperosmolar syndrome</td>
</tr>
</tbody>
</table>

Clinical Presentation

Many clinical features of rhabdomyolysis are nonspecific, and the course of the syndrome varies depending on the underlying condition. The syndrome has local and systemic features, and early or late complications may occur. Prompt recognition of rhabdomyolysis is critical to preventing late complications.

Screening may be performed with a urine dipstick test. The orthotolidine portion of the dipstick turns blue in the presence of hemoglobin or myoglobin. Positive urine “blood” can be used as a surrogate marker for myoglobin if freshly spun sediment of urine shows no red blood cells. In this setting, a serum sample with normal color indicates myoglobinuria, whereas a pigmented brown or red serum sample indicates hemoglobinuria.

In ambiguous cases, clinical suspicion of rhabdomyolysis is confirmed by a positive urine or serum test for myoglobin. Because it

TABLE 4
Genetic Causes of Rhabdomyolysis

<table>
<thead>
<tr>
<th>Lipid metabolism</th>
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<tbody>
<tr>
<td>Carnitine palmitoyltransferase deficiency</td>
</tr>
<tr>
<td>Carnitine deficiency</td>
</tr>
<tr>
<td>Short-chain and long-chain acyl-coenzyme A dehydrogenase deficiency</td>
</tr>
<tr>
<td>Carbohydrate metabolism</td>
</tr>
<tr>
<td>Myophosphorylase deficiency (McArdle's disease)</td>
</tr>
<tr>
<td>Phosphorylase kinase deficiency</td>
</tr>
<tr>
<td>Phosphofructokinase deficiency</td>
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<tr>
<td>Phosphoglycerate mutase deficiency</td>
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<tr>
<td>Lactate dehydrogenase deficiency (characteristic elevation of creatine kinase level with normal lactate dehydrogenase level)</td>
</tr>
<tr>
<td>Purine metabolism</td>
</tr>
<tr>
<td>Myoadenylate deaminase deficiency</td>
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<tr>
<td>Duchenne's muscular dystrophy</td>
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</table>
takes several days to obtain results, neither test should be relied on in making therapeutic decisions.

Clinical features of rhabdomyolysis are listed in Table 5. Local signs and symptoms may include muscle pain, tenderness and swelling. Systemic features may include tea-colored urine, which is usually the first sign, along with fever and malaise.

When a genetic disorder is suspected, forearm ischemic testing can be used to help differentiate among possible inherited causes (Table 6). A muscle biopsy with histochemical analysis is necessary to determine the specific cause of a genetic myopathy.

### Complications

The complications of rhabdomyolysis can be classified as early or late (Table 7). Severe hyperkalemia may occur secondary to massive muscle breakdown, causing cardiac arrhythmia and, possibly, cardiac arrest. Hypocalcemia is another early complication that can be potentiated by the release of large amounts of phosphate from the lysed muscle cells. Hepatic dysfunction occurs in approximately 25 percent of patients with rhabdomyolysis. Proteases released from injured muscle may be implicated in hepatic inflammation.

Acute renal failure and diffuse intravascular coagulation are late complications of rhabdomyolysis (i.e., past 12 to 24 hours). Acute renal failure, the more serious complication, develops in up to 15 percent of patients and is associated with high morbidity and mortality. Renal damage results from the mechanical obstruction of tubules by myoglobin precipitation, the direct toxic effect of free chelatable iron on tubules, and hypovolemia. In addition, the release of vasoactive kinins from muscle may interfere with renal hemodynamics. There is a loose predictive correlation between CK levels and the development of acute renal failure, with levels higher than 16,000 units per L more likely to be associated with renal failure.

The rate at which serum creatinine levels increase is typically faster in patients with

### Table 5

<table>
<thead>
<tr>
<th>Local features</th>
<th>Systemic features</th>
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<tbody>
<tr>
<td>Muscle pain</td>
<td>Tea-colored urine</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Fever</td>
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<tr>
<td>Swelling</td>
<td>Malaise</td>
</tr>
<tr>
<td>Bruising</td>
<td>Nausea</td>
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<tr>
<td>Weakness</td>
<td>Emesis</td>
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<td></td>
<td>Confusion</td>
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<td></td>
<td>Agitation</td>
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<tr>
<td></td>
<td>Delirium</td>
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<tr>
<td></td>
<td>Anuria</td>
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</tbody>
</table>

### Table 6

<table>
<thead>
<tr>
<th>Procedure</th>
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</thead>
<tbody>
<tr>
<td>1. Draw a blood sample from the antecubital vein for use in obtaining baseline ammonia and lactic acid levels.</td>
</tr>
<tr>
<td>2. Inflate the sphygmomanometer cuff to above 200 mm Hg. (Because this pressure is greater than the systolic pressure, ischemia is created.)</td>
</tr>
<tr>
<td>3. After the cuff is inflated, have the patient perform repeated hand-grip exercises to fatigue the forearm.</td>
</tr>
<tr>
<td>4. Remove the cuff and draw serial blood samples from the antecubital vein to obtain ammonia and lactic acid levels.</td>
</tr>
</tbody>
</table>

### Interpretation

A minimal rise or no rise in the lactic acid level suggests McArdle's disease or another disorder of carbohydrate metabolism (see Table 4). A slow rise or no rise in the ammonia level points to the diagnosis of pyruvate dehydrogenase deficiency. A normal rise in ammonia and lactic acid levels indicates the presence of a disorder of lipid metabolism.

myoglobinuric renal failure (up to 2.5 mg per dL per day [220 μmol per L]) than in those with other causes of acute renal failure.

Disseminated intravascular coagulation may develop in patients with rhabdomyolysis. This complication is usually worse on the third to fifth day of presentation. Prompt recognition and vigorous treatment of the underlying cause is necessary.

Compartment syndrome may be an early or late complication, resulting mainly from direct muscle injury or vigorous muscle activity. This complication occurs primarily in muscles whose expansion is limited by tight fascia, such as the anterior tibial muscles. Peripheral pulses may still be palpable, in which case nerve deficits (mainly sensory) are more important findings. A delay of more than six hours in diagnosing this complication can lead to irreversible muscle damage or death. Decompressive fasciotomy should be considered if the compartment pressure is greater than 30 mm Hg.22

Treatment

The treatment of rhabdomyolysis is primarily directed at preserving renal function. Up to 12 L of fluid may be sequestered in the necrotic muscle tissues, thereby contributing to hypovolemia, which is one cause of renal failure in patients with rhabdomyolysis.23

Intravenous (IV) hydration must be initiated as early as possible. In the patient with a crush injury, IV fluids should be started even before the trapped limb is freed and decompressed, and certainly no later than six hours after decompression. The longer it takes for rehydration to be initiated, the more likely it is that oliguric renal failure (less than 500 mL of urine per day) or anuric renal failure (less than 50 mL of urine per day) will be established.23 Investigators in one study24 found that forced diuresis within the first six hours of admission prevented all episodes of acute renal failure.

Initially, normal saline should be given at a rate of 1.5 L per hour. Urine output should be maintained at 300 mL per hour until myoglobinuria has ceased. High rates of IV fluid administration should be used at least until the CK level decreases to or below 1,000 units per L. If these measures successfully thwart the development of oliguria, the patient can be switched to 0.45 percent saline with the addition of one or two ampules of sodium bicarbonate (40 mEq) and 10 g per L of mannitol. Diuretics (loop or other types) should not be used because they do not improve, and may actually compromise, the final renal outcome.

The objectives are to alkalize urine to a pH of greater than 6.5 (thereby decreasing the toxicity of myoglobin to the tubules) and to enhance the flushing of myoglobin casts from renal tubules by means of osmotic diuresis. However, these measures should not be employed if oliguria is established despite initial generous hydration with normal saline. The use of mannitol remains controversial as it is mostly supported by experimental animal studies and retrospective clinical studies.25-26 In one study,27 mannitol did not confer additional protection compared with normal saline alone. There are also some concerns about the use of sodium bicarbonate, because it may worsen hypocalcemia or precipitate calcium phosphate deposition on various tissues.28

Elderly patients should be treated in an intensive care unit so that vital signs, intake and hourly output can be closely monitored.

<table>
<thead>
<tr>
<th>TABLE 7 Complications of Rhabdomyolysis</th>
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</thead>
<tbody>
<tr>
<td>Early complications</td>
</tr>
<tr>
<td>Hyperkalemia</td>
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<tr>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Hepatic inflammation</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Late complications</td>
</tr>
<tr>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Early or late complication</td>
</tr>
<tr>
<td>Compartment syndrome</td>
</tr>
</tbody>
</table>
Rhabdomyolysis

and fluid overload can be quickly detected. Invasive hemodynamic monitoring is critical to fine-tune treatment in patients with comorbid cardiovascular disorders or preexisting chronic renal dysfunction.

Hemodialysis may be a therapeutic modality. Despite treatment, patients with rhabdomyolysis often develop oliguric acute tubular necrosis. In this situation, hemodialysis should be started and carried out aggressively, frequently on a daily basis. If given enough time, many patients partially or completely recover renal function. The chances of recovery are obviously much higher in the absence of preexisting renal insufficiency.

Finally, initial hypocalcemia should not be corrected unless a patient is symptomatic. It is important to avoid further aggravating the hypocalcemia that commonly develops during the recovery phase of rhabdomyolysis, when calcium deposited in the injured muscles is mobilized back to the extracellular space.29

Figure 1 provided by Reid R. Heffner, M.D., Department of Pathology, State University of New York at Buffalo School of Medicine and Biomedical Sciences.

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Diagnosis of Gastrointestinal Bleeding in Adults

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The clinical evaluation of gastrointestinal bleeding depends on the hemodynamic status of the patient and the suspected source of the bleeding. Patients presenting with upper gastrointestinal or massive lower gastrointestinal bleeding, postural hypotension, or hemodynamic instability require inpatient stabilization and evaluation. The diagnostic tool of choice for all cases of upper gastrointestinal bleeding is esophagogastroduodenoscopy; for acute lower gastrointestinal bleeding, it is colonoscopy, or arteriography if the bleeding is too brisk. When bleeding cannot be identified and controlled, intraoperative enteroscopy or arteriography may help localize the bleeding source, facilitating segmental resection of the bowel. If no upper gastrointestinal or large bowel source of bleeding is identified, the small bowel can be investigated using a barium-contrast upper gastrointestinal series with small bowel follow-through, enteroclysis, push enteroscopy, technetium-99m–tagged red blood cell scan, arteriography, or a Meckel’s scan. These tests may be used alone or in combination. (Am Fam Physician 2005;71:1339-46. Copyright© 2005 American Academy of Family Physicians.)

Although gastrointestinal bleeding is most commonly a result of benign anal pathology, life-threatening hemorrhage, cancers, and polyps must be considered in making the diagnosis. Acute, massive upper gastrointestinal bleeding has an incidence of 40 to 150 episodes per 100,000 persons annually, with a mortality rate of 6 to 10 percent. Acute, massive lower gastrointestinal bleeding has an incidence of 20 to 27 episodes per 100,000 persons annually, with a mortality rate of 4 to 10 percent. Mortality rates increase in patients with advancing age and increasing number of associated underlying comorbidities, specifically renal and hepatic dysfunction, heart disease, and malignancies.

Gastrointestinal bleeding can present in several forms, depending on the rate of blood loss: microscopic blood loss presents as iron-deficiency anemia or hemocult-positive stools; hematemesis is vomiting of fresh blood; “coffee-ground” emesis is vomiting of altered black blood; melena is black tarry stools; hemechecia is the passing of red blood via the rectum (usually from the lower gastrointestinal tract, but sometimes from a briskly bleeding upper gastrointestinal source).

Most cases of gastrointestinal bleeding resolve spontaneously, regardless of the amount of blood lost. The stability of the patient and the rate of bleeding dictate the order in which various diagnostic procedures should be conducted. The goal is to identify and, if necessary, treat the source of bleeding, while maintaining hemodynamic stability.

Evaluation

The evaluation of the upper or lower gastrointestinal tract for sources of gastrointestinal bleeding depends on whether the bleeding is acute massive hemorrhage or chronic inter-
mittent bleeding.\textsuperscript{10,12} (Tables 1\textsuperscript{2-4,6,7,9,10,12-21} and 2\textsuperscript{13,15,22,23}). Hospitalization is required in patients who are hemodynamically unstable or elderly, and those who have comorbidities. These patients usually are admitted in an intensive care setting, based on risk stratification criteria (Table 3).\textsuperscript{24} Patients with minimal or intermittent bleeding who are stratified as low risk can be evaluated in an outpatient setting.\textsuperscript{5,13}

**Acute Massive Rectal Bleeding**

Acute massive rectal bleeding frequently arises from an upper gastrointestinal source\textsuperscript{2,10,16,25} (Table 1\textsuperscript{2-4,6,7,9,10,12-21}). When there is evidence or clinical suspicion of an upper gastrointestinal source of bleeding, the diagnostic work-up begins with an esophagogastroduodenoscopy (EGD), which is the diagnostic tool of choice for evaluation of lesions above the ligament of Treitz.\textsuperscript{5,9,10,16,26,27} Table 4\textsuperscript{3,4,10,21,28-30} describes the history and clinical findings associated with gastrointestinal sources of rectal bleeding. If the patient is not experiencing hematemesis and endoscopy is not immediately available, a nasogastric tube may be placed for gastric lavage while awaiting endoscopy.\textsuperscript{10,12} If no blood is returned and bile is identified, an upper gastrointestinal source is much less likely, and the work-up can focus on the large bowel.\textsuperscript{6,9,10,12,13}

Colonoscopy is one of two diagnostic tools of choice used to evaluate acute lower gastrointestinal bleeding\textsuperscript{6,10,12,13,26} (Table 1\textsuperscript{2-4,6,7,9,10,12-21}). Several studies have demonstrated that colonoscopy identifies definitive bleeding sites in more than 70 percent of patients.\textsuperscript{2,6,10,12,16,31,32} Colonoscopy may be performed urgently or electively, depending on the patient's hemodynamic status and risk-stratification criteria.

If bleeding stops or hemodynamic stability is achieved,

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper GI tract</strong></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>40 to 79</td>
</tr>
<tr>
<td>Gastritis/duodenitis</td>
<td>5 to 30</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>6 to 21</td>
</tr>
<tr>
<td>Mallory-Weiss tear</td>
<td>3 to 15</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>2 to 8</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Dieulafoy's lesion*</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastric arteriovenous malformations</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Portal gastropathy</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Lower GI tract</strong></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td></td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>70 to 80</td>
</tr>
<tr>
<td>Jejunoeal diverticula</td>
<td>—</td>
</tr>
<tr>
<td>Meckel's diverticulum</td>
<td>—</td>
</tr>
<tr>
<td>Neoplasms/lymphomas (benign and malignant)</td>
<td>—</td>
</tr>
<tr>
<td>Enteritis/Crohn's disease</td>
<td>—</td>
</tr>
<tr>
<td>Aortoduodenal fistula in patient with synthetic vascular graft</td>
<td>—</td>
</tr>
<tr>
<td>Large bowel</td>
<td></td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>17 to 40</td>
</tr>
<tr>
<td>Arteriovenous malformations</td>
<td>2 to 30</td>
</tr>
<tr>
<td>Colitis\textsuperscript{†}</td>
<td>9 to 21</td>
</tr>
<tr>
<td>Colonic neoplasms/post-polypectomy bleeding</td>
<td>11 to 14</td>
</tr>
<tr>
<td>Anorectal cause\textsuperscript{‡}</td>
<td>4 to 10</td>
</tr>
<tr>
<td>Colonic tuberculosis</td>
<td>—</td>
</tr>
</tbody>
</table>

GI = gastrointestinal.

* — Dieulafoy's lesion: thick-walled arterial vessel surrounded by a very shallow ulcer. Usually occurs in the stomach but also occurs in the esophagus, small bowel, colon, and rectum.\textsuperscript{1,10-12}
† — Includes ischemia, infectious anal fissures, inflammatory bowel disease, and radiation.
‡ — Includes hemorrhoids and rectal varices.

Information from references 2 through 4, 6, 7, 9, 10, and 12 through 21.

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### TABLE 2
Causes of Chronic Intermittent Rectal Bleed

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper GI tract</strong></td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>18 to 35</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>18 to 35</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>18 to 21</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>3 to 15</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>5 to 23</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>3 to 6</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Lower GI tract</strong></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td></td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>40</td>
</tr>
<tr>
<td>Small bowel tumors</td>
<td>33</td>
</tr>
<tr>
<td>Small bowel ulcers and erosions</td>
<td></td>
</tr>
<tr>
<td>Crohn's disease</td>
<td></td>
</tr>
<tr>
<td>Small bowel diverticulosis</td>
<td></td>
</tr>
<tr>
<td>Celiac sprue</td>
<td></td>
</tr>
<tr>
<td>Radiation enteritis</td>
<td></td>
</tr>
<tr>
<td>Meckel's diverticulum</td>
<td></td>
</tr>
<tr>
<td>Small bowel varices</td>
<td></td>
</tr>
<tr>
<td>Lymphangioma</td>
<td></td>
</tr>
<tr>
<td>Blue rubber bleb nevus syndrome</td>
<td></td>
</tr>
<tr>
<td>Osler-Weber-Rendu syndrome</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand's disease</td>
<td></td>
</tr>
<tr>
<td>Small bowel polyposis syndrome</td>
<td></td>
</tr>
<tr>
<td>Gardner's syndrome</td>
<td></td>
</tr>
<tr>
<td>Aortoenteric fistula</td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
</tr>
<tr>
<td>Hemosuccus pancreaticus hemobilia</td>
<td></td>
</tr>
<tr>
<td><strong>Large bowel</strong></td>
<td></td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>59</td>
</tr>
<tr>
<td>Colorectal polyps</td>
<td>38 to 52</td>
</tr>
<tr>
<td>Diverticulosis</td>
<td>34 to 51</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5 to 8</td>
</tr>
<tr>
<td>Proctitis/ulcerative colitis</td>
<td>2 to 6</td>
</tr>
<tr>
<td>Arteriovenous malformations</td>
<td>0 to 5</td>
</tr>
<tr>
<td>Colonic stricture</td>
<td>2</td>
</tr>
<tr>
<td>Post-polypectomy bleeding</td>
<td></td>
</tr>
<tr>
<td>Other colitis*</td>
<td></td>
</tr>
<tr>
<td>Anal neoplasms</td>
<td></td>
</tr>
</tbody>
</table>

GI = gastrointestinal.

* — Includes ischemia, infectious anal fissures, and radiation.

Adapted with permission from Zuckerman GR, Pukacz C, Askin MP, Lewis BS. AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. Gastroenterology 2000;118:211, with additional information from references 7, 13, and 23.

Gastrointestinal Bleeding

Colon preparation may precede colonoscopy to increase visibility and diagnostic yield. Advantages of colonoscopy include direct visualization; access for tissue biopsy; and the ability to treat bleeding lesions primarily with heat probe, epinephrine injection, laser therapy, band ligation, or hemoclipping. As an initial diagnostic test, colonoscopy has a higher yield and a lower complication rate than arteriography. When used to evaluate sub-massive lower gastrointestinal bleeding, colonoscopy is highly effective; however, in cases of massive hemorrhage it may be limited by poor visibility.

Arteriography is a radiographic contrast study that can identify briskly bleeding sources. In situations where massive bleeding impedes visualization of the colon, arteriography may be used as a second-line diagnostic tool of choice. Although several studies have shown a broad range of overall sensitivity with arteriography (40 to 78 percent), the largest study reported a diagnostic sensitivity of 41 percent. Mesenteric arteriography can identify bleeding from arteriovenous malformations by demonstrating extravasation of contrast material into the bowel lumen, which helps localize the bleeding site (Figure 1).

A technetium-99m–tagged red blood cell scan is a nuclear study best suited for identifying slow-bleeding sources with rates of 0.1 to 0.4 mL per minute. However, this test is not as accurate as arteriography in identifying the exact location of a bleeding site. When arteriography is used in association with a technetium-99m–tagged red blood cell blush, the sensitivity of the arteriogram is increased to 61 to 72 percent. One five-year, retrospective study of technetium-99m–tagged red blood cell scans showed that an “immediate blush” (positive scan) had a 60 percent positive predictive value for an associated positive angiogram. A “delayed blush” correlated with a predictive value of 93 percent for a negative angiogram. This finding suggests that a positive “immediate blush” is a good indication for urgent angiography or surgery, while a delayed blush or negative technetium-99m–tagged red blood cell scan is an indication for observation and elective colonoscopy (Figure 2).

Enhanced helical computed tomographic scanning, which uses intravenous contrast, is a new diagnostic tool being reported in the literature; its role has not yet been defined.

When the source of bleeding cannot be identified by endoscopic, radiographic, or nuclear intervention, the patient may need exploratory laparotomy. In most circumstances this is accompanied by intraoperative endoscopy, which has a sensitivity of more than...
### TABLE 3
**Rockall Scoring System for Risk of Rebleeding and Death After Admission to the Hospital for Acute GI Bleeding**

<table>
<thead>
<tr>
<th>Variable*</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt; 60</td>
<td>60 to 79</td>
<td>≥ 80</td>
<td>—</td>
</tr>
<tr>
<td>Shock</td>
<td>No shock; SBP ≥ 100 mm Hg; pulse &lt; 100 bpm</td>
<td>Tachycardia; SBP ≥ 100 mm Hg; pulse ≥ 100 bpm</td>
<td>Hypotension; SBP &lt; 100 mm Hg</td>
<td>—</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>No major comorbidity</td>
<td>No major comorbidity</td>
<td>Heart failure, ischemic heart disease, or any major comorbidity</td>
<td>—</td>
</tr>
<tr>
<td>Diagnosis based on endoscopy</td>
<td>Mallory-Weiss tear, no lesion identified, and no SRH†</td>
<td>All other diagnoses</td>
<td>Malignancy of upper GI tract</td>
<td>—</td>
</tr>
<tr>
<td>Major SRH†</td>
<td>None or dark spot only</td>
<td>—</td>
<td>Blood in upper GI tract, adherent clot, visible or spurring vessel</td>
<td>—</td>
</tr>
</tbody>
</table>

*GI = gastrointestinal; SBP = systolic blood pressure; bpm = beats per minute; SRH = stigmata of recent hemorrhage.

— Each variable is scored, and the total score is calculated by simple addition.
†Active arterial spurring or the oozing of blood; nonbleeding, visible vessels; and adherent clots.

Adapted with permission from Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after upper gastrointestinal haemorrhage. Gut 1996;38:318.

70 percent for identifying sources of bleeding and limits the extent of surgery in up to 10 percent of cases. However, the removal of identified colon lesions does not always result in effective treatment of the underlying source of bleeding. In these cases, arteriography can be used intraoperatively as an adjunct to localize a source of bleeding, facilitate segmental resection of the bowel, and prevent blind hemicolecotomy.

When rectal bleeding stops before the source is identified, evaluation can proceed in the outpatient setting in patients who remain stable and at low risk. Depending on clinical suspicion, it may be appropriate to repeat upper or lower endoscopy, because upper and lower gastrointestinal lesions occasionally are missed on the first endoscopic evaluation. The most commonly missed upper gastrointestinal lesions are erosions in large hiatal hernias, arteriovenous malformations, and peptic ulcers. The lower gastrointestinal lesions most commonly missed on initial endoscopy are arteriovenous malformations and neoplasms.

### Chronic Intermittent Rectal Bleeding

EGD is the diagnostic test of choice for suspected chronic intermittent rectal bleeding. A barium-contrast upper gastrointestinal series with small bowel follow-through (SBFT) may be considered if there is a relative contraindication to endoscopy (i.e., patient preference, concomitant anticoagulation treatment, comorbidity causing unacceptable risk for conscious sedation, or unavailability of an endoscopist). This procedure has a sensitivity of 54 percent and a specificity of 91 percent in the detection of upper gastrointestinal lesions located above the ligament of Treitz. Upper endoscopy has a 92 percent sensitivity and a 100 percent specificity.

Colonoscopy is the diagnostic tool of choice in a hemodynamically stable patient with a suspected lower gastrointestinal source of bleeding. One prospective study showed that colonoscopy had a higher positive predictive value than double-contrast barium enema with sigmoidoscopy in identifying all colonic lesions (87 versus 81 percent, respectively). Colonoscopy also has a higher sensitivity than double-contrast barium enema in identifying colon cancer (97.5 versus 83 percent, respectively), neoplastic polyps greater than 1 cm (91.4 versus 81.7 percent, respectively), and angiodysplasia. Most importantly, colonoscopy allows for evaluation of the entire colon while providing the opportunity to acquire tissue biopsy and facilitating therapeutic intervention.

Double-contrast barium enema with sigmoidoscopy may be an alternative in patients who have a relative contraindication to colonoscopy. Some physicians may consider a limited evaluation of the anorectosigmoid area in patients younger than 40
TABLE 4
History and Clinical Findings Associated with Specific GI Sources of Rectal Bleeding

<table>
<thead>
<tr>
<th>Cause</th>
<th>History and clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI tract</td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>Use of aspirin, NSAIDs, or tobacco</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>Alcohol abuse; jaundice; signs of portal hypertension, including ascites, palmar erythema, spider angiomata, hepatomegaly, splenomegaly, and rectal varices</td>
</tr>
<tr>
<td>Mallory-Weiss tear</td>
<td>Bleeding preceded by vomiting, retching, or seizures</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Left supraclavicular adenopathy; palpable mass; abdominal pain; weight loss; cachexia</td>
</tr>
<tr>
<td>Lower GI tract</td>
<td></td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>Age &gt; 60 years; painless bleeding; possible recent constipation</td>
</tr>
<tr>
<td>Arteriovenous malformations</td>
<td>Age &gt; 60 years; painless bleeding; chronic renal failure</td>
</tr>
<tr>
<td>Colonic neoplasms</td>
<td>Age &gt; 50 years; abdominal pain; weight loss; muscle wasting; protein calorie malnutrition; right-sided colon cancer may be associated with palpable right-sided abdominal mass; hepatomegaly; liver nodules; history of adenomatous polyps or longstanding ulcerative colitis; prior exposure to ionized radiation; family history of familial polyposis coli or cancer family syndrome</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Ulcerative colitis: starts in younger patients (20 to 40 years of age); usually involves the rectum; associated with diarrhea mixed with blood and mucus Crhôn's disease: starts in younger patients (20 to 40 years of age); perianal, peritoneal, and/or abdominal wall fistulas may be associated</td>
</tr>
<tr>
<td>Radiation colitis</td>
<td>History of radiation treatment to abdomen and/or pelvis</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>Perianal mass may be painful (external hemorrhoid) or painless (internal hemorrhoid); commonly starts in younger patients; associated with constipation, pregnancy, or postpartum period</td>
</tr>
<tr>
<td>Anal fissures</td>
<td>More common in patients with history of constipation; associated with severe sharp pain occurring with straining on defecation; pain resolves within an hour after defecation; commonly starts at 20 to 40 years of age</td>
</tr>
<tr>
<td>Colon tuberculosis</td>
<td>History of pulmonary tuberculosis or past exposure to tuberculosis</td>
</tr>
<tr>
<td>Aortoduodenal fistula</td>
<td>History of abdominal aortic aneurysm surgically repaired with synthetic vascular graft placement</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.
Information from references 3, 4, 10, 21, and 28 through 30.

Figure 1. Arteriogram of patient with acute massive gastrointestinal bleeding, localizing the source of the bleeding to the ascending colon (arrow).

years because only 5 percent of colorectal cancer cases occur in this population. In addition, the most common cause of rectal bleeding in patients younger than 30 years is anal pathology such as hemorrhoids or fissures. In cases where the source of bleeding cannot be confirmed, or if bleeding and anemia continue, a colonoscopy should be performed for complete evaluation of the large bowel.

Small Bowel Bleeding

Small bowel sources of gastrointestinal bleeding are uncommon, accounting for only 2 to 10 percent of all cases. Because of its location, evaluation is technically difficult. For these reasons, therefore, evaluation of the small bowel is less commonly indicated. However, when endoscopy is nondiagnostic, the small bowel should be evaluated. When evaluation of the small bowel is considered necessary, several procedures can be employed. One diagnostic tool is push enteroscopy, which is an extension of upper endoscopy that allows visualization.
Figure 2. Sequential one-minute picture frames of technetium-99m–tagged red blood cell scan in hemodynamically-stable patient presenting with painless bloody diarrhea occurring over the course of several hours. Note the immediate blush (Frame 6), followed by rapid antegrade bowel transit of intraluminal blood (Frame 11), and then retrograde transit of blood (Frame 15), which collectively helped localize the source of bleeding within the proximal sigmoid colon.

of 15 to 160 cm of small bowel distal to the ligament of Treitz.2,22,42 This procedure allows for tissue biopsy and treatment of bleeding lesions, but it is limited by its inability to visualize beyond 160 cm of the proximal small bowel.23,42 The diagnostic yield for push enteroscopy is approximately 54 percent.22

Two radiographic tools are used to evaluate the small bowel. One is a barium-contrast upper gastrointestinal series with SBFT, which has a low sensitivity (zero to 5.6 percent).22 The other diagnostic tool is enteroclysis, which has a sensitivity of 10 to 21 percent.22 The latter procedure requires a small tube or endoscopic placement of contrast material directly into the proximal small bowel.22 The advantages of enteroclysis over SBFT are its higher sensitivity, shorter procedure time, and greater usefulness in evaluating an unconscious or uncooperative patient.22 When enteroclysis is combined with push enteroscopy, the absolute yield over push enteroscopy alone increases from 54 to 58 percent.22

One of the nuclear studies routinely used in the evaluation of the small bowel is technetium-99m–tagged red blood cell scanning.23,43 The other is a Meckel’s scan, which uses technetium-99m pertechnate.22,42 A Meckel’s scan has a high sensitivity (75 to 100 percent) for identifying gastric mucosa in the small bowel, but cannot confirm the identified lesion as the source of bleeding.22 This study is most appropriately used in the evaluation of younger patients.6,22

Although arteriography is most useful in the evaluation of acute massive rectal bleeding, it also serves a role in the evaluation of obscure sources of bleeding that are not identified by endoscopy.16 It is particularly helpful in the evaluation of older patients in whom arteriovenous malformations or neoplasms are suspected, because
both of these lesions are associated with characteristic vascular patterns that can be identified on arteriogram.16 Helical computed tomography combined with angiography also may have a role in evaluating obscure sources of bleeding. More evidence-based studies need to be done to confirm the latter as an option.44

Capsule endoscopy is a new diagnostic tool consisting of a pill-shaped camera that the patient swallows12 (Figure 3). Only a few small studies have examined the usefulness of this diagnostic tool in the evaluation of sources of small bowel bleeding, but the preliminary results are promising.42,43,45,46 When compared with push enteroscopy (38 percent yield), capsule endoscopy has been shown to have the better diagnostic yield (66 to 69 percent) in identifying small bowel lesions.34,47

A recent prospective study45 comparing capsule endoscopy with barium-contrast upper gastrointestinal series with SBFT found capsule endoscopy to have a superior diagnostic yield in identifying obscure bleeding sites (31 versus 5 percent, respectively). Capsule endoscopy is painless and well tolerated, and requires no sedation.34,43 Although capsule endoscopy is helpful in identifying pathologic lesions, it must be followed by endoscopy or surgery for tissue diagnosis and treatment of significant sources of bleeding.43 Capsule endoscopy is contraindicated in patients when bowel stricture is suspected.34,42,46

When all diagnostic tools have failed to allow identification or effective treatment of chronic recurrent bleeding, and anemia persists or worsens, laparotomy with intraoperative enteroscopy may be indicated.57 This procedure is considered a last option in the diagnostic evaluation of nonemergent cases because it is more invasive and associated with higher rates of morbidity and mortality.12

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Figures 1 and 2 used with permission from Linda L. Manning-Dimmett, D.O.
Figure 3 used with permission from Gwin Imaging, Ltd., Norcross, Ga.

Members of various family practice departments develop articles for "Problem-Oriented Diagnosis." This article is one in a series coordinated by R. Whlt Curly, Jr., M.D., from the Department of Family Medicine at the University of Florida, Gainesville, Fla.

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REFERENCES

Gastrointestinal Bleeding

Primary Care

OCCULT GASTROINTESTINAL BLEEDING
DON C. ROCKEY, M.D.

OCCULT gastrointestinal bleeding typically refers to bleeding that is not apparent to the patient. The potential for occult bleeding is emphasized by the finding that for melena to be produced consistently, 150 to 200 ml of blood must be present in the stomach.1 Moreover, patients with gastroduodenal blood loss of 100 ml per day may have stools that appear normal.2 Thus, occult bleeding is usually identified only by tests that detect fecal blood or, if bleeding is sufficient, when it becomes manifest as iron deficiency. Occult gastrointestinal bleeding can also refer to bleeding that is clinically evident but from an obscure source. Obscure gastrointestinal bleeding is the least common form of occult gastrointestinal bleeding but represents a tremendous diagnostic and therapeutic challenge. This article reviews important concepts in the evaluation and care of patients with each type of occult gastrointestinal bleeding.

FECAL OCCULT BLOOD

The amount of blood lost from the gastrointestinal tract is normally approximately 0.5 to 1.5 ml per day,2-5 an amount that is typically not detected by occult-blood tests. Nonetheless, occult blood is commonly detected in the stool if fecal occult-blood tests when there has been no clinical evidence of bleeding or iron deficiency. In screening studies, 2 to 16 percent of the patients tested had positive tests, although many tests may have been falsely positive.6,7 A variety of fecal occult-blood tests have been designed, primarily to screen for colon cancer.8,9 However, they also detect blood from other lesions in the gastrointestinal tract (Fig. 1). The likelihood that fecal occult-blood tests will detect gastrointestinal bleeding is affected by the anatomical level of bleeding, factors relating to the patient—such as stool transit time, stool mixing, and intraluminal hemoglobin degradation—and the intrinsic features of the bleeding of gastrointestinal tract lesions (e.g., irregular bleeding).10

Fecal Occult-Blood Tests

Guaiac-based fecal occult-blood tests make use of the pseudoperoxidase activity of hemoglobin. Guaiac turns blue after oxidation by oxidants or peroxidases in the presence of an oxygen donor such as hydrogen peroxide. Several different guaiac-based tests are available, the characteristics of which vary considerably. For example, of the two most commonly used tests, Hemoccult II and Hemoccult II Sensa (SmithKline Diagnostics, Palo Alto, Calif.), the latter is much more sensitive than the former for detecting fecal heme.11,12

The likelihood that a guaiac-based test will be positive is generally proportional to the quantity of fecal heme, which in turn is related to the size and location of the bleeding lesion (Fig. 1).13,14 Guaiac-based tests are generally best at detecting large, more distal lesions. However, many factors contribute to the variation in the effectiveness of guaiac-based tests for the detection of fecal blood.15 The inconsistency of fecal occult-blood tests in detecting fecal blood is emphasized by the finding that fecal hemoglobin levels must exceed 10 mg per gram of stool (10 ml of daily blood loss) for Hemoccult II tests to be positive 50 percent of the time.16 Such data have raised questions about the accuracy of guaiac-based tests for detecting colonic lesions.17

Many variables influence guaiac-based tests, including dietary factors (Table 1). For this reason, it is important to consider (and modify) diet when performing guaiac-based tests. In addition, fecal rehydration markedly raises the sensitivity of guaiac-based tests but reduces specificity.7 Many believe that oral iron causes positive results on guaiac-based tests. Although the dark-green or black appearance of iron in stool can be confused with the blue typical of a positive guaiac-based test, iron administered orally does not cause positive guaiac reactions.18 Antacids and anti-diarrheal drugs containing bismuth also render the stool dark and may confound the reading of guaiac-based tests.

Immunochromatographic tests, which use antibodies directed against human globin epitopes, detect colonic blood with great sensitivity (at a level of as little as 0.3 ml of blood added to stool)19 and do not detect

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small quantities of blood from the upper gastrointestinal tract (Fig. 1). Thus, they have a theoretical advantage over guaiac-based tests in terms of localizing bleeding to the colon. Unfortunately, the tests are limited by loss of globin antigenicity at room temperature and require processing in a laboratory. Newer slide tests may help circumvent these problems.

The heme–porphyrin test, HemoQuat (Mayo Medical Laboratories, Rochester, Minn.), measures hemoglobin-derived porphyrin spectrophotometrically and allows exact measurement of total hemoglobin in stools. Moreover, substances that may interfere with or cause false positive guaiac-based tests (for example, vegetable peroxidases) do not affect the test. Unfortunately, the need for laboratory processing and the high false positive rate of this test have limited its clinical application.

**Differential Diagnosis and Approach to Evaluation**

Although many variables influence the results of fecal occult-blood tests, including variables that cause false positive results and those that cause false negatives, once it is determined that a patient has a positive test, the clinical focus is generally first on colonic

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**Table 1. Characteristics of Different Classes of Fecal Occult-Blood Tests.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Guaiac-Based</th>
<th>Heme-Porphyrin</th>
<th>Immunochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redline availability</td>
<td>+++</td>
<td>0</td>
<td>0 to ++</td>
</tr>
<tr>
<td>Time to develop</td>
<td>1 min</td>
<td>1 hr</td>
<td>5 min to 24 hr</td>
</tr>
<tr>
<td>Cost</td>
<td>$18</td>
<td>$33</td>
<td>$35</td>
</tr>
<tr>
<td>Reasons for false positive results:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhuman hemoglobin</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Dietary peroxidases</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rehydration</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Iron</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reasons for false negative results:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin degradation</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Storage</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

*Relative comparisons are shown on a scale of 0 to ++, with +++ indicating highly likely and 0 highly unlikely.

†Commonly used tests are Hemocult II and Hemoccult II Sensa for guaiac-based tests, HemoQuat for heme–porphyrin tests, and HemeSelect and FlexSure OBT (SmithKline Diagnostics, Palo Alto, Calif.) for immunochromel tests.

‡The dollar amounts shown, which represent 1998 values, are for reimbursements. The amount shown for the guaiac-based test is the price for three cards.
imaging. The choice of imaging mode — colonoscopy or air-contrast barium enema — is controversial.20-32 Flexible sigmoidoscopy is mandatory for patients undergoing air-contrast barium enema to evaluate the rectosigmoid colon fully.33 Some studies have found that air-contrast barium enema accurately detects colon cancer and large adenomas,24 but most studies have found air-contrast barium enema to be less accurate than colonoscopy.20,25 Both tests can miss important neoplastic lesions.20,36,37 In addition, other factors are important when choosing an evaluation strategy; not only is the accuracy of the test an issue, but cost, acceptance by the patient, and complication rates differ between the two methods.

On the basis of the available data, colonoscopy is recommended for the evaluation of the colon in patients with fecal occult blood; however, the use of air-contrast barium enema with flexible sigmoidoscopy may be an acceptable alternative. Computed tomographic studies of the colon (virtual colonoscopy) could eventually play a part in colonic evaluation,28 but clinical experience is limited. Further studies are required to assess colonic-imaging techniques in patients with fecal occult blood.

Many gastrointestinal lesions can bleed and cause a positive fecal occult-blood test (Table 2); indeed, patients with fecal occult blood detected by guaiac-based tests may have serious disease of the upper gastrointestinal tract. Upper endoscopic examinations detected abnormalities in 25 to 41 percent of patients with fecal occult blood, many of whom were asymptomatic.20,22 Although this finding is surprising given the intraluminal metabolism of hemoglobin (Fig. 1), currently available guaiac-based tests detect small amounts of blood in the upper gastrointestinal tract,11,23 and many upper gastrointestinal tract lesions bleed enough to produce positive results on guaiac-based tests.3,12 The highly sensitive Hemocult II Sensa test is substantially more likely to detect blood in the upper gastrointestinal tract than is the Hemocult II test.12 Therefore, the upper gastrointestinal tract must be considered as a potential source of bleeding in patients with normal results on colonoscopy, especially when highly sensitive guaiac-based tests are positive.

In the patient with a positive guaiac-based fecal occult-blood test and a negative colonoscopic examination, symptoms of upper gastrointestinal disorders (severe reflux, dyspepsia, and abdominal pain), weight loss, and iron deficiency should be assessed. If such signs and symptoms are present, the upper gastrointestinal tract should be studied. Whether asymptomatic patients should undergo evaluation of the upper gastrointestinal tract has not yet been determined.

Appropriate evaluation of patients with fecal occult blood detected by digital rectal examination is controversial, because obtaining stool by this means may lead to false positive tests. False positive tests may, in theory, result from anorectal trauma induced by the gloved finger during digital rectal examination. In addition, patients generally have not had dietary modification implemented at the time of digital rectal examination. However, in both symptomatic and asymptomatic patients with fecal occult blood detected by digital rectal examination, the number of new lesions identified by gastrointestinal evaluation is substantial.32,34 Thus, evaluation of these patients is indicated and, if symptoms are present, the investigation should be focused on the site or sites of the symptoms.

Occult gastrointestinal bleeding is often attributed to therapy with anticoagulants or aspirin. However, fecal blood levels in patients treated with anticoagulants or low-dose aspirin are normal or only minimally elevated, respectively.35,36 Neither warfarin nor low-dose aspirin alone appears to cause positive

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**Table 2. Differential Diagnosis of Occult Gastrointestinal Bleeding.**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass lesions</td>
</tr>
<tr>
<td>Carcinoma (any site)†</td>
</tr>
<tr>
<td>Large (&gt;1.5 cm) adenoma (any site)</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Erosive esophagitis‡</td>
</tr>
<tr>
<td>Ulcer (any site)†</td>
</tr>
<tr>
<td>Cameron lesion‡</td>
</tr>
<tr>
<td>Erosive gastritis</td>
</tr>
<tr>
<td>Cecal disease</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Colitis (nonspecific)</td>
</tr>
<tr>
<td>Idiopathic colonic ulcer</td>
</tr>
<tr>
<td>Vascular disorders</td>
</tr>
<tr>
<td>Vascular ectasia (any site)§</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy or colopathy</td>
</tr>
<tr>
<td>Watermelon stomach</td>
</tr>
<tr>
<td>Varices (any site)</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
</tr>
<tr>
<td>Arteriovenous malformations§</td>
</tr>
<tr>
<td>Infectious diseases</td>
</tr>
<tr>
<td>Hookworm</td>
</tr>
<tr>
<td>Whipple</td>
</tr>
<tr>
<td>Strongyloidias</td>
</tr>
<tr>
<td>Ascaris</td>
</tr>
<tr>
<td>Tuberculosis enterocolitis</td>
</tr>
<tr>
<td>Amebias</td>
</tr>
<tr>
<td>Suppurative bleeding</td>
</tr>
<tr>
<td>Hemohoma</td>
</tr>
<tr>
<td>Oropharyngeal bleeding (including epistaxis)</td>
</tr>
<tr>
<td>Other causes</td>
</tr>
<tr>
<td>Hemorrhagic pancreatitis</td>
</tr>
<tr>
<td>Hemobilia</td>
</tr>
<tr>
<td>Long-distance running</td>
</tr>
<tr>
<td>Farcious cause</td>
</tr>
</tbody>
</table>

*Potential lesions leading to all forms of occult gastrointestinal bleeding are listed here. Some lesions that may lead to recurrent obscure bleeding are not listed.
† These abnormalities are the most common.
‡ These are linear erosions within a hiatus hernia.
§ This is a large superficial artery underlying a small mucosal defect.
Normal obligate daily iron loss is from blood loss (presumably from gastrointestinal mucosal microerosions or mucosal ulcerations) and iron in sloughed epithelial cells of the gut. Total daily iron loss is approximately 1 mg. The usual Western diet contains mostly elemental iron, of which about 10 percent is absorbed. Heme iron, derived primarily from myoglobin in meats, is preferentially absorbed and accounts for 60 to 80 percent of the iron absorbed per day. Under normal circumstances, iron homeostasis is tightly regulated, and daily iron loss is precisely balanced by iron absorption. Iron deficiency results only when the dynamic, but limited, absorptive capacity of the small intestine is exceeded by iron excess. The time required for the development of iron deficiency depends on the size of initial iron stores, the rate of bleeding, and intestinal iron absorption. Iron deficiency generally occurs only with loss of more than 5 ml of blood per day. Anemia is a late manifestation of the iron-depleted state. The red cells indicate bleeding and potential sites of blood loss.

In a prospective study evaluating the gastrointestinal tract in patients taking anticoagulants who had positive guaiac-based fecal occult-blood tests, 36 in a prospective study evaluating the gastrointestinal tract in patients taking anticoagulants who had positive guaiac-based fecal occult-blood tests, 15 of 16 patients had new lesions, 20 percent of which were malignant.37 In addition, there was no difference in the frequency of lesions between patients receiving warfarin and those receiving standard heparin.37 Thus, positive fecal occult-blood tests should not be attributed solely to anticoagulant therapy — whether with therapeutic or prophylactic warfarin, heparin (including low-dose heparin), or aspirin — but, rather, should lead to formal evaluation.

In patients with fecal occult blood (or any occult gastrointestinal bleeding), too high a degree of anticoagulation diminishes the yield of a gastrointestinal tract evaluation. In those with intrinsic coagulopathy (hemophilia or von Willebrand's disease), particularly if bleeding is chronic, abnormalities of the gastrointestinal tract are also less likely to be identified; nevertheless, in both clinical scenarios, gastrointestinal evaluation must be given serious consideration.

Treatment and Outcome

The care of patients with fecal occult blood is based on the abnormalities identified. Likewise, outcomes are directly related to specific findings. Since nonsteroidal antiinflammatory drugs may lead to gastrointestinal injury, these should be discontinued if possible. Particularly problematic are vascular ectasias, which are often multiple and bleed chronically. (The medical management of vascular ectasias is discussed below.) The prognosis of patients with positive fecal occult-blood tests but no identifiable gastrointestinal disorder is generally favorable.

ANEMIA DUE TO IRON DEFICIENCY

In the United States, 5 to 11 percent of women and 1 to 4 percent of men have iron deficiency, and approximately 5 percent and 2 percent of women and men, respectively, have iron-deficiency anemia.38 In women, iron-deficiency anemia — a result of chronic iron loss (Fig. 2) — is most common during the reproductive years, because of menstrual and pregnancy-associated iron losses.39 Among other patients,
however, iron-deficiency anemia has been associated with chronic occult gastrointestinal bleeding.\textsuperscript{40}

**Differential Diagnosis and Approach to Evaluation**

Because a diagnosis of iron-deficiency anemia necessarily extends extensive and often costly evaluation, the diagnosis must be established carefully. Although the gold standard is bone marrow biopsy, iron deficiency is most often indicated by a serum ferritin level of less than 45 μg per liter; iron-deficiency anemia is most often diagnosed on the basis of a similarly low ferritin level plus a hemoglobin level of less than 12 g per deciliter for women and less than 13 g per deciliter for men.\textsuperscript{41} Iron deficiency without anemia also requires further investigation, because it may be associated with serious abnormalities of the gastrointestinal tract.\textsuperscript{42,43}

Cancers of the right side of the colon have traditionally been considered a leading cause of occult bleeding leading to iron-deficiency anemia, although practically any lesion in the gastrointestinal tract can bleed in an occult fashion (Table 2). Several cross-sectional studies have documented prominent abnormalities of the upper gastrointestinal tract. In studies of 381 patients with iron-deficiency anemia, lesions of the gastrointestinal tract consistent with chronic blood loss were identified in the following locations: the esophagus, stomach, or duodenum (in the form of severe esophagitis, presumably mediated by reflux, and ulcers) (41 percent), the small intestine (3 percent), and the colon (in the form of colon cancer and large adenoma) (22 percent).\textsuperscript{44-47} In this group of patients, 34 percent had no identifiable lesion consistent with blood loss, and only 5 percent had disease identified in both upper and lower gastrointestinal tracts.

Focused evaluation of the gastrointestinal tract should be considered in patients with iron-deficiency anemia. Gastrointestinal symptoms help direct the workup\textsuperscript{48} although symptoms may not localize the disease.\textsuperscript{45,46} If epigastric pain, a change in stool caliber, and reflux symptoms are present, the initial investigation should be directed toward these symptoms, especially if the onset was recent. Because multiple lesions are rare, the identification of an abnormality clearly consistent with bleeding, such as a mass lesion, large ulceration, or severe inflammation, generally makes further evaluation unnecessary. In the absence of gastrointestinal symptoms, particularly in elderly patients, evaluation should begin with the colon and, if the colonoscopic evaluation is negative, proceed to the upper gastrointestinal tract.

Large mass lesions, ulcerative gastrointestinal lesions, and even erosive gastritis associated with *Helicobacter pylori* infection commonly lead to serious occult blood loss (up to 60 ml per day).\textsuperscript{35,49} However, trivial lesions such as mild inflammation and small adenomas do not bleed substantially.\textsuperscript{3,10} Furthermore, not all patients with iron-deficiency anemia and gastrointestinal lesions have elevated levels of hemoglobin in gastrointestinal lavage fluid.\textsuperscript{50} Thus, it is unlikely that every identified gastrointestinal tract lesion is associated with occult bleeding; caution is therefore urged in attributing iron-deficiency anemia to trivial lesions.

The role of gastrointestinal evaluation in premenopausal women with iron-deficiency anemia is not yet settled. A recent retrospective study found that 23 of 186 premenopausal women with iron-deficiency anemia (12 percent) had serious gastrointestinal tract abnormalities, including lesions of the upper gastrointestinal tract (12 patients) and the lower gastrointestinal tract (11 patients).\textsuperscript{48} Surprisingly, gastric cancer was the most common lesion of the upper gastrointestinal tract (five patients) and colon cancer the most prevalent colonic lesion (six patients). Of 15 variables examined, the only clinical features predictive of a detectable lesion were severe anemia (hemoglobin, <10 g per deciliter), abdominal symptoms, weight loss, and a positive fecal occult-blood test. Although the design of the study limits its generalizability, it shows that evaluation can lead to important diagnoses. Because iron-deficiency anemia is extremely common in premenopausal women, the management strategy is of critical importance. Currently, the best strategy is to individualize management. Patients with gastrointestinal symptoms (abdominal pain, dyspepsia, or severe reflux), weight loss, fecal occult blood, a family history of gastrointestinal cancer, or severe anemia should undergo gastrointestinal tract evaluation. Furthermore, the threshold for evaluation of patients older than 40 or 45 years should be lower than for younger women. For asymptomatic patients or those with abnormal menses, evaluation of the gastrointestinal tract is most appropriate when the severity of iron deficiency is disproportionate to the menstrual blood loss.

Both endoscopic evaluations (esophagogastroduodenoscopy and colonoscopy) and radiographic tests (air-contrast barium enema and upper gastrointestinal series) have been used to evaluate the gastrointestinal tract in patients with iron-deficiency anemia. Radiographic studies are generally effective for detecting mass lesions and large ulcerating lesions.\textsuperscript{51} However, they are not as sensitive for detecting vascular ectasias and mucosal lesions (esophagitis or colitis) as are endoscopic procedures. Therefore, endoscopic investigation is likely to be the most cost-effective approach and is recommended.

The small bowel should be considered as a potential site of bleeding in patients with iron-deficiency anemia and negative results on examinations of the colon and upper gastrointestinal tract. For example, celiac disease, a classic disorder of the small bowel, can lead to malabsorption of iron as well as to occult bleeding.\textsuperscript{52,53} Especially in patients of northern Euro-
pean descent. Radiographic examination of the small bowel (either by small-bowel follow-through or by enteroclysis with barium instilled under pressure) is of limited value in patients with iron-deficiency anemia. In contrast, endoscopy of the small intestine (enteroscopy) is more sensitive for detecting mucosal lesions and possibly mass lesions; it has identified abnormalities in 6 to 27 percent of patients with iron-deficiency anemia. However, available data do not support the routine use of enteroscopy (or enteroclysis) in the initial evaluation of all patients with iron-deficiency anemia. Rather, investigation of the small bowel should be reserved for patients with negative studies of the colon and upper gastrointestinal tract but with persistent gastrointestinal symptoms or those for whom a short trial of iron therapy has failed. The role of routine biopsy of the small intestine in patients with negative evaluations of the upper and lower gastrointestinal tracts to investigate whether celiac disease is present is controversial, but the use of biopsy is reasonable in groups with a high underlying prevalence of celiac disease.

Some patients with iron-deficiency anemia have no identifiable abnormality of the gastrointestinal tract. Possible explanations for the iron-deficiency anemia include nongastrointestinal (especially oropharyngeal) blood loss, a misdiagnosis of the type of anemia, nutritional deficiency, and lesions that were not identified (especially vascular ectasias). Indeed, in a recent study, 35 percent of the patients with a negative workup had a source of bleeding that was subsequently identified by upper gastrointestinal endoscopy. In another study, approximately 20 percent of patients with iron-deficiency anemia were found to have gastric achlorhydria and atrophy, a finding that suggests that atrophic gastritis may contribute to the malabsorption of iron.

Treatment and Outcome

Iron therapy should be instituted for all patients once the diagnosis of iron-deficiency anemia has been confirmed. Oral ferrous sulfate is recommended because it is inexpensive and effective. Parenteral iron therapy is used only for patients with severe malabsorption or intolerance of all oral iron supplements (because of potential anaphylactic reactions to intravenous compounds). The prognosis for patients with iron-deficiency anemia and lesions amenable to medical therapy (duodenal ulcer, esophagitis, or adenoma) is excellent. Likewise, the prognosis for patients with normal results on evaluation of the gastrointestinal tract is favorable; very few of these patients are found to have serious gastrointestinal lesions during follow-up. The majority of patients respond to standard oral iron therapy; for patients who do not respond, the diagnosis of iron-deficiency anemia should be reevaluated. When unexplained iron-deficiency anemia persists, consideration should be given to careful reexamination of the colon, the esophagus (for linear esophageal ulceration, or Cameron lesions, within the mucosa), the stomach (for atrophic gastritis and other abnormalities), and the small bowel (including biopsy for celiac disease).

GASTROINTESTINAL HEMORRHAGE OF OBSCURE ORIGIN

In up to 5 percent of patients with overt gastrointestinal bleeding, the source of bleeding remains unidentified after readily identifiable causes of gastrointestinal bleeding (ulcers or carcinomas) have been ruled out by endoscopic procedures. After bleeding is recognized as recurrent, the focus of care shifts to identification of the site and determination of the cause of bleeding; only then can appropriate therapy be instituted.

Differential Diagnosis and Approach to Evaluation

History taking and physical examination often help to localize the site of bleeding. Melena and hematochezia are typically associated with bleeding of the upper and lower gastrointestinal tracts, respectively, although slow oozing from the distal small bowel or cecum may lead to melena, and aggressive bleeding from a site in the upper gastrointestinal tract can cause hematochezia. A bloody nasogastric-lavage fluid or a blood urea nitrogen level disproportionately high in relation to the creatinine level suggests bleeding from the upper rather than lower gastrointestinal tract, but these tests are not highly sensitive for the localization of bleeding.

The initial evaluation should entail the consideration of lesions that are easily overlooked, such as those due to linear inflammation and erosion in patients with portal hypertension (watermelon stomach), vascular ectasias, Dieulafoy's vascular malformation (a large superficial artery underlying a small mucosal defect), gastric and small intestinal varices, diverticula, aortoenteric fistulas, hemobilia, hemobilia pancreaticus (bleeding from the pancreatic duct), and in young patients, Meckel's diverticulum. Thus, a second endoscopic procedure, directed at the most likely site of bleeding, is usually warranted. For example, in patients with apparent upper gastrointestinal hemorrhage, a reexamination of the upper gastrointestinal tract by esophagogastroduodenoscopy leads to the identification of lesions in many patients. However, a familiarity with bleeding lesions that are rare or subtle is essential. If a lesion cannot be identified, the decision to evaluate further depends on the briskness of bleeding. For patients with active bleeding, technetium-99m radionuclide scanning or angiography should be performed. Technetium-99m scanning, although sensitive (as small a blood loss as 0.1 ml per minute can be detected), is useful only to confirm bleeding and its general area; its effect on treatment has been disappointing.
Enteric angiography is less sensitive than technetium-99m scanning (requiring a bleeding rate of more than 0.5 ml per minute), but it is reportedly more likely to help in the identification of a specific site of bleeding,64 perhaps as a result of selection bias in published studies. In some situations, other diagnostic tests (computed tomography or Meckel scanning) may be helpful. For patients with subacute bleeding in whom repeated endoscopy (including esophagogastroduodenoscopy, colonoscopy, or both) is negative, the focus of investigation should be broadened to include the small intestine. The lesions most commonly identified as sites of bleeding in the small bowel are tumors and vascular ectasias, both of which vary in frequency according to age. Among patients between 30 and 50 years of age, tumors are the most common abnormalities; among patients younger than 25, Meckel's diverticula are the most common source of bleeding in the small bowel, and among patients older than 50, vascular ectasias predominate.65

The chief diagnostic methods used to evaluate the small intestine are enterolysis and enteroscopy. Small-bowel follow-through is usually inadequate for evaluating the small intestine. Enterolysis is capable of detecting mass lesions of the small intestine, especially distal ones,66 but it is ineffective in detecting mucosal lesions, particularly vascular ectasias. Because vascular ectasias are often a major diagnostic concern in patients with small-bowel bleeding, radiographic studies are reserved for those in whom the clinical suspicion of a mass lesion or of small-bowel diverticula is high.

Enteroscopy, either of the push or Sonde type, is an integral component of the evaluation of most patients with obscure gastrointestinal bleeding.69 Push enteroscopy, which entails personal insertion of a long endoscope (usually a dedicated enteroscope or pediatric colonoscope), should be the first approach used in evaluating most patients. It is performed after mild sedation of the patient and allows thorough examination of the distal duodenum and proximal jejunum. The experience with push enteroscopy has been variable, but it has led to the identification of a source of bleeding in 24 to 75 percent of patients with obscure bleeding.54,59,60,67,68 The main advantages of push enteroscopy are that it is readily available and relatively safe and that biopsy and therapy can be performed through the procedure. Sonde enteroscopy involves placement of a long, small-caliber endoscope into the proximal small bowel; subsequent peristalsis carries the endoscope to the distal small intestine. Although this procedure permits visualization of almost the entire small bowel, it requires a highly specialized endoscope. Sonde enteroscopy is uncomfortable, does not permit therapy, and is not widely available. The role of Sonde enteroscopy is evolving, but it will probably be limited to use in patients whose examination by push enteroscopy was negative and who have serious coexisting conditions that preclude intraoperative enteroscopy. Intraoperative enteroscopy permits the visualization of the small intestine through the use of an endoscope (or standard colonscope) that is advanced through the small bowel during laparotomy. It has been reported to detect abnormalities in up to 70 to 100 percent of patients,69,70 although this high rate of detection has not been duplicated in the experience of all clinicians.

Treatment and Outcome

Vascular ectasias of the small bowel are the most common source of bleeding in patients with obscure gastrointestinal bleeding.71 Endoscopic and surgical therapy is most successful in those with large, focal vascular ectasias. Because vascular ectasias are often diffuse (limiting endoscopic and surgical intervention), hormonal therapy with compounds of estrogen and progesterone has been tried as a medical alternative. Although positive experiences with such pharmacologic therapy have been reported,72 controlled trials have failed to show an advantage.72 Nevertheless, for patients with severe, recurrent bleeding from vascular ectasias, mixed hormonal therapy should be considered.

Specific treatment for patients with obscure bleeding, as for patients with fecal occult-blood loss and iron-deficiency anemia, varies according to the abnormality identified. Enteroscopy, which often reveals putative bleeding lesions, has not always led to improved outcomes. Enteroscopic cauteterization of vascular ectasias can lead to a reduction in blood-transfusion requirements.74 Unfortunately, in only about 50 percent of patients treated at the time of intraoperative enteroscopy will bleeding stop,75,76 so this intervention is not ideal. Thus, further work is required to help determine which lesions respond best to endoscopic and surgical intervention. Finally, the care of patients with obscure gastrointestinal bleeding requires an experienced and highly dedicated team of care givers and endoscopic and imaging experts.

I am indebted to John Ballitte for his helpful discussion and careful review of the manuscript.

REFERENCES


Cirrhosis and Chronic Liver Failure: Part I. Diagnosis and Evaluation

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Cirrhosis and chronic liver failure are leading causes of morbidity and mortality in the United States, with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis, or nonalcoholic fatty liver disease. Cirrhosis often is an indolent disease; most patients remain asymptomatic until the occurrence of decompensation, characterized by ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or variceal bleeding from portal hypertension. Physical examination of patients with cirrhosis may reveal a variety of findings that necessitate a hepatic- or gastrointestinal-based work-up to determine the etiology. Some patients already may have had laboratory or radiographic tests that incidentally uncovered signs of cirrhosis and its comorbidities. No serologic or radiographic test can accurately diagnose cirrhosis. A significant correlation has been demonstrated between persistently elevated liver function tests and biopsy-proven underlying hepatic disease; thus, a more targeted serologic work-up is indicated in patients whose liver function test results are persistently abnormal. Unnecessary medications and surgical procedures should be avoided in patients with cirrhosis. Referral for liver biopsy should be considered only after a thorough, noninvasive serologic and radiographic evaluation has failed to confirm a diagnosis of cirrhosis; the benefit of biopsy outweighs the risk; and it is postulated that biopsy will have a favorable impact on the treatment of chronic liver disease. (Am Fam Physician 2006;74:756-62,781. Copyright © 2006 American Academy of Family Physicians.)

This is part I of a two-part article on cirrhosis and chronic liver failure. Part II, "Complications and Treatment," appears in this issue of AFP on page 767.

► Patient information:
A handout on cirrhosis and chronic liver failure, written by the authors of this article, is on page 781.

Cirrhosis and chronic liver failure together were the 12th most common cause of death in the United States in 2002, accounting for 27,257 deaths (9.5 per 100,000 persons), with a slight male predominance.1 Approximately 40 percent of patients with cirrhosis are asymptomatic, and the condition often is discovered during a routine examination with laboratory or radiographic studies, or at autopsy. In 2000, there were 360,000 U.S. hospital discharges related to cirrhosis and liver failure.1 This article, part I of a two-part series, outlines the diagnosis and evaluation of cirrhosis and chronic liver failure (Figure 1). Part II discusses complications and treatment.2

Single or multifactorial insults to the liver ultimately lead to cirrhosis, the most common being alcohol abuse, chronic hepatitis C, and obesity with concomitant nonalcoholic fatty liver disease (Table 1).3,4 Nonalcoholic fatty liver disease (NAFLD; formerly known as nonalcoholic steatohepatitis, or NASH) is an increasingly common cause of liver injury; risk factors include obesity, diabetes, hypertriglyceridemia, and profound weight loss after jejunoileal bypass.5

According to estimates from the United Network for Organ Sharing, 75 to 80 percent of cirrhosis cases could be prevented by eliminating alcohol abuse, and approximately 3.9 million Americans have chronic hepatitis C.6 In August 2005, there were 17,935 persons with cirrhosis (from various etiologies) in the United States who were awaiting a liver transplant.6 Mortality rates in patients with alcoholic liver disease are considerably higher than in patients with other forms of cirrhosis. The Centers for Disease Control and Prevention estimates that 75,766 deaths and 2.3 million years of potential life lost during 2001 were attributable to excessive alcohol use, an average of approximately 30 years of potential life lost for each alcohol-attributable death.7
SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Although no laboratory test can diagnose cirrhosis accurately, liver function tests, a complete blood count with platelets, and a prothrombin time test should be performed if a liver abnormality is suspected. If clinical, laboratory, and radiographic data are inconclusive, but suspicion of cirrhosis remains, a diagnostic liver biopsy should be performed. If serum transaminase levels are greater than twice the upper limit of normal or remain elevated for longer than six months, additional serologic studies should be performed to evaluate for various etiologies of cirrhosis. If clinical suspicion for liver disease is high, further serologic work-up is warranted earlier. Abdominal ultrasonography is a specific, reliable, noninvasive, fast, and cost-effective test that should be used as a first-line radiographic study for diagnosing cirrhosis.</td>
<td>C</td>
<td>14, 15, 17, 15, 20, 21</td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 699 or http://www.aafp.org/aafpsort.xml.

Diagnosis of Cirrhosis and Chronic Liver Failure

**History:**
Patient presents with signs and symptoms of chronic liver disease or has risk factors for chronic liver disease (e.g., alcohol abuse, risk of viral hepatitis, obesity).

**Physical examination:**
Patient has hallmark findings consistent with chronic liver disease (see Table 2). Physical examination findings consistent with liver disease (see Table 2) or high suspicion for chronic liver disease confirm history via signs and symptoms of chronic liver disease and possible risk factors (e.g., alcohol abuse, risk of viral hepatitis, obesity).

**Laboratory studies:**
Patient has incidental liver panel abnormalities (e.g., elevated ALT and/or AST) or positive screen for serologic markers of liver disease (see Table 3). Confirm history via signs and symptoms of chronic liver disease and positive risk factors (e.g., alcohol abuse, risk of viral hepatitis, obesity) and screen for hallmark physical examination findings (see Table 2).

**Radiographic studies:**
Patient has incidental findings suggestive of liver disease on routine studies (e.g., abdominal ultrasonography, CT, MRI).

Obtain liver panel (if not already obtained). CBC with platelets, prothrombin time, and targeted serologic studies to determine etiology of cirrhosis, highlighting risk factors and family history for liver disease (see Table 3).

Obtain abdominal ultrasonography with Doppler (if not already performed) to evaluate for morphologic abnormalities consistent with cirrhosis and to assess for potential complications (e.g., ascites, varices, portal hypertension, portal vein thrombosis).

Refer for possible liver biopsy if diagnosis of cirrhosis is uncertain, as well as possible determination of etiology via histology if not readily determinable through serologic testing and if potential benefit outweighs risk of procedure.

---
Tests included in standard liver panels vary but typically include the serum enzymes ALT, AST, alkaline phosphatase, and γ-glutamyltransferase; total, direct, and indirect serum bilirubin; and serum albumin.

**Figure 1.** Algorithm for the diagnosis of cirrhosis and chronic liver failure. (ALT = alanine transaminase; AST = aspartate transaminase; CT = computed tomography; MRI = magnetic resonance imaging; CBC = complete blood count.)

**Definitions and Etiologies**
The liver aids greatly in the maintenance of metabolic homeostasis by processing dietary amino acids, carbohydrates, lipids, and vitamins; metabolizing cholesterol and toxins; producing clotting factors; and storing glycogen. Injury to the liver parenchyma associated with an influx of acute or chronic inflammatory cells is termed hepatitis. Cirrhosis refers to a progressive, diffuse, fibrosing, nodular condition that disrupts the entire normal architecture of the liver (Figures 2 through 4; Table 1).4-6, 8-10

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previously was thought to be an irreversible scarring process formed in response to inflammation or direct toxic insult to the liver, but current evidence suggests that fibrosis may be reversible in some patients with chronic hepatitis B after antiretroviral therapy.  

Any chronic insult to the liver can cause progression to cirrhosis. Although numerous pathophysiologic mechanisms of injury exist, the final common pathway is persistent wound healing resulting in hepatic parenchymal fibrosis. In most persons, approximately 80 to 90 percent of the liver parenchyma must be destroyed before liver failure is manifested clinically. When complications of cirrhosis occur, they typically are related to impaired hepatic function or actual physical disruption and reorganization of the liver parenchyma.  

Clinical Presentation

HISTORY

Cirrhosis often is a silent disease, with most patients remaining asymptomatic until decompensation occurs. Physicians should inquire about risk factors that predispose patients to cirrhosis (Figure 1). Quantity and duration of alcohol consumption is an important factor in the early diagnosis of cirrhosis. Other risk factors include those for hepatitis B and C transmission (e.g., birthplace in endemic areas, sexual history exposure risk, intranasal or intravenous drug use, body piercing or tattooing, accidental contamination with blood or body fluids), as well as transfusion history and personal or family history of autoimmune or hepatic diseases.  

Early and well-compensated cirrhosis can manifest as anorexia and weight loss, weakness, fatigue, and even osteoporosis as a result of vitamin D malabsorption and subsequent calcium deficiency. Decompensated disease can result in complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding from portal hypertension (discussed further in part II). Clinical symptoms at presentation may include jaundice of the eyes or skin, pruritus, gastrointestinal bleeding, coagulopathy, increasing abdominal girth, and mental status changes. Each of these clinical findings is the result of impaired hepatocellular function with or without physical obstruction secondary to cirrhosis. Because hepatic enzyme synthesis is required

Figure 2. Inferior surface of liver, biliary tree, and gallbladder (gross) revealing normal hepatic tissue and structure.

Figure 4A. Normal hepatic tissue (microscopic, 10X, trichrome stain).

Figure 3. Inferior surface of liver and gallbladder (gross) revealing cirrhotic liver.

Figure 4B. Cirrhosis (microscopic, 10X, trichrome stain).

Photographs courtesy of Henry D. Apelman, M.D., Professor, Department of Pathology, University of Michigan Medical School, Ann Arbor, Mich.
TABLE 1
Etiologies of Hepatic Cirrhosis

<table>
<thead>
<tr>
<th>Most common causes</th>
<th>Less common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (60 to 70 percent)</td>
<td>Autoimmune chronic hepatitis types 1, 2, and 3</td>
</tr>
<tr>
<td>Biliary obstruction (5 to 10 percent)</td>
<td>Drugs and toxins</td>
</tr>
<tr>
<td>Biliary atresia/neonatal hepatitis</td>
<td>Alpha-methylldopa (Aldomet)</td>
</tr>
<tr>
<td>Congenital biliary cysts</td>
<td>Amiodarone (Cordarone)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Isoniazid (INH)</td>
</tr>
<tr>
<td>Primary or secondary biliary cirrhosis</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Chronic hepatitis B or C (10 percent)</td>
<td>Oxaprenasin (Prulet)*</td>
</tr>
<tr>
<td>Hemochromatosis (5 to 10 percent)</td>
<td>Penflexamine*</td>
</tr>
<tr>
<td>NAFLD (10 percent)—most commonly resulting from obesity, also can occur after jejunoleal bypass</td>
<td>Troglitazone (Rezulin)*</td>
</tr>
<tr>
<td></td>
<td>Vitamin A</td>
</tr>
<tr>
<td>Genetic metabolic disease</td>
<td>Genetic metabolic disease</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>α1-Antitrypsin deficiency</td>
</tr>
<tr>
<td>Amino acid disorders (e.g., tyrosinemia)</td>
<td>Amino acid disorders (e.g., tyrosinemia)</td>
</tr>
<tr>
<td>Bile acid disorders</td>
<td>Bile acid disorders</td>
</tr>
<tr>
<td>Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycosogen storage diseases)</td>
<td>Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycosogen storage diseases)</td>
</tr>
<tr>
<td>Lipid disorders (e.g., abetalipoproteinemia)</td>
<td>Lipid disorders (e.g., abetalipoproteinemia)</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Porphyria</td>
</tr>
<tr>
<td>Urea cycle defects (e.g., ornithine carbamoyltransferase deficiency)</td>
<td>Urea cycle defects (e.g., ornithine carbamoyltransferase deficiency)</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Wilson's disease</td>
</tr>
<tr>
<td>Idiopathic/miscellaneous</td>
<td>Idiopathic liver disease (e.g., sarcoidosis)</td>
</tr>
<tr>
<td>Granulomatous liver disease</td>
<td>Idiopathic liver disease (e.g., sarcoidosis)</td>
</tr>
<tr>
<td>Indian childhood cirrhosis</td>
<td>Indian childhood cirrhosis</td>
</tr>
<tr>
<td>Polycystic liver disease</td>
<td>Polycystic liver disease</td>
</tr>
<tr>
<td>Infection</td>
<td>Infection</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Brucellosis</td>
</tr>
<tr>
<td>Congenital or tertiary syphilis</td>
<td>Congenital or tertiary syphilis</td>
</tr>
<tr>
<td>Echinococcosis</td>
<td>Echinococcosis</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>Vascular abnormalities</td>
</tr>
<tr>
<td>Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis</td>
<td>Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)</td>
<td>Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>Veno-occlusive disease</td>
</tr>
</tbody>
</table>

NAFLD = nonalcoholic fatty liver disease.
* = Not available in the United States.

Information from references 3 and 4.
Cirrhosis and Chronic Liver Failure—Part 1

Patients with numerous large vascular spiders are at increased risk for variceal hemorrhage. (shifting dullness) or whether it can be percussed anteriorly. One study found absence of flank dullness to be the most accurate predictor against the presence of ascites; the probability of ascites without flank dullness was less than 10 percent. Approximately 1,500 mL of fluid must be present before dullness is detected on physical examination, whereas routine ultrasonography can detect as little as 50 mL of fluid in the abdomen.

Vascular spiders (spider angiomata, spider telangiectasias) are vascular lesions usually found on the trunk, face, and upper extremities. Although their pathogenesis is incompletely understood, it is believed that their presence in men is associated with an increase in the estradiol to free testosterone ratio. Vascular spiders are not specific for cirrhosis: they also occur during pregnancy, in patients with severe malnutrition, and in healthy persons. The number and size of vascular spiders have been shown to correlate with the severity of chronic liver disease. Patients with numerous large vascular spiders are at increased risk for variceal hemorrhage.

Laboratory Evaluation

No serologic test can diagnose cirrhosis accurately. The term liver function tests is a misnomer because the assays in most standard liver panels do not reflect the function of the liver correctly. Although liver function tests may not correlate exactly with hepatic function, interpreting abnormal biochemical patterns in conjunction with the clinical picture may suggest certain liver diseases. When a liver abnormality is suspected or identified, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time test should be performed.

Common tests in standard liver panels include the serum enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and γ-glutamyltransferase; total, direct, and indirect serum bilirubin; and serum albumin. The ALT is thought to be the most cost-effective screening test for identifying metabolic or drug-induced hepatic injury, but like other liver function tests, it is of limited use in predicting degree of inflammation and of no use in estimating severity of fibrosis. One study found that a platelet count of less than 160 K per mm³ has a sensitivity of 80 percent for detecting cirrhosis in patients with chronic hepatitis C.

A prospective study showed a strong correlation between liver function test results elevated to greater than twice the upper limit of normal for at least six months and underlying liver disease proved by liver biopsy. Additional serologic studies should be pursued in such circumstances to evaluate for various etiologies of cirrhosis (Table 3). If clinical suspicion for liver disease is high, then further serologic work-up is warranted within six months. If a patient has a persistently increased ALT level, viral hepatitis serologies should be assayed. If these are negative, the remaining serologic work-up should include an antinuclear antibodies test or anti-smooth muscle antibody test, or both, to evaluate for autoimmune hepatitis; and a fasting transferrin saturation level or unsaturated iron-binding capacity and ferritin level to evaluate for hereditary hemochromatosis. In patients younger than 40 years in whom Wilson's disease is suspected, serum ceruloplasmin and copper levels should be measured, but screening all patients with chronic hepatic injury for Wilson's disease is not indicated.

Primary biliary cirrhosis or primary sclerosing cholangitis should be suspected in patients with chronic cholestasis. Testing for α1-antitrypsin (A1AT) deficiency may be of benefit in patients with chronic hepatic injury and no other apparent cause. Although the role of A1AT deficiency in liver disease in adults is not clearly defined, testing is especially important in neonates with evidence of hepatic injury. Ultrasonography or biopsy is necessary to establish the diagnosis of NAFLD.

Radiographic Studies

Although various radiographic studies may suggest the presence of cirrhosis, no test is considered a diagnostic standard. The major use of radiographic studies is to detect ascites, hepatosplenomegaly, hepatic or portal vein thromboses, and hepatocellular carcinoma, all of which strongly suggest cirrhosis.

ULTRASONOGRAPHY

Abdominal ultrasonography with Doppler is a noninvasive, widely available modality that provides valuable information regarding the gross appearance of the liver and blood flow in the portal and hepatic veins in patients suspected to have cirrhosis. Ultrasonography should be the first radiographic study performed in the evaluation of cirrhosis because it is the least expensive and does not pose a radiation exposure risk or involve intravenous contrast with the potential for nephrotoxicity as does computed tomography (CT). Nodularity, irregularity, increased echogenicity, and atrophy are ultrasonographic hallmarks of cirrhosis. In advanced disease, the gross liver appears small and multinodular, ascites may be
TABLE 3
Clinical Laboratory Studies Used in Diagnosing Chronic Liver Disease

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Laboratory tests and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>AST:ALT ratio &gt; 2*</td>
</tr>
<tr>
<td></td>
<td>Elevated GGT</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>Decreased serum α1-antitrypsin</td>
</tr>
<tr>
<td></td>
<td>Genetic screening recommended in equivocal cases</td>
</tr>
<tr>
<td>Autoimmune hepatitis (type 1)</td>
<td>Positive ANA and/or ASMA in high titer</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>Positive HBsAg and HBeAg qualitative assays</td>
</tr>
<tr>
<td></td>
<td>Once HBeAg is negative and HBeAb is positive, HBsAg should be monitored periodically to</td>
</tr>
<tr>
<td></td>
<td>determine viral clearance</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B virus DNA quantification used to document viral clearance</td>
</tr>
<tr>
<td></td>
<td>Elevated AST and/or ALT*</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>Positive hepatitis C virus antibody qualitative assay</td>
</tr>
<tr>
<td></td>
<td>HCV RNA quantification used to document viral clearance</td>
</tr>
<tr>
<td></td>
<td>HCV viral genotype to determine potential response to antiretroviral therapy</td>
</tr>
<tr>
<td></td>
<td>Elevated AST and/or ALT*</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Elevated alpha fetoprotein, AST, and/or ALT*</td>
</tr>
<tr>
<td></td>
<td>Elevated ALP with obstruction or cholestasis</td>
</tr>
<tr>
<td>Hereditary hemochromatosis</td>
<td>Elevated fasting transferrin saturation, unsaturated iron-binding capacity, or ferritin. A</td>
</tr>
<tr>
<td></td>
<td>transferrin saturation ≥45 percent or an unsaturated iron-binding capacity 155 mcg per dl.</td>
</tr>
<tr>
<td></td>
<td>(27.7 μmol per L) should be followed by analysis for HFE (hemochromatosis) gene mutations.</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>Elevated AST and/or ALT*</td>
</tr>
<tr>
<td>Primary biliary cirrhosis and</td>
<td>Ultrasonography or biopsy necessary to establish diagnosis.</td>
</tr>
<tr>
<td>primary sclerosing cholangitis</td>
<td>Diagnosis made via contrast cholangiography, can be supported clinically by positive</td>
</tr>
<tr>
<td></td>
<td>antimitochondrial antibody (primary biliary cirrhosis) or antineutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td></td>
<td>(primary sclerosing cholangitis) in high titters.</td>
</tr>
<tr>
<td></td>
<td>Elevated AST, ALT, and ALP common</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Serum ceruloplasmin &lt; 20 mg per dl. (200 mg per L) (normal: 20 to 60 mg per dl. (200 to 600</td>
</tr>
<tr>
<td></td>
<td>mg per L), or low serum copper level (normal: 80 to 160 mg per dl. [12.6 to 25.1 μmol per L]</td>
</tr>
<tr>
<td></td>
<td>Basal 24-hour urinary copper excretion &gt; 100 mcg (1.57 μmol/L; normal: 10 to 80 mcg</td>
</tr>
<tr>
<td></td>
<td>[0.16 to 1.26 μmol/L])</td>
</tr>
<tr>
<td></td>
<td>Genetic screening recommended in equivocal cases, but must be able to detect multiple</td>
</tr>
<tr>
<td></td>
<td>mutations in Wilson’s disease gene.</td>
</tr>
</tbody>
</table>

AST = aspartate transaminase; ALT = alanine transaminase; GGT = γ-glutamyltransferase; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBeAb = hepatitis B e antibody; HCV = hepatitis C virus; ALP = alkaline phosphatase.

*—AST and ALT levels may be normal in advanced disease.

Information from references 14, 15, 18, and 19.

detected, and Doppler flow can be significantly decreased in the portal circulation. The discovery of hepatic nodules via ultrasonography warrants further evaluation because benign and malignant nodules can have similar ultrasonographic appearances. A study using high-resolution ultrasonography in patients with cirrhosis confirmed with biopsy or laparoscopy found a sensitivity and specificity for cirrhosis of 91.1 and 93.5 percent, respectively, and positive and negative predictive values of 93.2 and 91.5 percent, respectively.

CT AND MRI
CT and magnetic resonance imaging (MRI) generally are poor at detecting morphologic changes associated with early cirrhosis, but they can accurately demonstrate nodularity and lobar atrophic and hypertrophic changes, as well as ascites and varices in advanced disease. Although MRI sometimes differentiates among regenerating or dysplastic nodules and hepatocellular carcinoma, it is best used as a follow-up study to determine whether lesions have changed in appearance and size. CT portal phase imaging can be used to assess portal vein patency, although flow volume and direction cannot be determined accurately.

Although used rarely, magnetic resonance angiography (MRA) can assess portal hypertensive changes including flow volume and direction, as well as portal vein thrombosis. One study reported that MRI can accurately
Cirrhosis and Chronic Liver Failure—Part I

diagnose cirrhosis and provide correlation with its severity. Despite the potential of MRI and MRA in the diagnosis and evaluation of patients with cirrhosis, their widespread use is limited by their expense and by the ability of routine ultrasonography with Doppler to obtain adequate information for the diagnosis of cirrhosis and presence of complications.

Liver Biopsy

Referral for liver biopsy should be considered after a thorough, noninvasive serologic and radiographic evaluation has failed to confirm a diagnosis of cirrhosis; the benefit of biopsy outweighs the risk; and it is postulated that biopsy will have a favorable impact on the treatment of chronic liver disease. The sensitivity and specificity for an accurate diagnosis of cirrhosis and its etiology range from 80 to 100 percent, depending on the number and size of the histologic samples and on the sampling method.

Liver biopsy is performed via percutaneous, transjugular, laparoscopic, open operative, or ultrasonography- or CT-guided fine-needle approaches. Before the procedure, a CBC with platelets and prothrombin time measurement should be obtained. Patients should be advised to refrain from consumption of aspirin and nonsteroidal anti-inflammatory drugs for seven to 10 days before the biopsy to minimize the risk of bleeding.

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Author disclosure: Nothing to disclose.

REFERENCES


Cirrhosis and Chronic Liver Failure:
Part II. Complications and Treatment

JOEL J. HEIDELBAUGH, M.D., and MARYANN SHERBONDY, M.D.
University of Michigan Medical School, Ann Arbor, Michigan

Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding, and hepatorenal syndrome. Diagnostic studies on ascitic fluid should include a differential leukocyte count, total protein level, a serum-ascites albumin gradient, and fluid cultures. Therapy consists of sodium restriction, diuretics, and complete abstention from alcohol. Patients with ascitic fluid polymorphonuclear leukocyte counts of 250 cells per mm³ or greater should receive empiric prophylaxis against spontaneous bacterial peritonitis with cefotaxime and albumin. Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole. Patients with gastrointestinal hemorrhage and cirrhosis should receive norfloxacin or trimethoprim/sulfamethoxazole twice daily for seven days. Treatment of hepatic encephalopathy is directed toward improving mental status levels with lactulose; protein restriction is no longer recommended. Patients with cirrhosis and evidence of gastrointestinal bleeding should undergo upper endoscopy to evaluate for varices. Endoscopic banding is the standard treatment, but sclerotherapy with vasoconstrictors (e.g., octreotide) also may be used. Prophylaxis with propranolol is recommended in patients with cirrhosis once varices have been identified. Transjugular intrahepatic portosystemic shunt has been effective in reducing portal hypertension and improving symptoms of hepatorenal syndrome, and can reduce gastrointestinal bleeding in patients with refractory variceal hemorrhage. When medical therapy for treatment of cirrhosis has failed, liver transplantation should be considered. Survival rates in transplant recipients have improved as a result of advances in immunosuppression and proper risk stratification using the Model for End-Stage Liver Disease and Child-Turcotte-Pugh scoring systems. (Am Fam Physician 2006;74:767-76, 781. Copyright © 2006 American Academy of Family Physicians.)

Part I of this two-part series outlines the diagnosis and evaluation of cirrhosis and chronic liver failure. This article, part II, discusses complications and treatment. Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding, and hepatorenal syndrome.

Ascites

Ascites is defined as the pathologic accumulation of fluid in the peritoneal cavity. Approximately 85 percent of patients with ascites have cirrhosis, and the remaining 15 percent have a nonhepatic cause of fluid retention. The American Association for the Study of Liver Diseases recommends a diagnostic abdominal paracentesis be performed and ascitic fluid obtained from patients with clinically evident ascites. Paracentesis with ascitic fluid culture in blood culture bottles should be performed before the initiation of antibiotics to determine a true infection.

The initial laboratory investigation of ascitic fluid should include a differential leukocyte count, a total protein level, and a serum-ascites albumin gradient (SAAG). The SAAG is a useful prognosticator of portal pressure; it is calculated by subtracting the ascitic albumin concentration from the serum albumin concentration obtained on the same day. If the SAAG is 1.1 g per dL (11 g per L) or greater, there is a high likelihood of portal hypertension; if it is less than 1.1 g per dL, other causes of ascites should be explored, including peritoneal carcinomatosis, tuberculous peritonitis, and pancreatic ascites (Figure 1). The ascitic fluid total protein level typically has been used in defining ascitic fluid as transudative (protein content less than 2.5 g per dL [25 g per L]) or exudative (protein content of 2.5 g per dL or greater) and to help identify patients at higher risk of developing spontaneous bacterial peritonitis. However, this method is flawed because many patients with spontaneous bacterial peritonitis, in which ascitic fluid is infected, have a low rather
Cirrhosis and Chronic Liver Failure—Part II

than high ascitic fluid total protein level, and many fluid samples from patients with portal hypertension secondary to heart failure have a high rather than the expected low ascitic fluid total protein level.6

First-line treatment of patients with cirrhotic ascites consists of sodium restriction (i.e., no more than 2,000 mg per day) and diuretics (e.g., oral spironolactone [Aldactone], furosemide [Lasix]), as well as complete

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**Figure 1.** Algorithm for the differential diagnosis of ascites. (WBC = white blood cell; RBC = red blood cell; PMNL = polymorphonuclear leukocyte; TP = total protein; LDH = lactate dehydrogenase; CT = computed tomography.)

abstention from alcohol (Table 1). Fluid restriction is unnecessary unless serum sodium is less than 120 to 125 mEq per L (120 to 125 mmol per L). Patients who are sensitive to diuretics should be treated with sodium restriction and oral diuretics rather than with serial paracenteses, unless the ascites is refractory to these therapies or infection is suspected. Postparacentesis albumin infusion is unnecessary for a single paracentesis of less than 4 to 5 L, but for large-volume paracenteses, an albumin infusion of 8 to 10 g per liter of fluid removed can be considered. Referral for liver transplantation should be expedited for patients with refractory ascites. Transjugular intrahepatic portosystemic shunt (TIPS) should be considered in patients with refractory ascites who may require a transplant, whereas a peritoneovenous shunt should be considered in patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.

Spontaneous Bacterial Peritonitis
Patients with ascitic fluid polymorphonuclear leukocyte (PMNL) counts of 250 cells per mm³ or greater should receive empiric antibiotic therapy (e.g., cefotaxime [Claforan] 2 g intravenously every eight hours) and albumin (1.5 g per kg body weight within six hours of detection and 1 g per kg on day 3) to prevent spontaneous bacterial peritonitis (Table 1). Oral ofloxacin (Floxin; 400 mg twice daily) is an alternative to intravenous medications in patients without vomiting, shock, severe hepatic encephalopathy, or a creatinine level greater than 3 mg per dL (265 μmol per L). Patients with ascitic fluid PMNL counts less than 250 cells per mm³ and signs and symptoms of infection should receive empiric antibiotic therapy while awaiting culture results. Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with norfloxacin (Noroxin) or trimethoprim/sulfamethoxazole (Bactrim, Septra). Patients with gastrointestinal hemorrhage and cirrhosis should receive norfloxacin or trimethoprim/sulfamethoxazole twice daily for seven days (the drug is then discontinued).2

Hepatic Encephalopathy
Hepatic (portosystemic) encephalopathy represents a potentially reversible decrease in neuropsychiatric function caused by acute and chronic liver disease, occurring predominantly in patients with portal hypertension. The onset often is insidious and is characterized by subtle and sometimes intermittent changes in memory, personality, concentration, and reaction times. Hepatic encephalopathy is a diagnosis of exclusion; therefore, all other etiologies of altered mental status must be effectively ruled out. Treatment goals for hepatic encephalopathy include provision of supportive care, identification and removal of precipitating factors, reduction in the nitrogenous...
Cirrhosis and Chronic Liver Failure—Part II

**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment of patients with cirrhotic ascites consists of sodium restriction (i.e., no more than 2,000 mg per day) and diuretics (e.g., oral spironolactone [Aldactone] and furosemide [Lasix]), as well as complete abstinence from alcohol.</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>TIPS should be considered in patients with refractory ascites who may require a transplant, whereas a portacaval shunt should be considered in patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>Patients with ascitic fluid polymorphonuclear leukocyte counts of 250 cells per mm³ or greater should receive empiric antibiotic therapy (e.g., cefotaxime [Claforan] 2 g intravenously every eight hours) and albumin (1.5 g per kg body weight within six hours of detection and 1 g per kg on day 3) to prevent spontaneous bacterial peritonitis.</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term antibiotic prophylaxis with norfloxacin (Noroxin) or trimethoprim/sulfamethoxazole (Bactrim, Septra). Patients with gastrointestinal hemorrhage and cirrhosis should receive norfloxacin or trimethoprim/sulfamethoxazole twice daily for seven days.</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>Propranolol (Inderal) at a dosage of 40 mg twice daily is recommended for pharmacologic prophylaxis of variceal bleeding, increasing to 80 mg twice daily if necessary or a dosage titrated to a 25 percent reduction in pulse rate.</td>
<td>B</td>
<td>9, 15, 16</td>
</tr>
<tr>
<td>An early referral to a transplant subspecialist is recommended for potential transplant recipients to allow time for patients, referring physicians, and transplant centers to meet and identify any potential problems.</td>
<td>C</td>
<td>28</td>
</tr>
</tbody>
</table>

TIPS = transjugular intrahepatic portosystemic shunt.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 699 or http://www.aafp.org/afpsort.xml.

load from the gut, and optimization of long-term therapy (Table 2). Therapy should be directed toward improving mental status via bowel cleansing with lactulose orally or with enemas (Table 13-19). One randomized trial demonstrated that diets with normal protein content can be followed safely during episodic hepatic encephalopathy caused by cirrhosis, and that protein restriction has no beneficial effect during such episodes. In patients who are refractory to lactulose alone, neomycin can be added.

Increases in the ratio of plasma aromatic amino acids to branched-chain amino acids as a consequence of hepatic insufficiency also may contribute to encephalopathy. One meta-analysis suggested that mental recovery was consistently more rapid in patients whose treatment included a branched-chain amino acid infusion; three studies found lower mortality rates in patients who received this treatment, and two others suggested that the treatment increased mortality.

Another physiologic theory of hepatic encephalopathy is that endogenous benzodiazepines may bind to γ-aminobutyric acid receptors and exert neuroinhibitory effects. Use of the benzodiazepine receptor antagonists flumazenil (Romazicon) may improve mental status transiently, whereas bromocriptine (Parlodol) may improve extrapyramidal symptoms. No formal recommendation for the routine use of any of these agents has been suggested.

**Portal Hypertension and Variceal Bleeding**

Regardless of the etiology of cirrhosis, the development of portal hypertension is nearly universal and results from an increased resistance to portal flow secondary to scarring, narrowing, and compression of the hepatic sinusoids. When the portal pressure exceeds a certain threshold, it results in the development of varices. Approximately 50 percent of patients with cirrhosis develop varices, most commonly in the distal 2 to 5 cm of the esophagus. Variceal hemorrhage is defined as bleeding from an esophageal or gastric varix at the time of endoscopy, or the presence of large esophageal varices with blood in the stomach and no other recognizable source of bleeding. The rate of variceal bleeding is approximately 10 to 30 percent per year.

The British Society of Gastroenterology guidelines for the management of variceal hemorrhage recommend...
### TABLE 1
Treatment of Complications of Cirrhosis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Treatment</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Sodium restriction</td>
<td>Maximum 2,000 mg per day²</td>
</tr>
<tr>
<td></td>
<td>Spironolactone (Aldactone)</td>
<td>Start 100 mg orally per day; maximum 400 mg orally per day²</td>
</tr>
<tr>
<td></td>
<td>Furosemide (Lasix)</td>
<td>Start 40 mg orally per day; maximum 160 mg orally per day³</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>8 to 10 g/IV per liter of fluid (if greater than 5 L) removed for paracenteses³</td>
</tr>
<tr>
<td></td>
<td>Fluid restriction</td>
<td>Recommended if serum sodium is less than 120 to 125 mEq per L (120 to 125 mmol per L)³</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis†</td>
<td>Cefotaxime (Claforan)</td>
<td>2 g IV every eight hours³</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>1.5 g per kg IV within six hours of detection and 1 g per kg IV on day ³</td>
</tr>
<tr>
<td></td>
<td>Norfloxac (Noroxin)†</td>
<td>400 mg orally two times per day for treatment³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg orally two times per day for seven days with gastrointestinal hemorrhage³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg orally per day for prophylaxis³</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/sulfamethoxazole</td>
<td>1 single-strength tablet orally per day for prophylaxis³</td>
</tr>
<tr>
<td></td>
<td>(Bactrim, Septra)†</td>
<td>1 single-strength tablet orally two times per day for seven days with gastrointestinal hemorrhage³</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>Lactulose</td>
<td>30 to 45 ml syrup orally titrated up to three or four times per day or 300 mL retention enema until two to four bowel movements per day and mental status improvement³</td>
</tr>
<tr>
<td></td>
<td>Neomycin</td>
<td>4 to 12 g orally per day divided every six to eight hours; can be added to lactulose in patients who are refractory to lactulose alone³</td>
</tr>
<tr>
<td>Portal hypertension and variceal bleeding</td>
<td>Propranolol (Inderal)</td>
<td>40 to 80 mg orally two times per day⁹</td>
</tr>
<tr>
<td></td>
<td>Isosorbide mononitrate (Ismo)</td>
<td>20 mg orally two times per day⁹</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>Midodrine (ProAmatine) and octreotide (Sandostatin)</td>
<td>Dosed orally (midodrine) and IV (octreotide) to obtain a stable increase of at least 15 mm Hg mean arterial pressure¹⁰</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>2 to 4 mcg per kg per minute IV (nonpressor dosing to produce renal vasodilation)¹⁰</td>
</tr>
</tbody>
</table>

IV = Intravenously; PMNl = polymorphonuclear leukocyte.

*—Patients with ascites fluid PMNl counts greater than or equal to 250 cells per mm³ should receive empiric antibiotic therapy; patients with ascites fluid PMNl counts less than 250 cells per mm³ and signs and symptoms of infection should receive empiric antibiotic therapy while awaiting culture results.
†—Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with norfloxac or trimethoprim/sulfamethoxazole.

Information from references 3 and 7 through 10.

that patients with cirrhosis who present with evidence of upper gastrointestinal bleeding undergo an urgent upper endoscopic evaluation (Figure 2).⁸ If no varices are observed, these patients should have repeat endoscopy at three-year intervals. If small varices are diagnosed, patients should have repeat surveillance at one-year intervals. Primary prophylaxis of variceal bleeding is aimed at reducing the portal pressure gradient, azygous blood flow, and variceal pressure. These guidelines also suggest that the most effective pharmacotherapy is propranolol (Inderal) at a dosage of 40 mg twice daily, increasing to 80 mg twice daily if necessary (Table 1³⁵⁻⁷⁻⁶⁻¹⁰).⁹ If propranolol is contraindicated or not tolerated, isosorbide mononitrate (Ismo) at a dosage of 20 mg twice daily is the treatment of choice.⁹ Studies conducted since these guidelines have titrated the dosage of propranolol based on a reduction of the pulse rate by 25 percent.¹⁵,¹⁶

The goals of treatment in acute variceal bleeding include hemodynamic resuscitation, treatment of active bleeding, and prevention of rebleeding. Band ligation is the standard for the control of variceal bleeding.⁹ If banding is difficult because of continued variceal bleeding, endoscopic sclerotherapy with vasoconstrictors (e.g., octreotide [Sandostatin]) or a Sengstaken-Blakemore tube insertion (with adequate airway protection) may be
Cirrhosis and Chronic Liver Failure—Part II

Hepatic encephalopathy is a diagnosis of exclusion; therefore, all other etiologies of altered mental status must be effectively ruled out.

Banding ligation in reducing variceal bleeding, but it is associated with a higher risk of encephalopathy. This treatment option should be performed in medical centers with particular expertise. TIPS has been shown to reduce portal hypertension and can be effective in converting patients with diuretic-resistant ascites to diuretic-sensitive ascites, as well as reducing gastrointestinal bleeding in patients with refractory variceal hemorrhage. Evidence regarding whether or not TIPS improves survival is conflicting. Compared with large-volume paracentesis plus albumin, TIPS improves survival without liver transplantation in patients with refractory or recidivant ascites.

After the cessation of active variceal hemorrhage, the subsequent six weeks carry a high risk of recurrent hemorrhage. The greatest risk of rebleeding is within the first 48 to 72 hours, with more than 50 percent of episodes occurring within the first 10 days. Risk factors for early rebleeding include age older than 60 years, renal failure, large varices, and severe initial bleeding (i.e., hemoglobin less than 8 g per dL [80 g per L] at admission). A retrospective study showed that in-hospital mortality of patients with cirrhosis and variceal bleeding decreased from 43 percent in 1980 to 15 percent in 2000, in concurrence with an early and combined use of pharmacologic and endoscopic therapies and short-term antibiotic prophylaxis.

Hepatorenal Syndrome

Hepatorenal syndrome is defined as functional renal failure in cirrhotic patients in the absence of intrinsic renal disease. It is characterized by sodium and water retention in patients with renal vasoconstriction, resulting in decreased renal blood flow, glomerular filtration rate, and urinary output, which contribute to azotemia (Table 3). One prospective study of 229 patients with cirrhosis and ascites who did not have azotemia found an incidence of hepatorenal syndrome of 18 percent after one year and 39 percent after five years. The pathogenesis of hepatorenal syndrome is not completely understood, but it is likely the result of an extreme underfilling of the arterial circulation secondary to arterial vasodilatation in the splanchnic circulation. Although hepatorenal syndrome can occur with most forms of severe hepatic disease, patients with primary biliary cirrhosis appear to be relatively protected.

The International Ascites Club consensus conference on hepatorenal syndrome defined diagnostic criteria that distinguish between two types of hepatorenal syndrome. Type 1 hepatorenal syndrome is defined as a rapid deterioration of renal function indicated by a two-fold increase of serum creatinine to values above 2.5 mg per dL (221 µmol per L), or a decrease of creatinine clearance to values below 20 mL per minute (0.33 mL per second). This form of hepatorenal syndrome usually is precipitated by spontaneous bacterial peritonitis and occurs in approximately 25 percent of patients with spontaneous bacterial peritonitis, even with the clearance of infection. The median survival duration of these patients is less than two weeks without treatment, and almost all patients die within 10 weeks after the onset of renal failure. Patients with type 2 hepatorenal syndrome exhibit moderately increased serum creatinine levels above 1.5 mg per dL (133 µmol per L) that remain

---

TABLE 2

Treatment of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Identify and correct the precipitating causes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Assess vital signs and volume status</td>
</tr>
<tr>
<td>2. Evaluate for gastrointestinal bleeding</td>
</tr>
<tr>
<td>3. Eliminate sedatives or tranquilizers</td>
</tr>
<tr>
<td>4. Screen for hypoxia, hypoglycemia, anemia, hypokalemia, metabolic alkalosis, and other potential metabolic or endocrine factors; correct as indicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initiate ammonia-lowering therapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use nasogastric lavage, lactulose, and/or other cathartics or enemas to remove source of ammonia from colon</td>
</tr>
<tr>
<td>2. Initiate treatment with lactulose or lactitol to produce two to four bowel movements per day</td>
</tr>
<tr>
<td>3. Consider oral nonabsorbable antibiotics to reduce intestinal bacterial counts</td>
</tr>
<tr>
<td>4. Consider treatment with flumazenil (Romazicon) or another benzodiazepine receptor antagonist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimize potential complications of cirrhosis and depressed consciousness:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Provide supportive care with attention to airway, hemodynamic, and metabolic statuses</td>
</tr>
</tbody>
</table>

Management of Variceal Hemorrhage

**Figure 2. Algorithm for the management of variceal hemorrhage. (GI = gastrointestinal; TIPS = transjugular intrahepatic portosystemic shunt.)**


Stable over a longer period, and ascites that generally is resistant to diuretics. The median survival duration in these patients is three to six months.24

Hemodialysis is often used to control azotemia in hepatorenal syndrome and to correct electrolyte imbalances. Nonsteroidal anti-inflammatory drugs and potentially nephrotoxic medications should be avoided. One controlled trial demonstrated a substantial improvement in renal plasma flow, glomerular filtration rate, and urinary sodium excretion in patients with type 1 hepatorenal syndrome after 20 days of treatment with oral midodrine (ProAmatine) and parenteral octreotide compared with the use of nonpressor dose dopamine (Table 1). These therapies also appear to improve survival rates and may serve as a bridge to liver transplantation. In the future, endothelins, adenosine antagonists, long-acting vasoconstrictors, and antileukotriene antagonists may play a role in preventing and treating hepatorenal syndrome.25

Liver Transplantation

When standard medical and procedural therapy has failed to control the complications of cirrhosis, liver transplantation should be considered. Unnecessary surgical procedures should be avoided and risks versus benefits weighed before any surgical procedure is performed in patients with cirrhosis. Since the first successful liver transplant in 1967, there has been a growing disparity between the number of potential candidates and the number of donors. This disparity is attributed to a sixfold increase in patients on the transplant waiting list from 1991 to 2001 and a much slower rate of increase in the donor pool. A total of 6,169 liver transplants were performed in the United States in 2004; the current

Hepatorenal syndrome is defined as functional renal failure in cirrhotic patients in the absence of intrinsic renal disease.
TABLE 3
Diagnostic Criteria for Hepatorenal Syndrome

Major criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension
Low glomerular filtration rate, indicated by serum creatinine level > 1.5 mg per dl (130 μmol per l) or creatinine clearance < 40 mL per minute (0.67 mL per second)
Absence of treatment with nephrotoxic drugs, shock, infection, or significant recent fluid losses
No sustained improvement in renal function after diuretic withdrawal and volume expansion with 1.5 L isotonic saline
Proteinuria < 0.5 g per dl (5 g per l) and no ultrasonographic evidence of obstruction or parenchymal renal disease

Additional criteria
Urine volume < 500 mL per day
Urine sodium < 10 mEq per l (10 mmol per l)
Urine osmolality greater than plasma osmolality
Urine red blood cells < 50 per high-power field
Serum sodium concentration < 130 mEq per l (130 mmol per l)


The waiting list includes about 17,900 candidates. Survival rates have improved markedly since the first transplant as a result of substantial improvements in immunosuppression and medical and surgical care experience. For liver transplants performed in the United States from 1996 to 2001, survival rates after one, three, and five years were 87.6, 79.9, and 74.5 percent, respectively.

![Figure 3. Estimated three-month survival as a function of the MELD score. (MELD = model for end-stage liver disease; INR = International Normalized Ratio).](image)


The Clinical Practice Committee of the American Society of Transplantation suggests patients should be referred early to a transplant subspecialist to allow time for the patient, family, referring physician, and transplant center to meet and identify any potential problems. Transplant care is best provided by a team of health care professionals including a hepatologist, a surgeon, a psychiatrist, and a social worker. In addition to a standard medical evaluation, the initial assessment of a possible transplant recipient should incorporate education highlighting the risks and benefits of organ transplantation, including the potential for poor outcomes (i.e., organ rejection), and standard post-transplant care.

The statistical model for end-stage liver disease (MELD) predicts survival in patients with cirrhosis and has been adopted for routine use in the timing and allocation of transplantation (Figure 3). This system is an objective model based on the relationships among serum bilirubin, serum creatinine, and International Normalized Ratio values. The MELD score can be used as an accurate predictor of three-month mortality: a score of 40 out of 50 correlates to a three-month survival rate of less than 20 percent.

INDICATIONS
Potential candidates for liver transplantation include any patient with documented fulminant hepatic failure, decompensated cirrhosis (including hepatorenal syndrome), or a hepatocellular carcinoma with no single lesion greater than 5 cm or no more than three lesions with the largest being 3 cm or smaller. Fulminant hepatic failure is a rare syndrome that arises from the loss of hepatic parenchymal function accompanied by encephalopathy and coma in patients who have had liver disease for less than eight weeks.

The Child-Turcotte-Pugh (CTP) scoring classification, originally devised to risk-stratify patients undergoing shunt surgery for portal decompression, is a useful system to assess liver disease severity in patients with established cirrhosis (Table 4). In a retrospective study involving 92 patients with cirrhosis who underwent abdominal surgery, the mortality rate was 10 percent for patients with CTP grade A disease, 30 percent for those with grade B, and 82 percent for those with grade C. The CTP classification also correlates with the frequency.

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of postoperative complications including renal failure, hepatic encephalopathy, bleeding, infection, intractable ascites, and worsening liver failure.32

CONTRAINDICATIONS

Absolute contraindications to liver transplantation encompass clinical scenarios in which the expected outcome of transplantation is so poor that the procedure should not be considered. Examples include multisystem organ failure, extrahepatic or extrabiliary malignancy or infection, advanced cardiac or pulmonary disease, human immunodeficiency virus infection, and active alcohol or illicit substance abuse.34

Relative contraindications include comorbidities that have a potential to reduce survival but that allow for the option of transplantation. Examples include renal insufficiency, a primary hepatobiliary malignancy greater than 5 cm, hemochromatosis, spontaneous bacterial peritonitis, age older than 65 years, poor social support, and the inability to comply with an immuno-suppression protocol.34

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Author disclosure: Nothing to disclose.

REFERENCES

Cirrhosis and Chronic Liver Failure—Part II


MECHANISMS OF DISEASE

The Coagulopathy of Chronic Liver Disease

Armando Tripodi, Ph.D., and Pier Vanniatto Manucci, M.D.

CHRONIC LIVER DISEASE, PARTICULARLY IN THE END STAGE, IS CHARACTERIZED by clinical bleeding and decreased levels of most procoagulant factors, with the notable exceptions of factor VIII and von Willebrand factor, which are elevated. Decreased levels of the procoagulants are, however, accompanied by decreases in levels of such naturally occurring anticoagulants as antithrombin and protein C. In physiologic conditions, the coagulation system is balanced by these two opposing drivers (Fig. 1), but the mechanistic significance of the parallel decrease of both procoagulants and anticoagulants in patients with chronic liver disease escaped attention for many years. As a consequence, chronic liver disease is still considered the epitome of acquired bleeding disorders and is featured as such in most hematology textbooks. The basic laboratory tests of coagulation (i.e., measurement of the prothrombin time and activated partial-thromboplastin time) have been used to assess the risk of bleeding.

However, their results are poorly correlated with the onset and duration of bleeding after liver biopsy or other potentially hemorrhagic procedures. These test results are also poorly correlated with the occurrence of gastrointestinal bleeding, the prototype of hemorrhagic events in patients with end-stage liver disease. Additional evidence that argues against the clinical relevance of the coagulation defects as detected by conventional laboratory tests in determining the bleeding tendency in these patients can be drawn from the natural history of liver transplantation. In the past, this major surgical procedure required massive transfusions of plasma and other blood products to correct the marked abnormalities on tests of hemostasis (assessments of coagulation, platelets, and fibrinolysis) observed both preoperatively and perioperatively. The need for transfusions, however, has declined considerably over time — not because of any substantial change in medication, but rather because of improved surgical procedures. Finally and most important, randomized clinical trials involving patients with chronic liver disease have shown that powerful procoagulant agents, such as recombinant activated factor VII, fail to control bleeding from the upper intestinal tract or bleeding during liver transplantation, even though the postinfusion prothrombin time is considerably shortened. In this review, we consider the evidence regarding the balance in the hemostatic system (involving coagulation, platelets, and fibrinolysis).

THE HEMOSTATIC SYSTEM IN CHRONIC LIVER DISEASE

COAGULATION

The aforementioned observations question the validity of the prothrombin-time test and related tests for assessing the risk of hemorrhage and guiding the transfusion of fresh-frozen plasma or use of procoagulant agents in patients with chronic liver disease. An old dogma is being dispelled in favor of the newly emerging concept that
blood coagulation in such patients is rebalanced, owing to the parallel reduction of procoagulant and anticoagulant factors (Table 1). Indeed, studies show that plasma from patients with cirrhosis generates as much thrombin (the final enzyme of coagulation) as plasma from healthy subjects, provided that thrombin is measured by methods that reflect the action of both procoagulants and anticoagulants.\textsuperscript{23,24} Thrombin generation in vivo and in vitro is down-regulated by thrombomodulin, a transmembrane protein situated on vascular endothelial cells that acts as the main physiologic activator of protein C (Fig. 2).\textsuperscript{25} Plasma and reagents that are used to measure the prothrombin time do not contain thrombomodulin. Accordingly, this test measures the amount of thrombin generated in plasma as a function of the procoagulant drivers, but not the thrombin inhibited by the anticoagulant drivers, especially protein C, which is not fully activated in the absence of thrombomodulin. This might explain why the prothrombin-time test and related tests do not truly represent the balance of coagulation in vivo and are inadequate for assessing the risk of hemorrhage in those acquired conditions, such as the coagulopathies of liver disease and neonatal coagulopathies, in which there is a restored balance due to the concomitant decrease of procoagulants and anticoagulants.\textsuperscript{26}

As for end-stage liver disease, another problem is that the prothrombin time expressed as the international normalized ratio (INR) is widely used as a prognostic index to calculate the patient's Model for End-Stage Liver Disease (MELD) score, which is used to prioritize candidates for liver transplantation. However, the INR was devised and validated to standardize across laboratories the prothrombin times in patients receiving anti-coagulation therapy with vitamin K antagonists such as warfarin and its congeners. The INR cannot be used for patients with chronic liver disease unless an alternative system of standardization specifically developed for them is adopted.\textsuperscript{27} This alternative system involves using a different calibration based on plasma from patients with chronic liver disease rather than plasma from patients receiving vitamin K antagonists.

Together, the above observations indicate that the bleeding tendency frequently observed in patients with end-stage liver disease should be explained by mechanisms other than hypocoagulability, such as those triggered by underlying conditions that favor hemorrhage (i.e., hemodynamic alterations subsequent to portal hypertension, endothelial dysfunction, bacterial infections, and renal failure\textsuperscript{28-31}) (Table 2). It should also be understood that although rebalanced, the coagulation system in patients with chronic liver disease is not as stable as that in healthy persons, who have an excess of both procoagulants and anticoagulants. Therefore, the relative deficiency of both coagulation-system drivers makes the balance fragile in patients with liver disease and may tip it toward hemorrhage or thrombosis, depending on the prevailing circumstantial risk factors (Fig. 2C).

**PLATELETS**

Under normal conditions, platelets have a dual function. They adhere to damaged vessel walls through an interaction with the multimeric adhesive protein von Willebrand factor, thus promoting aggregation and ultimately the formation of the primary hemostatic plug. Platelets also support thrombin generation by assembling activated coagulation factors on their surfaces. Thrombocytopenia, a typical feature of chronic liver disease,\textsuperscript{17} may therefore be another cause of bleeding (Table 1). However, very high levels of von Willebrand factor, a common finding in patients with chronic liver disease, may restore platelet adhesion to the subendothelium at sites of vascular injury (Table 1), as shown by in vitro experiments carried out under flow conditions mimicking those that occur in vivo.\textsuperscript{15} Levels of ADAMTS 13, a naturally occurring plasma metalloprotease that limits in vivo the functions of von Willebrand factor on platelets, are reduced in patients with cirrhosis\textsuperscript{16}; this may further contribute to the restoration of platelet function (Table 1). Finally, a platelet count as low as $60 \times 10^9$ per liter in platelet-rich plasma from patients with cirrhosis is usually sufficient to preserve thrombin generation at a level equivalent to the lower limit of the normal range in healthy subjects.\textsuperscript{26}
Table 1. Patterns of Prohemostatic and Antihemostatic Drivers in the Different Phases of Hemostasis in Patients with Chronic Liver Disease.

<table>
<thead>
<tr>
<th>Hemostasis Phase</th>
<th>Prohemostatic Drivers</th>
<th>Antihemostatic Drivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hemostasis (platelet–vessel wall interactions)</td>
<td>High von Willebrand factor, low ADAMTS 13, low platelet count</td>
<td>Low procoagulant factors, fibrinogen, factors II, V, VII, IX, X, XI</td>
</tr>
<tr>
<td>Fibrinolysis (clot dissolution)</td>
<td>Low plasminogen, high PAI</td>
<td>High t-PA, low TAFI, low plasmin inhibitor</td>
</tr>
</tbody>
</table>

* ADAMTS 13 denotes disintegrin and metalloprotease with thrombospondin type 1 motif 13, PAI plasminogen activator inhibitor, TAFI thrombin-activatable fibrinolysis inhibitor, and t-PA tissue plasminogen activator.

FIBRINOLYSIS

Fibrinolysis is a highly regulated mechanism that, on deposition of fibrin within the vascular system, converts the proenzyme plasminogen into the active enzyme plasmin, which in turn degrades fibrin (Fig. 3). Under normal conditions, plasminogen-to-plasmin conversion is regulated by such activators as tissue plasminogen activator (t-PA), urokinase plasminogen activator, and activated factor XII. These activators (profibrinolytic) are opposed by such antiactivators as t-PA inhibitors (mainly, plasminogen activator inhibitor [PAI]), plasmin inhibitor, and thrombin-activatable fibrinolysis inhibitor (TAFI), which cumulatively act as antifibrinolytic drivers. Any perturbation of this balance may result in hyperfibrinolysis, which increases the risk of hemorrhage, or hypofibrinolysis, which increases the risk of thrombosis.

Plasma hyperfibrinolysis has been reported in patients with chronic liver disease, but its mechanistic role in bleeding is still debated. Uncertainty rests mainly on the lack of appropriate laboratory tests for its evaluation, because most observations are based on the measurement of the individual components of the system rather than on the overall activity stemming from the action of both profibrinolytic and antifibrinolytic drivers. Cirrhosis has been variably associated with laboratory changes favoring hyperfibrinolysis, such as increased levels of t-PA and reduced levels of plasmin inhibitor and TAFI, but also with changes favoring hypofibrinolysis, such as reduced levels of plasminogen and increased levels of PAI (Table 1). Hence, although contrasting results have been reported, the balance of fibrinolysis is probably restored in patients with liver disease by the parallel changes in profibrinolytic and antifibrinolytic drivers.

PROCOAGULANT IMBALANCE IN CHRONIC LIVER DISEASE

GENERAL FEATURES

Overall, the aforementioned observations suggest that patients with chronic liver disease are not naturally “autoanticoagulated,” as previously believed. This concept is reinforced by clinical evidence indicating that they are not protected from thrombosis, particularly but not exclusively in the portal venous system, and especially in the presence of inherited prothrombotic mutations.

Laboratory signs of a procoagulant imbalance, which was not evident in the previous studies, have been reported in association with chronic liver disease. As noted above, thrombin generation in vivo and in vitro is down-regulated by thrombomodulin (Fig. 2), which effectively quenches thrombin generation when added to plasma from healthy subjects but is much less effective when added to plasma from patients with chronic liver disease. This indicates that in such patients, the plasma is partially resistant to anticoagulation mediated by thrombomodulin. This resistance is evident only when the results of thrombin-generation tests are expressed as the ratio of thrombin activity in the presence of thrombomodulin to thrombin activity in its absence. The resistance is probably the result of two alterations typically found in patients with chronic liver disease; markedly increased plasma levels of factor VIII (one of the most potent drivers of thrombin generation) and the concomitant decrease in levels of protein C (one of the most potent anticoagulant drivers in quenching thrombin generation). Although protein C is reduced owing to the impaired synthetic capacity of the...
Figure 2. Protein C Activation by Thrombin on the Membrane of Endothelial Cells, and the Balance of Antihemostatic and Prohemostatic Drivers in the Different Phases of Hemostasis.

Thrombin and plasma protein C bind to the respective endothelial receptors, thrombomodulin and the endothelial protein C receptor (Panel A). On binding, protein C is quickly activated by thrombin (Panel B). Activated protein C forms a complex with its plasma co-factor, protein S, and eventually inhibits the activated forms of factor VIII (VIIa) and factor V (Va), thus quenching thrombin generation. Plasma and reagents that are used to perform the prothrombin-time test (the laboratory test most widely used until now to assess the risk of hemorrhage in patients with chronic liver disease) do not contain sufficient amounts of thrombomodulin. Accordingly, the test is responsive to the amount of thrombin generated as a function of the procoagulants, but not to the thrombin inhibited by the anticoagulants. Therefore, the prothrombin time does not represent the balance of coagulation as it occurs in vivo. This might explain why the prothrombin-time test and related tests are not effective in assessing the risk of hemorrhage in patients with acquired coagulopathies (e.g., chronic liver disease) in which there is a concomitant decrease of procoagulants and anticoagulants. Panel C shows the balance of antithrombotic and prohemostatic drivers in the different phases of hemostasis in patients with chronic liver disease. ADAMTS 13 denotes disintegrin and metalloprotease with thrombospondin type 1 motif 13, TAFI thrombin-activatable fibrinolysis inhibitor, and t-PA tissue plasminogen activator.
liver, the increased levels of factor VIII are likely to be explained by decreased clearance of this moiety from plasma, mediated by two mechanisms, one involving von Willebrand factor, and the other the low-density lipoprotein receptor–related protein. Von Willebrand factor binds factor VIII in vivo and protects it from cleavage by plasma proteases and from premature clearance. High plasma levels of von Willebrand factor in patients with cirrhosis may be mechanistically involved in maintaining high plasma levels of factor VIII through the stabilization of its procoagulant activity. The low-density lipoprotein receptor–related protein, a multifunctional ligand that mediates the cellular uptake and subsequent degradation of factor VIII, is inadequately expressed in patients with cirrhosis and, in conjunction with high levels of von Willebrand factor, may help sustain the high plasma levels of factor VIII.

**LABORATORY DETECTION**

The procoagulant imbalance associated with chronic liver disease can be detected by measuring thrombin generation in plasma in the presence and absence of thrombomodulin. An alternative method uses a snake-venom extract (Protac, Pentapharm) that acts as a surrogate activator of protein C in a manner similar to that of thrombomodulin. Whereas the results of the first test are expressed as the ratio of the thrombin concentration generated in the presence of thrombomodulin to the concentration generated in its absence, the results of the second test are expressed as the percentage of extract-induced coagulation inhibition, measured as the amount of thrombin generated in the presence versus the absence of the venom extract. By definition, the higher the ratio or the lower the percentage of extract-induced coagulation inhibition, the greater the degree of procoagulant imbalance. As detected by these assays in the context of chronic liver disease, the procoagulant imbalance is negatively correlated with levels of plasma protein C and positively correlated with levels of factor VIII. Furthermore, the degree of imbalance increases with the severity of cirrhosis as assessed by the Child–Pugh score. Whether the procoagulant imbalance detected in the laboratory as thrombomodulin resistance is a risk factor for thrombosis in patients with chronic liver disease remains to be established by prospective studies. It must be recognized that although thrombin-generation tests mimic the conditions operating in vivo much more closely than do conventional tests, they remain artificial because they use platelet-free plasma and the amount of thrombomodulin added in vitro is chosen arbitrarily, not on the basis of the density of the protein on endothelial cells.

**POSSIBLE CLINICAL IMPLICATIONS OF PROCOAGULANT IMBALANCE**

The in vitro procoagulant imbalance associated with chronic liver disease may have clinical implications. First, it calls into question the unrestricted use of plasma infusion to correct the results of conventional coagulation tests in patients undergoing invasive procedures. This is still a common practice, despite a lack of evidence from controlled, randomized trials and the recent guidelines of the American Association for the Study of Liver Diseases, which warn against the indiscriminate use of plasma therapy before liver biopsy. Second, the procoagulant imbalance may help explain mechanistically why these patients are not protected from clinical events such as peripheral-vein thrombosis, portal-vein thrombosis, atherothrombosis, and the progression of liver fibrosis. In the next sections, these potential clinical implications are discussed.

**PERIPHERAL-VEIN THROMBOSIS**

Retrospective studies showed that patients with chronic liver disease are not protected from venous thromboembolism (deep-vein thrombosis and pulmonary embolism). Recently, a nationwide, population-based case–control study involving 99,444 patients with venous thromboembolism and 496,872 controls showed that patients with liver disease had an increased relative risk of venous thromboembolism, with the risk being greater for deep-vein thrombosis than for pulmonary embolism and for cirrhosis than for noncirrhosis liver.
disease. However, other studies have shown a low prevalence of venous thromboembolism among patients with chronic liver disease.\textsuperscript{43,44} The retrospective design of all these studies makes it difficult to assess the true risk of venous thromboembolism among such patients. It is clear, however, that patients with chronic liver disease are not procoagulated and may eventually have clinical manifestations of thromboembolism, even though the abnormal results of conventional coagulation tests would suggest the opposite.

Thrombosis in patients with chronic liver disease might become an emerging issue owing to their increasing life expectancy and changing lifestyle, which expose them much more than in the past to such circumstantial risk factors as tumors, surgery, obesity, prolonged hospitalization, and inadequate physical activity. Thus, the logical consequence is that patients with chronic liver disease who have peripheral-vein thrombosis should be treated with anticoagulants just as any other patient would; it is important to note that the long-term safety of this approach has not been studied. Furthermore, the in vitro procoagulant imbalance associated with chronic liver disease, confirmed by many independent studies,\textsuperscript{45-47} suggests that these patients are eligible for antithrombotic prophylaxis when exposed to such risky situations as major surgery and prolonged immobilization. This notion contradicts current clinical practice, whereby patients with cirrhosis often receive no or suboptimal prophylaxis because of the perceived risk of bleeding.\textsuperscript{48} Clinical studies are needed to determine the appropriate care of these patients.

**ARTERIAL THROMBOSIS**

Even though it is not firmly established that patients with chronic liver disease have an increased risk of arterial thrombosis (i.e., coronary artery disease and stroke), they are not free from these and other clinical manifestations of atherothrombosis.\textsuperscript{49} Furthermore, the occurrence of hepatic-artery occlusion after liver transplantation worsens the prognosis for these patients. Therefore, early detection of this complication is important.\textsuperscript{50} Whether aspirin or other antiplatelet agents are indicated in the primary prophylaxis of this complication warrants evaluation in clinical trials.

**PORTAL-VEIN THROMBOSIS**

The prevalence of portal-vein thrombosis in patients with cirrhosis increases with the severity of the disease: approximately 1% among patients with compensated cirrhosis\textsuperscript{51} but 8 to 25% among those who are candidates for liver transplantation.\textsuperscript{52} Because not only reduced flow velocity\textsuperscript{53} but also procoagulant imbalance and vessel-wall abnormalities (Virchow's triad)\textsuperscript{54} are mechanistic factors in this complication, antithrombotic therapy (low-molecular-weight heparin or vitamin K antagonists) is commonly used.\textsuperscript{55,56} This approach is relatively safe,\textsuperscript{57} but varices may need to be treated (with vasoactive drugs or endoscopic ligation)\textsuperscript{58} before patients start taking anticoagulants. Portal-vein thrombosis worsens the post-transplantation prognosis, so primary prevention with low-molecular-weight heparin or vitamin K antagonists should be considered in patients awaiting liver transplantation. Randomized clinical trials to test the efficacy of these drugs are under way.\textsuperscript{59} However, because of the mechanistic role played by low levels of protein C in the balance of coagulation in patients with chronic liver disease,\textsuperscript{18,19} vitamin K antagonists are perhaps not the ideal drugs. Protein C is a vitamin K-dependent protein, and treatment with vitamin K antagonists might therefore further reduce levels of this naturally occurring anticoagulant in patients with end-stage liver disease, increasing the risk of thrombosis.
The newer direct thrombin inhibitors and inhibitors of activated factor X (e.g., dabigatran, rivaroxaban, and apixaban) may be attractive alternatives to vitamin K antagonists because they do not reduce protein C levels. Moreover, they do not require regular laboratory monitoring to adjust the dosage, whereas vitamin K antagonists require monitoring with the use of the INR, the validity of which has been questioned in patients with chronic liver disease. Other potential advantages of these new drugs over low-molecular-weight heparin are their oral route of administration and their mechanism of action, which is independent of antithrombin (low in these patients). However, specially designed clinical trials are needed because patients with chronic liver disease are usually excluded from the randomized clinical trials of these drugs.

LIVER FIBROSIS
Another consequence of procoagulant imbalance in chronic liver disease pertains to liver fibrosis and its progression. Two hypotheses are currently considered for the pathogenesis of this condition. Both involve coagulation, and they might be synergistic. One hypothesis centers on the role of microemboli. Obliterative lesions in the portal and hepatic veins frequently occur in patients with cirrhosis, owing to the formation of microthrombi that lead to tissue ischemia, cell death, and fibrosis through parenchymal extinction.

Another hypothesis suggests that coagulation activation within the liver’s vascular system may play a role in the development and progression of the fibrotic process. Thrombin, besides being a potent procoagulant, has many cellular effects that are mediated by a family of widely expressed G-protein–coupled receptors called protease-activated receptors (PARs). Thrombin signaling through PARs expressed on hepatic stellate cells, which are responsible for tissue repair, might therefore play a crucial role in the mechanisms and progression of fibrosis. The degree of thrombin-receptor expression is associated with the severity of liver disease, and it has also been observed that humans and mice with hypercoagulability due to a gain-of-function mutation in the factor V gene (factor V Leiden) have an accelerated progression of liver fibrosis. PAR1 antagonists can provide protection against experimental liver fibrosis in rodents, and anticoagulant drugs slow fibrosis progression in mice. Furthermore, low-molecular-weight heparin prevents hepatic fibrogenesis caused by the injection of carbon tetrachloride in rodents. These observations are consistent with the hypothesis that thrombin generation and fibrosis are directly associated. Accordingly, a controlled, randomized clinical trial is being carried out to investigate whether vitamin K antagonists can influence the progression of fibrosis in patients with hepatitis C (ClinicalTrials.gov number, NCT00180674).

CONCLUSIONS
Undoubtedly, patients with end-stage liver disease have prominent bleeding symptoms, particularly in the gastrointestinal tract. Yet evaluation of this bleeding tendency solely on the basis of abnormal levels of the conventional coagulation biomarkers should be reconsidered. When patients are assessed by means of global tests such as the thrombin-generation test, the results do not show hypercoagulability. Thus, the main culprits for the bleeding tendency observed in patients with end-stage liver disease should be sought among underlying conditions that favor hemorrhage, such as portal hypertension, endothelial dysfunction, bacterial infection, and renal failure (Table 2).

On the other hand, the restored balance of hemostasis afforded by the concomitant reduction of procoagulant and anticoagulant factors, together with increased levels of factor VIII (Table 1), might explain why patients with chronic liver disease are not protected from arterial and venous thrombosis. This apparent clinical paradox may be explained by the findings that these patients have a procoagulant imbalance in vitro owing to resistance to thrombomodulin and that their thrombocytopenia is compensated for by increased plasma levels of the adhesive protein von Willebrand factor. Another dogma is being challenged by the finding that platelet activation plays a crucial role in the immune-mediated progression of liver disease in an animal model of viral hepatitis.

In conclusion, the reassessment of hemostasis in patients with chronic liver disease challenges the dogma that the major coagulopathy in these patients leads consistently to bleeding. Other changes that accompany chronic liver disease may restore the balance of anticoagulant and procoagulant effects (Fig. 2C). In certain circumstances,
the risk of thrombotic events may be greater than the risk of hemorrhage. We speculate that drugs that are often regarded as contraindicated in patients with chronic liver disease may instead prove beneficial and should be tested in appropriate clinical trials.

Disclosures: provided by the authors are available with the full text of this article at NEJM.org.

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Acute Pancreatitis: Diagnosis, Prognosis, and Treatment

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Mild acute pancreatitis has a low mortality rate, but patients with severe acute pancreatitis are more likely to develop complications and have a much higher death rate. Although serum amylase and lipase levels remain the most widely used diagnostic assays for acute pancreatitis, other biomarkers and inflammatory mediators such as trypsinogen are being investigated for clinical use. Ranson’s criteria, the Imrie scoring system, the Acute Physiology and Chronic Health Evaluation (APACHE II) scale, and the Computed Tomography Severity Index are systems for classifying severity of this disease; the Atlanta classification is widely used to compare these systems and standardize clinical trials. New developments in imaging modalities such as endoscopic ultrasonography and magnetic resonance cholangiopancreatography increase the options available to physicians for determining the cause of pancreatitis and assessing for complications. Enteral nutrition is preferred to parenteral nutrition for improving patient outcomes. Clinical trials are ongoing to evaluate the role, selection, and timing of antibiotics in patients with infected necrosis. (Am Fam Physician 2007;75:1513-20. Copyright © 2007 American Academy of Family Physicians.)

Acute pancreatitis is a reversible inflammatory process of the pancreas. Although the disease process may be limited to pancreatic tissue, it also can involve peripancreatic tissues or more distant organ sites. Acute pancreatitis may occur as an isolated attack or may be recurrent. It has a variety of causes and can range in severity from mild to severe and life threatening. Some patients may require brief hospitalization, whereas others may be critically ill with multiple organ dysfunction requiring intensive care monitoring. Mild acute pancreatitis has a very low mortality rate (less than 1 percent), whereas the death rate for severe acute pancreatitis can be 10 to 30 percent depending on the presence of sterile versus infected necrosis. In the United States, up to 210,000 patients per year are admitted to a hospital for acute pancreatitis.

**Risk Factors**
The most common risk factors for acute pancreatitis are gallbladder disease (often caused by choledocholithiasis) and chronic alcohol consumption. Table 1 lists risk factors for acute pancreatitis. Given newly emerging

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for Acute Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic or functional disorders (e.g., pancreas divisum, sphincter of Oddi dysfunction)</td>
</tr>
<tr>
<td>Autoimmune (e.g., systemic lupus erythematosus)</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
</tr>
<tr>
<td>Chronic alcohol consumption</td>
</tr>
<tr>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Drug-induced hypertriglyceridemia (triglycerides greater than 1,000 mg per dl [11.30 mmol per L])</td>
</tr>
<tr>
<td>Gallstones</td>
</tr>
<tr>
<td>Hypercalcemia, hyperparathyroidism</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Infections (e.g., viral, bacterial, parasitic, fungal)</td>
</tr>
<tr>
<td>Pancreatic or ampullary tumors</td>
</tr>
<tr>
<td>Traumatic or postprocedure (e.g., endoscopic retrograde cholangiopancreatography or after abdominal surgery)</td>
</tr>
<tr>
<td>Vascular (e.g., vasculitis)</td>
</tr>
</tbody>
</table>

Information from reference 5.
SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enteral nutrition is equal to or more effective than total parenteral nutrition</td>
<td>A</td>
<td>36</td>
</tr>
<tr>
<td>for nutritional management of patients with severe pancreatitis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluate for less-common causes of pancreatitis (e.g., sphincter of Oddi dysfunction,</td>
<td>C</td>
<td>29</td>
</tr>
<tr>
<td>pancreas divisum, pancreatic duct strictures) with endoscopic retrograde</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholangiopancreatography.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnose acute pancreatitis with contrast-enhanced computed tomography.</td>
<td>C</td>
<td>27</td>
</tr>
<tr>
<td>It is controversial whether antibiotics reduce mortality in patients with necrotic</td>
<td>B</td>
<td>37, 38</td>
</tr>
<tr>
<td>pancreatitis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent endoscopic retrograde cholangiopancreatography is indicated in patients with</td>
<td>A</td>
<td>30</td>
</tr>
<tr>
<td>or at risk of biliary sepsis, biliary obstruction, cholangitis, or worsening or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>persistent jaundice.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1430 or http://www.aafp.org/afpsort.wml.

diagnostic modalities, recent guidelines have recommended against the diagnosis of “idiopathic acute pancreatitis.”

Clinical Presentation

The hallmark symptom of acute pancreatitis is the acute onset of persistent upper abdominal pain, usually with nausea and vomiting. The usual locations of the pain are the epigastric and periumbilical regions. The pain may radiate to the back, chest, flanks, and lower abdomen. Patients are usually restless and bend forward (the knee- chest position) in an effort to relieve the pain because the supine position may exacerbate the intensity of symptoms. Physical examination findings are variable but may include fever, hypotension, severe abdominal tenderness, guarding, respiratory distress, and abdominal distention.

Diagnosis

No single laboratory or clinical sign is pathognomonic for acute pancreatitis; many biomarkers and inflammatory mediators for predicting the severity of acute pancreatitis are being evaluated. The initial laboratory evaluation should include amylase and lipase levels; complete blood count with differential; metabolic panel (blood urea nitrogen, creatinine, glucose, and calcium levels); triglyceride level; urinalysis; and arterial blood gases. Elevated amylase and lipase levels can be nonspecific, depending on the time since onset of pain, other intra-abdominal processes, and concomitant chronic diseases such as renal insufficiency. Amylase levels may be normal in patients with alcoholism who present with acute pancreatitis, especially if they had previous attacks of alcoholic pancreatitis; thus, serial testing may not be helpful. Plasma lipase is more sensitive and specific than plasma amylase.

Recent research has examined potential biologic markers for predicting the severity and prognosis of pancreatitis. Trypsinogens and pancreatic proteases involved in the autodigestive processes of acute pancreatitis appear promising. Other investigational serologic markers include trypsinogen activation peptide, C-reactive protein, procalcitonin, phospholipase A2, and the cytokines interleukin-6 and interleukin-8. Currently, these markers have limited clinical availability, but there is significant interest in better understanding markers of immune response and pancreatic injury because these could be valuable tools for reliably predicting the severity of acute pancreatitis and supplementing imaging modalities.

Prognosis

Early evaluation and risk stratification for patients with acute pancreatitis are important
to differentiate patients with mild versus severe disease because patients with severe disease often need intensive care treatment. Several scoring systems can predict the severity of pancreatitis, and recent work has attempted to compare their relative predictive values.

Ranson's criteria,16 the Imrie scoring system,17 the Acute Physiology and Chronic Health Evaluation (APACHE II) scale,18 and the Computed Tomography (CT) Severity Index19 have been developed and validated to predict adverse outcomes, including mortality, in patients with pancreatitis (Table 36-19).

Research has shown some advantages of the CT Severity Index in predicting the severity of acute pancreatitis compared with the other systems. One study found that a CT Severity Index score of 5 or greater correlated with prolonged hospitalization and higher rates of mortality and morbidity.20 A CT Severity Index score of 5 or greater was associated with a mortality rate 15 times higher than in those with a score of less than 5. No association was found between Ranson's criteria and APACHE II scale scores and mortality or length of hospitalization.20

Another study demonstrated that the CT Severity Index was a stronger predictor of severe acute pancreatitis than Ranson's criteria or the APACHE II scale; however, the CT Severity Index was calculated 72 hours after admission, whereas the APACHE II scale and Ranson's criteria scores were calculated at 24 and 48 hours, respectively.21

An observational study showed that CT Severity Index scores, when obtained within 48 hours, correlated better with complications and mortality than Ranson's criteria.22 Because of the number of available scoring systems, the Atlanta Classification of Severe Acute Pancreatitis has become widely used as a means of comparing scores (Ranson's criteria, APACHE II scale, and contrast-enhanced CT) to define severe acute pancreatitis,23 which has helped standardize clinical research trials.

Table 2. Serum Markers for Determining Diagnosis and Prognosis in Acute Pancreatitis

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Time of onset (hours)</th>
<th>Purpose</th>
<th>Clinical observation/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine transaminase</td>
<td>12 to 24</td>
<td>Diagnosis and etiology</td>
<td>Associated with gallstone pancreatitis; threefold elevation or greater in the presence of acute pancreatitis has a positive predictive value of 95 percent in diagnosing acute gallstone pancreatitis</td>
</tr>
<tr>
<td>Amylase</td>
<td>2 to 12</td>
<td>Diagnosis</td>
<td>Most accurate when at least twice the upper limit of normal; amylase levels and sensitivity decrease with time from onset of symptoms</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>24 to 48</td>
<td>Predictive of severity</td>
<td>Late marker; high levels associated with pancreatic necrosis</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>18 to 48</td>
<td>Predictive of severity</td>
<td>Early indication of severity</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>12 to 24</td>
<td>Predictive of severity</td>
<td>Early indication of severity</td>
</tr>
<tr>
<td>Lipase</td>
<td>4 to 8</td>
<td>Diagnosis</td>
<td>Increased sensitivity in alcohol-induced pancreatitis; more specific and sensitive than amylase for detecting acute pancreatitis</td>
</tr>
<tr>
<td>Phospholipase A2</td>
<td>24</td>
<td>Predictive of severity</td>
<td>Associated with development of pancreatic necrosis and pulmonary failure</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>24 to 36</td>
<td>Predictive of severity</td>
<td>Early detection of severity; high concentrations in infected necrosis</td>
</tr>
<tr>
<td>Trypsinogen activation</td>
<td>Within a few hours</td>
<td>Diagnosis and predictive of severity</td>
<td>Early marker for acute pancreatitis and close correlation to severity</td>
</tr>
</tbody>
</table>

Information from references 5 and 11.
Table 3. Clinical Criteria Used in Prognostic Scoring Systems for Acute Pancreatitis

<table>
<thead>
<tr>
<th>APACHE II scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation includes the following factors: age, rectal temperature, mean arterial pressure, heart rate, PaO₂, arterial pH, serum potassium, serum sodium, serum creatinine, hematocrit, white blood cell count, Glasgow Coma Scale score, chronic health status</td>
</tr>
<tr>
<td>Scoring: Can be calculated at <a href="http://www.sfar.org/scores2/apache22.html/calcul">http://www.sfar.org/scores2/apache22.html/calcul</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CT Severity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT grade</td>
</tr>
<tr>
<td>A is normal pancreas (0 points)</td>
</tr>
<tr>
<td>B is edematous pancreas (1 point)</td>
</tr>
<tr>
<td>C is B plus mild extrapancreatic changes (2 points)</td>
</tr>
<tr>
<td>D is severe extrapancreatic changes plus one fluid collection (3 points)</td>
</tr>
<tr>
<td>E is multiple or extensive fluid collections (4 points)</td>
</tr>
<tr>
<td>Necrosis score:</td>
</tr>
<tr>
<td>None (0 points)</td>
</tr>
<tr>
<td>&gt; One third (2 points)</td>
</tr>
<tr>
<td>&lt; One third but less than one half (4 points)</td>
</tr>
<tr>
<td>&gt; One half (6 points)</td>
</tr>
<tr>
<td>Scoring: CT grade + necrosis score</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imrie scoring system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 55 years</td>
</tr>
<tr>
<td>White blood cell count &gt; 15,000 per mm³ (15.0 × 10⁹ per L)</td>
</tr>
<tr>
<td>Blood glucose &gt; 180 mg per dl (10 mmol per L) in patients without diabetes</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase &gt; 600 U per L</td>
</tr>
<tr>
<td>Serum AST or ALT &gt; 100 U per L</td>
</tr>
<tr>
<td>Serum calcium &lt; 8 mg per dl</td>
</tr>
<tr>
<td>PaO₂ &lt; 60 mm Hg</td>
</tr>
<tr>
<td>Serum albumin &lt; 3.2 g per dl (32 g per L)</td>
</tr>
<tr>
<td>Serum urea &gt; 45 mg per dl (16.0 mmol per L)</td>
</tr>
<tr>
<td>Scoring: One point for each criterion met 48 hours after admission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ranson’s criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission or diagnosis:</td>
</tr>
<tr>
<td>Age &gt; 55 years</td>
</tr>
<tr>
<td>White blood cell count &gt; 16,000 per mm³ (16.0 × 10⁹ per L)</td>
</tr>
<tr>
<td>Blood glucose &gt; 200 mg per dl (11.1 mmol per L)</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase &gt; 350 U per L</td>
</tr>
<tr>
<td>AST &gt; 250 U per L</td>
</tr>
<tr>
<td>During initial 48 hours:</td>
</tr>
<tr>
<td>Hematocrit decrease &gt; 10 percent</td>
</tr>
<tr>
<td>Blood urea nitrogen increase &gt; 5 mg per dl (1.8 mmol per L)</td>
</tr>
<tr>
<td>Serum calcium &lt; 8 mg per dl (2 mmol per L)</td>
</tr>
<tr>
<td>Base deficit &gt; 4 mmol per L (4 mEq per L)</td>
</tr>
<tr>
<td>Fluid sequestration &gt; 6,000 ml</td>
</tr>
<tr>
<td>PaO₂ &lt; 60 mm Hg</td>
</tr>
<tr>
<td>Scoring: One point for each criterion met</td>
</tr>
</tbody>
</table>

Table 4 summarizes evidence comparing these prognostic systems and patient-related outcomes such as ruling out severe acute pancreatitis.7,13,24 The higher the prognostic score, the poorer the clinical outcome, including mortality. Irrespective of scoring criteria, signs of organ failure within 24 hours of admission significantly increase the risk of death; and thus, physiologic response to treatment needs to be monitored closely.25

Advances in Radiologic Imaging Techniques

Radiologic imaging is used to confirm or exclude the clinical diagnosis, establish the cause, assess severity, detect complications, and provide guidance for therapy. In recent years, the range of imaging modalities has greatly expanded. Traditional imaging modalities include plain film radiography, abdominal ultrasonography, CT scans, and endoscopic retrograde cholangiopancreatography (ERCP); newer options include endoscopic ultrasonography and magnetic resonance cholangiopancreatography (MRCP). Recent research in this area has focused on development of these tests and the better understanding of their application to clinical care.

Transabdominal ultrasonography is used to determine cholelithiasis.9 Bowel gas can limit the accuracy of pancreatic imaging, but if the pancreas is visualized, then imaging can reveal pancreatic enlargement, exudational changes, and peripancreatic fluid.26 Contrast-enhanced CT is the standard imaging technique for detection of acute pancreatitis.27 CT generally is not indicated for patients with mild, uncomplicated pancreatitis but should be reserved for cases of clinical or biologic worsening.13 It is controversial whether routine use of CT increases length of hospital stay,28 and the potential risk of contrast media-induced morbidity limits its use in certain patients. Magnetic resonance imaging is not commonly used but may be indicated if better visualization of peripancreatic inflammation, necrosis, or fluid collections is needed.13

ERCP is helpful in evaluating less-
Table 4. Clinical Outcomes and Predictive Value of Prognostic Scoring Systems for Acute Pancreatitis

<table>
<thead>
<tr>
<th>Prognostic scoring system</th>
<th>Associated outcomes</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score ≥ 8 at 24 hours</td>
<td>Need for intensive care unit, severity, pancreatic necrosis, mortality, organ failure, and longer hospital stay</td>
<td>1.7 to 4.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Imrie score ≥ 3</td>
<td>Mortality, severity, pancreatic fluid collections</td>
<td>4.6</td>
<td>0.36</td>
</tr>
<tr>
<td>Ranson’s criteria score &gt; 3 at 48 hours</td>
<td>Major complications, severity, organ failure, pancreatic necrosis, mortality, longer hospital stay</td>
<td>2.4 to 2.5</td>
<td>0.47</td>
</tr>
</tbody>
</table>

LR = likelihood ratio; APACHE II = Acute Physiology and Chronic Health Evaluation.

Information from references 8, 21, and 24.

common causes of pancreatitis (e.g., micro-lithiasis; sphincter of Oddi dysfunction; pancreas divisum; and pancreatic duct strictures, which can be benign or malignant).\(^\text{29}\) Urgent ERCP is indicated in patients at risk of or with evidence of biliary sepsis, severe pancreatitis with biliary obstruction, cholangitis, elevated bilirubin, worsening and persistent jaundice, or signs of worsening pain in the setting of an abnormal ultrasound examination because these patients may need more immediate surgical or gastroenterologic intervention.\(^\text{30,31}\) In patients with severe gallstone pancreatitis, morbidity and mortality is reduced with the use of early selective ERCP.\(^\text{32}\)

MRCP is a newer, noninvasive technique that has been referred to as “the pancreatogram.”\(^\text{33}\) MRCP can be used preoperatively to determine which patients would benefit from ERCP.\(^\text{27}\) MRCP has been found to be as accurate as contrast-enhanced CT in predicting the severity of pancreatitis and identifying pancreatic necrosis.\(^\text{34}\) Unlike ERCP, MRCP does not have interventional capability for stone extraction, stent insertion, or biopsy. MRCP is less sensitive for detection of small stones (i.e., smaller than 4 mm), small ampullary lesions, and ductal strictures.\(^\text{35}\) MRCP can assess pancreatic and peripancreatic cysts.\(^\text{34}\) It is helpful in patients when ERCP is not possible or is unsuccessful.\(^\text{32}\)

Another new technology is endoscopic ultrasonography, which is highly accurate in documenting stones and tumors but is used less often than ERCP. Endoscopic ultrasonography is useful in obese patients and patients with ileus, and can help determine which patients with acute pancreatitis would benefit most from therapeutic ERCP.\(^\text{31}\) Endoscopic ultrasonography can assist with endoscopic transmural cyst and abscess drainage. Endoscopic ultrasonography and MRCP show promise in increasing the range of options available to search for the cause of acute pancreatitis. Table 5 compares the sensitivity and specificity of various imaging techniques.\(^\text{8,13,26,32}\)

Table 5. Comparison of Imaging Techniques for Acute Pancreatitis

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast-enhanced computed tomography</td>
<td>78 percent sensitivity and 86 percent specificity for severe acute pancreatitis</td>
</tr>
<tr>
<td>Endoscopic ultrasonography</td>
<td>100 percent sensitivity and 91 percent specificity for gallstones</td>
</tr>
<tr>
<td>Magnetic resonance cholangiopancreatography</td>
<td>81 to 100 percent sensitivity for detecting common bile duct stones</td>
</tr>
<tr>
<td></td>
<td>98 percent negative predictive value and 94 percent positive predictive value for bile duct stones</td>
</tr>
<tr>
<td></td>
<td>As accurate as contrast-enhanced computed tomography in predicting severity of pancreatitis and identifying pancreatic necrosis</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>83 percent sensitivity and 91 percent specificity for severe acute pancreatitis</td>
</tr>
<tr>
<td>Transabdominal ultrasonography</td>
<td>87 to 98 percent sensitivity for the detection of gallstones</td>
</tr>
</tbody>
</table>

Information from references 8, 13, 26, and 32.
Evaluation and Management of Acute Pancreatitis

Subjective
Acute onset steady, intense epigastric abdominal pain radiating to the back with nausea and vomiting; may be relieved with leaning forward; medical history: chronic alcoholism, gallstones

Objective
Mild: Restlessness, low-grade fever, tachycardia, mild epigastric tenderness
Severe: Same as mild plus marked tenderness with guarding and abdominal distension, absent bowel sounds, systemic signs of hypotension, possible shock, jaundice, and pulmonary findings (e.g., rales, pulmonary edema)

Laboratory results: Elevated serum and/or urinary levels of pancreatic enzymes (i.e., amylase, lipase, C-reactive protein, or trypsinogen activation peptide); consider liver function tests, calcium triglycerides, albumin, complete blood count, arterial blood gases, glucose

Imaging: Ultrasonography, contrast-enhanced CT or MRI (with elevated serum creatinine) and MRCP or ERCP (if high suspicion of common bile duct stones)

Differential diagnosis
Acute or chronic alcohol consumption; gallstone disease; peptic ulcer disease; perforated ulcer; early appendicitis; bowel obstruction; mesenteric ischemia; medications; hypertriglyceridemia; hypercalcemia; infection; post-traumatic injury; pregnancy; pulmonary, renal, or cardiovascular disorders

Assessment

<table>
<thead>
<tr>
<th>Ranson’s Criteria</th>
<th>APACHE II</th>
<th>CT Severity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pancreatitis</td>
<td>≤ 3</td>
<td>&lt; 8</td>
</tr>
<tr>
<td>Severe pancreatitis</td>
<td>&gt; 3</td>
<td>≥ 8</td>
</tr>
</tbody>
</table>

Plan

Management of mild pancreatitis
- Aggressive rehydration (i.e., dextrose in normal saline at 1 L per hour until adequate urine output)
- Pain relief (morphine)
- Enteral nutritional support once pain improves and laboratory results normalize
- Monitor hemodynamic and laboratory/serum parameters

Management of severe pancreatitis
- Consider intensive care unit admission
- Eliminate oral Intake for first 48 hours
- Aggressive volume replacement
- Nutritional support (enteral preferred)
- Consider emergent ERCP with suspected gallstones and obstructive jaundice
- Pain relief (morphine)
- Identify if pancreatic or peripancreatic necrosis is present
- Consider antibiotics if possible infection
- Consider consultation with gastroenterology, surgery, and/or interventional radiology subspecialists

Figure 1. Algorithm for the evaluation and management of acute pancreatitis. (CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; ERCP = endoscopic retrograde cholangiopancreatography; APACHE II = Acute Physiology and Chronic Health Evaluation.)

Information from references 4, 7 through 9, 11, 15, and 35.

Treatment Issues for Acute Pancreatitis

Aggressive volume repletion, pain control, close monitoring of hemodynamic and volume statuses, attention to nutritional needs, and monitoring for complications are essential in patients with acute pancreatitis. Because several clinical guidelines and reviews describe these management issues in detail, this article only provides a brief update based on recent developments in two important aspects of management: nutrition and the role of antibiotics.

Physicians often find the decision about nutritional management in patients with acute pancreatitis challenging because historically it was believed that pancreatic rest was needed. However, total enteral nutrition, when compared with total parenteral nutrition,
Acute Pancreatitis

has been shown to have clear benefits in patients with severe acute pancreatitis. A meta-analysis concluded that total enteral nutrition is equal to if not better than total parenteral nutrition. However, more research is needed to clarify which type of total enteral nutrition (i.e., oral, nasogastric, or nasojejunal feeding) most benefits patient outcomes. Several randomized studies have shown that nasojejunal feeding prevents morbidity and mortality, possibly by preventing development of infected necrosis by inhibiting bacterial translocation from the gut. It is often the preferred option in patients with severe pancreatitis but may not be possible if ileus is present.

One of the late complications of severe acute pancreatitis is pancreatic necrosis. Mortality increases when necrosis becomes infected. Antibiotics have been shown to improve patient outcomes in severe acute pancreatitis. A recent, double-blind, randomized controlled trial of 114 patients with acute necrotic pancreatitis receiving ciprofloxacin (Cipro), metronidazole (Flagyl), or placebo found no significant difference in the rate of infected pancreatic necrosis, systemic complications, or mortality. Yet, meta-analyses of studies of acute necrotic pancreatitis conclude that prophylactic antibiotics can decrease pancreatic sepsis, mortality, extrapancreatic infections, and surgical rates. Because evidence is mixed on the issue of prophylactic antibiotics for necrotic pancreatitis, the aforementioned benefits must be weighed carefully with risks (e.g., adverse effects, fungal infections, drug resistance).

Surgical debridement also may be indicated for infected necrosis. Surgery for sterile necrosis is indicated only if the patient clinically deteriorates or if there is no improvement. Surgery is usually performed no earlier than two weeks after the onset of symptoms. When compared with immediate surgery, this delay has been shown to decrease the mortality rate. Surgical techniques are evolving, and ongoing research is evaluating the effectiveness of various approaches.

Figure 1 is an overview and summary of the key principles and steps involved in the diagnostic evaluation, differential diagnosis, prognostic evaluations, and treatment of mild and severe acute pancreatitis.

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Author disclosure: Nothing to disclose.

REFERENCES
Acute Pancreatitis


Glucose Control in Hospitalized Patients

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Evidence indicates that hospitalized patients with hyperglycemia do not benefit from tight blood glucose control. Maintaining a blood glucose level of less than 180 mg per dL (9.99 mmol per L) will minimize symptoms of hyperglycemia and hypoglycemia without adversely affecting patient-oriented health outcomes. In the absence of modifying factors, physicians should continue patients' at-home diabetes mellitus medications and randomly check glucose levels once daily. Sulfonylureas should be withheld to avoid hypoglycemia in patients with limited caloric intake. Patients with cardiovascular conditions may benefit from temporarily stopping treatment with thiazolidinediones to avoid precipitating heart failure. Metformin should be temporarily withheld in patients who have worsening renal function or who will undergo an imaging study that uses contrast. When patients need to be treated with insulin in the short term, using a long-acting basal insulin combined with a short-acting insulin before meals (with the goal of keeping blood glucose less than 180 mg per dL) better approximates normal physiology and uses fewer nursing resources than sliding-scale insulin approaches. Most studies have found that infusion with glucose, insulin, and potassium does not improve mortality in patients with acute myocardial infarction. Patients admitted with acute myocardial infarction should have moderate control of blood glucose using home regimens or basal insulin with correctional doses. (Am Fam Physician. 2010;81(9):1121-1124. Copyright © 2010 American Academy of Family Physicians.)

Hyperglycemia commonly complicates the treatment of adult patients hospitalized for other reasons. Stress, medications, and changes in diet during hospitalization can elevate or lower blood glucose levels. Physicians often do not know whether high glucose levels are from acute changes or if the levels were present before admission.

Diabetic ketoacidosis or hyperosmolar states caused by critical increases in blood glucose levels have well-established management protocols. This article reviews the rationale and evidence for blood glucose control in hospitalized patients with non-critical hyperglycemia and recommends methods for achieving blood glucose goals.

Effects of Tight Glucose Control in Hospitalized Patients

The concern with hyperglycemia in hospitalized patients is the effect of elevated blood glucose on the immune system and the body's susceptibility to pathogens. Elevated blood glucose levels impair neutrophil adhesion and phagocytosis and may alter the virulence of some pathogens, resulting in increased risk of infection, including sepsis. There is no research assessing the value of tightly controlling blood glucose in hospitalized patients who are not in intensive care units. Hyperglycemic episodes occur in approximately 7.7 percent of patients admitted with diabetes mellitus to a general hospital ward; each episode is associated with an increased risk of inpatient mortality, as well as an increase in the risk of death in the following year.

In severely ill patients, preliminary research points to a benefit of controlling hyperglycemia. Studies that evaluated epidemiologic data or that were controlled studies of patients in surgical intensive care or of patients with acute myocardial infarction (MI) found that intensive control aimed at maintaining glucose concentrations between 80 to 110 mg per dL (4.44 to 6.11 mmol per L) decreased mortality, morbidity, and length of hospitalization.

However, confirmatory studies have found no benefit and have provided evidence of harm from tight glucose control in critically ill adult patients. A meta-analysis of 29 studies that enrolled a total of 8,432 patients found that intensive control decreased the risk of sepsis, but was not associated with a decrease in hospital mortality and was associated with an increased risk of severe hypoglycemia (i.e., blood glucose level less than 40 mg per dL [2.22 mmol per L]).

A recent study of more than 6,000 patients...
# SORT: Key recommendations for practice

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients who are in the surgical ICU, insulin drip and tight glucose control decreases the risk of septicemia, but increases hypoglycemic episodes and has no mortality benefit.</td>
<td>A</td>
<td>7</td>
<td>Meta-analysis of RCTs</td>
</tr>
<tr>
<td>Intensive blood glucose protocols (goal of 81 to 108 mg per dl. [4.50 to 5.99 mmol per L]) for patients in the ICU increase mortality compared with less intensive treatment (i.e., goal of 180 mg per dl. [9.99 mmol per L] or less).</td>
<td>B</td>
<td>8</td>
<td>Large RCT that showed increased mortality with strict glucose control, and no difference in length of hospitalization or need for mechanical ventilation or dialysis</td>
</tr>
<tr>
<td>In hospitalized patients, home diabetes mellitus treatment regimens should be continued in the absence of specific contraindications.</td>
<td>B</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Metformin (Glucophage) should be discontinued in patients with diabetes who have a serum creatinine level greater than 1.5 mg per dl. (132.60 μmol per L) for men, and greater than 1.4 mg per dl. (123.76 μmol per L) for women.</td>
<td>C</td>
<td>13, 14</td>
<td>Consensus statement from working group on contrast-induced nephropathy</td>
</tr>
<tr>
<td>Sliding-scale insulin regimens have no benefit over continuation of home diabetes treatment regimens.</td>
<td>B</td>
<td>19</td>
<td>Comparative study evaluating the benefit of sliding-scale insulin versus home regimens found no difference in glucose control</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; RCT = randomized controlled trial.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

also demonstrated that tight glucose control (81 to 108 mg per dl. [4.50 to 5.99 mmol per L]) in the treatment group versus 180 mg per dl. [9.99 mmol per L] or less in control group) increased mortality (odds ratio = 1.14; 95% confidence interval, 1.02 to 1.28; P = .02; number needed to harm = 39), with 7 percent of patients experiencing severe hypoglycemia. In this study, there were no differences in median number of days in intensive care or the hospital, or need for mechanical ventilation or dialysis.

**Approach to Hospitalized Patients with Hyperglycemia**

A reasonable goal for most patients is to maintain a random blood glucose level of less than 180 mg per dl., but only for patients in whom it is safe to do so. Instead of frequent blood glucose measurements throughout the day and night, which is bothersome to patients and results in many telephone calls from nursing staff reporting measurements outside of the normal range, a single, random daily determination is often all that is necessary. This level of control is thought to minimize the risk of hypoglycemia, the likelihood of symptoms in patients, and the adverse effect on immune function. Specific patient factors may require more frequent monitoring, such as poor outpatient control of blood glucose, changes in diet, and reactions to stress or medications.

When possible, the patient’s previous medications should be continued while in the hospital, except when the patient’s situation requires other approaches to treatment. Patients who have no oral intake of medications will need to be treated with subcutaneous or intravenous insulin. Patients with limited caloric intake are at risk of hypoglycemia if they are taking sulfonylureas, and these medications should be withheld until the patient is eating again. Thiazolidinediones should be avoided in patients with new or worsening cardiovascular conditions, given these agents potential to precipitate or worsen heart failure.

Metformin (Glucophage) does not cause hypoglycemia and may be continued in many hospitalized patients. It has a theoretical risk of inducing lactic acidosis, although the actual risk of this often fatal adverse effect is probably small, considering that a Cochrane review found no cases of fatal or nonfatal lactic acidosis in 59,321 patient-years of metformin use. Because the risk of lactic acidosis increases with declining renal function, product labeling recommends discontinuation of metformin in men with creatinine
levels greater than 1.5 mg per dL (132.60 μmol per L) and in women with levels greater than 1.4 mg per dL (123.76 μmol per L).13

Contrast-induced nephropathy can decrease renal function and, theoretically, cause lactic acidosis if a patient is receiving metformin. Current guidelines recommend stopping metformin use before imaging procedures that use contrast, and restarting use 48 hours after the procedure if renal function is unchanged.13,14 Although the necessity of this prohibition has been questioned,15 most radiologists will require withholding metformin in all patients for two days before they will perform the imaging study.

**Using Insulin in Hospitalized Patients**

If it is not possible to continue oral hypoglycemic therapy, insulin may be needed temporarily to maintain blood glucose levels less than 180 mg per dL. Common approaches to insulin dosing in the hospital are the sliding-scale insulin approach and the use of basal insulin dosing with prandial and correctional doses.

**SLIDING-SCALE INSULIN**

Protocols for reacting to fluctuations in blood glucose have been used for years, and these sliding-scale insulin regimens require measuring blood glucose levels several times per day and administering enough insulin to cover above-normal values. However, the sliding-scale approach makes no physiologic sense and has been compared with giving sliding-scale antibiotics to treat fever.16 Reacting to high glucose levels has the potential to lower glucose levels too much, creating a physiologic response that sends the glucose level higher than before, leading to higher doses of insulin that only magnify the fluctuations. Reports found that increased length of hospitalization was associated with the use of sliding-scale insulin protocols, prompting concern that it was harmful rather than helpful.17,18

One randomized trial evaluated the relative benefit of a sliding-scale approach compared with using patients’ prehospitalization dose.19 Sliding-scale insulin did not produce any greater degree of control than the home dose, with about one third of patients remaining hyperglycemic during their hospitalization, regardless of the method of blood glucose control.20 The duration of hospitalization was not different with sliding-scale insulin.

**BASAL INSULIN WITH PRANDIAL AND CORRECTIONAL DOSES**

A more physiologic approach to addressing inpatient hyperglycemia is a weight-based dosing (0.4 to 0.5 units per kg per day) of long-acting basal insulin (glargine [Lantus] or isophane insulin [NPH]), combined with short-acting insulin before meals. Used in insulin-naive patients, this approach will provide lower blood glucose levels than sliding-scale insulin (an average difference of 27 mg per dL [1.50 mmol per L] lower with no increase in hypoglycemic episodes), although it has not been demonstrated to decrease length of stay or affect any patient-oriented outcomes.20 In addition to making more physiologic sense than a sliding-scale protocol, a basal-insulin–based protocol decreases work for nursing and physician staff, and it decreases the number of finger sticks requested of patients.

**Insulin to Treat Patients with Acute MI**

A combination infusion of glucose, insulin, and potassium (the GIK regimen) was initially used in the 1960s in an attempt to decrease morbidity and mortality in patients with acute MI. The rationale behind the combination was that exogenous insulin would limit myocardial uptake of toxic free fatty acids; glucose would provide energy for the heart; and potassium would replete the losses that occur with ischemia and reduce the likelihood of arrhythmias.

Nine studies have assessed the benefit of the GIK regimen, but only one of these studies demonstrated a decrease in mortality.21 The other studies, many of them much larger, found no difference in short- or long-term mortality with treatment.22 Although hyperglycemia is associated with a worse prognosis in patients with acute MI,23 hypoglycemia
during hospitalization is also associated with increased mortality in patients who have diabetes with non-ST-elevation MI. Therefore, patients admitted with acute MI should have moderate control of blood glucose using home regimens or basal insulin with correctional doses. This is one in a series of "Clinical Pharmacology" articles coordinated by Allen F. Shaughnessy, PharmD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Mass.

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REFERENCES

Glycemic Control in Hospitalized Patients Not in Intensive Care: Beyond Sliding-Scale Insulin

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Glycemic control in hospitalized patients who are not in intensive care remains unsatisfactory. Despite persistent expert recommendations urging its abandonment, the use of sliding-scale insulin remains pervasive in U.S. hospitals. Evidence for the effectiveness of sliding-scale insulin is lacking after more than 40 years of use. New physiologic subcutaneous insulin protocols use basal, nutritional, and correctional insulin. The initial total daily dose of subcutaneous insulin is calculated using a factor of 0.3 to 0.6 units per kg body weight, with one half given as long-acting insulin (the basal insulin dose), and the other one half divided daily over three meals as short-acting insulin doses (nutritional insulin doses). A correctional insulin dose provides a final insulin adjustment based on the preprandial glucose value. This correctional dose resembles a sliding scale, but is only a small fine-tuning of therapy, as opposed to traditional sliding-scale insulin alone. Insulin sensitivity, nutritional intake, and total daily dosing review can alter the physiologic insulin-dosing schedule. Prospective trials have demonstrated reductions in hyperglycemic measurements, hypoglycemia, and adjusted hospital length of stay when physiologic subcutaneous insulin protocols are used. Transitions in care require special considerations and attention to glycemic control medications. Changing the sliding-scale insulin culture requires a multidisciplinary effort to improve patient safety and outcomes. (Am Fam Physician. 2010;81(9):1130-1135. Copyright © 2010 American Academy of Family Physicians.)

Defining Optimal Glucose Targets for Hospitalized Patients

Table 1 summarizes upper glucose limits for optimal glycemic control from guidelines developed by the American Association of Clinical Endocrinologists (AACE),7 the American Diabetes Association (ADA),8 and the Society of Hospital Medicine (SHM).9 These organizations have consensus recommendations to abandon traditional sliding-scale insulin as the sole method for glycemic control. Their guidelines identify two inpatient populations—the patients in critical care who typically require admission to an intensive care unit (ICU) and intravenous insulin infusions; and the patients with diabetes who are not in an ICU and are traditionally treated with oral agents and subcutaneous insulin.

Evidence Against Sliding-Scale Insulin

The sliding scale for insulin dosage that is based on levels of glycosuria was introduced in 1934,10 and the technique was gradually adapted to blood glucose measurements.
SORT Key Recommendations for Practice

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional sliding-scale insulin should be abandoned as the sole means of controlling blood glucose levels in hospitalized patients.</td>
<td>B</td>
<td>7, 8, 9, 11, 14</td>
</tr>
<tr>
<td>Physiologic subcutaneous insulin protocols with basal, nutritional, and correctional components should be used for patients with diabetes mellitus who are hospitalized (non-ICU).</td>
<td>B</td>
<td>18, 20, 21, 22</td>
</tr>
<tr>
<td>Long-acting insulin should be used for physiologic basal insulin.</td>
<td>B</td>
<td>18, 19, 20, 21, 22</td>
</tr>
<tr>
<td>Short-acting insulin should be used for physiologic nutritional and correctional insulin.</td>
<td>B</td>
<td>18, 20, 21, 22</td>
</tr>
<tr>
<td>Discontinuing outpatient oral diabetic medications should be considered upon hospitalization of patients who are not in an ICU.</td>
<td>C</td>
<td>8, 24, 26</td>
</tr>
<tr>
<td>Insulin therapy should be continued upon hospital discharge of capable patients already on two or more oral diabetic medications and with an admission A1C greater than 10 percent.</td>
<td>C</td>
<td>6, 21, 23</td>
</tr>
<tr>
<td>An A1C level should be obtained upon admission if none performed within the past 30 days.</td>
<td>C</td>
<td>7, 8, 18, 21</td>
</tr>
</tbody>
</table>

ICU = intensive care unit.
A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Table 1. Upper Limits for Glycemic Control in Hospitalized Patients

<table>
<thead>
<tr>
<th>Organization</th>
<th>Blood glucose limits in intensive care units</th>
<th>Blood glucose limits in general care units</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association of Clinical Endocrinologists*; American Diabetes Association*; Society of Hospital Medicine*</td>
<td>140 to 180 mg per dl (7.77 to 9.99 mmol per L)</td>
<td>Preprandial: 140 mg per dl. All others: &lt; 180 mg per dl.</td>
</tr>
<tr>
<td></td>
<td>110 to 140 mg per dl (6.11 to 7.77 mmol per L)</td>
<td>Preprandial: 130 mg per dl. (7.21 mmol per L.) All others: 180 mg per dl.</td>
</tr>
</tbody>
</table>

Information from references 7 through 9.

Medical articles have questioned the effectiveness of sliding-scale insulin since at least 1970;11 a Medline search of 52 trials from 1966 to 2003 showed no clinical trials demonstrating benefit from sliding-scale insulin;12 and most experts currently question the effectiveness and safety of traditional sliding-scale insulin.13 A retrospective observational study to determine the effectiveness of sliding-scale insulin therapy at a university hospital reported that patients had hyperglycemic glucose levels on 84 percent of measurements.14 Although normal glucose levels were infrequently achieved, adjustment of sliding-scale insulin occurred in only 19 percent of participants.14

The largest prospective cohort study to date revealed that sliding-scale insulin regimens failed to adequately control hyperglycemia, resulted in high rates of hypoglycemia, and were associated with longer hospital stays.15 Patients treated with sliding-scale insulin alone had blood glucose levels greater than 300 mg per dl (16.65 mmol per L) three times more often than patients treated with other glucose-lowering therapies. Most patients treated with sliding-scale insulin in this study never had their regimens adjusted, despite poor glycemic control. The authors concluded that although sliding-scale insulin regimens were prescribed for the majority (76 percent) of general medical inpatients with diabetes, they appeared to provide no benefit and, when used without a standing dose of long- or intermediate-acting insulin, were associated with an increased rate of hyperglycemic episodes.15

Traditional sliding-scale insulin regimens measure blood glucose taken preprandially and at bedtime if the patient is eating, or on a schedule of every six hours if the patient is taking nothing by mouth. The amount of regular insulin given is based on the fingerstick glucose level. Sliding-scale insulin does not take into account basal insulin needs, diet (type and amount), and personal characteristics (e.g., weight) or insulin history (e.g., previous demonstrated insulin need, insulin sensitivity or resistance). Sliding-scale insulin is a reactive approach to glucose elevation control. It is not a proactive strategy to prevent hyperglycemic states.16,17 Using sliding-scale insulin is playing catch-up with the glucose reading, and it usually does not treat sufficiently or aggressively enough to maintain glucose levels in a normal range.

In most sliding-scale insulin regimens, the physician is only notified of extremes of hypoglycemia (i.e., blood glucose less than 60 mg per dl [3.33 mmol per L]) or hyperglycemia (i.e., blood glucose greater than 300 mg per dl). Using sliding-scale insulin creates the possibility of insulin stacking, with the pharmacokinetics of regular
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insulin given every six hours. The sliding-scale insulin regimen has no way to anticipate nutritional status or illness-related changes in glucose levels, further leading to insulin inadequacies. These flaws in traditional sliding-scale insulin put patients on a roller coaster of fluctuations in blood glucose, which could be harmful. Variations in blood glucose and insulin levels create oxidative stress, endothelial dysfunction, and increased markers of inflammation, which can contribute to poor patient outcomes.

Although nurses find the traditional sliding-scale insulin regimen easy to use, the entire care team must prioritize the necessity for optimal glycemic control. The time has come to challenge clinical inertia and no longer accept the poor outcomes of this regimen.

Evidence for Physiologic Subcutaneous Insulin Regimens

Research shows that subcutaneous insulin administration in the non-ICU hospitalized patient should include three components to be effective: basal insulin (to inhibit hepatic gluconeogenesis), nutritional insulin (to facilitate mealtime glucose metabolism), and correctional insulin (to provide real-time adjustment of insulin dosing based on the patient’s insulin sensitivity). The importance of a long-acting basal insulin is illustrated by a randomized controlled trial of insulin glargine (Lantus) compared with sliding-scale insulin in patients who had bariatric surgery. Insulin glargine treatment resulted in superior glycemic control, with only three episodes of hypoglycemia in 926 measurements. The addition of short-acting nutritional and correctional insulin to a basal long-acting insulin are current best-practice recommendations. Prospective observational studies have documented superior glycemic control with this three-pronged physiologic approach.

The University of California-San Diego has a structured insulin protocol that produced significantly fewer hyperglycemic and hypoglycemic patient-days compared with sliding-scale insulin. Results from the Brigham and Women’s Hospital protocol showed increased days of euglycemia (i.e., blood glucose of 60 to 180 mg per dL [3.33 to 9.99 mmol per L]) and reduced adjusted length of stay in non-ICU hospitalized patients treated with the protocol compared with patients treated with sliding-scale insulin.

The Randomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes trial is the only prospective randomized controlled study that compared traditional sliding-scale insulin with a new basal-bolus subcutaneous insulin glargine (for long-acting insulin) and insulin glulisine (Apidra; for nutritional and supplemental doses). Participants who received the basal-bolus insulin achieved blood glucose averages of 27 mg per dL (1.50 mmol per L) less than the participants who received sliding-scale insulin, with significantly more participants in the basal-bolus group who had levels below the target blood glucose level of 140 mg per dL (7.77 mmol per L), and no significant difference in hypoglycemia.

Physiologic Subcutaneous Insulin Protocols

Practical guidelines for implementing physiologic subcutaneous insulin have been published. These regimens are designed for patients with type 1 or 2 diabetes who are not in diabetic ketoacidosis, and for patients with newly discovered hyperglycemia during a hospital stay (i.e., those with random blood glucose levels greater than 180 mg per dL or two or more fasting blood glucose values greater than 130 mg per dL [7.21 mmol per L]). Implementing quality protocols is neither simple nor accomplishment in a single week because it involves a change in the medical culture. This multidisciplinary change includes detailed education of physicians, nurses, and dietary and pharmacy professionals to ensure that all are working to replace sliding-scale insulin with more effective strategies. Table 2 summarizes the key concepts of any protocol promoting the use of physiologic subcutaneous insulin.

Physiologic insulin regimens that used the basal, nutritional, and correctional insulin approach were thoroughly reviewed for best practices by the 2007 to 2008 SHM Glycemic Control Task Force. These results and best practices are available at SHM’s online glycemic control resource room (http://www.hospitalmedicine.org/ResourceRoomRedesign/GlycemicControl.cfm). The ADA, AACE, and SHM published the University of California-San Diego protocol in their task force document as the highlighted best practice, but other institutional protocols might better fit individual needs and hospital resources (for more information, visit http://www.hospitalmedicine.org/ResourceRoomRedesign/html/12Clinical_Tools/00_Clinical_Landing.cfm).

Although most patients use different regimens in the hospital than at home, the benefit will be uniform, and coordinated implementation from the entire care team...
null
Non-ICU Glycemic Control

the flexibility of adding insulin beyond the calculated nutritional dose.

Transitions of Care

It is a challenge to transition patients with hyperglycemia across various care settings. Variables affecting glycemic control include the previous level of control (as represented by A1C level), current dietary intake, and the severity of illness and associated hyperglycemia. Oral medications prove difficult to use and present their own concerns during inpatient use. Changing renal function and potential use of contrast dye are contraindications to metformin (Glucophage) use. Changes in diet and caloric intake can lead to an increase in hypoglycemic episodes when sulfonylureas are used. In general, oral medications should be stopped on hospital admission and insulin protocols should be initiated. Patients who were using an insulin regimen as outpatients can be converted to the hospital protocol initially on a unit-for-unit ratio before making individualized adjustments for patient variables. Outpatient regimens with a high ratio of basal insulin should be modified so that only 50 to 60 percent of long-acting insulin is used.

Transitioning patients from insulin infusions used in critical care settings to the subcutaneous regimens used on general hospital wards requires adjustment of the hyperglycemic regimen. The insulin dose given to the patient during the previous six hours should be extrapolated to a 24-hour dose, and then reduced by 20 percent as a safety factor to calculate the new total daily dose. The daily total dose is then divided according to the guidelines in Table 2. It is important to give the basal insulin injection at least one to two hours before discontinuation of the insulin infusion to prevent rebound hyperglycemia. If a faster discontinuation of the infusion is required, a portion of basal insulin is given with a more rapid analog to cover until the basal insulin can take effect or preferred administration time is reached. If the patient is starting to eat and the infusion can be continued, bolus insulin injections are added in addition to the drip to cover these new requirements.

The final transition of care occurs with patient discharge to home. Considerations include the discharge location, the patient’s ability to comply with therapy, and, perhaps most importantly, the level of glycemic control at admission. For patients who were adequately controlled before admission (i.e., A1C level was below target goal), discharge on their home therapy is appropriate. However, for patients who were admitted with an elevated A1C level, the addition of another oral agent or basal insulin should be considered. Insulin is preferred if the patient was admitted while taking two or more oral medications. For patients with poor glycemic control (i.e., A1C level greater than 10 percent), the physician should consider continuing a basal-bolus regimen as long as the patient will monitor blood glucose aggressively and has been educated on the new regimen. In this circumstance, the basal insulin requirements can often be maintained, but less bolus insulin prescribed to account for less acute stress. For patients who were not treated by their primary care physician during hospitalization, it is important to communicate treatment changes to their primary care physician.

Glycemic “Never Ever” Events

In October 2008, Medicare announced that hospitals would no longer be paid for hospital-acquired diabetic ketoacidosis, hyperglycemic coma, or hypoglycemic coma. This is further incentive for hospitals to adopt physiologic subcutaneous insulin protocols. To avoid hypoglycemia, insulin regimens should be modified if the patient’s blood glucose level is less than 70 mg per dL (3.89 mmol per L).

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<table>
<thead>
<tr>
<th>Blood glucose level</th>
<th>Insulin-sensitive dosing (units of insulin)*</th>
<th>Standard dosing (units of insulin)†</th>
<th>Insulin-resistant dosing (units of insulin)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 to 199 mg per dL</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>(8.32 to 11.04 mmol per L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 to 249 mg per dL</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(11.10 to 13.82 mmol per L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 to 299 mg per dL</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>(13.88 to 16.59 mmol per L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 to 349 mg per dL</td>
<td>4</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>(16.65 to 19.37 mmol per L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 349 mg per dL</td>
<td>5 + call</td>
<td>8 + call</td>
<td>12 + call</td>
</tr>
</tbody>
</table>

*—Total daily dose: less than 40 units.
†—Total daily dose: 40 to 80 units.
‡—Total daily dose: greater than 80 units.

Non-ICU Glycemic Control

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Author disclosure: Nothing to disclose.

REFERENCES


Ulcerative Colitis: Diagnosis and Treatment

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Ulcerative colitis is a chronic disease with recurrent symptoms and significant morbidity. The precise etiology is still unknown. As many as 25 percent of patients with ulcerative colitis have extraintestinal manifestations. The diagnosis is made endoscopically. Tests such as perinuclear antineutrophilic cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies are promising, but not yet recommended for routine use. Treatment is based on the extent and severity of the disease. Rectal therapy with 5-aminosalicylic acid compounds is used for proctitis. More extensive disease requires treatment with oral 5-aminosalicylic acid compounds and oral corticosteroids. The side effects of steroids limit their usefulness for chronic therapy. Patients who do not respond to treatment with oral corticosteroids require hospitalization and intravenous steroids. Refractory symptoms may be treated with azathioprine or inflixiab. Surgical treatment of ulcerative colitis is reserved for patients who fail medical therapy or who develop severe hemorrhage, perforation, or cancer. Longstanding ulcerative colitis is associated with an increased risk of colon cancer. Patients should receive an initial screening colonoscopy eight years after the onset of pancolitis and 12 to 15 years after the onset of left-sided disease; follow-up colonoscopy should be repeated every two to three years. (Am Fam Physician 2007;76:1323-30, 1331. Copyright © 2007 American Academy of Family Physicians.)

Ulcerative colitis is a chronic disease characterized by diffuse mucosal inflammation of the colon. Ulcerative colitis always involves the rectum (i.e., proctitis), and it may extend proximally in a contiguous pattern to involve the sigmoid colon (i.e., proctosigmoiditis), the descending colon (i.e., left-sided colitis), or the entire colon (i.e., pancolitis). This article reviews the diagnosis and treatment of ulcerative colitis from a primary care perspective.

**Epidemiology**

Ulcerative colitis affects approximately 250,000 to 500,000 persons in the United States, with an annual incidence of two to seven per 100,000 persons. The overall incidence of the disease has remained constant over the past five decades. The financial cost is nearly $500 million annually, and the disease accounts for 250,000 physician visits and 20,000 hospitalizations per year.

The onset of ulcerative colitis is most common between 15 and 40 years of age, with a second peak in incidence between 50 and 80 years. The disease affects men and women at similar rates. The precise etiology of ulcerative colitis is not well understood. A current hypothesis suggests that primary dysregulation of the mucosal immune system leads to an excessive immunologic response to normal microflora.

Cigarette smokers have a 40 percent lower risk of developing ulcerative colitis than do nonsmokers; however, compared with those who have never smoked, former smokers are approximately 1.7 times more likely to develop the disease. No consistent link between diet and the development of ulcerative colitis has been found. Although an association between the use of nonsteroidal anti-inflammatory drugs and the development of ulcerative colitis has been suggested, careful epidemiologic studies have failed to confirm that this association is causal.

**Typical Presentation**

The hallmark symptoms of ulcerative colitis are intermittent bloody diarrhea, rectal urgency, and tenesmus. The extent of colonic involvement can often, but not always, be predicted by the degree of symptomatology exhibited by the patient; more fulminant presentations are often associated with pancolitis, severe inflammation, or both. The
Ulcerative Colitis

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with moderately active ulcerative colitis are more likely to achieve overall improvement with higher dosages (4.8 g per day) of 5-ASA.</td>
<td>B</td>
<td>22</td>
</tr>
<tr>
<td>Patients with ulcerative colitis proctitis should be treated with 5-ASA suppositories rather than oral 5-ASA.</td>
<td>B</td>
<td>23</td>
</tr>
<tr>
<td>Patients who take chronic steroids for their ulcerative colitis should be screened for osteoporosis, and they usually receive prophylactic therapy with calcium, vitamin D, and bisphosphonates.</td>
<td>C</td>
<td>28</td>
</tr>
<tr>
<td>Patients with ulcerative colitis can receive nonpathogenic Escherichia coli instead of 5-ASA to prevent disease relapse.</td>
<td>B</td>
<td>31</td>
</tr>
<tr>
<td>Patients with ulcerative colitis should receive an initial screening colonoscopy eight years after a diagnosis of pancolitis and 12 to 15 years after a diagnosis of left-sided disease, and then subsequently every one to three years.</td>
<td>B</td>
<td>1, 34</td>
</tr>
</tbody>
</table>

5-ASA = 5-aminosalicylic acid.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1282 or http://www.aafp.org/afpsort.xml.

reported frequency of extraintestinal manifestations in patients with ulcerative colitis is 6 to 47 percent (Table 1).8

In the 1950s, Truelove and Witts developed a classification scheme for the severity of ulcerative colitis,9 which was later modified (Table 2).10 Using this classification scheme, investigators in one series found that 54 percent of patients could be classified initially as having mild disease, 27 percent as having moderate disease, and 19 percent as having severe disease.10 Assessment of severity has important therapeutic considerations, because patients with more severe disease (based on these criteria) respond less well to therapy.11

Diagnosis

The differential diagnosis of ulcerative colitis includes any condition that produces chronic, intermittent diarrhea, such as Crohn's disease, ischemic colitis, infectious colitis, irritable bowel syndrome (IBS), and pseudomembranous colitis (Table 3).12

CLINICAL DIAGNOSIS

The clinical history can be used to differentiate the various etiologies of chronic diarrhea in patients who have not previously been diagnosed with ulcerative colitis. For example, recent antibiotic use might suggest pseudomembranous colitis; recent travel may indicate infectious colitis; and abdominal pain that is relieved with bowel movements could represent IBS.

For the patient with established ulcerative colitis, the presence of constitutional symptoms and extraintestinal manifestations, particularly arthritis and skin lesions, may
Table 2. Ulcerative Colitis Severity Index

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Mild disease</th>
<th>Moderate disease</th>
<th>Severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g per dl. [g per L])</td>
<td>Normal</td>
<td>3.0 to 3.5 [30 to 35]</td>
<td>3.0</td>
</tr>
<tr>
<td>Body temperature</td>
<td>Normal</td>
<td>99 to 100°C (37.2 to 37.8°C)</td>
<td>&gt; 100°F</td>
</tr>
<tr>
<td>Bowel movements</td>
<td>&lt; 4 per day</td>
<td>4 to 6 per day</td>
<td>&gt; 6 per day</td>
</tr>
<tr>
<td>ESR (mm per hour)</td>
<td>&lt; 20</td>
<td>20 to 30</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>Normal</td>
<td>30 to 40</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Pulse (beats per minute)</td>
<td>&lt; 90</td>
<td>90 to 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>None</td>
<td>1 to 10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate.


provide clues to the severity of the disease. Physical examination should target the gastrointestinal, dermatologic, and ocular systems. The presence of finger clubbing increases the likelihood of ulcerative colitis in patients with bowel symptoms (positive likelihood ratio [LR] = 3.8), but its absence does not reduce the likelihood (negative LR = 0.8).

**DIAGNOSTIC TESTING**

In patients with suspected ulcerative colitis, the most important laboratory studies are stool examinations for ova and parasites, stool culture, and testing for *Clostridium difficile* toxin to help eliminate other causes of chronic diarrhea. The results of tests that support systemic inflammation, such as erythrocyte sedimentation rate and C-reactive protein, may be elevated. A complete blood count may show anemia from chronic blood loss, and a basic metabolic profile may demonstrate electrolyte abnormalities such as hypokalemia from persistent diarrhea.

Neither the American College of Gastroenterology nor the British Society of Gastroenterology recommends routine radiographic testing in persons with suspected ulcerative colitis. However, when endoscopy is not readily available or when colonic strictures prevent a thorough evaluation, a double-contrast barium enema and small-bowel barium follow-through can demonstrate fine mucosal detail. A contiguous, superficial inflammatory process associated with loss of haustra suggests ulcerative colitis, whereas noncontiguous inflammation involving the small intestine would support a diagnosis of Crohn’s disease.

Colonoscopy or proctosigmoidoscopy and biopsy are the tests of choice to diagnose ulcerative colitis. In one study, endoscopy with biopsy was 99 percent sensitive for colonic pathology in patients with diarrhea. Characteristic changes include loss of the typical vascular pattern, friability, exudates, ulcerations, and granularity in a continuous, circumferential pattern. Although flexible sigmoidoscopy is an efficient method of evaluating patients with chronic diarrhea, it may miss lesions in the ascending

Table 3. Differential Diagnosis of Ulcerative Colitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s colitis</td>
<td>Perianal lesions common; frank bleeding less common than in ulcerative colitis</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>Sudden onset; pathogens present in stool; pain may be a predominant feature</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Meets Rome II criteria for irritable bowel syndrome</td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>Affects older age groups; vascular disease often present; sudden onset, often painful</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Recent antibiotic use; <em>Clostridium difficile</em> toxin detectable in stool</td>
</tr>
</tbody>
</table>

Information from reference 12.
Ulcerative Colitis

or transverse colon in patients with Crohn’s disease. Thus, patients who are diagnosed with inflammatory bowel disease based on sigmoidoscopy results should then undergo a complete colonoscopy.

Differentiating Crohn’s disease from ulcerative colitis can be challenging, particularly early in the course of the disease, but it is an important step because appropriate treatments and potential complications vary for these two conditions. Table 4 outlines key differences between ulcerative colitis and Crohn’s disease. Review of biopsies by an experienced pathologist is critical to making the final diagnosis, although as many as 10 to 15 percent of patients may still have a diagnosis of indeterminate colitis.17 A meta-analysis of observational studies to determine the utility of blood tests to detect perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) showed that the combination is specific, but not sensitive for diagnosing ulcerative colitis (Table 5).18 Further studies must be done before pANCA and ASCA testing can be routinely recommended.

**Table 4. Comparison of Ulcerative Colitis and Crohn’s Disease**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Variable</td>
<td>Common</td>
</tr>
<tr>
<td>Depth of inflammation</td>
<td>Mucosal</td>
<td>Transmural</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Severe</td>
<td>Less severe</td>
</tr>
<tr>
<td>Distribution</td>
<td>Diffuse, contiguous spread; always involves rectum; spares proximal gastrointestinal tract</td>
<td>Segmental, noncontiguous spread (“skip lesions”); less common rectal involvement; occurs in entire gastrointestinal tract</td>
</tr>
<tr>
<td>Fistula and sinus tracts</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

Information from references 1, 7, and 12.

**Table 5. Accuracy of pANCA and ASCA to Diagnose Ulcerative Colitis**

<table>
<thead>
<tr>
<th>Test combination</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>LR+*</th>
<th>LR+†</th>
</tr>
</thead>
<tbody>
<tr>
<td>pANCA only positive</td>
<td>55.3</td>
<td>88.5</td>
<td>4.6</td>
<td>0.5</td>
</tr>
<tr>
<td>pANCA positive plus</td>
<td>70.3</td>
<td>93.4</td>
<td>10.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Increasing values mean the test is better at ruling in disease when positive.
†Decreasing values (i.e., less than 1) mean the test is better at ruling out disease when negative.

Information from reference 18.

**Treatment**

**MEDICAL MANAGEMENT**

Management of ulcerative colitis involves acute treatment of all inflammatory symptoms, followed by maintenance of remission. In general, the therapeutic approach is determined by the severity of the symptoms and the degree of colonic involvement (Figure 1).1,2,19 Approximately 66 percent of patients will achieve clinical remission with medical therapy, and 80 percent of treatment-compliant patients maintain remission.20 Current medical therapies for ulcerative colitis are summarized in Table 6.

First-line medical therapies contain mesalamine (also known as 5-aminosalicylic acid [5-ASA]), which acts topically from the colonic lumen to suppress the production of numerous proinflammatory mediators.21 Response to 5-ASA appears to be dose-dependent.22 Proctitis has been shown to respond better to suppositories than to oral 5-ASA23; response may take three to four weeks. Patients with proctosigmoiditis require delivery of 5-ASA via an enema and may need four to six weeks of therapy to achieve remission. Patients unable to tolerate the anal irritation of topical 5-ASA may try oral preparations, although response might take longer and remission rates may not be as high as those with direct topical therapy.24 Patients with pancolitis often require a combination of oral and topical 5-ASA compounds in addition to corticosteroids.

For patients who fail to improve with the
maximal dosage of 5-ASA compounds or who cannot tolerate the side effects, oral steroid therapy should be considered. Prednisone is given to these patients in dosages of 40 to 60 mg per day. Full-dose therapy is continued until symptoms are completely controlled (usually 10 to 14 days); the dosage is then tapered gradually by 5 mg per week. Long-term oral steroid use is not recommended for chronic maintenance because of significant side effects.¹

When patients do not respond to orally administered steroids, they should be admitted to the hospital to receive intravenous corticosteroids, such as methylprednisolone sodium (Solu-Medrol), 40 mg daily. In a retrospective study of 85 patients hospitalized with severe ulcerative colitis, the highest failure rate with intravenous corticosteroids occurred when symptoms lasted more than six weeks or when severe lesions were noted on endoscopy.¹¹

Hospitalized patients who fail to respond to intravenous corticosteroids after five to seven days are candidates for intravenous cyclosporine (Sandimmune). A review of the available literature showed limited evidence for the effectiveness of cyclosporine A compared...
Table 6. Common Medical Therapies for Patients with Ulcerative Colitis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dosage*</th>
<th>Approximate cost†</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-aminosalicylic acid</td>
<td>2 to 6 g</td>
<td>$57 ($13 to $38) for 500-mg tablets</td>
<td>Agranulocytosis, diarrhea, headache, nausea, rash, renal impairment</td>
</tr>
<tr>
<td>Sulfasalazine (Azulfidine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesalamine (Asacol, Pentasa)</td>
<td>Asacol, 2.4 to 4.8 g</td>
<td>$120 for 90 400-mg tablets</td>
<td></td>
</tr>
<tr>
<td>Mesalamine enema (Rowasa)</td>
<td>2 to 4 g</td>
<td>$48 for 30 500-mg capsules</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>40 to 60 mg</td>
<td>$13 to $15 ($8 to $12) for 10 mg tablets</td>
<td>Adrenal insufficiency, hyperglycemia, osteoporosis</td>
</tr>
<tr>
<td>Steroid enema</td>
<td>100 mg</td>
<td>$85 for seven 100-mg/60-mL bottles</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Azathioprine (Imuran)</td>
<td>1.5 to 2.5 mg per kg</td>
<td>$96 ($37 to $39) for 500-mg tablets</td>
<td>Headache, diarrhea, hepatotoxicity, leukopenia, myalgias</td>
</tr>
<tr>
<td>Mercaptopurine (Purinethol)</td>
<td>0.75 to 1.5 mg per kg</td>
<td>$157 ($122 to $130) for 500-mg tablets</td>
<td>Headache, diarrhea, hepatotoxicity, leukopenia, myalgias</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>5 mg per kg</td>
<td>$670 for 100-mg vial</td>
<td>Arthralgias, fever, infection, malaise, myalgias</td>
</tr>
</tbody>
</table>

Note: Listed in order of pharmacologic treatments for least to most severe ulcerative colitis.
*—Relative range of commonly used dosages.
†—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book, Montvale, N.J.: Medical Economics Data, 2005. Cost to the patient will be higher, depending on prescription filling fee.

With standard therapy using 5-ASA compounds and corticosteroids for patients with severe ulcerative colitis (two studies with a total of 50 patients); information about long-term results and costs is not available.25

In two recent clinical trials, 60 percent of patients who failed to respond to corticosteroid therapy achieved symptom remission with infliximab (Remicade), a chimeric monoclonal antibody that neutralizes the proinflammatory cytokine tumor necrosis factor-α, compared with approximately 30 percent of patients who received placebo.26 Patients who fail to respond to maximal medical therapy are candidates for surgical therapy (see Surgical Management section).

The level of therapy that induces remission dictates the selection of maintenance therapy. Patients who achieve remission solely with 5-ASA compounds may remain on these same medications, although typically at lower dosages.27 If response is obtained with azathioprine (Imuran) or infliximab, these medications are continued to maintain remission.

If steroids are required to induce remission, higher dosages of 5-ASA are often needed. Because of the significant side effects from long-term use, steroids should be tapered to the lowest effective dosage and stopped altogether if possible. In 2001, the American College of Rheumatology published guidelines on the prevention and treatment of glucocorticoid-induced osteoporosis. All patients on chronic steroid therapy should be counseled to participate in regular weight-bearing exercise; screened for osteoporosis with dual energy x-ray absorptiometry; and considered for prophylaxis with calcium, vitamin D, and bisphosphonates.28

**SURGICAL MANAGEMENT**

No prospective randomized trials have compared medical treatment to surgery for any indication in patients with ulcerative colitis.7 Colectomy for the treatment of ulcerative colitis is warranted in patients who develop dysplasia or cancer (see Cancer Screening section); who have disease resistant to maximal medical therapy; or who experience massive hemorrhage, perforation, or toxic megacolon.19 Toxic megacolon, which is a presentation of fulminant ulcerative colitis, is characterized by dilatation of the transverse...
colon to more than 5.5 cm on supine abdominal radiography and requires emergent surgical evaluation.²⁹

Surgical treatment of ulcerative colitis is curative and has been shown to lead to durable improvements in quality of life.²⁹ However, potential complications include bowel obstruction, pouchitis, stricture, pouch dysfunction, and the possibility of decreased fertility in women.²⁹

**COMPLEMENTARY THERAPY**

Patients with ulcerative colitis may be motivated to attempt complementary medical therapies because of side effects and limited effectiveness of current medical therapy. Results of one study suggested that *Lactobacillus* was as effective as 5-ASA in preventing recurrence of ulcerative colitis, although the study was unblinded.³⁰ Other studies have shown the comparative effectiveness of non-pathogenic *Escherichia coli* to 5-ASA products in the treatment of ulcerative colitis and the prevention of relapse.³¹³²

**CANCER SCREENING**

Patients with ulcerative colitis are at increased risk of developing colon cancer. The anatomic extent and duration of the disease correlate with the degree of risk. In one meta-analysis, investigators found that the risk of colon cancer was 2 percent in the first 10 years of ulcerative colitis, 8 percent during the first 20 years, and 18 percent during the first 30 years.³³ Patients who have only proctitis or proctosigmoiditis are not considered to be at increased risk of developing colon cancer.

No randomized controlled trials have compared the outcomes of different surveillance strategies.⁷ The British Society of Gastroenterology recommends initial colonoscopy eight to 10 years after disease onset for patients with pancolitis and 15 to 20 years after the onset of left-sided disease, with follow-up colonoscopies every three years in the second decade of the disease.³⁴ The American Cancer Society recommends similar initial screening (i.e., eight years for pancolitis, 12 to 15 years for left-sided disease) but states that follow-up examinations should be done every one to two years.³⁵ Both guidelines suggest that colonoscopy include random mucosal biopsies of the colon every 10 cm. Family physicians need to be strong advocates for colon cancer screening in their patients with ulcerative colitis, who may be unwilling to undergo additional testing, particularly during periods of remission.

A meta-analysis of nine observational studies involving more than 1,900 patients found an association between 5-ASA use and a decreased likelihood of colorectal cancer.³⁶ However, additional studies are needed before a definitive recommendation can be made.

The authors thank Patti Forest, MD, and Tiana Shekari, DO, for their assistance in the preparation of the manuscript.

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Author disclosure: Nothing to disclose.

**REFERENCES**


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Ulcerative Colitis


Evaluation and Management of Intestinal Obstruction

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Georgetown University Hospital, Washington, District of Columbia

Acute intestinal obstruction occurs when there is an interruption in the forward flow of intestinal contents. This interruption can occur at any point along the length of the gastrointestinal tract, and clinical symptoms often vary based on the level of obstruction. Intestinal obstruction is most commonly caused by intra-abdominal adhesions, malignancy, or intestinal herniation. The clinical presentation generally includes nausea and emesis, colicky abdominal pain, and a failure to pass flatus or bowel movements. The classic physical examination findings of abdominal distension, tympany to percussion, and high-pitched bowel sounds suggest the diagnosis. Radiologic imaging can confirm the diagnosis, and can also serve as useful adjunctive investigations when the diagnosis is less certain. Although radiography is often the initial study, non-contrast computed tomography is recommended if the index of suspicion is high or if suspicion persists despite negative radiography. Management of uncomplicated obstructions includes fluid resuscitation with correction of metabolic derangements, intestinal decompression, and bowel rest. Evidence of vascular compromise or perforation, or failure to resolve with adequate bowel decompression is an indication for surgical intervention. (Am Fam Physician. 2011;83(2):159-165. Copyright © 2011 American Academy of Family Physicians.)

Intestinal obstruction accounts for approximately 15 percent of all emergency department visits for acute abdominal pain. Complications of intestinal obstruction include bowel ischemia and perforation. Morbidity and mortality associated with intestinal obstruction have declined since the advent of more sophisticated diagnostic tests, but the condition remains a challenging surgical diagnosis. Physicians who are treating patients with intestinal obstruction must weigh the risks of surgery with the consequences of inappropriate conservative management. A suggested approach to the patient with suspected small bowel obstruction is shown in Figure 1.

Pathophysiology
The fundamental concerns about intestinal obstruction are its effect on whole body fluid/electrolyte balances and the mechanical effect that increased pressure has on intestinal perfusion. Proximal to the point of obstruction, the intestinal tract dilates as it fills with intestinal secretions and swallowed air. Failure of intestinal contents to pass through the intestinal tract leads to a cessation of flatus and bowel movements. Intestinal obstruction can be broadly differentiated into small bowel and large bowel obstruction.

Fluid loss from emesis, bowel edema, and loss of absorptive capacity leads to dehydration. Emesis leads to loss of gastric potassium, hydrogen, and chloride ions, and significant dehydration stimulates renal proximal tubule reabsorption of bicarbonate and loss of chloride, perpetuating the metabolic alkalosis. In addition to derangements in fluid and electrolyte balance, intestinal stasis leads to overgrowth of intestinal flora, which may lead to the development of feculent emesis. Additionally, overgrowth of intestinal flora in the small bowel leads to bacterial translocation across the bowel wall.

Ongoing dilation of the intestine increases luminal pressures. When luminal pressures exceed venous pressures, loss of venous drainage causes increasing edema and hyperemia of the bowel. This may eventually lead to compromised arterial flow to the bowel, causing ischemia, necrosis, and...
Intestinal Obstruction

perforation. A closed-loop obstruction, in which a section of bowel is obstructed proximally and distally, may undergo this process rapidly, with few presenting symptoms. Intestinal volvulus, the prototypical closed-loop obstruction, causes torsion of arterial inflow and venous drainage, and is a surgical emergency.

**Causes and Risk Factors**
The most common causes of intestinal obstruction include adhesions, neoplasms, and herniation (Table 1). Adhesions resulting from prior abdominal surgery are the predominant cause of small bowel obstruction, accounting for approximately 60 percent of cases. Lower abdominal surgeries, including appendectomies, colorectal surgery, gynecologic procedures, and hernia repairs, confer a greater risk of adhesive small bowel obstruction. Less common causes of obstruction include intestinal intussusception, volvulus, intra-abdominal abscesses, gallstones, and foreign bodies.

---

**Management of Small Bowel Obstruction**

Patient presents with signs and symptoms of small bowel obstruction

Did the patient present clinically stable?

- No
  - Exploratory laparotomy

- Yes
  - Radiography or computed tomography

Vascular compromise or perforation? (Continued)

- No
  - Complete obstruction

- Yes
  - Partial obstruction

No oral intake, nasogastric intubation, intravenous hydration

Resolution within 24 to 48 hours?

- No
  - Exploratory laparotomy

- Yes
  - Upper gastrointestinal/small bowel follow-through/enteroclysis?

Resolution?

- Yes
  - Advance diet

- No
  - Exploratory laparotomy

---

Figure 1. Algorithm for evaluation and treatment of patients with suspected small bowel obstruction.
The development of metabolic acidosis, especially in a patient with an increasing serum lactate level, may signal bowel ischemia.

RADIOGRAPHY

The initial evaluation of patients with clinical signs and symptoms of intestinal obstruction should include plain upright abdominal radiography. Radiography can quickly determine if intestinal perforation has occurred; free air can be seen above the liver in upright films or left lateral decubitus films. Radiography accurately diagnoses intestinal obstruction in approximately 60 percent of cases, and its positive predictive value approaches 80 percent in patients with high-grade intestinal obstruction. However, plain abdominal films can appear normal in early obstruction and in high jejunal or duodenal obstruction. Therefore, when clinical suspicion for obstruction is high or persists despite negative initial radiography, non-contrast computed tomography (CT) should be ordered.

In patients with small bowel obstruction, supine views show dilation of multiple loops of small bowel, with a paucity of air in the large bowel (Figure 2). Those with large bowel obstruction may have dilation of the

### Table 1. Causes of Intestinal Obstruction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesive disease (60 percent)</td>
<td></td>
</tr>
<tr>
<td>Neoplasm (20 percent)</td>
<td></td>
</tr>
<tr>
<td>Herniation (10 percent)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease (5 percent)</td>
<td></td>
</tr>
<tr>
<td>Intussusception (&lt; 5 percent)</td>
<td></td>
</tr>
<tr>
<td>Volvulus (&lt; 5 percent)</td>
<td></td>
</tr>
<tr>
<td>Other (&lt; 5 percent)</td>
<td></td>
</tr>
</tbody>
</table>

### History and Physical Examination

Patients should be asked about their history of abdominal neoplasia, hernia or hernia repair, and inflammatory bowel disease, because these conditions increase the risk of obstruction. The hallmarks of intestinal obstruction include colicky abdominal pain, nausea and vomiting, abdominal distension, and a cessation of flatus and bowel movements. It is important to differentiate between true mechanical obstruction and other causes of these symptoms (Table 2). Distal obstructions allow for a greater intestinal reservoir, with pain and distension more marked than emesis, whereas patients with proximal obstructions may have minimal abdominal distension but marked emesis. The presence of hypotension and tachycardia is an indication of severe dehydration. Abdominal palpation may reveal a distended, tympanic abdomen; however, this finding may not be present in patients with early or proximal obstruction. Auscultation in patients with early obstruction reveals high-pitched bowel sounds, whereas those with late obstruction may present with minimal bowel sounds as the intestinal tract becomes hypotonic.

### Diagnostic Testing and Imaging

#### LABORATORY TESTS

Laboratory evaluation of patients with suspected obstruction should include a complete blood count and metabolic panel. Hypokalemic, hypochloremic metabolic alkalosis may be noted in patients with severe emesis. Elevated blood urea nitrogen levels are consistent with dehydration, and hemoglobin and hematocrit levels may be increased. The white blood cell count may be elevated if intestinal bacteria translocate into the bloodstream, causing the systemic inflammatory response syndrome or sepsis.

#### Table 2. Differential Diagnosis of Abdominal Pain, Distension, Nausea, and Cessation of Flatus and Bowel Movements

<table>
<thead>
<tr>
<th>Alternate diagnosis</th>
<th>Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Acute liver failure, history of hepatitis or alcoholism</td>
</tr>
<tr>
<td>Medications (e.g., tricyclic antidepressants, narcotics)</td>
<td>Review of medications; diagnosis of exclusion</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>History of peripheral vascular disease, hypercoagulable state, or postprandial abdominal angina; recent use of vasopressors</td>
</tr>
<tr>
<td>Perforated viscus/intra-abdominal sepsis</td>
<td>Fever, leukocytosis, acute abdomen, free air on imaging</td>
</tr>
<tr>
<td>Postoperative paralytic ileus</td>
<td>Recent abdominal surgery with no postoperative flatus or bowel movement</td>
</tr>
<tr>
<td>Pseudo-obstruction (Ogilvie syndrome)</td>
<td>Acutely dilated large intestine, history of intestinal dysmotility, diabetes mellitus, scleroderma</td>
</tr>
</tbody>
</table>
Intestinal Obstruction

Figure 2. Supine view of the abdomen in a patient with intestinal obstruction. Dilated loops of small bowel are visible (arrows).

Figure 3. Lateral decubitus view of the abdomen, showing air-fluid levels consistent with intestinal obstruction (arrows).

Figure 4. Axial computed tomography scan showing dilated, contrast-filled loops of bowel on the patient's left (yellow arrows), with decompressed distal small bowel on the patient's right (red arrows). The cause of obstruction, an incarcerated umbilical hernia, can also be seen (green arrow), with proximally dilated bowel entering the hernia and decompressed bowel exiting the hernia.

colon, with decompressed small bowel in the setting of a competent ileocecal valve. Upright or lateral decubitus films may show laddering air fluid levels (Figure 3). These findings, in conjunction with a lack of air and stool in the distal colon and rectum, are highly suggestive of mechanical intestinal obstruction.

COMPUTED TOMOGRAPHY

CT is appropriate for further evaluation of patients with suspected intestinal obstruction in whom clinical examination and radiography do not yield a definitive diagnosis. CT is sensitive for detection of high-grade obstruction (up to 90 percent in some series), and has the additional benefit of defining the cause and level of obstruction in most patients. In addition, CT can identify emergent causes of intestinal obstruction, such as volvulus or intestinal strangulation.

CT findings in patients with intestinal obstruction include dilated loops of bowel proximal to the site of obstruction, with distally decompressed bowel. The presence of a discrete transition point helps guide operative planning (Figure 4). Absence of contrast material in the rectum is also an important sign of complete obstruction. For this
Intestinal Obstruction

reason, rectal administration of contrast material should be avoided. A C-loop of distended bowel with radial mesenteric vessels with medial conversion is highly suspicious for intestinal volvulus. Thickened intestinal walls and poor flow of contrast material into a section of bowel suggests ischemia, whereas pneumatosis intestinalis, free intraperitoneal air, and mesenteric fat stranding suggest necrosis and perforation. Although CT is highly sensitive and specific for high-grade obstruction, its value diminishes in patients with partial obstruction. In these patients, oral contrast material may be seen traversing the length of the intestine to the rectum, with no discrete area of transition. Fluoroscopy may be of greater value in confirming the diagnosis.

The American College of Radiology recommends non-contrast CT as the initial imaging modality of choice. However, because most causes of small bowel obstruction will have systemic manifestations or fail to resolve—necessitating operative intervention—the additional diagnostic value of CT compared with radiography is limited. Radiation exposure is also significant. Therefore, in most patients, CT should be ordered when the diagnosis is in doubt, when there is no surgical history or hernias to explain the etiology, or when there is a high index of suspicion for complete or high-grade obstruction.

**CONTRAST FLUOROSCOPY**

Contrast studies, such as a small bowel follow-through, can be helpful in the diagnosis of a partial intestinal obstruction in patients with high clinical suspicion and in clinically stable patients in whom initial conservative management was not effective. The use of water-soluble contrast material is not only diagnostic, but may also be therapeutic in patients with partial small-bowel obstruction. A randomized controlled trial of 124 patients showed a 74 percent reduction in the need for surgical intervention in patients receiving gastrografin fluoroscopy within 24 hours of initial presentation. Contrast fluoroscopy may also be useful in determining the need for surgery; the presence of contrast material in the rectum within 24 hours of administration has a 97 percent sensitivity for spontaneous resolution of intestinal obstruction.

There are several variations of contrast fluoroscopy. In the small-bowel follow-through study, the patient drinks contrast material, then serial abdominal radiographs are taken to visualize the passage of contrast through the intestinal tract. Enteroclysis involves naso- or oro-duodenal intubation, followed by the instillation of contrast material directly into the small bowel. Although this study has superior sensitivity compared with small-bowel follow-through, it is more labor-intensive and is rarely performed. Rectal fluoroscopy can be helpful in determining the site of a suspected large bowel obstruction.

**ULTRASONOGRAPHY**

In patients with high-grade obstruction, ultrasound evaluation of the abdomen has high sensitivity for intestinal obstruction, approaching 85 percent. However, because of the wide availability of CT, it has largely replaced ultrasonography as the first-line investigation in stable patients with suspected intestinal obstruction. Ultrasonography remains a valuable investigation for unstable patients with an ambiguous diagnosis and in patients for whom radiation exposure is contraindicated, such as pregnant women.

**MAGNETIC RESONANCE IMAGING**

Magnetic resonance imaging (MRI) may be more sensitive than CT in the evaluation of intestinal obstruction, which involves intubation of the duodenum and infusion of contrast material directly into the small bowel, can more reliably determine the location and cause of obstruction. However, because of the ease and cost-effectiveness of abdominal CT, MRI remains an investigational or adjunctive imaging modality for intestinal obstruction.

**Treatment**

Management of intestinal obstruction is directed at correcting physiologic derangements caused by the obstruction, bowel rest, and removing the source of obstruction. The
<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal radiography is an effective initial examination in patients with suspected intestinal obstruction.</td>
<td>C</td>
<td>6, 7</td>
<td>Radiography has greater sensitivity in high-grade obstruction than in partial obstruction.</td>
</tr>
<tr>
<td>Computed tomography is warranted when radiography indicates high-grade intestinal obstruction or is inconclusive.</td>
<td>C</td>
<td>8-10</td>
<td>Computed tomography can reliably determine the cause of obstruction, and whether serious complications are present, in most patients with high-grade obstructions.</td>
</tr>
<tr>
<td>Upper gastrointestinal fluoroscopy with small bowel follow-through can determine the need for surgical intervention in patients with partial obstruction.</td>
<td>C</td>
<td>14, 15</td>
<td>Contrast material that passes into the cecum within four hours of oral administration is highly predictive of successful nonoperative management.</td>
</tr>
<tr>
<td>Antibiotics can protect against bacterial translocation and subsequent bacteremia in patients with intestinal obstruction.</td>
<td>C</td>
<td>22</td>
<td>Enteric bacteria have been found in cultures from serosal scrapings and mesenteric lymph node biopsy in patients requiring surgery.</td>
</tr>
<tr>
<td>Clinically stable patients can be treated conservatively with bowel rest, intubation and decompression, and intravenous fluid resuscitation.</td>
<td>A</td>
<td>22-26</td>
<td>Several randomized controlled trials have shown that surgery can be avoided with conservative management.</td>
</tr>
<tr>
<td>Surgery is warranted in patients with intestinal obstruction that does not resolve within 48 hours after conservative therapy is initiated.</td>
<td>B</td>
<td>25</td>
<td>Study found that conservative management beyond 48 hours does not diminish the need for surgery, but increases surgical morbidity.</td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

The former is addressed by intravenous fluid resuscitation with isotonic fluid. The use of a bladder catheter to closely monitor urine output is the minimum requirement for gauging the adequacy of resuscitation; other invasive measures, such as arterial cannulation or central venous pressure monitoring, can be used as the clinical situation warrants. Antibiotics are used to treat intestinal overgrowth of bacteria and translocation across the bowel wall. The presence of fever and leukocytosis should prompt inclusion of antibiotics in the initial treatment regimen. Antibiotics should have coverage against gram-negative organisms and anaerobes, and the choice of a specific agent should be determined by local susceptibility and availability. Aggressive replacement of electrolytes is recommended after adequate renal function is confirmed.

The decision to perform surgery for intestinal obstruction can be difficult. Peritonitis, clinical instability, or unexplained leukocytosis or acidosis are concerning for abdominal sepsis, intestinal ischemia, or perforation; these findings mandate immediate surgical exploration. Patients with an obstruction that resolves after reduction of a hernia should be scheduled for elective hernia repair, whereas immediate surgery is required in patients with an irreducible or strangulated hernia. Stable patients with a history of abdominal malignancy or high suspicion for malignancy should be thoroughly evaluated for optimal surgical planning. Abdominal malignancy can be treated with primary resection and reconstruction or palliative diversion, or placement of ventilating and feeding tubes.

Treatment of stable patients with intestinal obstruction and a history of abdominal surgery presents a challenge. Conservative management of a high-grade obstruction should be attempted initially, using intestinal intubation and decompression, aggressive intravenous rehydration, and antibiotics. The inclusion of oral magnesium hydroxide, simethicone, and probiotics decreased the length of hospitalization in a randomized controlled trial of 144 patients with partial small bowel obstructions (number needed to treat = 7). Caution should be used when clinical and radiologic evidence suggest complete obstruction, because the use of intestinal stimulation can exacerbate the obstruction and precipitate intestinal ischemia.
Intestinal Obstruction

Conservative management is successful in 40 to 70 percent of clinically stable patients, with a higher success rate in those with partial obstruction.24-26 Although conservative management is associated with shorter initial hospitalization (4.9 versus 12 days), there is also a higher rate of eventual recurrence (40.5 versus 26.8 percent).27 With conservative management, resolution generally occurs within 24 to 48 hours. Beyond this time frame, the risk of complications, including vascular compromise, increases. If intestinal obstruction is not resolved with conservative management, surgical evaluation is required.25

Figures 2 through 4 provided by Citrelda J. Cooper, MD.

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Author disclosure: Nothing to disclose.

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Infectious Disease
Diagnosis and Management of Community-Acquired Pneumonia in Adults

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TRACY L. LEMONOVICH, MD, University Hospitals Case Medical Center, Cleveland, Ohio

Community-acquired pneumonia is diagnosed by clinical features (e.g., cough, fever, pleuritic chest pain) and by lung imaging, usually an infiltrate seen on chest radiography. Initial evaluation should determine the need for hospitalization versus outpatient management using validated mortality or severity prediction scores. Selected diagnostic laboratory testing, such as sputum and blood cultures, is indicated for inpatients with severe illness but is rarely useful for outpatients. Initial outpatient therapy should include a macrolide or doxycycline. For outpatients with comorbidities or who have used antibiotics within the previous three months, a respiratory fluoroquinolone (levofloxacin, gemifloxacin, or moxifloxacin), or an oral beta-lactam antibiotic plus a macrolide should be used. Inpatients not admitted to an intensive care unit should receive a respiratory fluoroquinolone, or a beta-lactam antibiotic plus a macrolide. Patients with severe community-acquired pneumonia or who are admitted to the intensive care unit should be treated with a beta-lactam antibiotic, plus azithromycin or a respiratory fluoroquinolone. Those with risk factors for Pseudomonas should be treated with a beta-lactam antibiotic (piperacillin/tazobactam, imipenem/cilastatin, meropenem, doripenem, or ceftazidime), plus an aminoglycoside and azithromycin or an antipseudomonal fluoroquinolone (levofloxacin or ciprofloxacin). Those with risk factors for methicillin-resistant Staphylococcus aureus should be given vancomycin or linezolid. Hospitalized patients may be switched from intravenous to oral antibiotics after they have clinical improvement and are able to tolerate oral medications, typically in the first three days. Adherence to the Infectious Diseases Society of America/American Thoracic Society guidelines for the management of community-acquired pneumonia has been shown to improve patient outcomes. Physicians should promote pneumococcal and influenza vaccination as a means to prevent community-acquired pneumonia and pneumococcal bacteremia. (Am Fam Physician. 2011;83(11):1299-1306. Copyright © 2011 American Academy of Family Physicians.)

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality in adults. CAP is defined as an infection of the lung parenchyma that is not acquired in a hospital, long-term care facility, or other recent contact with the healthcare system. Table 1 includes common etiologies of CAP. This article discusses the important studies and guidelines for CAP that have been published since the topic was last reviewed in American Family Physician.

Epidemiology

Pneumonia and influenza combined is the eighth leading cause of death in the United States and the most common cause of infection-related mortality. In 2007, about 52,700 persons died from the conditions. The overall annual incidence of CAP ranges from five to 11 per 1,000 persons, with more cases occurring in the winter months. In 2006, there were approximately 4.2 million ambulatory care visits for CAP in the United States, with Streptococcus pneumoniae as the most commonly identified pathogen. The estimated annual economic burden of CAP in the United States exceeds $17 billion.

Diagnosis

DIFFERENTIAL DIAGNOSIS

Many microbiologic pathogens can cause CAP. Pneumonia traditionally has been classified as typical, usually caused by S. pneumoniae, or atypical, caused by Mycoplasma pneumoniae, Chlamydophila pneumoniae (formerly Chlamydia pneumoniae), Legionella species, and respiratory viruses. However, it is often not possible to distinguish typical versus atypical pneumonia solely on clinical grounds.

HISTORY AND PHYSICAL EXAMINATION

Common symptoms include fever (positive likelihood ratio [LR+] = 4.5), chills, pleuritic
SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendations                                                                 Evidence rating References
In patients with clinically suspected CAP, chest radiography should be obtained to confirm the diagnosis. C 12
Evaluation for specific pathogens that would alter standard empiric therapy should be performed when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues; this testing usually is not required in outpatients. C 12
Mortality and severity prediction scores should be used to determine inpatient versus outpatient care for patients with CAP. A 22-24
All patients with CAP who are admitted to the intensive care unit should be treated with dual therapy. A 28
Prevention of CAP should focus on universal influenza vaccination and pneumococcal vaccination for patients at high risk of pneumococcal disease. B 12, 35-37

CAP = community-acquired pneumonia.
A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence; usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

cHEST PAIN, AND A COUGH PRODUCING MUCOPURULENT SPUTUM. OVERALL, PHYSICIAN JUDGMENT IS MODERATELY ACCURATE FOR DIAGNOSIS OF PNEUMONIA, ESPECIALLY FOR RULING IT OUT (LR+ = 2.0, NEGATIVE LIKELIHOOD RATIO [LR−] = 0.24).7 ABSENCE OF FEVER AND SPUTUM ALSO SIGNIFICANTLY REDUCES THE LIKELIHOOD OF PNEUMONIA IN OUTPATIENTS.8

HIGH FEVER (GREATER THAN 104°F [40°C]), MALE SEX, MULTIPLE INVOLVEMENT, AND GASTROINTESTINAL AND NEUROLOGIC ABNORMALITIES HAVE BEEN ASSOCIATED WITH CAP CAUSED BY Legionella INFECTION.9 THE CLINICAL PRESENTATION OF CAP IS OFTEN MORE SUBTLE IN OLDER PATIENTS, AND MANY OF THESE PATIENTS DO NOT EXHIBIT CLASSIC SYMPTOMS.10 THEY OFTEN PRESENT WITH WEAKNESS AND DECLINE IN FUNCTIONAL AND MENTAL STATUS.

THE PATIENT HISTORY SHOULD FOCUS ON DETECTING SYMPTOMS CONSISTENT WITH CAP, UNDERLYING DEFECTS IN HOST DEFENSES, AND POSSIBLE EXPOSURE TO SPECIFIC PATHOGENS. PERSONS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE OR HUMAN IMMUNODEFICIENCY VIRUS INFECTION HAVE AN INCREASED INCIDENCE OF CAP. PATIENTS SHOULD BE ASKED ABOUT OCCUPATION, ANIMAL EXPOSURES, AND SEXUAL HISTORY TO HELP IDENTIFY A SPECIFIC INFECTION AGENT. A RECENT TRAVEL HISTORY (WITHIN TWO WEEKS) MAY HELP IDENTIFY Legionella PNEUMONIA, WHICH HAS BEEN ASSOCIATED WITH STAYS AT HOTELS AND ON CRUISE SHIPS. INFLUENZA IS OFTEN SUGGESTED ON THE BASIS OF TYPICAL SYMPTOMS DURING PEAK INFLUENZA SEASON.

PHYSICAL EXAMINATION MAY REVEAL FEVER, DULLNESS TO PERCUSSION, EGOPHONY, TACHYCARDIA (LR+ = 2.1), AND TACHYPIA (LR+ = 3.5). ASYMMETRIC BREATH SOUNDS, PLURAL RUBS, EGOPHONY, AND INCREASED FREMITUS ARE RELATIVELY UNCOMMON, BUT ARE HIGHLY SPECIFIC FOR PNEUMONIA (LR+ = 8.0); THESE SIGNS HELP RULE IN PNEUMONIA WHEN PRESENT, BUT ARE NOT HELPFUL WHEN ABSENT.8 RALES OR BRONCHIAL BREATH SOUNDS ARE HELPFUL, BUT MUCH LESS ACCURATE THAN CHEST RADIOGRAPHY.10 TACHYPIA IS COMMON IN OLDER PATIENTS WITH CAP, OCCURRING IN UP TO 70 PERCENT OF THOSE OLDER THAN 65 YEARS.11 PULSE OXIMETRY SCREENING SHOULD BE PERFORMED IN ALL PATIENTS WITH SUSPECTED CAP.12

Table 1. Common Etiologies of Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Frequency (median percentage)</th>
<th>Etiology</th>
<th>Frequency (median percentage)</th>
<th>Etiology</th>
<th>Frequency (median percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients</td>
<td></td>
<td>Inpatients not admitted to ICU</td>
<td></td>
<td>Inpatients admitted to ICU</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>16</td>
<td>S. pneumoniae</td>
<td>25</td>
<td>S. pneumoniae</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>15</td>
<td>Respiratory viruses</td>
<td>10</td>
<td>Legionella species</td>
<td>10</td>
</tr>
<tr>
<td>Streptococcal pneumoniae</td>
<td>14</td>
<td>M. pneumoniae</td>
<td>6</td>
<td>Gram-negative bacilli</td>
<td>5</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>12</td>
<td>H. influenzae</td>
<td>5</td>
<td>Staphylococcus aureus</td>
<td>5</td>
</tr>
<tr>
<td>Legionella species</td>
<td>2</td>
<td>C. pneumoniae</td>
<td>3</td>
<td>Respiratory viruses</td>
<td>4</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1</td>
<td>Legionella species</td>
<td>3</td>
<td>H. influenzae</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>44</td>
<td>Unknown</td>
<td>37</td>
<td>Unknown</td>
<td>41</td>
</tr>
</tbody>
</table>

ICU = intensive care unit.
Information from references 1 through 3.
**Table 2. Patients with Acute Respiratory Illness Who Benefit from Chest Radiography**

**Chest radiography should be performed in:**
- Any patient with at least one of the following abnormal vital signs:
  - Temperature > 100°F (37.8°C)
  - Heart rate > 100 beats per minute
  - Respiratory rate > 20 breaths per minute
- Any patient with at least two of the following clinical findings:
  - Decreased breath sounds
  - Crackles (rales)
  - Absence of asthma


**RADIOLOGIC EXAMINATION**

An infiltrate on lung imaging, usually chest radiography, is required for the diagnosis of CAP; therefore, the test should be performed in patients with clinically suspected CAP. Table 2 includes a tool for identifying patients with respiratory illness who would benefit from chest radiography. The extent of radiographic findings may help identify the severity of illness and assist with initial point-of-care decisions. Lobar consolidation, cavitation, and pleural effusions suggest a bacterial etiology. Diffuse parenchymal involvement is more often associated with *Legionella* or viral pneumonia. Because overuse of antibiotics for treatment of upper respiratory tract infections promotes drug resistance and can have adverse effects, identifying patients who will benefit from antimicrobial therapy is important.

**LABORATORY TESTING**

Routine laboratory testing to establish an etiology in outpatients with CAP is usually unnecessary. However, evaluation for specific pathogens that would alter standard empiric therapy should be performed when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues (Table 3). A randomized clinical trial comparing pathogen-driven therapy versus empiric therapy in patients with CAP found no

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**Table 3. Recommended Diagnostic Testing in Patients with Suspected Community-Acquired Pneumonia**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Blood culture</th>
<th>Sputum culture</th>
<th>Legionella urine antigen test</th>
<th>Pneumococcal urine antigen test</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to intensive care unit</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Endotracheal aspirate if intubated</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asplenia</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavitary infiltrates</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Fungal and tuberculosis cultures</td>
</tr>
<tr>
<td>Chronic severe liver disease</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient therapy ineffective</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Thoracentesis and pleural fluid cultures</td>
</tr>
<tr>
<td>Positive <em>Legionella</em> urine antigen test result</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive pneumococcal urine antigen test result</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent travel (within past two weeks)</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Severe obstructive lung disease</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Community-Acquired Pneumonia

statistically significant differences in mortality rate or length of hospitalization.14

Hypoglycemia (blood glucose level less than 70 mg per
dL [3.89 mmol per L]) at presentation is associated with increased 30-day mortality even after adjustment for other variables, including comorbid illness and Pneumonia Severity Index (PSI) score.15 Procalcitonin levels are elevated in many patients with bacterial infections, and several studies have shown procalcitonin tests to be potentially useful in CAP.16,17 However, the turnaround time for procalcitonin results can be prolonged, limiting their clinical usefulness. A white blood cell count greater than 10,400 per mm3 (10.40 × 103 per L; LR+ = 3.4, LR− = 0.52) and a C-reactive protein level of 5.0 mg per dL (47.62 nmol per L) or greater (LR+ = 3.1, LR− = 0.7) are modestly helpful when positive, but it is important to note that normal values do not rule out pneumonia.18

Blood cultures are not recommended for most hospitalized patients with CAP and should be performed according to the recommendations in Table 3.12 The most common blood isolate in patients with CAP is S. pneumoniae. A study comparing 125 patients with CAP caused by pneumococcal bacteremia and 1,847 patients with nonbacteremic CAP found no increase in poor outcomes among those with bacteremia.19 In addition, false-positive blood culture results have been associated with prolonged hospitalization and more vancomycin use.20 Blood cultures should be ordered for patients with severe CAP (Table 4) because they are more likely to be infected with bacteria other than S. pneumoniae.12 Blood cultures in patients with severe CAP have a higher yield, are more likely to grow pathogens not covered by empiric therapy, and have higher potential to influence antibiotic management.12

Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend that sputum specimens be obtained before the initiation of antibiotic therapy in inpatients.12 A negative sputum culture result from a good-quality sample (i.e., positive for neutrophils, but less than 25 epithelial cells per low-power field) is strong evidence that gram-negative bacilli and Staphylococcus aureus are absent, and can prompt safe de-escalation of antibiotic therapy. Necrotizing or cavitary pneumonia may be caused by methicillin-resistant S. aureus (MRSA). Physicians should maintain a high clinical suspicion for MRSA pneumonia in patients with a history of MRSA skin lesions or other risk factors. In patients with suspected Legionella pneumonia, sputum culture can help identify a causative environmental exposure.12

Pleural effusions greater than 5 cm on lateral chest radiography should be drained by thoracentesis, and the fluid sent for Gram stain and aerobic and anaerobic cultures. Urine antigen tests are helpful when an adequate sputum culture is unobtainable or when antibiotic therapy has already been started. The sensitivity of the pneumococcal urine antigen test is 50 to 80 percent with a specificity of greater than 90 percent. Although the urine antigen test only detects Legionella serogroup 1, this serogroup causes 80 to 95 percent of CAP from Legionella; the test is 70 to 90 percent sensitive and 99 percent specific for serogroup 1. Urine antigen test results are positive on the first day of illness and remain positive for several weeks.13 In general, urine antigen tests are better at ruling in disease when positive; a negative test result does not rule out infection with a specific pathogen given its somewhat limited sensitivity.

Acute- and convalescent-phase serologic testing is the standard for other atypical causes of pneumonia. However, treating patients based on a positive acute-phase titer result has been shown to be unreliable.21 Therefore, serology for other atypical pathogens should not be routinely ordered. Rapid antigen testing or direct fluorescent antibody testing for influenza can help with consideration of antiviral therapy and may decrease use of antibacterial agents.12

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### Table 4. Criteria for Severe Community-Acquired Pneumonia

**Minor criteria**
- Blood urea nitrogen level ≥ 20 mg per dL (7.14 mmol per L)
- Confusion/disorientation
- Hypotension requiring aggressive fluid resuscitation
- Hypothermia (core temperature < 96.8°F [36°C])
- Leukopenia (white blood cell count < 4,000 per mm3 [4.00 × 103 per L])
- Multilobar infiltrates
- PaO2/FiO2 ratio ≤ 250
- Respiratory rate ≥ 30 breaths per minute
- Thrombocytopenia (platelet count < 100 × 103 per mm3 [100 × 109 per L])

**Major criteria**
- Invasive mechanical ventilation
- Septic shock with need for vasopressors

*Note.* Any major criterion is an absolute indication for admission to an intensive care unit. One or more minor criteria indicate increased risk of death, and admission to an intensive care unit may be appropriate. FiO2 = fraction of inspired oxygen; PaO2 = partial arterial oxygen pressure.

Table 5. CURB-65 Mortality Prediction Tool for Patients with Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Prognostic variables*</th>
<th>30-day mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatient vs. outpatient</td>
</tr>
<tr>
<td>Confusion</td>
<td>0 or 1 point: Treat as outpatient 0.7 to 2.1</td>
</tr>
<tr>
<td>Blood urea nitrogen level &gt; 20 mg per dL (7.14 mmol per L)</td>
<td>2 points: Treat as inpatient 9.2</td>
</tr>
<tr>
<td>Respiratory rate ≥ 30 breaths per minute</td>
<td>≥3 points: Treat in intensive care unit 15 to 40</td>
</tr>
<tr>
<td>Blood pressure (systolic &lt; 90 mm Hg or diastolic ≤ 60 mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td></td>
</tr>
</tbody>
</table>

*—Assign 1 point for each variable.
Information from reference 1.

Management

The initial management of CAP depends on the patient’s severity of illness; underlying medical conditions and risk factors, such as smoking; and ability to adhere to a treatment plan. The need for hospitalization is the first decision that needs to be made after CAP is diagnosed or suspected.

Inpatient vs. Outpatient Care

The estimated direct cost of a single CAP hospitalization ranges from $3,000 to $13,000. Patients admitted to the hospital are at risk of hospital-acquired complications, such as thromboembolic events, superinfections (e.g., Clostridium difficile colitis), and catheter-associated urinary tract infections. Mortality and severity prediction scores have been designed to identify patients with CAP who can be treated safely as outpatients. The PSI is the most extensively validated prediction score, but it is limited by its complexity and failure to always recognize the most severely ill patients, especially those without comorbid illness.22

Table 5 summarizes the CURB-65 (confusion, uremia, respiratory rate, blood pressure), a prediction score developed by the British Thoracic Society.1 It is simpler than the PSI but does not specifically account for decompensated chronic illness that occurs with CAP. CURB-65 has been shown to predict death from CAP in hospital and outpatient settings.23

More recently, SMART-COP (systolic blood pressure, multilobar chest radiography, albumin level, respiratory rate, tachycardia, confusion, oxygen level, arterial pH) was created to predict which patients will require intensive respiratory or vasopressor support (Table 6).24 A SMART-COP score of 3 or more points identifies 92 percent of those who will receive intensive respiratory or vasopressor support, whereas sensitivities for PSI and CURB-65 are 74 and 39 percent, respectively.24 Patients admitted to the intensive care unit (ICU) with CAP are more likely to be men who have congestive heart failure or chronic obstructive pulmonary disease.25

Antibiotic Therapy

Because the exact causative organism is not identified in many patients with CAP, treatment is usually empiric. Recommendations for antibiotic therapy in these patients

Table 6. SMART-COP Score to Predict Need for IRVS in Patients with Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure &lt; 90 mm Hg</td>
<td>2</td>
</tr>
<tr>
<td>Multilobar involvement on chest radiography</td>
<td>1</td>
</tr>
<tr>
<td>Albumin level &lt; 3.5 g per dL (35 g per L)</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
</tr>
<tr>
<td>50 years and younger: ≥ 25 breaths per minute</td>
<td>1</td>
</tr>
<tr>
<td>Older than 50 years: ≥ 30 breaths per minute</td>
<td></td>
</tr>
<tr>
<td>Tachycardia (≥ 125 beats per minute)</td>
<td>1</td>
</tr>
<tr>
<td>Confusion (new onset)</td>
<td>1</td>
</tr>
<tr>
<td>Oxygen level</td>
<td>2</td>
</tr>
<tr>
<td>50 years and younger: PaO2 &lt; 70 mm Hg, oxygen saturation ≤ 93 percent, or (if on oxygen) PaO2/FiO2 ratio &lt; 333</td>
<td></td>
</tr>
<tr>
<td>Older than 50 years: PaO2 &lt; 60 mm Hg, oxygen saturation ≤ 90 percent, or (if on oxygen) PaO2/FiO2 ratio &lt; 250</td>
<td></td>
</tr>
<tr>
<td>Arterial pH &lt; 7.35</td>
<td>Total: 2</td>
</tr>
</tbody>
</table>

Score | Risk of needing IRVS |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 2 points</td>
<td>Low</td>
</tr>
<tr>
<td>3 or 4 points</td>
<td>Moderate (one in eight patients)</td>
</tr>
<tr>
<td>5 or 6 points</td>
<td>High (one in three patients)</td>
</tr>
<tr>
<td>≥7 points</td>
<td>Very high (two in three patients)</td>
</tr>
</tbody>
</table>

Alternative interpretation for primary care physicians (disregard albumin level, arterial pH, and PaO2):

Score | Risk of needing IRVS |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 points</td>
<td>Very low</td>
</tr>
<tr>
<td>1 point</td>
<td>Low (one in 20 patients)</td>
</tr>
<tr>
<td>2 points</td>
<td>Moderate (one in 10 patients)</td>
</tr>
<tr>
<td>3 points</td>
<td>High (one in six patients)</td>
</tr>
<tr>
<td>≥4 points</td>
<td>High (one in three patients)</td>
</tr>
</tbody>
</table>

FiO2 = fraction of inspired oxygen; IRVS = intensive respiratory or vasopressor support; PaO2 = partial arterial oxygen pressure.
Community-Acquired Pneumonia

Table 7. Empiric Therapy for Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Initial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously healthy outpatients; no antibiotic use in past three months</td>
<td>A macrolide or doxycycline</td>
</tr>
<tr>
<td>Outpatients with comorbidities* or antibiotic use in past three months†</td>
<td>A respiratory fluoroquinolone (levofloxacin [Levaquin], gemifloxacin [Factive], or moxifloxacin [Avelox]), or a beta-lactam antibiotic (high-dose amoxicillin, amoxicillin/clavulanate [Augmentin], or cefpodoxime) plus a macrolide§</td>
</tr>
<tr>
<td>Inpatients, non-ICU</td>
<td>A respiratory fluoroquinolone, or a beta-lactam antibiotic plus a macrolide</td>
</tr>
<tr>
<td>Inpatients, ICU</td>
<td>A beta-lactam antibiotic (ceftriaxone [Rocephin], cefotaxime [Claforan], or ampicillin/subactam [Unasyn]), plus azithromycin (Zithromax) or a respiratory fluoroquinolone§</td>
</tr>
<tr>
<td>Special considerations</td>
<td></td>
</tr>
<tr>
<td>Risk factors for Pseudomonas species</td>
<td>A beta-lactam antibiotic (piperacillin/tazobactam [Zosyn], cefepime, imipenem/cilastatin [Primaxin], meropenem [Merrem], or doripenem [Doribax], plus either ciprofloxacin (Cipro) or levofloxacin or The above beta-lactam antibiotic plus an aminoglycoside and azithromycin or The above beta-lactam antibiotic plus an aminoglycoside and an antipneumococcal respiratory fluoroquinolone</td>
</tr>
<tr>
<td>Risk factors for methicillin-resistant Staphylococcus aureus</td>
<td>Vancomycin or linezolid (Zyvox)</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Oseltamivir (Tamiflu) or zanamivir (Relenza)</td>
</tr>
</tbody>
</table>

ICU = intensive care unit.
*—Chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; asplenia.
†—Antibiotic from a different class should be used.
§—Also recommended in regions with a rate of high-level macrolide-resistant Streptococcal pneumoniae of greater than 25 percent.
§—For patients allergic to penicillin, a respiratory fluoroquinolone plus aztreonam (Azactam) are recommended.


are listed in Table 7. One of the major differences between U.S. and European guidelines for treatment of CAP is that all patients in the United States receive treatment for *S. pneumoniae* and atypical organisms because CAP is more often caused by these pathogens in North America. Macrolides (e.g., azithromycin [Zithromax], clarithromycin [Biaxin]) can be used for outpatients with no cardiopulmonary disease or recent antibiotic use.

Drug-resistant *S. pneumoniae* is a concern in patients with comorbid illness or recent antibiotic therapy (within previous three months) and should be treated with an oral beta-lactam antibiotic (e.g., high-dose amoxicillin, amoxicillin/clavulanate [Augmentin], cefpodoxime) combined with a macrolide. A respiratory fluoroquinolone is another choice. If a patient has used an antibiotic in the previous three months, a drug from a different class should be prescribed to decrease the risk of pneumococcal resistance. For hospitalized patients not admitted to the ICU, an intravenous respiratory fluoroquinolone alone or an intravenous beta-lactam antibiotic combined with a macrolide or doxycycline should be given. A study showed doxycycline to be comparable to levofloxacin (Levaquin) in effectiveness, length of hospital stay, and failure rate for empiric treatment of CAP; doxycycline is also a less expensive option for hospitalized patients who are not admitted to the ICU. However, the sample size in the study was small and IDSA/ATS guidelines recommend doxycycline only for outpatients.

All patients with CAP who are admitted to the ICU should be treated with dual therapy, which is associated with lower mortality from bacteremic pneumococcal pneumonia and improves survival in patients with CAP and shock. Some patients with severe CAP, especially after an episode of influenza or viral illness, who are admitted to the ICU need added coverage for *S. aureus*, including MRSA. MRSA-associated CAP is characterized by a severe, bilateral, necrotizing pneumonia induced by Panton-Valentine leukocidin and other toxins.
Duration of therapy for patients with CAP has traditionally been 10 to 14 days, but more recent evidence suggests a shorter course of up to seven days is equally effective.\textsuperscript{29} Hospitalized patients may be switched from intravenous to oral antibiotic therapy after they have clinical improvement and are able to tolerate oral medications. An early switch from intravenous to oral antibiotics after three days in patients with severe CAP has been shown to be effective and may decrease length of hospital stay.\textsuperscript{28} A course of oral azithromycin after completing intravenous azithromycin and ceftriaxone (Rocephin) is effective and well-tolerated.\textsuperscript{31} Treatment of patients who do not respond well to initial treatment is summarized in Table 8.\textsuperscript{12}

**ADJUNCTIVE THERAPIES**

Prednisolone therapy (40 mg once daily) for one week did not improve outcomes in hospitalized patients with CAP.\textsuperscript{35} The IDSA/ATS guidelines recommend considering drotrecogin alfa (Xigris) within 24 hours of hospital admission in patients with severe CAP and persistent septic shock.\textsuperscript{12}

**Quality Improvement and Prevention**

The Centers for Medicare and Medicaid Services has developed a set of core measures for CAP that is collected for every hospital and reported on the Hospital Compare Web site (http://www.healthcare.gov/compare). Adhering to national guidelines has been shown to improve length of hospital stay and other outcomes\textsuperscript{33,34}; however, they do not take into account individual patient differences and should not supplant physician judgment. Pneumococcal vaccination is recommended for all persons 65 years and older, adults younger than 65 years who have chronic illness or asplenia, and all adults who smoke or have asthma.\textsuperscript{35} However, effectiveness may decrease with age, and studies evaluating its effectiveness against pneumonia without bacteremia have been mixed.\textsuperscript{36-38}

The influenza vaccine is also important for the prevention of CAP. However, its effectiveness is influenced by host factors and how closely the antigens in the vaccine are matched with the circulating influenza strain.\textsuperscript{12} The influenza vaccine has also been shown to effectively prevent pneumonia, hospitalization, and death in older persons.\textsuperscript{39}

**Table 8. Management of Unresponsive Community-Acquired Pneumonia**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed response to therapy with no improvement after 72 hours</td>
<td>Resistant microorganism or uncovered pathogen</td>
</tr>
<tr>
<td>Noninfectious condition, such as pulmonary embolism, drug fever, bronchiolitis obliterans, organizing pneumonia, congestive heart failure, vasculitis</td>
<td>Nosocomial superinfection</td>
</tr>
<tr>
<td>Clinical deterioration or continued progression of illness</td>
<td>Severity of illness at presentation</td>
</tr>
<tr>
<td>Metastatic infection, such as empyema, endocarditis, meningitis, arthritis</td>
<td>Inaccurate diagnosis, such as acute respiratory distress syndrome, aspiration</td>
</tr>
<tr>
<td>Exacerbation of comorbid illness or coexisting noninfectious disease, such as renal failure, acute myocardial infarction, pulmonary embolism</td>
<td></td>
</tr>
</tbody>
</table>

*No improvement within 72 hours of treatment is not considered abnormal.
*Further workup and management for unresponsive illness include blood cultures, repeat sputum culture (interpret with caution because of possible colonization), urine antigen testing for Streptococcus pneumoniae and Legionella if not previously done, chest computed tomography, thoracentesis if significant pleural effusion is present with fluid analysis and culture, and bronchoscopy with bronchoalveolar lavage and transbronchial biopsies.


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Author disclosure: Nothing to disclose.

**REFERENCES**


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**DATA SOURCES:** A PubMed search was completed in Clinical Queries using the key term community-acquired pneumonia. The search included meta-analyses, randomized controlled trials, clinical trials, practice guidelines, and reviews. The limits included English language, humans, and all adults 19 years and older. We also searched the National Guideline Clearinghouse, Agency for Healthcare Research and Quality Evidence Reports, Cochrane Database of Systematic Reviews, and the U.S. Preventive Services Task Force. Search date: September 19, 2010.
Community-Acquired Pneumonia


Diagnosis and Treatment of Community-Acquired Pneumonia

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Patients with community-acquired pneumonia often present with cough, fever, chills, fatigue, dyspnea, rigors, and pleuritic chest pain. When a patient presents with suspected community-acquired pneumonia, the physician should first assess the need for hospitalization using a mortality prediction tool, such as the Pneumonia Severity Index, combined with clinical judgment. Consensus guidelines from several organizations recommend empiric therapy with macrolides, fluoroquinolones, or doxycycline. Patients who are hospitalized should be switched from parenteral antibiotics to oral antibiotics after their symptoms improve, they are afebrile, and they are able to tolerate oral medications. Clinical pathways are important tools to improve care and maximize cost-effectiveness in hospitalized patients. (Am Fam Physician 2006;73:442-50. Copyright © 2006 American Academy of Family Physicians.)

Members of various family medicine departments develop articles on "Practical Therapeutics." This article is one in a series coordinated by the Department of Family Medicine at the University of Illinois at Chicago College of Medicine, Chicago, Ill. Guest editor of the series is Eric Henley, M.D., M.P.H.

Community-acquired pneumonia (CAP) is defined as pneumonia not acquired in a hospital or a long-term care facility. Despite the availability of potent new antimicrobials and effective vaccines, 1 an estimated 5.6 million cases of CAP occur annually in the United States. 2 The estimated total annual cost of health care for CAP in the United States is $8.4 billion. 2 Table 1 presents an overview of CAP including definition, signs and symptoms, etiology, and risk factors.

Epidemiology
The epidemiology of CAP is unclear because few population-based statistics on the condition alone are available. The Centers for Disease Control and Prevention (CDC) combines pneumonia with influenza when collecting data on morbidity and mortality, although they do not combine them when collecting hospital discharge data. In 2001, influenza and pneumonia combined were the seventh leading causes of death in the United States, 3 down from sixth in previous years, and represented an age-adjusted death rate of 21.8 per 100,000 patients. 3 Death rates from CAP increase with the presence of comorbidity and increased age; the condition affects persons of any race or sex equally. The decrease in death rates from pneumonia and influenza are largely attributed to vaccines for vulnerable populations (e.g., older and immunocompromised persons).

Clinical Presentation
Pneumonia is an inflammation or infection of the lungs that causes them to function abnormally. Pneumonia can be classified as typical or atypical, although the clinical presentations are often similar. Several symptoms commonly present in patients with pneumonia.

Types of CAP
Typical pneumonia usually is caused by bacteria such as Streptococcus pneumoniae. Atypical pneumonia usually is caused by the influenza virus, mycoplasma, chlamydia, legionella, adenovirus, or other unidentified microorganisms. The patient's age is the main differentiating factor between typical and atypical pneumonia; young adults are more prone to atypical causes, 5,6 and very
**SORT: Key Recommendations for Practice**

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with suspected community-acquired pneumonia (CAP) should receive chest radiography.</td>
<td>C</td>
<td>8</td>
</tr>
<tr>
<td>The Pneumonia Severity Index should be used to assist in decisions regarding hospitalization of patients with CAP.</td>
<td>A</td>
<td>8, 9, 15, 16</td>
</tr>
<tr>
<td>The initial treatment of CAP is empiric, and macrolides or doxycycline (Vibramycin) should be used in most patients.</td>
<td>C</td>
<td>8, 9, 29</td>
</tr>
<tr>
<td>Respiratory fluoroquinolones should be used when patients have failed first-line regimens, have significant comorbidities, have had recent antibiotic therapy, are allergic to alternative agents, or have a documented infection with highly drug-resistant pneumococci.</td>
<td>C</td>
<td>8, 9, 28, 29</td>
</tr>
</tbody>
</table>

* A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 374 or http://www.aafp.org/afpsort.xml.

Young and older persons are more predisposed to typical causes.

**SYMPTOMS**

Common clinical symptoms of CAP include cough, fever, chills, fatigue, dyspnea, rigors, and pleuritic chest pain. Depending on the pathogen, a patient's cough may be persistent and dry, or it may produce sputum. Other presentations may include headache and myalgia. Certain etiologies, such as legionella, also may produce gastrointestinal symptoms.

**Diagnosis**

**PHYSICAL EXAMINATION**

Physical examination may reveal dullness to percussion of the chest, crackles or rales on auscultation, bronchial breath sounds,

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overview of Community-Acquired Pneumonia</strong></td>
</tr>
<tr>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>Lower respiratory tract infection in a nonhospitalized person that is associated with symptoms of acute infection with or without new infiltrate on chest radiographs</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
</tr>
<tr>
<td>Temperature greater than 38°C (100.4°F)</td>
</tr>
<tr>
<td>Cough with or without sputum, hemoptysis</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Malaise, fatigue</td>
</tr>
<tr>
<td>Rales, rhonchi, wheezing</td>
</tr>
<tr>
<td>Egophony, bronchial breath sounds</td>
</tr>
<tr>
<td>Dullness to percussion</td>
</tr>
<tr>
<td>Atypical symptoms in older patients</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>Bacterial</td>
</tr>
<tr>
<td>Chlamydia species</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Legionella species</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Viral</td>
</tr>
<tr>
<td>Adenovirus</td>
</tr>
<tr>
<td>Influenza A and B</td>
</tr>
<tr>
<td>Parainfluenza</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>Endemic fungi</td>
</tr>
<tr>
<td>Blastomycosis</td>
</tr>
<tr>
<td>Coccioidiomycosis</td>
</tr>
<tr>
<td>Histoplasmosis</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
</tr>
<tr>
<td>Age older than 65 years</td>
</tr>
<tr>
<td>Human immunodeficiency virus or immunocompromised</td>
</tr>
<tr>
<td>Recent antibiotic therapy or resistance to antibiotics</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Liver disease</td>
</tr>
<tr>
<td>Neoplastic disease</td>
</tr>
</tbody>
</table>
tactile fremitus, and egophony ("E" to "A" changes). The patient also may be tachypneic. A prospective study showed that patients with typical pneumonia were more likely than not to present with dyspnea and bronchial breath sounds on auscultation.

**RADIOGRAPHY**

Chest radiography (posteroanterior and lateral views) has been shown to be a critical component in diagnosing pneumonia. According to the latest American Thoracic Society (ATS) guidelines for the diagnosis and treatment of adults with CAP, "all patients with suspected CAP should have a chest radiograph to establish the diagnosis and identify complications (pleural effusion, multilobar disease)." Chest radiography may reveal a lobar consolidation, which is common in typical pneumonia; or it could show bilateral, more diffuse infiltrates than those commonly seen in atypical pneumonia. However, chest radiography performed early in the course of the disease could be negative.

**LABORATORY TESTS**

Historically, common laboratory tests for pneumonia have included leukocyte count, sputum Gram stain, two sets of blood cultures, and urine antigens. However, the validity of these tests has recently been questioned after low positive culture rates were found (e.g., culture isolates of *S. pneumoniae* were present in only 40 to 50 percent of cases). Such low positive culture rates are likely due to problems with retrieving samples from the lower respiratory tract, previous administration of antibiotics, contamination from the upper airways, faulty separation of sputum from saliva when streaking slides or plates, or viral etiology. Furthermore, sputum samples are adequate in only 52.3 percent of patients with CAP, and only 44 percent of those samples contain pathogens. Nonetheless, initial therapy often is guided by the assumption that the presenting disease is caused by a common bacterial pathogen.

Findings also cast doubt on the clinical utility of obtaining blood cultures from patients with suspected CAP. In a study of CAP cases in 19 Canadian hospitals over a six-month period, positive blood cultures were obtained in only 5.2 to 6.2 percent of patients, including those with the most severe disease. Based on these findings, other researchers concluded that a positive blood culture had no correlation with the severity of the illness or outcome. Another prospective study showed that blood cultures were positive in only 10.5 percent of patients with pneumonia. Despite these and

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**TABLE 2**

**Sensitivity and Specificity of Diagnostic Tests for CAP**

<table>
<thead>
<tr>
<th>Diagnostic tests by pathogen</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chlamydia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid PCR (sputum, BAL fluid)</td>
<td>30 to 95</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>Serology (fourfold rise in serum</td>
<td>10 to 100</td>
<td>—</td>
</tr>
<tr>
<td>and convalescent titers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum culture</td>
<td>10 to 80</td>
<td>&gt; 95</td>
</tr>
<tr>
<td><strong>Gram-negative rods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum Gram stain</td>
<td>15 to 100</td>
<td>11 to 100</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae, Moraxella catarrhalis, Pneumoniae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum culture</td>
<td>Diagnostic yield</td>
<td>Diagnostic yield</td>
</tr>
<tr>
<td></td>
<td>20 to 79⁺</td>
<td>20 to 79⁺</td>
</tr>
<tr>
<td><strong>Influenza</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid DFA (sputum, BAL fluid)</td>
<td>22 to 75</td>
<td>90</td>
</tr>
<tr>
<td><strong>Legionella pneumophilia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFA (sputum, BAL fluid)</td>
<td>22 to 75</td>
<td>90</td>
</tr>
<tr>
<td>PCR (sputum, BAL fluid)</td>
<td>83 to 100</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>Serum acute titer</td>
<td>10 to 27</td>
<td>&gt; 85</td>
</tr>
<tr>
<td>Urinary antigen</td>
<td>55 to 90</td>
<td>&gt; 95</td>
</tr>
<tr>
<td><strong>Mycoplasma pneumoniae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic titers</td>
<td>75 to 95</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Cold agglutinins</td>
<td>50 to 60</td>
<td>—</td>
</tr>
<tr>
<td>PCR (sputum, BAL fluid)</td>
<td>30 to 95</td>
<td>&gt; 95</td>
</tr>
<tr>
<td><strong>Pneumococcal pneumoniae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest radiography (lobar infiltrate)</td>
<td>40⁺</td>
<td>—</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>Diagnostic yield</td>
<td>Diagnostic yield</td>
</tr>
<tr>
<td></td>
<td>20 to 79⁺</td>
<td>20 to 79⁺</td>
</tr>
<tr>
<td>Sputum Gram stain</td>
<td>15 to 100</td>
<td>11 to 100</td>
</tr>
</tbody>
</table>

CAP = community-acquired pneumonia; PCR = polymerase chain reaction; BAL = bronchoalveolar lavage; DFA = direct fluorescence antibody.  
⁺—Overgrowth of oral flora, isolation of atypical agents requires special media.  
₁—Acute symptoms.  
Information from references 2, 6, 11, and 13.
other research findings, current ATS guidelines recommend that patients hospitalized for suspected CAP receive two sets of blood cultures. Blood cultures, however, are not necessary for outpatient diagnosis.6

Legionella antigens were found in the urine of 48 percent of patients with suspected Legionella pneumophilia serogroup 1 infection.14 Table 23,8,11,13 includes the sensitivity and specificity of diagnostic tests for CAP.

**Treatment**

Initial treatment of CAP is based on physical examination findings, laboratory results, and patient characteristics (e.g., age, chronic illnesses, history of smoking, history of the illness).15 Physicians should begin their treatment decisions by assessing the need for hospitalization using a prediction tool for increased mortality, such as the Pneumonia Severity Index (Table 315), combined with clinical judgment.9

**OUTPATIENT VS. INPATIENT TREATMENT**

Choosing between outpatient and inpatient treatment is a crucial decision because of the possible risk of death.8,15,16 This decision not only influences diagnostic testing and medication choices, it can have a psychological impact on patients and their families. On average, the estimated cost for inpatient care of patients with CAP is $7,500. Outpatient care can cost as little as $150 to $350.17-19 Hospitalization of a patient should depend on patient age, comorbidities, and the severity of the presenting disease.9,20

Physicians tend to overestimate a patient’s risk of death14; therefore, many low-risk patients who could be safely treated as outpatients are admitted for more costly inpatient care. The Pneumonia Severity Index (Table 315) was developed to assist physicians in identifying patients at a higher risk of complications and who are more likely to benefit from hospitalization.8,15,16 Investigators developed a risk model based on a prospective cohort study of 2,287 patients with CAP in Pittsburgh, Boston, and Halifax, Nova Scotia. By using the model, the authors found that 26 to 31 percent of the hospitalized patients were good outpatient candidates, and an additional 13 to 19 percent only needed brief hospital observation. They validated this model using data from more than 50,000 patients with CAP in 275 U.S. and Canadian hospitals.15-17,21,22

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumonia Severity Index</strong></td>
</tr>
<tr>
<td><strong>Patient Characteristics</strong></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Nursing home resident</td>
</tr>
<tr>
<td><strong>Comorbid Illness</strong></td>
</tr>
<tr>
<td>Neoplastic disease</td>
</tr>
<tr>
<td>Liver disease</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Renal disease</td>
</tr>
<tr>
<td><strong>Physical examination findings</strong></td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Respiratory rate &gt; 30 breaths per minute</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 90 mm Hg</td>
</tr>
<tr>
<td>Temperature &lt; 35°C (95°F) or &gt; 40°C (105°F)</td>
</tr>
<tr>
<td>Pulse rate &gt; 125 beats per minute</td>
</tr>
<tr>
<td><strong>Laboratory and radiographic findings</strong></td>
</tr>
<tr>
<td>Arterial pH &lt; 7.35</td>
</tr>
<tr>
<td>Blood urea nitrogen &gt; 64 mg per dl. (22.85 mmol per l)</td>
</tr>
<tr>
<td>Sodium &lt; 130 mEq per l (130 mmol per l)</td>
</tr>
<tr>
<td>Glucose &gt; 250 mg per dl. (13.87 mmol per l)</td>
</tr>
<tr>
<td>Hematocrit &lt; 30 percent</td>
</tr>
<tr>
<td>Partial pressure of arterial oxygen &lt; 60 mm Hg or oxygen percent saturation &lt; 90 percent</td>
</tr>
<tr>
<td>Pleural effusion</td>
</tr>
</tbody>
</table>

| Total points: |  |

**Point total** | **Risk** | **Risk class** | **Mortality % (No. of patients)** | **Recommended site of care** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No predictors</td>
<td>Low</td>
<td>I</td>
<td>0.1 (3,034)</td>
<td>Outpatient</td>
</tr>
<tr>
<td>≤ 70</td>
<td>Low</td>
<td>II</td>
<td>0.6 (5,778)</td>
<td>Outpatient</td>
</tr>
<tr>
<td>71 to 90</td>
<td>Low</td>
<td>III</td>
<td>2.8 (6,790)</td>
<td>Inpatient (briefly)</td>
</tr>
<tr>
<td>91 to 130</td>
<td>Moderate</td>
<td>IV</td>
<td>8.2 (13,104)</td>
<td>Inpatient</td>
</tr>
<tr>
<td>&gt; 130</td>
<td>High</td>
<td>V</td>
<td>29.2 (9,333)</td>
<td>Inpatient</td>
</tr>
</tbody>
</table>

Information from reference 15.
Community-Acquired Pneumonia

Although the Pneumonia Severity Index can serve as a general guideline for management, clinical judgment should always supersede the prognostic score.9

PHARMACOTHERAPY

The primary goals of pharmacotherapy for patients with CAP include eradicating the causative pathogens, resolving the clinical signs and symptoms, minimizing hospitalization, and preventing reinfection.23-27 Physicians should choose a medication based on the pharmacokinetic profile, adverse reactions, drug interactions, and cost-effectiveness.23-27 Further, patient evaluation should focus on severity of illness, patient age, comorbidities, clinical presentation, epidemiologic setting, and previous exposure.8 The majority of patients with CAP are treated empirically based on the most common pathogen(s) associated with the condition.23-27

Consensus guidelines from ATS,9 Infectious Diseases Society of America,9 and Canadian Guidelines for the Initial Management of Community-Acquired Pneumonia28 (Figure 1) recommend initial empiric therapy with macrolides, fluoroquinolones, or doxycycline (Vibramycin). A fourth guideline29 developed by the Therapeutic Working Group of the CDC, however, recommends using fluoroquinolones sparingly because of resistance concerns.

Although data are limited on duration of CAP therapy, current research30 recommends seven to 10 days of therapy for S. pneumoniae and 10 to 14 days of therapy for Mycoplasma pneumoniae and Chlamydia pneumoniae. After a hospitalized patient is clinically stable (i.e., temperature less than 37.8° C [100.0° F], pulse under 100 beats per minute, respiratory rate below 24 breaths per minute, systolic blood pressure above 90 mm Hg, and blood oxygen saturation over 90 percent) and able to tolerate oral intake, the patient may be treated with oral antibiotics for the remainder of the therapy course. This can save money and allow for earlier hospital discharge, which minimizes a patient’s risk of hospital-acquired infection.

Pneumococcal Resistance

S. pneumoniae, which accounts for 60 to 70 percent of all bacterial CAP cases, can affect all patient groups and can cause a fatal form of CAP. The alarming rate of resistance to many commonly used antibiotics raises great concern. Penicillin-resistant S. pneumoniae was uncommon in the early 1990s but has since become increasingly prevalent.29,31

Resistant strains are classified as having intermediate or high-level resistance. Surveillance data in the United States30 revealed that, overall, pneumococcal strains had a 28 percent immediate resistance rate and a 16 percent high-level resistance rate. Decreased susceptibility to other commonly used antibiotics has also been observed (Table 4).32-34 The clinical importance of these data is questionable because recruiting patients infected with resistant pathogens for clinical trials is difficult. Furthermore, available outcomes on the treatment of

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Management of CAP

[Diagram showing CAP diagnosis process with decisions and treatments based on comorbidities, risk classes, and antibiotics]

**Figure 1. Algorithm for the management of CAP. (CAP = community-acquired pneumonia.)**

TABLE 4
Patterns of Resistance to Antibiotics in North America*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>4.1</td>
</tr>
<tr>
<td>(Augmentin)</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>21.3</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
</tr>
<tr>
<td>Cefepime (Maxipime)</td>
<td>0.4</td>
</tr>
<tr>
<td>Cefprozil (Cecef)</td>
<td>23.9</td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin)</td>
<td>1.9</td>
</tr>
<tr>
<td>Cefuroxime (Ceftin)</td>
<td>24.7</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>23.0</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin)</td>
<td>26.6</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>28.3</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin (Tequin)</td>
<td>0.7</td>
</tr>
<tr>
<td>Levofloxacin (Levaquin)</td>
<td>0.7</td>
</tr>
<tr>
<td>Moxifloxacin (Avelox)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Clindamycin (Cleocin)</td>
<td>9.2</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>18.8</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>29.9</td>
</tr>
<tr>
<td>(Bactrim, Septra)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin (Vancocin)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*—Antibiotics tested against Streptococcus pneumonia isolates.
†—Resistance rates averaged across all patient age groups.
Information from reference 32.

pneumonia caused by resistant pneumococcal strains are conflicting.30

The CDC and others recommend outpatient oral empirical antibiotics with a macrolide, doxycycline, or an oral beta-lactam (amoxicillin, cefuroxime [Ceftin], or amoxicillin/clavulanate [Augmentin]) or inpatient treatment with an intravenous beta-lactam (cefuroxime, ceftriaxone [Rocephin], cefotaxime [Claforan]) or a combination of ampicillin/sulbactam (Unasyn) with a macrolide (Figure 1).38,29 Conservative use of new fluoroquinolones (levofloxacin [Levaquin], gatifloxacin [Tequin], moxifloxacin [Avelox]) also is recommended to minimize resistance patterns.28,29 The new fluoroquinolones (minimum inhibitory concentration: 4 mcg per mL or greater) should be used only when patients have failed recommended first-line regimens, are allergic to alternative agents, or have a documented infection with highly drug-resistant pneumococci such as those resistant to penicillin.28,29

Cost of Antimicrobial Therapy

Economic pressures have accentuated the focus on reducing health care costs and utilizing resources while maintaining or improving quality of care.31 These pressures are exacerbated by the growing resistance of *Streptococcus pneumoniae* to penicillin.31,32 This pattern of resistance increases the cost of treatment because of prolonged hospitalization, relapses, and the use of more expensive antibacterial agents.33-37

**REducing Costs**

Numerous methods for reducing costs when treating patients with bacterial infections can be applied to CAP (Table 5). Choosing monotherapy instead of combination therapy

| TABLE 5 |
| Strategies for Reducing the Cost of Antibiotic Therapy |

<table>
<thead>
<tr>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use the shortest appropriate course possible.</td>
</tr>
<tr>
<td>Switch from parenteral to oral antibiotics as soon as clinically appropriate.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid agents with serious or costly adverse effects.</td>
</tr>
<tr>
<td>Avoid agents known to induce resistance.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compare low impact with total hospital costs (but significant to pharmacy costs).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use knowledge of local resistance to initiate early therapy with appropriate spectrum agent (few data available).</td>
</tr>
<tr>
<td>Consider availability and cost-effectiveness of intravenous versus oral administration.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitoring</th>
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</thead>
<tbody>
<tr>
<td>Avoid agents that require therapeutic monitoring or laboratory safety tests.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
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</thead>
<tbody>
<tr>
<td>Use long-acting antibiotics.</td>
</tr>
<tr>
<td>Use potent bactericides.</td>
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<tr>
<td>Avoid antibiotics with poor tissue penetration.</td>
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<tr>
<td><strong>Agent</strong></td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
</tr>
<tr>
<td>Cefotaxime (Claforan)</td>
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<tr>
<td>Cefpodoxime (Vantin)</td>
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<tr>
<td>Cefprozil (Cefzil)</td>
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<tr>
<td>Ceftriaxone (Rocephin)</td>
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<td>Cefuroxime (Ceftin)</td>
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<tr>
<td><strong>Clindamycins</strong></td>
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<tr>
<td>Clindamycin (Cleocin)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
</tr>
<tr>
<td>Gatifloxacin (Tequin)</td>
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<tr>
<td>Levofloxacin (Levaquin)</td>
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<tr>
<td>Moxifloxacin (Avelox)</td>
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<td></td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
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<tr>
<td></td>
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<tr>
<td>Clarithromycin (Biaxin)</td>
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<tr>
<td>Erythromycin</td>
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<td></td>
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<tr>
<td><strong>Penicillins</strong></td>
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<tr>
<td>Amoxicillin</td>
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<td></td>
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<tr>
<td>Amoxicillin/clavulanate</td>
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<tr>
<td>(Augmentin)</td>
</tr>
<tr>
<td>Penicillin G</td>
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<tr>
<td>Penicillin V</td>
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<tr>
<td><strong>Tetracyclines</strong></td>
</tr>
<tr>
<td>Doxycline (Vibramycin)</td>
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</tbody>
</table>

CAP = community-acquired pneumonia; IV = intravenously.

*—Usual duration for adults with CAP and normal renal function is 10 to 14 days.
†—Estimated cost to the pharmacist based on average wholesale prices in Red Book: Montvale, N.J.: Medical Economics Data, 2005. Cost to the patient will be higher, depending on prescription filling fee.
‡—Adverse events occurring at a rate of approximately 1 to 10 percent.

Table 6. Antimicrobial Therapies for CAP

Reduces costs associated with administering an antibacterial. Using agents with longer half-lives allows for once-daily administration, which in turn leads to improved compliance and outcomes and decreased costs. In addition, transitioning patients to oral therapy as soon as they are clinically stable can significantly reduce the length of hospitalization—the major contributing factor to health care costs.
COST-EFFECTIVE CARE

When choosing a treatment, it is essential to compare costs and outcomes of all recommended drug therapies. Table 6 includes the costs of and common adverse reactions to antimicrobial therapies for CAP.

The goal of a formal pharmacoeconomic assessment is to enhance overall patient care using available resources. The evaluation should lead to a decision that will maximize the value of health care services, not simply reduce the costs of drug therapy. For instance, a particular drug may be more expensive, but it may also be more effective, thus lowering overall costs. Another drug may have a higher rate of treatment failures, creating added costs associated with managing the failures. The overall cost of each therapy should be obtained by comparing the end cost with the probability of achieving a positive outcome. Depending on the relative costs associated with treatment failures compared with the costs of cures, the decision to choose one agent over another may change.

The best way to apply cost-saving approaches to the treatment of patients with CAP is by using a clinical pathway. This is a method of facilitating multidisciplinary patient care by moving processes of care sequentially through various stages, within specified time frames, toward a desired outcome. These pathways should be specific to each institution, taking into account resistance rates in the community and encouraging the use of the most active, cost-effective agents to produce rapid, positive clinical outcomes.

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Author disclosure: Nothing to disclose.

REFERENCES

Community-Acquired Pneumonia

Treatment of Nursing Home–Acquired Pneumonia

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Pneumonia is an important cause of morbidity and mortality in nursing home residents, with 30-day mortality rates ranging from 10 to 30 percent. Streptococcus pneumoniae is the most common cause of nursing home–acquired pneumonia, although Staphylococcus aureus and gram-negative organisms may be more common in severe cases. Antibiotic therapy for nursing home–acquired pneumonia should target a broad range of organisms, and drug-resistant microbes should be considered when making treatment decisions. In the nursing home setting, treatment should consist of an antipseudomococcal fluoroquinolone alone or either a high-dose beta-lactam/beta-lactamase inhibitor or a second- or third-generation cephalosporin, in combination with azithromycin. Treatment of hospitalized patients with nursing home–acquired pneumonia requires broad-spectrum antibiotics with coverage of many gram-negative and gram-positive organisms, including methicillin-resistant S. aureus. Appropriate dosing of antibiotics for nursing home–acquired pneumonia is important to optimize effectiveness and avoid adverse effects. Because many nursing home residents take multiple medications, it is important to consider possible drug interactions. (Am Fam Physician. 2009;79(11):976-982. Copyright © 2009 American Academy of Family Physicians.)

Pneumonia is the second most common cause of infection in nursing home residents, and is associated with notable morbidity and mortality.1 Attributable 30-day mortality rates range from 10 to 30 percent.2-4 Prompt diagnosis and management are therefore essential. This article reviews the clinical management of nursing home–acquired pneumonia, with an emphasis on antimicrobial therapy.

Etiology
Nursing home–acquired pneumonia is usually bacterial in origin, although the specific microbiologic cause of infection is often not identified.5-12 Common bacterial etiologies are listed in Table 1.5-12 Streptococcus pneumoniae is the most common causative agent. However, in severe cases of nursing home–acquired pneumonia requiring hospitalization and mechanical ventilation, the rates of infection with Staphylococcus aureus and enteric gram-negative organisms appear to exceed those of S. pneumoniae.5 These organisms can be associated with antimicrobial resistance, especially in the nursing home setting. Risk factors for infection with multidrug-resistant pathogens include antibiotic therapy within the preceding 90 days, a high incidence of antibiotic resistance in the community or facility, chronic hemodialysis, and immunosuppression.7 One study found that recent antibiotic use and the inability to perform activities of daily living were independently associated with antibiotic-resistant nursing home–acquired pneumonia requiring intensive care unit (ICU) admission or mechanical ventilation.10

Nursing home–acquired pneumonia can also be caused by viral infection (Table 1). Influenza and respiratory syncytial virus (RSV) are important causes of respiratory illness and mortality in nursing home residents.13,14 Physicians should suspect viral etiologies from late fall through early spring, and whenever outbreaks of respiratory infection occur. Influenza predisposes patients to a secondary bacterial pneumonia.15 In a population-based analysis involving 381 nursing homes over a period of four years, investigators found that each year influenza infection was associated with approximately 28 hospitalizations; 147 courses of antibiotics;
Physicians should suspect infection with resistant organisms in nursing home patients who received antibiotics within the previous 90 days; when there is a high incidence of antibiotic resistance in the community or facility; and in patients who receive chronic dialysis, are immunosuppressed, or have difficulty performing activities of daily living.

Nursing home–acquired pneumonia should be suspected in patients with new or progressive infiltrate plus a new-onset fever, leukocytosis, purulent sputum, or hypoxia.

Nonhospitalized nursing home patients requiring treatment for pneumonia should be treated with an antipneumococcal fluoroquinolone, or either a high-dose beta-lactam/beta-lactamase inhibitor or a second- or third-generation cephalosporin, in combination with azithromycin (Zithromax).

Empiric coverage of methicillin-resistant Staphylococcus aureus and double coverage of Pseudomonal pneumonia should be prescribed for patients requiring intensive care unit admission.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afsp/sort.xml.

and 15 deaths per 1,000 residents with heart or lung disease, diabetes mellitus, or immunosuppression. Similarly, RSV accounted for approximately 15 hospitalizations, 76 courses of antibiotics, and 17 deaths per 1,000 residents with similar conditions. A recent report described human metapneumovirus as the cause of an outbreak of respiratory infections, including pneumonia, in a Canadian nursing home.

Diagnosis

The clinical manifestations of pneumonia in older adults may be subtle. In one study, investigators found that persons 65 years and older are less likely to complain of fever, chills, myalgia, and pleuritic chest pain than younger persons. One prospective study revealed that 80 percent of nursing home residents with pneumonia exhibit three or fewer respiratory signs or symptoms, but 92 percent have at least one identifiable respiratory manifestation, such as cough, respiratory rate of 30 breaths per minute or more, presence of crackles, or absence of wheezes on auscultation. The 2005 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guideline recommends that the clinical diagnosis of health care–associated pneumonia, including nursing home–acquired pneumonia, be based on a new or progressive infiltrate on chest radiography plus clinical findings consistent with pneumonia (i.e., new-onset fever [temperature greater than 100.4°F (38°C)], leukocytosis, purulent sputum, or hypoxia). The 2005 ATS/IDSA guideline also recommends that lower respiratory tract samples be obtained from nursing home residents hospitalized with nursing home–acquired pneumonia, particularly from those who are intubated, to guide treatment. Although respiratory cultures from nonintubated patients, and from those managed in the nursing home, could be considered, it is important to note that these are infrequently obtained, tend to produce a low yield of pathogenic microorganisms, and are commonly contaminated with oropharyngeal microflora, making interpretation difficult. Blood cultures are infrequently positive in patients with pneumonia, but may be considered in those who require intensive care. Rapid antigen tests of respiratory secretions, such as nasal washings, nasopharyngeal swabs, or throat swabs, can assist with the diagnosis of influenza and RSV during the appropriate seasons. Urinary antigen testing for S. pneumoniae and Legionella pneumophila serotype 1 may be considered, although most studies examining its use have been performed in patients with community-acquired pneumonia (CAP). One limitation of urinary antigen testing is the lack of information about antibiotic susceptibility. Therefore, a sputum Gram stain and culture should be considered if patients are able to generate a useful sample and the results can be obtained in time to influence therapeutic decision-making.

### Table 1. Common Etiologies of Nursing Home–Acquired Pneumonia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacilli</td>
<td>Up to 55</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Up to 48</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Up to 33</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Up to 22</td>
</tr>
<tr>
<td>Viruses</td>
<td>Up to 10</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Up to 7</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>Up to 6</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>Up to 1</td>
</tr>
</tbody>
</table>

Information from references 5 through 12.
Nursing Home–Acquired Pneumonia

In many nursing home residents with pneumonia, a diagnosis of aspiration pneumonitis or aspiration pneumonia should be considered. Aspiration pneumonitis is an inflammatory syndrome that does not typically require antibiotic therapy, whereas aspiration pneumonia is an infection for which antibiotic therapy should be initiated. Risk factors for these conditions include a history of stroke, dementia, gastroesophageal reflux disease, and tube-feeding requirements. Pathogens isolated from nursing home patients with severe aspiration pneumonia have included enteric gram-negative bacteria, *S. aureus*, and anaerobes. The results of a recent prospective cohort study validated a new algorithm for diagnosis of aspiration pneumonitis versus aspiration pneumonia (Figure 1).

**Treatment**

**IN THE NURSING HOME SETTING**

There is little evidence to suggest the clinical superiority of one antibiotic over another for nursing home–acquired pneumonia, particularly in the nursing home setting. Previous guidelines have recommended antibiotic therapy based primarily on microbiologic data. The 2005 ATS/IDSA guideline for the treatment of health care–associated pneumonia does not specifically address treatment of nursing home–acquired pneumonia in the nursing home setting. Guidelines based on limited data and expert opinion recommend the use of an antipseudomonal fluoroquinolone (e.g., levofloxacin [Levaquin] or moxifloxacin [Avelox]) alone or either a high-dose beta-lactam/beta-lactamase inhibitor (e.g., amoxicillin/clavulanate [Augmentin]) or a second- or third-generation cephalosporin (e.g., cefuroxime [Ceftin], cepodoxime [Vantin], ceftriaxone [Rocephin]), in combination with azithromycin (Zithromax). Oral therapy is preferred over parenteral therapy in mild to moderate cases. Intramuscular cephalosporins may also be used.

A randomized, double-blind trial compared the safety and effectiveness of once-daily intramuscular injections of cefepime (Maxipime) and ceftriaxone for nursing home–acquired pneumonia treated within the nursing home. Sixty-nine residents 60 years and older with radiographically-confirmed pneumonia and creatinine clearances of less than 60 mL per minute were included in the study. Most patients were switched to oral therapy after three days of parenteral therapy. Successful response was documented in 78 percent of patients treated with cefepime and 66 percent of patients treated with ceftriaxone (*P* = not significant). Each year, the Centers for Disease Control and Prevention (CDC) recommendations for influenza treatment should be consulted for updates on recent resistance patterns and treatment or prevention recommendations.

When a viral etiology of nursing home–acquired pneumonia is diagnosed and there is low suspicion of secondary bacterial infection, antibiotics often can be discontinued. However, it should be noted that older patients with influenza are at high risk of bacterial superinfection. Oseltamivir (Tamiflu) and zanamivir (Relenza) are approved for the treatment of influenza A and B in adults, but therapy should begin within two days of symptom onset to confer the most benefit, and increasing resistance to oseltamivir has recently been reported. These agents may lessen the severity of influenza manifestations and may reduce the incidence of post-influenza bacterial pneumonia.

Influenza vaccination is recommended for the prevention of influenza in nursing home residents, but does not provide complete protection. Similarly, pneumococcal
vaccination is recommended for all nursing home patients in accordance with the latest CDC guidelines for the prevention of pneumococcal pneumonia. Oseltamivir should be used prophylactically when an outbreak of influenza A or B occurs within a nursing home. There are no data to support specific treatments for RSV and human metapneumovirus in nursing home residents.

**IN HOSPITALIZED PATIENTS**

Intravenous antimicrobial therapy should be initiated for nursing home patients hospitalized with pneumonia, with empiric coverage of methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa*. Antibiotic coverage of atypical organisms is controversial, and there are no data to support such therapy. If an etiologic agent is identified, antibiotic therapy should be narrowed to minimize antibiotic resistance, toxicity, and cost. Hospitalized patients are more likely to have drug-resistant and highly pathogenic organisms. Antibiotics administered in the past 90 days generally should not be prescribed again, because the risk of infection with resistant pathogens is increased.

Nursing home residency is a major risk factor for MRSA colonization, which can lead to subsequent infection. Rates of MRSA from six nursing homes and one skilled-nursing facility in the United States ranged from 24 to 77 percent. Vancomycin (Vancocin; given intravenously) and linezolid (Zyvox; given orally or intravenously) are recommended for the treatment of MRSA pneumonia.

Risk factors for pneumonia caused by *P. aeruginosa* were identified in a study of 559 cases of CAP, including 45 cases of nursing home–acquired pneumonia. They include hospitalization within the previous 30 days or pulmonary comorbid illness (e.g., chronic obstructive pulmonary disease, asthma, chronic bronchitis, bronchiectasis, interstitial lung disease). When choosing antipseudomonal agents, the physician should refer to local pseudomonal susceptibility patterns.

One prospective, randomized trial compared the effectiveness of cefepime, with or without metronidazole (Flagyl), versus ertapenem (Invanz) for hospital- or skilled facility–acquired pneumonia in nonventilated, non-ICU patients. The addition of vancomycin was permitted for patients with suspected MRSA infection. *Enterobacteriaceae, S. pneumoniae*, and *S. aureus* comprised 19.5, 12.9, and 11.6 percent of the pathogens recovered, respectively. Forty percent of the *S. aureus* isolates were methicillin-resistant. Outcomes were similar; 87.3 percent of patients who received ertapenem and 86.0 percent of patients who received cefepime improved.

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**Table 2. Initial Intravenous, Adult Doses of Antibiotics for Empiric Therapy of Hospital-Acquired Pneumonia, Including Ventilator-Associated Pneumonia, and Healthcare-Associated Pneumonia in Patients with Late-Onset Disease or Risk Factors for Multidrug–Resistant Pathogens**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipseudomonal cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1–2 g every 8–12 h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 g every 8 h</td>
</tr>
<tr>
<td>Carbenems</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg every 6 h or</td>
</tr>
<tr>
<td></td>
<td>1 g every 8 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g every 8 h</td>
</tr>
<tr>
<td>β-lactam/β-lactamase inhibitor</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>4.5 g every 6 h</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7 mg/kg per 8 h</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>7 mg/kg per 8 h</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20 mg/kg per 8 h</td>
</tr>
<tr>
<td>Antipseudomonal quinolones</td>
<td></td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>750 mg every 8 h</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg every 8 h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg every 12 h</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg every 12 h</td>
</tr>
</tbody>
</table>

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* Dosages are based on normal renal and hepatic function.
† Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4–5 μg/ml.
‡ Trough levels for vancomycin should be 15–20 μg/ml.


For hospitalized patients with nursing home–acquired pneumonia, the 2005 ATS/IDSA guideline recommends a combination antibiotic therapy consisting of the following:

- An antipseudomonal cephalosporin, an antipseudomonal carbapenem, or an extended-spectrum beta-lactam/beta-lactamase inhibitor
- An antipseudomonal fluoroquinolone or an aminoglycoside
  - An anti-MRSA agent (vancomycin or linezolid).

The broad empiric therapy includes coverage of MRSA and double-coverage of *P. aeruginosa*. Specific antibiotics and recommended dosages are provided in (Table 2). These recommendations are based on microbiologic data from patients with severe pneumonia. Treatment should be tailored to the local microbiology, resistance patterns,
Nursing Home–Acquired Pneumonia

and specific patient risk factors. Aminoglycoside use increased mortality in a retrospective review. If chosen as therapy, aminoglycosides should be used with caution in patients with impaired renal function. Tigecycline (Tygacil) and doripenem (Doribax) are newer antibiotics being investigated in the treatment of health care-associated pneumonia, but they are not approved by the U.S. Food and Drug Administration for this indication. These medications may play a role in the treatment of hospitalized patients with nursing home–acquired pneumonia in the near future.

Pharmacotherapeutics

TIMING AND DURATION OF ANTIBIOTIC THERAPY

The timing of initiation of antibiotic therapy in hospitalized patients with nursing home–acquired pneumonia may be an important predictor of outcome. Therapy given within four hours of admission was associated with decreased length of stay and decreased mortality in one retrospective study, and is an important outcome measure for the Centers for Medicare and Medicaid Services. However, other studies have not demonstrated a survival benefit or a more rapid clinical response. The 2007 IDSA/ATS guideline recommends initiation of antibiotic therapy for CAP within the emergency department or as soon as possible after the diagnosis is made, rather than within a specified time period. Although no studies have specifically measured outcomes for nursing home patients, similar recommendations apply to this population.

The IDSA/ATS guideline recommends a seven-to-eight-day duration of therapy for health care–associated pneumonia that has been treated with appropriate empiric antibiotics, has clinically improved, and that is not caused by nonfermenting gram-negative bacteria such as P. aeruginosa.

DOSING OF ANTIBIOTICS IN THE NURSING HOME PATIENT

Critically ill patients often have altered pharmacokinetics and pharmacodynamics, and antibiotics must be dosed more aggressively than in other patients. Empiric antibiotics in critically ill patients with nursing home–acquired pneumonia should be dosed as outlined in Table 2. As renal function declines with age, proper dosing of antibiotic agents must be ensured to avoid adverse effects. The Cockcroft-Gault equation is commonly used to estimate creatinine clearance; manufacturers generally use this equation to estimate creatinine clearance when making recommendations about drug dosing in patients with renal insufficiency. Aminoglycosides, which can cause nephro- and ototoxicity, and imipenem/cilastatin (Primaxin), which can cause seizures, should be avoided in older patients with renal impairment.

Vancomycin dosing should be optimized to maintain trough concentrations in the range of 15 to 20 mcg per mL. However, a retrospective review of patients with MRSA pneumonia did not demonstrate any correlation between serum vancomycin trough concentrations and mortality.

ADVERSE EFFECTS OF ANTIMICROBIAL AGENTS IN OLDER ADULTS

Adverse drug events are more likely to occur in older adults than in other patients. The safest and most effective medication should be prescribed in an appropriate dose for the shortest duration possible to adequately treat the infection. In a study of nursing home patients, use of antibiotics was associated with preventable adverse drug reactions (Table 3).

DRUG INTERACTIONS WITH ANTIMICROBIAL AGENTS IN OLDER ADULTS

Increasing age is associated with an increasing number of medications used on a daily or weekly basis. Up to 67 percent of nursing home patients will experience an adverse drug reaction during a six- to 12-month stay, and use of more than eight medications is associated with

<table>
<thead>
<tr>
<th>Table 3. Adverse Effects of Antibiotics in Older Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial class/agent</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Beta-lactams</td>
</tr>
<tr>
<td>Clindamycin (Cleocin)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
</tr>
<tr>
<td>(Primaxin)</td>
</tr>
<tr>
<td>Linezolid (Zyvox)</td>
</tr>
<tr>
<td>Macrolides</td>
</tr>
</tbody>
</table>

### Table 4. Selected Drug Interactions of Common Antibiotics

<table>
<thead>
<tr>
<th>Antimicrobial class/agent(s)</th>
<th>Interacting agents</th>
<th>Potential clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Loop diuretics, nonsteroidal anti-inflammatory drugs, vancomycin (Vancoycin)</td>
<td>Additive nephrotoxicity</td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>Warfarin (Coumadin)</td>
<td>Increased anticoagulant effect (minor)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Aluminum, magnesium, iron, zinc, calcium, sucralfate (Carafate)</td>
<td>Decreased absorption</td>
</tr>
<tr>
<td></td>
<td>Class IA and III antihypertensics</td>
<td>QT prolongation, arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Increased anticoagulant effect</td>
</tr>
<tr>
<td>Linezolid (Zyvox)</td>
<td>Serotonergic agents (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, tramadol (Ultrim))</td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td>Metronidazole (Flagyl)</td>
<td>Warfarin</td>
<td>Increased anticoagulant effect (major)</td>
</tr>
<tr>
<td>(Bactrim, Septra)</td>
<td>Phenytoin (Dilantin)</td>
<td>Increased concentration of phenytoin</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Increased anticoagulant effect (major)</td>
</tr>
</tbody>
</table>


increased rates of adverse drug reactions. Because of the large number of medications prescribed in nursing home patients, the potential for drug interactions is very high. Table 4 lists some common drug interactions with which prescribers should be familiar. Most antibiotics alter the anticoagulant effects of warfarin (Coumadin), primarily by increasing these effects. All patients concurrently taking antibiotics and warfarin should have their International Normalized Ratio monitored closely during antibiotic therapy.

This is one in a series of "Clinical Pharmacology" articles coordinated by Allen F. Shaughnessy, PharmD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Mass.

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Author disclosure: Nothing to disclose.

### REFERENCES

Diagnosis and Management of Acute Pyelonephritis in Adults

KALYANAKRISHNAN RAMAKRISHNAN, M.D., and DEWEY C. SCHEID, M.D., M.P.H.

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

There are approximately 250,000 cases of acute pyelonephritis each year, resulting in more than 100,000 hospitalizations. The most common etiologic cause is infection with *Escherichia coli*. The combination of the leukocyte esterase test and the nitrite test (with either test proving positive) has a sensitivity of 75 to 84 percent and a specificity of 82 to 98 percent for urinary tract infection. Urine cultures are positive in 90 percent of patients with acute pyelonephritis, and cultures should be obtained before antibiotic therapy is initiated. The use of blood cultures should be reserved for patients with an uncertain diagnosis, those who are immunocompromised, and those who are suspected of having hemotogenous infections. Outpatient oral antibiotic therapy with a fluoroquinolone is successful in most patients with mild uncomplicated pyelonephritis. Other effective alternatives include extended-spectrum penicillins, amoxicillin-clavulanate potassium, cephalosporins, and trimethoprim-sulfamethoxazole. Indications for inpatient treatment include complicated infections, sepsis, persistent vomiting, failed outpatient treatment, or extremes of age. In hospitalized patients, intravenous treatment is recommended with a fluoroquinolone, aminoglycoside with or without ampicillin, or a third-generation cephalosporin. The standard duration of therapy is seven to 14 days. Urine culture should be repeated one to two weeks after completion of antibiotic therapy. Treatment failure may be caused by resistant organisms, underlying anatomic/functional abnormalities, or immunosuppressed states. Lack of response should prompt repeat blood and urine cultures and, possibly, imaging studies. A change in antibiotics or surgical intervention may be required. (Am Fam Physician 2005;71:933-42. Copyright© 2005 American Academy of Family Physicians.)

Acute pyelonephritis is an infection of the upper urinary tract, specifically the renal parenchyma and renal pelvis (Figure 1). Acute pyelonephritis is considered uncomplicated if the infection is caused by a typical pathogen in an immunocompetent patient who has normal urinary tract anatomy and renal function. Misdiagnosis can lead to sepsis, renal abscesses, and chronic pyelonephritis that may cause secondary hypertension and renal failure. Risk factors for complicated acute pyelonephritis are those that increase susceptibility or reduce host response to infections (Table 1).

Approximately 250,000 cases of acute pyelonephritis occur each year, resulting in more than 100,000 hospitalizations. Women are approximately five times more likely than men to be hospitalized with this condition (11.7 versus 2.4 hospitalizations per 10,000 cases, respectively); however, women have a lower mortality rate than men (7.3 versus 16.5 deaths per 1,000 cases, respectively). Acute pyelonephritis occurs in 1 to 2 percent of pregnant women, increasing the risk for premature labor and low-birth-weight infants.

Pathogenesis

Most renal parenchymal infections occur secondary to bacterial ascent through the urethra and urinary bladder. In men, prostatitis and prostatic hypertrophy causing urethral obstruction predispose to bacteriuria. Hematogenous acute pyelonephritis occurs most often in debilitated, chronically ill patients and those receiving immunosuppressive therapy. Metastatic staphylococcal or fungal infections may spread to the kidney from distant foci in the bone or skin.

In more than 80 percent of cases of acute pyelonephritis, the etiologic agent is *Escherichia coli*. Other etiologic causes include aerobic gram-negative bacteria, *Staphylococcus saprophyticus*, and enterococci. The microbial spectrum associated with different types of urinary tract infections (UTIs) is
Strength of Recommendations

<table>
<thead>
<tr>
<th>Key clinical recommendation</th>
<th>Label</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures should be obtained in patients with acute pyelonephritis only if there is diagnostic uncertainty, the patient is immunosuppressed, or a hematogenous source is suspected.</td>
<td>C</td>
<td>24, 25</td>
</tr>
<tr>
<td>Outpatient oral therapy is successful in 90 percent of selected patients with uncomplicated acute pyelonephritis who can tolerate oral intake, will be compliant with the treatment regimen, will return for early follow-up, and have adequate social support.</td>
<td>B</td>
<td>27, 28</td>
</tr>
<tr>
<td>Patients hospitalized with acute pyelonephritis should be treated with one of three initial intravenous therapies: a fluoroquinolone; an aminoglycoside with or without ampicillin; or an extended-spectrum cephalosporin with or without an aminoglycoside.</td>
<td>B</td>
<td>29</td>
</tr>
</tbody>
</table>

\( \text{A} = \text{consistent, good-quality patient-oriented evidence; } \text{B} = \text{inconsistent or limited-quality patient-oriented evidence; } \text{C} = \text{consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 835 for more information.} \)

In elderly patients, *E. coli* is a less common (60 percent) cause of acute pyelonephritis. The increased use of catheters and instruments among these patients predisposes them to infections with other gram-negative organisms such as Proteus, Klebsiella, Serratia, or Pseudomonas.

Patients who have diabetes mellitus tend to have infections caused by Klebsiella, Enterobacter, Clostridium, or Candida. They also are at an increased risk of developing emphysematous pyelonephritis and papillary necrosis, leading to shock and renal failure.\(^1,10^\) Bacteriuria, which frequently is polymicrobial, develops in more than 50 percent of patients who require catheterization for more than five days, and in virtually all patients who have indwelling urinary catheters for more than one month.\(^1^\)

Immunosuppression favors the development of subclinical (silent) pyelonephritis and infections caused by nonenteric, aerobic, gram-negative rods and Candida. Acute pyelonephritis occurs within two months following renal transplant in 30 to 50 percent of patients because of concomitant immunosuppression and postsurgical vesicoureteric reflux.\(^2^\) Acute pyelonephritis is considered complicated in men because they have a higher probability of urinary tract abnormalities, prostatic enlargement causing urethral obstruction with incomplete voiding, or an age-related decrease of antibacterial activity in prostatic secretions.

**Clinical Presentation**

The spectrum of acute pyelonephritis is wide, ranging from a mild illness to sepsis syndrome.\(^1^\) To diagnose acute pyelonephri-
Pyelonephritis

### TABLE 1
*Risk Factors for Complicated Acute Pyelonephritis*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Immunosuppressed state</th>
<th>Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly (&gt; 60 years of age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anatomic/functional abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double ureter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureterocele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesicoureteric reflux</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign body</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary, ureteric, or nephroscopy catheters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>Foreign body</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td></td>
<td>CalcuI</td>
</tr>
<tr>
<td>Transplantation</td>
<td></td>
<td>Bladder neck obstruction</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td>Posterior urethral valve</td>
</tr>
<tr>
<td>Chemoradiation</td>
<td></td>
<td>Benign prostatic hypertrophy</td>
</tr>
<tr>
<td>HIV infections</td>
<td></td>
<td>Neurogenic bladder</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Anatomic abnormalities</td>
<td></td>
<td>Inappropriate antibiotics</td>
</tr>
<tr>
<td>Prostatic obstruction</td>
<td></td>
<td>Resistant organisms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Instrumentation</td>
</tr>
</tbody>
</table>

*HIV = human immunodeficiency virus.*

*Information from references 1 and 2.*

Tis, physicians must rely on evidence of UTI from urinalysis or culture, along with signs and symptoms suggesting upper UTI (fever, chills, flank pain, nausea, vomiting, costovertebral angle tenderness). Symptoms that are suggestive of cystitis (dysuria, urinary bladder frequency and urgency, and suprapubic pain) also may be present.

In a study of young and middle-aged women presenting to an emergency depart-

### TABLE 2
*Microbial Organisms Causing Specific Types of Urinary Tract Infections*

<table>
<thead>
<tr>
<th>Microbial organism</th>
<th>Acute uncomplicated cystitis (%)</th>
<th>Acute uncomplicated pyelonephritis (%)</th>
<th>Complicated UTI (%)</th>
<th>Catheter-associated UTI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>68</td>
<td>89</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Proteus</em></td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><em>Enterococci</em></td>
<td>3</td>
<td>0</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td><em>Yeast</em></td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

*UTI = urinary tract infection.*

*—One study showed that 25 percent of E. coli isolates were resistant to ampicillin, 24 percent to tetracyclines, and 11 percent to trimethoprim-sulfamethoxazole (TMP-SMX; Bactrim, Septra).*

ment with fever, pyuria, and other features of upper UTI, 98 percent had acute pyelonephritis. In the absence of fever, 16 percent were given alternative diagnoses. However, up to one third of elderly patients with acute pyelonephritis have no fever; in 20 percent of elderly patients, the predominant symptoms are gastrointestinal or pulmonary. Fever and leukocytosis are of little value in diagnosing acute pyelonephritis in patients who have indwelling bladder catheters, especially when infections are caused by gram-positive cocci or Candida. The differential diagnosis of acute pyelonephritis includes pelvic inflammatory disease, cholecystitis, appendicitis, lower lobe pneumonia, perforated viscus, and the prodrome of herpes zoster.

Up to 30 percent of women presenting with cystitis-like symptoms have upper urinary tract involvement (subclinical pyelonephritis), but these infections rarely cause any cortical damage. This situation is more common in pregnant women and patients with recurrent UTI, diabetes, immunosuppression, renal tract pathology, or previous UTI occurring before 12 years of age. In the presence of obstruction (stone, tumor, bladder neck obstruction, enlarged prostate), acute pyelonephritis can be extremely severe and recalcitrant to treatment, and may progress to renal abscess.

**Diagnostic Testing**

Urinalysis and urine culture confirm the diagnosis of acute pyelonephritis. The consensus definition of pyelonephritis established by the Infectious Diseases Society of America (IDSA) is a urine culture showing at least 10,000 colony-forming units (CFU) per mm³ and symptoms compatible with the diagnosis. Lower counts (1,000 to 9,999 CFU per mm³) are of concern in men and pregnant women. Urine specimens generally are obtained by a midstream clean-catch technique, and one study showed that cleansing does not decrease contamination rates in adults.

Pyuria is present in almost all patients with acute pyelonephritis and can be detected rapidly with the leukocyte esterase test or the nitrite test. The combination of the leukocyte esterase and nitrite tests (with a positive result on either) for UTI is more specific but less sensitive than either test alone (Table 3). Although white cell casts may be observed in other conditions, they are, along with other features of UTI, specific for acute pyelonephritis. Hematuria may be present in patients with cystitis and pyelonephritis.

In some complicated cases, Gram stain analysis of urine can aid in the choice of initial antibiotic therapy. Another option is the use of the antibody-coated bacteria assay, which may be helpful in localizing subclinical upper UTIs.

Urine cultures are positive in 90 percent of patients with acute pyelonephritis, and culture specimens should be obtained before initiation of antibiotic therapy. Blood cultures have been recommended for hospitalized patients; up to 20 percent of these patients have positive cultures. In two studies, however, completion of blood cultures did not result in changes in management strategies in patients with acute pyelonephritis. There is no evidence that positive blood cultures indicate a more complicated course in otherwise healthy persons with pyelonephritis. Therefore, blood cultures are indicated only if there is diagnostic uncertainty, the patient is immunosuppressed, or a hematogenous source is suspected.

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TABLE 3
Laboratory Diagnosis of Urinary Tract Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis&lt;sup&gt;16,17&lt;/sup&gt;</td>
<td>&gt; 5 WBCs/HPF</td>
<td>72 to 95</td>
<td>48 to 82</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 WBCs/HPF</td>
<td>58 to 82</td>
<td>65 to 86</td>
</tr>
<tr>
<td>Leukocyte esterase test&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Positive</td>
<td>74 to 96</td>
<td>94 to 98</td>
</tr>
<tr>
<td>Nitrite test&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Positive</td>
<td>92 to 100</td>
<td>35 to 85</td>
</tr>
<tr>
<td>Leukocyte esterase and nitrite tests&lt;sup&gt;15,19&lt;/sup&gt;</td>
<td>Either test positive</td>
<td>75 to 84</td>
<td>82 to 98</td>
</tr>
<tr>
<td>Dipstick hematuria&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Positive</td>
<td>44</td>
<td>88</td>
</tr>
<tr>
<td>Gram stain of uncentrifuged urine&lt;sup&gt;21&lt;/sup&gt;</td>
<td>&gt; 1 bacterium per HPF</td>
<td>93</td>
<td>95</td>
</tr>
</tbody>
</table>

WBCs/HPF = white blood cells per high-power field.

*—For identification of > 100,000 colony-forming units per mm<sup>3</sup>.

Information from references 3 and 15 through 21.

Treatment

Although patients with acute pyelonephritis traditionally have been hospitalized and treated with intravenous antibiotics, outpatient oral therapy is successful in 90 percent of selected patients with uncomplicated acute pyelonephritis who can tolerate oral intake, will be compliant with the treatment regimen,

will return for early follow-up, and have adequate social support<sup>27,28</sup> (Figure 2). Patients with complicated acute pyelonephritis who are more ill or have not responded to outpatient therapy should be hospitalized. Using specific hospitalization criteria (Table 4),<sup>1</sup> up to 70 percent of patients can be selected for outpatient management. Another option is initial therapy with parenteral antibiotics in an inpatient observation unit, followed by oral therapy as an outpatient.<sup>26,29</sup>

Of the common uropathogens, resistance to fluoroquinolones remains very low (1 to 3 percent).<sup>30</sup> Fluoroquinolones are absorbed well from the gastrointestinal tract and have excellent kidney penetration. In selected patients with moderate or severe acute pyelonephritis, clinical outcomes are equivalent with intravenous and oral ciprofloxacin (Cipro) therapy.<sup>31</sup> Therefore, for empiric therapy in uncomplicated acute pyelonephritis, the IDSA recommends the use of an oral fluoroquinolone<sup>29</sup> (Table 5). Oral amoxicillin-clavulanate potassium (Augmentin), a cephalosporin, and trimethoprim-sulfamethoxazole (TMP-SMX; Bactrim, Septra) provide acceptable alternatives for susceptible organisms.<sup>29</sup>

The U.S. Food and Drug Administration has classified fluoroquinolones as pregnancy
Evaluation and Management of Acute Pyelonephritis

Patient with UTI and signs and symptoms of acute pyelonephritis
- Fever/chills
- Flank pain
- Nausea/Vomiting
- Costovertebral angle tenderness

Specific management depends on risk factors (see text)

Yes

High risk for complications?
- Anatomic/functional abnormality
- Foreign body
- Immunosuppressed state
- Obstruction
- Pregnancy
- Inappropriate antibiotics
- Failure to respond
- Instrumentation

No

Hospitalization indicated?
- Anatomic urinary tract abnormality
- Immunocompromised state
- Urinary tract obstruction
- Outpatient treatment failure
- Uncomplicated UTI progression
- Persistent nausea/Vomiting
- Suspected sepsis
- Age > 60 years
- Poor social support
- Inadequate access to follow-up care
- Uncertain diagnosis

Urine culture and sensitivity
- IV antibiotics
- Fluoroquinolone
- Aminoglycoside with or without ampicillin, or
- Extended-spectrum cephalosporin with or
- Without an aminoglycoside
- Ampicillin-sulbactam (Unasyn) with or without
- An aminoglycoside (gram-positive cocci)
- Hydration
- Fever control
- Pain management

Yes

No

Improvement in 72 hours?
- Afebrile
- Tolerates fluids, foods, and oral medications
- Decreased pain

Yes

Oral antibiotics for a total of 14 days
- Test for cure one week after completion of antibiotics

No

Hospitalization if ambulatory
- Check sensitivities
- Check obstruction (ultrasoundography)
- Consider other causes

Figure 2. Algorithm for the evaluation and management of acute pyelonephritis (UTI = urinary tract infection; IV = intravenous).

category C drugs, and their use should be avoided in pregnant women. Amoxicillin or amoxicillin-clavulanate potassium is preferred during pregnancy and in the treatment of infections caused by gram-positive organisms. Some physicians administer a single parenteral dose of an antibiotic (ceftriaxone [Rocephin], gentamicin [Garamy-
cin), or a fluoroquinolone) before initiating oral therapy, but there is little evidence that this step improves outcomes. Table 5 reviews antimicrobial agents used in the treatment of acute pyelonephritis.

If the patient requires hospitalization, the IDSA guidelines recommend one of three initial intravenous therapies: (1) a fluoroquinolone; (2) an aminoglycoside with or without ampicillin; or (3) an extended-spectrum

### TABLE 5
Antimicrobial Agents Used in the Treatment of Acute Pyelonephritis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing schedule</th>
<th>Oral dose (mg)</th>
<th>IV dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Every 8 to 12 hours</td>
<td>500</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate potassium (Augmentin)</td>
<td>Every 8 to 12 hours</td>
<td>500/125</td>
<td>—</td>
<td>GI side effects*</td>
</tr>
<tr>
<td>Ampicillin-sulbactam (Unasyn)</td>
<td>Every 4 to 6 hours</td>
<td>—</td>
<td>150 to 200 mg per kg per day</td>
<td>GI side effects*</td>
</tr>
<tr>
<td>Aztreonam (Azactam)</td>
<td>Every 6 to 8 hours</td>
<td>—</td>
<td>1 to 2 g</td>
<td>Phlebitis; GI side effects*</td>
</tr>
<tr>
<td>Imipenem (Primaxin I.V.)</td>
<td>Every 6 hours</td>
<td>—</td>
<td>0.5 g</td>
<td>None</td>
</tr>
<tr>
<td>Piperacillin (Pipracil)</td>
<td>Every 6 hours</td>
<td>—</td>
<td>3 g</td>
<td>GI side effects*; phlebitis</td>
</tr>
<tr>
<td>Piperacillin-tazobactam (Zosyn)</td>
<td>Every 6 to 8 hours</td>
<td>—</td>
<td>3.375 g/4.5 g</td>
<td>GI side effects*; rash; headaches; insomnia</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate (Timentin)</td>
<td>Every 4 to 6 hours</td>
<td>—</td>
<td>3.1 g</td>
<td>GI side effects*; rash; phlebitis</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime (Claforan)</td>
<td>Every 8 to 12 hours</td>
<td>—</td>
<td>1 to 2 g</td>
<td>Thrombophlebitis</td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin)</td>
<td>Once in 24 hours</td>
<td>—</td>
<td>1 to 2 g</td>
<td>Leukopenia; elevated BUN and liver enzyme levels</td>
</tr>
<tr>
<td>Cephalexin (Keflex)</td>
<td>Every 6 hours</td>
<td>500</td>
<td>—</td>
<td>GI side effects*</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>Every 12 hours</td>
<td>500</td>
<td>400 mg</td>
<td>Nausea; headache; photosensitivity; pregnancy category C</td>
</tr>
<tr>
<td>Enoxacin (Penetrex)</td>
<td>Every 24 hours</td>
<td>400</td>
<td>—</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td>Gatifloxacin (Tequin)</td>
<td>Every 24 hours</td>
<td>—</td>
<td>400 mg</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td>Levofloxacin (Levaquin)</td>
<td>Every 24 hours</td>
<td>250 to 750</td>
<td>250 to 750 mg</td>
<td>ECG QT prolongation; pregnancy category C</td>
</tr>
<tr>
<td>Lomefloxacin (Maxaquin)</td>
<td>Every 24 hours</td>
<td>400</td>
<td>—</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td>Norfloxacin (Noroxin)</td>
<td>Every 12 hours</td>
<td>400</td>
<td>—</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td>Ofloxacin (Floxin)</td>
<td>Every 12 hours</td>
<td>200 to 400</td>
<td>400 mg</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin (Amikin)</td>
<td>Every 12 hours</td>
<td>—</td>
<td>7.5 mg per kg</td>
<td>Ototoxicity; nephrotoxicity</td>
</tr>
<tr>
<td>Gentamicin (Garamycin)</td>
<td>Every 24 hours</td>
<td>—</td>
<td>5 to 7 mg per kg</td>
<td>Ototoxicity; nephrotoxicity</td>
</tr>
<tr>
<td>Tobramycin (Nebcin)</td>
<td>Every 24 hours</td>
<td>—</td>
<td>5 to 7 mg per kg</td>
<td>Ototoxicity; nephrotoxicity</td>
</tr>
<tr>
<td><strong>Other antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP-SMX (Bactrim; Septra)</td>
<td>Every 12 hours</td>
<td>160/800</td>
<td>8 to 10 mg per kg (TMP)</td>
<td>G6PD deficiency; sulf allergy; do not use in third trimester</td>
</tr>
</tbody>
</table>

*IV = intravenous; GI = gastrointestinal; BUN = blood urea nitrogen; ECG = electrocardiogram; TMP-SMX = trimethoprim-sulfamethoxazole; G6PD = glucose-6-phosphate dehydrogenase.

* GI side effects include nausea, vomiting, and diarrhea.
cephalosporin with or without an aminoglycoside. With gram-positive cocci, ampicillin-sulbactam (Unasyn) with or without an aminoglycoside is recommended. Amino-glycosides should be avoided in patients with pre-existing renal disease. Oral treatment is feasible as soon as the patient becomes afebrile, has improved clinically, and can tolerate oral hydration and medications. It is not necessary to use the same agent for both parenteral and oral therapy.36 There is no benefit from additional hospital observation to determine the success of switching to an oral antibiotic.32

A seven- to 14-day course of antibiotics is effective in women who are immunocompetent and do not have underlying illness.127,30 Studies29,33,34 suggest that therapy lasting only five to seven days is comparable to seven to 14 days in terms of clinical and bacteriologic outcome in patients with mild pyelonephritis and in those having a dramatic initial response to therapy. Acute pyelonephritis associated with immunosuppressive states responds well to a 14- to 21-day course of a fluoroquinolone or TMP-SMX.2 Post-treatment urine cultures are recommended in all patients at the follow-up visit, one to two weeks after completion of antibiotic therapy.35

Fever generally resolves within 72 hours of starting antibiotic therapy. In a study36 of hospitalized patients who had no complications, however, 26 percent remained febrile at 48 hours, and 13 percent were febrile at 72 hours. Thus, persistence of fever after 72 hours in an otherwise stable and improving patient may not necessarily warrant a change in therapy or further investigation.

The two most common causes of initial treatment failure are resistant organisms and nephrolithiasis. In the absence of clinical response, many physicians obtain a blood count, urinalysis, and blood and urine cultures, seeking an indication of persisting infection and antibiotic resistance; however, there is little evidence to support the routine use of these tests. A rectal or vaginal examination should be performed.

Imaging studies may identify complicating factors such as anatomic abnormalities, obstruction, acute bacterial nephritis (localized, non-acute interstitial inflammation), or subjacent infections such as appendicitis, cholecystitis, or perinephric abscess (Figure 2). Options include plain radiography of the kidneys, ureter, and bladder; renal ultrasonography; computed tomographic (CT) scan; magnetic resonance imaging; and intravenous pyelography. In most patients, ultrasound examination identifies acute bacterial nephritis, abscesses, ureteral obstruction, and hydronephrosis.37 Acute bacterial nephritis may progress to frank abscess and requires a protracted course of antibiotics. If renal ultrasonography fails to define a lesion but shows marked renal enlargement, or if invasive intervention is being considered, a CT scan can exclude renal and perinephric abscesses.

Differences between UTI in men and women support the classification of male acute pyelonephritis as complicated. Men younger than 60 years without obstruction, renal abnormalities, or prostatitis respond well to 14 days of antibiotic therapy.3 Men who have recurrent UTIs require a six-week regimen. Men with acute prostatitis require four weeks of treatment with an antibiotic that has high penetration into prostatic tissue, such as doxycycline (Vibramycin), TMP-SMX, or a fluoroquinolone; men with chronic prostatitis require six to 12 weeks of such therapy.38 The optimal duration of treatment for hospitalized patients is 14 days.

Short-term antibiotic therapy (three days), which is appropriate in the treatment of cystitis, results in a 50 percent relapse rate in patients who have subclinical acute pyelonephritis.
ate release of any existing obstruction combined with a 14-day course of appropriate antibiotics minimizes failure and recurrence. Relief of obstruction and antibiotic therapy may be successful in emphysematous pyelonephritis, but nephrectomy must be strongly considered in patients with unresponsive infections. If parenchymal involvement including abscesses is observed, longer courses of antibiotics (intravenous or oral) or sequential therapy may be necessary.

Pregnant women with pyelonephritis require hospitalization (for at least a short observation period) for aggressive hydration and parenteral antibiotics. Antibiotic treatment is similar to the treatments of other adult regimens. During pregnancy, 86 percent of women have uterine contractions in the first hour after initiation of antimicrobial therapy, and 50 percent continue to have contractions after five hours of therapy. One study found no difference in clinical responses among pregnant women treated with ampicillin and gentamicin, cefazolin (Ancef), or ceftriaxone. Fluoroquinolones should be avoided because of concerns about their teratogenic effects on the fetus.

Most patients with mild acute pyelonephritis who are pregnant (90 percent) can be treated successfully with parenteral antibiotics under brief (two to 24 hours) observation, followed by outpatient oral therapy. Although some experts state that selected patients may be treated safely with oral antibiotics, there have been no outpatient trials in which oral therapy alone was used. Because 25 percent of patients with mild acute pyelonephritis who are pregnant have a recurrence, these patients should have monthly urine cultures or antimicrobial suppression with oral nitrofurantoin (Macrodantin), 100 mg daily, until four to six weeks postpartum. All pregnant women, especially those who have diabetes and had a previous UTI, should be screened for asymptomatic bacteriuria during the first prenatal visit.

No antibiotic prophylaxis is effective in reducing complications associated with indwelling catheters. Sterile insertion and care of the catheter, minimizing the duration of catheterization, intermittent catheterization, closed drainage systems, and silver-alloy-coated catheters may reduce the risk of symptomatic infection.

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REFERENCES
Laboratory Diagnosis of Urinary Tract Infections in Adult Patients

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Urinary tract infections (UTIs) are among the most common bacterial infections and account for a significant part of the workload in clinical microbiology laboratories. Enteric bacteria (in particular, Escherichia coli) remain the most frequent cause of UTIs, although the distribution of pathogens that cause UTIs is changing. More important is the increase in resistance to some antimicrobial agents, particularly the resistance to trimethoprim-sulfamethoxazole seen in E. coli. Physicians distinguish UTIs from other diseases that have similar clinical presentations with use of a small number of tests, none of which, if used individually, have adequate sensitivity and specificity. Among the diagnostic tests, urinalysis is useful mainly for excluding bacteriuria. Urine culture may not be necessary as part of the evaluation of outpatients with uncomplicated UTIs, but it is necessary for outpatients who have recurrent UTIs, experience treatment failures, or have complicated UTIs, as well as for inpatients who develop UTIs.

Urinary tract infections (UTIs) are among the most common bacterial infections. It has been estimated that symptomatic UTIs result in as many as 7 million visits to outpatient clinics, 1 million visits to emergency departments, and 100,000 hospitalizations annually [1]. UTIs have become the most common hospital-acquired infection, accounting for as many as 35% of nosocomial infections, and they are the second most common cause of bacteremia in hospitalized patients [2, 3]. The annual cost to the health care system of the United States attributable to community-acquired UTI alone is estimated to be approximately $1.6 billion [4].

UTIs are challenging, not only because of the large number of infections that occur each year, but also because the diagnosis of UTI is not always straightforward. Physicians must distinguish UTI from other diseases that have a similar clinical presentation, some UTIs are asymptomatic or present with atypical signs and symptoms, and the diagnosis of UTIs in neutropenic patients (who do not typically have pyuria) may require different diagnostic criteria than those used for the general patient population. Because of these factors, physicians frequently rely on a small number of imperfect laboratory tests to augment clinical impressions; even when clinical diagnoses are unequivocal, physicians may order laboratory tests to identify the cause of the infection and/or to provide isolates for antimicrobial susceptibility testing. It therefore comes as no surprise that the laboratory examination of urine specimens accounts for a large part of the workload in many hospital-based laboratories. In fact, in many clinical laboratories, urine cultures are the most common type of culture, accounting for 24%–40% of submitted cultures; as many as 80% of these urine cultures are submitted from the outpatient setting.

The purpose of this review is to summarize the laboratory diagnosis of routine UTI using current diagnostic methods. The review will not cover the diagnosis of UTI in special patient populations, a topic that merits a separate review.

CAUSES OF UTIs

The etiological agents of community-acquired and hospital-acquired UTIs differ (Table 1) [5–14]. Only a limited amount of data has been published regarding changes in the frequency of causative agents among outpatients. Enteric bacteria (in particular, Escherichia coli) have been and remain the most frequent
cause of UTI, although there is some evidence that the percentage of UTIs caused by *E. coli* is decreasing [6, 15]. In contrast, significant changes in the causes of nosocomial UTI have been reported since 1980. Bronsma et al. [13] reported that, from 1980 through 1991, the percentage of UTIs caused by *E. coli*, *Proteus* species, and *Pseudomonas* species decreased, whereas the percentage of UTIs caused by yeasts, group B streptococci, and *Klebsiella pneumoniae* increased. Weber et al. [6] reported different changes in the causative agents of UTI, with a decrease in the percentage of UTIs caused by *Enterobacter* species, but with an increase in the percentage of UTIs caused by *Acinetobacter* species and *Pseudomonas aeruginosa*. *Candida albicans* is the most common cause of funguria, followed by *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and other yeasts [16].

**SPECIMEN COLLECTION, TRANSPORTATION, AND PROCESSING**

**Specimen collection.** Suprapubic aspiration is the best method to avoid contamination of specimens with bacteria in the distal urethra. This collection method is used infrequently because it is not indicated clinically (except in rare circumstances), it is invasive and uncomfortable, and it requires too much time and too many resources to be practical. Collection of urine by use of a single catheter (straight catheter technique) is the next-best technique for obtaining urine specimens with minimal contamination, but, again, it is not indicated clinically for most patients because it is too labor intensive and costly for routine use and it is invasive. It has added disadvantages, because the process of inserting a catheter through the urethra can introduce bacteria into the bladder (and thereby cause UTI), and rare complications have been reported.

Most urine specimens are obtained from adult patients via the clean-catch midstream technique. This technique has the following advantages: it is neither invasive nor uncomfortable, it is simple and inexpensive, it can be performed in almost any clinical setting, there is no risk of introducing bacteria into the bladder by catheterization, and there is no risk of complications. Colony counts from urine specimens collected by this method correlate reasonably well with those of specimens collected via suprapubic aspiration or straight catheterization [15]. The obvious disadvantage of this technique is that the urine sample passes through the distal urethra and can become contaminated with commensal bacteria. Simple procedures that have been developed to decrease the contamination rate include cleansing of the skin and mucous membranes adjacent to the urethral orifice before micturition, allowing the first part of the urine stream to pass into the toilet, and collecting urine for culture from the midstream [17]. Although the clean-catch midstream method is accepted and used widely, the available evidence suggests that the cleansing procedures may not decrease urine contamination rates significantly and, therefore, may be unnecessary as a routine [18–23]. There may be difficulties with proper collection of samples from elderly patients, as well as from those patients who have physical or other types of impairments, which adds to the importance of collecting specimens properly to avoid contamination.

As discussed below, correct processing and handling of urine specimens, as well as correct interpretation of test results, is dependent on the method used to collect the specimen. It is, therefore, of obvious importance for clinicians to specify the method of collection on the test requisition slip. Other information that should be included on the test requisition slip includes the date and time of specimen collection, patient demographic information, and any clinically relevant information (e.g., whether the patient was treated with antimicrobial agents or whether anatomic abnormalities, stones, or an indwelling urinary catheter were present).

**Specimen transportation.** Several studies have demonstrated the adverse effect of delays in transportation or processing of urine specimens on their quality [24–26]. In each study, urine specimens were plated within 2 h after collection and then were plated again after delays of up to 24 h; results were compared to determine whether delays in plating resulted in an increase in colony counts. In each of the studies, some of the cultures that were delayed showed increases in the number of colony forming units (cfu) per mL to >10⁵ cfu/mL; thereby leading to false-positive results. It should be noted that these studies were performed before the publication of current criteria for interpreting quantitative urine cultures and that the effect on interpretation would have been even greater if colony counts of 10⁵ or 10⁶ cfu/mL were used to define probable infection in specific patients [15]. On the basis of the results of these and other similar studies, it is currently recommended that urine specimens be plated within 2 h after collection unless specimens have been refrigerated or kept in a preservative [17].

**Specimen processing.** Routine urine cultures should be plated using calibrated loops for the semiquantitative method. This method has the advantage of providing information regarding the number of cfu/mL, as well as providing isolated colonies for identification and susceptibility testing. The types of media used for routine cultures should be limited to blood agar and MacConkey’s agar. For urine specimens obtained from outpatients, it is not necessary to routinely inoculate a medium that is selective for gram-positive bacteria, because nearly all UTIs in outpatients are caused by aerobic and facultative gram-negative bacteria (table 1) [27, 28]. Even in patient populations in which *Staphylococcus saprophyticus* is a common cause of UTIs, it is not necessary to use selective media. In contrast, urine specimens obtained from hospitalized patients are likely to contain enterococci, which have emerged as the second most
Table 1. Percentage distribution of etiologic agents of urinary tract infections among outpatients and inpatients, by pathogen.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Outpatients (Percentage with pathogen)</th>
<th>Reference(s)</th>
<th>Inpatients (Percentage with pathogen)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>53-72</td>
<td>[5-9]</td>
<td>17.5-56.7</td>
<td>[5, 6, 8-14]</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>2-7.5</td>
<td>[5, 7]</td>
<td>2.1-12.5</td>
<td>[5, 8-14]</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>6-12</td>
<td>[5-7]</td>
<td>6.2-15.0</td>
<td>[5, 6, 8-14]</td>
</tr>
<tr>
<td>Proteus species</td>
<td>4-6</td>
<td>[5-7]</td>
<td>3.8-8.2</td>
<td>[5, 6, 8-13]</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>0.6-5.8</td>
<td>[5-7]</td>
<td>0.9-6.6</td>
<td>[5, 6, 8-14]</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>0.1</td>
<td>[5]</td>
<td>0.2-3</td>
<td>[5, 8, 9, 11-13]</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>1.7-12</td>
<td>[5-7]</td>
<td>6.5-15.8</td>
<td>[5, 6, 8-14]</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
<td>[5, 7]</td>
<td>1.6-3.5</td>
<td>[5, 8-12,14]</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>0.2-2</td>
<td>[5, 7]</td>
<td>0.4</td>
<td>[5]</td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>0.1-4</td>
<td>[5-7]</td>
<td>1.3-11</td>
<td>[5, 6, 8-14]</td>
</tr>
<tr>
<td>Candida species</td>
<td>...</td>
<td>...</td>
<td>9.4-15.8</td>
<td>[8, 9, 14]</td>
</tr>
<tr>
<td>Other</td>
<td>3-8</td>
<td>[5-7]</td>
<td>1.8-26.3</td>
<td>[5, 6, 8, 10-14]</td>
</tr>
</tbody>
</table>

Common cause of nosocomial infections. Laboratories may want to consider inoculating urine specimens obtained from hospitalized patients, or from patients in whom gram-positive bacterial infection is suspected but not documented, to a medium that is selective for gram-positive cocci. A medium such as phenylethyl alcohol suppresses the growth of swarming *Proteus* species and other gram-negative bacilli that can overgrow gram-positive cocci in the specimen. Urine cultures should be incubated overnight at 35°C-37°C in ambient air before being read. There is no added benefit to incubating routine urine cultures for 48 h, provided that specimens are incubated for a full 24 h and that urine specimens containing <10^3*<sup>3</sup>* uropathogens or specimens from patients with suspected funguria are incubated for 48 h [29-31].

Most pathogenic yeasts grow well on blood agar plates, so it is unnecessary to use selective fungal media for urine cultures, even for samples obtained from patients with suspected funguria. Selective fungal media can be used in those rare instances in which there is a high clinical probability that a UTI is caused by a more fastidious yeast or mold. Urine specimens obtained from patients with suspected mycobacterial UTIs should be processed and plated to the appropriate mycobacterial media [32].

**NONCULTURE METHODS FOR THE LABORATORY DIAGNOSIS OF UTI**

**Detection of bacteriuria by urine microscopy.** Bacteriuria can be detected microscopically using Gram staining of uncentrifuged urine specimens, Gram staining of centrifuged specimens, or direct observation of bacteria in urine specimens. Gram stain of uncentrifuged urine specimens is a simple method. A volume of urine is applied to a glass microscope slide, allowed to air dry, stained with Gram stain, and examined microscopically. The performance characteristics of the test are not well-defined, because different criteria have been used to define a positive test result. In one study, the test was found to be sensitive for the detection of >10^5 cfu/mL but insensitive for the detection of lower numbers of bacteria (table 2) [28]. Other investigators have found the test to be of low sensitivity for the detection of UTI [33-42].

The urine Gram stain test has the important advantage of providing immediate information as to the nature of the infecting bacterium or yeast (rarely infectious agents such as mycosporidia) and thereby guiding the physician in selecting empiric antimicrobial therapy. This is of importance in some settings, but the Gram stain test has 3 disadvantages that limit its usefulness in most clinical settings. First, it is an insensitive test, being reliably positive only if the concentration of bacteria in the urine is >10^5 cfu/mL; infections with bacterial concentrations of 10^5-10^6 cfu/mL may not be detected by this test. Second, the test is too labor intensive for it to be practical for most clinical microbiology laboratories to offer it on more than a select basis. Last, because it may not detect bacteria at concentrations of 10^2-10^4 cfu/mL, it should not be used in the outpatient setting for patients with uncomplicated UTIs. Because of these limitations, its use should be limited to patients with cases of acute pyelonephritis, patients with invasive UTIs, or other patients for whom it is important to have immediate information as to the nature of the infecting pathogen.

**Detection of bacteriuria by nitrite test.** Bacteriuria can be detected chemically when bacteria produce nitrite from nitrate.
Table 2. Performance characteristics of Gram staining for detection of bacteriuria.

<table>
<thead>
<tr>
<th>Specimen, colony count</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive</th>
<th>Negative</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncentrifuged urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ND^a</td>
<td>96</td>
<td>95</td>
<td>54</td>
<td>100</td>
<td>[33]</td>
</tr>
<tr>
<td>ND^b</td>
<td>91</td>
<td>99</td>
<td>93</td>
<td>99</td>
<td>[33]</td>
</tr>
<tr>
<td>≥10⁶ cfu/mL</td>
<td>81–97</td>
<td>71–96</td>
<td>31–90</td>
<td>92–100</td>
<td>[34–36, 38]</td>
</tr>
<tr>
<td>≥10⁶ cfu/mL</td>
<td>86–96</td>
<td>75–99</td>
<td>59–98</td>
<td>80–99</td>
<td>[28, 40]</td>
</tr>
<tr>
<td>Centrifuged urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10⁶ cfu/mL</td>
<td>92–100</td>
<td>9–94</td>
<td>7–77</td>
<td>99–100</td>
<td>[37, 39, 41]</td>
</tr>
<tr>
<td>≥10⁶ cfu/mL</td>
<td>74</td>
<td>86</td>
<td>78</td>
<td>84</td>
<td>[38]</td>
</tr>
<tr>
<td>≥10⁶ cfu/mL</td>
<td>63</td>
<td>91</td>
<td>89</td>
<td>69</td>
<td>[39]</td>
</tr>
</tbody>
</table>

**NOTE.** The criteria used to assess the clinical importance of isolates and the laboratory methods used varied between studies; the data are presented only as an overview of reported performance characteristics of the test. All numbers are rounded to the nearest whole number. ND, not done.

^a ≥1 bacterium per oil immersion field.

^b ≥5 bacteria per oil immersion field.

The biochemical reaction that is detected by the nitrite test is associated with members of the family Enterobacteriaceae (the pathogens most commonly responsible for UTIs), but the usefulness of the test is limited because nitrite production is not associated with urinary-tract pathogens such as S. saprophyticus, Pseudomonas species, or enterococci [43]. Another limitation to the test is that it requires testing a specimen of the first urine produced in the morning, as ≥4 h are required for bacteria to convert nitrate to nitrite at levels that are reliably detectable.

**Detection of pyuria by urine microscopy.** Pyuria can be detected and quantified microscopically by measuring the urinary leukocyte excretion rate, counting leukocytes with a hemocytometer, counting leukocytes in urine specimens using Gram staining, or counting leukocytes in a centrifuged specimen. The advantages to urine microscopy are that leukocytes, leukocyte casts, and other cellular elements are observed directly. One disadvantage to urine microscopy is that leukocytes deteriorate quickly in urine that is not fresh or that has not been adequately preserved. In addition, each of these methods has disadvantages that limit its usefulness as a routine test [28]. Because of these disadvantages, urine microscopy should be limited to patients in whom pyelonephritis or other more serious infections are suspected.

The most accurate microscopic method for quantitating pyuria is to measure the urinary leukocyte excretion rate [43]. Patients with symptomatic UTIs have urinary leukocyte excretion rates of ≥400,000 leukocytes/h [43]. The test is impractical for clinical use, however, making it necessary for laboratories to use other methods. A simple and inexpensive alternative is to count urine leukocytes with a hemocytometer. Comparison of hemocytometer counts with urinary leukocyte excretion rates has shown that a hemocytometer count of ≥10 leukocytes/mm² correlates with a urinary leukocyte excretion rate of ≥400,000 leukocytes/h [43]. Moreover, the correlation of hemocytometer counts with urine colony counts has shown that patients with symptomatic UTIs and bacterial concentrations of ≥10⁶ cfu/mL have urine leukocyte counts of ≥10 leukocytes/mm² [43]. The correlation of hemocytometer cell counts for patients with bacterial concentrations of <10⁶ cfu/mL was studied by Stamm et al. [15], who found that urine leukocyte counts of ≥8 cells/mm² correlated with bacterial concentrations of <10⁶ cfu/mL in specimens obtained by suprapubic aspiration or straight catheterization from acutely dysuric female subjects. Although using a hemocytometer to count leukocytes is easier than measuring urinary leukocyte excretion rates, it is impractical for clinical laboratories to use a hemocytometer to count leukocytes on a routine basis. The most practical microscopic method involves counting the number of leukocytes in the sediment of centrifuged urine specimens. As reviewed by Pappas [43], this method is inaccurate because of inadequate standardization of the method. For these reasons, and to facilitate the processing of large numbers of specimens, most laboratories use rapid tests for leukocyte esterase as a surrogate for microscopic leukocyte counts.

**Detection of pyuria by leukocyte esterase tests.** Leukocyte esterase tests are based on the hydrolysis of ester substrates by proteins with esterolytic activity [44]. Human neutrophils produce as many as 10 proteins with esterolytic activity. These proteins react with ester substrates to produce alcohols and acids that then react with other chemicals to produce a color change that is proportional to the amount of esterase in the specimen [44]. These tests have the advantage of detecting both esterases in intact leukocytes and esterases released after cell lysis; therefore, even specimens that have not been preserved
properly may yield a positive test result. Leukocyte esterase tests can yield false-positive test results when the urine is contaminated with bacteria present in vaginal fluid; when the specimen contains eosinophils or Trichomonas species, both of which can act as sources of esterases; and when oxidizing agents or formalin react with the test strips to generate false-positive test results [44, 45]. Leukocyte esterase tests may show a decrease in positive test results when the specimen has an elevated specific gravity and/or elevated levels of protein and glucose; when boric acid preservatives are present; when large amounts of ascorbic or oxalic acid are present; and when the patient has received antimicrobial agents, such as cephalothin, cephalexin, or tetracycline [44, 45]. High concentrations of tetracycline may result in false-negative test results [45]. As shown in table 3, when it is used alone, the leukocyte esterase test has a relatively low sensitivity and specificity and low positive predictive values as a test for UTIs, with higher negative predictive values [28, 35, 38, 46-54].

**Simultaneous detection of bacteriuria and pyuria.** Commercial urinalysis products include tests for both nitrite and leukocyte esterase, thus providing tests for both bacteriuria and pyuria. As shown in table 3, a number of clinical evaluations have defined the performance characteristics of these tests. The evaluations are not directly comparable because the studies occurred over a 20-year period in a number of different laboratories and health care settings, there were a multiplicity of study designs, and various commercial products were used in the studies. Nonetheless, the results are sufficiently consistent to allow some conclusions to be made. First, the 2 tests, when used together, perform better than either test performs when used alone. Second, the tests have better performance characteristics for detecting bacteriuria at high colony counts than at low colony counts [51]. Third, these tests have low sensitivity, high specificity, low positive-predictive values, and high negative-predictive values. Taken together, the performance characteristics of these tests make them useful as a way to rule out bacteriuria on the basis of a negative test result.

A number of drugs can change the color of urine; abnormal urine color may affect urine tests that are based on the interpretation of color changes. In some cases, this can mask color changes, and in others, it may result in false-positive interpretations [45].

### CULTURES AND THE LABORATORY DIAGNOSIS OF UTIs

**Routine bacterial urine cultures.** Urine culture may not be necessary as part of the evaluation of outpatients with uncomplicated UTIs [55, 56]. However, urine cultures are necessary for outpatients who have recurrent UTIs, experience treatment failures, or have complicated UTIs. Urine cultures are also necessary for inpatients who develop UTIs. The bacterial culture remains an important test in the diagnosis of UTI, not only because it helps to document infection, but also because it is

<table>
<thead>
<tr>
<th>Test, colony count</th>
<th>Performance characteristics</th>
<th>Predictive values</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Positive</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10^5 cfu/mL</td>
<td>69-88</td>
<td>59-96</td>
<td>19-86</td>
</tr>
<tr>
<td>&gt;10^6 cfu/mL</td>
<td>64-77</td>
<td>59-83</td>
<td>16-52</td>
</tr>
<tr>
<td>&gt;10^7 cfu/mL</td>
<td>62-79</td>
<td>55-84</td>
<td>3-81</td>
</tr>
<tr>
<td>Nitrite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10^9 cfu/mL</td>
<td>19-45</td>
<td>96-98</td>
<td>50-78</td>
</tr>
<tr>
<td>&gt;10^10 cfu/mL</td>
<td>8-39</td>
<td>97-98</td>
<td>27-81</td>
</tr>
<tr>
<td>&gt;10^11 cfu/mL</td>
<td>0-50</td>
<td>48-96</td>
<td>0-82</td>
</tr>
<tr>
<td>Leukocyte esterase and nitrite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10^12 cfu/mL</td>
<td>35-84</td>
<td>99-100</td>
<td>84</td>
</tr>
<tr>
<td>&gt;10^13 cfu/mL</td>
<td>0-45</td>
<td>62-98</td>
<td>0-86</td>
</tr>
<tr>
<td>Leukocyte esterase and/or nitrite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10^14 cfu/mL</td>
<td>67-100</td>
<td>67-98</td>
<td>40-95</td>
</tr>
<tr>
<td>&gt;10^15 cfu/mL</td>
<td>74-79</td>
<td>66-82</td>
<td>42-54</td>
</tr>
<tr>
<td>&gt;10^16 cfu/mL</td>
<td>71-84</td>
<td>41-83</td>
<td>49-81</td>
</tr>
</tbody>
</table>

**NOTE.** The criteria used to assess the clinical importance of isolates and the laboratory methods used varied between studies; the data are presented only as an overview of reported performance characteristics of the tests. All numbers are rounded to the nearest whole number. cfu, colony-forming units,
Table 4. Interpreting culture results for urine specimens yielding common urinary tract pathogens.

<table>
<thead>
<tr>
<th>Probability of contamination, no. of microorganisms isolated</th>
<th>Quantitation, cfu/mL</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low probability&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;10⁵</td>
<td>Probable contaminant</td>
</tr>
<tr>
<td>1</td>
<td>≥10⁴</td>
<td>Significant isolate</td>
</tr>
<tr>
<td>2</td>
<td>&lt;10⁷ for each</td>
<td>Probable contaminants</td>
</tr>
<tr>
<td>2</td>
<td>≥10⁴ for each</td>
<td>Significant isolates</td>
</tr>
<tr>
<td>2</td>
<td>≥10² for 1</td>
<td>Significant isolate and contaminant</td>
</tr>
<tr>
<td>≥3</td>
<td>≥10⁴ for 1</td>
<td>Significant isolate and contaminant</td>
</tr>
<tr>
<td>≥3</td>
<td>≥10⁵ for each</td>
<td>Probable contaminants</td>
</tr>
<tr>
<td>High probability&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;10⁵</td>
<td>Probable contaminant</td>
</tr>
<tr>
<td>1</td>
<td>≥10⁴</td>
<td>Significant isolate</td>
</tr>
<tr>
<td>2</td>
<td>≥10⁵ for each</td>
<td>Significant isolates</td>
</tr>
<tr>
<td>2</td>
<td>≥10⁷ for 1</td>
<td>Significant isolate and contaminant</td>
</tr>
<tr>
<td>2</td>
<td>&lt;10⁵ for each</td>
<td>Probable contaminants</td>
</tr>
<tr>
<td>≥3</td>
<td>≥10⁷ for 1</td>
<td>Significant isolate and contaminant</td>
</tr>
<tr>
<td>≥3</td>
<td>≥10⁸ for each</td>
<td>Probable contaminants</td>
</tr>
</tbody>
</table>

NOTE. cfu, colony-forming units.
<sup>a</sup> Urine specimens obtained via aspiration (suprapubic, bladder, ureter, renal pelvis, kidney) or single (straight) catheterization; specimens obtained in the operating room, and urine specimens obtained from patients receiving antimicrobial therapy.
<sup>b</sup> Urine specimens obtained via clean catch technique, from indwelling catheters (urinary or suprapubic), or from nephrostomy tubes, ureterostomy tubes, or feal loops.

necessary for determination of the identity of the infecting microorganism(s) and for antimicrobial susceptibility testing. This is particularly true because of the increased incidence of antimicrobial resistance.

The most commonly used criterion for defining significant bacteriuria is the presence of ≥10⁵ cfu per milliliter of urine [15, 57, 58]. This criterion was established only for women with acute pyelonephritis or women who were asymptomatic but had multiple urine cultures that yielded this number of bacteria; however, the criterion is often applied to other patient populations [15]. Most patients with UTIs, however, do not fall into either category, and 30%–50% of patients with acute urethral syndrome will have colony counts of <10⁵ cfu/mL [15]. For this reason, many laboratories have opted to use lower colony counts as a criterion for interpreting and reporting results. One common criterion is a colony count of 10⁵ cfu/mL, which would be expected to increase the sensitivity of the test without making the test impractical for clinicians and laboratories to use.

Catheterized patients (who may have low concentrations of bacteria that can progress to higher concentrations) and many patients with infections of the lower urinary tract have colony counts much lower than 10⁵ cfu/mL if the specimens are obtained via suprapubic aspirate or catheterization [59]. Accordingly, the most appropriate diagnostic criterion for urine culture specimens obtained via suprapubic aspirate or catheterization is a bacterial concentration of ≥10⁵ cfu/mL [15, 59].

Routine follow-up cultures for test-of-cure are not recommended for patients who have been treated for asymptomatic bacteriuria, acute uncomplicated cystitis, or acute uncomplicated pyelonephritis [60] and for whom there is evidence of an appropriate clinical response to therapy [2]. Follow-up cultures are, however, recommended for patients with infections that do not respond to therapy, patients who have recurrent UTIs, patients who have anatomic or functional abnormalities of the urinary tract, or patients who continue to have unexplained abnormal urinalysis findings.

Anaerobic bacterial urine cultures. The normal flora of the large intestine, vagina, and skin contain large numbers of anaerobic bacteria. Because anaerobic bacteria cause UTIs only in rare circumstances, however, recovery of anaerobic bacteria from urine by culture is of no clinical relevance for most patients with UTIs. Urine cultures for anaerobic bacteria should be limited to patients with anatomic abnormalities (e.g., enterovesical fistulae) that increase the likelihood of infection with anaerobic bacteria.

Fungal urine cultures. As stated previously, microbiologic detection of almost all cases of funguria can be achieved using
routine bacterial media. There are limited data regarding the use of tests other than culture to detect funguria. Huang et al. [61] reported that pyuria did not correlate with funguria, regardless of whether patients had concomitant bacteriuria or an indwelling urinary catheter. Kauffman et al. [16] reported that, of 648 patients with funguria whose urine specimens underwent urinalysis, 354 (54.6%) had pyuria and 230 (35.5%) had hematuria. Of the 648 patients, only 410 had urine specimen reports that included a comment as to the presence or absence of yeasts; 247 (60.2%) of these 410 patients had urine specimens that were positive for yeasts [16]. On the basis of these observations, and because the nitrite test would be of no use in the detection of funguria, there appears to be limited value in using urinalysis in the detection of funguria at this time. This conclusion may change as further information is published regarding the clinical outcomes of patients with funguria, the results of laboratory testing of urine specimens, and the effects of chemotherapy.

Mycobacterial urine cultures. Although it is an uncommon finding in the United States, extrapulmonary tuberculosis may involve the genitourinary tract. The traditional laboratory diagnosis of mycobacterial UTI is by use of acid-fast smears and mycobacterial cultures [62], but more recent data suggests that the diagnosis can also be made by use of nucleic acid amplification tests [63, 64]. There are, however, only limited data about the use of such assays for the diagnosis of genitourinary tuberculosis, and none of these assays have been cleared or approved by the US Food and Drug Administration for this indication. Until better data are available, the authors recommend against the routine use of nucleic acid amplification tests, particularly with patients for whom there is low clinical suspicion of genitourinary tuberculosis.

Because nontuberculous mycobacteria, such as Mycobacterium smegmatis, may be present as colonizing flora (and to reduce the number of contaminating bacteria), the external genitalia should be washed before specimens are obtained [64]. The best specimen for mycobacterial urine cultures is the first voided urine. Multiple specimens may be needed, because mycobacterial culture results are positive for 25%-95% of patients and smears are positive for 50%-70% of patients with tuberculous genitourinary tract infections [62].

Interpretation of urine culture results. Microbiologists need to interpret the microbiologic relevance of growth on culture plates to determine whether further identification and antimicrobial susceptibility testing are necessary. Most culture results can be interpreted readily; no growth and gross contamination are both unambiguous results, as are pure cultures of common pathogens growing in a quantity of >10^8 cfu per milliliter of urine. The interpretation of cultures that yield pure growth in lower quantities is also clear for specimens obtained via suprapubic aspiration or straight catheterization.

On the other hand, interpretation of urine cultures that yield mixed flora in varying quantities can be difficult. Although a number of algorithms have been developed to guide the interpretation of urine cultures, the large number of potential combinations of microorganisms—in varying quantities—and the need to correlate these results with different types of UTIs limits the usefulness of any algorithm. One algorithm is presented in table 4.

Irrespective of the algorithm used to guide interpretation, laboratories should report culture results with interpretive guidelines to help the ordering physician assess the clinical relevance of the results. Cultures that yield unambiguous culture results should be interpreted and reported as such. Test reports for cultures that yield mixed flora in varying quantities should specify the microorganisms that were recovered, the quantity of each microorganism, and the probable clinical importance of each isolate.

Antimicrobial susceptibility testing. Each laboratory should have guidelines by which pathogens are tested for antimicrobial susceptibility. These guidelines should be developed and antimicrobial susceptibility tests should be performed and reported according to the most recent version of the NCCLS guidelines. Bacterial or fungal isolates of uncertain clinical importance should not be tested for antimicrobial susceptibility for purposes of routine patient care.

CONCLUSION

Most patients with uncomplicated acute cystitis have cases that are clinically straightforward, and they may not require any laboratory testing beyond urinalysis. For a significant number of patients, however, the clinical history and physical findings alone may be insufficient to make a definitive diagnosis of UTI. For those patients and for patients with complicated UTIs, laboratory tests are necessary to make the diagnosis and to provide specific information regarding the identity and the antimicrobial susceptibility pattern of pathogens. Both the laboratory diagnosis and the clinical diagnosis of laboratory test results must be made in light of the method of collection used; clinicians should specify the method of collection on test requisition forms. Of the available laboratory tests, urinalysis is helpful primarily as a means of excluding bacteriuria, but it is not a surrogate for culture. Although cultures identify pathogens, the accurate interpretation of culture results requires clinical information that is usually available only to the clinician. We hope that infectious diseases physicians, in particular, will understand both the strengths and the limitations of the laboratory-based diagnostic studies for UTIs that have been reviewed in this article, and we hope that they will incorporate this understanding with current treatment guidelines [65] to optimize patient care.
References


Diagnosis, Initial Management, and Prevention of Meningitis

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Although the annual incidence of bacterial meningitis in the United States is declining, it remains a medical emergency with a potential for high morbidity and mortality. Clinical signs and symptoms are unreliable in distinguishing bacterial meningitis from the more common forms of aseptic meningitis; therefore, a lumbar puncture with cerebrospinal fluid analysis is recommended. Empiric antimicrobial therapy based on age and risk factors must be started promptly in patients with bacterial meningitis. Empiric therapy should not be delayed, even if a lumbar puncture cannot be performed because results of a computed tomography scan are pending or because the patient is awaiting transfer. Concomitant therapy with dexamethasone initiated before or at the time of antimicrobial therapy has been demonstrated to improve morbidity and mortality in adults with Streptococcus pneumoniae infection. Within the United States, almost 30 percent of strains of pneumococci, the most common etiologic agent of bacterial meningitis, are not susceptible to penicillin. Among adults in developed countries, the mortality rate from bacterial meningitis is 21 percent. However, the use of conjugate vaccines has reduced the incidence of bacterial meningitis in children and adults. (Am Fam Physician. 2010;82(12):1491-1498. Copyright © 2010 American Academy of Family Physicians.)

Acute meningitis is a medical emergency with a potential for high morbidity and mortality. Bacterial meningitis is life threatening, and must be distinguished from the more common aseptic (viral) meningitis. With increased use of conjugate vaccines, the annual incidence of bacterial meningitis in the United States declined from 1.9 to 1.5 cases per 100,000 persons between 1998 and 2003, with an overall mortality rate of 15.6 percent. Incidence rates in developing countries remain significantly higher.

Etiology
Age, immunosuppression, and neurosurgical procedures increase the likelihood of infection from specific pathogens (Table 1). In persons with community-acquired meningitis, aseptic meningitis is significantly more common than bacterial meningitis; 96 percent of children with cerebrospinal fluid (CSF) pleocytosis have aseptic meningitis. The most common etiologies of aseptic meningitis are enterovirus, herpes simplex virus (HSV), and Borrelia burgdorferi infections. In adults, the incidence of aseptic meningitis is 7.6 cases per 100,000 persons, and the most common etiologies are enterovirus, HSV, and varicella-zoster virus infections. Other pathogens and diseases associated with aseptic meningitis include Treponema pallidum, Mycoplasma pneumoniae, Rocky Mountain spotted fever, ehrlichiosis, mumps, lymphocytic choriomeningitis virus, and acute retroviral syndrome associated with human immunodeficiency virus (HIV) infection.

Patients with mosquito-borne arboviral infections (e.g., West Nile virus, St. Louis encephalitis, the California encephalitis group) often present with encephalitis; however, they may present with meningeal involvement alone and no neurologic manifestations. Seasonality is important in predicting the likelihood of aseptic meningitis, because most enteroviral and arboviral infections occur in the summer or fall in temperate climates. Tuberculous and fungal meningitis are less common in the United States, and usually produce more chronic symptoms. Cryptococcal meningitis is common in patients with altered cellular immunity, especially in those with advanced HIV infection (e.g., CD4 cell count of less than 200 cells per mm³ [200 × 10⁶ per L]).

Clinical Presentation
In adults with community-acquired bacterial meningitis, 25 percent have recent otitis or sinusitis, 12 percent have pneumonia, and
Table 1. Common Etiologies of Bacterial Meningitis and Recommended Empiric Therapy

<table>
<thead>
<tr>
<th>Population</th>
<th>Likely pathogen</th>
<th>Empiric therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants younger than one month</td>
<td><em>Streptococcus agalactiae</em> (group B streptococcus), <em>Listeria monocytogenes</em>, <em>Escherichia coli</em>, other gram-negative bacilli</td>
<td>Ampicillin and cefotaxime (Cilastan)</td>
</tr>
<tr>
<td>Children one to 23 months of age</td>
<td><em>Streptococcus pneumoniae</em>, <em>Neisseria meningitidis</em>, <em>S. agalactiae</em>, <em>Haemophilus influenzae</em>, <em>E. coli</em></td>
<td>Vancomycin and ceftriaxone (Rocephin)</td>
</tr>
<tr>
<td>Children and adults two to 50 years of age</td>
<td><em>N. meningitidis</em>, <em>S. pneumoniae</em></td>
<td>Vancomycin and ceftriaxone</td>
</tr>
<tr>
<td>Adults older than 50 years, with altered cellular immunity, or with alcoholism</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>E. monocytogenes</em>, aerobic gram-negative bacilli</td>
<td>Vancomycin, ceftriaxone, and ampicillin</td>
</tr>
<tr>
<td>Patients with basilar skull fracture or cochlear implant</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em>, group A beta-hemolytic streptococci</td>
<td>Vancomycin and ceftriaxone</td>
</tr>
<tr>
<td>Patients with penetrating trauma or postneurosurgery</td>
<td><em>Staphylococcus aureus</em>, coagulase-negative staphylococci, aerobic gram-negative bacilli (including <em>Pseudomonas aeruginosa</em>)</td>
<td>Vancomycin and ceftriaxone (Maxaquin)</td>
</tr>
<tr>
<td>Patients with cerebrospinal fluid shunt</td>
<td>Coagulase-negative staphylococci, <em>S. aureus</em>, aerobic gram-negative bacilli (including <em>P. aeruginosa</em>), <em>Propanobacterium acnes</em></td>
<td>Vancomycin and ceftriaxone</td>
</tr>
</tbody>
</table>

*In 2002-2003 among all age groups in the United States, 61 percent of bacterial meningitis was caused by *S. pneumoniae*, 16 percent by *N. meningitidis*, 14 percent by group B streptococci, 2 percent by *H. influenzae*, and 2 percent by *E. monocytogenes.*


16 percent are immunocompromised. Typical clinical features are listed in Table 2. At least one of the cardinal features of fever, neck stiffness, and altered mental status is present in 99 to 100 percent of patients with meningitis; when headache is included, two of the four features are observed in 95 percent of patients with meningitis. The Kernig and Brudzinski signs are poorly sensitive but highly specific for bacterial meningitis. Sixty-three percent of patients with meningococcal meningitis present with a rash that is usually petechial. Petechial rash may also be caused by *Haemophilus influenzae* or *Streptococcus pneumoniae* infection. Pneumococcal meningitis is more likely than meningococcal meningitis to be associated with seizures, focal neurologic findings, and altered consciousness.

Compared with younger adults, persons 65 years and older with bacterial meningitis are less likely to have headache, nausea, vomiting, and nuchal rigidity, and are more likely to have seizures and hemiparesis. Similarly, the classical features of bacterial meningitis are not observed as often in younger children, who may present with subtle findings, such as lethargy and irritability. A recent history of upper respiratory tract infection is common in children with bacterial meningitis; children are also more likely than adults to experience a seizure. The illness course varies, with progression over hours to several days. The clinical features are nonspecific. For example, in a study of 297 adults who underwent a lumbar puncture for suspected meningitis, only 80 (27 percent) had any degree of CSF pleocytosis, only 20 (6.7 percent) had a white blood cell count of 100 cells per μL [0.10 × 10⁹ per L] or higher, and only three (1 percent) had culture-confirmed bacterial meningitis.

**Table 2. Clinical and Laboratory Findings in Adults with Bacterial Meningitis**

<table>
<thead>
<tr>
<th>Clinical or laboratory feature</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two of the following features, fever, neck stiffness, altered mental status, and headache</td>
<td>95</td>
</tr>
<tr>
<td>Cerebrospinal fluid white blood cell count ≥ 100 per μL [0.10 × 10⁹ per L]</td>
<td>93</td>
</tr>
<tr>
<td>Headache</td>
<td>87</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>85</td>
</tr>
<tr>
<td>Fever ≥ 100.4°F (38°C)</td>
<td>77</td>
</tr>
<tr>
<td>Nausea</td>
<td>74</td>
</tr>
<tr>
<td>Altered mental status (Glasgow Coma Scale score &lt; 14)</td>
<td>69</td>
</tr>
<tr>
<td>Growth of organism in blood culture</td>
<td>66</td>
</tr>
<tr>
<td>Triad of fever, neck stiffness, and altered mental status</td>
<td>44</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>33</td>
</tr>
<tr>
<td>Seizure</td>
<td>5</td>
</tr>
<tr>
<td>Papilledema</td>
<td>3</td>
</tr>
</tbody>
</table>

Information from reference 3.
Initial Management of Suspected Acute Meningitis

Patient presents with suspected meningitis
→ Initiate dropper precaution
→ Adequate respiratory and circulatory status, and likely normal coagulation status based on history and physical examination?
  → No → Initiate therapy for respiratory, circulatory, and coagulation status
  → Yes
→ Central nervous system disease*: adult with a new-onset seizure or moderately to severely impaired level of consciousness, or delay in ability to perform lumbar puncture?\textsuperscript{4,10-14}
  → No → Perform lumbar puncture and blood cultures
  → Yes → Spinal fluid cloudy? → Yes → CSF suggestive of bacterial meningitis?
    → No → Initiate (or continue) antimicrobial therapy
    → Yes → Initiate concomitant dexamethasone in an adult with likely pneumococcal meningitis
→ Obtain blood cultures and initiate antimicrobial therapy
  → If patient is an adult with likely pneumococcal meningitis, initiate concomitant dexamethasone
  → Perform computed tomography or magnetic resonance imaging
  → Scan reveals mass effect or cerebral edema?
    → No → Perform lumbar puncture
    → Yes → Reconsider diagnosis based on clinical, laboratory, and radiographic findings
→ Meningitis likely?
  → No → Reconsider diagnosis
  → Yes → Continue therapy
  → CSF suggestive of bacterial meningitis?
    → No → Continue therapy
    → Yes → Suspicion of bacterial meningitis
      → Yes → Initiate antimicrobial therapy
      → No → Reconsider diagnosis based on clinical, laboratory, and radiographic findings
→ Conclusion

*Includes CSF shunts, hydrocephalus, trauma, space-occupying lesions or recent neurosurgery, immunocompromised state, papilledema, or focal neurological signs

Figure 1. Algorithm for the initial management of suspected acute meningitis. (CSF = cerebrospinal fluid.)

Information from references 4, and 16 through 18.

particularly in young children (i.e., a normal white blood cell count does not rule out bacterial meningitis).\textsuperscript{4} Meningitis should be suspected in patients with those features previously noted that cannot be fully explained by other diagnoses. Lumbar puncture is a safe procedure, although postprocedure headache occurs in about one third of patients.\textsuperscript{12} (A video of a lumbar puncture is available at http://content.nejm.org/cgi/content/short/355/13/e12.) The concern with lumbar puncture is the poorly quantified risk of herniation in patients with a space-occupying lesion or severe diffuse cerebral swelling, and the degree to which the risk can be recognized by a previous computed tomography scan. Life-threatening herniation from lumbar puncture has not been reported in patients who are neurologically unremarkable before the procedure.\textsuperscript{16}

Based on patient series\textsuperscript{4} and guidelines,\textsuperscript{4,18} patients with risk factors for occult intracranial abnormalities should undergo computed tomography of the brain before lumbar puncture. This includes patients with central nervous system disease (including CSF shunts, hydrocephalus, trauma, space-occupying lesions or recent neurosurgery, immunocompromised state, papilledema, focal neurologic signs) and adults with new-onset seizures or moderately to severely impaired consciousness (Figure 1\textsuperscript{4,16-18}). During the initial evaluation of a patient with suspected meningitis, diagnostic and therapeutic maneuvers should begin concomitantly. If a computed tomography scan is required before a lumbar puncture, blood cultures should be obtained, followed by prompt initiation of empiric antimicrobial therapy before the scan. Adjunctive therapy with dexamethasone should be added in adults with suspected S. pneumoniae infection.\textsuperscript{19}

After CSF is obtained, the Gram stain results, white and red blood cell counts, glucose levels, and protein...
levels should be evaluated immediately. Although no single measure is diagnostic, a combination of abnormal CSF findings is highly suggestive of meningitis and helpful in determining the likely etiology (Table 3). Rarely, patients with bacterial meningitis may present with normal or near-normal white blood cell counts, glucose levels, and protein levels. This has been observed in young children with neutropenia and other immunocompromised states, and very early in the course of meningococcal meningitis.28 Lack of CSF leukocytosis and normal CSF glucose levels are also common in patients with HIV infection and cryptococcal meningitis, but the CSF cryptococcal antigen test is highly sensitive and specific. Patients with partially treated bacterial meningitis and those with Listeria infection may have a CSF profile that is similar to aseptic meningitis. In children who have not received previous antimicrobial agents, clinical decision rules are useful in identifying those at low risk of bacterial meningitis and, if otherwise clinically stable, who are eligible for careful observation without antimicrobial therapy (Table 4).31

### Table 3. Typical CSF Parameters in Patients with Meningitis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>White blood cells per µL (× 10^9 per L)</th>
<th>Percentage of neutrophils</th>
<th>Glucose level</th>
<th>Protein level in mg per dl (g per l)</th>
<th>Likelihood of observing organism on CSF stain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyogenic (not Listeria monocytogenes)</td>
<td>&gt; 500 (0.50)</td>
<td>&gt; 80</td>
<td>Low</td>
<td>&gt; 100 (1.00)</td>
<td>-70 percent</td>
</tr>
<tr>
<td><em>L. monocytogenes</em></td>
<td>&gt; 100 (0.10)</td>
<td>-50</td>
<td>Normal</td>
<td>&gt; 50 (0.50)</td>
<td>-30 percent</td>
</tr>
<tr>
<td>Partially treated pyogenic</td>
<td>&gt; 100</td>
<td>-50</td>
<td>Normal</td>
<td>&gt; 70 (0.70)</td>
<td>-60 percent</td>
</tr>
<tr>
<td>Aseptic, often viral</td>
<td>10 to 1,000</td>
<td>Early &gt; 50</td>
<td>Normal</td>
<td>&lt; 200 (2.00)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Tubercular</td>
<td>50 (0.05) to 500</td>
<td>&lt; 30</td>
<td>Low</td>
<td>&gt; 100</td>
<td>Rare</td>
</tr>
<tr>
<td>Fungal</td>
<td>50 to 500</td>
<td>&lt; 30</td>
<td>Low</td>
<td>Varies</td>
<td>Often high in cryptococcus</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid

### Table 4. Clinical Decision Rules to Distinguish Bacterial from Aseptic Meningitis in Children with CSF Pleocytosis

<table>
<thead>
<tr>
<th>Rule</th>
<th>Bacterial Meningitis Score†</th>
<th>Meningitis†/‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria</td>
<td>Neurosurgical history</td>
<td>Neurosurgical history</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>CSF red blood cell count ≥ 0.01 × 10^6 per µL (0.01 × 10^6 per L)</td>
<td>CSF red blood cell count ≥ 0.01 × 10^6 per µL</td>
</tr>
<tr>
<td></td>
<td>Antibiotic use in the previous 48 hours</td>
<td>Antibiotic use in the previous 48 hours</td>
</tr>
<tr>
<td>Purpura</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criteria (further evaluation; including lumbar puncture, is needed in patients with one or more findings)</td>
<td>Positive CSF Gram stain</td>
<td>Positive CSF Gram stain</td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>Seizure</td>
</tr>
<tr>
<td></td>
<td>Blood neutrophil count ≥ 10,000 per µL (10.00 × 10^6 per L)</td>
<td>Toxic appearance (unfitability, lethargy, or low capillary refill)</td>
</tr>
<tr>
<td></td>
<td>CSF neutrophil count ≥ 1,000 per µL (1.00 × 10^6 per L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSF protein level ≥ 80 mg per dl (0.80 g per L)</td>
<td>Serum procalcitonin level ≥ 0.5 ng per mL</td>
</tr>
</tbody>
</table>

Sensitivity (95% confidence interval): 93% (99 to 100) 100% (96 to 100)

CSF = cerebrospinal fluid

*†—White blood cell count ≥ 10 per µL (0.01 × 10^6 per L).


### Bacterial Meningitis

Initial empiric therapy of bacterial meningitis is based on the patient's age, risk factors, and clinical features (Table 1).44 In patients with suspected bacterial meningitis, empiric therapy should not be delayed for more than one hour while awaiting diagnostic testing or
Table 5. Pathogen-Specific Therapy for Common Causes of Bacterial Meningitis

<table>
<thead>
<tr>
<th>Pathogen*</th>
<th>Recommended therapy</th>
<th>Adult dose (intravenous)</th>
<th>Days of therapy</th>
<th>Alternative therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Penicillin</td>
<td>4 million units every four hours</td>
<td>10 to 14</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td>Penicillin MIC  &lt; 0.1 mcg per ml</td>
<td>Penicillin</td>
<td>4 million units every four hours</td>
<td>10 to 14</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td>Penicillin MIC 0.1 to 1 mcg per ml</td>
<td>Ceftriaxone (Rocephin)</td>
<td>2 g every 12 hours</td>
<td>10 to 14</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td>Penicillin MIC  &gt; 2 mcg per ml</td>
<td>Vancomycin</td>
<td>15 to 22.5 mg per kg every 12 hours</td>
<td>10 to 14</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Ceftaxone</em></td>
<td>Ceftriaxone</td>
<td>15 to 22.5 mg per kg every 12 hours</td>
<td>10 to 14</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Aerococcus meningitidis</em></td>
<td>Ceftriaxone</td>
<td>2 g every 12 hours</td>
<td>5 to 7</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Ceftriaxone</td>
<td>2 g every 12 hours</td>
<td>5 to 7</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (group B <em>Streptococcus</em>)</td>
<td>Ampicillin</td>
<td>150 mg every 4 hours</td>
<td>14 to 21</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Gentamicin</td>
<td>1 to 2 mg per kg every 8 hours</td>
<td>14 to 21</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Ceftazidime, ceftriaxone (Targen), or ceftiraxone (Mazentril) with or without Gentamicin</td>
<td>2 g every 8 hours</td>
<td>14 to 21</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Enterobacteraceae</em></td>
<td>Ceftazidime, ceftriaxone (Targen), or ceftiraxone (Mazentril) with or without</td>
<td>2 g every 8 hours</td>
<td>21 to 28</td>
<td>Meropenem (Merrem), imipenem (Ifex), or chloramphenicol</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Nalidixin or Tobramycin</td>
<td>1 g every 8 hours</td>
<td>6 to 10</td>
<td>Nalidixin or Tobramycin</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> resistant</td>
<td>Nalidixin, Tobramycin</td>
<td>1 g every 8 hours</td>
<td>6 to 10</td>
<td>Nalidixin or Tobramycin</td>
</tr>
</tbody>
</table>

*MIC = minimal inhibitory concentration
* Listed in order of most likely to least likely.
+ Gentamicin may be used instead.
3 Consider adding rifampin. Vancomycin concentration into cerebrospinal fluid may be diminished with concomitant dexamethasone. Adequate levels are achieved with continuous infusion at 50 mg per kg.†
6 For the first seven to 10 days.
Information from references 1, 2, 11, 16, 18, 26, and 27.

transfers. Although no prospective comparative trials have been performed, observational studies have found that delays in therapy of as little as two to six hours are associated with adverse outcomes. Factors associated with a delay in antimicrobial therapy include failure to receive antimicrobials before transfer from another facility; performance of head computed tomography before lumbar puncture and antimicrobial administration; and the absence of the cardinal features of fever, neck stiffness, and altered mental status. When administered just before antimicrobial therapy is initiated, concomitant use of dexamethasone for four days has been shown to reduce mortality and improve neurologic outcomes in adults with *S. pneumoniae* infection. It has not been shown to improve outcomes in other patient groups. Studies of patients in the developing world who have a high likelihood of HIV infection have not shown a clear benefit with adjunctive dexamethasone for pyogenic bacterial meningitis. Fluid management includes treatment for possible dehydration or hyponatremia from the syndrome of inappropriate antidiuretic hormone.

After the results of the Gram stain, culture, and susceptibility tests are available, specific therapy targeting the pathogen should be administered (Table 5). Blood cultures drawn before antimicrobial administration are positive in 61 to 66 percent of patients. Initiation of antimicrobials before lumbar puncture decreases the yield of CSF culture, the likelihood of a low CSF
glucose level, and the degree of elevation of CSF protein; however, it does not markedly influence the results of CSF Gram stain, which is positive in 60 to 70 percent of patients.\textsuperscript{6,18}

Polymerase chain reaction testing of CSF is more sensitive than CSF culture, particularly in patients who received previous antimicrobials.\textsuperscript{29,30} However, antimicrobial susceptibility testing, which is important in the treatment and prevention of meningitis, can be performed only when the organism is grown in culture. In one series in the United States, 28 percent of pneumococci from patients with meningitis were not susceptible to penicillin, 6 percent were not susceptible to chloramphenicol, 17 percent were not susceptible to meropenem (Merrem), and 12 percent were not susceptible to cefotaxime (Claforan).\textsuperscript{1} Because of this degree of resistance, the administration of empiric therapy with vancomycin and a third-generation cephalosporin (cefotaxime or ceftriaxone [Rocephin]) is recommended until the results of susceptibility tests are known.

\section*{Aseptic Meningitis}

Enteroviruses are the most common etiologic pathogens in persons with aseptic meningitis and do not require specific antimicrobial therapy. They can be diagnosed by CSF polymerase chain reaction testing,\textsuperscript{4} which is not always needed, but a positive test may be useful in discontinuing antimicrobials initiated presumptively for bacterial meningitis. If suggested by the patient's sexual or substance use history, it is appropriate to order serum reactive plasma reagin (RPR), CSF Venereal Disease Research Laboratory (VDRL), serum HIV antibody, and serum HIV polymerase chain reaction tests. In acute HIV seroconversion, the serum HIV antibody test may be negative at the time of clinical presentation.

HSV aseptic meningitis is usually a self-limited infection that must be distinguished from HSV encephalitis based on clinical and radiographic features; therapy with acyclovir (Zovirax) can be lifesaving in patients with HSV encephalitis. In contrast with HSV encephalitis, most patients with HSV aseptic meningitis have normal mental status and neurologic function, and do not have enhancement observed on magnetic resonance imaging of the temporal lobe. Both forms of HSV central nervous system disease are diagnosed by CSF HSV polymerase chain reaction testing. Infection with HSV may cause recurrent disease (e.g., Mollaret meningitis). Varicella-zoster virus infection may cause aseptic meningitis in the absence of cutaneous manifestations.\textsuperscript{5} Although it has not been studied in clinical trials, therapy with acyclovir at 10 mg per kg every eight hours is suggested, based on expert opinion. Central nervous system Lyme disease is treated with ceftriaxone for 14 to 28 days, and central nervous system syphilis is treated with intravenous penicillin for 10 to 14 days.

\section*{Tuberculous and Cryptococcal Meningitis}

A high index of suspicion is needed to diagnose tuberculous meningitis because culture results are often delayed and stains are often negative. Empiric therapy may be lifesaving. Polymerase chain reaction testing may be useful. Initial treatment is a combination of isoniazid (5 mg per kg per day in adults, 10 mg per kg per day in children, up to 300 mg); rifampin (10 mg per kg per day in adults, 10 to 20 mg per kg per day in children, up to 600 mg); pyrazinamide (15 to 30 mg per kg per day, up to 2 g); and ethambutol (15 to 25 mg per kg per day). Streptomycin (20 to 40 mg per kg per day, up to 1 g) should be used in lieu of ethambutol in young children.\textsuperscript{31} Adding dexamethasone to the treatment regimen improves mortality in patients older than 14 years with tuberculous meningitis.\textsuperscript{32}

Cryptococcal meningitis is the most common fungal meningitis, and usually occurs in patients with altered cellular immunity. Initial treatment includes amphotericin B (0.7 to 1.0 mg per kg per day intravenously) plus fluocytosine (Ancobon; 25 mg per kg every six hours orally).\textsuperscript{33}

\section*{Prognosis}

The mortality rate in adults with bacterial meningitis in developed countries is 21 percent; it is higher in patients with pneumococcal disease than in those with meningococcal disease.\textsuperscript{7} Neurologic sequelae include hearing loss in 14 percent of patients and hemiparesis in 4 percent.\textsuperscript{7} Risk factors for adverse outcomes include advanced age, alteration of mental status on admission, bacteremia, and a CSF white blood cell count of less than 1,000 per \(\mu\)L (1.00 \(\times\) 10\(^3\) per L).\textsuperscript{7} The mortality rate in children with bacterial meningitis is 3 percent; the incidence of stroke in children with bacterial meningitis is 3 percent.\textsuperscript{24}

\section*{Prevention}

Conjugate vaccines for \textit{H. influenzae} type B and \textit{S. pneumoniae} initiated in early childhood have been highly effective in reducing the incidence of bacterial meningitis, not only in children but also in adults.\textsuperscript{1,12} Although the overall incidence of pneumococcal meningitis has declined with the use of the conjugate vaccine, the percentage of meningitis cases caused by nonvaccine serotypes has increased, as did the percentage of isolates that were not susceptible to penicillin and cefotaxime. A newer conjugate vaccine for \textit{Neisseria meningitidis} (active against serogroups A, C, W135, and Y, but not serogroup B) is recommended in all
### SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of cerebrospinal fluid is key to the diagnosis of meningitis. Decision rules using clinical and laboratory findings are highly sensitive in diagnosing meningitis in children.</td>
<td>C</td>
<td>5, 8, 13, 21</td>
</tr>
<tr>
<td>Patients with risk factors for occult intracranial abnormalities should undergo computed tomography of the brain before lumbar puncture.</td>
<td>C</td>
<td>17</td>
</tr>
<tr>
<td>If bacterial meningitis is suspected, empiric therapy with antimicrobials should not be delayed for more than one hour in patients awaiting diagnostic testing or transfers.</td>
<td>C</td>
<td>4, 18, 22, 23</td>
</tr>
<tr>
<td>Adults with <em>Streptococcus pneumoniae</em> or <em>Mycobacterium tuberculosis</em> infection should receive concomitant dexamethasone with antimicrobial therapy to reduce mortality and improve neurologic outcomes.</td>
<td>B</td>
<td>19, 25, 32</td>
</tr>
<tr>
<td>Conjugate vaccines for <em>S. pneumoniae</em> and <em>Haemophilus influenzae</em> type B are recommended for patients in appropriate risk groups to reduce the incidence of bacterial meningitis.</td>
<td>B</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.*

### Table 6: Chemoprophylaxis for Bacterial Meningitis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication</th>
<th>Antimicrobial agent</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Close contact (for more than 8 hours) with someone with N. meningitidis infection</td>
<td>Rifampin or Clindamycin</td>
<td>Adults: 600 mg every 12 hours for 2 days; Children: 1 mg/kg every 12 hours for 2 days</td>
<td>Not fully effective and rare resistant isolates</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Contact with oral secretions of someone with N. meningitidis infection</td>
<td>Ciprofloxacin or Rifampin</td>
<td>Adults: single dose of 600 mg; Children: &lt;1 month 8 mg/kg every 12 hours for 2 days; 1-11 months 16 mg/kg every 12 hours for 2 days</td>
<td>Rare resistant isolates</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Living in a household with one or more unvaccinated or unvaccinated, unvaccinated children younger than 1 year</td>
<td>Ceftriaxone or Rifampin</td>
<td>Single intramuscular dose of 250 mg (125 mg if younger than 1 year); 20 mg/kg per day for 4 days</td>
<td>Cephalosporins may be used in the first week of life if fluoroquinolones are contraindicated.</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (Group B)</td>
<td>Recent birth to an infant with invasive S. agalactiae infection</td>
<td>Penicillin G or Ceftriaxone</td>
<td>Initial dose of 5 million units intravenously; then 2 to 3 million units every 4 hours during the first 24 hours of life; 5 to 10 mg/kg every 12 hours</td>
<td>Ceftriaxone may be used in the first week of life if penicillin is contraindicated.</td>
</tr>
<tr>
<td><em>Streptococcus, women in the intrapartum period</em></td>
<td>Recent labor during pregnancy</td>
<td>Clindamycin or Cefazolin</td>
<td>Initial dose of 500 mg every 6 hours; then 500 mg every 30 hours for 4 days</td>
<td>Clindamycin susceptibility must be confirmed by antimicrobial susceptibility test</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>High risk because of severe macromnism, fluid rupture for more than 18 hours, or delivery before 37 weeks gestation</td>
<td>Cefazolin or Vancocin</td>
<td>Initial dose of 2 g followed by 1 g every 8 hours; then 750 mg every 6 hours for 4 days</td>
<td>Cefazolin susceptible isolates must be confirmed by antimicrobial susceptibility test</td>
</tr>
</tbody>
</table>

Information from references 11, 18, and 36.

Children 11 to 18 years of age; freshmen entering college dormitories; travelers to regions in which meningococcal disease is endemic (e.g., sub-Saharan Africa; Mecca, Saudi Arabia, during the Hajj); and persons with complement component deficiencies. Patients with functional or anatomic asplenia should receive the meningococcal, pneumococcal, and *H. influenzae* vaccines. Patients hospitalized with *N. meningitidis* infection or meningitis of uncertain etiology require droplet precautions for the first 24 hours of treatment, or until *N. meningitidis* can be ruled out. Chemoprophylaxis recommendations are listed in Table 6.11,18,36

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Meningitis

The Author

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Author disclosure: Nothing to disclose.

REFERENCES


Hematology & Oncology
Anemia in Older Persons

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KATHLEEN SOCH, MD, Texas A&M Health Science Center, College Station, Texas
TERESA SMITH-KNUPPEL, MD, Christus Spohn Family Medicine Residency Program, Corpus Christi, Texas

Anemia in older persons is commonly overlooked despite mounting evidence that low hemoglobin levels are a significant marker of physiologic decline. Using the World Health Organization definition of anemia (hemoglobin level less than 13 g per dL [130 g per L] in men and less than 12 g per dL [120 g per L] in women), more than 10 percent of persons older than 65 years are anemic. The prevalence increases with age, approaching 50 percent in chronically ill patients living in nursing homes. There is increasing evidence that even mild anemia is associated with increased morbidity and mortality. Anemia warrants evaluation in all older persons, except those at the end of life or who decline interventions. About one third of persons have anemia secondary to a nutritional deficiency, one third have anemia caused by chronic inflammation or chronic kidney disease, and one third have unexplained anemia. Nutritional anemia is effectively treated with vitamin or iron replacement. Iron deficiency anemia often is caused by gastrointestinal bleeding and requires further investigation in most patients. Anemia of chronic inflammation or chronic kidney disease may respond to treatment of the underlying disease and selective use of erythropoiesis-stimulating agents. The treatment of unexplained anemia is difficult, and there is little evidence that treatment decreases morbidity and mortality, or improves quality of life. Occasionally, anemia may be caused by less common but potentially treatable conditions, such as autoimmune hemolytic anemia, malignancy, or myelodysplastic syndrome. (Am Fam Physician. 2010;82(5):480-487. Copyright © 2010 American Academy of Family Physicians.)

Anemia is a common problem with serious consequences in older persons. Using the World Health Organization definition of anemia (hemoglobin level less than 13 g per dL [130 g per L] in men and less than 12 g per dL [120 g per L] in women), a large cohort study found that the corrected annual incidence of anemia increased steadily with age. From 65 to 69 years of age, the incidence of new-onset anemia was 6 percent in men and 4 percent in women. In persons 85 years and older, the annual incidence rose to 14 percent in men and 13 percent in women. In one study, approximately 50 percent of chronically ill patients living in nursing homes had anemia.2

Anemia is often overlooked in older persons despite considerable evidence that low hemoglobin levels indicate physiologic decline in these patients. Multiple studies demonstrate that anemia is an independent risk factor for increased morbidity and mortality, and decreased quality of life in community-dwelling older persons (Table 1).3-7 Increasing functional deterioration is associated with decreasing hemoglobin concentration in an inverse and linear manner.4,6 It is important to note, however, that even low normal hemoglobin levels may be a marker for decline.3 For example, one study of 1,146 community-dwelling older persons found that women with borderline anemia (hemoglobin level of 12 to 13 g per dL) perform worse than women with a hemoglobin level of 13 to 15 g per dL (130 to 150 g per L) on tests of walking speed, balance, and ability to rise from a chair.8

These implications of anemia should lead physicians to investigate for causes of anemia that can be readily addressed, with treatments that have the potential to improve quality of life. Despite the possible benefits of treating anemia in older adults who are...
frail or who are at the end of life, discomfort from medical tests and interventions may exceed the benefits when disease burden and disability become severe. Limited overall benefits, the risk of false-positive test results, and patient preferences are valid reasons to defer evaluation. This article outlines potential causes of anemia and treatments that may be beneficial in older persons.

Etiologies
The Third National Health and Nutrition Examination Survey studied the prevalence and etiologies of anemia in a large national sample of community-dwelling persons. Most cases of anemia were mild, with only 2.8 percent of women and 1.6 percent of men having a hemoglobin level of less than 11 g per dL (110 g per L). Approximately one third of persons with anemia had a nutritional deficiency; one third had anemia of chronic inflammation, chronic kidney disease, or both; and one third had unexplained anemia. A breakdown of specific etiologies are found in Table 2.

Clinical Diagnosis
Anemia often has an insidious onset in older persons. Although an acute drop in hemoglobin will cause symptoms of volume depletion, such as dizziness and increased falls, slower onset of anemia is better tolerated, with symptoms developing as compensatory mechanisms fail. Older persons cannot increase heart rate and cardiac output as readily as younger persons, with dyspnea, fatigue, and confusion becoming more common as anemia worsens. Preexisting cardiac diseases, such as coronary artery disease and congestive heart failure, often become more symptomatic as hemoglobin levels decrease.

There are few signs on physical examination that are specific for mild or moderate anemia. Pale conjunctiva are usually noted when the hemoglobin level drops below 9 g per dL (90 g per L). In persons with multiple chronic illnesses, physicians may overlook anemia or attribute its symptoms to the underlying disease process. Thus, it is important to have a high index of suspicion

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia is an independent risk factor for increased morbidity and mortality, and decreased quality of life in community-dwelling older persons.</td>
<td>B</td>
<td>3-6, 8, 11, 12</td>
</tr>
<tr>
<td>Most older persons with iron deficiency anemia should be evaluated for gastrointestinal bleeding.</td>
<td>C</td>
<td>35, 36</td>
</tr>
<tr>
<td>Normal levels of homocysteine and methylmalonic acid virtually exclude folate and vitamin B12 deficiencies.</td>
<td>C</td>
<td>32, 33</td>
</tr>
<tr>
<td>High-dose oral vitamin B12 replacement for vitamin B12 deficiency is effective and well tolerated.</td>
<td>B</td>
<td>41-43</td>
</tr>
</tbody>
</table>

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus; disease-oriented evidence; usual practice; expert opinion; or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afp/sort.xml.

Table 1. Risks Associated with Anemia in Older Persons

<table>
<thead>
<tr>
<th>Increased morbidity</th>
<th>Increased mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased mobility in community-dwelling older persons²⁴</td>
<td>Community-dwelling older persons¹¹,¹²</td>
</tr>
<tr>
<td>Decreased quality of life⁶</td>
<td>Nursing home residents⁹</td>
</tr>
<tr>
<td>Increased risk of fatigue, depression, dementia, delirium (in hospitalized patients), and falls¹⁰</td>
<td>Persons with preexisting heart or kidney disease¹⁵-¹⁸</td>
</tr>
<tr>
<td>Persons undergoing noncardiac surgery¹⁷</td>
<td></td>
</tr>
</tbody>
</table>

Information from references 3 through 17.

Table 2. Etiologies of Anemia in Noninstitutionalized Persons 65 Years and Older

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Subtype</th>
<th>Percentage of anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional</td>
<td>Iron deficiency</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td>Folate deficiency</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Vitamin B₁₂ deficiency</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency plus folate or vitamin B₁₂ deficiency, or all three</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Folate and vitamin B₁₂ deficiencies</td>
<td>2.0</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>Anemia of chronic inflammation</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>Renal insufficiency</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Renal insufficiency and anemia of chronic inflammation</td>
<td>4.3</td>
</tr>
<tr>
<td>Unexplained</td>
<td>---</td>
<td>33.6</td>
</tr>
</tbody>
</table>

Anemia

when older persons present with even subtle symptoms of decline. A complete blood count or a point-of-care hematocrit measurement will quickly confirm the diagnosis of anemia.

Additional history and physical examination findings often clarify the etiology of anemia. Questions should address signs and symptoms associated with blood loss, such as chronic indigestion or dark stools suggestive of gastrointestinal bleeding, dark urine suggestive of hematuria, and recent surgery. Dietary history is important, with strict vegan diets increasing the risk of vitamin B₁₂ deficiency.¹² Heavy alcohol consumption increases the risk of folate deficiency and bleeding from peptic ulcer disease and varices. Chronic inflammatory diseases and chronic kidney disease are associated with anemia.¹⁰ A history of long-standing anemia warrants consideration of familial disorders, such as thalassemias and hereditary spherocytosis.

Medications should be reviewed, with attention to those that increase the risk of bleeding (e.g., nonsteroidal anti-inflammatory drugs, warfarin [Coumadin]). A careful review of systems may identify alarming signs such as recent immobility, anorexia, and night sweats. Weight loss, lymphadenopathy, and localized bony pain are signs of serious illness and warrant consideration of underlying malignancy and chronic infection.

**Laboratory Testing and Evaluation**

Once anemia is confirmed, a complete blood count is helpful. If bleeding or iron deficiency anemia is clinically suspected, measurement of serum ferritin is also warranted. The red blood cell size or mean corpuscular volume (MCV) is used to distinguish microcytic, normocytic, and macrocytic anemias. Many patients have a previously documented complete blood count that can be compared for changes in the baseline MCV. Three algorithms (Figures 1²³⁻²⁰, ²³⁻²², and ²³⁻²⁴) are presented to help identify the underlying etiology or etiologies for anemia. The algorithms are based on probabilities, with the understanding that many anemias are multifactorial, and that it is difficult to conclusively identify the underlying causes.

**MICROCYTIC ANEMIA**

Microcytic anemias (Figure 1²³⁻²⁰) are usually caused by iron deficiency.²³ Ferritin is a marker of iron storage, and a ferritin level below 35 ng per mL (78.64 pmol per L) is highly suggestive of iron deficiency anemia.²³ It is important to note that ferritin levels increase with acute illness and inflammation, and in some persons with iron deficiency anemia and an acute inflammatory process, ferritin levels may be spuriously elevated. A cutoff of 45 ng per mL (101.11 pmol per L) has a higher sensitivity in older adults (Table 3).²⁴

Iron deficiency anemia often is caused by gastrointestinal bleeding and requires further investigation in most older persons.²⁵,²⁶ The presence of iron deficiency anemia markedly increases the likelihood of gastrointestinal malignancy, especially in persons 65 years and older.²⁵ Even in asymptomatic

---

**Diagnosis of Microcytic Anemia**

Mean corpuscular volume < 80 fl.

- Serum ferritin level

  - ≤ 45 ng per mL (101.11 pmol per L)
  - 46 to 100 ng per mL (103.36 to 224.70 pmol per L)
  - > 100 ng per mL (224.70 pmol per L)

- Iron deficiency anemia
- Blood urea nitrogen/creatinine ratio, hemoglobin electrophoresis
- Anemia of chronic disease

- Creatinine clearance ≤ 30 mL per minute per 1.73 m² (0.50 mL per second per m²)

- Abnormal hemoglobin electrophoresis

- Both normal

- Determination of soluble transferrin receptor

- Thalassemia likely

- Anemia of chronic kidney disease

**Figure 1. Algorithm for the diagnosis of microcytic anemia.**

Information from references 23 through 30.
Diagnosis of Normocytic Anemia

Mean corpuscular volume 80 to 100 fl.

Peripheral blood smear, reticulocyte count, vitamin B₁₂ and folate levels
Abnormal peripheral blood smear?

No

Reticulocyte index* ≤ 2%?

No

Lactate dehydrogenase, indirect bilirubin, and haptoglobin levels; direct Coombs test

High lactate dehydrogenase level, high indirect bilirubin level, haptoglobin level ≤ 25 mg per dl (250 mg per L), or positive direct Coombs test

Hemolysis

Vitamin B₁₂ level < 100 pg per mL (73.78 pmol per L) or folate level < 5 ng per mL (11.33 nmol per L)

Vitamin B₁₂ or folate deficiency

Vitamin B₁₂ or folate level borderline low

Methylmalonic acid and homocysteine levels

Elevated methylmalonic acid level

Vitamin B₁₂ deficiency

Ferritin level ≤ 45 ng per mL (101.11 pmol per L)

Iron deficiency anemia

Ferritin level 46 to 100 ng per mL (103.36 to 224.70 pmol per L)

Anemia of chronic disease with possible iron deficiency (see Figure 1)

Ferritin level >100 ng per mL (224.70 pmol per L)

Anemia of chronic disease

Creatinine clearance ≤ 30 mL per minute per 1.73 m² (0.50 mL per second per m²)

Anemia of chronic kidney disease

Yes

Consider myelodysplastic syndrome, malignancy, multiple myeloma

Consider bone marrow biopsy

Vitamin B₁₂ and folate levels

Normal tests

Recent blood loss, hypersplenism

Figure 2. Algorithm for the diagnosis of normocytic anemia.

Information from references 23 through 33.
Diagnosis of Macrocytic Anemia

![Diagram of the diagnosis process for macrocytic anemia]

Figure 3. Algorithm for the diagnosis of macrocytic anemia.

Information from references 31 through 34.

patients, more than one half are found to have a bleeding-related lesion on endoscopic evaluation with esophagogastroduodenoscopy and colonoscopy. Advanced age, low MCV (60 fl or less), and positive fecal occult blood test results are associated with higher rates of gastrointestinal bleeding.56 Despite the potential benefits of diagnosing malignancies and other pathologies, it is important to remember that the risks of perforation with colonoscopy increase with age, significant comorbidity, obstruction, and invasive interventions.57 Invasive diagnostic interventions are best used when they are likely to affect disease management and improve prognosis.

NORMOCYTIC ANEMIA

Normocytic anemias (Figure 233-33) have a wide differential diagnosis. Although many normocytic anemias are secondary to chronic disease, including chronic kidney disease, it is important to exclude early nutritional deficiencies and hemolysis. A peripheral blood smear, reticulocyte count, and vitamin

<table>
<thead>
<tr>
<th>Table 3. Ferritin Testing in Older Persons with Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin level (ng per mL)</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>&lt; 19 (42.69 pmol per L)</td>
</tr>
<tr>
<td>19 to 45 (42.69 to 101.11 pmol per L)</td>
</tr>
<tr>
<td>45 to 100 (103.36 to 224.70 pmol per L)</td>
</tr>
<tr>
<td>&gt; 100 (224.70 pmol per L)</td>
</tr>
</tbody>
</table>

*—Based on an estimated 33 percent prevalence of iron deficiency anemia.

Information from reference 24.
B₁₂ and folate levels should be ordered. Many patients with vitamin B₁₂ or folate deficiency have a normal MCV.³³ If the reticulocyte index (reticulocyte count times hematocrit level, divided by normal hematocrit level) is greater than 2 percent, hemolysis and subsequent confirmatory tests should be considered. A positive direct Coombs test result strongly supports autoimmune hemolytic anemia. Autoimmune hemolytic anemia, both warm and cold antibody types, is life-threatening if untreated, but has good outcomes with immunosuppression.³⁴ Other causes of reticulocytosis include recent blood loss and hypersplenism. Most persons with anemia have a low reticulocyte count, which indicates that the bone marrow is not producing adequate red blood cells. If vitamin B₁₂ and folate levels are adequate, these patients should be evaluated for iron deficiency anemia and kidney disease. Many older persons have a mixed anemia with more than one etiology. The soluble transferrin receptor level is typically increased to 2.5 mg per L (29.5 nmol per L) or greater with iron deficiency anemia.²⁷ When dividing the soluble transferrin receptor level by the log of the ferritin level, a value of 1.5 or less suggests anemia of chronic disease and a value greater than 1.5 supports iron deficiency with chronic disease.²⁸⁻²⁹

MACROCYTIC ANEMIA

Macrocyclic anemias (Figure 3³¹-³⁴) may be caused by drug therapy, alcoholism, liver disease, hypothyroidism, vitamin B₁₂ deficiency, or folate deficiency.²³,²⁴ An elevated reticulocyte count suggests hemolysis, hypersplenism, or recent blood loss. When the reticulocyte count is low, the next step is to obtain serum vitamin B₁₂ and folate levels. If the vitamin B₁₂ or folate level is borderline low, serum homocysteine level (to confirm folate deficiency) and methylmalonic acid level (to confirm vitamin B₁₂ deficiency) should be obtained. Normal levels of homocysteine and methylmalonic acid virtually exclude folate and vitamin B₁₂ deficiencies.²³,²⁵

An abnormal peripheral blood smear result in patients with anemia warrants strong consideration for myelodysplastic syndrome and malignancies, especially multiple myeloma. Macrocytic anemia is associated with myelodysplastic syndrome and myeloproliferative conditions. In such cases, bone marrow biopsy should be considered if the findings would potentially affect treatment.

Treatment

Almost all older persons with nutritional anemia should be treated, because treatment is usually simple and cost-effective. The only exceptions may be very ill patients at the end of life and those who decline interventions. For iron deficiency anemia, the usual replacement dose is ferrous sulfate, 325 mg (65 mg of elemental iron) per day, or ferrous gluconate, 325 mg (38 mg of elemental iron) per day.³⁹ Low-dose iron therapy, with 15 mg of elemental iron per day as liquid ferrous gluconate, effectively corrects hemoglobin and ferritin concentrations with fewer gastrointestinal adverse effects than higher iron doses.⁴⁰ Treatment is usually continued for six months to replete iron stores. For persons who fail to respond to oral iron therapy, parenteral treatment with iron dextran or iron sucrose is usually therapeutic. High-dose oral therapy (cyanocobalamin, 1 to 2 mg per day) to treat vitamin B₁₂ deficiency is effective and well tolerated.¹⁻⁴³ Folate deficiency should be treated with folic acid, 1 mg per day. Effective treatment of nutritional anemia is noted by reticulocytosis within one week, followed by a more gradual increase in hemoglobin level.

Treatment of anemia of chronic disease, chronic kidney disease anemia, and unexplained anemia is more difficult. The initial and preferred treatment is to correct the underlying disorder. Optimal management of chronic diseases will minimize inflammation and lessen bone marrow suppression. Most anemias in older persons are mild and do not require further intervention. When anemia is severe (hemoglobin level less than 10 g per dL [100 g per L]), symptoms that warrant additional treatment often develop. Two options to treat severe anemia are blood transfusions and erythropoiesis-stimulating agents, both of which have significant limitations. Blood transfusions provide immediate relief of common symptoms, including dyspnea, fatigue, and dizziness. Risks of transfusions include volume overload, iron overload, infections, and acute reactions.

Erythropoiesis-stimulating agents have been approved for the treatment of anemia of chronic disease in limited situations (Table 4⁴⁴⁻⁴⁷), but their use remains controversial. Erythropoietin is produced mainly by the kidneys and stimulates the production of red blood cells in the bone marrow. Two recent randomized trials of the use of erythropoiesis-stimulating agents in persons with chronic kidney disease and anemia found that increasing the hemoglobin level to a target of 13.5 g per dL (135 g per L)⁴⁸ or 13 g per dL⁴⁹ resulted in an increased rate of death and cardiovascular events. Goals of treatment with erythropoiesis-stimulating agents for chronic kidney disease are avoiding transfusions and maintaining a hemoglobin level significantly below 12 g per dL.⁵⁰ Although some studies have shown modest benefits of erythropoiesis-stimulating agents in persons with cancer and anemia, several have found decreased survival with these agents.⁵¹⁻⁵⁴ For selected chemotherapy-
Anemia

Table 4. Guidelines for Use of Erythropoiesis-Stimulating Agents in Patients with Anemia

Indications approved by the U.S. Food and Drug Administration
Persons with anemia of chronic kidney disease undergoing dialysis to maintain a hemoglobin level of 10 to 12 g per dL (100 to 120 g per L)
Persons with a hemoglobin level less than 10 g per dL who currently are on chemotherapy for cancer
Persons with human immunodeficiency virus infection and anemia secondary to zidovudine (Retrovir) therapy
Persons with anemia scheduled for surgery who are at risk of needing surgery-associated blood transfusion (epoetin alfa [Eprex] or darbepoetin alfa [Procrit] only)

Other indications covered by Medicare
Certain persons with myelodysplastic syndrome
Persons undergoing treatment for hepatitis C
Inflammatory bowel disease
Rheumatoid arthritis
Systemic lupus erythematosus

Information from references 44 through 47.

Associated anemias, erythropoiesis-stimulating agents are recommended as the hemoglobin level approaches or falls below 10 g per dL to avoid transfusions.56,66

For most persons with anemia of chronic disease or unexplained anemia, there is little evidence that correcting the hemoglobin level decreases morbidity and mortality, or improves quality of life. In these patients, anemia may be a marker of frailty and physiologic decline. Therefore, it is prudent to limit erythropoiesis-stimulating agents to the treatment of severe anemia associated with chronic kidney disease and other approved indications, unless patients are part of clinical trials to evaluate erythropoiesis-stimulating agents.

Newer treatment modalities for myelodysplastic syndrome and multiple myeloma may prove beneficial regardless of patient age.56,59 Hematology consultation should be obtained if treatment is desired.

The authors thank Sally P. Stabler, MD, professor of medicine and co-head of the Division of Hematology at the University of Colorado Denver, for her review of the manuscript.

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Author disclosure: Nothing to disclose.

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Evaluation of Microcytosis

MICHELE VAN VRANKEN, MD, Children’s Hospital of Minneapolis, Minneapolis, Minnesota

Microcytosis is typically an incidental finding in asymptomatic patients who received a complete blood count for other reasons. The condition is defined as a mean corpuscular volume of less than 80 μm³ (80 fl) in adults. The most common causes of microcytosis are iron deficiency anemia and thalassemia trait. Other diagnoses to consider include anemia of chronic disease, lead toxicity, and sideroblastic anemia. Serum ferritin measurement is the first laboratory test recommended in the evaluation of microcytosis. Low ferritin levels suggest iron deficiency. Once a presumptive diagnosis of iron deficiency anemia has been made, an underlying cause for the deficiency should be determined. Iron deficiency anemia in adults is presumed to be caused by blood loss; the most common source of bleeding is the gastrointestinal tract. The possibility of gastrointestinal malignancy must be considered. If the serum ferritin level is not initially low, further evaluation should include total iron-binding capacity, transferrin saturation level, serum iron level, and possibly hemoglobin electrophoresis. Anemia of chronic disease is suggested with low iron levels and decreased total iron-binding capacity. Patients with beta-thalassemia trait usually have elevated levels of hemoglobin A2. (Am Fam Physician. 2010;82(9):1117-1122. Copyright © 2010 American Academy of Family Physicians.)

Microcytosis is usually encountered incidentally when a complete blood count (CBC) is performed for various reasons. The condition is defined as a mean corpuscular volume of less than 80 μm³ (80 fl) in adults and is often associated with anemia. Normal mean corpuscular volume and hemoglobin levels vary during childhood, and normal hemoglobin levels can vary based on factors such as ethnicity, tobacco use, and altitude (Table 1).

Differential Diagnosis

In the United States, the most common cause of microcytosis is iron deficiency anemia. Other causes include anemia of chronic disease, lead toxicity, sideroblastic anemia, and thalassemia trait. Table 2 presents the differential diagnosis of microcytosis.

The diagnosis of iron deficiency anemia warrants additional evaluation for an underlying cause. The most common etiologies of iron deficiency anemia differ based on patient age and sex (Table 3). Nutritional deficiency is the most common source of iron deficiency anemia in children, and menstrual blood loss is the most common source in menstruating women. Iron deficiency anemia in adult men and nonmenstruating women warrants further gastrointestinal investigation for occult blood loss, including evaluation for gastrointestinal malignancy.

History and Physical Examination

Once microcytosis is diagnosed, the history can sometimes provide clues to the underlying etiology. Important history information includes nutritional intake (especially whole milk intake in children), pica or craving for ice, which are symptoms of iron deficiency anemia; occupational or residential exposure to toxins, such as lead; family history of anemia or ethnicity suggestive of anemia due to an underlying hemoglobinopathy; and systemic symptoms of an underlying chronic infectious or inflammatory process. A review of gastrointestinal symptoms, including abdominal discomfort, hematochezia, and bright red rectal bleeding, is warranted in adults, and a menstrual history should be obtained in menstruating women. Finally, depending on the severity and acuity of the anemia, the patient may have varying levels of fatigue or dyspnea.

Most patients with microcytosis are asymptomatic, and physical examination findings are often limited. As the severity of anemia increases, physical findings may include a systolic murmur and pallor of the mucous membranes, nail beds, and palmar creases.

Laboratory Evaluation

Laboratory tests that may help in differentiating the cause of microcytosis include red blood cell distribution width using the CBC, serum iron levels, serum ferritin levels,
Table 1. Variations in Hemoglobin Level and Mean Red Blood Cell Volume

<table>
<thead>
<tr>
<th>Age</th>
<th>Hemoglobin level in g per dL (g per L)</th>
<th>Mean corpuscular volume in μm³ (fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean*</td>
<td>Diagnostic of anemia</td>
</tr>
<tr>
<td>3 to 6 months</td>
<td>11.5 (115)</td>
<td>9.5 (95)</td>
</tr>
<tr>
<td>6 months to 2 years</td>
<td>12.0 (120)</td>
<td>10.5 (105)</td>
</tr>
<tr>
<td>2 to 6 years</td>
<td>12.5 (125)</td>
<td>11.5 (115)</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>13.5 (135)</td>
<td>11.5 (115)</td>
</tr>
<tr>
<td>12 to 18 years (female)</td>
<td>14.0 (140)</td>
<td>12.0 (120)</td>
</tr>
<tr>
<td>12 to 18 years (male)</td>
<td>14.5 (145)</td>
<td>13.0 (130)</td>
</tr>
<tr>
<td>20 to 59 years (white men)</td>
<td>—</td>
<td>13.7 (137)</td>
</tr>
<tr>
<td>60 years and older (white men)</td>
<td>—</td>
<td>13.2 (132)</td>
</tr>
<tr>
<td>20 to 59 years (white women)</td>
<td>—</td>
<td>12.2 (122)</td>
</tr>
<tr>
<td>60 years and older (white women)</td>
<td>—</td>
<td>12.2 (122)</td>
</tr>
<tr>
<td>20 to 59 years (black men)</td>
<td>—</td>
<td>12.9 (129)</td>
</tr>
<tr>
<td>60 years and older (black men)</td>
<td>—</td>
<td>12.7 (127)</td>
</tr>
<tr>
<td>20 to 59 years (black women)</td>
<td>—</td>
<td>11.5 (115)</td>
</tr>
<tr>
<td>60 years and older (black women)</td>
<td>—</td>
<td>11.5 (115)</td>
</tr>
</tbody>
</table>

*—No data available for some age groups.

Information from reference 2 and 4.

total iron-binding capacity (TIBC), transferrin saturation, hemoglobin electrophoresis, and occasionally reticulocyte blood count and peripheral blood smears. Data do not support the routine use of other CBC parameters in the evaluation of microcytosis. Table 4 provides a summary of laboratory results that suggest etiologies of microcytosis.

Red blood cell distribution width measures the variation in red blood cell size and is often increased in persons with iron deficiency, but normal in those with anemia of chronic disease. However, this measurement is not sensitive or specific enough to differentiate iron deficiency and beta-thalassemia trait. The red blood cell count can help differentiate the two causes because it is often in the high to normal range with beta-thalassemia trait.

Serum iron levels are decreased in iron deficiency anemia and, to a lesser extent, in anemia of chronic disease. Serum iron levels can have diurnal variations with higher concentrations later in the day. Transient increases in serum iron levels may occur with meat ingestion or iron supplementation, but do not represent an increase in true iron stores.

Ferritin and transferrin saturation levels and TIBC are useful in differentiating iron deficiency anemia and beta-thalassemia trait. The red blood cell count can help differentiate the two causes because it is often in the high to normal range with beta-thalassemia trait. Serum iron levels are decreased in iron deficiency anemia and, to a lesser extent, in anemia of chronic disease. Serum iron levels can have diurnal variations with higher concentrations later in the day. Transient increases in serum iron levels may occur with meat ingestion or iron supplementation, but do not represent an increase in true iron stores.

Table 2. Differential Diagnosis of Microcytosis

<table>
<thead>
<tr>
<th>Children and adolescents</th>
<th>Menstruating women</th>
<th>Men and nonmenstruating women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>Iron deficiency anemia</td>
<td>Iron deficiency anemia</td>
</tr>
<tr>
<td>Thalassemia trait</td>
<td>Thalassemia trait</td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>Other hemoglobinopathies</td>
<td>Pregnancy</td>
<td>Unexplained anemia</td>
</tr>
<tr>
<td>Lead toxicity</td>
<td>Anemia of chronic disease</td>
<td>Thalassemia trait</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Sideroblastic anemia</td>
<td></td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Listed in descending order of frequency.

Information from references 2, 5, and 6.
deficiency anemia and anemia of chronic disease when the serum iron level is decreased. TIBC refers to the ability of unsaturated transferrin, the transport protein for iron, to bind to iron. This measure is usually increased in iron deficiency, decreased in anemia of chronic disease, and normal in the less severe thalassemias. Similar to iron, TIBC is affected by diurnal variations.

Transferrin saturation is a percentage calculated as serum iron concentration/TIBC × 100. Levels indicate the number of free binding sites on transferrin. A value less than 16 percent is often indicative of iron deficiency anemia. Ferritin is a complex of iron and the binding protein apoferritin. Ferritin reflects true iron stores and is not susceptible to the short-term variations that occur with serum iron levels and TIBC. However, ferritin is also an acute phase reactant and can be elevated with liver disease, malignancy, and chronic renal disease. Iron deficiency anemia is likely if the ferritin level is less than 15 ng per mL (15 mcg per L) in an otherwise healthy person, or less than 50 ng mL (50 mcg per L) in a person with an underlying source of chronic inflammation. Iron deficiency can usually be excluded when the ferritin level is greater than 100 ng per mL (100 mcg per L).18,20

**Diagnostic Strategy**

*Figure 1* is a suggested algorithm for diagnosing the cause of microcytosis in adults.1,2,5,7,10,20,21 After confirmation of microcytosis on CBC, physicians should first order a serum ferritin level.18-20 If the ferritin level is consistent with iron deficiency anemia, identifying the underlying cause of the anemia is the priority. It is critical to exclude gastrointestinal malignancy in men and nonmenstruating women.1,5,21,22 Gastrointestinal sources of blood loss should also be considered in menstruating women and adolescent girls when the anemia is

### Table 3. Etiologies of Iron Deficiency Anemia

<table>
<thead>
<tr>
<th>Children and adolescents</th>
<th>Menstruating women</th>
<th>Men and nonmenstruating women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional deficiency (and blood loss</td>
<td>Blood loss</td>
<td>Gastrointestinal blood loss (i.e., malignancy,</td>
</tr>
<tr>
<td>with cow's milk intolerance)</td>
<td>Menstrual</td>
<td>other gastrointestinal lesions, autoimmune</td>
</tr>
<tr>
<td>Blood loss</td>
<td>Gastrointestinal (i.e., esophagitis,</td>
<td>atrophic gastritis)</td>
</tr>
<tr>
<td>Gastrointestinal (i.e., esophagitis,</td>
<td>Meckel diverticulum)</td>
<td>Other gastrointestinal lesions)</td>
</tr>
<tr>
<td>Meckel diverticulum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation in females</td>
<td>Pregnancy (increasing iron needs)</td>
<td>Decreased absorption</td>
</tr>
<tr>
<td>Decreased absorption</td>
<td>Decreased absorption</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Celiac disease</td>
<td><em>H. pylori</em> infection</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td></td>
<td>Poor nutritional intake</td>
</tr>
</tbody>
</table>

Note: Listed in descending order of frequency.
Information from references 2, 5, 8, and 9.

### Table 4. Laboratory Tests in the Differential Diagnosis of Microcytosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Suggested diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin level</td>
<td>Decreased</td>
</tr>
<tr>
<td>Red blood cell distribution width</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum iron level</td>
<td>Decreased</td>
</tr>
<tr>
<td>Total iron-binding capacity</td>
<td>Increased</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Suggested diagnosis</td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Increased</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>Normal to increased</td>
</tr>
</tbody>
</table>

Information from reference 1.
Microcytosis

Diagnosing the Cause of Microcytosis

Adult with microcytosis (mean corpuscular volume < 80 µm³ [80 fl])

Check ferritin level

- Ferritin level < 15 ng per mL (15 mcg per L), or < 50 ng per mL (50 mcg per L) with chronic inflammation
  - Iron deficiency anemia

- Ferritin level normal to high
  - Check serum iron level, TIBC, and transferrin saturation

Serum iron level decreased
  - TIBC increased
    - Transferrin saturation decreased
      - Suggests iron deficiency anemia

Serum iron level decreased
  - TIBC decreased
    - Transferrin saturation decreased
      - Suggests anemia of chronic disease

Perform hemoglobin electrophoresis (consider earlier in the evaluation of children and young adults)

Normal hemoglobin A2 level
  - Sideroblastic anemia
    - Alpha-thalassemia trait

Increased hemoglobin A2 level
  - Beta-thalassemia trait

Diagnose other hemoglobinopathy

Figure 1. Suggested algorithm for diagnosing the cause of microcytosis in adults. (TIBC = total iron-binding capacity.)

Information from references 1, 2, 5, 17, 18, 20, and 21.

refractory to iron treatment or when gastrointestinal symptoms are present.2-4

If the serum ferritin level is not consistent with iron deficiency anemia, the next stage of the evaluation should include measurement of serum iron level, TIBC, and transferrin saturation. Iron deficiency anemia is still probable if the serum iron level and transferrin saturation are decreased and TIBC is increased. On the other hand, if the serum iron level is decreased and the TIBC and transferrin saturation are decreased or normal, anemia of chronic disease is most likely.2,23

If the diagnosis remains unclear, hemoglobin electrophoresis can identify beta-thalassemia trait and less common inherited causes of microcytosis. Hemoglobin electrophoresis may be considered earlier in the evaluation of children and young adults, in whom beta-thalassemia trait is more common.2,4,14 A bone marrow biopsy can help identify sideroblastic anemia (a group of disorders in which iron is deposited in bone marrow erythrocytes). A serum lead test can detect lead toxicity, and the Centers for Disease Control and Prevention provide guidelines on which high-risk groups of children to screen.24,27 Even in the presence of lead toxicity, microcytic anemia can be caused by coexisting iron deficiency anemia.24

Specific Causes of Microcytosis

IRON DEFICIENCY ANEMIA

Iron deficiency anemia occurs when the absorption of iron through dietary intake does not match the needs of the body. The
mismatch occurs from inadequate dietary intake or increased needs, which usually cause only mild anemia, or from blood loss or malabsorption, which can lead to more significant anemia. Young children, women of childbearing age, and pregnant women have the highest prevalence of the condition. Complications include developmental delays and behavior disturbances in children and preterm delivery in pregnant women. Heavy menstrual losses leading to significant anemia warrant additional evaluation for clotting disorders (e.g., von Willebrand disease).

THALASSEMIA

Beta-thalassemia is an autosomal recessive genetic condition in which the normal beta globin chains that make up hemoglobin are underproduced. Beta-thalassemia trait is the heterozygous form of the disease. Beta-thalassemia major (also known as Cooley anemia) is the homozygous form. Both are more common in black persons, and in persons of Southeast Asian, Greek, Italian, or Mediterranean descent.

Most patients with beta-thalassemia trait have mild anemia (hemoglobin level is rarely less than 9.3 g per dl [93 g per L]). In addition, the mean corpuscular volume can sometimes reach much lower levels than with iron deficiency anemia alone. Ultimately, the diagnosis of beta-thalassemia trait is made when hemoglobin electrophoresis shows a slight increase in hemoglobin A2. Coexisting iron deficiency anemia can lower hemoglobin A2 levels; therefore, iron deficiency anemia must be corrected before hemoglobin electrophoresis results can be appropriately evaluated.

Alpha-thalassemia is caused by an underproduction of alpha globin chains, and is most prevalent in persons of African or Southeast Asian descent. The production of alpha globin chains is controlled by four genes on two chromosomes. One gene deletion results in a silent carrier status with normal hematologic findings. Two gene deletions result in alpha-thalassemia trait, which usually leads to microcytosis without anemia. Hemoglobin electrophoresis is often normal in patients with silent carrier status or with alpha-thalassemia trait. The diagnosis is usually one of exclusion.

ANEMIA OF CHRONIC DISEASE

Anemia of chronic disease can be caused by chronic infections or inflammatory processes. Increased levels of cytokines cause a decrease in erythropoietin production, a decreased response to erythropoietin, and interference with iron metabolism. Although anemia of chronic disease is usually normocytic, about one fourth to one third of cases are mildly microcytic. The anemia is usually mild and not progressive. Additionally, although serum iron levels are decreased in anemia of chronic disease (similar to iron deficiency anemia), ferritin levels are increased because ferritin is an acute phase reactant.

The Author

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Microcytosis

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Author disclosure: Nothing to disclose.

REFERENCES


Point-of-Care Guides

Predicting the Risk of Bleeding in Patients Taking Warfarin

MARK H. EBELE, MD, MS, University of Georgia, Athens, Georgia


Clinical Question
What is the best way to predict the risk of bleeding in patients taking warfarin (Coumadin)?

Evidence Summary
When considering anticoagulation therapy in patients with atrial fibrillation or venous thromboembolism (VTE), physicians and patients must balance the benefits of anticoagulation with the risk of bleeding, particularly major bleeding complications. For example, in patients who are at high risk of bleeding, physicians may wish to consider aspirin instead of warfarin, especially if the risk of stroke or recurrent VTE is relatively low.

The Outpatient Bleeding Risk Index (OBRI; Table 1) is one of several models that have been developed to predict the risk of bleeding with warfarin (Table 2). The OBRI, which assigns one point for each of four variables, was developed in a population of 556 patients with VTE who were discharged on warfarin therapy. It was validated in a similar group of 264 patients. The OBRI was a good predictor of bleeding risk in the initial study and in two subsequent validation studies, but a more recent and larger study found it less helpful in identifying patients at high risk of major bleeding. However, this study did not include data for patients with renal impairment, and because all patients were 65 years or older (two of the four variables), the score could not be fully calculated.

<p>| TABLE 1. Outpatient Bleeding Risk Index |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 years or older</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke</td>
<td>1</td>
</tr>
<tr>
<td>History of gastrointestinal bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Recent myocardial infarction, severe anemia, diabetes mellitus, or renal impairment*</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Major bleeding at one year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beyth, 1998</td>
</tr>
<tr>
<td>Low risk: 0</td>
<td>3%</td>
</tr>
<tr>
<td>Intermediate risk: 1 or 2</td>
<td>12%</td>
</tr>
<tr>
<td>High risk: 3 or more</td>
<td>48%</td>
</tr>
</tbody>
</table>

*—Anemia is defined as hematocrit level < 30%, and renal impairment is defined as serum creatinine level > 1.5 mg per dL (133 μmol per L).
†—Only two patients in this risk group.
TABLE 2. 
Decision Rules to Predict Bleeding Risk in Patients Taking Warfarin (Coumadin)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants and Indications</th>
<th>Demographics</th>
<th>Prediction of major bleeding by risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyth, 1998 (n = 820)</td>
<td>Patients discharged on warfarin therapy (VTE, 47%; cardiac surgery, 18%; other, 35%)</td>
<td>Mean age = 60 years; 53% women</td>
<td>One-year bleeding risk using OBRI:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low risk: 3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk: 12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: 48%</td>
</tr>
<tr>
<td>Kuijer, 1999 (n = 1,021)</td>
<td>Patients discharged on warfarin therapy after diagnosis of VTE</td>
<td>Mean age = 61 years; 51% men</td>
<td>90-day bleeding risk:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low risk: 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: 7%</td>
</tr>
<tr>
<td>Wells, 2003 (n = 222)</td>
<td>Pulmonary embolism or deep venous thrombosis; started on low-molecular-weight heparin as outpatients and then switched to warfarin</td>
<td>Mean age = 58 years; 43% women</td>
<td>Bleeding risk per person-year using OBRI:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low risk: 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk: 4.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: not applicable*</td>
</tr>
<tr>
<td>Aspinall, 2005 (n = 1,269)</td>
<td>Patients treated with warfarin at a Veterans Affairs anticoagulation clinic</td>
<td>Mean age = 68 years; 92% men</td>
<td>Bleeding risk per person-year using OBRI:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low risk: 0.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk: 2.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: 10.6%</td>
</tr>
<tr>
<td>Shireman, 2006 (n = 26,345)</td>
<td>Registry of patients hospitalized with atrial fibrillation and discharged on warfarin therapy</td>
<td>All 65 years or older (88% 70 years or older); 53% women</td>
<td>90-day bleeding risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shireman rule:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low risk: 0.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk: 2.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: 5.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate- plus high-risk: 2.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OBRI†:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk: 1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: 2.5%</td>
</tr>
</tbody>
</table>
Another model that uses only three variables (60 years or older, female sex, and presence of malignancy) predicts 90-day bleeding risks of 1 percent in low-risk patients and 7 percent in high-risk patients. However, this rule was not validated in a larger, more recent study, and does not include important risk factors such as anemia, history of bleeding, or use of antiplatelet agents. Therefore, it cannot be recommended for clinical use.

Most recently, Shireman and colleagues developed a new prediction model using 19,875 patients hospitalized with atrial fibrillation and discharged on warfarin therapy. The multivariate model was validated in 6,470 patients. It has eight clinical variables and identifies groups at low, intermediate, and high risk of major bleeding within 90 days of hospital discharge (Table 3). The Shireman model has good face validity, and because it was developed and validated in a large group of patients, it can distinguish between recent and remote bleeding, and can account for concurrent use of antiplatelet agents. However, as with the OBRI, only a small percentage of patients are identified as high risk (3.4 percent). When the intermediate- and high-risk groups are combined, two groups are created (low- and intermediate/high-risk) with bleeding risks of 0.9 and 2.3 percent, respectively. These results are remarkably similar to the 90-day risks found in the same study when it evaluated the OBRI (1.0 percent for intermediate risk, and 2.5 percent for high risk). Thus, these rules provide similar results. The difference between 1 and 2.5 percent over 90 days seems small, but becomes more significant over time as large numbers of patients (especially those with atrial fibrillation) are on anticoagulation therapy for many years.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>86</td>
</tr>
<tr>
<td>Alcohol or drug abuse</td>
<td>71</td>
</tr>
<tr>
<td>Recent bleeding</td>
<td>62</td>
</tr>
<tr>
<td>Remote bleeding</td>
<td>58</td>
</tr>
<tr>
<td>70 years or older</td>
<td>49</td>
</tr>
<tr>
<td>Female sex</td>
<td>32</td>
</tr>
<tr>
<td>Antiplatelet use (e.g., aspirin, clopidogrel [Plavix])</td>
<td>32</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27</td>
</tr>
</tbody>
</table>

**Total points:**

**Score**

<table>
<thead>
<tr>
<th>Risk of major bleeding at 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk: &lt; 108</td>
</tr>
<tr>
<td>Intermediate risk: 108 to 218</td>
</tr>
</tbody>
</table>

\[ OBRI = \text{Outpatient Bleeding Risk Index}; \text{VTE = venous thromboembolism.} \]

\[ *— \text{Only two patients in high-risk group.} \]

\[ †— \text{Because all patients were 65 years or older, all were at intermediate or high risk. No data were available for patients with renal impairment, one of the four variables in the OBRI.} \]

Information from references 1 through 5.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: &gt; 218</td>
<td>5.4% (12 / 222)</td>
</tr>
<tr>
<td>Intermediate/high risk combined</td>
<td>2.3% (60 / 2,622)</td>
</tr>
</tbody>
</table>

NOTE: The original score was presented as an equation with factors between 0 and 1.0. Factors have been multiplied by 100 to create whole numbers and an additive score. The denominator for major bleeding was calculated from the percentage and numerator, because it was not reported in the original article.

Information from reference 5.

There are potentially important differences between the two models. Although the Shireman model was developed and validated in a large population, it is somewhat complex to calculate and is limited to patients 65 years or older with atrial fibrillation. The OBRI is simpler and has been validated in patients with atrial fibrillation or VTE, and in younger patients. Either rule can be used confidently—in combination with predictors of the risk of stroke or recurrent VTE—to help make decisions about the treatment strategy that best balances potential benefits and harms.

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Author disclosure: Nothing to disclose.

REFERENCES

This guide is one in a series that offers evidence-based tools to assist family physicians in improving their decision making at the point of care.

A collection of Point-of-Care Guides published in AFP is available at http://www.aafp.org/afp/poc.
Transfusion of Blood and Blood Products: Indications and Complications

SANJEEV SHARMA, MD; POONAM SHARMA, MD; and LISA N. TYLER, MD
Creighton University School of Medicine, Omaha, Nebraska

Red blood cell transfusions are used to treat hemorrhage and to improve oxygen delivery to tissues. Transfusion of red blood cells should be based on the patient's clinical condition. Indications for transfusion include symptomatic anemia (causing shortness of breath, dizziness, congestive heart failure, and decreased exercise tolerance), acute sickle cell crisis, and acute blood loss of more than 30 percent of blood volume. Fresh frozen plasma infusion can be used for reversal of anticoagulant effects. Platelet transfusion is indicated to prevent hemorrhage in patients with thrombocytopenia or platelet function defects. Cryoprecipitate is used in cases of hypofibrinogenemia, which most often occurs in the setting of massive hemorrhage or consumptive coagulopathy. Transfusion-related infections are less common than noninfectious complications. All noninfectious complications of transfusion are classified as noninfectious serious hazards of transfusion. Acute complications occur within minutes to 24 hours of the transfusion, whereas delayed complications may develop days, months, or even years later. (Am Fam Physician. 2011;83(6):719-724. Copyright © 2011 American Academy of Family Physicians.)

Blood transfusion can be a lifesaving procedure, but it has risks, including infectious and noninfectious complications. There is debate in the medical literature concerning the appropriate use of blood and blood products. Clinical trials investigating their use suggest that waiting to transfuse at lower hemoglobin levels is beneficial. This review will consider the indications for transfusion of blood and blood products, and will discuss common noninfectious complications associated with transfusion.

Red Blood Cells

Packed red blood cells (RBCs) are prepared from whole blood by removing approximately 250 mL of plasma. One unit of packed RBCs should increase levels of hemoglobin by 1 g per dL (10 g per L) and hematocrit by 3 percent. In most areas, packed RBC units are filtered to reduce leukocytes before storage, which limits febrile nonhemolytic transfusion reactions (FNHTRs), and are considered cytomegalovirus safe.

RBC transfusions are used to treat hemorrhage and to improve oxygen delivery to tissues. Transfusion of RBCs should be based on the patient's clinical condition. Indications for RBC transfusion include acute sickle cell crisis (for stroke prevention), or acute blood loss of greater than 1,500 mL or 30 percent of blood volume. Patients with symptomatic anemia should be transfused if they cannot function without treating the anemia. Symptoms of anemia may include fatigue, weakness, dizziness, reduced exercise tolerance, shortness of breath, changes in mental status, muscle cramps, and angina or severe congestive heart failure. The 10/30 rule—transfusion when a patient has a hemoglobin level less than or equal to 10 g per dL (100 g per L) and a hematocrit level less than or equal to 30 percent—was used until the 1980s as the trigger to transfuse, regardless of the patient's clinical presentation.

In 1999, a randomized, multicenter, controlled clinical trial evaluated a restrictive transfusion trigger (hemoglobin level of 7 to 9 g per dL [70 to 90 g per L]) versus a liberal transfusion trigger (hemoglobin level of 10 to 12 g per dL [100 to 120 g per L]) in patients who were critically ill. Restrictive transfusion practices resulted in a 54 percent relative decrease in the number of units transfused and a reduction in the 30-day mortality rate. The authors recommended transfusion when hemoglobin is less than 7 g per dL, and maintenance of a
hemoglobin level between 7 to 9 g per dL. A recently updated Cochrane review supports the use of restrictive transfusion triggers in patients who do not have cardiac disease. A similar study was carried out in critically ill children. The restrictive transfusion trigger was a hemoglobin level of 7 g per dL, with a target level of 8.5 to 9.5 g per dL (85 to 95 g per L). The liberal transfusion trigger was a hemoglobin level of 9.5 g per dL, with a target level of 11 to 12 g per dL (110 to 120 g per L). Patients in the restrictive group received 44 percent fewer blood transfusions, with no difference in rates of multiple organ dysfunction syndrome or death. The restrictive transfusion strategy is useful for children who are stable patients in intensive care. It should not be used in preterm neonates or in children with severe hypoxemia, active blood loss, hemodynamic instability, or cyanotic heart disease.

### Table 1. Indications for Transfusion of Plasma Products

<table>
<thead>
<tr>
<th>Indication</th>
<th>Associated condition/additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Normalized Ratio &gt; 1.6</td>
<td>Inherited deficiency of single clotting factors with no virus-safe or recombinant factor available—anticoagulant factors II, V, X, or XI Prevent active bleeding in patient on anticoagulant therapy before a procedure Active bleeding</td>
</tr>
<tr>
<td>Emergent reversal of warfarin (Coumadin)</td>
<td>Major or intracranial hemorrhage Prophylactic transfusion in a surgical procedure that cannot be delayed</td>
</tr>
<tr>
<td>Acute disseminated intravascular coagulopathy</td>
<td>With active bleeding and correction of underlying condition</td>
</tr>
<tr>
<td>Microvascular bleeding during massive transfusion</td>
<td>≥ 1 blood volume (replacing approximately 5,000 mL in an adult who weighs 155.56 lb [70 kg])</td>
</tr>
<tr>
<td>Replacement fluid for apheresis in thrombotic microangiopathies</td>
<td>Thrombotic thrombocytopenic purpura; hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Hereditary angioedema</td>
<td>When C1 esterase inhibitor is unavailable</td>
</tr>
</tbody>
</table>

Information from references 7 through 9.

### Plasma

Plasma products available in the United States include fresh frozen plasma and thawed plasma that may be stored at 33.8 to 42.8°F (1 to 6°C) for up to five days. Plasma contains all of the coagulation factors. Fresh frozen plasma infusion can be used for reversal of anticoagulant effects. Thawed plasma has lower levels of factors V and VIII and is not indicated in patients with consumption coagulopathy (diffuse intravascular coagulation).

Plasma transfusion is recommended in patients with active bleeding and an International Normalized Ratio (INR) greater than 1.6, or before an invasive procedure or surgery if a patient has been anticoagulated. Plasma is often inappropriately transfused for correction of a high INR when there is no bleeding. Supportive care can decrease high-normal to slightly elevated INRs (1.3 to 1.6).
Table 2. Indications for Transfusion of Platelets in Adults

<table>
<thead>
<tr>
<th>Prophylactic transfusion indications</th>
<th>Platelet count (x 10^9 per µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery or invasive procedure, no active bleeding</td>
<td>≤ 50</td>
</tr>
<tr>
<td>Ocular surgery or neurosurgery, no active bleeding</td>
<td>≤ 100</td>
</tr>
<tr>
<td>Surgery with active bleeding</td>
<td>&lt; 50 (usually) &gt; 100 (rarely)</td>
</tr>
<tr>
<td>Stable, nonbleeding</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Stable, nonbleeding, and body temperature &gt; 100.4°F (38°C) or undergoing invasive procedure</td>
<td>&lt; 20</td>
</tr>
</tbody>
</table>

Information from reference 9.

Table 3. Indications for Transfusion of Platelets in Neonates

<table>
<thead>
<tr>
<th>Platelet count (x 10^9 per µL)</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Always transfuse</td>
</tr>
<tr>
<td>20 to &lt; 30</td>
<td>Consider transfusion; transfuse for clinical reasons (e.g., active bleeding, lumbar puncture)</td>
</tr>
<tr>
<td>30 to 50</td>
<td>Transfuse if any of the following Indications exist: First week of life with birth weight &lt; 1,000 g (2 lb, 4 oz) Intraventricular or intraparenchymal cerebral hemorrhage Coagulation disorder Sepsis or fluctuating arterial venous pressures Invasive procedure Allergic neonate thrombocytopenia*</td>
</tr>
</tbody>
</table>

*—Select a donor (possibly the mother) whose platelets lack the causative antigen. If the mother’s platelets are used, unit must be washed, irradiated, and resuspended in plasma that is ABO compatible with the neonate.

Information from references 9 through 12.

without transfusion of plasma. Table 1 gives indications for plasma transfusion.

Platelets

Table 4. Indications for Transfusion of Cryoprecipitate

<table>
<thead>
<tr>
<th>Adults</th>
<th>Neonates (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage after cardiac surgery</td>
<td>Anticoagulant factor XIII deficiency</td>
</tr>
<tr>
<td>Massive hemorrhage or transfusion</td>
<td>Congenital dysfibrinogenemia</td>
</tr>
<tr>
<td>Surgical bleeding</td>
<td>Congenital fibrinogen deficiency</td>
</tr>
<tr>
<td>Neonates</td>
<td>von Willebrand disease*</td>
</tr>
<tr>
<td>Anticoagulant factor VIII deficiency*</td>
<td></td>
</tr>
</tbody>
</table>

*—Use when recombinant factors are not available.

Information from references 12 and 15.

One unit of apheresis platelets should increase the platelet count in adults by 30 to 60 x 10^9 per µL (30 to 60 x 10^9 per L).5 In neonates, transfusing 5 to 10 mL per kg of platelets should increase the platelet count by 50 to 100 x 10^9 per µL (50 to 100 x 10^9 per L). One apheresis platelet collection is equivalent to six pooled random donor platelet concentrates.5

Spontaneous bleeding through intact endothelium does not occur unless the platelet count is no greater than 5 x 10^9 per µL (5 x 10^9 per L). One randomized controlled trial evaluated a threshold for prophylactic platelet transfusion in patients with acute myeloid leukemia.14 Patients were randomized based on platelet transfusion triggers of 10 x 10^9 per µL (10 x 10^9 per L) or 20 x 10^9 per µL (20 x 10^9 per L). Patients in the lower trigger group received 21.5 percent fewer transfusions than the higher trigger group. Gastrointestinal bleeding was more common in the lower trigger group; however, there was no difference in blood transfusions between groups. Tables 2 and 3 give indications for platelet transfusion in adults and neonates, respectively.

Cryoprecipitate

Cryoprecipitate is prepared by thawing fresh frozen plasma and collecting the precipitate. Cryoprecipitate contains high concentrations of factor VIII and fibrinogen. Cryoprecipitate is used in cases of hypofibrinogenemia, which most often occurs in the setting of massive hemorrhage or consumptive coagulopathy. Indications for cryoprecipitate transfusion are listed in Table 4.15 Each unit will raise the fibrinogen level by 5 to 10 mg per dL (0.15 to 0.29 µmol per L), with the goal of maintaining a fibrinogen level of at least 100 mg per dL (2.94 µmol per L).15 The usual dose in adults is 10 units of pooled cryoprecipitate. Recommendations for dosing regimens in neonates vary, ranging from 2 mL of cryoprecipitate per kg to 1 unit of cryoprecipitate (15 to 20 mL) per 7 kg.12

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Blood Transfusion

Transfusion Complications

Transfusion-related complications can be categorized as acute or delayed, which can be divided further into the categories of noninfectious (Table 5) and infectious (Table 6). Acute complications occur within minutes to 24 hours of the transfusion, whereas delayed complications may develop days, months, or even years later. The AABB (formerly known as the American Association of Blood Banks) uses the term "noninfectious serious hazards of transfusion" to classify noninfectious complications. Transfusion-related infections are less common because of advances in the blood screening process; the risk of contracting an infection from transfusion has decreased 10,000-fold since the 1980s. Noninfectious serious hazards of transfusion are up to 1,000 times more likely than an infectious complication. However, there has been no progress in preventing noninfectious serious hazards of transfusion, despite improvements in blood screening tests and other related medical advances. Therefore, patients are far more likely to experience a noninfectious serious hazard of transfusion than an infectious complication.

Acute Transfusion Reactions

ACUTE HEMOLYTIC REACTIONS

Hemolytic transfusion reactions are caused by immune destruction of transfused RBCs, which are attacked by the recipient's antibodies. The antibodies to the antigens of the ABO blood group or alloantibodies to other RBC antigens are produced after immunization through a previous transfusion or pregnancy. There are two categories of hemolytic transfusion reactions: acute and delayed. Nonimmune causes of acute reactions include bacterial overgrowth, improper storing, infusion with incompatible medications, and infusion of blood through lines containing hypertonic solutions or small-bore intravenous tubes.

In acute hemolytic transfusion reactions, there is a destruction of the donor's RBCs within 24 hours of transfusion. Hemolysis may be extravascular or intravascular. The most common type is extravascular hemolysis, which occurs when donor RBCs coated with immunoglobulin G (IgG) or complement are attacked in the liver or spleen. Intravascular hemolysis is a severe form of hemolysis caused by ABO antibodies. Symptoms of acute hemolytic transfusion reactions include fever, chills, rigors, nausea, vomiting, dyspnea, hypotension, diffuse bleeding, hemoglobinuria, oliguria, anuria, pain at the infusion site; and chest, back, and abdominal pain. Associated complications are clinically significant anemia, acute or exacerbated renal failure, disseminated intravascular coagulation, need for dialysis, and death secondary to complications.

The incidence of acute hemolytic reactions is approximately one to five per 50,000 transfusions. From 1996 to 2007, there were 213 ABO-incompatible RBC transfusions with 24 deaths. Systems using bar codes for blood and patient identification have decreased errors.

Table 5. Noninfectious Serious Hazards of Transfusion

<table>
<thead>
<tr>
<th>Complication</th>
<th>Estimated risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>Hemolytic reaction</td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td></td>
</tr>
<tr>
<td>Coagulation problems in massive transfusion</td>
<td></td>
</tr>
<tr>
<td>Febrile nonhemolytic reaction</td>
<td></td>
</tr>
<tr>
<td>Metabolic derangements</td>
<td></td>
</tr>
<tr>
<td>Mistransfusion (transfusion of the incorrect product to the incorrect recipient)</td>
<td></td>
</tr>
<tr>
<td>Septic or bacterial contamination</td>
<td></td>
</tr>
<tr>
<td>Transfusion-associated circulatory overload</td>
<td></td>
</tr>
<tr>
<td>Transfusion-related acute lung injury</td>
<td></td>
</tr>
<tr>
<td>Urticarial reaction</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Infectious Complications of Blood Transfusions

<table>
<thead>
<tr>
<th>Complication</th>
<th>Estimated risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus</td>
<td>1 in 350,000</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1 in 1.8 million</td>
</tr>
<tr>
<td>Human T-lymphotropic virus 1 or 2</td>
<td>1 in 2 million</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>1 in 2.3 million</td>
</tr>
<tr>
<td>Creutzfeld-Jakob disease</td>
<td>Rare*</td>
</tr>
<tr>
<td>Human herpesvirus 8</td>
<td>Rare*</td>
</tr>
<tr>
<td>Malaria and babesiosis</td>
<td>Rare*</td>
</tr>
<tr>
<td>Pandemic influenza</td>
<td>Rare*</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Rare*</td>
</tr>
</tbody>
</table>

*—Exact risk unknown.
Information from references 16 and 17.
ALLERGIC REACTIONS
Allergic reactions range from mild (urticarial) to life threatening (anaphylactic). Urticarial allergic reactions are defined by hives or pruritus. Patients experiencing allergic transfusion reactions have been sensitized to the antigens in the donor unit. These antigens are soluble, and the associated reaction is dose-dependent. Allergic transfusion reactions occur in 1 to 3 percent of transfusions. Patients with anaphylactic transfusion reactions, like those with urticarial reactions, may present with hives, but they are distinct in that they also develop hypotension, bronchospasm, stridor, and gastrointestinal symptoms. Anaphylaxis occurs in response to a recipient's presensitization to a variety of proteins in donor plasma. For example, anaphylaxis occurs because of donor IgA being infused into a recipient who is IgA deficient and has preexisting circulating anti-IgA. In addition, anti-human leukocyte antigen (HLA) antibodies and anticomplement antibodies have been linked to anaphylactic reactions, which are estimated to occur in one in 20,000 to 50,000 transfusions. Prevention of anaphylactic transfusion reactions includes avoiding plasma transfusions with IgA in patients known to be IgA deficient. Cellular products (e.g., RBCs, platelets) may be washed to remove plasma in patients with an IgA deficiency. The best precaution is observation of the patient during the initial 15 minutes of transfusion.

TRANSFUSION-RELATED ACUTE LUNG INJURY
Transfusion-related acute lung injury (TRALI) is noncardiogenic pulmonary edema causing acute hypoxemia that occurs within six hours of a transfusion and has a clear temporal relationship to the transfusion. Patients with TRALI do not have any other risk factors for acute lung injury. Antineutrophil cytoplasmic antibodies or anti-HLA antibodies activate the recipient's immune system, resulting in massive pulmonary edema. Activated neutrophils in the lungs may also secrete proteolytic enzymes, leading to more tissue damage. Optimal methods for detecting these antibodies in donated products have yet to be determined.
Donor products that contain large amounts of plasma from multiparous women are associated with TRALI. Mortality in the United Kingdom decreased significantly after donor plasma from men was used exclusively. In 2006, TRALI was the leading cause of transfusion-related mortality, contributing to 50.7 percent of transfusion-related deaths. The TRALI working group of the AABB recommends using male-predominant plasma for transfusions. Because this policy excludes a large number of female donors, maintaining an adequate supply of plasma and platelets is a concern.

FEBRILE NONHEMOLYTIC TRANSFUSION REACTIONS
An FNHTR is defined as a rise in body temperature of at least 1.8°F (1°C) above 98.6°F (37°C) within 24 hours after a transfusion; it may involve chills, rigors, and discomfort. The fever occurs more often in patients who have been transfused repeatedly and in patients who have been pregnant. Leukoreduction, which is the removal or filtration of white blood cells from donor blood, has decreased FNHTR rates. FNHTRs are caused by platelet transfusions more often than RBC transfusions and have an incidence that ranges from less than 1 percent to more than 35 percent.

Two mechanisms have been proposed to explain FNHTRs: a release of antibody-mediated endogenous pyrogen, and a release of cytokines. Common cytokines that may be associated with FNHTRs include interleukin-1, interleukin-6, interleukin-8, and tumor necrosis factor. FNHTR is a diagnosis of exclusion that can be made only after ruling out other causes of fever (e.g., hemolytic, sepsis).

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD
Transfusion-associated circulatory overload is the result of a rapid transfusion of a blood volume that is more than what the recipient's circulatory system can handle. It is not associated with an antibody-mediated reaction. Those at highest risk are recipients with underlying cardiopulmonary compromise, renal failure, or chronic anemia, and infants or older patients. Signs and symptoms include tachycardia, cough, dyspnea, hypertension, elevated central venous pressure, elevated pulmonary wedge pressure, and widened pulse pressure. Cardiomegaly and pulmonary edema are often seen on chest radiography.

The diagnosis is made clinically, but may be assisted by measuring brain natriuretic peptide levels, which are elevated in response to an increase in filling pressure. A study comparing patients who have transfusion-associated circulatory overload with patients who have TRALI found significantly greater levels of brain natriuretic peptide in those with transfusion-associated circulatory overload. Transfusion of lower volumes or at a slower rate may help prevent it. The treatment is diuresis to decrease volume overload.

Delayed Transfusion Reactions

TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE
Transfusion-associated graft-versus-host disease is a consequence of a donor's lymphocytes proliferating and causing an immune attack against the recipient's tissues and organs. It is fatal in more than 90 percent of cases. Patients vulnerable to this condition are those who are
immunocompromised or immunocompetent and who are receiving transfusion with shared HLA haplotypes (i.e., donor is a relative).\(^9\) Symptoms include rash, fever, diarrhea, liver dysfunction, and pancytopenia occurring one to six weeks after transfusion.\(^6\)

Risk factors include a history of fludarabine (Ofarta) treatment, Hodgkin disease, stem cell transplant, intensive chemotherapy, intrathecal transfusion, or erythroblastosis fetalis. Other probable risk factors include a history of solid tumors treated with cytotoxic drugs, transfusion in premature infants, and recipient-donor pairs from homogenous populations.\(^29\) Gamma irradiation of blood products keeps the donor lymphocytes from proliferating and can prevent transfusion-associated graft-versus-host disease.\(^6\)

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Treatment of Oncologic Emergencies

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Most oncologic emergencies can be classified as metabolic, hematologic, structural, or side effects from chemotherapy agents. Tumor lysis syndrome is a metabolic emergency that presents as severe electrolyte abnormalities. The condition is treated with allopurinol or urate oxidase to lower uric acid levels. Hypercalcemia of malignancy is treated with aggressive rehydration, furosemide, and intravenous bisphosphonates. Syndrome of inappropriate antidiuretic hormone should be suspected if a patient with cancer presents with normovolemic hyponatremia. This metabolic condition usually is treated with fluid restriction and furosemide. Febrile neutropenia is a hematologic emergency that usually requires inpatient therapy with broad-spectrum antibiotics, although outpatient therapy may be appropriate for low-risk patients. Hyperviscosity syndrome usually is associated with Waldenström’s macroglobulinemia, which is treated with plasmapheresis and chemotherapy. Structural oncologic emergencies are caused by direct compression of nontumor structures or by metastatic disease. Superior vena cava syndrome presents as neck or facial swelling and development of collateral venous circulation. Treatment options include chemotherapy, radiation, and intravenous stenting. Epidural spinal cord compression can be treated with dexamethasone, radiation, or surgery. Malignant pericardial effusion, which often is undiagnosed in cancer patients, can be treated with pericardiocentesis or a pericardial window procedure. (Am Fam Physician 2006;74:1873-80. Copyright © 2006 American Academy of Family Physicians.)

Family physicians are more likely to encounter emergencies related to the treatment or presence of cancer because of increases in outpatient cancer treatments and improved survival rates. Physicians should be familiar with these oncologic emergencies because treatment often is necessary before consultation with a subspecialist. Some oncologic emergencies are insidious and take months to develop, whereas others manifest over hours, causing devastating outcomes such as paralysis and death. In many patients, cancer is not diagnosed until a related condition emerges. Various clinical syndromes often are evident before an emergency occurs; therefore, a patient-focused approach that includes education and cancerspecific monitoring is needed. Most oncologic emergencies (Table 1) can be categorized as metabolic, hematologic, structural, or side effects from chemotherapy agents.

**Metabolic**

Metabolic emergencies include tumor lysis syndrome, hypercalcemia of malignancy, and syndrome of inappropriate antidiuretic hormone (SIADH).

**TUMOR LYsis SYNDROME**

Tumor lysis syndrome is acute cell lysis caused by chemotherapy and radiation therapy. The release of intracellular products (e.g., uric acid, phosphates, calcium, potassium) overwhelms the body’s homeostasis mechanisms. Tumor lysis syndrome is more common with hematologic malignancies or cancers with rapidly growing tumors, particularly acute leukemias and high-grade lymphomas. Tumor lysis syndrome usually presents within one to five days of chemotherapy or radiation.

Patients with tumor lysis syndrome commonly present with azotemia, acidosis, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute renal failure. Treatment includes inpatient monitoring, vigorous fluid resuscitation, allopurinol (Zyloprim) or urate oxidase (uricase) therapy to lower uric acid levels, urinary alkalinization, and hemodialysis.
HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia of malignancy occurs in 20 to 30 percent of patients with cancer. This condition most commonly is associated with multiple myeloma and cancers of the lung, breast, and kidney. Mechanisms that are thought to be important in the development of hypercalcemia of malignancy include bone-resorbing cytokines; parathyroid hormone-related peptide, secreted by the tumor, that binds to parathyroid hormone receptors; tumor-mediated calcitriol production; and, occasionally, ectopic parathyroid hormone secretion.

Symptoms of this condition include nausea, vomiting, constipation, progressive decline in mental function, renal failure, and coma. Occasionally, serum calcium levels are 14 mg per dL (3.50 mmol per L) or more. Hypercalcemia of malignancy is associated with a poor prognosis, with more than 50 percent of patients dying within 30 days of diagnosis. However, treating hypercalcemia of malignancy allows time for treatment of the underlying tumor.

Treatment of hypercalcemia of malignancy (Table 2) includes aggressive rehydration followed by diuresis with furosemide (Lasix). Serum phosphorus should be monitored because hypophosphatemia is common and can worsen the condition. Phosphorus should be replaced orally or via a nasogastric tube. Intravenous bisphosphonate therapy can inhibit osteoclastic bone resorption. Although pamidronate (Aredia) and zoledronic acid (Zometa) can effectively manage hypercalcemia of malignancy, a pooled analysis of two clinical trials showed that the more potent zoledronic acid is superior. Zoledronic acid and pamidronate have been shown to improve quality of life in patients with metastatic bone disease by reducing skeletal complications, bone pain, and the need for analgesic medications. Adjunctive treatments include dialysis and glucocorticoid, calcitriol (Miacalcin), plicamycin (Mithracin), and gallium nitrate (Ganite) therapies.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

When a patient with cancer presents with normovolemic hyponatremia, SIADH should be suspected. A bronchogenic carcinoma often is the ectopic source of antidiuretic hormone production, although certain chemotherapy agents can cause SIADH. Patients may present with anorexia nervosa, nausea, myalgia, headaches, and severe neurologic symptoms (e.g., seizures, coma). Laboratory testing may reveal hyponatremia (i.e., serum sodium level less than 135 meq per L [135 mmol...
<table>
<thead>
<tr>
<th>Emergency</th>
<th>Associated cancer or cause</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia of</td>
<td>Lung, breast, and kidney cancers; multiple myeloma</td>
<td>Fatigue, anorexia, nausea, vomiting, constipation, mental decline, renal failure, coma, myalgia, headache, altered sensorium</td>
</tr>
<tr>
<td>malignancy</td>
<td></td>
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<tr>
<td>Syndrome of inappropriate</td>
<td>Bronchogenic carcinoma</td>
<td>Anorexia, nausea, vomiting, constipation, muscle weakness, myalgia, polyuria, polydipsia, severe neurologic symptoms (e.g., seizures, coma)</td>
</tr>
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<td>antidiuretic hormone</td>
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<tr>
<td>Tumor lysis syndrome</td>
<td>Hematologic malignancies; cancers with rapidly growing tumors, particularly acute leukemias and high-grade lymphoma</td>
<td>Azotemia, acidosis, hyperphosphatemia, hyperkalemia, acute renal failure, hypocalcemia</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
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<tr>
<td>Febrile neutropenia</td>
<td>Chemotherapy-associated bacterial or fungal infections</td>
<td>Temperature greater than 101°F (38.3°C), absolute neutrophil count less than 500 per mm³ (0.5 × 10⁹ per L)</td>
</tr>
<tr>
<td>Hyperviscosity syndrome</td>
<td>Waldenström's macroglobulinemia, multiple myeloma, leukemia</td>
<td>Spontaneous bleeding, &quot;sausage-like&quot; hemorrhagic retinal veins, neurologic defects, serum viscosity levels greater than 5 cP</td>
</tr>
<tr>
<td>Structural</td>
<td></td>
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<tr>
<td>Epidural spinal cord</td>
<td>Breast, lung, renal, and prostate cancers and myeloma</td>
<td>New back pain that worsens when lying down, late paraplegia, late incontinence, and loss of sensory function</td>
</tr>
<tr>
<td>compression</td>
<td></td>
<td></td>
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<tr>
<td>Malignant pericardial</td>
<td>Metastatic lung and breast cancer, melanoma, leukemia, lymphoma, chemotherapy to the chest wall</td>
<td>Dyspnea, fatigue, distended neck veins, distant heart sounds, tachycardia, orthopnea, nanow pulse pressure, pulsus paradoxus, water-bottle heart</td>
</tr>
<tr>
<td>effusion</td>
<td></td>
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<tr>
<td>Superior vena cava</td>
<td>Lung cancer, metastatic mediastinal tumors, lymphoma, indwelling venous catheters</td>
<td>Cough; dyspnea; dysphagia; head, neck, or upper extremity swelling or discoloration; development of collateral venous circulation</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Side effects from treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Chemotherapy</td>
<td>Dehydration, poor skin turgor, dry mucous membranes, weight loss</td>
</tr>
<tr>
<td>Extravasations</td>
<td>Current chemotherapy infusion</td>
<td>Pain and erythema at infusion site, swelling, necrosis, contractures</td>
</tr>
<tr>
<td>Obstipation</td>
<td>Narcotic medications, chemotherapy (specifically neurotoxic agents)</td>
<td>Abdominal pain, constipation, hard stools every three to five days</td>
</tr>
</tbody>
</table>

Information from references 1, 2, and 4 through 12.

per L), decreased serum osmolarity (less than 280 mOsm per L [280 mmol per L]), and concentrated urine (100 mOsm per L or more). There are few physical examination findings associated with SIADH, although papilledema and pathologic reflexes occasionally are present.4 Treatment of the underlying tumor is the cornerstone of therapy. Acute care includes fluid restriction (limit of 500 to 1,000 mL per day) and furosemide therapy. Slow correction of serum sodium levels is necessary to avoid central pontine myelinolysis. Hypertonic saline should be considered for patients with severe neurologic symptoms.1 Demedocycline (Declomycin) is recommended for persistent hyponatremia or for outpatient treatment of minor symptoms.2,21

Hematologic
Hematologic emergencies include febrile neutropenia and hyperviscosity syndrome.

FEBRILE NEUTROPENIA
Febrile neutropenia is one of the most common complications related to cancer treatment, particularly chemotherapy. The condition contributes to 50 percent of deaths associated with leukemia, lymphomas, and solid tumors.22 Bacterial infections are common in patients
TABLE 2
Treatment of Hypercalcemia of Malignancy

with febrile neutropenia, but fungal sources are increasingly prevalent. Symptoms include a temperature of 101°F (38.3°C) or more and an absolute neutrophil count (ANC) less than 500 per mm³ (0.5 x 10⁹ per L).²

A patient usually is considered to have low risk if he or she has a cancer that is under good control or is in remission and has no evidence of hepatic insufficiency, hypotension, or comorbid conditions.²⁴⁻²⁶ However, patients with cancer presenting with fever soon after chemotherapy should receive inpatient treatment with empiric antibiotics until the ANC is more than 500 per mm³ for 72 hours.²³ Initial laboratory evaluation includes targeted cultures; complete blood count; and serum creatinine, blood urea nitrogen, and transaminase measurements. If respiratory symptoms are present, chest radiography is recommended, although it may not detect an infiltrate until the patient's ANC has improved enough to enable an inflammatory response.²³ Outpatient treatment of low-risk patients who are older than 16 years has been validated in several clinical trials.²⁷

Antibiotic treatment for febrile neutropenia depends on the patient's risk of life-threatening infection. A prospective, multinational study of 1,139 patients with febrile neutropenia validated a scoring system (Table 3)²³ to classify patients as high or low risk.²⁷ Generally, multi-drug regimens are used when gram-positive and gram-negative organisms are suspected.²³ Empiric vancomycin therapy is added in hospitals where methicillin-resistant, gram-positive organisms are common or if specific clinical findings are present.²³ Antifungals are recommended if there is no improvement within the first three days of treatment. Routine use of antivirals, granulocyte transfusions, and colony-stimulating factors is not recommended.²³ Figure 1 is an algorithm for the treatment of febrile neutropenia.²²,²³

TABLE 3
Clinical Decision Rule for Determining Infection Risk in Patients with Febrile Neutropenia

HYPERVERSOSITY SYNDROME

Hyperviscosity syndrome is most common in patients with Waldenström's macroglobulinemia (although most patients with Waldenström's macroglobulinemia do not experience hyperviscosity syndrome),
leukemia, or multiple myeloma. Elevated levels of circulating serum immunoglobulins coat the cells, causing increased blood viscosity, sludging of blood, and hypoperfusion.

Signs and symptoms of hyperviscosity syndrome include spontaneous bleeding, neurologic defects (e.g., peripheral neuropathies), and vision changes (“sausage-like” hemorrhagic retinal veins are pathognomonic). A serum viscosity of more than 5 cP suggests hyperviscosity syndrome. Treatment includes plasmapheresis followed by targeted chemotherapy. Occasionally, repeat plasmapheresis is needed to control refractory episodes.

**Structural**

Structural emergencies include superior vena cava syndrome, epidural spinal cord compression, and malignant pericardial effusion.

**SUPERIOR VENA CAVA SYNDROME**

This syndrome is caused by the gradual compression of the superior vena cava, leading to edema and retrograde flow. Lung cancer is the most common malignant cause, although lymphoma, metastatic mediastinal tumors, and indwelling catheters also can cause superior vena cava syndrome. Symptoms may include cough, dyspnea, dysphagia; and swelling or discoloration of the neck, face, or upper extremities. Often, collateral venous circulation causes distension of the superficial veins in the chest wall.

Although superior vena cava syndrome is a clinical diagnosis, plain radiography, computed tomography, and venography are used for confirmation. Recommended treatments include chemotherapy and radiation to reduce the tumor that is causing the obstruction. However, treatment with
intravenous stents is becoming increasingly common. Tissue diagnosis (i.e., sputum cytology, thoracentesis, bronchoscopy, or needle aspiration) often is necessary to direct treatment decisions. Adjunctive therapies include diuretics, corticosteroids, thrombolytics, anticoagulation, and elevating the head of the patient’s bed. Patients with superior vena cava syndrome usually have advanced disease, and less than 10 percent survive more than 30 months after treatment.

Epidural Spinal Cord Compression

Epidural spinal cord compression is caused by a tumor compressing the dural sac. This can cause permanent neurologic impairment even if treatment is delayed for only a few hours. Epidural spinal cord compression is associated with renal, prostate, and, most commonly, breast and lung cancers. The thoracic spine is most often affected, accounting for 70 percent of patients with the condition. Patients with epidural spinal cord compression should receive prompt treatment to improve outcomes. Approximately 90 percent of patients who are ambulatory at the time of diagnosis do not lose this ability posttreatment.

New back pain in patients with cancer suggests epidural spinal cord compression. Pain that worsens when the patient is lying down or with percussion of vertebral bodies is characteristic of this condition. Late neurologic signs such as incontinence and loss of sensory function are associated with permanent paraplegia. Plain radiographs usually show lesions in patients with solid tumors. Magnetic resonance imaging (MRI) has surpassed myelography as the imaging study of choice. If possible, the spinal column should be imaged with non-contrast MRI. Figure 2 is an MRI scan showing spinal cord compression. If neurologic symptoms are present, the patient should receive a dexamethasone (Cortistat) bolus (10 mg intravenously) followed by 4-mg doses every six hours. This treatment should not be delayed while awaiting diagnostic study results. Use of high-dose dexamethasone (up to 100 mg) is controversial; clinical trials have shown that it has unclear benefits and significantly more serious side effects at higher doses. Most patients with epidural spinal cord compression need radiation treatment (up to 3,000 Gy) or surgery. Asymptomatic patients should be considered for immediate radiation therapy, and patients with progressive symptoms despite radiation therapy should be considered for surgical intervention.

Malignant Pericardial Effusions

Malignant pericardial effusions often are undiagnosed in patients with cancer, although as many as 10 to 15 percent of patients with cancer will have some degree
of pericardial effusion at autopsy,¹ and some patients with otherwise treatable cancer succumb to undiagnosed pericardial effusion.⁴ Most effusions develop from metastatic lung or breast cancer. Other causes include malignant melanoma, leukemia, lymphoma, radiation therapy to the chest wall, and chemotherapy agents.⁴,²⁶,²⁷

Clinical symptoms include dyspnea, orthopnea, fatigue, heart palpitations, and dizziness. Pulsus paradoxus, tachycardia, distended neck veins, narrow pulse pressure, and distant heart sounds may be present.²⁹ Echocardiography is the preferred diagnostic study. Acute symptoms are treated with pericardiocentesis or a pericardial window procedure.⁴,²⁶ Fluid samples should be analyzed with cytology. Chemotherapy, radiation, or sclerosis therapy can prevent fluid reaccumulation.⁵

Side Effects of Chemotherapy Agents
There are a multitude of side effects and allergic reactions associated with the use of chemotherapy agents. Many of these adverse reactions initially are managed by family physicians.

EXTRAVASATION INJURIES
Many chemotherapy agents (e.g., anthracyclines, vinca alkaloids) are irritants or vesicants.⁵ Leakage of these agents onto the skin during infusion therapy can cause extravasation injuries such as severe scarring or contractures if the injury is near joints.²⁸ Clinical signs of extravasation injuries include erythema, swelling, and necrosis at the infusion site, usually occurring within hours of chemotherapy. Prompt diagnosis is crucial to avoid extensive skin damage.

Treatment includes cessation of infusion treatments, application of heat or ice, avoidance of site compression, and initiation of antidotes.⁴,⁵ Patients presenting with erythema should receive rapid referral to an oncologist or plastic surgeon, because extensive debridement occasionally is needed.⁴

GASTROINTESTINAL COMPLAINTS
Dehydration is a serious side effect of cancer treatment that often is missed. Up to 30 percent of patients with cancer who have delirium are dehydrated, and as many as 50 percent of patients treated for colon cancer develop dehydration from vomiting, diarrhea, and mucositis.⁵,⁶ Treatment includes fluid resuscitation and initiation of antiemetics and antidiarrheals.

Obstipation, characterized by hard stools every three to five days and abdominal pain, also is commonly associated with narcotic medications and occasionally with neurotoxic chemotherapy agents. If severe, an oncologist should be consulted to consider a change of treatment.⁵

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army or the U.S. Army Service at large.

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