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Gout

Tuhina Neogi, M.D., Ph.D.

A 54-year-old man with crystal-proven gout has a history of four attacks during the previous year. Despite receiving 300 mg of allopurinol daily, his serum urate level is 7.2 mg per deciliter (428 μmol per liter). He is moderately obese and has hypertension, for which he receives hydrochlorothiazide, and his serum creatinine level is 1.0 mg per deciliter (88 μmol per liter). How should his case be managed?

THE CLINICAL PROBLEM

SYMPTOMS AND PREVALENCE

Gout is a type of inflammatory arthritis induced by the deposition of monosodium urate crystals in synovial fluid and other tissues. It is associated with hyperuricemia, which is defined as a serum urate level of 6.8 mg per deciliter (404 μmol per liter) or more, the limit of urate solubility at physiologic temperature and pH.1 Humans lack uricase and thus cannot convert urate to soluble allantoin as the end product of purine metabolism. Hyperuricemia that is caused by the overproduction of urate or, more commonly, by renal urate underexcretion is necessary but not sufficient to cause gout. In one cohort study, gout developed in only 22% of subjects with urate levels of more than 9.0 mg per deciliter (535 μmol per liter) during a 5-year period.2

Gout has two clinical phases. The first phase is characterized by intermittent acute attacks that spontaneously resolve, typically over a period of 7 to 10 days, with asymptomatic periods between attacks. With inadequately treated hyperuricemia, transition to the second phase can occur, manifested as chronic tophaceous gout, which often involves polyarticular attacks, symptoms between attacks, and crystal deposition (tophi) in soft tissues or joints. Although the prevalence of tophaceous gout varies among populations, in one study, tophi were detected in three quarters of patients who had had untreated gout for 20 years or more.3 Recurrent attacks are common. In one study, approximately two thirds of patients with at least one gout attack in the previous year had recurrent attacks.4

An estimated 6.1 million adults in the United States have had gout.5 The prevalence increases with age and is higher among men than among women, with a ratio of 3 or 4 to 1 overall.5,6 However, this sex disparity decreases at older ages, at least in part because of declining levels of estrogen, which has uricosuric effects in women. The rising incidence and prevalence of gout are probably related to the aging of the population, increasing levels of obesity, and dietary changes.6,7

RISK FACTORS

The use of thiazide diuretics, cyclosporine, and low-dose aspirin (<1 g per day) can cause hyperuricemia, whereas high-dose aspirin (≥3 g per day) is uricosuric. Factors
that are associated with hyperuricemia and gout include insulin resistance, the metabolic syndrome, obesity, renal insufficiency, hypertension, congestive heart failure, and organ transplantation.8,9 The uricosuric effects of glycosuria in diabetes may reduce the risk of gout.10,11 Rare X-linked inborn errors of metabolism can cause gout.8 Genomewide association studies have identified common polymorphisms in several genes involved in renal urate transport that are associated with gout, including SLC2A9, ABCG2, SLC17A3, and SLC22A12.11,12 The risk of incident gout is increased in persons with an increased intake of dietary purines (particularly meat and seafood), ethanol (particularly beer and spirits), soft drinks, and fructose and is decreased in those with an increased intake of coffee, dairy products, and vitamin C (which lower urate levels).15,17,18

Triggers for recurrent flares include recent diuretic use, alcohol intake, hospitalization, and surgery.19,20 Urate-lowering therapy, which reduces the risk of gout attacks in the long term, can trigger attacks in the early period after its initiation, presumably as a result of mobilization of bodily urate stores.21,22

The diagnostic standard remains synovial fluid or tophus aspiration with identification of negatively birefringent monosodium urate crystals under polarizing microscopy. Crystals are detectable during attacks and also potentially between attacks, primarily in previously inflamed joints in patients with hyperuricemia.23 However, crystal evaluation is not performed routinely in clinical practice.15 Hyperuricemia may not be present during acute gout attacks and therefore may not be a helpful criterion for diagnosis. A typical presentation that is strongly suggestive of the diagnosis includes rapid development of severe pain (i.e., within 24 hours), erythema, and swelling in a characteristic joint distribution — for example, in the first metatarsophalangeal joint (podagra). In a population with a 0.5% prevalence of gout overall, a patient with hyperuricemia and this presentation has an 82% chance of having gout.23

The differential diagnosis of acute gout includes other crystal-induced arthritides (e.g., calcium pyrophosphate dihydrate) and a septic joint. Joint aspiration with Gram’s staining and culture must be performed if a septic joint is suspected, even if monosodium urate crystals are identified. Older adults, particularly women, may present with polyarticular involvement, which may be mistaken for rheumatoid arthritis; a tophus may be mistaken for a rheumatoid nodule. Tophaceous deposits that are not clinically apparent may be visualized by plain radiography or another imaging method. A diagnosis of gout should prompt evaluation for potentially modifiable risk factors (e.g., dietary habits and associated coexisting illnesses (e.g., hypertension and hyperlipidemia) that may require intervention.

**TREATMENT OPTIONS**

**ACUTE GOUT**

The main aim of therapy for acute gout is rapid relief of pain and disability caused by intense inflammation. Options for managing acute attacks include the use of nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, glucocorticoids, and possibly corticotropin.24 The choice of agent, dose, and duration of therapy is guided by consideration of coexisting illnesses that preclude the safe use of a particular regimen, as well as the severity of the gout. Adjunctive measures include applying ice to and resting the affected joint.25

NSAIDs and colchicine are first-line agents for acute attacks (Table 1).24 Oral colchicine has long been used, although it has only recently (in 2009) been approved by the Food and Drug Administration (FDA) for use in patients with acute gout. In a randomized trial, colchicine (at a dose of 1.2 mg at the onset of a flare, followed by 0.6 mg 1 hour later) was significantly more likely than placebo to result in a reduction in pain of 50% or more 24 hours later (rates, 37.8% and 15.5%, respectively).20 This regimen had efficacy similar to that of a high-dose regimen (1.2 mg, then 0.6 mg per hour for 6 hours), with fewer gastrointestinal side effects. This study did not address treatment after the first 24 hours.

The relative efficacy of colchicine as compared with NSAIDs is unknown. In head-to-head studies, various NSAIDs have had similar benefits for acute gout, and a controlled trial showed the efficacy of tenoxicam over placebo.24,27

When the use of NSAIDs or colchicine is poorly tolerated or contraindicated, glucocorticoids or corticotropin may be used, although evidence for the use of intraarticular and intramuscular glucocorticoids and corticotropin is limited by a lack

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**STRATEGIES AND EVIDENCE**

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When the use of NSAIDs or colchicine is poorly tolerated or contraindicated, glucocorticoids or corticotropin may be used, although evidence for the use of intraarticular and intramuscular glucocorticoids and corticotropin is limited by a lack
Table 1. Pharmacologic Management Options for Acute Gout Attacks.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Examples of Regimens from Randomized Clinical Trials</th>
<th>Alternative Regimens for Complete Attack Resolution*</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsteroidal antiinflammatory drug†</td>
<td>500 mg orally twice daily for 5 days</td>
<td>375–500 mg orally twice daily for 3 days, then 250–375 mg orally twice daily for 4–7 days or until attack resolves</td>
<td>Avoid in patients with renal or hepatic insufficiency, bleeding disorder, congestive heart failure, or allergy; associated with an increased risk of adverse thrombotic and gastrointestinal events; may be administered with a proton-pump inhibitor in patients at risk for gastrointestinal events.</td>
</tr>
<tr>
<td>Naproxen</td>
<td>50 mg orally three times daily for 2 days, then 25 mg orally three times daily for 3 days</td>
<td>50 mg orally three times daily for 3 days, then 25 mg orally three times daily for 4–7 days or until attack resolves</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1.2 mg orally at first sign of gout flare, followed by 0.6 mg orally 1 hr later</td>
<td>Consider additional acute gout regimen to continue managing attack 12–24 hr after colchicine regimen (e.g., 0.6 mg of colchicine twice daily, a nonsteroidal antiinflammatory drug regimen, or an oral glucocorticoid regimen until attack resolves)</td>
<td>Avoid (or use lower dose) in older adults and those with renal insufficiency, hepatic dysfunction, or known gastrointestinal symptoms; adjust dose (and avoid in patients with renal or hepatic impairment) if used in conjunction with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine, clarithromycin, certain antiretroviral agents, certain antifungal agents, certain calcium-channel blockers, and grapefruit juice); avoid for gout-flare therapy in patients with renal or hepatic impairment who are already receiving colchicine prophylaxis; monitor for gastrointestinal symptoms, myotoxicity, and blood dyscrasias (details are available at <a href="http://www.fda.gov">www.fda.gov</a>).</td>
</tr>
<tr>
<td>Oral glucocorticoids (prednisone or prednisolone)‡</td>
<td>Prednisolone, 30–35 mg daily for 5 days</td>
<td>Prednisone, 30–60 mg daily for 2 days (depending on severity of attack), then reduce by 5–10 mg every 2 days (depending on starting dose) in 10-day taper</td>
<td>Use caution in patients with hyperglycemia or congestive heart failure; may be used in patients with moderate-to-severe renal impairment.</td>
</tr>
</tbody>
</table>

* Longer durations of therapy may be necessary for patients with long-standing disease and severe flares.
† There are no published trials establishing the efficacy of celecoxib, the only selective cyclooxygenase-2 inhibitor available in the United States, for use in acute gout.
‡ Although there are insufficient data to recommend the use of intraarticular glucocorticoid injection, it may be a useful alternative for attacks that are limited to one or two joints and amenable to aspiration and in the absence of joint sepsis.
of data from blinded, randomized, placebo-controlled trials24,27-29 (Table 1). Monoarticular attacks are often managed with the use of intraarticular glucocorticoids. In two randomized, placebo-controlled trials of a 5-day course of oral prednisolone (one evaluating a dose of 30 mg daily and the other a dose of 35 mg daily), the efficacy of prednisolone was equivalent to that of standard regimens of indomethacin (vs. the 30-mg dose of prednisolone) and naproxen (vs. the 35-mg dose).30,31

The dose and duration of therapy for acute gout should be sufficient to eradicate the profound inflammatory response. Although randomized trials have generally studied the effects of short courses of treatment on pain reduction, clinical experience suggests that 7 to 10 days of treatment may be necessary to ensure the resolution of symptoms. Increased doses of antinflammatory drugs are typically prescribed for the first few days, with a reduction in the dose once symptoms begin to improve.32 Flares should be treated without interruption of urate-lowering therapy. A “medications in the pocket” strategy should be considered for patients with established gout so that therapy can be started promptly at the onset of symptoms that are consistent with typical attacks.

There is evidence that attacks of gout are caused by the activation of the NLRP3 inflammasome by urate crystals, leading to the release of interleukin-1β33 (Fig. 1). For this reason, interleukin-1 antagonists are being studied as potential options for patients in whom other treatments are not feasible.34 In a randomized trial, the fully human monoclonal antibody canakinumab significantly reduced pain from acute gout, as compared with 40 mg of intramuscular triamcinolone acetonide, 72 hours after administration of the study drug.35 Anakinra and rilonacept improved acute and chronic gout symptoms, respectively, in two small, uncontrolled pilot studies; however, rilonacept did not significantly reduce pain, as compared with indomethacin, in a randomized trial.34,36,37 More data are needed to assess the potential role of these agents.

HYPERURICEMIA
Pharmacologic Approaches
The purpose of lowering serum urate levels is to prevent acute flares and development of tophi. However, gout does not develop in all patients with hyperuricemia, and antihyperuricemic therapies are not without risk. Recommendations that are based on both consensus and evidence support the consideration of urate-lowering therapy in patients with hyperuricemia who have at least two gout attacks per year or tophi (as determined by either clinical or radiographic methods).38 However, the severity and frequency of flares, the presence of coexisting illnesses (including nephrolithiasis), and patient preference are additional considerations.34 Urate-lowering therapy should not be initiated during acute attacks but rather started 2 to 4 weeks after flare resolution, with a low initial dose that is increased as needed over a period of weeks to months, and with close monitoring of urate levels, renal function, and adverse effects. The dose should be adjusted as necessary to maintain a serum urate level below 6 mg per deciliter (357 μmol per liter), which is associated with a reduced risk of recurrent attacks and tophi.22,39,40 It is uncertain whether a more stringent target of less than 5 mg per deciliter (297 μmol per liter) results in greater disease control.41,42 Therapy is generally continued indefinitely.

Three classes of drugs are approved for lowering urate levels: xanthine oxidase inhibitors, uricosuric agents, and uricase agents (Table 2 and Fig. 2). Xanthine oxidase inhibitors block the synthesis of uric acid and can be used regardless of whether there is overproduction of urate. In this class of drugs, the one most commonly prescribed to lower urate levels is allopurinol, which is effective in decreasing flares and tophi, particularly among patients in whom target urate levels are achieved.22,39 Although allopurinol has an acceptable side-effect profile in most patients, a mild rash develops in approximately 2%.22,39,43 Severe allopurinol hypersensitivity is much less common but can be life-threatening. Allopurinol desensitization can be attempted in patients with mild cutaneous reactions, but its safety in those with more serious reactions is unknown.44 The majority of patients receive 300 mg of allopurinol daily, but this dose is often inadequate to achieve target urate levels. Daily doses up to 800 mg may be used in patients with normal renal function. The dose is typically reduced in patients with renal impairment, owing to concerns about an increased risk of hypersensitivity in such patients. However, studies have not shown an association between dose and risk of hypersensitivity, and a reduced dose may contribute to suboptimal gout control.43
In 2009, another xanthine oxidase inhibitor, febuxostat, was approved by the FDA for the treatment of hyperuricemia in patients with gout. As compared with a daily dose of 300 mg of allopurinol, febuxostat at daily doses of 80 mg and 120 mg was 2.5 and 3 times as likely, respectively, to achieve serum urate levels of less than 6 mg per deciliter in a 52-week trial. During the initial 8 weeks of the study, the frequency of gout attacks was higher among patients receiving 120 mg of febuxostat than among those receiving either 80 mg of febuxostat or 300 mg of allopurinol, but there was no significant difference among the three groups for the remainder of the trial. In another study involving patients with renal impairment (defined as a creatinine clearance of 30 to 89 ml per minute), daily doses of 80 mg and 40 mg of febuxostat were superior to 300 mg of allopurinol (or 200 mg in patients with moderate renal impairment) for lowering serum urate to a level below 6 mg per deciliter. There was no increase in cardiovascular risk or hypersensitivity associated with the use of either dose of febuxostat, as compared with allopurinol, although the trial was not powered for such comparisons. Postmarketing surveillance is needed to better understand the risks and benefits of febuxostat. Its efficacy as compared with increased doses of allopurinol is not known, nor is its safety in persons with allopurinol hypersensitivity.

Uricosuric drugs (including probenecid, sulfinpyrazone, and benzbromarone) block renal tubular urate reabsorption. Although these drugs can be used in patients with underexcretion of urate (accounting for up to 90% of patients with gout), they are used less frequently than xanthine oxidase inhibitors and are contraindicated in patients with a history of nephrolithiasis. Benzbromarone (not available in the United States) may be used in patients with mild-to-moderate renal insufficiency but is potentially hepatotoxic, whereas the other two drugs are generally ineffective in patients with renal impairment. In two open-label, randomized trials, benzbromarone was equivalent to allopurinol (the latter at a daily dose of as much as 600 mg) and superior to probenecid (among patients in whom target urate levels were not achieved with 300 mg of allopurinol) in lowering serum urate to 5 mg per deciliter or less.

Uricase converts uric acid into soluble allantoin. Pegloticase, a polyethylene glycolated ( pegylated) modified porcine recombinant uricase, was approved by the FDA in 2010 for chronic gout that is refractory to conventional treatments. The approval was based on data from two double-blind, randomized, placebo-controlled, 6-month trials showing the drug’s urate-lowering and tophus-reducing effects. However, pegloticase must be administered intravenously, and infusion reactions were common.

Figure 1. Mechanisms of Inflammation in Gout.

In acute gout, monosodium urate crystals that have undergone phagocytosis activate the NLRP3 inflammasome, leading to secretion of interleukin-1β. In turn, this secretion can induce further production of interleukin-1β and other inflammatory mediators and further the activation of synovial lining cells and phagocytes. Monosodium urate crystals also induce many other inflammatory cytokines (e.g., tumor necrosis factor α [TNF-α], interleukin-6 and 8, leukotrienes, and alarmins) by mechanisms that are both dependent on and independent of interleukin-1. Experimental models of gout have demonstrated a role for the activation of the terminal complement pathway (C5b-9 membrane attack complex) induced by monosodium urate crystals. Binding of interleukin-1β to the interleukin-1 receptor results in signal transduction, leading to altered expression of adhesion molecules and chemokines, which together with the other inflammatory events results in the neutrophil recruitment that is a major driver of the intense inflammation in gout. In chronic gout, with low-grade synovitis and frequently recurring or nonresolving flares, these inflammatory processes are probably ongoing with potentially continued release of inflammatory mediators, including interleukin-1β, in the presence of persistent monosodium urate crystals.
Table 2. Pharmacologic Options for Hyperuricemia Therapy in Gout.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example of Regimen</th>
<th>Considerations or Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urate-lowering therapy</strong></td>
<td>Aim to maintain serum urate levels below 6 mg per deciliter, which requires regular monitoring and may require dose adjustments. Accompany the initiation of therapy with flare prophylaxis.</td>
<td></td>
</tr>
<tr>
<td>Xanthine oxidase inhibitor</td>
<td>Use in patients with urate overproduction or underexcretion. Avoid use (or monitor closely) in patients receiving azathioprine or 6-mercaptopurine because these drugs are metabolized by xanthine oxidase.</td>
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<tr>
<td><strong>Allopurinol</strong></td>
<td>Starting dose: 50–100 mg orally daily; increase dose every 2–4 wk to achieve serum urate target, with dose based on creatinine clearance; average daily dose, 300 mg, although many patients require higher doses</td>
<td>Use with caution in patients with renal insufficiency (based on creatinine clearance). The maximal dose may be as high as 800 mg daily, but there are limited data for doses above 300 mg daily. A mild rash occurs in approximately 2% of patients, and the risk is potentially increased by concomitant use of ampicillin, amoxicillin, thiazide diuretics, or ACE inhibitors. Allopurinol hypersensitivity is rare, occurring in approximately 0.1% of patients, but can be fatal (rate of death, 20%). If the target serum urate level is not achieved, consider dose escalation beyond the level suggested by guidelines in patients with renal impairment (with close monitoring) or consider the use of an alternative therapy (e.g., febuxostat). Allopurinol can increase the anticoagulant effect of warfarin.</td>
</tr>
<tr>
<td><strong>Febuxostat</strong></td>
<td>Starting dose: 40 mg orally daily; increase to 80 mg orally daily after 2–4 wk to achieve serum urate target, if necessary†</td>
<td>Use as a second-line agent for patients who have contraindications or an inadequate response to allopurinol or uricosuric therapy. Although no dose adjustment is required for patients with mild-to-moderate renal or hepatic insufficiency, there are insufficient data for use in patients with a creatinine clearance of &lt;30 ml per minute or severe hepatic impairment. Currently contraindicated for use with theophylline. Febuxostat has a higher cost than allopurinol.</td>
</tr>
<tr>
<td><strong>Uricosuric agent (probenecid)</strong>‡</td>
<td>Starting dose: 250 mg orally daily; increase by 500 mg per mo to a maximal dose of 2–3 g per day (2 divided doses) in patients with normal renal function to achieve serum urate target</td>
<td>Avoid in patients with a history of nephrolithiasis and a creatinine clearance of &lt;30 ml per minute. Adequate hydration is required to reduce risk of nephrolithiasis. The use of this drug can increase serum penicillin levels. Evaluate for renal uric acid excretion in patients with a family history of early onset of gout, onset of gout at &lt;25 yr, or a history of nephrolithiasis, since this may identify patients with an overproduction of urate in whom uricosuric therapy should be avoided because of the risk of nephrolithiasis.</td>
</tr>
</tbody>
</table>
drome, is not appropriate for use in patients with gout because of its immunogenicity and short half-life.

Lifestyle, Nutrition, and Adjunctive Therapies
Observational data indicate that nonpharmacologic approaches, such as avoiding alcohol or modifying one’s diet, can reduce serum urate levels but may not be sufficient to control established gout. In one randomized trial involving persons without gout, 500 mg of vitamin C per day for 2 months resulted in serum urate levels that were 0.5 mg per deciliter (30 μmol per liter) lower than in those receiving placebo. The intake of dairy milk reduced serum urate levels by approximately 10% during a 3-hour period in a small, randomized, crossover trial involving healthy volunteers. Whether these approaches would have similar effects in persons with gout, or with a longer duration of therapy, is not known. Losartan and fenofibrate, which have uricosuric effects, may be considered in patients with gout who have hypertension or hypertriglyceridemia, although it is not known whether their use reduces the frequency of gout attacks.

Flare Prophylaxis during Initiation of Urate-Lowering Therapy
Because rapid lowering of urate levels is associated with gout flares, with an increased risk associated with therapies that more effectively lower urate levels, proflaxis against acute flares is advised during the initiation of urate-lowering therapy (Table 2). In a study of patients with normal renal function who were starting allopurinol therapy, oral colchicine (at a dose of 0.6 mg twice daily for an average of 5.2 months) significantly reduced the likelihood of gout attacks and lessened the severity of flares that did occur, as compared with placebo. Diarrhea was common, resulting in a once-daily regimen of colchicine for many patients. Thus, the general recommendation for flare prophylaxis is to use colchicine at a dose of 0.6 mg once or twice daily, with dose adjustments as needed for renal impairment, potential drug interactions, or intolerance. Although NSAIDs are also used for prophylaxis, there are few studies that support their use. For patients without tophi, prophylaxis should be continued for 6 months. The optimal duration for those with tophi is uncertain; ongoing prophylaxis until tophus resolution may be necessary.
Areas of Uncertainty

Data are limited regarding the safety and efficacy of combination therapies for the treatment of gout (e.g., the use of a xanthine oxidase inhibitor and a uricosuric agent for hyperuricemia or the use of multiple drugs for acute gout attacks). The safety and cost-effectiveness of new agents for gout, including inhibitors of urate transporter 1 and purine nucleoside phosphorylase, which are under development, and interleukin-1 antagonists, require further study. Preliminary data have suggested the potential efficacy of the interleukin-1 antagonists canakinumab and rilonacept for flare prophylaxis.44

Figure 2. Management Strategies in Patients with Hyperuricemia.

Hyperuricemia can be targeted at many levels. Restriction of exogenous purine intake through dietary modifications or the use of xanthine oxidase inhibitors to block uric acid synthesis from endogenous purine metabolism can reduce the amount of urate that contributes to the total-body urate pool. Modified uricase agents reduce the total-body urate pool by converting uric acid into soluble allantoin. In patients with normal renal function, uricosuric agents can promote renal elimination of urate, thereby reducing total-body urate pools. However, decreased renal urate excretion in patients with renal impairment leads to increased total-body urate stores.

Risk factors for recurrent gout flares may differ from those that predispose patients to the initial attack. Whether factors that lower serum urate levels over the long term in persons without gout would have similar effects with short-term or episodic exposure in persons with gout requires clarification.

It is not known to what level urate can be safely lowered. Observational data have suggested associations between low urate levels and an increased risk of Parkinson’s disease,50 but it is unclear whether the low levels are a cause or consequence of disease. The optimal duration of urate-lowering therapy is also uncertain, and such therapy is recommended indefinitely at this time. In one study, the withdrawal of urate-lowering therapy was associated with prolonged symptom-free intervals (3 to 4 years) in a cohort of 89 patients after long-term control of urate levels (<7 mg per deciliter), flares, and tophi resolution,51 but further study is needed.

Finally, the concept of asymptomatic hyperuricemia as a benign condition is being challenged. Experimental data suggest that urate may contribute to vascular remodeling and hypertension, although it remains uncertain whether urate plays a causal role in cardiovascular disease.9

Guidelines

The American College of Rheumatology is currently developing guidelines for the management of gout. The European League against Rheumatism and the British Society for Rheumatology have published guidelines for the evaluation and management of gout on the basis of trial data (when available) and expert consensus.23,24,42 The present recommendations are largely consistent with these guidelines.

Conclusions and Recommendations

In patients presenting with suspected gout, the diagnosis should be confirmed by examination of synovial fluid or tophus aspirate for monosodium urate crystals. Management should be tailored to the stage of disease and coexisting illnesses. The patient who is described in the vignette has crystal-proven gout, with multiple attacks and a serum urate level of more than 6 mg per deciliter despite receipt of allopurinol at a dose of 300 mg per day.
Since his renal function is normal, the allopurinol dose should be increased (e.g., 100-mg increments every 2 to 4 weeks until the target urate level is reached), with monitoring of renal function and serum urate levels and assessment for potential adverse reactions. Colchicine prophylaxis (0.6 mg once or twice daily) is reasonable while the dose of allopurinol is escalated. If target serum urate levels cannot be achieved or if the patient has serious side effects at higher allopurinol doses, the use of either febuxostat or a uricosuric agent is another option, given his normal renal function.

The patient should understand that the intake of alcohol and an excessive amount of meat or seafood and sugar-sweetened drinks may contribute to elevated urate levels and should be minimized. He should be advised to keep well hydrated and to lose weight. Associated cardiovascular risk factors should be identified and treated. Although the use of hydrochlorothiazide may contribute to the increased urate level, I would not necessarily change that medication if it is effectively controlling his blood pressure, and I would advise him to take the diuretic consistently, since intermittent use may precipitate flares. The addition of losartan for the hypertension might be considered.

He should be advised to maintain his urate-lowering regimen during flares, which can be managed with colchicine. Follow-up is necessary to ensure that appropriate serum urate levels are achieved and maintained and to monitor the patient for adverse effects.

Dr. Neogi reports serving as a core expert panel leader for the American College of Rheumatology Gout Treatment Guidelines. No other potential conflict of interest relevant to this article was reported.

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

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43. Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. J Rheumatol 2006;33:1646-50.


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Calcium Kidney Stones

Elaine M. Worcester, M.D., and Fredric L. Coe, M.D.

In the United States, the prevalence of kidney stones has risen over the past 30 years. By 70 years of age, 11.0% of men and 5.6% of women will have a symptomatic kidney stone. The risk among white persons is approximately three times that among black persons. About 80% of stones are composed of calcium oxalate with variable amounts of calcium phosphate. Diagnosis of a calcium stone requires analysis after passage or removal of the stone. After passage of a first stone, the risk of recurrence is 40% at 5 years and 75% at 20 years. Among patients with recurrent calcium stones who have served as control subjects in randomized, controlled trials of interventions, new stones formed in 43 to 80% of subjects within 3 years. Hospitalizations, surgery, and lost work time that are associated with kidney stones cost more than $5 billion annually in the United States. Stone formation is associated with increased rates of chronic kidney disease and hypertension, increases that are not completely explained by obesity, which is a risk factor for each of these conditions.

Although many inherited and systemic diseases are associated with calcium kidney stones, most such stones are idiopathic. The majority of patients with idiopathic stones have at least one metabolic abnormality, as identified by 24-hour urine testing. Prevention requires evaluation to identify systemic disease and modifiable factors.

PATHOGENESIS

PHYSICOCHEMICAL FACTORS

Supersaturation, often expressed as the ratio of urinary calcium oxalate or calcium phosphate concentration to its solubility, is the driving force in stone formation. At levels of supersaturation below 1, crystals dissolve, whereas at supersaturation levels above 1, crystals can nucleate and grow, promoting stone formation. Supersaturation is generally higher in patients with recurrent kidney stones than in those without the condition, and the type of stone that is formed correlates with urinary
supersaturation. Calcium oxalate supersaturation is independent of urine pH, but calcium phosphate supersaturation increases rapidly as urine pH rises from 6 to 7. Since calcium oxalate stones form over an initial calcium phosphate layer, treatment optimally should lower the supersaturation of both types. Most 24-hour analyses of kidney-stone risk that are performed at specialized laboratories include calculated supersaturation values.

Urine also contains substances that can accelerate or retard urinary crystallization. The only such substance that can be modified in practice at this time is citrate, which can slow the growth of calcium crystals. Anatomic abnormalities, in particular those that result in urinary stasis (such as ureteropelvic junction obstruction, horseshoe kidney, or polycystic kidney), may precipitate or worsen stone formation. Patients with a single functioning kidney are at particular risk, since stone passage with ureteral obstruction can result in acute kidney failure.

**METABOLIC FACTORS**

Imbalances between excretions of calcium, oxalate, and water create supersaturation. Hypercalciuria, the most common metabolic abnormality found in patients with recurrent calcium stones, is most often familial and idiopathic and is strongly influenced by diet. Gut calcium absorption is increased in persons with idiopathic hypercalciuria, but serum calcium values remain unchanged, since absorbed calcium is promptly excreted. On a low-calcium diet, such persons often excrete more calcium than they eat, and urinary calcium excretion also rises markedly after the intake of calcium-free nutrients such as simple oral glucose; in such cases, the only source possible is bone. Although hypercalciuria is sometimes divided into subtypes (absorptive, resorptive, and renal leak), this classification is not helpful in guiding treatment. However, measurement of serum calcium is indicated to identify patients with primary hyperparathyroidism.

The level of oxalate excretion is modestly higher among patients with recurrent calcium stones than among those without the condition, possibly because of increased oxalate absorption in the gut. The intake of ascorbic acid and a high level of protein may increase oxalate production. Because calcium binds with oxalate in the gut and hinders its absorption, oxalate is more readily absorbed when dietary calcium is low. This may be why a low-calcium diet does not successfully prevent stone recurrence.

Citrate chelates calcium in the urine, decreasing supersaturation and reducing the growth of crystals; hypocitraturia is a risk factor for stone formation. Distal renal tubular acidosis, hypokalemia, and the use of carbonic anhydrase inhibitors (e.g., topiramate) lead to hypocitraturia, but the cause of this condition in most patients with recurrent kidney stones is unknown. Hyperuricosuria, often from high dietary intake of purines, is thought to promote the formation of calcium stones by reducing the solubility of calcium oxalate.

**HISTOPATHOLOGY**

Intraoperative papillary biopsy specimens obtained from patients with recurrent kidney stones show that the pattern of crystal deposition differs according to the type of stone. Idiopathic calcium oxalate stones form over regions of interstitial calcium phosphate deposits (Randall’s plaque) on the papillary surface, whereas idiopathic calcium phosphate stones are associated with crystal deposits in inner medullary collecting ducts that contain mainly apatite, sometimes mixed with other crystals. (For additional details, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

**STRATEGIES AND EVIDENCE**

Patients with recurrent calcium stones should be evaluated to rule out systemic disease and guide preventive therapy. Evaluation includes history taking directed at detecting potential causes of stones (Table 1). All stones should be analyzed to classify the type and to detect conversion from one stone type to another — for example, from calcium oxalate to struvite in the presence of infection or to calcium phosphate if the urinary pH rises in response to treatment.

Computed tomography (CT) without the use of contrast material provides information regarding the presence, size, and location of stones, as well as ruling out anatomic abnormalities and providing a baseline for assessing whether subsequent stones that are passed are old or new (with the latter indicating a need for improved preventive treatment). Given the expense and radiation exposure of CT, renal ultrasonography
or abdominal plain radiography may be used in follow-up imaging of known stones, although these methods are less sensitive than CT.

Metabolic testing should be done after the resolution of the acute episode of stone passage, when patients have resumed their usual diet and activity. Evaluation includes a blood test to screen for hypercalcemia, chronic kidney disease, and renal tubular acidosis. Analysis of a 24-hour urine collection to detect metabolic abnormalities should preferably be performed twice, since mineral excretions may vary from day to day.31 Tables 2 and 3 provide a suggested framework for testing and interpretation. Whether to evaluate patients after a single kidney-stone episode is controversial, although it seems prudent to rule out systemic disease, especially in patients with a first stone before adulthood.

### Treatment

#### Management of Symptomatic Stones

Stones that have formed in kidneys do not require removal or fragmentation unless they cause obstruction, infection, serious bleeding, or persistent pain. Ureteral stones of less than 10 mm in

---

Table 1. Key Coexisting Medical Conditions, Medication Use, Diet, and Other Factors Associated with Calcium Kidney Stones.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Features</th>
<th>Type of Kidney Stone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Calcium Oxalate</td>
</tr>
<tr>
<td><strong>Medical or surgical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel disease</td>
<td>Chronic diarrhea, malabsorption</td>
<td>Yes</td>
</tr>
<tr>
<td>Intestinal surgery</td>
<td>Small-bowel resection, ileostomy</td>
<td>Yes</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>Duodenal switch, Roux-en-Y gastric bypass</td>
<td>Yes</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Gout</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Bone disease or fracture</td>
<td>Primary hyperparathyroidism, idiopathic hypercalciuria, myeloma</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Trauma, prolonged illness</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Untreated, iatrogenic</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Renal anomaly</td>
<td>Urinary stasis</td>
<td>Yes Yes</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Seizures, migraine</td>
<td>Yes</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>Antacids, dietary supplement</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitor</td>
<td>Glaucoma</td>
<td>Yes</td>
</tr>
<tr>
<td>Alkali</td>
<td>Bicarbonate, citrate</td>
<td>Yes</td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
<td>Yes Yes</td>
</tr>
<tr>
<td><strong>Occupational or recreational factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>Hot environment, inability to drink</td>
<td>Yes Yes</td>
</tr>
<tr>
<td><strong>Dietary factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxalate loads</td>
<td>Nuts, spinach, ascorbic acid</td>
<td>Yes</td>
</tr>
<tr>
<td>Excess salt</td>
<td>Prepared foods, snack foods</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>Vomiting, use of laxatives</td>
<td>Yes Yes</td>
</tr>
<tr>
<td>Strange diets*</td>
<td>Protein powder, sugar loads</td>
<td>Yes Yes</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of kidney stones in a first-degree relative</td>
<td>Idiopathic hypercalciuria, primary hyperoxaluria</td>
<td>Yes Yes</td>
</tr>
</tbody>
</table>

* Strange diets include very restrictive choices of food or the use of a large number or amount of supplements.
Table 2. Diagnostic Testing for Patients with Recurrent Kidney Stones.*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Value or Range for Adults</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>8.8–10.3 mg/dl</td>
<td>Detection of primary hyperparathyroidism, excessive vitamin D intake, sarcoidosis</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.5–5.0 mg/dl</td>
<td>Detection of primary hyperparathyroidism</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6–1.2 mg/dl</td>
<td>Detection of chronic hyperparathyroidism</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>20–28 mmol/liter</td>
<td>Detection of renal tubular acidosis</td>
</tr>
<tr>
<td>Chloride</td>
<td>95–105 mmol/liter</td>
<td>Detection of renal tubular acidosis</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5–4.8 mmol/liter</td>
<td>Detection of renal tubular acidosis, eating disorders, gastrointestinal disease</td>
</tr>
<tr>
<td><strong>Urine collection over 24-hour period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>&gt;1.5 liter/day</td>
<td>Detection of low volume as cause of stones</td>
</tr>
<tr>
<td>Calcium</td>
<td>&lt;300 mg/day for men, &lt;250 mg/day for women; &lt;140 mg/g creatinine/day</td>
<td>Detection of hypercalcemia</td>
</tr>
<tr>
<td>Oxalate</td>
<td>&lt;40 mg/day</td>
<td>Detection of hyperoxaluria</td>
</tr>
<tr>
<td>pH</td>
<td>5.8–6.2</td>
<td>Calculation of calcium phosphate and uric acid supersaturation, diagnosis of renal tubular acidosis</td>
</tr>
<tr>
<td>Phosphate</td>
<td>500–1500 mg/day</td>
<td>Calculation of calcium phosphate supersaturation</td>
</tr>
<tr>
<td>Citrate</td>
<td>&gt;450 mg/day for men, &gt;550 mg/day for women</td>
<td>Detection of low citrate level and diagnosis of renal tubular acidosis; calculation of calcium phosphate supersaturation</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&lt;800 mg/day for men, &lt;750 mg/day for women</td>
<td>Detection of hyperuricosuria as cause of stones; calculation of uric acid supersaturation</td>
</tr>
<tr>
<td>Sodium</td>
<td>50–150 mmol/day</td>
<td>Diet counseling; calculation of supersaturation</td>
</tr>
<tr>
<td>Potassium</td>
<td>20–100 mmol/day</td>
<td>Use of potassium salts; calculation of supersaturation</td>
</tr>
<tr>
<td>Magnesium</td>
<td>50–150 mg/day</td>
<td>Detection of malabsorption; calculation of supersaturation</td>
</tr>
<tr>
<td>Sulfate</td>
<td>20–80 mmol/day</td>
<td>Calculation of supersaturation; measure of net acid production</td>
</tr>
<tr>
<td>Ammonium</td>
<td>15–60 mmol/day</td>
<td>Calculation of supersaturation</td>
</tr>
<tr>
<td>Creatinine</td>
<td>20–24 mg/kg/day for men, 15–19 mg/kg/day for women</td>
<td>Comparison of actual with predicted creatinine to assess the completeness of the urine collection</td>
</tr>
<tr>
<td>Protein catabolic rate†</td>
<td>0.8–1.0 g/kg/day</td>
<td>Estimation of protein intake</td>
</tr>
<tr>
<td>Calculated supersaturation‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium oxalate</td>
<td>6–10</td>
<td>Guidance of treatment</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>0.5–2</td>
<td>Guidance of treatment</td>
</tr>
<tr>
<td>Other screening tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary cystine screening§</td>
<td>Negative</td>
<td>Detection of cystinuria</td>
</tr>
<tr>
<td>Stone analysis</td>
<td>Basic classification of condition</td>
<td></td>
</tr>
</tbody>
</table>

* Blood testing for renal tubular acidosis, chronic kidney disease, and hypercalcemia, along with urinary cystine screening and kidney-stone analysis, are appropriate for all patients with recurrent kidney stones. Collection of urine over a 24-hour period is appropriate if medical prevention of kidney-stone formation is planned. To convert the values for calcium to millimoles per day, multiply by 0.025. To convert the values for phosphate to millimoles per day, multiply by 0.0323. To convert the values for creatinine to micromoles per day multiply by 0.00884. To convert the values for urinary oxalate to micromoles per day, multiply by 11.11. To convert the values for urinary citrate to mmol per day, multiply by 0.0052. To convert the values for urinary uric acid to millimoles per day, multiply by 0.00595. To convert the values for urinary magnesium to mmol per day, multiply by 0.0411. To convert the values for urinary urea nitrogen to moles per day, multiply by 0.0357. † The protein catabolic rate is calculated by multiplying the urea nitrogen excretion in grams per day by 6.25 and dividing by body weight in kilograms. ‡ Supersaturation is expressed as the ratio of urinary calcium oxalate or calcium phosphate concentration to its solubility. § Urinary cystine was tested with the use of the cyanide nitroprusside test. A negative test means that the cystine concentration is less than 75 mg per liter.
diameter may be followed with conservative treat-
ment in the absence of fever, infection, or renal
failure, if pain is controlled. Opioid analgesics
and nonsteroidal antiinflammatory agents are
both effective for pain control in acute colic.
Therapy with drugs that block α1-adrenergic re-
ceptors or calcium-channel blockers may facili-
tate passage of ureteral stones.

In general, stones
larger than 10 mm in diameter will not pass, and
those smaller than 5 mm will; stones from 5 mm
to 10 mm have variable outcomes. Stones in the
distal ureter are more likely to pass than those
located more proximally.

If stones do not pass, there are several surgi-
cal options for removal.33 Data to guide surgical
recommendations are derived largely from meta-
analyses of small trials. For ureteral stones, the
treatment of choice is either shock-wave litho-
tripsy or ureteroscopy with laser lithotripsy. Stone-
free rates are better with ureteroscopy, but com-
plication rates are higher, including sepsis and
ureteral injury. For stones lodged in the kidney,
the size, location, and presumed composition
play a role in determining treatment. Not all
stone types fragment equally well; for example,
calcium oxalate monohydrate and brushite stones
are more resistant to fragmentation than calci-
um oxalate dihydrate or apatite stones. Shock-
wave lithotripsy and ureteroscopy are frequently
used for smaller stones. Percutaneous nephro-
lithotomy may be used for single large stones
(above 2 cm) or a large or obstructing stone bur-
den. This procedure requires general anesthesia
and hospitalization and carries more risk of com-
plications, including bleeding and infection, than
other techniques but can result in a stone-free
kidney.34 Open or laparoscopic procedures are
occasionally used for stone removal in challeng-
ing cases.

Prevention of Idiopathic Calcium Oxalate
Stones
Prevention of recurrent stones requires decreasing
urinary supersaturation, which is generally
achieved by raising urine volume and lowering
calcium and oxalate excretion. It should be rec-
ognized that urinary abnormalities are graded
risk factors, and thresholds for the definition of
normal urinary function are not absolute cut-
offs.35 Table 4 summarizes treatment strategies.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Serum Calcium</th>
<th>Serum Parathyroid Hormone</th>
<th>Urine Calcium</th>
<th>Urine pH</th>
<th>Urine Citrate</th>
<th>Urine Oxalate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic calcium oxalate</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>Normal</td>
<td>Normal or decreased</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>Idiopathic calcium phosphate</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>Increased</td>
<td>Normal or decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Sarcoideosis</td>
<td>Increased</td>
<td>Decreased</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Lithium use</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Oral supplementation with calcium or vitamin D</td>
<td>Normal or increased</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>Normal or decreased</td>
<td>Normal</td>
<td>Increased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Short-bowel syndrome</td>
<td>Normal or decreased</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>Normal or decreased</td>
<td>Normal</td>
<td>Decreased</td>
<td>Normal</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

* NA denotes not available because histologic analyses have not been reported for patients with the listed conditions.
A randomized trial of increased fluid intake that was targeted to maintain a daily urine volume of more than 2 liters showed a significant reduction in recurrent stone passage among patients with first-time kidney stones. A target urine volume of 2 to 2.5 liters is reasonable and can be achieved by an increased intake of fluids, especially water, although most low-sodium, low-carbohydrate fluids are acceptable in moderation for this purpose.

In a randomized, controlled trial involving Italian men with hypercalciuria, a diet that was low in animal protein (52 g per day), sodium (50 mmol per day), and oxalate (200 mg per day) with normal calcium intake (1200 mg per day) was associated with a reduction in stone formation of almost 50% over a period of 5 years, as compared with a diet that was low in calcium (400 mg per day) and oxalate. But data on the effect of a sodium-restricted diet alone on stone recurrence are lacking. Calcium restriction should be avoided in patients with hypercalciuria, since it may result in a reduction in bone mineral density and an increased rate of fracture.

Thiazide-type diuretics decrease urine calcium excretion, and in randomized, controlled trials, these medications significantly reduced recurrence rates of calcium stones by more than 50% during a 3-year period, as compared with placebo. Long-acting agents like chlorthalidone and indapamide are effective with once-daily doses, whereas twice-daily doses are recommended for hydrochlorothiazide.

Hyperoxaluria may occur when dietary calcium is low or oxalate intake is unusually high or (less commonly) when oxalate is overproduced. Dietary oxalate restriction to less than 100 mg per day and the avoidance of an intake of ascorbic acid above 100 mg per day are prudent if hyperoxaluria is present. Foods that are very high in oxalate include spinach, rhubarb, wheat bran, chocolate, beets, miso, tahini, and most nuts. (A list of the oxalate content of various foods is available at www.ohf.org under Resources.)

### Treatment

<table>
<thead>
<tr>
<th>Supersaturation</th>
<th>Tissue Changes</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric Acid</td>
<td>Calcium Oxalate</td>
<td>Interstitial Plaque</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>Calcium Phosphate</td>
<td>Collecting-Duct Plugging</td>
</tr>
<tr>
<td>Normal or increased</td>
<td>High</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Normal</td>
<td>Decreased</td>
<td>High</td>
</tr>
<tr>
<td>Normal</td>
<td>Decreased</td>
<td>High</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Thiazide for idiopathic hypercalciuria; potassium citrate for calcium oxalate (and perhaps calcium phosphate) stones; allopurinol for hyperuricosuria; sodium restriction and possible protein or oxalate restriction; increased fluid intake

Parathyroid surgery

Glucocorticoids, possible ketoconazole

Discontinuation of supplements

Fluids, alkali; supplements to reduce urine oxalate excretion for the short-bowel syndrome and bariatric surgery

 alkali, possible thiazides

Hyperoxaluria should prompt consideration of malabsorption or one of the primary hyperoxaluria syndromes. Two randomized trials have shown substantial reductions in stone recurrence among patients with hypocitraturia who were treated with potassium alkali three times daily. One trial of sodium–potassium citrate had negative results. Potassium alkali may be safely combined with thiazide when indicated, but no trials have compared the combination against either agent alone for the prevention of stone recurrence. Hyperuricosuria can decrease the solubility of calcium oxalate and increase the incidence of calcium oxalate stones. Allopurinol (at a dose of 300 mg daily) decreased stone recurrence in a randomized trial involving patients with idiopathic calcium oxalate stones who had hyperuricosuria.

A reduction in the intake of protein (and therefore purine) is also prudent but has not been explicitly tested among patients with hyperuricosuria and recurrent kidney stones. In long-term clinical follow-up, preventive treatment resulted in persistent reductions in stone recurrence during a period of 20 years or more. However, compliance tended to wane over time, with rates of nonadherence approaching 20% per year.

**Table 4. Treatment Recommendations for the Prevention of Idiopathic Calcium Kidney Stones in Adults.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Selection Criteria</th>
<th>Potential Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids</td>
<td>Lowers supersaturation by dilution of solutes</td>
<td>Adequate to maintain urine volume &gt;2 liters daily</td>
<td>Useful for all patients; possible sole treatment for patients with a single stone episode</td>
<td>Need to avoid fluids containing excess salt or carbohydrates</td>
</tr>
<tr>
<td>Diet</td>
<td>Lowers supersaturation by decreasing calcium and oxalate excretion; maintains bone mineral, prevents hyperoxaluria</td>
<td>Sodium, &lt;100 mmol/day; protein, &lt;0.8–1 g of animal protein/kg/day; oxalate, &lt;100 mg/day; calcium, 800–1000 mg/day</td>
<td>Recommendations for sodium and protein especially useful in patients with hypercalciuria or hyperuricosuria; for oxalate in patients with hyperoxaluria; and for calcium in all patients with calcium stones</td>
<td>Difficult in maintaining diet; should obtain calcium from dietary sources and avoid supplements</td>
</tr>
<tr>
<td>Thiazide-type diuretic</td>
<td>Lowers supersaturation by decreasing calcium excretion</td>
<td>Chlorthalidone, 12.5–50 mg/day; indapamide, 1.25–2.5 mg/day; hydrochlorothiazide, 12.5–25 mg twice daily</td>
<td>Patients with hypercalciuria; may be useful for some with normocalciuria</td>
<td>Hypokalemia, reduced blood pressure (may be desirable); allergy and sun sensitivity</td>
</tr>
<tr>
<td>Potassium alkali</td>
<td>Lowers supersaturation by chelating calcium; inhibits growth of calcium crystals</td>
<td>Potassium citrate, 10–20 mmol two or three times daily</td>
<td>Patients with hypocitraturia</td>
<td>Need to monitor urine pH and calcium phosphate supersaturation; avoid supersaturation of &gt;1</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Lowers urinary uric acid concentration, which may improve solubility of calcium salts</td>
<td>100–300 mg/day (may be taken once daily)</td>
<td>Patients with hyperuricosuria and calcium stones</td>
<td>Allergy (may be severe)</td>
</tr>
</tbody>
</table>

**PREVENTION OF CALCIUM PHOSPHATE STONES**

Most calcium stones consist of more than 90% calcium phosphate, but the proportion of calcium phosphate in stones has increased over time. Calcium phosphate stones are associated with poorer stone-free rates after percutaneous nephrolithotomy and with more shock-wave lithotripsy treatments than are calcium oxalate stones.

Among patients with calcium phosphate stones, treatment is similar to that of patients with calcium oxalate stones except that potassium alkali should prompt consideration of malabsorption or one of the primary hyperoxaluria syndromes. Two randomized trials have shown substantial reductions in stone recurrence among patients with hyperuricosuria who were treated with potassium alkali three times daily. One trial of thiazide, when indicated, but no trials have compared the combination against either agent alone for the prevention of stone recurrence.

**Table 4. Treatment Recommendations for the Prevention of Idiopathic Calcium Kidney Stones in Adults.**

<table>
<thead>
<tr>
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<th>Dose</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>Adequate to maintain urine volume &gt;2 liters daily</td>
<td>Useful for all patients; possible sole treatment for patients with a single stone episode</td>
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</tr>
<tr>
<td>Diet</td>
<td>Lowers supersaturation by decreasing calcium and oxalate excretion; maintains bone mineral, prevents hyperoxaluria</td>
<td>Sodium, &lt;100 mmol/day; protein, &lt;0.8–1 g of animal protein/kg/day; oxalate, &lt;100 mg/day; calcium, 800–1000 mg/day</td>
<td>Recommendations for sodium and protein especially useful in patients with hypercalciuria or hyperuricosuria; for oxalate in patients with hyperoxaluria; and for calcium in all patients with calcium stones</td>
<td>Difficult in maintaining diet; should obtain calcium from dietary sources and avoid supplements</td>
</tr>
<tr>
<td>Thiazide-type diuretic</td>
<td>Lowers supersaturation by decreasing calcium excretion</td>
<td>Chlorthalidone, 12.5–50 mg/day; indapamide, 1.25–2.5 mg/day; hydrochlorothiazide, 12.5–25 mg twice daily</td>
<td>Patients with hypercalciuria; may be useful for some with normocalciuria</td>
<td>Hypokalemia, reduced blood pressure (may be desirable); allergy and sun sensitivity</td>
</tr>
<tr>
<td>Potassium alkali</td>
<td>Lowers supersaturation by chelating calcium; inhibits growth of calcium crystals</td>
<td>Potassium citrate, 10–20 mmol two or three times daily</td>
<td>Patients with hypocitraturia</td>
<td>Need to monitor urine pH and calcium phosphate supersaturation; avoid supersaturation of &gt;1</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Lowers urinary uric acid concentration, which may improve solubility of calcium salts</td>
<td>100–300 mg/day (may be taken once daily)</td>
<td>Patients with hyperuricosuria and calcium stones</td>
<td>Allergy (may be severe)</td>
</tr>
</tbody>
</table>

**PREVENTION OF CALCIUM PHOSPHATE STONES**

Most calcium stones consist of more than 90% calcium phosphate, but the proportion of calcium phosphate in stones has increased over time. Calcium phosphate stones are associated with poorer stone-free rates after percutaneous nephrolithotomy and with more shock-wave lithotripsy treatments than are calcium oxalate stones.

Among patients with calcium phosphate stones, treatment is similar to that of patients with calcium oxalate stones except that potassium alkali should prompt consideration of malabsorption or one of the primary hyperoxaluria syndromes. Two randomized trials have shown substantial reductions in stone recurrence among patients with hyperuricosuria who were treated with potassium alkali three times daily. One trial of thiazide, when indicated, but no trials have compared the combination against either agent alone for the prevention of stone recurrence.

**Table 4. Treatment Recommendations for the Prevention of Idiopathic Calcium Kidney Stones in Adults.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Selection Criteria</th>
<th>Potential Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids</td>
<td>Lowers supersaturation by dilution of solutes</td>
<td>Adequate to maintain urine volume &gt;2 liters daily</td>
<td>Useful for all patients; possible sole treatment for patients with a single stone episode</td>
<td>Need to avoid fluids containing excess salt or carbohydrates</td>
</tr>
<tr>
<td>Diet</td>
<td>Lowers supersaturation by decreasing calcium and oxalate excretion; maintains bone mineral, prevents hyperoxaluria</td>
<td>Sodium, &lt;100 mmol/day; protein, &lt;0.8–1 g of animal protein/kg/day; oxalate, &lt;100 mg/day; calcium, 800–1000 mg/day</td>
<td>Recommendations for sodium and protein especially useful in patients with hypercalciuria or hyperuricosuria; for oxalate in patients with hyperoxaluria; and for calcium in all patients with calcium stones</td>
<td>Difficult in maintaining diet; should obtain calcium from dietary sources and avoid supplements</td>
</tr>
<tr>
<td>Thiazide-type diuretic</td>
<td>Lowers supersaturation by decreasing calcium excretion</td>
<td>Chlorthalidone, 12.5–50 mg/day; indapamide, 1.25–2.5 mg/day; hydrochlorothiazide, 12.5–25 mg twice daily</td>
<td>Patients with hypercalciuria; may be useful for some with normocalciuria</td>
<td>Hypokalemia, reduced blood pressure (may be desirable); allergy and sun sensitivity</td>
</tr>
<tr>
<td>Potassium alkali</td>
<td>Lowers supersaturation by chelating calcium; inhibits growth of calcium crystals</td>
<td>Potassium citrate, 10–20 mmol two or three times daily</td>
<td>Patients with hypocitraturia</td>
<td>Need to monitor urine pH and calcium phosphate supersaturation; avoid supersaturation of &gt;1</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Lowers urinary uric acid concentration, which may improve solubility of calcium salts</td>
<td>100–300 mg/day (may be taken once daily)</td>
<td>Patients with hyperuricosuria and calcium stones</td>
<td>Allergy (may be severe)</td>
</tr>
</tbody>
</table>
kali should be used cautiously because it raises urine pH, potentially worsening calcium phosphate supersaturation. Levels of urine pH and citrate and the degree of supersaturation should be assessed after starting therapy. If the citrate level does not rise and the degree of supersaturation worsens, the medication is unlikely to be of benefit.

**Areas of Uncertainty**

Treatment trials for calcium stones have not looked specifically at outcomes in patients with calcium phosphate stones. Dietary recommendations to increase fluids, lower salt and protein intake, and maintain a normal intake of calcium are supported by an Italian randomized trial, but no women were included in this study, and it is unclear whether many Americans can comply with the necessary dietary pattern sufficiently to successfully prevent stones. The Dietary Approaches to Stop Hypertension (DASH)—Sodium diet, when modified to remove high-oxalate foods, replicates many of the features of the study diet and may provide a model to follow, but its effects on stone recurrence have not been explicitly studied. Stone formation is associated with an increased risk of bone disease, chronic kidney disease, and hypertension, but it is not known whether effective stone prevention decreases these risks.

**Guidelines**

Guidelines of the American Urological Association (www.auanet.org) recommend that patients who require surgery for ureteral stones should be informed about benefits and risks of all current treatment approaches. Shock-wave lithotripsy and ureteroscopy with laser lithotripsy are both considered acceptable first-line treatments, although ureteroscopy achieves greater stone-free rates. Percutaneous access and open or laparoscopic surgery are used as needed for selected cases. The guidelines do not address evaluation or treatment to prevent recurrent stones.

**Conclusions and Recommendations**

Preventive treatment to decrease stone recurrence is indicated for patients with recurrent calcium stones, such as the patient in the vignette. If systemic disease is not present, treatment should focus on metabolic abnormalities uncovered during the workup, such as hypercalcemia, hypocitraturia, hyperuricosuria, or hyperoxaluria. Although data comparing specific supersaturation targets are lacking, a logical strategy is to lower calcium oxalate and calcium phosphate supersaturation to the low end of the normal range.

Patients should be advised to increase fluid intake to at least 2 liters daily and reduce sodium intake to 2300 mg and protein intake to 0.8 to 1 g per kilogram of body weight per day, since these dietary interventions have reduced stone recurrence in randomized trials. Calcium intake should not be reduced below the recommended intake for sex and age and should be supplied by food rather than by supplements, which may increase the risk of stone formation. In many patients, medication is also needed; the choice of medication is influenced by the metabolic abnormalities identified, the type of stone, and the preference of patients.

The stones of the patient in the vignette contain 20% phosphate, despite a low urine pH while the patient was not receiving medications; the increased phosphate level may reflect his previous treatment with citrate. Both hypocitraturia and hypercalcemia may contribute to his stone formation. In addition to the recommendations above, we would initiate therapy with a thiazide-type diuretic (e.g., 25 mg of chlorthalidone daily) to lower the urinary calcium level. A reduction in sodium intake will also reduce a thiazide-induced loss of potassium.

A follow-up 24-hour urine collection and serum chemical analysis should be performed in 4 to 6 weeks to assess the efficacy of treatment and possible side effects, particularly hypokalemia, which can worsen hypocitraturia. If potassium supplementation is needed, it may be added as potassium alkali, but the urine pH level and the level of calcium phosphate supersaturation should be monitored. If the level of calcium phosphate supersaturation rises and is consistently above 1, potassium chloride should be substituted. Primary treatment with potassium alkali would be an alternative to a thiazide but may not lower the level of urinary calcium phosphate supersaturation as effectively. Ongoing attention is warranted at follow-up visits to monitor whether the patient is adhering to preventive recommendations.
Drs. Worcester and Coe report receiving consulting fees from LabCorp. No other potential conflict of interest relevant to this article was reported.

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

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REFERENCES


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The New England Journal of Medicine

CLINICAL PRACTICE

Emergency Treatment of Asthma
Stephen C. Lazarus, 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 46-year-old woman who has had two admissions to the intensive care unit (ICU) for asthma during the past year presents with a 4-day history of upper respiratory illness and a 6-hour history of shortness of breath and wheezing. An inhaled corticosteroid has been prescribed, but she takes it only when she has symptoms, which is rarely. She generally uses albuterol twice per day but has increased its use to six to eight times per day for the past 3 days. How should this case be managed in the emergency department?

THE CLINICAL PROBLEM

Asthma is one of the most common diseases in developed countries and has a worldwide prevalence of 7 to 10%. It is also a common reason for urgent care and emergency department visits. From 2001 through 2003 in the United States, asthma accounted for an average 4210 deaths annually and an average annual total of approximately 504,000 hospitalizations and 1.8 million emergency department visits. The average annual rate of emergency department visits for asthma was 8.8 per 100 persons with current asthma. Rates were higher among children than among adults (11.2 vs. 7.8 visits per 100 persons), among blacks than among whites (21 vs. 7 visits per 100 persons), and among Hispanics than among non-Hispanics (12.4 vs. 8.4 visits per 100 persons). Women made twice the number of emergency department visits as men. Approximately 10% of visits result in hospitalization.

Asthma is a heterogeneous disease, with varied triggers, manifestations, and responsiveness to treatment. Some patients with acute severe asthma presenting to the emergency department have asthma that responds rapidly to aggressive therapy, and they can be discharged quickly; others require admission to the hospital for more prolonged treatment. The reasons for this difference in responsiveness to treatment include the degree of airway inflammation, presence or absence of mucus plugging, and individual responsiveness to β2-adrenergic and corticosteroid medications. The major challenge in the emergency department is determining which patients can be discharged quickly and which need to be hospitalized.

STRATEGIES AND EVIDENCE

INITIAL ASSESSMENT IN THE EMERGENCY DEPARTMENT

Patients presenting to the emergency department with asthma should be evaluated and triaged quickly to assess the severity of the exacerbation and the need for urgent intervention (Fig. 1). A brief history should be obtained, and a limited physical examination performed. This assessment should not delay treatment; it can be performed while patients receive initial treatment. Clinicians should search for signs...
of life-threatening asthma (e.g., altered mental status, paradoxical chest or abdominal movement, or absence of wheezing), which necessitate admission. Attention should be paid to factors that are associated with an increased risk of death from asthma, such as previous intubation or admission to an ICU, two or more hospitalizations for asthma during the past year, low socioeconomic status, and various coexisting illnesses. The measurement of lung function (e.g., forced expiratory volume in 1 second [FEV1] or peak expiratory flow [PEF]) can be helpful for assessing...
the severity of an exacerbation and the response to treatment but should not delay the initiation of treatment. Laboratory and imaging studies should be performed selectively, to assess patients for impending respiratory failure (e.g., by measuring the partial pressure of arterial carbon dioxide [PaCO₂]), suspected pneumonia (e.g., by obtaining a complete blood count or a chest radiograph), or certain coexisting conditions such as heart disease (e.g., by obtaining an electrocardiogram).

**TREATMENT IN THE EMERGENCY DEPARTMENT**

All patients should be treated initially with supplementary oxygen to achieve an arterial oxygen saturation of 90% or greater, inhaled short-acting β₂-adrenergic agonists, and systemic corticosteroids (Fig. 1). The dose and timing of these agents and the use of additional pharmacologic therapy depend on the severity of the exacerbation.

**β₂-Adrenergic Agonists**

Inhaled short-acting β₂-adrenergic agonists should be administered immediately on presentation, and administration can be repeated up to three times within the first hour after presentation. The use of a metered-dose inhaler with a valved holding chamber is as effective as the use of a pressurized nebulizer in randomized trials, but proper technique is often difficult to ensure in ill patients. Most guidelines recommend the use of nebulizers for patients with severe exacerbations; metered-dose inhalers with holding chambers can be used for patients with mild-to-moderate exacerbations, ideally with supervision from trained respiratory therapists or nursing personnel (see the Supplementary Appendix and a Video, both available at NEJM.org, for descriptions of how to use inhalers with and inhalers without a holding chamber, respectively). The dose administered by means of metered-dose inhalers for exacerbations is substantially greater than that used for routine relief: four to eight puffs of albuterol can be administered every 20 minutes for up to 4 hours and then every 1 to 4 hours as needed (Table 1). Albuterol can be delivered by means of a nebulizer either intermittently or continuously. A meta-analysis of results from six randomized trials indicated that intermittent administration and continuous administration have similar effects on both lung function and the overall rate of hospitalization, whereas a Cochrane review of findings from eight trials suggested that continuous administration resulted in greater improvement in PEF and FEV₁ and a greater reduction in hospital admissions, particularly among patients with severe asthma.

Albuterol is the inhaled β₂-adrenergic agonist most widely used for emergency management. Levalbuterol, the R-enantiomer of albuterol, has been shown to be effective at half the dose of albuterol, but randomized trials conducted in the emergency department have not consistently shown a clinical advantage of levalbuterol over racemic albuterol. Pirbuterol and bitolterol are effective for mild or moderate exacerbations, but a higher dose is required than with albuterol or levalbuterol, and their use for severe exacerbations has not been studied.

Oral or parenteral administration of β₂-adrenergic agonists is not recommended, since neither has been shown to be more effective than inhaled β₂-adrenergic agonists, and both are associated with an increased frequency of side effects. The long-acting inhaled β₂-adrenergic salmeterol has not been studied for the treatment of exacerbations, though trials with formoterol (ClinicalTrials.gov numbers, NCT00819637 and NCT00900874) are under way.

**Anticholinergic Agents**

Because of its relatively slow onset of action, inhaled ipratropium is not recommended as monotherapy in the emergency department but can be added to a short-acting β₂-adrenergic agonist for a greater and longer-lasting bronchodilator effect. In patients with severe airflow obstruction, the use of ipratropium together with a β₂-adrenergic agonist in the emergency department, as compared with a β₂-adrenergic agonist alone, has been shown to reduce rates of hospitalization by approximately 25%, although there is no apparent benefit of continuing ipratropium after hospitalization.

**Systemic Corticosteroids**

In most patients with exacerbations that necessitate treatment in the emergency department, systemic corticosteroids are warranted. The exception is the patient who has a rapid response to initial therapy with an inhaled β₂-adrenergic agonist. Although most randomized, controlled
Table 1. Medications for Treatment of Asthma Exacerbation in the Emergency Department. *

<table>
<thead>
<tr>
<th>Drug and Available Formulation</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting β₂-adrenergic agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metered-dose inhaler (90 μg/puff)</td>
<td>4–8 puffs every 20 min up to 4 hr, then every 1–4 hr as needed</td>
<td>For optimal delivery, dilute solution to a minimum of 3 ml at a gas flow of 6–8 liters/min. Use large-volume nebulizers for continuous administration.</td>
</tr>
<tr>
<td>Nebulizer solution (0.63 mg/3 ml, 1.25 mg/3 ml, 2.5 mg/3 ml, or 5.0 mg/ml)</td>
<td>2.5–5 mg every 20 min over the first hr, then 2.5–10 mg every 1–4 hr as needed or 10–15 mg/hr continuously</td>
<td></td>
</tr>
<tr>
<td>Levalbuterol†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metered-dose inhaler (45 μg/puff)</td>
<td>Same as for albuterol, metered-dose inhaler; levalbuterol administered at half the milligram dose of albuterol has similar efficacy and safety</td>
<td></td>
</tr>
<tr>
<td>Nebulizer solution (0.63 mg/3 ml, 1.25 mg/0.5 ml, or 1.25 mg/3 ml)</td>
<td>1.25–2.5 mg every 20 min over the first hr, then 1.25–5 mg every 1–4 hr as needed; levalbuterol administered at half the milligram dose of albuterol has similar efficacy and safety; continuous nebulization has not been evaluated</td>
<td></td>
</tr>
<tr>
<td>Bitolterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metered-dose inhaler (370 μg/puff)</td>
<td>Same as for albuterol, metered-dose inhaler; bitolterol thought to be half as potent as albuterol on a milligram basis</td>
<td>Has not been studied in patients with severe asthma exacerbations. Not available in the United States.</td>
</tr>
<tr>
<td>Nebulizer solution (2 mg/ml)</td>
<td>Same as for albuterol, nebulizer solution; bitolterol thought to be half as potent as albuterol on a milligram basis</td>
<td></td>
</tr>
<tr>
<td>Pirbuterol, metered-dose inhaler (200 μg/puff)</td>
<td>Same as for albuterol, metered-dose inhaler; pirbuterol thought to be half as potent as albuterol on a milligram basis</td>
<td>Has not been studied in patients with severe asthma exacerbations.</td>
</tr>
<tr>
<td><strong>Anticholinergic agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metered-dose inhaler (18 μg/puff)</td>
<td>8 puffs every 20 min as needed, for up to 3 hr</td>
<td>Adverse effects include dry mouth, cough, and blurred vision.</td>
</tr>
<tr>
<td>Nebulizer solution (0.25 mg/ml)</td>
<td>0.5 mg every 20 min for 1 hr (three doses), then as needed; can be used with albuterol in one nebulizer</td>
<td>Should not be used as first-line therapy; should be added to short-acting β₂-adrenergic agonist therapy for severe exacerbations. The addition of ipratropium to a short-acting β₂-adrenergic agonist has not been shown to provide further benefit once the patient is hospitalized.</td>
</tr>
</tbody>
</table>
trials of corticosteroids in patients seen in the emergency department and those admitted to the hospital have been small, these studies individually\(^{14,15}\) and collectively\(^{16-18}\) show that the use, as compared with nonuse, of systemic corticosteroids is associated with a more rapid improvement in lung function, fewer hospitalizations, and a lower rate of relapse after discharge from the emergency department. Because comparisons of oral prednisone and intravenous corticosteroids have not shown differences in the rate of improvement of lung function, fewer hospitalizations, and a lower rate of relapse after discharge from the hospital, there is no known advantage of higher doses of corticosteroids to treat severe asthma exacerbations or of intravenous administration over oral therapy, provided that gastrointestinal absorption is not impaired. The total course of systemic corticosteroids for an asthma exacerbation necessitating an emergency department visit or hospitalization may be 3 to 10 days. For corticosteroid courses of <1 wk, there is no need to taper the dose; for courses of 7–10 days, there is probably no need to taper, especially if patients are concurrently receiving inhaled corticosteroids.

Adverse effects include adrenal suppression, growth suppression, osteoporosis, muscle weakness, hypertension, weight gain, diabetes, cataracts, Cushing's syndrome, and dermal thinning.

Ipratropium bromide and albuterol

<table>
<thead>
<tr>
<th>Ipratropium bromide and albuterol</th>
<th>8 puffs every 20 min as needed, up to 3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metered-dose inhaler (each puff containing 18 μg of ipratropium and 90 μg of albuterol)</td>
<td>3 ml every 20 min for 3 doses, then as needed</td>
</tr>
<tr>
<td>Nebulizer solution (each 3-mL vial contains 0.5 mg of ipratropium bromide and 2.5 mg of albuterol)</td>
<td>40–80 mg/day in one dose or two divided doses, given until peak expiratory flow reaches 70% of predicted value or a personal best value</td>
</tr>
</tbody>
</table>

Systemic corticosteroids: prednisone, prednisolone, and methylprednisolone

May be used for up to 3 hr during initial management of severe exacerbations. The addition of ipratropium to albuterol has not been shown to provide further benefit once the patient is hospitalized.

Inhaled Corticosteroids

Although high-dose inhaled corticosteroids are often used to treat worsening of asthma control and to try to prevent exacerbations, the evidence does not support the use of inhaled corticosteroids as a substitute for systemic corticosteroids in the emergency department. Inhaled corticosteroids are, however, preferred for long-term asthma control. At the time of discharge from the emergency department, these agents should be continued in patients who have been taking them for long-term control and should be prescribed for patients who have not previously taken them. In a randomized, controlled trial of 1006 consecutively enrolled patients with acute asthma, the addition at discharge of inhaled budesonide (for 21 days) to treatment with oral corticosteroids (for 5 to 10 days) was associated with a 48% reduction in the rate of relapse at 21 days and with improvement in the quality of life with respect to asthma (as measured by the Asthma Quality of Life Questionnaire and symptoms as compared with treatment with oral corticosteroids alone.\(^7\)

Adverse effects include adrenal suppression, growth suppression, osteoporosis, muscle weakness, hypertension, weight gain, diabetes, cataracts, Cushing's syndrome, and dermal thinning.

* Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3.\(^3\)

† Levalbuterol is the R-enantiomer of albuterol.

\(^7\) Levalbuterol is the R-enantiomer of albuterol.
Treatments That Are Not Recommended

Although methylxanthines were once a standard treatment for asthma in the emergency department, it is now clear that their use increases the risk of adverse events without improving outcomes. Antibiotics should not be used routinely but rather should be reserved for patients in whom bacterial infection (e.g., pneumonia or sinusitis) seems likely. Similarly, neither aggressive hydration nor administration of mucolytic agents is recommended for acute exacerbations.

Assessment of Response to Treatment

Patients should be reassessed after the first treatment with an inhaled bronchodilator and again at 60 to 90 minutes (i.e., after three treatments). This assessment should include a survey of symptoms, a physical examination, and measurement of FEV₁ or PEF (Fig. 2). For the most severe exacerbations, this repeat assessment should probably include the measurement of arterial blood gases. Most patients will have clinically significant improvement after one dose of an inhaled...
bronchodilator, and 60 to 70% will meet the criteria for discharge from the emergency department (see below) after three doses.29-31 The degree of subjective and objective improvement that occurs in response to treatment predicts the need for hospitalization.32-38 In a study of 720 patients treated in 36 Australian emergency departments, the need for hospital admission among patients assessed as having moderate asthma, as well as the need for ICU care of patients assessed as having severe asthma, was better predicted by the assessment of asthma severity after 1 hour of treatment than by the initial assessment in the emergency department.38

**INDICATIONS FOR ADMISSION**

After treatment in the emergency department for 1 to 3 hours, patients who have an incomplete or poor response, defined as an FEV₁ or PEF of less than 70% of the personal best or predicted value, should be evaluated for admission to the hospital. Patients who have an FEV₁ of less than 40%, persistent moderate-to-severe symptoms, drowsiness, confusion, or a PaCO₂ of 42 mm Hg or greater should be admitted. Patients who have an FEV₁ of 40 to 69% and mild symptoms should be assessed individually for risk factors for death, ability to adhere to a prescribed regimen, and the presence of asthma triggers in the home. The NAEPP Expert Panel Report 3 suggests that the decision to admit or discharge a patient should be made within 4 hours after presentation to the emergency department.3

**MANAGEMENT OF RESPIRATORY INSUFFICIENCY**

Patients with altered mental status, exhaustion, or hypercapnia should be considered for immediate intubation and ventilatory support. Because of high positive intrathoracic pressures, intubation and ventilation may lead to hypotension and barotrauma. Care should be taken to ensure adequate intravascular volume, and to avoid high airway pressures. A strategy of “permissive hypercapnia,” achieved by adjusting the ventilator to correct hypoxemia while avoiding high airway pressures, was associated in an observational study with decreased mortality among patients with status asthmaticus,39 and this approach has become standard.

Guidelines suggest that once a decision has been made in the emergency department to intubate a patient, the procedure should be semi-elective and performed under controlled conditions (vs. performed as an emergency procedure by the first available staff). Randomized trials have shown a benefit from noninvasive positive-pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease, but most information used to guide the ventilation strategy for treating acute asthma comes from case reports or noncontrolled studies. A randomized crossover study that compared the use of bilevel positive airway pressure for 2 hours with standard care in children with acute asthma showed a significantly lower respiratory rate and improved scores on a questionnaire regarding asthma symptoms with bilevel positive airway pressure but no significant difference in arterial oxygen saturation, transcutaneous carbon dioxide levels, or other outcomes.40 In a randomized, sham-controlled trial of the use of bilevel positive airway pressure in 30 adults with acute asthma, bilevel positive airway pressure was associated with a higher FEV₁ value at 4 hours and a lower rate of hospitalization (17.6%, vs. 62.5% with sham treatment).41 These data suggest that noninvasive positive-pressure ventilation could be considered for patients who decline intubation and for selected patients who are likely to cooperate with mask therapy, but more data are needed to recommend this approach.

**DISCHARGE FROM THE EMERGENCY DEPARTMENT**

Patients may be discharged if the FEV₁ or PEF after treatment is 70% or more of the personal best or predicted value and if the improvements in lung function and symptoms are sustained for at least 60 minutes.3 After discharge, patients should continue to use inhaled short-acting β₂-adrenergic agonists as needed and should be given oral corticosteroids for 3 to 10 days3 (Table 2). Inhaled corticosteroids can be started at any time during treatment of the exacerbation, but initiation at the time of discharge, if not before, is prudent to reduce the risk of relapse.27,42,43

**EDUCATION OF PATIENTS**

The need for treatment in the emergency department often reflects inadequate maintenance therapy and insufficient knowledge of how to deal with a worsening of asthma control. Presentation to the emergency department provides a unique opportunity to educate patients about medications, inhaler technique, and steps that can reduce exposure to household triggers of allergic reaction and to ensure that discharged
patients have an asthma action plan and instructions for monitoring their symptoms and implementing their plan. A follow-up appointment should be scheduled with the patient’s primary care provider or with an asthma specialist to occur 1 to 4 weeks after discharge. Guidelines also recommend that patients be encouraged to contact their asthma care provider within 3 to 5 days after discharge, when the risk of relapse is greatest, although data are lacking to show that this action improves outcomes.

**Areas of Uncertainty**

In patients with severe asthma that is refractory to standard treatment, intravenous magnesium sulfate is widely used, but there is controversy regarding its efficacy. A meta-analysis of 1669 patients in 24 studies who received either intravenous magnesium sulfate (used in 15 studies) or nebulized magnesium sulfate (used in 9 studies) showed that intravenous treatment was weakly associated with improved lung function in adults but had no significant effect on hospital admissions; in children, the use of intravenous magnesium sulfate significantly improved lung function and reduced rates of hospital admission. The effect of nebulized magnesium sulfate is less substantiated. Expert opinion and guidelines suggest that clinicians consider the use of intravenous magnesium sulfate in patients who have severe exacerbations and whose FEV₁ or PEF remains less than 40% of the personal best or predicted value after initial treatments. The results of a large multicenter trial in the United Kingdom (Current Controlled Trials number, ISRCTN04417063) comparing treatment with intravenous or nebulized magnesium sulfate and standard treatment in patients with severe asthma are expected in 2011.

Heliox is a mixture of helium and oxygen, usually 79% and 21%, respectively, with a density about one third that of air, that reduces airflow resistance within regions of the bronchial tree where turbulent flow predominates. It is thought to reduce the work of breathing and to improve delivery of aerosolized medications. However, its role in the management of acute severe asthma is unclear. A Cochrane analysis of 544 patients in 10 trials led to the conclusion that heliox might be beneficial in patients with severe airflow obstruction who have not had a response to initial treatment, and current guidelines reflect this conclusion.

Since the administration of oral leukotriene inhibitors results in increases in the FEV₁ within 1 to 2 hours, there has been interest in using these agents in the emergency department, but their usefulness in that setting is unclear. In a randomized, placebo-controlled trial of intravenous montelukast in 583 adults whose FEV₁ remained at 50% or less of the predicted value after 60 minutes of standard care, the use of montelukast significantly improved the FEV₁ at 60 minutes but did not reduce the rate of hospitalization.

**Table 2. Recommendations for Discharge from the Emergency Department**

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue inhaled short-acting β₂-adrenergic agonists every 1–2 hr, as needed</td>
</tr>
<tr>
<td>Continue oral corticosteroids at a dose of 40–80 mg/day for 3–10 days</td>
</tr>
<tr>
<td>If course is &lt;1 wk, no need to taper the dose</td>
</tr>
<tr>
<td>If course is 7–10 days, probably no need to taper, especially if patients are concurrently receiving inhaled corticosteroids</td>
</tr>
<tr>
<td>Continue or start an inhaled corticosteroid at a “medium dose” (e.g., beclomethasone [HFA], 240–480 μg/day; budesonide [DPI], 600–1200 μg/day; or fluticasone [DPI], 300–500 μg/day)</td>
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<table>
<thead>
<tr>
<th>Education</th>
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<tbody>
<tr>
<td>Review purposes and doses of asthma medications with patient</td>
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<tr>
<td>Review inhaler technique with patient</td>
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<tr>
<td>Teach patient to monitor for signs and symptoms of poor asthma control</td>
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<tr>
<td>Provide patient with an asthma action plan</td>
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<table>
<thead>
<tr>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Advise patient to call primary care provider within 3–5 days after discharge</td>
</tr>
<tr>
<td>Schedule a follow-up appointment with provider to occur within 1–4 wk</td>
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</tbody>
</table>

* DPI denotes dry-powder inhaler, and HFA hydrofluoroalkane formulation.
daily controller therapy. Her history of ICU admissions and excessive albuterol use indicate that she is at increased risk for death related to asthma.

Treatment with oxygen, aerosolized albuterol and ipratropium, and systemic corticosteroids should be initiated. The patient should be monitored closely and her signs and symptoms reassessed frequently, and a decision to admit or discharge her should be made within 4 hours after presentation. If she is discharged from the emergency department, she should be educated about medications, inhaler technique, and steps for monitoring symptoms and for managing exacerbations. Emergency department staff should provide her with a discharge plan, schedule a follow-up appointment, and ensure that she has adequate medications or prescriptions to last until that appointment. Because of her previous admissions to the ICU and her history of consistently poor asthma control, referral to an asthma specialist would be prudent.

No potential conflict of interest relevant to this article was reported.

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

REFERENCES
27. Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: a randomized controlled trial. JAMA 1999;281:2119-26.
42. NIHR Health Technology Assessment Program. The 3Mg Trial: randomised controlled trial of intravenous or nebulised magnesium sulphate or standard therapy for acute severe asthma. 2010. (Accessed July 23, 2010, at http://www.hta.ac.uk/project/1619.asp.)
Early Alzheimer’s Disease
Richard Mayeux, 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 72-year-old man who is still managing investments at a brokerage firm seeks consultation at the urging of his wife for increasing difficulty with memory over the past 2 years. Clients have expressed concern about his occasional lapses in memory. His wife reports that he frequently repeats questions about social appointments and becomes angry when she points this out. The physical examination is normal, but the patient has difficulty remembering elements of a brief story and adding a small amount of change. He has a score of 28 out of 30 on the Mini–Mental State Examination, indicating slightly impaired cognitive function. Early Alzheimer’s disease is suspected. How should the patient be further evaluated and treated?

THE CLINICAL PROBLEM

Alzheimer’s disease is the most frequent cause of dementia in Western societies, affecting an estimated 5 million people in the United States and 17 million worldwide. The annual incidence worldwide increases from 1% between the ages of 60 and 70 years to 6 to 8% at the age of 85 years or older. In countries in which survival to the age of 80 years or older is not uncommon, the proportion of persons in this age group with Alzheimer’s disease now approaches 30% and is expected to continue to increase substantially. The disease onset is insidious, and manifestations evolve over a period of years from mildly impaired memory to severe cognitive loss. A transitional state, referred to as mild cognitive impairment, often precedes the earliest manifestations of Alzheimer’s disease. The course of Alzheimer’s disease is inevitably progressive and terminates in mental and functional incapacity and death. Plateaus sometimes occur in which the degree of cognitive impairment is stable for 1 or 2 years, but progression usually resumes thereafter.

An inability to retain recently acquired information is typically the initial symptom, whereas memory for remote events is relatively spared until later. With disease progression, impairment in other areas of cognition (e.g., language, abstract reasoning, and executive function or decision making) occurs to varying degrees and typically coincides with difficulty at work or in social situations or household activities. Changes in mood and affect often accompany the decline in memory. Delusions and psychotic behavior are not typically presenting signs but can occur at any time during the disease course. The occurrence of psychosis during the initial stages of dementia suggests other diagnoses, such as dementia with Lewy bodies.

At autopsy, the most frequent pathological features in the brains of patients with Alzheimer’s disease include extracellular beta-amyloid protein in diffuse plaques and in plaques containing elements of degenerating neurons, termed neuritic plaques. Intracellular changes include deposits of hyperphosphorylated tau protein, a microtubule assembly protein, in the form of neurofibrillary tangles. These pathological lesions first appear in the entorhinal regions of the hippocampus and
then become widespread. Over time, there is widespread loss of neurons and synapses. The pathogenic mechanisms that are responsible for the development of these changes are unknown.

A family history of dementia is one of the most consistently reported risk factors for Alzheimer’s disease.\(^3\) There are rare cases of families with autosomal dominant inheritance of Alzheimer’s disease that develops between the ages of 30 and 50 years; about half these cases result from mutations in genes encoding amyloid precursor protein, presenilin 1, or presenilin 2.\(^9\) Studies of these mutated genes have led to the assertion that Alzheimer’s disease is caused by the generation and aggregation of beta-amyloid peptide, which then forms neuritic plaques. Although several hundred families carry these mutations, they account for less than 1% of cases.

First-degree relatives of patients with late-onset disease have approximately twice the expected lifetime risk of the disease. The disease is also more often concordant among monozygotic twins than among dizygotic twins.\(^19\) Individuals from families that have many members with late-onset Alzheimer’s disease are at increased risk for dementia, but the distribution of cases is rarely consistent with mendelian inheritance.

The genetic variant encoding apolipoprotein (APOE) \(\varepsilon4\) is the only well-established mutation associated with the late-onset form of Alzheimer’s disease.\(^11\) Risks that are associated with the APOE \(\varepsilon4\) allele peak between the ages of 60 and 80 years. As compared with the absence of the APOE \(\varepsilon4\) allele, the presence of one such allele is associated with a doubling or tripling of the lifetime risk of disease, and the presence of two copies is associated with an increase in risk by a factor of five or more. Associations between Alzheimer’s disease and variants in sortilin-related receptor 1 (SORL1),\(^12\) clusterin, phosphatidylinositol-binding clathrin assembly protein, and a complement component (3b/4b) receptor have been reported,\(^13,14\) but mechanisms underlying these associations remain uncertain.

**Strategies and Evidence**

Impaired memory is typically one of the first signs of Alzheimer’s disease, but difficulty recalling the names of friends or recent events is also common among normal elderly persons. The clinician is thus faced with the difficulty of distinguishing between normal aging and the early stages of Alzheimer’s disease. Mild cognitive impairment is an intermediate state in which persons have more memory problems than would be considered normal for their age, but their symptoms are not as severe as the symptoms of Alzheimer disease and they do not have functional impairment.\(^5\) Alzheimer’s disease develops at a much higher frequency among persons with mild cognitive impairment than among those with normal aging. Determining when patients have reached the very early stage of Alzheimer’s disease is not easy, particularly because it is likely that a preclinical stage of Alzheimer’s disease exists in which senile plaques, neuritic plaques, and neurofibrillary tangles occur in sufficient numbers to meet standard neuropathological criteria for Alzheimer’s disease in the absence of overt symptoms or signs of dementia.\(^15\) Other causes of memory impairment must also be considered, such as cerebrovascular disease, hydrocephalus, hypothyroidism, vitamin B\(_{12}\) deficiency, central nervous system infection, a cognitive disorder related to human immunodeficiency virus infection, adverse effects of prescribed medications, substance abuse, and cancer.

A substantial decline in verbal memory and executive function (e.g., the ability to perform sequential tasks) typically occurs at the onset of Alzheimer’s disease but may be difficult to document without formal neuropsychological testing (Fig. 1). Reduced independence in daily activities (often recognized by the patient’s family) is one of the strongest predictors of disease.\(^16\) Functional status can be measured by the Clinical Dementia Rating (CDR) scale, which evaluates cognitive and functional performance on a scale ranging from 0 to 3, with higher scores indicating a greater severity of impairment.\(^17\) This assessment requires a collateral source of information gathering concerning the patient’s ability to function independently but can be performed in the primary care setting and is particularly useful for clinicians who do not have ready access to formal neuropsychological testing. The assessment requires 30 to 45 minutes to administer, and training is provided online. (Additional details are available in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The CDR score was the strongest predictor of Alzheimer’s disease in a study involving community volunteers without dementia, and scores on a functional rating scale that is based on the CDR effectively identified patients in the early stages of Alzheimer’s disease in a clinical setting.\(^18\)

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testing that shows a substantial decline in verbal memory and executive function supports the diagnosis of Alzheimer’s disease but requires a trained professional for administration and interpretation.

Occasionally, patients with early Alzheimer’s disease present with impaired language or perceptual dysfunction rather than memory loss. Over time, both memory impairment and functional decline become apparent in such patients.

Patients with early disease are at increased risk for motor vehicle accidents. The American Academy of Neurology recommends that clinicians perform a careful assessment of driving ability, including asking the caregiver to rate the patient’s driving ability and reviewing any traffic citations and accidents. Cognitive assessments that include visual perception and sequential-task performance may also be helpful in assessing the capacity to drive. Many state motor vehicle agencies have simulated driving laboratories or are willing to assess driving ability for a nominal fee. Information regarding resources for evaluating potentially impaired drivers is available through the National Highway Traffic Safety Administration (www.nhtsa.dot.gov).

**TREATMENT OPTIONS**

**DRUG THERAPIES**

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate receptor antagonist memantine are the only treatments for Alzheimer’s disease that have been approved by the Food and Drug Administration (Table 1). Randomized, placebo-controlled clinical trials of cholinesterase inhibitors have included patients with mainly mild-to-moderate Alzheimer’s disease and have shown a modest improvement in cognitive function.
Alzheimer’s disease and have shown significant but clinically marginal benefits with respect to cognition, daily function, and behavior.\textsuperscript{24-26} The condition of patients who are taking these drugs remains stable for a year or more and then may decline, though at a rate that is slower than that among untreated patients.

Although there are few studies directly comparing the three cholinesterase inhibitors, a systematic review and meta-analysis of data from 27 randomized trials concluded that there were no significant differences in effects on cognitive performance among these medications.\textsuperscript{27} During the study period (usually, 3 to 6 months), the use of each of these drugs as prescribed at a standard dose resulted in a mean improvement of 2 to 3 points on the Alzheimer’s Disease Assessment Scale for cognition (a scale ranging from 0 to 70, with higher scores indicating worse cognition) or a decreased rate of decline, as compared with the placebo group (approximately a 3-point difference, with a minimal clinically important difference of 4 points).

On the basis of 14 studies that measured daily function, donepezil was modestly but significantly more effective than rivastigmine. Donepezil was likewise modestly but significantly better than rivastigmine and galantamine with regard to behavior, as measured by the Neuropsychiatric Inventory (on a scale ranging from 1 to 144, with higher scores indicating a greater severity of disease). Patients receiving donepezil had a mean reduction of 4.3 points in the baseline score, as compared with a reduction of 1.4 for those receiving the other agents. The likelihood of an overall improvement in score was 1.9 times as great with donepezil as with placebo, 1.2 times as great with rivastigmine as with placebo, and 1.6 times as great with galantamine as with placebo. Adverse effects (including nausea, vomiting, diarrhea, dizziness, and weight loss) were frequent with all three medications, although slightly less frequent with donepezil than with the other medications.

Initial randomized trials of memantine involving patients with moderate-to-severe disease showed a small but significant reduction in cognitive deterioration.\textsuperscript{28} Subsequent randomized trials involving patients with mild-to-moderate disease showed that memantine resulted in marginal benefits over a period of 6 months, with absolute changes in cognitive and functional measures of 1 percentage point.\textsuperscript{29} However, studies that were limited to patients with mild or early-stage disease have shown no significant benefit of memantine therapy.\textsuperscript{30} Memantine has also been used in patients with late-stage disease in combination with cholinesterase inhibitors, such as donepezil.

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**Table 1. Drug Therapy for Alzheimer’s Disease.**

<table>
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<tr>
<th>Medication</th>
<th>Dose</th>
<th>Common Adverse Side Effects</th>
<th>Comments</th>
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<tr>
<td>Donepezil (Aricept)</td>
<td>5 mg/day at bedtime with or without food for 4 to 6 weeks; 10 mg/day there-after, if tolerated</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams</td>
<td>Available in a single daily dose</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>3 mg daily, split into morning and evening doses with meals; dose increased by 3 mg/day every 4 weeks as tolerated, with a maximum daily dose of 12 mg</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, indigestion, dizziness, drowsiness, headache, diaphoresis, weakness</td>
<td>Available as a patch</td>
</tr>
<tr>
<td>Galantamine (Razadyne)</td>
<td>8 mg daily, split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks, as tolerated, with a maximum daily dose of 16 to 24 mg</td>
<td>Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue</td>
<td>Available as an extended-release capsule</td>
</tr>
<tr>
<td>Memantine (Namenda)</td>
<td>5 mg/day with or without food; dose increased by 5 mg every week, with a maximum daily dose of 20 mg</td>
<td>Constipation, dizziness, headache, pain (nonspecific)</td>
<td>Often used as an adjunct to cholinesterase inhibitors; not recommended alone for treatment of early disease</td>
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with modest improvements (a relative change in score of 2 to 5%) on the Severe Impairment Battery and the activities of daily living inventory of the Alzheimer’s Disease Cooperative Study.31

More data are needed to guide the optimal timing of treatment of early Alzheimer’s disease. In a small, randomized, placebo-controlled trial of donepezil, patients in whom Alzheimer’s disease had been diagnosed within the preceding year showed improvement in cognitive performance over a period of 24 weeks.32 In an open-label study, patients who were treated early in the disease course had improvement that was only slightly greater than that of patients who began treatment later.26 In another observational study, a duration of treatment with cholinesterase inhibitors or memantine of at least 3 years was associated with a significantly slower rate of decline in cognitive ability and daily function.33

In practice, subjective reports of improvement in patients receiving cholinesterase inhibitors or memantine are common, but objective improvements are modest, if detectable at all. A rational approach is to try a cholinesterase inhibitor first, switching to another agent in the same class if the initial agent is ineffective or if intolerable side effects emerge.23 Memantine may be added to any of the cholinesterase inhibitors in patients who have little or no improvement with cholinesterase inhibitor monotherapy.

OTHER STRATEGIES

The use of nonsteroidal antiinflammatory drugs, estrogen therapy, antioxidant vitamins, or statins has been proposed for the prevention of Alzheimer’s disease, but the results of randomized trials have been inconsistent or negative.34-37 Similarly, the efficacy of commonly used complementary therapies (e.g., ginkgo biloba, acetyl-L-carnitine, lecithin, huperzine A, piracetam, curcumin, periwinkle, and phosphatidylserine) has not been shown in randomized trials.38 A review of nine randomized clinical trials of cognitive training and rehabilitation therapies that were used to address loss of memory and other intellectual functions showed no significant effects.39

MANAGEMENT OF PSYCHIATRIC SYMPTOMS

Behavioral and psychiatric symptoms typically increase with disease progression. However, depression and anxiety are frequent even in the early stage of Alzheimer’s disease. In one study, 25% of patients with Alzheimer’s disease were reported to have received the diagnosis of depression at the time of or just before the onset of symptoms of the disease.40 In patients in whom pharmacotherapy is considered appropriate, selective serotonin-reuptake inhibitors are commonly used; tricyclic antidepressants are generally avoided, since their anticholinergic effects can cause or exacerbate confusion.41

Psychosis that is characterized by hallucinations and delusions may occur infrequently in patients with early Alzheimer’s disease. The occurrence of agitation, delusions, hallucinations, and irritability early in the disease course also raises the possibility of an alternative diagnosis, such as dementia with Lewy bodies. Treatment with conventional or atypical antipsychotic agents may be helpful, but such drugs should be used with caution because of the potential adverse effects (e.g., parkinsonism, extrapyramidal signs, sedation, and confusion).42

CAREGIVER SUPPORT

Persons who live with and provide care for patients with Alzheimer’s disease, even in the early phases of the disease, often report emotional stress, in part related to the need to give up vacations, hobbies, or even work to care for the patient. Caregivers should routinely be offered counseling and support. Resources for caregivers and patients are available through the Alzheimer’s Association (www.alz.org).

AREAS OF UNCERTAINTY

Further study of brain-imaging methods and biomarkers that may facilitate the identification of patients with early Alzheimer’s disease is needed. Focal atrophy on magnetic resonance imaging (MRI) of the inferior temporal region, particularly the hippocampus, has been shown to predict the conversion from mild cognitive impairment to Alzheimer’s disease.43 However, there is no standard technique to quantify atrophy in the clinical setting, and the diagnostic sensitivity and specificity of MRI are unclear.

Studies have shown that evidence of decreased metabolism and perfusion in the parietal lobes on 18F-fluorodeoxyglucose–positron-emission tomography (FDG–PET) is as accurate as evidence...
of focal atrophy on MRI in predicting progression from mild cognitive impairment to Alzheimer’s disease.\textsuperscript{43,44} However, PET scanning is costly and not widely available at present, and its role in diagnosis remains uncertain. PET imaging with the use of amyloid-binding compounds, such as carbon 11–labeled Pittsburgh compound B (PIB),\textsuperscript{45} has been reported to identify patients with early Alzheimer’s disease.\textsuperscript{46} Some normal elderly persons without dementia have PIB retention similar to that observed in patients with Alzheimer’s disease, but progression to Alzheimer’s disease occurs more rapidly in persons with mild cognitive impairment who have PIB retention than in those without retention, indicating that amyloid deposition may be an early biomarker of incipient disease.\textsuperscript{47,48}

Measurement of markers in cerebrospinal fluid has also been proposed to identify early Alzheimer’s disease. Among persons with mild cognitive impairment, reduced levels of beta-amyloid peptide and increased levels of total tau and tau phosphorylated at threonine 181 have predicted the diagnosis of Alzheimer’s disease.\textsuperscript{49,50} Assessment requires lumbar puncture, and the threshold diagnostic levels of these markers have varied across studies.\textsuperscript{51,52} These measures are now commercially available with clinical interpretation, but their role in practice remains unclear.

**GUIDELINES**

The European Federation of Neurological Societies has published recommendations for the diagnosis and management of Alzheimer’s disease.\textsuperscript{53} On the basis of available randomized trials, treatment with cholinesterase inhibitors is recommended even for mild or early disease; no specific cholinesterase inhibitor is recommended over another. The American Academy of Neurology published practice recommendations in 2001\textsuperscript{54} that have not yet been updated. In 2006, the American Association for Geriatric Psychiatry published practice recommendations that also emphasize treatment with approved medications for cognitive symptoms, as well as symptomatic treatment for neuropsychiatric manifestations, such as depression and psychosis, and attention to issues related to safety, such as driving, living alone, and medication administration.\textsuperscript{55}

**CONCLUSIONS AND RECOMMENDATIONS**

The 72-year-old patient who is described in the vignette has a history of memory and functional impairment, with a relatively high Mini–Mental State Examination\textsuperscript{1} score and a normal neurologic examination. Basic blood chemical analysis and measures of thyrotropin should be performed, along with additional laboratory studies as deemed clinically relevant. Brain MRI to rule out other brain diseases and assess atrophy and a detailed neuropsychological assessment are warranted to make a preliminary diagnosis. If the diagnosis of Alzheimer’s disease is established, I would discuss with the patient and caregiver potential safety issues, including the current living situation and driving, and I would initiate treatment with one of the cholinesterase inhibitors, probably donepezil (starting at 5 mg each night at bedtime). I would plan a follow-up visit in 4 to 6 weeks to assess the side effects and efficacy of the medication (both subjective and objective) by repeating the Mini–Mental State Examination. At that time, the dose of the cholinesterase inhibitor could be increased to 10 mg daily if the drug has been well tolerated. The patient should be closely followed clinically, with repeated neuropsychological assessment within 2 years.

Dr. Mayeux reports receiving an honorarium from Quintiles for serving on a data and safety monitoring board for a trial of a product manufactured by Eli Lilly. No other potential conflict of interest relevant to this article was reported.

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

**REFERENCES**

Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006;63:530-8.

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Helicobacter pylori Infection
Kenneth E.L. McColl, 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 29-year-old man presents with intermittent epigastric discomfort, without weight loss or evidence of gastrointestinal bleeding. He reports no use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs). Abdominal examination reveals epigastric tenderness. A serologic test for Helicobacter pylori is positive, and he receives a 10-day course of triple therapy (omeprazole, amoxicillin, and clarithromycin). Six weeks later, he returns with the same symptoms. How should his case be further evaluated and managed?

Helicobacter pylori, a gram-negative bacterium found on the luminal surface of the gastric epithelium, was first isolated by Warren and Marshall in 1983 (Fig. 1). It induces chronic inflammation of the underlying mucosa (Fig. 2). The infection is usually contracted in the first few years of life and tends to persist indefinitely unless treated. Its prevalence increases with older age and with lower socioeconomic status during childhood and thus varies markedly around the world. The higher prevalence in older age groups is thought to reflect a cohort effect related to poorer living conditions of children in previous decades. At least 50% of the world’s human population has H. pylori infection. The organism can survive in the acidic environment of the stomach partly owing to its remarkably high urease activity; urease converts the urea present in gastric juice to alkaline ammonia and carbon dioxide.

Infection with H. pylori is a cofactor in the development of three important upper gastrointestinal diseases: duodenal or gastric ulcers (reported to develop in 1 to 10% of infected patients), gastric cancer (in 0.1 to 3%), and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (in <0.01%). The risk of these disease outcomes in infected patients varies widely among populations. The great majority of patients with H. pylori infection will not have any clinically significant complications.

Gastric and Duodenal Ulcers
In patients with duodenal ulcers, the inflammation of the gastric mucosa induced by the infection is most pronounced in the non–acid-secreting antral region of the stomach and stimulates the increased release of gastrin. The increased gastrin levels in turn stimulate excess acid secretion from the more proximal acid-secreting fundic mucosa, which is relatively free of inflammation. The increased duodenal acid load damages the duodenal mucosa, causing ulceration and gastric metaplasia. The metaplastic mucosa can then become colonized by H. pylori, which may contribute to the ulcerative process. Eradication of the infection provides a long-term cure of duodenal ulcers in more than 80% of patients whose ulcers are not associated with the use of NSAIDs. NSAIDs are the main cause of H. pylori–negative ulcers.
Ulceration of the gastric mucosa is believed to be due to the damage to the mucosa caused by *H. pylori*. As with duodenal ulcers, eradicating the infection usually cures the disease, provided that the gastric ulcer is not due to NSAIDs.8

**GASTRIC CANCER**
Extensive epidemiologic data suggest strong associations between *H. pylori* infection and noncardia gastric cancers (i.e., those distal to the gastroesophageal junction).9 The infection is classified as a human carcinogen by the World Health Organization.10 The risk of cancer is highest among patients in whom the infection induces inflammation of both the antral and fundic mucosa and causes mucosal atrophy and intestinal metaplasia.11 Eradication of *H. pylori* infection reduces the progression of atrophic gastritis, but there is little evidence of reversal of atrophy or intestinal metaplasia,12 and it remains unclear whether eradication reduces the risk of gastric cancer.13

**GASTRIC MALT LYMPHOMA**
Epidemiologic studies have also shown strong associations between *H. pylori* infection and the presence of gastric MALT lymphomas.14 Furthermore, eradication of the infection causes regression of most localized gastric MALT lymphomas.15

**OTHER GASTROINTESTINAL CONDITIONS**
At least 50% of persons who undergo endoscopy for upper gastrointestinal symptoms have no evidence of esophagitis or gastric or duodenal ulceration and are considered to have nonulcer or functional dyspepsia. In such patients, biopsy specimens of the gastric mucosa often reveal the presence of *H. pylori* and associated inflammation, although this finding is also common in persons without upper gastrointestinal symptoms. Most randomized trials of therapy for *H. pylori* eradication in patients with nonulcer dyspepsia have shown no significant benefit regarding symptoms; a few have shown a marginal benefit,16,17 but this can be explained by the presence of unrecognized ulceration.18 There is thus little evidence that chronic *H. pylori* infection in the absence of gastric or duodenal ulceration causes upper gastrointestinal symptoms.

The prevalence of *H. pylori* infection is lower among patients with gastroesophageal reflux disease (GERD)19 and those with esophageal adenocarcinoma (which may arise as a complication of GERD) than among healthy controls.20 *H. pylori*-associated atrophic gastritis, which reduces acid secretion, may provide protection against these diseases. A recent meta-analysis showed no significant association between *H. pylori* eradication and an increased risk of GERD.21

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**Figure 1. Helicobacter pylori.**
*H. pylori* is a gram-negative bacterium with a helical rod shape. It has prominent flagellae, facilitating its penetration of the thick mucous layer in the stomach.

**Figure 2. Gastric-Biopsy Specimen Showing Helicobacter pylori Adhering to Gastric Epithelium and Underlying Inflammation.**
*H. pylori* is visible as small black rods (arrows) on the epithelial surface and within the glands. The underlying mucosa shows inflammatory-cell infiltrates.

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**STRATEGIES AND EVIDENCE**

**CANDIDATES FOR TESTING FOR *H. pylori* INFECTION**

Since the vast majority of patients with *H. pylori* infection do not have any related clinical disease, routine testing is not considered appropriate.22,23 Definite indications for identifying and treating
the infection are confirmed gastric or duodenal ulcers and gastric MALT lymphoma. Testing for infection, and subsequent eradication, also seems prudent after resection of early gastric cancers. In addition, European guidelines recommend eradicating *H. pylori* infection in first-degree relatives of patients with gastric cancer and in patients with atrophic gastritis, unexplained iron-deficiency anemia, or chronic idiopathic thrombocytopenic purpura, although the data in support of these recommendations are scant.

Patients with uninvestigated, uncomplicated dyspepsia may also undergo testing for *H. pylori* infection by means of a nonendoscopic (noninvasive) method; eradication therapy is prescribed for patients with positive test results. The rationale for this strategy is that in some patients with dyspepsia, underlying *H. pylori*–induced ulcer disease is causing their symptoms. This nonendoscopic strategy is not appropriate for patients with accompanying alarm symptoms (e.g., weight loss, persistent vomiting, or gastrointestinal bleeding) or for older patients (≥45 or ≥55 years of age, depending on the specific set of guidelines) with new-onset dyspepsia, in whom endoscopy is warranted. The nonendoscopic strategy is also not generally recommended for patients with NSAID-associated dyspepsia, since NSAIDs can cause ulcers in the absence of *H. pylori* infection.

An attraction of the test-and-treat strategy is that it avoids the discomfort and costs of endoscopy. However, because only a minority of patients with dyspepsia who have a positive *H. pylori* test have underlying ulcer disease, most patients treated by means of the test-and-treat strategy incur the inconvenience, costs, and potential side effects of therapy without a benefit. In a placebo-controlled trial of empirical treatment involving 294 patients with uninvestigated dyspepsia and a positive *H. pylori* breath test, the 1-year rate of symptom resolution was 50% in those receiving *H. pylori*–eradication therapy, as compared with 36% of those receiving placebo (P = 0.02); 7 patients would need to receive eradication therapy for 1 patient to have a benefit. A greater benefit would be expected if treatment were limited to patients with an increased probability of having an ulcer. However, neither the characteristics of the symptoms nor the presence of other risk factors for ulcer (e.g., male sex, smoking, and family history of ulcer disease) are particularly useful in clinical practice for identifying patients with ulcer dyspepsia and those with nonulcer dyspepsia.

In randomized trials comparing a noninvasive test-and-treat strategy with early endoscopy or with proton-pump–inhibitor therapy, the three strategies resulted in a similar degree of symptom improvement, but early endoscopy was more expensive than the other two strategies. However, the test-and-treat strategy is unlikely to be cost-effective in populations with a prevalence of *H. pylori* infection below 20%. Information is lacking on the longer-term outcomes of these strategies.

**Tests for *H. pylori* Infection**

Table 1 summarizes the various tests for *H. pylori* infection.

**Nonendoscopic Tests**

Serologic testing for IgG antibodies to *H. pylori* is often used to detect infection. However, a meta-analysis of studies of several commercially available quantitative serologic assays showed an overall sensitivity and specificity of only 85% and 79%, respectively. The appropriate cutoff values vary among populations, and the test results are often reported as positive, negative, or equivocal. Also, this test has little value in confirming eradication of the infection, because the antibodies persist for many months, if not longer, after eradication.

The urea breath test involves drinking 13C-labeled or 14C-labeled urea, which is converted to labeled carbon dioxide by the urease in *H. pylori*. The labeled gas is measured in a breath sample. The test has a sensitivity and a specificity of 95%. The infection can also be detected by identifying *H. pylori*–specific antigens in a stool sample with the use of polyclonal or monoclonal antibodies (the fecal antigen test). The monoclonal-antibody test (which also has a specificity and a sensitivity of 95%) is more accurate than the polyclonal-antibody test. For both the breath test and the fecal antigen test, the patient should stop taking proton-pump inhibitors 2 weeks before testing, should stop taking *H₂* receptor antagonists for 24 hours before testing, and should avoid taking antimicrobial agents for 4 weeks before testing, since these medications may suppress the infection and reduce the sensitivity of testing.
Endoscopic Tests

*H. pylori* infection can be detected on endoscopic biopsy of the gastric mucosa, by means of several techniques. The biopsy specimens are usually taken from the prepyloric region, but an additional biopsy specimen obtained from the fundic mucosa may increase the test’s sensitivity, especially if the patient has recently been treated with a proton-pump inhibitor.

The urease-based method involves placement of the endoscopic biopsy specimen in a solution of urea and pH-sensitive dye. If *H. pylori* is present, its urease converts the urea to ammonia, increasing the pH and changing the color of the dye. Recommendations for avoiding proton-pump inhibitors, *H*₂ receptor antagonists, and antimicrobial therapy before testing apply to this test as well, to minimize the chance of false negative results.

Another means of diagnosis involves routine histologic testing of a biopsy specimen; if there is *H. pylori* infection, the organism and associated gastritis are apparent on sections stained with hematoxylin and eosin or Giemsa. Although culturing of the organism is also possible and permits testing for sensitivity to antimicrobial agents, facilities for the culture of *H. pylori* are not widely available and the method is relatively insensitive.

**Table 1. Tests for *Helicobacter pylori* infection.**

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<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonendoscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serologic test</td>
<td>Widely available; the least expensive of available tests</td>
<td>Positive result may reflect previous rather than current infection; not recommended for confirming eradication</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>High negative and positive predictive values; useful before and after treatment</td>
<td>False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations; considerable resources and personnel required to perform test</td>
</tr>
<tr>
<td>Fecal antigen test</td>
<td>High negative and positive predictive values with monoclonal-antibody test; useful before and after treatment</td>
<td>Process of stool collection may be distasteful to patient; false negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations</td>
</tr>
<tr>
<td><strong>Endoscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urease-based tests</td>
<td>Rapid, inexpensive, and accurate in selected patients</td>
<td>False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations</td>
</tr>
<tr>
<td>Histologic assessment</td>
<td>Good sensitivity and specificity</td>
<td>Requires trained personnel</td>
</tr>
<tr>
<td>Culture</td>
<td>Excellent specificity; provides opportunity to test for antibiotic sensitivity</td>
<td>Variable sensitivity; requires trained staff and properly equipped facilities</td>
</tr>
</tbody>
</table>

*PPI denotes proton-pump inhibitor.*

**TREATMENT OF *H. PYLORI* INFECTION**

Various drug regimens are used to treat *H. pylori* infection (Table 2). Most include two antibiotics plus a proton-pump inhibitor or a bismuth preparation (or both). The most commonly used initial treatment is triple therapy consisting of a proton-pump inhibitor plus clarithromycin and amoxicillin, each given twice per day for 7 to 14 days. Metronidazole is used in place of amoxicillin in patients with a penicillin allergy.

The recommended duration of triple therapy is typically 10 to 14 days in the United States and 7 days in Europe. A recent meta-analysis of 21 randomized trials showed that the rate of eradication was increased by 4 percentage points with the use of triple therapy for 10 days as compared with 7 days and by 5 percentage points with the use of triple therapy for 14 days as compared with 7 days — absolute differences that are statistically significant but of marginal clinical significance.

Another possible initial therapy in areas with a high prevalence of clarithromycin-resistant *H. pylori* infection (i.e., >20%) is quadruple therapy comprising the use of a proton-pump inhibitor, tetracycline, metronidazole, and a bismuth salt for 10 to 14 days; however, bismuth salts are not available in some countries. A recent meta-analysis of 93 studies showed a higher rate of eradication with quadruple therapy that included...
both clarithromycin and metronidazole than with triple therapy that included both these agents in populations with either clarithromycin or metronidazole resistance.\textsuperscript{39}

An alternative initial regimen is 10-day sequential therapy, involving a proton-pump inhibitor plus amoxicillin for 5 days followed by a proton-pump inhibitor plus clarithromycin and tinidazole for 5 more days. This regimen was reported to achieve an eradication rate of 93%, as compared with a rate of 77% with standard triple therapy, in a meta-analysis of 10 randomized trials in Italy.\textsuperscript{40} However, in a trial in Spain, the eradication rate among patients randomly assigned to receive sequential therapy was only 84%, indicating a need to confirm its efficacy before it is used widely.\textsuperscript{41}

**Confirmation of Eradication**

It is important to confirm the eradication of \textit{H. pylori} infection in patients who have had an \textit{H. pylori}-associated ulcer or gastric MALT lymphoma or who have undergone resection for early gastric cancer.\textsuperscript{22,23} In addition, to avoid repeated treatment of patients whose symptoms are not attributable to \textit{H. pylori}, follow-up testing is indicated in patients whose symptoms persist after \textit{H. pylori} eradication treatment for dyspepsia. Eradication may be confirmed by means of a urea breath test or fecal antigen test; these are performed 4 weeks or longer after completion of therapy, to avoid false negative results due to suppression of \textit{H. pylori}.\textsuperscript{22} Eradication can also be confirmed by testing during repeat endoscopy (Table 1) for patients in whom endoscopy is required.

**Management of Persistent Infection After Treatment**

Before prescribing a second course of therapy, it is important to confirm that the infection is still present and consider whether additional antimicrobial treatment is appropriate. Further attempts at eradication are indicated in patients with confirmed ulcer or gastric MALT lymphoma or after resection for early gastric cancer. However, if the initial therapy was for uninvestigated dyspepsia, which is associated with a low likelihood of underlying ulcer and symptomatic benefit from eradication, the appropriateness of further eradication therapy is unclear; data from studies designed to determine the optimal management of such cases are lacking. Options for treatment include empirical acid-inhibitory therapy, endoscopy to check for underlying ulcer or another cause of symptoms, and repeat use of the noninvasive test-and-treat strategy. The possibility that symptoms may be due to a different cause (e.g., biliary tract, pancreatic, musculoskeletal, or cardiac disease or psychosocial stress) should routinely be considered. If another course of therapy is administered to eradicate \textit{H. pylori} infection, the importance of adherence to the treatment regimen should be

\begin{table}
\centering
\begin{tabular}{|l|}
\hline
\textbf{Table 2. Regimens Used to Treat Helicobacter pylori Infection.} \\
\hline
\textbf{Standard initial treatment (use one of the following three options)} \\
\hline
Triple therapy for 7–14 days \\
\hline
\begin{tabular}{l}
PPI, healing dose twice/day\textsuperscript{a} \\
Amoxicillin, 1 g twice/day\textsuperscript{f} \\
Clarithromycin, 500 mg twice/day \\
Quadruple therapy for 10–14 days\textsuperscript{c} \\
\begin{tabular}{l}
PPI, healing dose twice/day\textsuperscript{a} \\
Tripotassium dicitratobismuthate, 120 mg four times/day \\
Tetracycline, 500 mg four times/day \\
Metronidazole, 250 mg four times/day\textsuperscript{g} \\
\end{tabular}
\end{tabular}
\hline
Sequential therapy \\
Days 1–5 \\
\begin{tabular}{l}
PPI, healing dose twice/day\textsuperscript{a} \\
Amoxicillin, 1 g twice/day \\
\end{tabular}
Days 6–10 \\
\begin{tabular}{l}
PPI, healing dose twice/day\textsuperscript{a} \\
Clarithromycin, 500 mg twice/day \\
Tinidazole, 500 mg twice/day\textsuperscript{g} \\
\end{tabular}
\hline
\textbf{Second-line therapy, if triple therapy involving clarithromycin was used initially (use one or the other)} \\
\hline
Triple therapy for 7–14 days \\
\begin{tabular}{l}
PPI, healing dose once/day\textsuperscript{a} \\
Amoxicillin, 1 g twice/day \\
Metronidazole, 500 mg (or 400 mg) twice/day\textsuperscript{g} \\
\end{tabular}
\hline
Quadruple therapy, as recommended for initial therapy \\
\hline
\textsuperscript{a} Examples of healing doses of proton-pump inhibitors (PPIs) include the following regimens, all twice per day: omeprazole at a dose of 20 mg, esomeprazole at a dose of 20 mg, rabeprazole at a dose of 20 mg, pantoprazole at a dose of 40 mg, and lansoprazole at a dose of 30 mg. In some studies, esomeprazole has been given at a dose of 40 mg once per day.
\hline
\textsuperscript{f} If the patient has an allergy to amoxicillin, substitute metronidazole (at a dose of 500 mg or 400 mg) twice per day and (in initial triple therapy only) use clarithromycin at reduced dose of 250 mg twice per day.
\hline
\textsuperscript{c} Quadruple therapy is appropriate as first-line treatment in areas in which the prevalence of resistance to clarithromycin or metronidazole is high (>20%) or in patients with recent or repeated exposure to clarithromycin or metronidazole.
\hline
\textsuperscript{g} Alcohol should be avoided during treatment with metronidazole or tinidazole, owing to the potential for a reaction resembling the reaction to disulfiram with alcohol use.
\hline
\end{tabular}
\end{table}
Alarm symptoms include dysphagia, weight loss, evidence of gastrointestinal bleeding, and persistent vomiting. The age cutoff varies among countries, depending on the prevalence of upper gastrointestinal symptoms but uninvestigated dyspepsia. The effect of eradication of *H. pylori* infection on the risk of gastric cancer is unclear but is currently under study.

### Areas of Uncertainty

Data from randomized trials are lacking to guide the care of patients whose symptoms persist after completion of *H. pylori* eradication therapy for uninvestigated dyspepsia. The effect of eradication of *H. pylori* infection on the risk of gastric cancer is unclear but is currently under study.

### Guidelines

The noninvasive test-and-treat strategy for *H. pylori* infection is reasonable for younger patients who have upper gastrointestinal symptoms but not alarm symptoms, like the patient in the vignette. Noninvasive testing can be performed with the use of the urea breath test, fecal antigen test, or serologic test; the serologic test is the least accurate. Triple therapy with a proton-pump inhibitor, clarithromycin, and amoxicillin or metronidazole remains an appropriate first-line therapy, provided that there is not a high local rate of clarithromycin resistance. Recurrence or persistence of symptoms after eradication therapy for uninvestigated dyspepsia is much less likely to indicate that treatment has failed than to indicate that the symptoms are unrelated to *H. pylori* infection. Further eradication therapy should not be considered unless persistent *H. pylori* infection is confirmed. Data are lacking to inform the op-

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**Table 3. Guidelines for Evaluation and Management of Helicobacter pylori Infection.**

<table>
<thead>
<tr>
<th>Criteria for testing</th>
<th>American College of Gastroenterology</th>
<th>Maastricht III Consensus Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active gastric or duodenal ulcer, history of active gastric or duodenal ulcer not previously treated for <em>H. pylori</em> infection, gastric MALT lymphoma, history of endoscopic resection of early gastric cancer, or uninvestigated dyspepsia</td>
<td>Same as American College of Gastroenterology criteria, with the following additional criteria: gastric cancer in first-degree relative, atrophic gastritis, unexplained iron-deficiency anemia, or chronic idiopathic thrombocytopenic purpura†</td>
<td></td>
</tr>
<tr>
<td>Criteria for test-and-treat strategy</td>
<td>Age &lt;55 yr and no alarm symptoms§</td>
<td>Age &lt;45 yr and no alarm symptoms‡§</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>10–14 Days</td>
<td>7 Days</td>
</tr>
</tbody>
</table>

* The American College of Gastroenterology guidelines are reported by Chey, Wong, and the Practice Parameters Committee of the American College of Gastroenterology; the Maastricht III consensus report guidelines are reported by Malfertheiner and colleagues. MALT denotes mucosa-associated lymphoid tissue.
† Eradication of *H. pylori* in patients with chronic idiopathic thrombocytopenic purpura has been reported to increase the platelet count, although the data are limited.
‡ The age cutoff varies among countries, depending on the prevalence of upper gastrointestinal cancer.
§ Alarm symptoms include dysphagia, weight loss, evidence of gastrointestinal bleeding, and persistent vomiting.

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emphasized, since poor adherence may underlie the failure of initial therapy.

The choice of second-line treatment is influenced by the initial treatment (Table 2). Treatment failure is often related to *H. pylori* resistance to clarithromycin or metronidazole (or both agents). If initial therapy did not include a bismuth salt, bismuth-based quadruple therapy is commonly used as second-line therapy, with eradication rates in case series ranging from 57 to 95%. Triple therapies have also been tested as second-line therapies in patients in whom initial therapy failed. A proton-pump inhibitor used in combination with metronidazole and either amoxicillin or tetracycline is recommended in patients previously treated with a proton-pump inhibitor, amoxicillin, and clarithromycin. Clarithromycin should be avoided as part of second-line therapy unless resistance testing confirms that the *H. pylori* strain is susceptible to the drug.

Patients in whom *H. pylori* infection persists after a second course of treatment and for whom eradication is considered appropriate should be referred to a specialist with access to facilities for culturing *H. pylori* and performing sensitivity testing and experience with alternative treatments for the infection. Several regimens have been reported to be effective as salvage therapy in case series. For example, retreatment after treatment failure with a triple regimen consisting of levofloxacin or rifabutin, along with a proton-pump inhibitor and amoxicillin, has been associated with high rates of eradication. However, caution is warranted in the use of rifabutin, which may lead to resistance of mycobacteria in patients with preexisting mycobacterial infection.
timal management of recurrent or persistent dyspepsia after noninvasive testing and treatment of *H. pylori* infection. Options include symptomatic acid-inhibitory therapy, endoscopy to check for underlying ulcer or another cause of symptoms, and repeat of the *H. pylori* test-and-treat strategy; other potential reasons for the symptoms should also be reconsidered.

Dr. McColl reports receiving lecture fees from AstraZeneca and Nycomed and consulting fees from Sacoor. No other potential conflict of interest relevant to this article was reported.

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

REFERENCES


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**CLINICAL PRACTICE**

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Clinical Therapeutics articles provide practical guidance for the use of specific medications, devices, and procedures in patient care. Topics include: how the therapy is used, evidence that supports (or fails to support) its use, adverse effects and areas of uncertainty, guidelines from major professional societies, and author recommendations.
Iron-Chelating Therapy for Transfusional Iron Overload

Gary M. Brittenham, 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, if they exist, are presented. The article ends with the author’s clinical recommendations.

A 16-year-old boy with sickle cell anemia undergoes routine screening with transcranial Doppler ultrasonography to assess the risk of stroke. This examination shows an abnormally elevated blood-flow velocity in the middle cerebral artery. The hemoglobin level is 7.2 g per deciliter, the reticulocyte count is 12.5%, and the fetal hemoglobin level is 8.0%. Long-term treatment with red-cell transfusion is initiated to prevent stroke. A hematologist recommends prophylactic iron-chelating therapy.

The Clinical Problem

Long-term treatment with red-cell transfusion effectively prevents stroke and other complications of sickle cell anemia and can sustain patients with chronic congenital and acquired refractory anemia, including thalassemia major, Diamond–Blackfan anemia, myelodysplastic syndromes, myelofibrosis, aplastic anemia, and other disorders. In the United States, 10,000 to 20,000 patients with sickling disorders receive repeated transfusions. An estimated 4000 to 5000 patients with myelodysplastic syndromes and other forms of acquired refractory anemia require red-cell transfusions. The number of patients with transfusion-dependent thalassemia in the United States is smaller — probably less than 1000. However, globally, almost 100,000 patients with thalassemia syndromes undergo transfusions. The majority of these patients are in low- and middle-income countries.

Because humans lack any effective means to excrete excess iron, long-term transfusion alone inexorably produces the clinical problem of iron overload. In patients with thalassemia who undergo transfusion from infancy, iron-induced liver disease and endocrine disorders develop during childhood and are almost inevitably followed in adolescence by death from iron-induced cardiomyopathy. In patients with sickle cell anemia, although iron-induced complications appear to develop later, eventually, liver disease with cirrhosis as well as cardiac and pancreatic iron deposition can develop. The annual per-patient costs of care for complications of iron overload are estimated at $15,000 to $20,000.

Pathophysiology and Effect of Therapy

At the end of their life span, transfused red cells are phagocytosed by reticuloendothelial macrophages in the liver, bone marrow, and spleen (Fig. 1). Their hemoglobin is digested, and the iron is freed from heme and released into the cytosol. Early in the course of long-term transfusion, most of this additional iron can be stored within reticuloendothelial macrophages. Gradually, limits on the capacity of macrophages to retain iron result in the release of excess iron into plasma. Transferrin...
binds the released iron, with an increase in the plasma iron concentration and transferrin saturation. As the transferrin saturation increases, hepatocytes are recruited to serve as storage sites for the excess iron.

With continued transfusion, macrophages and hepatocytes can no longer retain all the surplus iron. Iron then enters plasma in amounts that exceed the transport capacity of circulating transferrin. As a consequence, non–transferrin-bound iron appears in the plasma (Fig. 1) as a heterogeneous assortment of iron complexes that appear to be the major mediators of extrahepatic tissue damage in transfusional iron overload. Non–transferrin-bound plasma iron enters specific cells, particularly hepatocytes, cardiomyocytes, anterior pituitary cells, and pancreatic beta-cells. In these cells, iron accumulation leads to the generation of reactive oxygen species, resulting in damage to lipids, proteins, DNA, and subcellular organelles, including lysosomes and mitochondria. This injury may result in cellular dysfunction, apoptosis, and necrosis.

Therapy with chelating agents that form a complex with iron and promote its excretion can clear plasma non–transferrin-bound iron, remove excess iron from cells, and maintain or return body iron to safe levels (Fig. 1). (An interactive graphic depicting iron supply and storage in sickle cell anemia with long-term red-cell transfusion and iron-chelating therapy is available with the full text of this article at NEJM.org.) Two iron-chelating agents are approved for use in North America (Table 1): parenteral deferoxamine mesylate (Desferal, Novartis) and oral deferasirox (Exjade, Novartis).

Deferoxamine is a siderophore (an iron-binding compound) produced by the bacterium Strep tomyces pilosus. It is poorly absorbed after oral administration and is rapidly cleared; consequently, subcutaneous or intravenous administration is necessary. One molecule of deferoxamine binds a single atom of iron, forming a ferroxamine complex that is virtually inert metabolically. Plasma iron chelated with deferoxamine is eliminated predominantly by the kidneys. Hepatocytes efficiently take up deferoxamine, which then chelates hepatocellular iron, with the ferroxamine excreted in the bile. Within cells, deferoxamine is localized to lysosomes, where it induces autophagy of cytosolic ferritin. Lysosomal degradation of cytosolic ferritin releases iron that is bound by deferoxamine, and the chelated iron is then cleared from the cell.

In contrast to deferoxamine, the synthetic chelator deferasirox is well absorbed from the gastrointestinal tract and is cleared from the circulation slowly. Two molecules of deferasirox are needed to bind a single atom of iron. Like deferoxamine, deferasirox forms complexes with plasma iron, but deferasirox–iron complexes are eliminated predominantly through a hepatobiliary route. Hepatocytes readily take up deferasirox, which chelates hepatocellular iron. The deferasirox–iron complexes are then excreted in the bile. Within cells, deferasirox chelates cytosolic iron, leading to ferritin degradation by the proteasome.

A third iron chelator, the synthetic oral agent deferiprone (Ferriprox, Apotex; Kelfer, Cipla), is not approved for use in the United States or Canada. In the European Union and some other countries, it is approved specifically for patients with thalassemia major when deferoxamine is contraindicated or inadequate (Table 1).

### CLINICAL EVIDENCE

The use of deferoxamine therapy antedates the common use of randomized, controlled trials to establish the efficacy of medical treatments. Only one small, randomized trial has compared chelation plus deferoxamine with no therapy; this trial enrolled 20 children with β-thalassemia. After a mean of 5.8 years of treatment with intramuscu-

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**Figure 1** (see next two pages). Iron Supply and Storage in Sickle Cell Anemia with Long-Term Red-Cell Transfusion and Iron-Chelating Therapy.

In all four panels, the area of the red and blue circles is roughly proportional to the amount of iron in each pool, and the width of the arrows is roughly proportional to the daily magnitude of the iron flux. Panel A shows normal iron supply and storage in a healthy person without sickle cell disease (i.e., with hemoglobin A). The major pathway of internal iron exchange is a unidirectional flow from plasma transferrin to the erythroid marrow to circulating red cells to reticuloendothelial macrophages and back to plasma transferrin (orange arrows). In the circulating plasma, virtually all iron is bound to transferrin. Panel B shows that in sickle cell anemia, hemolysis shortens the average life span of the red cells from about 4 months to 5 or 6 weeks, increasing red-cell catabolism by reticuloendothelial macrophages and increasing iron delivery to the erythroid marrow by 6 to 8 times the normal rate. There is little ineffective erythropoiesis, and iron absorption from the gastrointestinal tract is not increased. Panel C shows that long-term red-cell transfusion decreases erythroid marrow activity to 2 to 3 times the normal rate but results in accumulation of iron in reticuloendothelial macrophages and hepatocytes. Eventually, the capacity for safe storage is exceeded, with the appearance of plasma non–transferrin-bound iron (dashed arrow) and its progressive deposition in the heart and endocrine organs. In Panel D, the green arrows show that iron-chelating therapy with deferasirox can clear plasma non–transferrin-bound iron and remove excess iron from the liver, heart, and other organs, with subsequent excretion through the bile into the stool.
A Normal Iron Supply and Storage

- Functional iron
- Storage iron

Circulating red cells

Reticuloendothelial macrophages

Transferrin-bound iron

Heart and endocrine organs

Muscle and other parenchymal cells

Hepatocytes

Gastrointestinal tract

B Sickle Cell Anemia

Circulating red cells

Reticuloendothelial macrophages

Transferrin-bound iron

Heart and endocrine organs

Muscle and other parenchymal cells

Hepatocytes

Gastrointestinal tract
Sickle Cell Anemia with Long-Term Red-Cell Transfusion

Circulating red cells

Erythrocyte production

Erythrocytes

Transferrin-bound iron

Hepatocytes

Reticuloendothelial macrophages

Non-transferrin-bound iron

Muscle and other parenchymal cells

Heart and endocrine organs

Gastrointestinal tract

Muscle and other parenchymal cells

Heart and endocrine organs

Gastrointestinal tract

Sickle Cell Anemia with Transfusion and Iron-Chelating Therapy

Circulating red cells

Erythrocyte production

Erythrocytes

Transferrin-bound iron

Hepatocytes

Reticuloendothelial macrophages

Non-transferrin-bound iron

Muscle and other parenchymal cells

Heart and endocrine organs

Gastrointestinal tract

Muscle and other parenchymal cells

Heart and endocrine organs

Gastrointestinal tract

Chelator-bound iron
lar deferoxamine, the mean hepatic iron concentration was 25.9 mg per gram of liver tissue (dry weight) in the deferoxamine group and 42.2 mg per gram in the control group. At 14 years, one death had occurred in the deferoxamine group and six deaths had occurred in the control group.

In lieu of randomized trials, observational studies have investigated the effects of deferoxamine in the management of transfusion-related iron overload. One study involved 977 children with transfusion-dependent thalassemia major who survived beyond the first decade of life. Subsequent survival was examined according to 5-year birth cohorts beginning in 1960; deferoxamine was introduced in 1975. The survival rate increased progressively in each 5-year cohort (see Fig. 1 in the Supplementary Appendix, available at NEJM.org). The survival rate was significantly higher among children born after 1975 than among those in previous cohorts.

Deferasirox has been compared with deferoxamine in a few short-term trials sponsored by Novartis. In the largest of these trials, 586 children with β-thalassemia were randomly assigned to either agent, with dosing according to the baseline hepatic iron concentration. The primary end point was the percentage of subjects with either a maintained or reduced hepatic iron concentration at 1 year; this end point was reached in 52.9% of patients assigned to deferasirox and in 66.4% of patients assigned to deferoxamine. This result, which did not meet a prespecified noninferiority target, was attributed to the relative underdosing of deferasirox. The total hepatic iron concentration decreased by a mean of 2.4 mg per gram (dry weight) in the deferasirox group and by 2.9 mg per gram in the deferoxamine group. No trial has established the long-term effectiveness of deferasirox in preventing organ toxicity or improving survival.

Deferiprone has also been compared with deferoxamine in several small, randomized trials. As is the case with deferasirox, no long-term trials have been performed to evaluate the effect of deferiprone on organ function or survival.

**CLINICAL USE**

Iron-chelating therapy should be considered in all patients who require long-term red-cell transfusion. Such patients include those with sickle cell disease, myelodysplastic syndromes, thalassemia major, Diamond–Blackfan anemia, aplastic...
anemia, and other congenital and acquired forms of refractory anemia.

There are alternatives to chelation in some patients. Some of the underlying disorders requiring transfusion may be cured by hematopoietic stem-cell transplantation. In some patients with sickle cell disease, exchange transfusion may reduce or obviate the need for iron chelation. Infrequently, phlebotomy may be an option for the removal of excess iron in the event of cure or remission of a refractory anemia. Iron-chelating therapy itself may sometimes decrease or eliminate the need for transfusion in patients with myelodysplasia or myelofibrosis. Chelation therapy may not be needed in patients with myelodysplasia or other acquired refractory anemias who have an estimated survival of less than 1 year.

With the exception of these groups, iron-chelating therapy is indicated in almost all patients requiring long-term red-cell transfusion. Iron chelation is contraindicated in patients who are hypersensitive to the chelating agent or excipients in the chelator formulation, and it requires specialized management in patients with several renal disease or anuria. Chelators should be avoided or used with great caution in patients who are pregnant or breast-feeding.

Ideally, iron-chelating therapy should be initiated prophylactically, before clinically significant iron accumulation has occurred. Treatment should begin when patients have received between 10 and 20 red-cell transfusions. Patients who have already undergone repeated transfusion without sufficient chelation can also be successfully treated, but they may require more intensive regimens (see below).

Evaluation of the patient before the initiation or adjustment of iron-chelating therapy includes a detailed characterization of the underlying disorder, with thorough documentation of the history of transfusion and chelation; determination of the body iron load by measurement of the hepatic iron and serum ferritin concentrations; estimation of the rate of transfusional iron loading; and assessment of cardiac iron deposition. The techniques for assessing cardiac iron overload, transfusional iron loading, and body iron burden are described in the Supplementary Appendix. The extent of any existing iron-induced hepatic, cardiac, or endocrine dysfunction should be established, and in children and adolescents, growth and maturation should be assessed. Nutritional evaluation with correction of deficiencies is recommended.

In the United States and Canada, the choice of an iron chelator for transfusional iron overload is either parenteral deferoxamine or oral deferasirox. The decision is best made with the patient and, if the patient is a child, with his or her parents. Despite the lack of data on long-term effectiveness, most patients now opt for deferasirox because of the ease of oral administration. Deferasirox is preferred for prophylactic or maintenance therapy. Deferoxamine, which has been proved to reverse iron-induced heart disease and increase long-term survival, may be indicated if deferasirox is ineffective in a particular patient, and it may be favored for severe iron overload, especially with cardiac involvement. Conversely, deferasirox may be the better choice in patients who are unable to tolerate subcutaneous infusions of deferoxamine. Deferasirox also may be substituted for deferoxamine after successful clearance of cardiac iron. Deferiprone is available in the United States on a compassionate-use basis, usually in combination with deferoxamine, in patients in whom iron-induced heart failure has developed or who are at high risk for the development of heart failure.

Deferoxamine is administered subcutaneously or intravenously, usually with a portable pump, for 8 to 10 hours each day, 5 to 7 days per week. Subcutaneous administration is preferred except in patients with severe cardiac iron deposition, for whom continuous intravenous deferoxamine therapy is recommended. Deferasirox is administered orally once daily, and deferiprone is administered orally three times daily.

The dose of an iron-chelating agent is determined by three principal factors: the presence or absence of cardiac iron overload, the rate of transfusional iron loading, and the body iron burden (see the Supplementary Appendix and Table 2). In brief, if cardiac iron overload is present, ridding the heart of the excess iron becomes the critical therapeutic goal. In the absence of cardiac iron overload, the long-term objective is to maintain the body iron at a level that permits safe storage while avoiding chelator toxicity. The greater the rate of transfusional iron loading, the greater the dose of an iron chelator that will be needed to control the accumulation of iron.

During treatment, tests to monitor chelator-associated toxicity should be performed, depending on the potential adverse effects of the specific agent to be used (see Table 1 and the Adverse Effects section below). In patients who receive...
Table 2. Usual Doses of Deferoxamine or Deferasirox for Transfusional Iron Overload.*

<table>
<thead>
<tr>
<th>Hepatic Iron Concentration</th>
<th>No Cardiac Iron Overload ($T_2^*, \geq 20$ msec)</th>
<th>Cardiac Iron Overload ($T_2^*, \leq 20$ msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Transfusional Iron Intake</td>
<td>Mild to Moderate</td>
</tr>
<tr>
<td></td>
<td>$&lt;0.3$ mg/kg of body weight</td>
<td>$0.3$ to $0.5$ mg/kg of body weight</td>
</tr>
<tr>
<td>$\geq15$ mg/kg, dry weight</td>
<td>Deferoxamine: 40–50 mg/kg/day, 8 to 10 hr/day, 6 or 7 days/wk, by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily</td>
<td>Deferoxamine: 40–50 mg/kg/day, 8 to 10 hr/day, 6 or 7 days/wk, by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily</td>
</tr>
<tr>
<td></td>
<td>Deferoxamine: 40–50 mg/kg/day, 8 to 10 hr/day, 6 or 7 days/wk, by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily</td>
<td>Deferoxamine: 50 mg/kg/day by continuous intravenous infusion; deferasirox: oral dose of 40 mg/kg daily, but uncertain efficacy in reducing cardiac iron</td>
</tr>
<tr>
<td>$7$ to $&lt;15$ mg/kg, dry weight</td>
<td>Deferoxamine: 30–40 mg/kg/day, 8 to 10 hr/day, 5 days/wk, by subcutaneous infusion; deferasirox: oral dose of 20–30 mg/kg daily</td>
<td>Deferoxamine: 40–50 mg/kg/day, 8 to 10 hr/day, 6 or 7 days/wk, by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily</td>
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<td>$3$ to $&lt;7$ mg/kg, dry weight</td>
<td>Deferoxamine: 30–40 mg/kg/day, 8 to 10 hr/day, 5 days/wk, by subcutaneous infusion; deferasirox: oral dose of 20–30 mg/kg daily</td>
<td>Deferoxamine: 40–50 mg/kg/day, 8 to 10 hr/day, 6 or 7 days/wk, by subcutaneous infusion; deferasirox: oral dose of 30–40 mg/kg daily</td>
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* To minimize interference with growth and skeletal development, the dose of deferoxamine in young children should not exceed 25 to 30 mg per kilogram of body weight. The dose should be adjusted according to the therapeutic index. The bioavailability of deferasirox may affect the response. $T_2^*$ denotes the cardiac effective transverse relaxation time on magnetic resonance imaging.
deferoxamine, these tests include annual assessments of auditory function and vision. In patients who receive deferasirox, serum creatinine, serum aminotransferases, and bilirubin levels and complete blood counts should be assessed monthly. In patients who receive deferiprone, weekly assessment of complete blood counts and monthly assessments of serum aminotransferases should be performed.

The effectiveness of iron-chelating therapy is best monitored by periodic measurements of cardiac iron concentrations by magnetic resonance imaging (MRI), of cardiac function, and of hepatic iron concentrations and by review of the actual rate of transfusional iron loading once or twice a year, depending on the severity of the iron overload (see the Supplementary Appendix). Dose adjustments can be made according to the guidelines in Table 2. Serum ferritin concentrations are usually measured at least quarterly.

In the United States, on the basis of 2006 wholesale acquisition prices, the annual costs of deferoxamine for iron-chelating therapy have been estimated to range from $6,824 to $29,209, plus $9,286 for infusion, and the estimated annual costs of deferasirox range from $24,404 to $53,095, with the actual cost depending on dose and body weight. Administration of a chelator will be needed as long as transfusion is continued and will be lifelong in most patients.

**ADVERSE EFFECTS**

Discomfort or pain at the site of subcutaneous infusion develops in almost all patients treated with subcutaneous deferoxamine, and induration or erythema develops in some patients. These symptoms can often be mitigated with topical anesthetic or glucocorticoid creams. Visual and auditory toxicity associated with deferoxamine has been reported, and in one series involving 89 patients treated with this agent, 13 presented with vision loss, deafness, or both. Subsequent studies suggest a much lower incidence of toxicity, and these risks can be minimized by not exceeding doses of 50 mg per kilogram of body weight in patients with iron overload and by decreasing the dose as the hepatic iron concentration approaches normal levels. Although treatment with deferoxamine may reduce endocrine complications of iron overload, such as a delay of puberty, the chelator itself can interfere with growth, apparently as a result of skeletal dysplasia. To minimize this effect, the dose of deferoxamine in young children should not exceed 25 to 30 mg per kilogram.

In the United States, on the basis of 2006 wholesale acquisition prices, the annual costs of deferasirox described above, gastrointestinal disturbances occurred in approximately 15% of patients, rash in 11%, and increases in serum creatinine levels in 38%. Similar rates have been observed in subsequent trials. In January 2010, on the basis of postmarketing studies, the Food and Drug Administration required a change in the prescribing information for deferasirox. The new information states that the drug could cause potentially fatal renal and hepatic impairment or failure as well as gastrointestinal hemorrhage. These adverse effects were reported to occur more frequently in older patients and in patients with high-risk myelodysplastic syndromes, thrombocytopenia, or underlying renal or hepatic impairment.

The most common adverse effects of deferiprone are diarrhea and gastrointestinal effects, arthropathy (including severe arthritis with clinically significant disability), increased levels of serum liver enzymes, and progression of hepatic fibrosis associated with an increase in iron overload or hepatitis C. The most serious adverse effects are agranulocytosis (incidence, 1.1%) and neutropenia (incidence, 4.9%); weekly monitoring of the neutrophil count is recommended. Neurologic abnormalities have been reported with higher-than-recommended doses of deferiprone.

**AREAS OF UNCERTAINTY**

Several areas of uncertainty exist with regard to the optimal approach to iron-chelating therapy. First, a variety of binary combinations of chelating agents are being examined in off-label uses, with either synchronous or sequential administration. The clinical usefulness of such combination therapies is unclear at present, in the absence of unequivocal evidence of the superiority of any specific combination over treatment with a single agent.
Second, MRI performed to evaluate the iron content of the liver, heart, and other organs has become the method of choice for guiding iron-chelating therapy, but calibrated methods are not available for all patients. A 1-year study of deferasirox involving patients with various types of anemias used an alternative approach; the investigators based the initial dose on the rate of transfusional iron loading and subsequently adjusted the dose according to measurements of serum ferritin levels and safety markers.23 The long-term efficacy and safety of this strategy are uncertain.

Third, in patients with myelodysplastic syndromes who have undergone long-term transfusion and for whom prolonged survival is anticipated, iron-chelating therapy may be appropriate. In individual patients, the benefit of such treatment may vary, given the morbidity associated with chelation, the variable prognosis for the underlying disorder, and the latency period between the onset of the transfusion and the development of clinical manifestations of iron overload. Data are lacking from prospective, randomized trials examining the clinical circumstances in which morbidity and mortality improve with iron-chelating therapy in these patients39; one such trial is currently recruiting patients.

Fourth, there is evidence to suggest that iron overload is associated with lower rates of cardiomyopathy, endocrinopathy, and other conditions among patients with sickle cell disease than among patients with thalassemia.41 The effects of the systemic inflammatory state on iron handling in patients with sickle cell disease,42 as well as differences in the rate and duration of transfusion and in the age of the patient at the initiation of long-term transfusion, the extent of ineffective erythropoiesis, and gastrointestinal iron absorption, may be involved. It is unclear whether these data provide sufficient grounds to recommend a higher body iron threshold for chelation therapy in patients with sickle cell disease, especially given the potential risks of iron-induced liver disease.

Finally, there is a lack of certainty with respect to the optimal hepatic iron concentrations (Table 2) for minimizing the risk that hepatic fibrosis will progress to cirrhosis and its ultimate complication, hepatocellular carcinoma.43,44

Guidelines and consensus statements on the management of sickle cell disease,45,46 thalassemia,32,47 Diamond–Blackfan anemia,48 aplastic anemia,49 and myelodysplastic syndromes 26,50 all include recommendations for iron-chelating therapy for transfusional iron overload. All these guidelines are generally consistent with the approach outlined in this review, although there are variations in the individual recommendations, depending in part on the year of publication and the specific underlying disorder. For example, the guidelines for iron chelation in thalassemia32,47 generally endorse measurement of serum ferritin levels as a useful way to monitor iron overload, whereas the guidelines for the management of sickle cell disease45,46 emphasize that ferritin levels can be altered by liver disease and inflammation. The guidelines on the management of thalassemia by the Italian Society of Hematology47 endorse deferoxamine as first-line therapy over the oral chelators, whereas most of the other guidelines do not state an explicit preference in this regard.

After discussing the need for iron-chelating therapy with the patient and his family, I would describe the advantages and disadvantages of subcutaneous deferoxamine and oral deferasirox so that a genuinely informed decision can be made. At present, the most frequent choice is oral deferasirox. Before the initiation of treatment, I would obtain information about the number of previous transfusions and the rate of ongoing transfusion and would arrange for cardiac $T_2^*$ and hepatic transverse relaxation rate ($R_2^*$) measurements, an MRI evaluation of cardiac function, and echocardiographic and electrocardiographic studies. Auditory and ophthalmic testing, including slit-lamp examination and dilated-fundus examination, should be performed. Laboratory tests should include a complete blood count with a differential count and measurement of serum creatinine, serum aminotransferases, bilirubin levels, and iron indexes. After transfusion of a total of 10 to 20 units of blood, or with the hepatic iron concentration between 3 and 7 mg per gram, I would administer once-daily oral therapy...
with deferasirox at a dose of 20 mg per kilogram.

With good support and careful monitoring, this regimen, adjusted as needed, should provide long-term protection against the complications of transfusional iron overload in this patient.

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Dr. Brittenham reports that his institution filed a patent application in April 2010 for a rapid MRI method. No other potential conflict of interest relevant to this article was reported.

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

REFERENCES


40. Novartis Pharmaceuticals. Myelodysplastic syndromes (MDS) event free survival with iron chelation therapy study (TELESTO). (ClinicalTrials.gov identifier no. NCT00940602.) (http://www.clinicaltrials.gov/ct2/show/NCT00940602?term=telesto&rank=1.)


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SPECIALTIES AND TOPICS AT NEJM.ORG

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Bisphosphonates for Osteoporosis
Murray J. Favus, 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.

A 67-year-old woman was referred by her primary care physician for treatment of osteoporosis and progressive bone loss. One year before the visit, the patient had discontinued hormone-replacement therapy. She had subsequently begun to experience midback pain and lost 3.8 cm (1.5 in.) in height. A dual-energy x-ray absorptiometry (DXA) scan showed bone mineral density T scores of −3.1 at the lumbar spine and −2.8 at the femoral neck, which are consistent with a diagnosis of osteoporosis. One year later, a second scan showed a further decrease of 5.4% in bone mineral density at the lumbar spine (Fig. 1), as well as a compression fracture of the 11th thoracic vertebra (Fig. 2). Results of blood and urine tests ruled out the common secondary causes of osteoporosis. To prevent additional vertebral fractures, oral bisphosphonate therapy was recommended.

THE CLINICAL PROBLEM

Osteoporosis is a systemic skeletal disorder that is characterized by the loss of bone tissue, disruption of bone architecture, and bone fragility, leading to an increased risk of fractures.1 Bone loss and low bone mass are asymptomatic until fractures occur. Estrogen deficiency after menopause is the most common cause of osteoporosis, but secondary causes2 must be ruled out before treatment is undertaken (Table 1).

Osteoporosis is the most common metabolic bone disease and the most common cause of fractures in older adults in the United States. Ten million people in the United States have osteoporosis, and an additional 33 million people have low bone mass (osteopenia) and are at increased risk for fractures.4,5 More than 2 million fractures occur each year as a result of osteoporosis or osteopenia, including 300,000 hip fractures, 547,000 vertebral fractures, and 135,000 pelvic fractures. Postmenopausal white women have a 40% lifetime risk of at least one osteoporotic fracture.4

Osteoporotic hip fractures are associated with the highest morbidity and mortality. Up to 50% of patients with such fractures have permanently impaired mobility, and 25% lose the skills necessary to live independently.6,7 A recent meta-analysis showed that among older men and women, the rate of death from any cause is increased by a factor of 5 to 8 during the first 3 months after a hip fracture.8

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Estrogen deficiency due to either spontaneous or surgical menopause9 increases the production by bone marrow stromal cells and osteoblasts of the receptor activator of nuclear factor κB ligand (RANKL), which, in turn, increases the binding of RANKL10 to the osteoclast cell-surface receptor nuclear factor κB (RANK). Increased
binding of RANKL to RANK initiates the proliferation of osteoclast precursors and their differentiation into mature osteoclasts.\textsuperscript{10-12} The expanded osteoclast population increases bone turnover and the depth and number of resorption pits (Fig. 3). Later in the course of menopause, age-related bone loss and accompanying changes in the properties of bone material exacerbate the bone loss and fragility associated with estrogen deficiency.\textsuperscript{10} At the microscopical level, the increased number and activity of osteoclasts disrupt trabecular connectivity and increase cortical porosity.\textsuperscript{9,11} Resorption pits are incompletely filled, since osteoblastic new bone formation does not keep pace with rates of bone resorption.\textsuperscript{10} Reduced bone density and bone quality compromise the mechanical weight-bearing properties of the skeleton and confer a predisposition to fractures occurring either spontaneously or when falls cause mechanical overload.\textsuperscript{11}

Bisphosphonates reduce fractures by suppressing bone resorption.\textsuperscript{12,13} The molecular structure of the bisphosphonates (P-C-P) is analogous to that of the naturally occurring pyrophosphates (P-O-P), with two short side chains (R1 and R2) attached to the C core.

The R1 side chain determines bone-binding affinity, and the R2 side chain determines antiresorptive potency. Bisphosphonates that are approved for use in the United States (ibandronate, risedronate, and zoledronate) have nitrogen-containing R2 side chains\textsuperscript{14} that enhance antiresorptive and antifracture potency. Variations in the structure of the side chains determine the strength with which the bisphosphate binds to bone, the distribution through bone, and the amount of time it remains in the bone after treatment is discontinued.\textsuperscript{15}

In bone, bisphosphonates accumulate in the hydroxyapatite mineral phase, and the concentration of the bisphosphonates is increased by a factor of 8 at sites of active bone resorption.\textsuperscript{14,16,17} The bound nitrogen-containing bisphosphonates enter osteoclasts and reduce resorption through inhibition of farnesyl pyrophosphate synthase (FPPS), an enzyme in the mevalonate-to-cholesterol pathway.\textsuperscript{18,19} Inhibition of FPPS interferes with prenylation of small guanosine triphosphatases (GTases) at the ruffled border of the osteoclasts and disrupts the attachment of osteoclasts to the bone surface, which stops resorption and promotes early cell death.\textsuperscript{16,20}

**Clinical Evidence**

Three of the most important phase 3 trials of the use of bisphosphonates for the treatment of osteoporosis are described below. In these trials, a reduction in the rate of fractures was the primary end point, and increases in bone mineral density at the lumbar spine and a reduction in markers of bone turnover were secondary end points.

In the Fracture Intervention Trial (FIT),\textsuperscript{21} 2,027 postmenopausal women at high risk for fracture, with low bone density at the femoral neck and at least one vertebral fracture, were randomly assigned to either placebo or alendronate, at a dose of 5 mg daily for 24 months, followed by 10 mg daily for the final 12 months of the trial. At 36 months, 15.0\% of the women who received the placebo and 8.0\% of the women who were treated with alendronate had sustained one or more new vertebral fractures, as assessed by radiography (P=0.001). New hip fractures occurred in 2.1\% of the women in the placebo group and 1.1\% of the women in the alendronate group (P=0.05).

In the Vertebral Efficacy with Risedronate Therapy (VERT) trial,\textsuperscript{22} 2,458 postmenopausal women with at least one vertebral fracture and a T score at the lumbar spine of \(-2.0\) or less were randomly assigned to either placebo or risedronate at a dose of 2.5 mg or 5 mg daily. During the course of the trial, data from other studies suggested that a dose of 2.5 mg was less effective than a dose of 5 mg; therefore the 2.5-mg group was discontinued. In the two remaining groups, the rate of new vertebral fractures after 3 years was 11.3\% among subjects treated with 5 mg of risedronate daily, as compared with 16.3\% in the placebo group (P=0.003). In a subsequent trial, risedronate was shown to be effective in reducing the rate of hip fractures as well.\textsuperscript{23}

The efficacy of zoledronic acid in the treatment of osteoporosis was evaluated in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly trial (HORIZON; ClinicalTrials.gov number, NCT00049829).\textsuperscript{24} In this trial,
7765 postmenopausal women with osteoporosis (T score of –2.5 or less or –1.5 or less with evidence of vertebral fracture) were randomly assigned to either zoledronic acid, at a dose of 5 mg administered at baseline, 12 months, and 24 months, or placebo. At 36 months, the absolute rate of new vertebral fractures as assessed by standard radiography was 3.3% in the zoledronic acid group, as compared with 10.9% in the placebo group (P<0.001). There were 52 new hip fractures (1.4%) in the zoledronic acid group, as compared with 88 (2.5%) in the placebo group (P<0.001).

Randomized, placebo-controlled trials of other oral bisphosphonates, including ibandronate,25 clodronate,26 and etidronate,27 have shown that these drugs also have efficacy in reducing the risk of new vertebral fractures. However, because these trials were not powered to show efficacy for the treatment of hip fractures, the clinical usefulness of these agents for preventing hip fractures is currently unknown. Pamidronate has been used to treat a variety of bone diseases in children and adults. However, no randomized, placebo-controlled trial has been performed with sufficient power to assess the efficacy of the drug for the treatment of hip fracture in women with postmenopausal osteoporosis.

**Clinical Use**

All postmenopausal women with measurements of bone mineral density at either the spine or the hip that meet World Health Organization (WHO) criteria for osteoporosis (T score of less than –2.5)
should receive long-term therapy with an agent that has been proven to prevent fractures. In contrast, it may be difficult to decide whom to treat among the large number of patients who have osteopenia (T score of −1.0 to −2.5). Many postmenopausal women in whom fractures develop have osteopenia rather than osteoporosis; in these women, the fractures may occur because of the contributions of risk factors that are independent of bone mineral density. I often use the WHO Fracture Risk Assessment Tool (FRAX; www.sheffield.ac.uk/FRAX/) to assist in making treatment decisions. FRAX is a calculator algorithm that incorporates risk factors with measurements of bone mineral density, generating a quantitative estimate of the 10-year probability of a major osteoporotic fracture (hip, vertebral, humerus, or forearm) or of a hip fracture alone in patients who have not yet begun therapy. In general, I initiate pharmacologic treatment in patients who have a 10-year probability of a hip fracture that exceeds 3% or a 10-year probability of a major osteoporotic fracture that exceeds 20%.29

In addition to weighing the objective evidence, I consider the patient’s lifestyle. I am more likely to initiate treatment for low bone mass in a patient who wishes to continue participating in sports or recreational activities such as cycling, tennis, skiing, and running. Such patients are likely to have a greater risk of falls and fractures than are sedentary patients.

A major consideration in selecting therapy is the risk of hip fracture. All treatments that have been approved by the Food and Drug Administration (FDA) have shown efficacy in reducing the rates of vertebral fracture, but not all have been clearly shown to reduce the rate of hip fractures. If bone mineral density at the hip is low, I usually select an agent for which there are trials showing efficacy in preventing hip fractures. I recommend either alendronate or risedronate if the patient is capable of taking an oral agent. If the patient cannot tolerate oral bisphosphonates, then I may select intravenous zoledronic acid. If bone density at the hip is normal or only mildly reduced, I may select oral or intravenous ibandronate, which has not been shown to be effective in reducing the risk of hip fracture.

Alternatives to bisphosphonates include the anabolic agent teriparatide (parathyroid hormone 1-34), which reduces the risk of vertebral and nonvertebral fractures but, among subjects in a large, pivotal trial, did not reduce the risk of hip fracture alone.30 Teriparatide is also more expensive than the bisphosphonates and requires daily subcutaneous injection. Estrogen is effective in decreasing the risk of vertebral and hip fractures in postmenopausal women31 but may confer increased risks of breast cancer and cardiovascular disease. Raloxifene is an oral selective estrogen-receptor modulator (SERM) that decreases the risk of vertebral fractures by 40 to 49%, but it may not reduce the risk of nonvertebral fractures.32 Calcitriol administered by means of a nasal spray is an antiresorptive agent that has limited efficacy in reducing the risk of vertebral fractures and lacks efficacy in preventing hip fracture.33

Oral bisphosphonates must be taken after an overnight fast either once weekly (alendronate at a dose of 70 mg or risedronate at a dose of 35 mg),
once monthly (ibandronate at a dose of 150 mg or risedronate at a dose of 150 mg), or on 2 consecutive days once monthly (risedronate at a dose of 75 mg). The tablets are taken with 6 to 8 oz of tap water. The patient should remain upright for at least 30 minutes after taking the drug to minimize gastroesophageal reflux. To optimize absorption, food, medications, and liquids other than tap or filtered water should be avoided for at least 30 to 45 minutes to allow for dissolution of the tablet and gastric emptying.

Intravenous bisphosphonates include ibandronate (at a dose of 3 mg every 3 months) and zoledronic acid (at a dose of 5 mg every 12 months). They are usually administered in an outpatient facility that has the resources for administering and monitoring intravenous infusions.

Oral and intravenous bisphosphonates are contraindicated in patients who have had a prior allergic reaction to a bisphosphonate or who have an estimated creatinine clearance of 35 ml per minute or less, vitamin D depletion (serum 25-hydroxyvitamin D levels should be more than 30 ng per milliliter before initiating bisphosphonates), osteomalacia (vitamin D depletion or deficiency causing defective mineralization), or hypocalcemia. Oral bisphosphonates are contraindicated in patients who have impaired swallowing or esophageal disorders such as achalasia, esophageal varices, or severe gastroesophageal reflux or who are unable to sit up for at least 30 minutes after taking the medication. There are no known interactions between bisphosphonates and other medications.

After initiating bisphosphonate therapy, I typically reevaluate the patient in 1 month to assess tolerance and thereafter at 3 months, 6 months, and 1 year. At 3 months and 6 months, I obtain measurements of bone-turnover markers, such as osteocalcin or serum C-terminal telopeptide of type 1 collagen (CTX). At 1 year, and every 2 years thereafter, I repeat the assessment of bone mineral density with the use of DXA. An increase in bone mineral density is not required for a therapy to be considered effective, but a substantial decline in bone mineral density requires further evaluation.

Poor adherence to therapy should be suspected if the patient has an otherwise unexplained decline in bone mineral density, a new fracture, continued bone loss, or high rates of bone turnover that persist after 12 months of therapy. When I suspect poor adherence, I ask the patient whether he or she has had any side effects and attempt to document the patient’s use of the drug by measuring markers of bone turnover. Evidence of treatment failure in a patient with good adherence to an oral bisphosphonate regimen requires a change to either intravenous zoledronic acid or another class of medications such as anabolic agents (e.g., teriparatide).

The optimal duration of bisphosphonate therapy remains unresolved. However, on the basis of available data, it seems likely that discontinuing therapy after 5 years, at least for a temporary drug holiday, is not harmful and may be advantageous. Patients with mildly reduced bone mineral density may be the most suitable candidates for a 1-year to 2-year drug holiday, because the risk of fracture will be low if bone loss occurs while the person is not receiving therapy.

Generic alendronate was introduced in 2008 and is less expensive than other agents, with cost ranging from $4 to $40 per month. The cost of risedronate ranges from $60 to $120 per month; generic risedronate will become available in the near future. The cost of oral ibandronate ranges from $90 to $130 per month. One infusion of zoledronic acid is estimated to cost $1,300; intravenous ibandronate costs about $1,300 per year.

### Adverse Effects

An acute-phase reaction characterized by fever, myalgia, bone pain, and weakness occurs in 20% of patients after an initial intravenous infusion of 

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* Additional information regarding secondary causes of osteoporosis can be found in Tannenbaum et al. and Jamal et al.
bisphosphonates and in a very small number of patients during oral therapy. Erosive esophagitis, ulceration, and bleeding have been associated with daily oral alendronate or risedronate therapy but occur rarely with current (nondaily) regimens. Heartburn, chest pain, hoarseness, and vocal-cord irritation may occur with weekly (alendronate or risedronate) or monthly (ibandronate or risedronate) therapy. A relationship between esophageal cancer and oral bisphosphonates, suggested on the basis of a small number of case reports, has not been substantiated.

Transient renal toxic effects can occur after rapid intravenous administration. Slow infusion rates (no less than 15 minutes) and lower doses minimize peak drug serum levels and the risk of renal damage. Bisphosphonates are not recommended when creatinine clearance is less than 35 ml per minute. Dose reductions may be required for patients with stage III chronic kidney disease (as defined by an estimated glomerular filtration rate between 59 and 30 ml per minute per 1.73 m² of body-surface area). Mild transient hypocalcemia is a rare complication of intravenous bisphosphonate therapy that may require an interruption in treatment, but once the serum calcium level has returned to the normal range, therapy can be resumed. Severe hypocalcemia is a contraindication for continued administration.

Osteonecrosis of the jaw is a rare but serious complication of long-term bisphosphonate therapy that may appear either spontaneously or after an oral surgical procedure. Exposed mandibular or maxillary dead bone, nonhealing mucosa, and chronic infection may persist for weeks to years. More than 95% of cases of osteonecrosis of the jaw occur in patients who are receiving zoledronic acid or pamidronate for the treatment of myeloma, breast cancer, or other bone cancers at doses 10 to 12 times as high as those used for the treatment of osteoporosis.

Case reports suggest that atypical femoral fractures (in the subtrochanteric and mid-diaphyseal portions of the femur) may be more common during bisphosphonate therapy. Recent data from a cross-sectional study of femur fractures recorded in the Danish national health registry and a pooled post hoc analysis of the trials that
studied the effects of alendronate and zoledronic acid on the incidence of fractures. They showed no relationship between the use of bisphosphonates and atypical femur fractures. However, these reports are not definitive, and the possibility of a relationship continues to be investigated.

**Areas of Uncertainty**

The optimal duration of bisphosphonate therapy remains uncertain. Recent retrospective studies and case reports suggest that long-term bisphosphonate therapy may result in the suppression of bone turnover and confer a predisposition to increased bone fragility, with an increased risk for atypical femur fractures. Markers of bone turnover underestimate the extent of suppressed bone formation, and their usefulness in monitoring long-term safety may therefore be limited. An accumulation of microcracks in bone-biopsy specimens was found in one study of patients receiving alendronate therapy when the analysis was adjusted for potential confounders such as age and bone mineral density at the femoral neck but not in another study of long-term alendronate therapy (mean, 6.5 years). Prospective studies are needed to estimate the long-term risk of side effects associated with bisphosphonate therapy, including osteonecrosis of the jaw and atypical femur fractures. Until a better estimate of the risk of these complications emerges, one must balance the long-term risk of these uncommon complications against the known efficacy of the agents in reducing rates of common osteoporotic fractures. It is also not known whether these complications can be minimized by periodic rotation of treatment from one class of agents to another.

**Guidelines**

Guidelines for the management of osteoporosis published by the National Osteoporosis Foundation, the American Association of Clinical Endocrinologists, the American College of Physicians, the American College of Obstetricians and Gynecologists, and the North American Menopause Society agree that persons with osteoporosis (bone mineral density T score of less than −2.5) or low bone mass and hip or vertebral fractures should receive treatment. These guidelines also suggest that persons with T scores higher than −1.5 should not receive therapy unless there is clinical evidence of osteoporosis. Thus, controversy remains regarding the indications for treatment among people with mild reductions in bone density. The guidelines include oral bisphosphonates among the first-line therapies for osteoporosis but do not name specific FDA-approved drugs.

**Recommendations**

The patient described in the vignette is at high risk for additional fractures on the basis of her history of vertebral compression fracture and a bone mineral density T score in the osteoporosis range. A drug with efficacy in preventing hip and spinal fractures is required, and I would treat the patient with either alendronate or risedronate for 5 years. After 5 years of treatment, I would decide whether a drug holiday might be appropriate for this patient, taking into consideration the fact that she is at high risk for recurrent fracture. I would suggest a calcium intake of 1200 mg per day from dietary sources, with calcium supplements as a second choice. I would also measure the serum 25-hydroxyvitamin D level and select an appropriate level of vitamin D intake, encourage regular weight-bearing exercise, and emphasize the importance of adherence to procedures for taking the medication. I would use measurements of bone mineral density to monitor her response to therapy 12 months after treatment is initiated and then at 24-month intervals as needed. A decline in bone mass or another low-trauma fracture would require careful review of the treatment plan and possible selection of another agent.

Dr. Favus reports receiving honoraria and consulting fees from CVS Caremark and Amgen. No other potential conflict of interest relevant to this article was reported.

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

**References**

4. Bone health and osteoporosis: a report of the Surgeon General. Rockville,
Ranibizumab Therapy for Neovascular Age-Related Macular Degeneration

James C. Folk, M.D., and Edwin M. Stone, M.D., Ph.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 authors’ clinical recommendations.

An ophthalmologist refers a 66-year-old man for consultation with a retinal specialist. The patient has had blurred and distorted vision in his right eye for the past 2 weeks. Examination reveals drusen beneath the retina in both eyes. His right eye also has a subretinal hemorrhage just temporal to the center of the macula, as well as subretinal fluid (Fig. 1A). A fluorescein angiogram shows subfoveal neovascularization (Fig. 1B). Optical coherence tomography reveals fluid beneath and within the layers of the retina (Fig. 1C). The retinal specialist diagnoses neovascular age-related macular degeneration (AMD) and recommends intraocular injections of ranibizumab.

The Clinical Problem

AMD is the leading cause of blindness in the United States. All patients initially have a form of the disorder called dry AMD, characterized by the development and accumulation of drusen, which are localized deposits of extracellular material that appear as yellow spots in the retina on ophthalmoscopy. As dry AMD progresses, focal areas of atrophy of the retinal pigment epithelium appear. Wet, or neovascular, AMD then develops in some patients with established dry AMD. Wet AMD is characterized by the growth of abnormal vessels beneath the retinal pigment epithelium and between the retinal pigment epithelium and the overlying retina.

The Eye Diseases Prevalence Research Group estimates that in the year 2000, a total of 1.2 million residents of the United States had neovascular AMD, 973,000 had dry AMD with atrophy of the retinal pigment epithelium, and 7.3 million had large drusen (≥125 μm in diameter) and were therefore at increased risk for atrophy or neovascularization. The same group estimates that these numbers will increase by more than 50% by the year 2020 as a result of aging of the population.

Many patients with AMD have moderate vision loss, between 20/50 and 20/100 in the better eye. These patients have quality-of-life measurements that are 32% below normal, similar to those among patients with severe angina or hip fractures. A person with very severe neovascular disease may have 20/800 vision in the better eye and will have a reduction in quality of life of 60%, similar to that of a patient who is bedridden with a catastrophic stroke. AMD is estimated to cost the United States $30 billion a year.

Pathophysiology and Effect of Therapy

Despite decades of intensive investigation, the molecular mechanisms underlying the pathogenesis of AMD are still obscure. It is likely that in most patients, a num-
ber of genetic factors\textsuperscript{3}\textsuperscript{-12} and environmental factors (e.g., smoking)\textsuperscript{13} contribute incrementally to the development of the disease. Genomewide association studies of patients with AMD and control subjects have shown that the largest single genetic factor contributing to AMD is a variant of codon 402 in the gene encoding complement factor H. This observation strongly supports the long-held belief that the immune system is an important contributor to AMD.\textsuperscript{3\textsuperscript{-5,14,15}}

The photoreceptor cells of the retina depend on the underlying retinal pigment epithelium for phagocytosis of their continuously renewed outer segments, as well as for reisomerization of their light-sensitive, vitamin-A–based chromophore\textsuperscript{16} (Fig. 2A). Both the photoreceptors and the retinal pigment epithelium depend on the choriocapillaris for oxygen, nutrients, and removal of metabolic waste products.\textsuperscript{37} In patients with AMD, drusen form between the retinal pigment epithelium and Bruch’s membrane. In some patients with AMD, there is apoptotic atrophy of the retinal pigment epithelium and choriocapillaris in the macula (the central region of the fundus).\textsuperscript{14,18}

Neovascularization occurs in about 10% of patients with AMD for reasons that are still unknown but that may be due in part to injury or degeneration of Bruch’s membrane. This complication is responsible for most (perhaps as much as 90%) of the severe vision loss caused by this disease.\textsuperscript{19} In neovascular AMD, abnormal capillaries grow from the choroid through Bruch’s membrane and into spaces beneath the retinal pigment epithelium and retina (Fig. 2B). As these vessels proliferate, they leak serum or blood, which causes swelling beneath and within the retina and loss of visual acuity. If left unchecked, the vessels eventually cause a subretinal fibrotic scar and permanent loss of vision.\textsuperscript{20,21}

Vascular endothelial growth factor A (VEGF-A) is closely associated with the growth and permeability of neovascular vessels.\textsuperscript{22\textsuperscript{-26}} Ranibizumab is the Fab fragment of a recombinant, humanized, monoclonal antibody that binds to all forms of VEGF-A. The inhibition of VEGF-A reduces the permeability of the neovascular vessels, as well as their further growth.\textsuperscript{27} In tumors, long-term VEGF blockade results in vessel maturation and remodeling, decreased numbers of endothelial cells, increased coverage of the vessel wall by pericytes, and a more stable, nonleaking vessel\textsuperscript{28} (Fig. 2C). When vessel growth and leakage are stopped, the retinal swelling usually diminishes and vision can stabilize or improve. Studies in primate models have shown that when ranibizumab is injected into the eye, effective retinal concentrations are maintained for about 1 month.\textsuperscript{27}
Two main patterns of choroidal neovascularization are seen on fluorescein angiography in patients with AMD. Classic neovascularization fluoresces brightly in the early phases of the angiogram and leaks profusely in the late phases, whereas occult neovascularization fills more slowly and leaks much less. Large, randomized, controlled trials have evaluated the benefit of ranibizumab for the treatment of both forms of neovascularization.

In the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trial (ClinicalTrials.gov number, NCT00056836), investigators compared monthly intraocular injections of ranibizumab with placebo in patients who had AMD with the predominantly occult type of choroidal neovascularization. At 1 year, only 5% of patients who were treated with either 0.3 mg or 0.5 mg of ranibizumab had lost 15 letters of vision (about three lines on a standard eye chart), as compared with 38% of control subjects. Of the patients who were treated with ranibizumab, 34% of those receiving the 0.5-mg dose and 25% of those receiving the 0.3-mg dose gained 15 letters of vision, as compared with only 5% of control subjects. Ranibizumab had a positive treatment effect in all subgroups of patients with neovascular AMD.
In the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study (NCT00061594), investigators compared monthly intraocular injections of ranibizumab with photodynamic therapy in patients who had AMD with the predominantly classic type of neovascularization. Photodynamic therapy involves the intravenous injection of verteporfin, a photosensitizing dye, followed by application of a nonthermal red laser light (at a wavelength of 689 nm) to the area of neovascularization. The red laser light stimulates the dye, which causes the formation of singlet oxygen and secondary damage to the vessels. Only 4% of patients who were treated with 0.5 mg of ranibizumab and 5% of those treated with 0.3 mg lost 15 letters of vision at 1 year, as compared with 36% of patients who were treated with laser-activated verteporfin. Among patients who were treated with ranibizumab, 40% of those receiving the 0.5-mg dose and 36% of those receiving the 0.3-mg dose gained 15 letters of vision, as compared with only 6% in the verteporfin group.

**Clinical Use**

In the absence of anti-VEGF therapy, neovascular AMD usually results in a substantial loss of vision. An alternative treatment is thermal laser photocoagulation, but this therapy damages the overlying and surrounding retina and is associated with a high rate of recurrent neovascularization. At 24 months after laser treatment of neovascularization that extended beneath the center of the macula, only 1% of treated eyes had better than 20/100 vision. Another alternative is photodynamic therapy, but the ANCHOR study showed that treatment with ranibizumab is superior.

Bevacizumab is an agent that is commonly used as an alternative to ranibizumab. Bevacizumab is also a monoclonal antibody that binds to VEGF-A, but the Food and Drug Administration (FDA) has approved it only for the treatment of colon cancer. The similarity between the two molecules has led many clinicians to hypothesize that the two drugs might be equally effective for the treatment of neovascular AMD, although this hypothesis has not been formally confirmed. When bevacizumab is used for the treatment of AMD, a pharmacy can split a vial into small doses that can be administered intraocularly. Generally, the dose that is used is 1.25 mg, which costs about $75, as compared with approximately $2,000 for a dose of ranibizumab. It should be emphasized that this use of bevacizumab for neovascular AMD is considered off-label therapy.

Ranibizumab is injected into the eye in an outpatient clinic (see video, available with the full text of this article at NEJM.org). Hospitalization is not needed. We perform injections in a room specially designed for minor surgery. Informed consent should be obtained before the procedure. We begin the injection procedure by giving anesthetic drops of proparacaine hydrochloride 0.5% and tetracaine hydrochloride 0.5%, followed by an antibiotic drop. Many retinal specialists do not use subconjunctival anesthesia, but for most of our patients, we inject about 0.2 ml of 1% lidocaine without epinephrine beneath the conjunctiva in the superotemporal quadrant, 3 mm posterior to the corneal limbus. After waiting about 4 minutes, we place a lid speculum into the eye to hold the lids open and drop 5% povidone–iodine onto the conjunctiva.

We use calipers to mark the injection site 3.5 mm posterior to the limbus (the outer border of the cornea). We use a 30-gauge needle on a 1-mm tuberculin syringe to inject 0.05 ml (0.5 mg of ranibizumab) into the middle of the vitreous cavity, then place a sterile cotton swab firmly over the injection site as the needle is withdrawn to prevent backflush of fluid through the injection site. We then remove the lid speculum and gently irrigate the eye to remove any residual povidone–iodine.

We give an additional drop of antibiotic and instruct the patient to use the drops twice more that day and then four times per day for the next 3 days. Some retinal specialists no longer use prophylactic antibiotic drops because they believe that the drops do not reduce the risk of infectious endophthalmitis. We tell the patient to call if vision decreases or the eye becomes painful. We give the patient a sheet that contains the instructions for using the antibiotic drops, warnings, and numbers to call if there are problems. The patient makes an appointment to return in 1 month.

Intraocular hemorrhage is rare after injections of ranibizumab. As noted, the needle is small (30 gauge), and the injection site is chosen to avoid major ocular blood vessels. The injection of the
The injection of either anesthetic or ranibizumab can cause mild subconjunctival hemorrhage. The blood is cosmetically unappealing but resolves without sequelae. Many clinicians use topical anesthetics only, but in our experience, most patients who are treated in this manner feel some pain when the needle pierces the wall of the eye.

Any intraocular injection can cause bacterial endophthalmitis, a serious complication that threatens vision. In the MARINA study, the presumed rate of endophthalmitis (presumed because not all eyes showed positive cultures) was 1.0% (infection in 5 of 477 patients); the rate per injection was 0.05% (infection associated with 5 of 10,443 injections).30 Patients in whom endophthalmitis develops have vision loss or an increase in floaters, almost always within the first week after the injection. The eye is red and may be painful. Patients with such symptoms after ranibizumab injection should be seen promptly by their retinal specialist.

In the MARINA and ANCHOR trials, the respective risks of nonocular hemorrhage were 9% and 6% in the treated groups versus 6% and 2% in the comparator groups, which may indicate a systemic anti-VEGF effect.30,32 In the MARINA trial, rates of stroke were 2.5% in the 0.5-mg group and 1.3% in the 0.3-mg group versus 0.8% in the sham group. Rates of myocardial infarction were 1.3% in the 0.5-mg group and 2.5% in the 0.3-mg group versus 1.7% in the sham group.30 Similar effects were seen in the 2-year results from the ANCHOR trial.37 None of these differences were statistically significant.

As noted above, bevacizumab is also an anti-VEGF-A monoclonal antibody. In a meta-analysis of trials of bevacizumab in patients with metastatic cancer, arterial thromboembolic events, including cardiac ischemia and stroke, occurred in 3.3% of patients who had received the drug, as compared with 2.0% who had not.38 The total-body dose of bevacizumab that was used in these trials was more than 1000 times the dose used in the treatment of AMD.

Areas of Uncertainty

A major area of uncertainty is whether bevacizumab is as effective as ranibizumab in the treatment of neovascular AMD. This issue has been evaluated in several small studies, with encouraging results.39-42 However, these findings are provisional. To answer the question definitively, a large, randomized clinical trial, called the Comparison of AMD Treatments Trial (CATT; NCT00593450), is currently being conducted. Results from this trial are expected in the spring of 2011.43 Since the cost of the dose of bevacizumab...
that is commonly used in AMD is so much less than the cost of the standard dose of ranibizumab ($75 vs. $2,000), the majority of our patients choose to be treated with bevacizumab on the basis of currently available data.

Another area of uncertainty is the optimal treatment schedule. Some specialists administer ranibizumab on a fixed monthly schedule, whereas others administer the agent only when fluid is present on optical coherence tomography or when leakage is seen on fluorescein angiography. In CATT, investigators are comparing these two approaches to treatment, as well as comparing ranibizumab with bevacizumab. If the study shows that the difference in outcome between the fixed and as-needed approaches is minimal, patients and physicians may opt for less-frequent injections. All the groups in CATT are being followed monthly, but most patients dislike having to return for a visit every month. An additional trial may be warranted in the future, comparing monthly visits with gradual extension of the follow-up interval for patients whose condition is stable. Some pharmacokinetic data, though not conclusive, support the hypothesis that bevacizumab may have a longer intraocular half-life than ranibizumab.

GUIDELINES

The American Academy of Ophthalmology included ranibizumab in its September 2008 Preferred Practice Pattern Guidelines for Age-Related Macular Degeneration, grading such therapy as level A (most important to the care process) and level I (greatest strength of evidence). The same guidelines also listed bevacizumab as a recommended treatment, grading it level A for importance but only level III (the lowest level) with respect to strength of evidence. The guidelines state that when using bevacizumab, “the ophthalmologist should provide appropriate informed consent with respect to the off-label status.” The guidelines committee of the European Society of Retina Specialists make similar recommendations in a statement published in August 2007.

RECOMMENDATIONS

The patient described in the vignette is an appropriate candidate for either ranibizumab or bevacizumab therapy. We would explain to the patient that only ranibizumab has been approved by the FDA for use in AMD. We would also explain that the efficacy of bevacizumab is thought to be similar to that of ranibizumab, although such efficacy has not been evaluated in definitive trials, and that bevacizumab is substantially less expensive.

Regardless of the patient’s choice of agent, we would carry out the initial injection in our outpatient minor surgery unit, as described in the Clinical Use section. After the first injection of either bevacizumab or ranibizumab, we would ask the patient to return for another injection in 4 weeks. After the second injection, we would ask him to return in 4 weeks if he received ranibizumab and in 6 weeks if he received bevacizumab. We would continue injections at these intervals until the retina was dry. We would then gradually extend the interval between follow-up visits, depending on the examination findings.

In our experience, most treatment failures are due to missed follow-up visits. Patients should be reminded repeatedly to call if their vision worsens. Physicians should have a system in place for calling patients who have been lost to follow-up because such patients have a high risk of recurrent neovascularization with permanent scarring and vision loss. Finally, ophthalmologists should be aware of the patient’s overall medical condition and should communicate clearly with the patient’s other physicians when warranted.

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REFERENCES

4. Hageman GS, Anderson DH, Johnson...


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Palmyra, Syria

Christian Müller, M.D.
Dietary Therapy in Hypertension
Frank M. Sacks, M.D., and Hannia Campos, Ph.D.

From the Department of Nutrition, Harvard School of Public Health (F.M.S., H.C.); and Channing Laboratory and Cardiology Division, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School (F.M.S.) — all in Boston. Address reprint requests to Dr. Sacks at the Department of Nutrition, Harvard School of Public Health, Bldg. 1, 2nd Fl., Boston, MA 02115, or at fsacks@hsph.harvard.edu.


A 57-year-old woman presents to an outpatient clinic for evaluation of hypertension. She has no history or symptoms of cardiovascular disease and reports having gained 15 kg over the past 30 years. Her blood pressure is 155/95 mm Hg, her weight 86 kg, her height 165 cm, her body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) 31, and her waist circumference 98 cm. Her serum triglyceride level is 175 mg per deciliter (2.0 mmol per liter), high-density lipoprotein cholesterol 42 mg per deciliter (1.1 mmol per liter), low-density lipoprotein cholesterol 110 mg per deciliter (2.8 mmol per liter), and glucose 85 mg per deciliter (4.7 mmol per liter). Her clinical profile is thus consistent with the metabolic syndrome. She is a nonsmoker, is sedentary, and eats a diet that is high in white bread, processed meats, and snacks and drinks containing sugars and sodium and is low in fruits and vegetables. She is interested in adopting a healthier lifestyle.

THE CLINICAL PROBLEM

Hypertension is defined as a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher. However, morbidity increases among persons whose blood pressure is above 115/75 mm Hg. High blood pressure is associated with an increased risk of stroke, myocardial infarction, heart failure, renal failure, and cognitive impairment. Systolic blood pressure above 115 mm Hg is the most important determinant of the risk of death worldwide, being responsible for 7.6 million cardiovascular deaths annually.

From 1960 through 1991, blood pressure decreased in the United States, and after the first 10 years of this interval, the rate of cardiovascular deaths decreased. Effective hypertension screening and treatment were probably the reason for these beneficial trends. However, from 1990 through 2002, blood pressure increased, and intake of fruits and vegetables and adherence to healthful dietary patterns declined during this period and the prevalence of abdominal obesity increased; both trends have contributed to hypertension.

Among most populations in industrialized countries, the prevalence of hypertension increases dramatically with age; in the United States it rises from about 10% in persons 30 years of age to 50% in those 60 years of age. However, some persons, including strict vegetarians, populations whose diet consists mostly of vegetable products, and those whose sodium intake is low, have virtually no increase in hypertension with age.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Essential hypertension is the name for hypertension that cannot be attributed to a specific renal or adrenal disease, such as chronic renal failure or an adrenal tumor;
the vast majority of patients with hypertension have essential hypertension. The pathophysiology of essential hypertension is complex, with much remaining to be discovered (Fig. 1, and Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The three cornerstones of dietary treatment of hypertension — a healthful dietary pattern, reduced sodium intake, and reduced body fat — influence the pathophysiology of hypertension at many of its points of control.

High sodium intake is strongly correlated with the development of hypertension.\textsuperscript{16-18} Sodium intake initiates an autoregulatory sequence that leads to increased intravascular fluid volume and cardiac output, peripheral resistance, and blood pressure. The elevation in blood pressure results in a phenomenon called pressure natriuresis, in which increased renal perfusion pressure leads to increased excretion of fluid and sodium. In essential hypertension, however, sodium excretion is impaired. It is hypothesized that in most cases essential hypertension is a genetic disorder involving many individual genes, each of which influences the body’s handling of sodium to varying degrees\textsuperscript{19} and becomes expressed in the context of an unhealthful dietary environment, particularly one characterized by excessive intake of salt.

Numerous other factors contribute to the pathophysiology of hypertension. Especially in the elderly, large conduit arteries such as the aorta and carotid arteries become stiff and less compliant, increasing systolic blood pressure.\textsuperscript{20} Proliferation of smooth-muscle cells and endothelial dysfunction occur in resistance vessels, including small arteries and arterioles, causing vasoconstriction and increasing peripheral vascular resistance.\textsuperscript{21-22} Although the systemic renin–angiotensin–aldosterone axis is often suppressed in the presence of elevated blood pressure, angiotensin II activity is increased locally in various tissues, including the kidneys, vascular endothelium, and adrenal glands.\textsuperscript{23,24} Increased activity in the sympathetic nervous system may also be a factor.\textsuperscript{25-30} Both aging\textsuperscript{19,31-33} and obesity\textsuperscript{25-30} contribute to the pathogenesis of hypertension through several mechanisms (Fig. 1, and Section 1 in the Supplementary Appendix).

Two effective interventions for lowering blood pressure in patients with hypertension are reducing sodium intake and reducing weight. Reductions in dietary salt lessen the amount of sodium the kidney has to excrete to restore normal blood volume. Compliance in the aorta and carotid artery in older patients with hypertension is improved when sodium intake is reduced.\textsuperscript{34} Reduction in sodium intake also improves arterial vasodilatation.\textsuperscript{21,22} Weight loss moderates activation of the renin–angiotensin–aldosterone axis\textsuperscript{35-36} and the sympathetic nervous system\textsuperscript{37,38} and diminishes sodium retention.\textsuperscript{39} Decreases in abdominal visceral fat also improve the functioning of both conduit and resistance vessels.\textsuperscript{40}

In addition to sodium restriction and weight loss, several other dietary modifications that are collectively termed “a healthful dietary pattern” have been shown to reduce blood pressure. Although the mechanisms of these diets have not been fully clarified, adherence to these diets has been found to reset the pressure–natriuresis curve so that a lower pressure suffices to excrete sodium and reduce blood volume,\textsuperscript{41} reduce aortic stiffness,\textsuperscript{42} and improve vasodilatation in small resistance vessels.\textsuperscript{43,44} As compared with the typical U.S. diet, the kinds of dietary patterns that have been proved to lower blood pressure emphasize fruits, vegetables, and low-fat dairy products; include whole grains, poultry, fish, and nuts; make use of unsaturated vegetable oils; and contain smaller amounts of red meat, sweets, and sugar-containing beverages.\textsuperscript{45,46} Clinical trials of such diets have not usually emphasized the identification of specific nutrients or single foods that lower blood pressure but rather have used epidemiologic data to define dietary patterns, such as Mediterranean-style diets\textsuperscript{47,48} and vegetarian diets.\textsuperscript{11,12} (see Section 2 in the Supplementary Appendix for a discussion of the effects of specific foods and nutrients on blood pressure).

**Clinical Evidence**

The most carefully studied and established healthful dietary patterns are the Dietary Approaches to Stop Hypertension (DASH) diet,\textsuperscript{45,49} variants of that diet,\textsuperscript{46,50} and variations of the Mediterranean diet.\textsuperscript{51,52} In the original DASH trial,\textsuperscript{49} 459 adults whose systolic blood pressure was less than 160 mm Hg and whose diastolic blood pressure was 80 to 95 mm Hg, 133 of whom had hypertension, were randomly assigned to a control diet typical of the average U.S. diet, a diet rich in fruits and vegetables, or a combination diet rich in fruits, vegetables, and low-fat dairy products and relatively low in saturated and total fat. Sodium intake and body weight were maintained at
Figure 1. Mechanisms Linked to Increases in Blood Pressure and the Therapeutic Effects of Healthful Dietary Patterns, Sodium Reduction, and Weight Loss.
constant levels. After 8 weeks, among the participants with hypertension, the diet rich in fruits and vegetables reduced systolic and diastolic blood pressure by 7.2 and 2.8 mm Hg more, respectively, than the control diet (P<0.001 and P=0.01, respectively). The combination diet resulted in greater reductions (11.4 and 5.5 mm Hg, respectively, as compared with the control diet; P<0.001 for each). The effects were less pronounced among participants who did not have hypertension at baseline.

In a subsequent trial, the effect of various levels of sodium intake was studied in the context of the DASH diet in 412 participants with blood pressure levels at enrollment similar to those of participants in the original DASH trial. Patients were randomly assigned to either the DASH “combination” diet (now commonly termed the DASH diet) or a control diet. Participants in each group were then given a diet with high, intermediate, and low levels of sodium (3.5, 2.3, and 1.2 g per day, respectively) for 30 days each in random order. Body weight was held constant by adjusting total caloric intake. Reducing sodium intake resulted in a significant incremental reduction in blood pressure levels at each level of dietary sodium. Numbers shown represent the mean changes with 95% confidence intervals. Adapted from Bray et al.14

In a secondary analysis from the sodium trial, the blood-pressure–lowering effects of the DASH diet and low sodium were each accentuated as age increased (Fig. 3). Systolic blood pressure was 12 mm Hg higher among participants between 55 and 76 years of age than among those between 21 and 41 years of age when they were given a typical U.S. diet that was high in sodium. This difference in systolic blood pressure is similar to that in the U.S. population when the same age groups are compared. In marked contrast, systolic blood pressure was the same among older and younger participants when they were given the DASH diet with low sodium content. This finding suggests that the typical rise in blood pressure that occurs with age during adult life may be prevented or reversed if the low-sodium DASH diet is followed.

Women, blacks, and those with the metabolic syndrome have a mildly enhanced reduction in blood pressure in response to a low-sodium diet. It is not possible to identify individual patients for whom sodium reduction is especially effective (see Section 3 in the Supplementary Appendix).

Two reduced-carbohydrate versions of the DASH diet were studied in 164 adults enrolled in the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart). One diet higher in unsaturated fat and another higher in protein were compared with a diet similar to the standard DASH diet but slightly higher in carbohydrates. As compared with the high-carbohydrate diet, the high-protein diet reduced mean systolic blood pressure in participants with hypertension by 3.5 mm Hg and mean diastolic blood pressure by 2.4 mm Hg (P=0.006 and P=0.008, respectively). The comparable effects of the diet high in unsaturated fat were 2.9 and 1.9 mm Hg, respectively (P=0.02 for both). As with the DASH diet itself, these effects were less pronounced in participants who did not have hypertension at baseline.

The traditional Mediterranean diet has many similarities to DASH-type diets, especially

![Figure 2. Sodium Reduction, the DASH Diet, and Changes in Systolic Blood Pressure.](image-url)
to the diet from the OmniHeart study that was higher in unsaturated fat. In controlled trials involving patients with the metabolic syndrome or type 2 diabetes, a reduced-carbohydrate Mediterranean diet lowered blood pressure and improved serum lipid levels more than a low-fat diet. In these trials, unlike the DASH trials, weight was not held constant through caloric adjustment; in both cases, patients assigned to the Mediterranean diet lost more weight than those assigned to the low-fat diet.

Epidemiologic studies generally support evidence from clinical trials on the effects of dietary management, as do community-based and clinic-based intervention programs (see Sections 4 and 5 in the Supplementary Appendix).

The effect of adding weight loss to the DASH diet was evaluated in 144 adults in the Exercise and Nutrition Interventions for Cardiovascular Health (ENCORE) study. Participants were randomly assigned to a control diet, to the DASH diet alone, or to a reduced-calorie modification of the DASH diet. At 4 months, blood pressure was reduced by 3.4/3.8 mm Hg in the control group, by 11.2/7.5 mm Hg in the group given the DASH diet alone (P<0.001 for both systolic and diastolic pressures as compared with the control diet), and 16.1/9.9 mm Hg with the DASH diet plus weight management (P = 0.02 for systolic blood pressure and P = 0.05 for diastolic blood pressure as compared with the DASH diet alone).

**CLINICAL USE**

Dietary management is appropriate for all patients with hypertension. In addition, patients with prehypertension (systolic blood pressure between 120 and 139 mm Hg or diastolic blood pressure between 80 and 89 mm Hg) should adopt the same dietary changes, given the benefit of dietary therapy at these blood-pressure levels.

Drug therapy plays an essential role in treating hypertension. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure emphasizes that in patients for whom lifestyle modification (including dietary therapy, physical activity, and moderation of alcohol consumption) does not reduce blood pressure below 140/90 mm Hg (or 130/80 mm Hg for patients with diabetes or chronic renal disease), drug therapy should be implemented and modified over time given a patient’s response. However, medication should not supplant dietary management; rather, the two forms of treatment should be considered complementary. The DASH diet is effective in combination with angiotensin-receptor blockers. Sodium reduction is highly effective in older patients with hypertension who are taking antihypertensive medicines and in those with resistant hypertension taking several antihypertensive agents.

We guide patients in adopting a healthful diet with the use of a chart or table such as that shown in Table 1. In simple terms, we encourage patients to eat poultry, fish, nuts, and legumes instead of red meat; low-fat and nonfat dairy products instead of full-fat dairy products; vegetables and fruit instead of snacks and desserts high in sugars; breads and pastas made from whole grain instead of white flour; fruit itself...
rather than fruit juice; and polyunsaturated and monounsaturated cooking oils such as olive, canola, soybean, peanut, corn, sunflower, or safflower rather than butter, coconut oil, or palm-kernel oil. Table 1 provides information about the number of servings and portion sizes for each type of food that should be consumed in 1 week.

Adopting a healthful dietary approach means making the correct choices at the market so that the most healthful foods will be available at home. The recommendations in Table 1 include a food-shopping guide. In the United States, it is common to place healthful foods at the periphery of the market; most weekly shopping should be concentrated there. Use of canned and processed foods should be limited, unless their salt content has been reduced or virtually eliminated. For convenience, low-sodium, frozen, or canned vegetables can be substituted for fresh ones. Sections of the market that contain sweetened beverages, candies, and cookies should be avoided entirely.

Sodium restriction is central to the dietary management of hypertension. Patients should become familiar with reading the food labels that specify the sodium content of packaged and processed foods. Processed foods are often high in sodium. A low sodium diet is sometimes less palatable for patients who are accustomed to a high-sodium diet; however, tastes adapt quickly, and studies have shown that low-sodium diets can be as acceptable to patients as higher-sodium diets. Herbs, spices, and citrus fruit (juice or peel) and other acidic ingredients such as vinegar can be added to dishes to compensate for low sodium content and may even be preferred over foods with higher amounts of sodium.

Patients should not skip meals, should consume one third of their daily food intake at breakfast, and should limit eating in restaurants to no more than once weekly. Eating in many restaurants subverts the goal of a low-sodium diet, since one serving of some soups, sandwiches, fried chicken, or pizza can far exceed the total recommended daily amount of sodium. The health care reform law includes a requirement that all chain restaurants with more than 20 locations provide information for consumers regarding the amount of sodium and other dietary components in menu items.

Compliance with dietary therapy is better, and success rates in achieving blood-pressure control are higher, when accompanied by active guidance or counseling of the patient by clinicians or ancillary medical personnel with expertise in dietary management. We always recommend that patients record their dietary intake for 1 or 2 weeks and discuss this record with a dietician, who will provide specific meal plans. This is especially important when weight loss is needed. Follow-up with a dietician is essential, whether arranged in individual or group appointments. In addition, numerous Web sites and books can provide patients with further information and guidance on healthful diets.

The costs associated with dietary treatment of hypertension are relatively modest. In one study in the Boston area conducted in 2006, the cost of the DASH meal plan was $31 per week in areas with low socioeconomic status and $40 per week in areas with high socioeconomic status; perceived affordability was similar for patients interviewed in clinics in both areas. An initial consultation with a dietician costs approximately $150, and follow-up consultations about $100. Coverage of this service by health insurance or employer programs varies.

**ADVERSE EFFECTS**

Adverse events generally occurred less frequently in persons following the DASH diet and its variants or Mediterranean diets (see Section 6 in the Supplementary Appendix).

**AREAS OF UNCERTAINTY**

One crucial frontier of dietary research is that of devising and evaluating effective behavioral and community-based interventions. In the DASH trials, dietary modifications were studied over a short time span, and participants were carefully monitored for compliance. Compliance is an essential element in the long-term dietary treatment therapy of hypertension, and we need to learn what components of behavioral interventions lead to adherence. In addition, no large, long-term, clinical-outcomes trial of these diets has been performed, although one long-term observational study of an earlier randomized trial and one relatively short-term randomized trial reported a decrease in the incidence of cardiovascular events with sodium reduction (see Section 7 in the Supplementary Appendix). However, we believe that it is not necessary to conduct a large-scale, randomized trial to address this question in...
Table 1. Recommended Weekly and Occasional Food Purchases for One Person Following a Healthful Diet Containing 2100 kcal and 1500 mg of Sodium per Day.6

<table>
<thead>
<tr>
<th>Type of Food</th>
<th>Servings per Wk</th>
<th>Serving Size</th>
<th>Total Amount Purchased per Wk</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly purchases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Market periphery</td>
<td></td>
<td></td>
<td></td>
<td>Do most weekly shopping in this section</td>
</tr>
<tr>
<td><strong>Vegetables†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salad greens</td>
<td>4</td>
<td>1 cup</td>
<td>1–2 bags or heads</td>
<td>Lettuce, mixed spring greens, spinach bunch (about 1 lb)</td>
</tr>
<tr>
<td>Other greens</td>
<td>4</td>
<td>1/2 cup</td>
<td>1–2 bunches</td>
<td>Kale, collard greens, mustard greens (about 1 lb)</td>
</tr>
<tr>
<td>Cruciferous</td>
<td>3</td>
<td>1/2 cup</td>
<td>1–2 heads</td>
<td>Broccoli, cabbage, cauliflower (about 1 lb)</td>
</tr>
<tr>
<td>Colorful‡</td>
<td>15</td>
<td>1/2 cup</td>
<td>8–12 individual items</td>
<td>Tomatoes, carrots, squash, peppers, sweet potatoes, corn, eggplant, avocados (about 3 lb)</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1/2 cup</td>
<td>1/2 lb</td>
<td>Celery, green beans, peas, lima beans, sprouts</td>
</tr>
<tr>
<td><strong>Fruits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh</td>
<td>20</td>
<td>1 medium or 1/2 cup chopped</td>
<td>15–20 individual items</td>
<td>Apples, pears, grapes, bananas, peaches, plums, oranges, tangerines, berries, cantaloupe, pineapple</td>
</tr>
<tr>
<td>Dried</td>
<td>8</td>
<td>1/4 cup</td>
<td>1 bag</td>
<td>Raisins, apricots, prunes, cherries (about 1/2 lb)</td>
</tr>
<tr>
<td>Juice</td>
<td>4</td>
<td>1 glass (8 oz)</td>
<td>1 qt</td>
<td>Orange, grapefruit, unsweetened carrot</td>
</tr>
<tr>
<td><strong>Herbs, alliums, and other seasonings</strong></td>
<td>Use freely</td>
<td></td>
<td></td>
<td>Thyme, ginger, garlic, onion, bay leaf, lemon juice</td>
</tr>
<tr>
<td><strong>Meat, poultry, and fish</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish and shellfish</td>
<td>2</td>
<td>6–8 oz</td>
<td>1 lb</td>
<td>Cod, sea bass, halibut; fresh or canned salmon, tuna, or sardines; mollusks, shrimp, crab meat</td>
</tr>
<tr>
<td>Poultry</td>
<td>2</td>
<td>6–8 oz</td>
<td>1 lb</td>
<td>Turkey, chicken, low-sodium cold cuts</td>
</tr>
<tr>
<td>Red meats</td>
<td>1</td>
<td>2–4 oz</td>
<td>1/4 lb</td>
<td>Beef, pork, lamb, low-sodium cold cuts</td>
</tr>
<tr>
<td><strong>Dairy products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>10</td>
<td>1 glass (8 oz)</td>
<td>1/2 gallon</td>
<td>Choose low-fat or nonfat products</td>
</tr>
<tr>
<td>Yogurt</td>
<td>3</td>
<td>1 cup</td>
<td>1 container</td>
<td>Choose low-fat or nonfat products (about 32 oz)</td>
</tr>
<tr>
<td>Cheese</td>
<td>4</td>
<td>1 slice</td>
<td>1/4 lb</td>
<td>Soft or hard</td>
</tr>
</tbody>
</table>
**Processed-food aisles**§

<table>
<thead>
<tr>
<th>Item</th>
<th>Amount</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuts (whole or butter)</td>
<td>10</td>
<td>1 oz</td>
</tr>
<tr>
<td>Legumes</td>
<td>3</td>
<td>1 cup</td>
</tr>
<tr>
<td>Olives</td>
<td>2</td>
<td>1/2 cup</td>
</tr>
<tr>
<td>Spices</td>
<td>Use freely</td>
<td></td>
</tr>
<tr>
<td>Baked goods</td>
<td>20</td>
<td>1 slice</td>
</tr>
<tr>
<td>Tomato products</td>
<td>4</td>
<td>2/3 cup</td>
</tr>
<tr>
<td>Chips and other snacks</td>
<td>3</td>
<td>1/2 cup</td>
</tr>
<tr>
<td>Chocolate or sweets</td>
<td>1</td>
<td>1 oz</td>
</tr>
</tbody>
</table>

*Choose only low-sodium products¶*

- Walnuts, almonds, peanuts (about 1/2 lb)
- Chickpeas, lentils, black beans (about 1 lb)
- Black, green, stuffed (about 1/4 lb)
- Bread, rolls, pancakes, waffles (about 1 1/2 lb); choose whole-grain products

**Less frequent purchases¶**

<table>
<thead>
<tr>
<th>Item</th>
<th>Amount</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast cereals</td>
<td>2</td>
<td>1/2 cup</td>
</tr>
<tr>
<td>Pasta, rice, and grains</td>
<td>3</td>
<td>1 cup (cooked)</td>
</tr>
<tr>
<td>Cooking oils</td>
<td>12</td>
<td>1 tbs</td>
</tr>
<tr>
<td>Table fats</td>
<td>16</td>
<td>1 tsp</td>
</tr>
<tr>
<td>Salad dressings and mayonnaise</td>
<td>21</td>
<td>1 tsp</td>
</tr>
<tr>
<td>Sugars</td>
<td>24</td>
<td>1 tsp</td>
</tr>
<tr>
<td>Desserts</td>
<td>1</td>
<td>1/2 cup</td>
</tr>
<tr>
<td>Eggs</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Salt</td>
<td>7</td>
<td>1/3 tsp</td>
</tr>
</tbody>
</table>

*Patients should observe the following general recommendations: don’t skip meals, and consume one third of daily calorie intake at breakfast; limit eating out to once weekly and choose meals with a low salt content — just one slice of pizza, a turkey sandwich, or a pasta dish can easily contain 2000 mg of sodium. Examples of conversion from standard to metric measures: 1 oz equals 28 g; 1 teaspoon, 5 g; 1 cup leafy greens, about 75 g.*

† Unsalted frozen or canned vegetables can be substituted for fresh vegetables.

‡ Choose at least four different types of vegetables from this category.

§ Also visit the processed-food aisle as needed for other food items in the less frequent purchases category.

¶ Look for lower-sodium, unsalted, or reduced-salt items. Compare brands and choose those with lower sodium content. The total amount of sodium consumed in a week from processed foods or eating out should not exceed 2000 mg.

∥ Weekly allowances are provided for items that are generally purchased less than once a week. The amounts for weekly intake should be set aside in individual containers to make it easier to keep track of how much is consumed.
view of the known benefits of healthful diets with regard to blood pressure and other risk factors.

GUIDELINES

We recommend the American Heart Association guidelines for cardiovascular health and the dietary management of hypertension. These guidelines endorse foods and approaches to diet similar to those included in the DASH diet and cite intake of 65 mmol, or 1.5 g, of sodium per day as optimal. In addition, a target BMI of less than 25 is recommended. Finally, the guidelines recommend no more than two alcoholic drinks per day for men and one for women and people of lighter weight. (One drink is equivalent to 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor, each of which represents approximately 14 g of ethyl alcohol.)

CONCLUSIONS AND RECOMMENDATIONS

The diet of the patient described in our vignette is very different from the healthful diets recommended for the management of hypertension, and it is therefore reasonable to assume that dietary change could normalize her blood pressure. The patient should be given written instructions on how to adopt a healthful diet such as the DASH diet, a reduced-carbohydrate version of the DASH diet, or a Mediterranean-style diet. The instructions should include ways to substantially reduce sodium intake. We also recommend a small consistent daily reduction in caloric intake of 200 to 300 kcal per day, coupled with an increase in physical activity. Her physician should schedule a consultation with a dietician, including a regular schedule of follow-up visits. The patient should monitor her blood pressure at home, with an automated machine, at least once a month, preferably more frequently. A trial of intensive dietary treatment is warranted for 6 months to try to achieve the targeted goal for blood pressure (systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg) before medication is introduced.

REFERENCES


82. Your guide to lowering your blood pressure with DASH. Bethesda, MD: National Heart, Lung, and Blood Institute, 2006.


Mitral-Valve Repair for Mitral-Valve Prolapse

Subodh Verma, M.D., Ph.D., and Thierry G. Mesana, M.D., Ph.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 authors’ clinical recommendations.

A 55-year-old man with a holosystolic murmur of increasing intensity has been seen regularly by his family physician for the past 3 years. He is referred to a cardiologist. The patient reports no shortness of breath, chest pain, or palpitations. An electrocardiogram shows normal sinus rhythm. A transthoracic echocardiogram reveals severe, anteriorly directed mitral regurgitation with isolated prolapse of the middle scallop of the posterior leaflet. Flow reversal is detected in the pulmonary veins. The calculated regurgitant volume is 75 ml, the regurgitant fraction 63%, and the effective regurgitant orifice 53 mm², features consistent with severe mitral regurgitation. The transthoracic echocardiogram also shows mildly depressed left ventricular function (ejection fraction, 58%), slightly elevated left ventricular dimensions (end-systolic dimension, 42 mm), and normal right ventricular systolic pressure. The patient is referred to a cardiac surgeon for consideration of mitral-valve repair.

The Clinical Problem

Mitral-valve prolapse is defined as the displacement of some portion of one or both leaflets of the mitral valve into the left atrium during systole. In developed countries, it is the most common cause of chronic mitral regurgitation; in a study of the Framingham Offspring Study cohort, the prevalence of mitral-valve prolapse was 2.5%. More than 150 million people worldwide may be affected. The disorder has both genetic and acquired forms, and several chromosomal loci for autosomal dominant mitral-valve prolapse have been identified. Although mitral-valve prolapse is more common in women, more men are referred for surgery; whether this reflects a difference between the sexes in the morphologic features or natural history of the disorder or referral bias is unclear.

The natural history of mitral-valve prolapse is heterogeneous and is largely determined by the severity of mitral regurgitation. Although a majority of patients remain asymptomatic and may have a near-normal life expectancy, approximately 5 to 10% have progression to severe mitral regurgitation. Left untreated, mitral-valve prolapse with severe mitral regurgitation results in limiting symptoms, left ventricular dysfunction, heart failure, pulmonary hypertension, and atrial fibrillation. Spontaneous rupture of mitral chordae may occur, and endocarditis and stroke are serious complications. The mortality rate of persons who have mitral-valve prolapse with severe mitral regurgitation is approximately 6 to 7% per year.

Pathophysiology and the Effect of Therapy

The mitral valve and subvalvular apparatus include the annulus, valve leaflets, chordae tendineae, papillary muscles, and left ventricular wall. The valve has anterior and posterior leaflets, and each leaflet typically consists of three discrete segments or scallops. These are designated P1, P2, and P3 in the posterior mitral-valve leaflet.
The mitral valve has anterior and posterior leaflets, which are separated by the anterior commissure (AC) and the posterior commissure (PC) (Panel A). The leaflets are inserted on the circumference of the mitral annulus, which is in continuity with the aortic annulus and the left and right fibrous trigones. The circumflex coronary artery, coronary sinus, aortic valve, and bundle of His are all close to the mitral valve. Panel B shows the mitral-valve leaflets, each of which usually consists of three discrete segments or scallops. These are designated A1, A2, and A3 for the anterior leaflet and P1, P2, and P3 for the posterior leaflet. The valve leaflets each receive chordae tendineae from the anterolateral and posteromedial papillary muscles (Panel C). Primary chordae are attached to the free edge of the valve leaflet, and secondary chordae are attached to the ventricular surface of the leaflet.

and A1, A2, and A3 in the anterior leaflet (Fig. 1). The valve leaflets receive chordae tendineae from the anterolateral and posteromedial papillary muscles. Competence of the mitral valve relies on coordinated interaction of the valve and subvalvular apparatus. During systole, the papillary mus-
cles contract, increasing tension on the chordae tendineae and preventing the valve leaflets from evertting into the left atrium.

Mitral-valve prolapse is characterized predominantly by myxomatous degeneration. In younger patients, the disease is often manifested by excess leaflet tissue and is known as Barlow’s syndrome, the most extreme form of myxomatous degeneration. On the other hand, in older patients, the prolapsing mitral valve tends not to have excess leaflet tissue, an entity known as fibroelastic deficiency. Both conditions can lead to leaflet leaflet tissue, an entity known as fibroelastic prolapsing mitral valve tends not to have excess leaflet tissue and is known as Barlow’s syndrome. These anatomic abnormalities result in the mitral orifice not closing completely during systole, causing regurgitation. Annular dilatation may also develop over time, leading to further progression of mitral regurgitation.

Patients with mild-to-moderate mitral regurgitation from mitral-valve prolapse may remain asymptomatic and without clinical deterioration for many years. However, increasing severity of mitral regurgitation, even among asymptomatic patients, imposes a volume load on the left ventricle, which, if sustained over time, results in ventricular dilatation, hypertrophy, neurohumoral activation, and heart failure. In addition, elevation in the mean left atrial pressure leads to left atrial enlargement, atrial fibrillation, pulmonary congestion, and pulmonary hypertension.

The goal of surgical correction for mitral-valve prolapse is to restore a competent mitral valve. There are two options for surgical correction of severe mitral regurgitation due to mitral-valve prolapse: valve replacement or valve repair.

Mitral-valve replacement can be performed with the use of either a mechanical or a biologic prosthesis. However, there are several drawbacks to mitral-valve replacement. These include the need for lifelong anticoagulation therapy and the risk of thromboembolism with the use of mechanical valves; the risk of prosthetic-valve deterioration and failure with the use of bioprosthetic valves; and the risk of prosthetic-valve endocarditis. In addition, if the chordae tendineae are severed during surgery, the ventricular wall is no longer anchored to the valve apparatus, and the tethering effect of the chordae is lost. As a result, left ventricular wall stress increases and left ventricular function deteriorates. The goals of mitral-valve repair are to obtain a proper line of coaptation on both leaflets, to correct annular dilatation, and to preserve (or repair, if necessary) the subvalvular apparatus.

**Clinical Evidence**

We are unaware of any randomized trials that have compared medical management to surgery for severe mitral regurgitation due to mitral-valve prolapse. However, evidence from observational series strongly suggests that surgical intervention is beneficial. One study evaluated the effect of early surgery on long-term outcomes in 221 patients who had mitral regurgitation with flail leaflets. The 63 patients undergoing surgery within 1 month after diagnosis had a significantly better 10-year survival rate than those whose mitral regurgitation was managed conservatively (79% vs. 65%; adjusted risk ratio, 0.30; 95% confidence interval [CI], 0.12 to 0.71; P=0.008). In another report, 394 patients with mitral regurgitation and flail leaflets were studied. During a median follow-up period of 3.9 years, the linearized mortality rate associated with nonsurgical management was 2.6% per year. Mitral-valve surgery was performed in 315 patients (repair in 250, replacement in 65). Surgical intervention was independently associated with a reduced risk of death (adjusted hazard ratio for death, 0.42; 95% CI, 0.21 to 0.84; P = 0.01).

To our knowledge, there are also no randomized trials comparing mitral-valve repair with replacement. Again, however, data from observational studies suggest a benefit of mitral repair. A meta-analysis of 29 studies compared mitral-valve repair with replacement for various conditions, including myxomatous degeneration. Mitral-valve replacement was associated with lower survival than was repair (hazard ratio for death, 1.58; 95% CI, 1.41 to 1.78).

In a study from Finland, mitral-valve repair was compared with replacement in 184 consecutive patients who were followed for a mean of 7.3 years. There was a significant survival benefit for the patients who underwent mitral-valve repair as compared with those who underwent replacement (5-year survival, 81.2% vs. 73.5%), which persisted after adjustment for baseline propensity score (P=0.02). In contrast, in a report from the Cleveland Clinic, 3286 patients who underwent an isolated primary operation for degenerative mitral-valve disease (mitral repair, 93%; mitral replacement, 7%) between 1985 and 2005 were studied. Propensity scoring was...
used to select 195 matched pairs for analysis. Among the propensity-matched patients, there was no significant difference in survival at 5, 10, or 15 years.

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**Clinical Use**

Patients with mitral-valve prolapse should have a careful assessment of symptoms and should undergo electrocardiography (primarily to evaluate cardiac rhythm) and transthoracic echocardiography to assess the mechanism and severity of mitral regurgitation, as well as left ventricular size and function. A semiquantitative scale is often used to grade mitral regurgitation: 1+ (trace), 2+ (mild), 3+ (moderate), and 4+ (severe). However, quantitative Doppler assessments are recommended to define severe mitral regurgitation more precisely; these variables include a regurgitant volume of at least 60 ml, a regurgitant fraction of at least 50%, and an effective regurgitant orifice of at least 40 mm².²⁷

Patients who have severe mitral regurgitation with symptoms or with left ventricular dysfunction (ejection fraction, <60%), dilatation (left ventricular end-systolic dimension, >40 mm), or both should be offered surgery.²⁸,²⁹ Likewise, asymptomatic patients without left ventricular dysfunction or dilatation but with atrial fibrillation or pulmonary hypertension should be considered for surgery. Asymptomatic persons with mild-to-moderate mitral regurgitation and no evidence of left ventricular dysfunction or dilatation should be observed until the development of either symptoms or severe mitral regurgitation.

Before the advent of mitral-valve repair, valve replacement was the preferred procedure for severe mitral regurgitation. Valve replacement may still be preferred in certain situations, such as in patients with advanced age, infective endocarditis, a requirement for a combined or complex surgical procedure, or extensive calcifications of the leaflets or annulus. In such cases, chordal-sparing valve replacement for mitral regurgitation may be a suitable alternative to repair.

Individual and institutional experience is crucial in determining the likelihood of success of a repair procedure. High-volume centers have the lowest mortality rates and the highest proportion of patients undergoing mitral-valve repair rather than replacement.³⁰ In counseling the patient, the surgeon should precisely evaluate the likelihood of successful repair in light of his or her own experience and may recommend a second opinion. If there is a possibility that intraoperative conversion to mitral replacement may be necessary, the decision between a mechanical valve and a bioprosthesis should be discussed with the patient before the operation.

Mitral-valve surgery is not recommended in patients with clinically significant coexisting conditions, such as advanced respiratory, hepatic, or renal dysfunction, or those with marked extracardiac arteriopathy or recent cerebrovascular events. Depressed left ventricular function is an independent predictor of poor outcomes but is not a contraindication to mitral-valve repair.³¹ In patients with coexisting coronary artery disease, mitral-valve repair combined with coronary-artery bypass surgery should be the procedure of choice.³² Two validated scoring systems for determining risk during cardiac surgery are commonly used to determine perioperative risk:³³,³⁴

We routinely perform intraoperative transesophageal echocardiography during all mitral-valve repair procedures.²⁸,²⁹ Transesophageal echocardiography provides precise anatomic and functional information that is helpful in planning the operation, including the extent of leaflet deformity, the mechanism and severity of mitral regurgitation, the condition of the subvalvular apparatus, the diameter of the mitral annulus, left atrial dimensions, and ventricular function.³⁵

Successful mitral-valve repair encompasses four general principles.³⁶ First, repair must restore an adequate surface of coaptation of both leaflets in systole.³⁶,³⁷ Second, full leaflet motion should be restored or preserved. Third, to prevent progressive dilatation, an annuloplasty ring or band should be used to reinforce the repair by stabilizing the annulus. Mitral-valve repair without annuloplasty reinforcement is not recommended. Last, the surgeon should ensure that no more than trace-to-mild mitral regurgitation is present at the completion of the repair.

In patients with isolated prolapse of the posterior middle scallop (P2), which is encountered in the majority of patients with degenerative mitral regurgitation, repair usually involves limited resection of this scallop, including the removal of the minimum number possible of adjacent chordae and supporting apparatus. The remaining segments of the posterior leaflet, namely P1 and P3, are then brought together (Fig. 2). If excessive posterior-leaflet tissue is present, the
Figure 2. Mitral-Valve Prolapse.

The most common leaflet abnormality seen in mitral-valve prolapse is isolated prolapse of the posterior middle scallop (P2) (Panel A1). In patients with isolated prolapse of P2, repair usually involves limited resection of this scallop by means of a quadrangular or triangular incision (Panel A2). The remaining parts of the posterior leaflet, namely P1 and P3, are then brought together (Panel A3). After the leaflet repair is complete, an annuloplasty ring or band is used to reinforce and stabilize the annulus, thus preventing progressive dilatation (Panel A4). If excessive posterior leaflet tissue is present (Panel B1), the height of the posterior leaflet is reduced by incising P1 and P3 from the annulus (Panel B2), followed by reapproximation of the free edges (“sliding plasty”) (Panel B3). After the leaflet repair is complete, an annuloplasty ring or band is inserted (Panel B4).
height of the posterior leaflet is reduced by incisions in P1 and P3, followed by reapproximation of the free edges (“sliding plasty”) (Fig. 2). Finally, the annulus, which is distorted or dilated or both, is stabilized with an annuloplasty ring or band (Fig. 2). Limited resection, artificial chordal replacement (with Gore-Tex expanded polytetrafluoroethylene sutures), or both may be appropriate, followed by annuloplasty reinforcement, in cases of mitral-valve prolapse without redundant leaflet tissue.

Repairs of the anterior leaflet, either in isolation or with concomitant posterior leaflet repair, are more complex procedures that are best handled by surgeons who are experienced in mitral repair. Various techniques may be used, including limited triangular resection of the anterior leaflet, chordal transposition, chordal shortening, artificial (Gore-Tex) chordal replacement, and edge-to-edge repair. Various techniques may be used, including limited triangular resection of the anterior leaflet, chordal transposition, chordal shortening, artificial (Gore-Tex) chordal replacement, and edge-to-edge repair. Various techniques may be used, including limited triangular resection of the anterior leaflet, chordal transposition, chordal shortening, artificial (Gore-Tex) chordal replacement, and edge-to-edge repair (Fig. 3).

The repair is assessed initially by visual inspection and by injecting saline through the mitral valve to look for regurgitation (the “saline test”), and then by intraoperative transesophageal echocardiography after the patient is weaned from cardiopulmonary bypass. Patients should not leave the operating theater with more than 1+ mitral regurgitation on transesophageal echocardiography. Since anesthesia may result in substantial changes in preload and afterload, it is important to perform the intraoperative transesophageal echocardiography under conditions that approximate postoperative conditions in a patient who is awake. This can be achieved by adjusting inotropes and vasopressors to raise the afterload and blood pressure.

After mitral-valve repair, the left ventricle must be able to eject the entire stroke volume into the aorta. This constitutes a substantial increase in afterload as compared with ejection into the left atrium. Therefore, afterload reduction is important to maintain optimal cardiac output. In addition, because myocardial dysfunction may be present (even in patients with an apparently normal preoperative ejection fraction), inotropic support may be necessary to improve contractility. Patients with a low preoperative ejection fraction and heart failure may require more intensive treatment to allow the left ventricle to recover, including temporary pacing, intraaortic balloon counterpulsation, or in rare cases, support with a ventricular assist device.

In the absence of preoperative atrial fibrillation, and if normal sinus rhythm is maintained throughout hospital admission, aspirin alone may be sufficient for patients who had mitral-valve repair with ring annuloplasty. Otherwise, patients typically undergo anticoagulation with warfarin for 3 months, with a target international normalized ratio of 2.0 to 2.5. Antibiotic prophylaxis for dental procedures is recommended in all patients receiving an annuloplasty ring or other prosthetic material.

There are currently no standard recommendations regarding postoperative echocardiographic follow-up after mitral-valve repair. It is customary at our center to perform transthoracic echocardiography once before discharge and again at 6 to 8 weeks after discharge. Usually patients are then transferred to the care of their cardiologist and family physician, and we recommend that echocardiography be performed annually thereafter.

We estimate that the overall costs for mitral-valve repair, including hospital admission, professional fees, operating time, and prosthetic material (annuloplasty ring or band), are currently approximately $40,000 at our institution. Data from the Nationwide Inpatient Sample indicate that the mean estimated institutional cost for mitral repair in the United States increased from $28,405 in 2001 to $38,642 in 2005.

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**ADVERSE EFFECTS**

Mitral-valve repair is associated with an operative mortality of 3% or less. This figure is nearer 1% in high-volume centers. The most common cause of death is heart failure. Predictors of death include advanced age, poorer New York Heart Association class, atrial fibrillation, lower preoperative ejection fraction, greater preoperative left ventricular end-systolic dimension, and coexisting conditions including diabetes, renal disease, chronic lung disease, and obesity.

In an analysis from the Society of Thoracic Surgeons National Adult Cardiac Surgery Database, major postoperative complications before discharge included prolonged (>24 hours) ventilatory support (7.3% of patients), renal failure (2.6%), and stroke (1.4%). Reoperation during initial hospitalization was required in 6.3% of patients. Thromboembolism after mitral-valve repair occurs in approximately 5% of patients within the first 5 years after surgery.
Intraoperative conversion to mitral-valve replacement occurs in 2 to 10% of cases. Systolic anterior motion of the mitral valve may occur postoperatively if leaflet coaptation is not optimal, and mitral stenosis can occur if the annuloplasty ring is too small. Other rare adverse effects of mitral-valve repair include damage to important structures around the mitral apparatus, such as the circumflex coronary artery, the aortic valve, and the bundle of His.

The most important late complication of mitral-valve repair is recurrent mitral regurgitation, which may occur in as many as 30% of patients. Reoperation to treat recurrent mitral regurgitation after primary repair is required in approximately 0.5 to 1.5% of patients per year.

Areas of Uncertainty

We are unaware of any randomized trials that have compared mitral-valve repair with mitral-valve replacement for mitral-valve prolapse, and it is unlikely that such a trial will be conducted. Therefore, the current recommendation for mitral-valve repair in the treatment of severe degenerative mitral regurgitation is based on observational data.

It is unclear whether asymptomatic patients who have severe mitral regurgitation without left ventricular dysfunction or dilatation, atrial fibrillation, or pulmonary hypertension should undergo early surgery. Some investigators have found evidence of reduced morbidity and mortality with surgery and recommend early intervention, whereas others have found that watchful waiting does not seem to result in worse outcomes.

The guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend mitral-valve repair for such patients if the operative success rate is expected to exceed 90%. Conversely, the European So-
The ACC and AHA established guidelines for the management of valvular disease in 2006, with an update in 2008. These guidelines gave a class I recommendation to mitral-valve surgery for chronic severe mitral regurgitation in the presence of symptoms, a left ventricular ejection fraction of less than 60%, or an end-systolic dimension of more than 40 mm. Mitral-valve repair was recommended over replacement for most patients (class I recommendation). The guidelines advise that such persons be referred to surgical centers at which the surgeons are experienced in mitral-valve repair. The ESC guidelines of 2007 made similar recommendations. As noted above, the societies differ somewhat in terms of their recommendations for patients who have asymptomatic mitral-valve prolapse with severe mitral regurgitation but normal left ventricular volumes and function; the ACC–AHA guidelines give a class IIA recommendation in this regard.

The patient in the vignette is asymptomatic but has signs of ventricular dysfunction and elevated left ventricular dimensions. He should therefore be offered mitral-valve surgery and should be referred to a center with demonstrated expertise in mitral-valve repair. His operative risk should be formally assessed with the use of one of the validated risk-scoring algorithms. Intraoperative transesophageal echocardiography should be performed to provide a detailed anatomical and functional assessment at the time of surgery that would permit a final decision to be made about the specifics of the operative procedure. Unless severe deformity of the valve leaflets or subvalvular apparatus is present, we would recommend mitral-valve repair rather than replacement. Since mitral-valve prolapse is often genetically transmitted, it may be worth considering echocardiographic screening of first-degree relatives.

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REFERENCES


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Current Concepts articles present current approaches to a wide variety of clinical problems. These concise reviews are intended for the practicing physician.
CURRENT CONCEPTS

Point-of-Care Ultrasonography

Christopher L. Moore, M.D., and Joshua A. Copel, M.D.

Ultrasonography is a safe and effective form of imaging that has been used by physicians for more than half a century to aid in diagnosis and guide procedures. Over the past two decades, ultrasound equipment has become more compact, higher quality, and less expensive, which has facilitated the growth of point-of-care ultrasonography — that is, ultrasonography performed and interpreted by the clinician at the bedside. In 2004, a conference on compact ultrasonography hosted by the American Institute of Ultrasound in Medicine (AIUM) concluded that “the concept of an ‘ultrasound stethoscope’ is rapidly moving from the theoretical to reality.” This conference included representatives from 19 medical organizations; in November 2010, the AIUM hosted a similar forum attended by 45 organizations. Some medical schools are now beginning to provide their students with hand-carried ultrasound equipment for use during clinical rotations.

Although ionizing radiation from computed tomographic (CT) scanning is increasingly recognized as a potentially major cause of cancer, ultrasonography has been used in obstetrics for decades, with no epidemiologic evidence of harmful effects at normal diagnostic levels. However, ultrasonography is a user-dependent technology, and as usage spreads, there is a need to ensure competence, define the benefits of appropriate use, and limit unnecessary imaging and its consequences.

This article provides an overview of the history and current status of compact, point-of-care ultrasonography, with examples and discussion of its use.

HISTORY OF ULTRASONOGRAPHY AND THE BASIC TECHNOLOGY

Medical ultrasonography was developed from principles of sonar pioneered in World War I, and the first sonographic images of a human skull were published in 1947. The first ultrasound images of abdominal disease were published in 1958, and ultrasonography was widely adopted in radiology, cardiology, and obstetrics over the next several decades. Although clinicians from other specialties occasionally reported using ultrasonography, point-of-care ultrasonography did not really begin to progress until the 1990s, when more compact and affordable machines were developed. The early portable machines were hampered by poor image quality, but in 2010, many point-of-care units can nearly match the imaging quality of the larger machines.

Ultrasound is defined as a frequency above that which humans can hear, or more than 20,000 Hz (20 kHz). Therapeutic ultrasound, designed to create heat using mechanical sound waves, is typically lower in frequency than diagnostic ultrasound and is not discussed in this article. The frequency of diagnostic ultrasound is in the millions of Hertz (MHz). Lower-frequency ultrasound has better penetration, but at lower resolution. Higher-frequency ultrasound provides better images, but it does not visualize deep structures well. A typical transabdominal or
cardiac probe has a frequency in the range of 2 to 5 MHz, whereas some dermatologic ultrasound probes have frequencies as high as 100 MHz.

Ultrasonography uses a “crystal” — a quartz or composite piezoelectric material — that generates a sound wave when an electric current is applied. When the sound wave returns, the material in turn generates a current. The crystal thus both transmits and receives the sound. Early ultrasonography used a single crystal to create a one-dimensional image known as A-mode. The standard screen image that machines now generate is known as B-mode (also called two-dimensional or gray-scale ultrasonography), and is created by an array of crystals (often 128 or more) across the face of the transducer. Each crystal produces a scan line that is used to create an image or frame, which is refreshed many times per second to produce a moving image on the screen (Fig. 1). Additional modes, including three-dimensional, four-dimensional, Doppler, and tissue Doppler modes, are now commonly available but are not addressed in this article.

Ultrasound penetrates well through fluid and solid organs (e.g., liver, spleen, and uterus); it does not penetrate well through bone or air, limiting its usefulness in the skull, chest, and areas of the abdomen where bowel gas obscures the image. Fluid (e.g., blood, urine, bile, and ascites), which is completely anechoic, appears black on ultrasound images, making ultrasonography particularly useful for detecting fluid and differentiating cystic or vascular areas from solid structures.

Two-dimensional ultrasound is used to visualize a plane that is then shown on the screen. This plane may be directed by the user in any anatomical plane on the patient: sagittal (or longitudinal), transverse (or axial), coronal (or frontal), or some combination (oblique). An indicator on the probe is used to orient the user to the orientation of the plane on the screen. By convention, in general and obstetrical imaging, the indicator corresponds to the left side of the screen as it is viewed. Cardiology uses the opposite convention for echocardiography, with the indicator corresponding to the right of the screen. Users should be aware of these conventions when conducting integrated examinations that include both general and cardiac imaging.14

Point-of-care ultrasonography is defined as ultrasonography brought to the patient and performed by the provider in real time. Point-of-care ultrasound images can be obtained nearly immediately, and the clinician can use real-time dynamic images (rather than images recorded by a sonographer and interpreted later), allowing findings to be directly correlated with the patient’s presenting signs and symptoms.15 Point-of-care ultrasonography is easily repeatable if the patient’s condition changes. It is used by various specialties in diverse situations (Table 1) and may be broadly divided into procedural, diagnostic, and screening applications.

**PROCEDURAL GUIDANCE**

Ultrasound guidance may improve success and decrease complications in procedures performed by multiple specialties, including central and peripheral vascular access, thoracentesis, paracentesis, arthrocentesis, regional anesthesia, incision and drainage of abscesses, localization and removal of foreign bodies, lumbar puncture, biopsies, and other procedures.16

Procedural guidance may be static or dynamic. With static guidance, the structure of interest is identified, and the angle required by the needle is noted, with the point of entry marked on the skin. In dynamic procedures, ultrasonography visualizes the needle in real time. Static guidance may initially be easier to perform, but properly performed dynamic guidance provides more accurate guidance and is generally preferred by experienced users.

In response to the 1999 Institute of Medicine report *To Err Is Human*, the Agency for Healthcare Research and Quality listed “use of real-time ultrasound guidance during central line insertion to prevent complications” as 1 of the 12 most highly rated patient safety practices designed to decrease medical errors.17 The use of ultrasound to guide central venous access has been shown to reduce the failure rate, the risk of complications, and the number of attempts, as compared with the landmark technique, particularly in the case of less experienced users or patients with more complex conditions.18,19 The evidence for these benefits of ultrasound guidance is greatest.
Figure 1. Basic (B-Mode) Two-Dimensional Ultrasound Image.

A typical ultrasound transducer, shown in Panel A, has 128 or more crystals arranged across the face of the probe. Each crystal transmits and receives bursts of sound (typically in the megahertz range), creating a scan line. The scan lines together make up a frame, which is refreshed many times per second and displayed on a two-dimensional screen to create a moving image. As shown in Panel B, the plane of the ultrasound can be directed in any anatomical plane or between planes. By convention, in abdominal imaging, the probe indicator (a bump or groove on the probe) is to the left of the screen and is generally directed toward the patient’s right side in a transverse plane. The ultrasound image shown is a transverse image of the abdominal aorta. The indicator is directed to the patient’s right side, corresponding to the left side of the screen. The aorta is black (fluid-filled) and located just anterior to the vertebral bodies. (See also Video 4, available with the full text of this article at NEJM.org.)
for the internal jugular site, with less evidence for the femoral and subclavian sites and in pediatric patients.20

A needle may be imaged dynamically with the use of either an “in-plane” or “out-of-plane” ultrasound approach (Fig. 2, and Video 1, available at NEJM.org). For vascular access, an in-plane approach corresponds to the long axis of the vessel. An in-plane, or long-axis, approach is generally preferred for dynamic vascular access, particularly for central venous access, because the entire length of the needle, including the tip, can be visualized throughout the procedure. However, it may be more difficult to keep the needle in view with the use of an in-plane approach, and for smaller vessels, it may be challenging to image the entire vessel in the long axis.

An out-of-plane approach is perpendicular to the needle and corresponds to the short axis of the vessel. The advantage of this approach is that the needle can be centered over the middle of the vessel. It is also easier to keep the vessel and the needle in view in the short axis. However, an out-of-plane approach may underestimate the depth of the needle tip if the ultrasound plane cuts across the shaft of the needle, proximal to the tip. A detailed description of ultrasound-guided central venous access of the internal jugular vein is provided by Ortega et al. as part of the Journal’s Videos in Clinical Medicine series.21

Table 1. Selected Applications of Point-of-Care Ultrasonography, According to Medical Specialty.5

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Ultrasound Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia</td>
<td>Guidance for vascular access, regional anesthesia, intraoperative monitoring of fluid status and cardiac function</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Echocardiography, intracardiac assessment</td>
</tr>
<tr>
<td>Critical care medicine</td>
<td>Procedural guidance, pulmonary assessment, focused echocardiography</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Assessment of skin lesions and tumors</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>FAST, focused emergency assessment, procedural guidance</td>
</tr>
<tr>
<td>Endocrinology and endocrine surgery</td>
<td>Assessment of thyroid and parathyroid, procedural guidance</td>
</tr>
<tr>
<td>General surgery</td>
<td>Ultrasonography of the breast, procedural guidance, intraoperative assessment</td>
</tr>
<tr>
<td>Gynecology</td>
<td>Assessment of cervix, uterus, and adnexa; procedural guidance</td>
</tr>
<tr>
<td>Obstetrics and maternal–fetal medicine</td>
<td>Assessment of pregnancy, detection of fetal abnormalities, procedural guidance</td>
</tr>
<tr>
<td>Neonatology</td>
<td>Cranial and pulmonary assessments</td>
</tr>
<tr>
<td>Nephrology</td>
<td>Vascular access for dialysis</td>
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<tr>
<td>Neurology</td>
<td>Transcranial Doppler, peripheral-nerve evaluation</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Corneal and retinal assessment</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Musculoskeletal applications</td>
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<tr>
<td>Otolaryngology</td>
<td>Assessment of thyroid, parathyroid, and neck masses; procedural guidance</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>Assessment of bladder, procedural guidance</td>
</tr>
<tr>
<td>Pulmonary medicine</td>
<td>Transthoracic pulmonary assessment, endobronchial assessment, procedural guidance</td>
</tr>
<tr>
<td>Radiology and interventional radiology</td>
<td>Ultrasonography taken to the patient with interpretation at the bedside, procedural guidance</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>Monitoring of synovitis, procedural guidance</td>
</tr>
<tr>
<td>Trauma surgery</td>
<td>FAST, procedural guidance</td>
</tr>
<tr>
<td>Urology</td>
<td>Renal, bladder, and prostate assessment; procedural guidance</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>Carotid, arterial, and venous assessment; procedural assessment</td>
</tr>
</tbody>
</table>

* FAST denotes focused assessment with sonography for trauma.
sonography to examine a particular organ, disease, or procedure that is directly relevant to their area of expertise, whereas imaging specialists typically perform more comprehensive examinations (Table 1).

Point-of-care ultrasonography may involve the use of a series of focused ultrasonographic examinations to efficiently diagnose or rule out certain conditions in patients presenting with particular symptoms or signs, such as hypoten-
The use of point-of-care ultrasonography for pulmonary assessment.

**FAST Examination**

FAST was a term coined at an international consensus conference in 1996 to describe an integrated, goal-directed, bedside examination to detect fluid, which is likely to be hemorrhage in cases of trauma. The extended FAST (e-FAST) also includes examination of the chest for pneumothorax.

The e-FAST examination combines five focused examinations for the detection of: free intraperitoneal fluid, free fluid in the pelvis, pericardial fluid, pleural effusion, and pneumothorax. Peritoneal fluid is detected using views of the hepatorenal space (Morison’s pouch), splenorenal space, and retrovesicular spaces. The thorax is evaluated for fluid at the flanks and for pneumothorax anteriorly. The pericardium may be evaluated for effusion, particularly in cases of penetrating trauma.

A FAST examination may be completed in less than 5 minutes and has been shown to have a sensitivity of 73 to 99%, a specificity of 94 to 98%, and an overall accuracy of 90 to 98% for clinically significant intraabdominal injury in trauma. The use of the FAST examination has been shown to reduce the need for CT or diagnostic peritoneal lavage and to reduce the time to appropriate intervention, resulting in a shorter hospital stay, lower costs, and lower overall mortality, although more rigorous study of patient-centered outcomes is recommended.

A complete or partial FAST examination may also be helpful in evaluating patients who do not have trauma for ascites, intraperitoneal hemorrhage, pleural effusion, pneumothorax, or pericardial effusion.

**Pulmonary Ultrasonography**

The use of ultrasound to detect pneumothorax was first described in a horse in 1986, and then in humans shortly afterward. In a normal lung, the visceral and parietal pleura are closely associated, and ultrasound shows shimmering or sliding at the pleural interface during respiration (Fig. 3, and Video 3). The absence of sliding indicates a pneumothorax. A small pneumothorax may be missed with the use of ultrasonography, and patients with blebs or scarring may have false positive findings. However, for assessing pa-
tients with trauma for pneumothorax, ultrasonography has been shown to be more than twice as sensitive as conventional supine chest radiography for detecting occult pneumothorax (pneumothorax seen only on CT), with similarly high specificity (>98%).23 The presence of a “lung point” sign, where the visceral pleura intermittently comes in contact with the parietal pleura, is nearly 100% specific for the detection of pneumothorax.

Comet tails are an ultrasound artifact that arises when ultrasound encounters a small air–fluid interface. In 1997, Lichtenstein et al. described the sonographic identification of alveolar interstitial syndrome, diagnosed on the basis of comet tails that extend from the pleural line to the bottom of the screen, also known as “B lines” (Fig. 3B). Alveolar interstitial syndrome is an ultrasonographic finding in several different conditions.29 In an acute condition, alveolar interstitial syndrome usually represents pulmonary edema, but it may also be seen in the acute respiratory distress syndrome and more chronic interstitial diseases and may be a focal finding in infectious or ischemic processes. Characteristics of the artifacts may be helpful in distinguishing these conditions.

Ultrasonography has been shown to be more accurate than auscultation or chest radiography for the detection of pleural effusion, consolidation, and alveolar interstitial syndrome in the critical care setting.30 In the emergency care setting, the presence of B lines on pleural ultrasonography predicts fluid overload, adding diagnostic accuracy to the physical examination and measurement of brain natriuretic peptide.31 The presence of B lines has been shown to be dynamic, disappearing in patients undergoing hemodialysis.31,32

SCREENING

Screening with ultrasonography is attractive because it is noninvasive and lacks ionizing radiation. Ultrasonography has been described as a screening test for cardiovascular and gynecologic disease, and compact ultrasonography has been incorporated into “mobile screening labs.”33 However, the benefits of screening must be weighed against the harms, particularly false positive findings that lead to unnecessary testing, intervention, or both. The U.S. Preventive Services Task Force (USPSTF) has specifically recommended that ultrasonography not be used for routine screening for carotid stenosis, peripheral vascular disease, or ovarian cancer in the general population (class D recommendation — “ineffective or harms outweigh benefits”), although research is ongoing to determine whether more narrowly defined populations may benefit from such screening.34

In 2005, the USPSTF gave a class B recommendation for one-time ultrasound screening for abdominal aortic aneurysm in men between the ages of 65 and 75 years who had ever smoked, leading to the incorporation of screening for abdominal aortic aneurysm into Medicare reimbursement.35,36 The USPSTF reports that ultrasonography has a sensitivity of 95% and a specificity of nearly 100% when performed in a “setting with adequate quality assurance.”

Imaging of the abdominal aorta is performed with a curvilinear probe of 2 to 5 MHz. With the patient in a supine position, gentle pressure is applied to move bowel gas out of the way. The aorta should be imaged as completely as possible from the proximal (celiac trunk) to the distal bifurcation and should include assessment of the iliac arteries when possible. It should be measured at its maximum diameter from outside wall to outside wall in two planes, transverse and longitudinal. Challenges include ensuring that the aorta is imaged, not the inferior vena cava or another fluid-filled structure, and ensuring that the entire diameter is measured (Fig. 1, and Video 4).

Ultrasonography of the abdominal aorta has been shown to be fairly straightforward to learn as a focused examination, and screening by primary care providers using point-of-care ultrasonography may provide an economical method for wider screening, although more study is needed in this area.

POINT-OF-CARE ULTRASONOGRAPHY IN OTHER SETTINGS

Point-of-care ultrasonography is increasingly being used in resource-limited settings. The World Health Organization states that plain radiography and ultrasonography, singly or in combination, will meet two thirds of all imaging needs in developing countries.37 Ultrasonography has been used at the Mount Everest base camp to diagnose high-altitude pulmonary edema, and ultrasonography is the only diagnostic imaging technique
used on the International Space Station, where astronauts obtain images that are interpreted on earth.\textsuperscript{38,39} The use of hand-carried ultrasonographic devices has been described in prehospital settings, including ambulance and disaster settings, as well as in battlefield medicine (the scenario for which hand-carried ultrasonography was initially developed).\textsuperscript{40-42} The e-FAST examination for internal bleeding and pneumothorax has been the most extensively described application in the prehospital setting (Video 2).

**POLICY CONSIDERATIONS**

From 2000 to 2006, physician fees billed for medical imaging in the United States more than doubled, with the proportion of billing for “in-office” imaging rising from 58 to 64%.\textsuperscript{43} Although the rate of imaging increased among both radiologists and nonradiologists, the rate of increase was faster among nonradiologists.\textsuperscript{44,45} Most of this increase was related to “advanced” imaging (CT, magnetic resonance imaging, and nuclear medicine), but certain applications of ultrasonography by nonradiologists (particularly breast and cardiac applications) increased at a very rapid rate.\textsuperscript{46}

With appropriate use, point-of-care ultrasonography can decrease medical errors, provide more efficient real-time diagnosis, and supplement or replace more advanced imaging in appropriate situations. In addition, point-of-care ultrasonography may allow more widespread, less-expensive screening for defined indications. It may be particularly cost-effective in a reimbursement scheme based on episodes of care (“bundling”), in some cases obviating the need for more resource-intensive imaging performed by a consulting radiologist.\textsuperscript{47} However, indiscriminate use of ultrasonography could lead to further unnecessary testing, unnecessary interventions in the case of false positive findings, or inadequate investigation of false negative findings. More imaging could simply lead to increased expense without added benefit, or might even be harmful.

As a user-dependent technology, point-of-care ultrasonography requires consideration of appropriate training and quality assurance. In addition, methodologically rigorous studies are needed to assess patient-centered outcomes for point-of-care ultrasonography.\textsuperscript{25,48-50}

**CONCLUSIONS**

The use of point-of-care ultrasonography will continue to diffuse across medical specialties and care situations. Future challenges include gaining a better understanding of when and how point-of-care ultrasonography can be used effectively, determining the training and assessment that will be required to ensure competent use of the technology, and structuring policy and reimbursement to encourage appropriate and effective use.

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

**REFERENCES**

13. Moore C. Current issues with emer-

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Myocardial Infarction Due to Percutaneous Coronary Intervention

Abhiram Prasad, M.D., and Joerg Herrmann, M.D.

From the Department of Internal Medicine and the Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Prasad at the Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at prasad.abhiram@mayo.edu.


Approximately 1.5 million patients undergo percutaneous coronary intervention (PCI) in the United States every year. Depending on local practices and the diagnostic criteria used, 5 to 30% of these patients (75,000 to 450,000) have evidence of a periprocedural myocardial infarction. At the higher estimate, the incidence of these events is similar to the annual rate of major spontaneous myocardial infarction. Thus, many cardiologists and internists are likely to encounter patients with coronary artery disease who have sustained a periprocedural myocardial infarction. However, the clinical significance of these events and their management remain a matter of considerable controversy and uncertainty (Table 1). Questions that often arise include the following: Do we need to routinely screen patients for periprocedural myocardial infarction? Which patients should be observed in the hospital for a prolonged period after periprocedural myocardial infarction? What are the therapeutic implications, and what should we tell patients who sustained a periprocedural myocardial infarction despite an otherwise successful procedure? Is a periprocedural myocardial infarction prognostically equivalent to a spontaneous myocardial infarction? Is periprocedural myocardial infarction a valid end point in clinical trials? The aim of this review is to address these questions and to provide a current perspective on this issue.

Definitions and Predictors of PCI-Related Myonecrosis

Current PCI guidelines give a class I recommendation for the measurement of cardiac biomarkers (the MB fraction of creatine kinase [CK-MB], cardiac troponin, or both) in patients who have signs or symptoms suggestive of myocardial infarction during or after PCI and for those who have undergone complicated procedures. In addition, a class IIa recommendation is given for routine measurements of cardiac biomarkers 8 to 12 hours after the procedure. In either case, “a new CK-MB or troponin I or T rise greater than 5 times the upper limit of normal would constitute a clinically significant periprocedural MI [myocardial infarction].” The more recent consensus document on the universal definition of myocardial infarction specifically classifies cardiac-biomarker levels that are more than 3 times the upper reference limit as indicative of a periprocedural myocardial infarction and recommends measurement of cardiac troponin as the preferred biomarker. Given the availability of high-sensitivity cardiac troponin assays, this guideline establishes the threshold for a diagnosis of periprocedural myocardial infarction at very low levels of myonecrosis.

The predictors of periprocedural myocardial infarction can be broadly categorized as patient-, lesion-, and procedure-related risk factors. The major risk factors, in terms of both frequency and potency, are complex lesions (e.g., the presence of thrombus, stenosis of a saphenous-vein graft, or a type C lesion), complex procedures...
(e.g., treatment of multiple lesions or use of rotational atherectomy), and associated complications (e.g., abrupt vessel closure, side-branch occlusion, distal embolization, or no reflow).\textsuperscript{2,9–12} In contrast, patient-related factors, such as advanced age, diabetes mellitus, renal failure, multivessel disease, and left ventricular dysfunction, are the important determinants of clinical outcomes after PCI.\textsuperscript{2,9–11}

The occurrence of peri-procedural ischemic symptoms, particularly chest pain at the end of the procedure, or electrocardiographic evidence of ischemia defines the subgroup of patients most likely to have periprocedural myocardial infarction.\textsuperscript{11,13}

**Mechanisms of PCI-Related Myonecrosis**

Large periprocedural myocardial infarcts are usually due to angiographically visible complications; however, this is generally not the case in the vast majority of patients with elevated biomarker levels after PCI.\textsuperscript{6,14,15} Cardiac magnetic resonance imaging (MRI) has confirmed two distinct locations for procedural myonecrosis: adjacent to the site of the intervention, where the injury is most likely due to epicardial side-branch occlusion, and downstream from the intervention site, where it is most likely due to compromise of the microvascular circulation (Fig. 1).\textsuperscript{2,16} Acute myocardial injury occurs with equal frequency at the two locations and is detected on MRI in 25% of patients after PCI, with a mean infarct size of approximately 5% of the left ventricular mass.\textsuperscript{3} The size of distal infarcts correlates directly with the extent to which the plaque volume is reduced (embolized) by PCI, since more debris is sent downstream, but this is not so for the proximal type of injury. Moreover, the composition of the plaque influences the extent of periprocedural myonecrosis. PCI for plaques with large necrotic cores leads to greater degrees of myonecrosis, whereas fibrous plaques are relatively inert in this regard.\textsuperscript{17,18}

Embolization of plaque material has been detected on intracoronary Doppler ultrasonography during PCI. Although it occurs at each phase of the intervention, embolization is most pronounced during stent implantation.\textsuperscript{19} Even though the number of microemboli correlates positively with the severity of myocardial microvascular dysfunction and myonecrosis, there is considerable overlap with regard to the magnitude of plaque microembolization between patients with and those without periprocedural myocardial infarction.\textsuperscript{19,20} This finding suggests that factors other than the burden of plaque microembolization influence the likelihood of periprocedural myocardial infarction, such as the release of vasoactive factors from the atherosclerotic plaque, platelet activation, and preexisting vulnerability of the myocardium.\textsuperscript{2}

**Table 1. Evidence for and against the Clinical Significance of Periprocedural Myocardial Infarction.\textsuperscript{2}**

<table>
<thead>
<tr>
<th>Evidence for Clinical Significance</th>
<th>Evidence against Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with elevated cardiac biomarkers after PCI have evidence of focal infarction on cardiac imaging</td>
<td>Virtually all data correlating PMI to adverse clinical outcomes are derived from retrospective studies that have shown associations but not causal relationships</td>
</tr>
<tr>
<td>A large number of studies have shown a correlation between PMI and adverse clinical outcomes (see the Supplementary Appendix, available with the full text of this article at NEJM.org), and these studies greatly outnumber those that do not</td>
<td>Retrospective studies are generally limited because they cannot adequately adjust for all possible confounding variables with respect to baseline clinical, angiographic, and procedural characteristics that may determine the likelihood of both PMI and adverse outcomes</td>
</tr>
<tr>
<td>There is a positive correlation between the magnitude of postprocedural biomarker elevation and the likelihood of adverse outcomes</td>
<td>Most studies did not use high-sensitivity cardiac troponin assays; when these assays were used, the studies did not apply the currently recommended 99th percentile cutoff value for the upper limit of the normal range</td>
</tr>
<tr>
<td>Studies have shown that pre-PCI interventions such as statin therapy reduce the frequency of PMI and improve long-term outcomes</td>
<td>In most cases, PMI results in minimal myonecrosis and therefore does not substantially impair cardiac function — one of the most important determinants of outcome in coronary artery disease</td>
</tr>
</tbody>
</table>

* PCI denotes percutaneous coronary intervention, and PMI periprocedural myocardial infarction.\textsuperscript{2}
of cardiac-biomarker elevations after PCI, and these studies have been systematically reviewed in a previous publication.² The general conclusion from the retrospective analyses was that a CK-MB elevation higher than 5 times the upper limit of normal was independently associated with an increased risk of in-hospital adverse cardiac events, whereas lower levels did not appear to influence in-hospital outcomes significantly (Table 2).²¹,²⁶,⁴⁰⁻⁴⁳ Data indicating a relationship between the CK-MB level and long-term survival were less consistent. The results of several studies sug-
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Incidence of ACS %</th>
<th>Type of Intervention</th>
<th>Incidence</th>
<th>In-Hospital Outcomes†</th>
<th>Length of Follow-up mo</th>
<th>Multivariate Adjusted Long-Term Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone et al. 21</td>
<td>7147</td>
<td>68.9</td>
<td>PCI</td>
<td></td>
<td>Increased risk of death (odds ratio, 8 for CK-MB &gt;8× ULN; 67 for Q-wave MI)</td>
<td>24</td>
<td>Increased risk of death (hazard ratio, 2.2 for CK-MB &gt;8× ULN; 9.9 for Q-wave MI)</td>
</tr>
<tr>
<td>CK-MB, &gt;4–32 ng/ml</td>
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<td>CK-MB, &gt;32 ng/ml</td>
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<td>Q-wave MI</td>
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<tr>
<td>Dangas et al. 22</td>
<td>4085</td>
<td>67.3</td>
<td>PCI</td>
<td></td>
<td>NA</td>
<td>12</td>
<td>Increased risk of death or MI (odds ratio, 1.5 for CK-MB &gt;5× ULN)</td>
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<tr>
<td>CK-MB, 4–20 ng/ml</td>
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<tr>
<td>CK-MB, &gt;20 ng/ml</td>
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</tr>
<tr>
<td>Ajani et al. 23</td>
<td>1326</td>
<td>85.4</td>
<td>PCI</td>
<td></td>
<td>NA</td>
<td>12</td>
<td>Increased risk of death or MI (odds ratio, 1.57 for CK-MB &gt;3× ULN)</td>
</tr>
<tr>
<td>CK-MB, 4–12 ng/ml</td>
<td></td>
<td></td>
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<td>CK-MB, &gt;12 ng/ml</td>
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<tr>
<td>Kini et al. 24, 25</td>
<td>1675</td>
<td>NA</td>
<td>PCI</td>
<td></td>
<td>Increased risk of chest pain (58% vs. 9–12%), heart failure (35% vs. 6–7%), and increased length of stay for CK-MB &gt;5× ULN vs. other elevations and normal levels</td>
<td>13±3</td>
<td>No association</td>
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<td>CK-MB, 1–3× ULN</td>
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<tr>
<td>Brener et al. 25</td>
<td>3478</td>
<td>64.0</td>
<td>Stent placement</td>
<td></td>
<td>NA</td>
<td>15±15</td>
<td>Increased risk of death (odds ratio, 1.89 for CK-MB &gt;3× ULN; 6.36 for CK-MB &gt;10× ULN)</td>
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<td>CK-MB, &gt;8.8–26.4 ng/ml (CK-MB, &gt;1–3× ULN)</td>
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<td>CK-MB, &gt;44–88 ng/ml (CK-MB, &gt;5–10× ULN)</td>
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<td>CK-MB, &gt;88 ng/ml (CK-MB, &gt;10× ULN)</td>
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<td>Ellis et al. 26</td>
<td>8409</td>
<td>63.0</td>
<td>PCI</td>
<td></td>
<td>Increased length of stay for CK-MB &gt;1× ULN</td>
<td>4</td>
<td>Increased risk of death (1.2, 1.9, and 8.9% for CK-MB &lt;1, 1–5, and &gt;5× ULN, respectively)</td>
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</table>
Brener et al.\textsuperscript{27}  & 3573 & NA & PCI & NA & 36 & Increased risk of death (hazard ratio, 1.1 for CK-MB >10× ULN) \\
| CK-MB, >8.8–26.4 ng/ml (CK-MB, >1–3× ULN) | & | & | & | & | \\
| CK-MB, >26.4–44 ng/ml (CK-MB, >3–5× ULN) | & | & | | & | \\
| CK-MB, >44–88 ng/ml (CK-MB, >5–10× ULN) | & | | | | | \\
| CK-MB, >88 ng/ml (CK-MB, >10× ULN) | & | & | | & | \\
| Hong et al.\textsuperscript{28}  & 1693 & 79.0 & Saphenous-vein graft PCI & Increased need for balloon pump (7.8% vs. 1.1%) and repeat PCI (4.2% vs. 1.2%) for CK-MB elevation vs. no elevation & 12 & Increased risk of death (hazard ratio, 3.3 for CK-MB >5× ULN) \\
| CK-MB, 4–20 ng/ml | & | | & | | \\
| CK-MB, >20 ng/ml | & | | | | | \\
| Andron et al.\textsuperscript{29}  & 3864 & 30.4 & PCI & NA & 6–42 & Increased risk of death (hazard ratio, 1.3, 1.76, and 2.26 for CK-MB 1–3, >3–5 and >5× ULN, respectively) \\
| CK-MB, 4–12 ng/ml | & | | | | | \\
| CK-MB, >12–20 ng/ml | & | | | | | \\
| CK-MB, >20 ng/ml | & | | | | | \\
| Jang et al.\textsuperscript{30}  & 1807 & 40.9 & Drug-eluting stenting PCI & No association & 13±7 & Increased risk of death (0.5, 1.1, and 2.6% for CK-MB <1, 1–5, and >5× ULN, respectively) \\
| CK-MB, 5–25 ng/ml | & | | | | | \\
| CK-MB, >25 ng/ml | & | | | | | \\
| Natarajan et al.\textsuperscript{31}  & 1128 & 61.0 & PCI & Increased risk of major cardiac events (3.8 for cTnl ≥5× ULN) & 12 & No association \\
| cTnl, 1–4× ULN | & | | | | | \\
| cTnl, ≥5× ULN | & | | | | | \\
| Nallamothu et al.\textsuperscript{32}  & 1157 & 36.5 & PCI & NA & 11±7 & Increased risk of death (hazard ratio, 2.4 for cTnl ≥8× ULN, 8.9 for Q-wave MI) \\
| cTnl, 2–5.9 ng/ml | & | | | | | \\
| cTnl, 6–9.9 ng/ml | & | | | | | \\
| cTnl, 10–15.9 ng/ml | & | | | | | \\
| cTnl, ≥16.0 ng/ml | & | | | | | \\
| Q-wave MI | & | | | | |
Table 2. (Continued.)

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<th>Study</th>
<th>No. of Patients</th>
<th>Incidence of ACS</th>
<th>Type of Intervention</th>
<th>Incidence</th>
<th>In-Hospital Outcomes†</th>
<th>Length of Follow-up</th>
<th>Multivariate Adjusted Long-Term Outcomes</th>
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<td>Prasad et al.33</td>
<td>1949</td>
<td>47.9</td>
<td>PCI</td>
<td></td>
<td>Increased length of stay</td>
<td>26</td>
<td>Increased risk of death (hazard ratio, 1.2 per ( \log_2 ) increase in cTnT)</td>
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<td>cTnT, ≥0.03 ng/ml</td>
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<td>Hubacek et al.34</td>
<td>1208</td>
<td>31.0</td>
<td>PCI</td>
<td></td>
<td>NA</td>
<td>24</td>
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<td>Increase in cTnT &gt;0.1 ng/ml</td>
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<td>Feldman et al.35</td>
<td>1601</td>
<td>43.3</td>
<td>PCI</td>
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<td>No association</td>
<td>25±8</td>
<td>Increased risk of death (hazard ratio, 1.6)</td>
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<td>cTnl, ≥0.15 ng/ml</td>
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<td>De Labriolle et al.36</td>
<td>3200</td>
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<td>Cavallini et al.37</td>
<td>2362</td>
<td>45.1</td>
<td>PCI</td>
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<td>Fuchs et al.38</td>
<td>1129</td>
<td>70.9</td>
<td>PCI</td>
<td></td>
<td>Increased risk of major adverse cardiovascular events (odds ratio, 2.1 for cTnl &gt;3× ULN)</td>
<td>8</td>
<td>No association</td>
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<td>cTnl, 0.15–0.45 ng/ml</td>
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<tr>
<td>Cavallini et al.39</td>
<td>3494</td>
<td>50.8</td>
<td>PCI</td>
<td></td>
<td>NA</td>
<td>24</td>
<td>Increased risk of death (odds ratio, 1.04 per peak CK-MB ratio unit)§</td>
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<tr>
<td>cTnl, &gt;0.15 ng/ml</td>
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* Plus–minus values are means ±SD. Only data from studies that included at least 1000 patients, long-term outcome data, and concentration-based biomarker analysis are shown.
Hazard ratios were determined by means of a multivariate Cox proportional-hazards regression model, if available; otherwise, odds ratios were determined by multivariate analysis.
Acute coronary syndromes (ACS) included angina at rest and urgent priority interventions. CK-MB denotes the MB fraction of creatine kinase, cTnl cardiac troponin I, cTnT cardiac troponin T, MI myocardial infarction, NA not available, and ULN upper limit of the normal range.
† Outcomes other than evolving myocardial infarction are shown. \( P<0.05 \) for all comparisons.
‡ In this study, the final analysis was based on mass immunoassay.
§ This ratio was calculated by dividing the maximum post-PCI level by the ULN or baseline level of CK-MB.
suggested that any elevation in CK-MB was associated with reduced long-term survival and that there was a direct correlation between the magnitude of myonecrosis and mortality. In contrast, other studies have shown that only large myocardial infarctions, variably defined as a CK-MB level exceeding 5 or 8 times the upper limit of normal or the presence of new Q waves, were predictive of a poor long-term outcome, especially if they were related to an unsuccessful revascularization procedure (Table 2).

Studies evaluating the relationship between the postprocedural cardiac troponin level and long-term mortality, in general, have not excluded patients with acute coronary syndromes, many of whom would have had abnormal cardiac-biomarker levels at baseline. Thus, the reported frequency of postprocedural elevations in cardiac troponin has been highly variable, and although some studies showed that the serum concentration of cardiac troponin was an independent predictor of survival, others did not (Table 2). The inconsistent findings were most likely due to heterogeneity of the inclusion criteria, variations in the sensitivity and specificity of the biomarker assays, different sample sizes, and differences in the duration of follow-up. Two recent meta-analyses concluded that an elevated cardiac troponin level after PCI does provide prognostic information. Both analyses were influenced by studies from our catheterization laboratories on postprocedural cardiac troponin T elevations in which we had reached a similar conclusion. However, the studies included in the meta-analyses (including our own) had used cardiac troponin cutoff values for normal that were higher than the currently recommended 99th percentile, thereby limiting the accuracy of their conclusions.

FOCUS ON PREPROCEDURAL RISK

To date, virtually all studies of periprocedural myocardial infarction have been limited by the lack of precision with which they determined preprocedural risk. Contemporary cardiac troponin assays have greatly enhanced our ability to detect myonecrosis before and after PCI. In a recent analysis, using the currently recommended 99th percentile value as the cutoff for a normal cardiac troponin T level, we found that approximately one third of patients who underwent nonemergency PCI had evidence of preprocedural myonecrosis. These patients had a greater atherosclerotic burden and more unstable disease than patients without evidence of preprocedural myonecrosis, a finding that is consistent with previous reports. Applying the universal definition of myocardial infarction to patients with normal preprocedural cardiac troponin T levels, another one third of patients sustained a periprocedural myocardial infarction after the procedure when cardiac troponin T was used to detect myonecrosis, as compared with only 1 in 15 patients when CK-MB was used. The preprocedural rather than postprocedural cardiac-biomarker level was a powerful independent predictor of short-term and long-term mortality. Similar findings have been reported in two additional recent studies that used cardiac troponin I within the framework of the universal definition of myocardial infarction and in an analysis from the Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry.

These observations may seem surprising, since one might argue that the clinical effect of myocardial infarction should be the same regardless of its cause. However, most periprocedural myocardial infarcts are very small in relation to the magnitude of myonecrosis, especially in patients with stable coronary artery disease. Among patients with normal preprocedural cardiac troponin values, less than 5% have CK-MB values that are higher than 5 times the upper reference limit after PCI, and Q-wave infarctions are rare (<0.1%). Instead, CK-MB levels that are higher than 5 times the upper reference limit are generally observed in patients with elevated preprocedural cardiac troponin T. Thus, it is likely that in the older studies that explored the effect of periprocedural myocardial infarction on outcomes, a large proportion of the patients who had been classified as biomarker-negative on the basis of CK or CK-MB levels at the time of PCI actually had non–ST-segment elevation myocardial infarction according to contemporary definitions. This conclusion is supported by the high proportion of patients (about 50% on average) who had acute coronary syndromes in the previous studies (Table 2, and the Supplementary Appendix, available with the full text of this article at NEJM.org).

In summary, recent studies reveal that the preprocedural cardiac troponin level is a powerful independent predictor of prognosis after PCI.
Moreover, these studies suggest that the association between postprocedural myonecrosis and outcomes after an otherwise successful PCI is, in general, a reflection of the preprocedural risk, which can be estimated by measuring baseline cardiac troponin levels with the use of contemporary high-sensitivity assays in conjunction with the clinical and angiographic characteristics of the patient.

Prognostic Significance of Periprocedural versus Spontaneous Events

On the basis of the traditional concept of periprocedural myocardial infarction described above, this complication has often been equated with spontaneous myocardial infarction in clinical trials.44 The validity of this assumption has not been examined in detail, and it has been confounded by the variable definitions of periprocedural myocardial infarction used in the past. The current universal definition of myocardial infarction attempts to address this issue by introducing a specific category (type 4a) for periprocedural myocardial infarction to distinguish it from spontaneous myocardial infarction (types 1 and 2).8

Akkerhuis and colleagues compared the effect of periprocedural myocardial infarction as detected by CK-MB elevation with that of spontaneous myocardial infarction on 6-month mortality in a heterogeneous group of patients who had acute coronary syndromes without ST-segment elevation; the data were derived from five different clinical-trial databases.55 The authors reported a positive correlation between CK-MB levels and mortality in both groups, although the absolute mortality was significantly higher among patients who had spontaneous myocardial infarction than among those who had periprocedural myocardial infarction. The authors concluded that the clinical significance of periprocedural myocardial infarction should be considered similar to the adverse consequences of spontaneous myocardial infarction. However, the study was conducted in the era of balloon angioplasty, before the widespread use of stents, and the analysis was not adjusted for confounding clinical variables.

To address these limitations, an analysis was conducted of data from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial (Clinical.Trials.gov number, NCT00093158) involving 7773 patients with moderate-to-high-risk, non–ST-segment elevation acute coronary syndromes who underwent PCI.55 Periprocedural myocardial infarction and spontaneous myocardial infarction during follow-up developed in 6.0% and 2.6% of the cohort, respectively. Among patients with either type of myocardial infarction, as compared with those without myocardial infarction, unadjusted mortality at 1 year was significantly higher. After adjustment for differences in baseline and procedural characteristics between the two groups, spontaneous myocardial infarction was a powerful independent predictor of an increased risk of death, whereas periprocedural myocardial infarction was not significantly associated with an increased risk of death. Similar observations have been made among patients with diabetes and stable coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (NCT00006305), in which a first spontaneous, symptomatic myocardial infarction was associated with higher mortality, as compared with myocardial infarction induced by percutaneous or surgical revascularization.56

Taken together, contemporary studies indicate that spontaneous myocardial infarction is a powerful predictor of mortality. Periprocedural myocardial infarction, although frequent, is a marker of atherosclerotic burden and procedural complexity, but in most cases, it does not have important independent prognostic significance in stable coronary artery disease or in non–ST-elevation acute coronary syndromes. Although large periprocedural myocardial infarcts may affect prognosis, they rarely occur in the absence of procedural complications or in patients with normal baseline cardiac troponin levels.

Areas of Uncertainty

There is a pressing need for the interventional community and the associated professional organizations to examine the new data and provide more practical guidelines for defining periprocedural myocardial infarction. This process should include an assessment of the appropriateness of relying on biomarkers alone and of the low threshold used for the universal definition, as compared with a definition that includes clinical criteria such as symptoms or evidence of ischemia or infarction on electrocardiography or cardiac imaging.
Since most of the data on periprocedural myocardial infarction are derived from patients with normal levels of cardiac biomarkers before the procedure (predominantly those with stable or unstable angina), clearer guidelines are needed with regard to whether periprocedural myocardial infarction can be diagnosed in patients with non–ST-elevation myocardial infarction in whom biomarkers are rising before PCI and, if so, what diagnostic criteria should be used. This is probably not feasible in contemporary practice, since PCI is often performed within 24 hours after hospital admission. Another practical issue that needs to be addressed is whether the class IIa recommendation to routinely measure biomarkers after PCI is still appropriate and, if so, what the therapeutic implications of an elevated post-PCI level would be. A recent report from the National Cardiovascular Data Registry indicates that the majority of hospitals in the United States do not routinely measure cardiac biomarkers at the time of PCI.  

The improved understanding of the clinical significance of periprocedural myocardial infarction has important implications for the design of future randomized trials (i.e., periprocedural myocardial infarction and spontaneous myocardial infarction should not be considered equivalent clinical end points). This issue has most recently been relevant with respect to the interpretation of data from the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PLATFORM trial (NCT00385138). In that study, the majority of patients had acute coronary syndromes without ST-segment elevation and underwent PCI within 24 hours after presentation. This did not allow a reliable distinction between spontaneous myocardial infarction and periprocedural myocardial infarction, and led the investigators to conclude that the result of the trial “calls into question the definition of periprocedural MI used.” Differentiating spontaneous myocardial infarction from periprocedural myocardial infarction will be increasingly difficult in clinical practice, since most invasively managed cases involve cardiac catheterization during a period when pre-
procedural biomarker levels would generally be rising. Thus, we would caution against including myocardial infarction as a component of the primary composite end point in future clinical trials of PCI in acute coronary syndromes or using it as a surrogate for long-term outcomes, although one might reasonably consider it as a secondary efficacy end point or a safety end point.

**Implications for Practice**

Our recommendation is that cardiac troponin levels be routinely measured before PCI is performed (Fig. 2). A normal preprocedural level of cardiac troponin will assist in risk stratification by identifying patients in whom PCI can be performed with very low risk and who may be considered for early discharge from the hospital. In addition, a pre-PCI elevation in cardiac troponin identifies high-risk patients with complex or thrombotic lesions who may benefit from the preprocedural initiation of potent antiplatelet therapies and statins to improve outcomes. Post-PCI levels should be routinely measured in patients who have undergone complex procedures, who have suboptimal angiographic results, or who have procedural complications, as well as in those who have signs or symptoms of myocardial ischemia, in order to quantify the extent of myocardial injury. However, a reasonable case can be made for not routinely measuring postprocedural cardiac troponin levels in uncomplicated, successful PCI, since it is not likely that in such cases relevant additional information can be gained that will be independent of the preprocedural risk and procedural outcomes. The role of postprocedural monitoring of biomarkers for risk stratification in the secondary prevention of coronary artery disease or as a metric of quality remains to be established.

There are no established cutoff values for cardiac troponin that define a “large” periprocedural myocardial infarct, and until such values can be clearly identified, a CK-MB level that is more than 5 times the upper reference limit, the presence of new Q waves, or both would appear to be reasonable criteria for defining a periprocedural myocardial infarction as extensive. We believe that, in general, this definition can reliably be applied only to patients with normal cardiac troponin levels before PCI. In the absence of data that can be used to help direct practice, we recommend that patients with large periprocedural myocardial infarction be monitored in the hospital for an additional day because of the reported risks of arrhythmias, hemodynamic instability, heart failure, and death (Table 2, and the Supplementary Appendix). For the purpose of preprocedural consent, one should discuss the frequency of a large periprocedural myocardial infarction (<5%) with the patient and inform the patient if it occurs after the intervention.

The care of patients with acutely elevated preprocedural cardiac troponin who sustain major periprocedural myonecrosis should, in general, be based on the guidelines for managing acute coronary syndromes. Patients whose condition unexpectedly deteriorates soon after PCI (e.g., those with recurrent and unrelenting chest pain, particularly in combination with ST-segment shifts or echocardiographic evidence of ischemia or peri-cardial effusion) should undergo repeat coronary angiography. The goal is to identify procedural complications that are amenable to further intervention, such as acute stent thrombosis, coronary dissection, or perforation, to limit myocardial necrosis and relieve symptoms. In most cases, this involves repeat PCI; it is rare in current practice for patients to require cardiac surgery.

Perhaps the most important implication for the long-term care of the vast majority of patients with periprocedural myocardial infarction is the realization that they represent a higher-risk cohort owing to a greater disease burden and more unstable disease. These patients should therefore be targeted for optimal secondary prevention based on the current guidelines. Occasionally, patients with stable coronary artery disease have extensive periprocedural myocardial infarction. The long-term care of such patients should be similar to that for patients with spontaneous myocardial infarction.

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

**References**


MDR Tuberculosis — Critical Steps for Prevention and Control

Eva Nathanson, M.Sc., Paul Nunn, F.R.C.P., Mukund Uplekar, M.D., Katherine Floyd, Ph.D., Ernesto Jaramillo, M.D., Ph.D., Knut Lönnroth, M.D., Ph.D., Diana Weil, M.Sc., and Mario Raviglione, M.D.

From the Stop TB Department, World Health Organization, Geneva. Address reprint requests to Dr. Jaramillo at the Stop TB Dept., World Health Organization, CH-1211 Geneva, Switzerland, or at jaramiloe@who.int.


Multidrug-resistant (MDR) tuberculosis is defined as disease caused by strains of Mycobacterium tuberculosis that are at least resistant to treatment with isoniazid and rifampicin; extensively drug-resistant (XDR) tuberculosis refers to disease caused by multidrug-resistant strains that are also resistant to treatment with any fluoroquinolone and any of the injectable drugs used in treatment with second-line anti-tuberculosis drugs (amikacin, capreomycin, and kanamycin). MDR tuberculosis and XDR tuberculosis are serious threats to the progress that has been made in the control of tuberculosis worldwide over the past decade.1,2

In 2008, an estimated 440,000 cases of MDR tuberculosis emerged globally.1 India and China carry the greatest estimated burden of MDR tuberculosis, together accounting for almost 50% of the world’s total cases. More than three quarters of the estimated cases of MDR tuberculosis occur in previously untreated patients. The proportion of MDR cases among new cases and previously treated cases of tuberculosis reported globally from 1994 through 2009 ranged from 0 to 28.3% and from 0 to 61.6%, respectively (Fig. 1). The highest proportions of MDR cases, and the most severe drug-resistance patterns, appear in the countries of the former Soviet Union. By 2009, a total of 58 countries had reported at least one case of XDR tuberculosis. In eight countries, reported cases of XDR tuberculosis account for more than 10% of all cases of MDR tuberculosis, and six of these countries were part of the former Soviet Union. By far the largest number of cases of XDR tuberculosis has been reported from South Africa (10.5% of all cases of MDR tuberculosis in that country), owing to rapid spread among people infected with the human immunodeficiency virus (HIV).

National programs are failing to diagnose and treat MDR tuberculosis. Globally, just under 30,000 cases of MDR tuberculosis were reported to the World Health Organization (WHO) in 2008 (7% of the estimated total), of which less than one fifth were managed according to international guidelines. The vast majority of the remaining cases probably are not diagnosed or, if diagnosed, are mismanaged. This problem remains despite the evidence that management of MDR tuberculosis is cost-effective3 and that treatment of MDR tuberculosis, and even treatment of XDR tuberculosis, is feasible in persons who are not infected with HIV.4,5

In some countries, the incidence of tuberculosis is rising, and the incidence of MDR tuberculosis appears to be rising even faster (e.g., in Botswana and South Korea).6 However, in Estonia, Hong Kong, the United States, and Orel and Tomsk Oblasts (in the Russian Federation), the incidence of tuberculosis is falling, and the incidence of MDR tuberculosis appears to be falling even faster.1,6 This trend is
the result of high-quality care and control practices that result in high rates of case detection and cure, drug-susceptibility testing for all patients, and the provision of appropriate treatment for all patients carrying drug-resistant strains. In short, preventing initial infection with MDR tuberculosis and managing the treatment of existing cases appropriately are the keys to containing the spread of this disease.

The WHO-recommended Stop TB Strategy provides the framework for treating and caring for those who are sick and controlling the epidemic of drug-susceptible and drug-resistant disease. The DOTS approach, which underpins the Stop TB Strategy, calls for political commitment to national programs designed to control disease by means of early diagnosis with the use of bacteriologic testing, standardized treatment with supervision and patient support, and provision and management of the drugs used in treatment; the approach also includes the monitoring of treatment and evaluation of its effectiveness. Between 1995 and 2008, a total of 36 million people were treated successfully with the use of the DOTS approach, and 6 million lives were saved.

Specific guidelines for controlling drug-susceptible and drug-resistant disease already exist, and the Global Plan to Stop TB, 2006 through 2015, developed by the Stop TB Partnership, specifies the scale at which these interventions need to be funded and implemented to achieve global targets. However, to date, planning, funding, and implementation are falling far behind the milestones that have been set.

Prompted by concern that political support for the management of MDR tuberculosis is insufficient, WHO, the Bill and Melinda Gates Foundation, and the Chinese Ministry of Health organized a ministerial conference in Beijing in April 2009. The report from the conference in Beijing and the subsequent resolution (number 62.15) approved by the World Health Assembly in May 2009 state that significant changes in several components of the health care system must be made if MDR tuberculosis is to be eliminated.

This review assesses the critical factors impeding control and discusses the solutions required to address them.

Figure 1. Distribution of the Proportion of Cases of MDR Tuberculosis among New Cases of Tuberculosis, 1994–2009.

The following 27 countries are responsible for 85% of the world’s estimated cases of MDR tuberculosis and are classified as countries with a high burden of MDR tuberculosis: China, India, Russia, Pakistan, Bangladesh, South Africa, Ukraine, Indonesia, Philippines, Nigeria, Uzbekistan, Democratic Republic of Congo, Kazakhstan, Vietnam, Ethiopia, Myanmar, Tajikistan, Azerbaijan, Moldova, Kyrgyzstan, Belarus, Georgia, Bulgaria, Lithuania, Armenia, Latvia, and Estonia. Adapted from the 2010 report on MDR and XDR tuberculosis from the WHO.
Critical Weaknesses and How to Address Them

Prevention is better than cure. Thus, the top priority for the control and, ultimately, elimination of MDR tuberculosis is prevention of its emergence.\textsuperscript{15} Once MDR tuberculosis has emerged, however, urgent measures are required to curb its effects on efforts to control the disease. The major obstacles and approaches to controlling MDR tuberculosis are described below and summarized in Table 1. Three topics of great importance — the global shortage of health care workers,\textsuperscript{16} the need for improvements in surveillance systems,\textsuperscript{1} and the urgent need for intensified research on new diagnostic tests, drugs, and vaccines\textsuperscript{17} — have been well described elsewhere and are beyond the scope of this article.

Financing Control and Care

To achieve the goal of universal access to diagnosis and treatment described in the Global Plan to Stop TB, 1.3 million cases of MDR tuberculosis in the 27 countries with the highest burden of MDR disease will need to be treated between 2010 and 2015.\textsuperscript{5} The total estimated cost of such treatment is several billion U.S. dollars, an amount far in excess of the existing level of funding. The national strategic plans in these countries must incorporate the preparation of ambitious budgets for the prevention and control of MDR tuberculosis. These plans must be consistent with policies on health care financing, including social-protection schemes (the delivery of commodities to reduce the social vulnerability of poor populations), and with broader planning and financing frameworks. These countries — especially the middle-income countries among them — must mobilize their domestic resources. In 2001, the WHO Commission on Macroeconomics and Health indicated that these middle-income countries could finance all, or almost all, of their health care needs.\textsuperscript{18} While maximizing the use of domestic resources, they should also target resources available from international financing organizations, such as the Global Fund to Fight AIDS (Acquired Immunodeficiency Syndrome), Tuberculosis, and Malaria and UNITAID, an organization that provides grants allowing countries to purchase diagnostic tests and drugs used in the treatment of HIV–AIDS, malaria, and tuberculosis. The failure to adequately fund a response to MDR tuberculosis would have catastrophic consequences in terms of both human lives and tuberculosis control in general.

Abolishing Financial Barriers

Health expenditures that account for more than 40% of household income (after deducting the cost of basic subsistence) have been defined as catastrophic.\textsuperscript{19} In virtually all countries with a high burden of MDR tuberculosis, treatment costs (per course of treatment) for one person are more than 100% of the gross national income per capita (the cost of second-line anti-tuberculosis drugs alone is typically $2,000 to $4,000 per patient).\textsuperscript{1} Collective financing mechanisms are therefore required to guarantee universal access to health care. The main source of funding should be domestic resources, such as contributions from taxes, payroll deductions, or mandatory insurance premiums.\textsuperscript{20,21} Most countries in Africa, Asia, and the Middle East have not attained universal health coverage,\textsuperscript{22} although there are exceptions. Lessons need to be drawn from universal health-financing schemes applied in such diverse settings as Mexico, Rwanda, and Thailand, where access to care may facilitate early detection and treatment of all tuberculosis cases. Even before universal health coverage is achieved, immediate steps can be taken to reduce catastrophic health expenditures for patients with tuberculosis and their households.\textsuperscript{23} These steps include decentralization of services to reduce the indirect costs that patients seeking care incur, provision of patient incentives and social support to promote adherence to treatment, and subsidization of care provided in the private sector that is in line with guidelines from national tuberculosis programs.

Engaging All Care Providers

A substantial proportion of patients with tuberculosis or MDR tuberculosis seek care with providers who are not linked to national tuberculosis programs.\textsuperscript{24,25} In five countries with a high burden of MDR tuberculosis, more than half of all sales of first-line anti-tuberculosis drugs occur in the private sector, and the proportion is even higher for sales of second-line drugs.\textsuperscript{26} Many physicians in the private sector and some in the public sector do not follow internationally recommended treatment regimens for tuberculosis, use medicines of questionable quality, and ne-
### Table 1. Critical Challenges in the Control of MDR Tuberculosis and XDR Tuberculosis and Potential Solutions Supported by the WHO.*

<table>
<thead>
<tr>
<th>Goal</th>
<th>Problem</th>
<th>Proposed Solution</th>
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<tbody>
<tr>
<td>Finance control and treatment for MDR-TB and XDR-TB</td>
<td>Finance control and treatment for MDR-TB and XDR-TB is critical. Estimated cost for 2010–2015 is $16.2 billion (in U.S. $), increasing annually from &lt;$1.3 billion in 2010 to $4.4 billion in 2015; funding needed is already in excess of the planned national MDR-TB budgets for 2010.</td>
<td>Maximize use of domestic resources while targeting resources from the Global Fund to Fight AIDS, Tuberculosis, and Malaria, UNITAID, and other external funding mechanisms in the private sector.</td>
</tr>
<tr>
<td>Abolish financial barriers</td>
<td>A substantial proportion of patients seek care from providers who do not follow internationally recommended treatment protocols, leading to delayed diagnosis and initiation of treatment with second-line anti-TB drugs. Persons with infectious MDR-TB and XDR-TB remain in the community for long periods of time because of delayed diagnosis and treatment, and initial treatment failure of MDR-TB remains a major problem.</td>
<td>Engage all care providers in appropriate MDR-TB prevention and control.</td>
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<tr>
<td>Optimize MDR-TB and XDR-TB management and care</td>
<td>Persons with infectious MDR-TB and XDR-TB remain in the community for long periods of time because of delayed diagnosis and treatment, and initial treatment failure of MDR-TB remains a major problem.</td>
<td>Strengthen laboratory services by using new molecular technologies.</td>
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<tr>
<td>Ensure timely diagnosis and treatment initiation for patients with MDR-TB and XDR-TB</td>
<td>Estimated cost for 2010–2015 is $16.2 billion (in U.S. $), increasing annually from &lt;$1.3 billion in 2010 to $4.4 billion in 2015; funding needed is already in excess of the planned national MDR-TB budgets for 2010.</td>
<td>Engage all care providers in appropriate MDR-TB prevention and control.</td>
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<td>Address laboratory crisis</td>
<td>In 2008, in 77 countries with the highest burden of MDR-TB, only 1% of patients with newly diagnosed TB and 3% of patients with previously treated TB underwent drug-susceptibility testing.</td>
<td>Strengthen laboratory services by using new molecular technologies.</td>
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<tr>
<td>Ensure access to quality-assured anti-TB drugs</td>
<td>Use of counterfeit and poor-quality anti-TB drugs, which can lead to development and amplification of drug resistance, is well documented, but there is no accurate estimate of the scale of the problem.</td>
<td>Secure affordable, quality-assured anti-TB drugs using national procurement mechanisms while building up a reliable second-line anti-TB drug market, with manufacturers investing in increased volumes and improved quality.</td>
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<tr>
<td>Address global health workforce crisis</td>
<td>Shortage of trained staff to effectively manage the 1.6 million MDR-TB cases expected by 2015 is exacerbated in many low-income countries by active recruitment of staff by industrialized countries.</td>
<td>Revise or update strategic plans for increasing the TB health care workforce (including TB care providers), to improve basic TB care and to scale up MDR-TB control.</td>
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<tr>
<td>Improve surveillance systems</td>
<td>Establish or strengthen continuous surveillance systems for drug-resistant TB.</td>
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</tr>
<tr>
<td>Address global health workforce crisis</td>
<td>Estimates of the burden of drug-resistant TB globally and by country remain incomplete and less than accurate.</td>
<td>Ensure collaboration between development and technical agencies to facilitate development and field testing of new tools for prevention, diagnosis, and treatment of TB.</td>
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glect essential principles of case management.\textsuperscript{27,28} Such practices lead to the development, amplification, and spread of drug resistance. In addition, collaboration with public and private hospitals warrants special attention.\textsuperscript{29}

Guidance on implementing a mix of public and private approaches to tuberculosis care is available,\textsuperscript{30} and many national tuberculosis programs have begun to incorporate diverse sources of care, including public, voluntary, private, and corporate providers. Nonetheless, only a fraction of the tuberculosis cases diagnosed by practitioners outside the public sector are registered with or referred to national tuberculosis programs.\textsuperscript{31,32}

These approaches should therefore be scaled up and applied to the prevention and management of MDR tuberculosis as well. National tuberculosis programs need to play a stewardship role and provide guidelines, training, technical and financial support, and the supervision needed to align the practices of private providers with the International Standards for TB Care.\textsuperscript{33} Effective engagement of diverse care providers will require national tuberculosis programs to both augment their own capacities and strengthen private provider networks to enable them to shoulder their responsibility for managing tuberculosis and MDR tuberculosis. Professional associations need to act as intermediaries between national tuberculosis programs and private providers. Nongovernmental organizations have introduced successful programs for the management of MDR tuberculosis in a number of countries and are key players in scaling up diagnosis and treatment.\textsuperscript{34,35}

But collaborative approaches and appropriate incentives alone may not enlist the support of all relevant care providers — some regulation may be necessary. In some countries with a high burden of tuberculosis, providers are not required to notify the government when a new case of tuberculosis has been diagnosed. And even in countries where notification is required, systems have not been established to ensure that the requirement is met. Case notification for both tuberculosis and MDR tuberculosis must be made mandatory; providers who follow best practices should be certified and accredited and should be offered access to free supplies of quality-assured anti-tuberculosis drugs for their patients.\textsuperscript{30} Sustainable engagement of all care providers will require national tuberculosis programs to work in close partnership with health professionals, representatives of the pharmaceutical industry, pharmacists, and drug regulatory authorities, in addition to consumer and patient associations.

**Optimizing Disease Management and Care**

Transmission of drug-resistant tuberculosis occurs in the community,\textsuperscript{36} as indicated by the high frequencies of MDR tuberculosis among previously untreated patients in some countries. In most countries with limited resources, patients with MDR or XDR tuberculosis must complete two unsuccessful courses of treatment with first-line anti-tuberculosis drugs before being eligible for treatment with second-line drugs.\textsuperscript{37} Moreover, in many countries, treatment of MDR tuberculosis is started only after the diagnosis has been confirmed, a process that takes months when conventional methods are used. As a result, persons with infectious MDR or XDR tuberculosis remain in the community for long periods of time. Prompt diagnosis and treatment of tuberculosis and MDR tuberculosis can keep the case reproduction number of MDR strains below their replacement rate — and perhaps even below that of non-MDR strains.\textsuperscript{8}

Outbreaks of MDR tuberculosis have occurred in hospitals, and patients with tuberculosis who are hospitalized have a higher risk of acquiring MDR tuberculosis than do those who are treated as outpatients.\textsuperscript{38,39} Treating MDR tuberculosis in a hospital is more expensive than doing so on an ambulatory basis. Hospital treatment is also more socially and economically disruptive for most patients.\textsuperscript{40} In addition, the number of hospital beds may become insufficient as countries expand treatment for MDR tuberculosis. Despite the complexities involved in caring for patients with MDR tuberculosis, including lengthy therapy with poorly tolerated drugs, clinic-based or community-based care has proved to be feasible and effective in several countries, including Nepal\textsuperscript{41} and Peru.\textsuperscript{42} However, the effectiveness of outpatient care depends on the availability of primary care facilities, qualified health care workers, and social support networks to promote adherence to treatment. Countries need to select the model of care that is right for them, taking into account the personal rights and needs of patients and communities,\textsuperscript{43} the numbers of patients who have both MDR tuberculosis and
HIV–AIDS, the social circumstances of patients, the health care infrastructure, and the ability of the country to mobilize resources.

**RESPONDING TO THE LABORATORY CRISIS**

Weak laboratory capacity remains a serious impediment to prompt diagnosis and better control of MDR tuberculosis. The goal of universal access to drug-susceptibility testing has not yet been achieved. In 2008, drug-susceptibility testing was performed in only 1% of new tuberculosis cases and 3% of previously treated cases in the 27 countries with the highest burden of MDR tuberculosis.

Today, rapid molecular tests for MDR tuberculosis are available. For instance, one new automated rapid test for rifampicin resistance holds promise for easier detection of MDR tuberculosis even in community settings. The implementation of this and other rapid tests, especially in countries with a high prevalence of concurrent HIV infection and MDR tuberculosis, can prevent fatal delays in detection. The establishment of quality-assured diagnostic capacity, including rapid diagnostic technologies to identify MDR tuberculosis, is feasible in resource-limited settings. Use of the new molecular technologies offers one of the best avenues for improving overall diagnostic capacity in the laboratory. At present, however, the adoption of the new rapid tests will not eliminate the need for conventional drug-susceptibility testing with the use of solid or liquid culture. Conventional susceptibility testing is required to determine susceptibility to drugs other than rifampicin and isoniazid. While countries expand laboratory capacity and introduce the new rapid tests, targeted drug-susceptibility testing should be performed in specific groups of patients at risk for drug resistance. Expansion of diagnostic capacity for MDR tuberculosis must be coupled with access to second-line anti-tuberculosis drugs. Efforts to shorten the time required for diagnosis must occur in tandem with measures that minimize organizational delay to ensure prompt initiation of treatment.

**ENSURING ACCESS TO QUALITY-ASSURED DRUGS**

In 2007, only 15% of reported new cases of tuberculosis were treated with fixed-dose combinations of anti-tuberculosis drugs, despite their logistic advantages and potential to reduce the risk of the development of drug resistance. The use of counterfeit and poor-quality anti-tuberculosis drugs, which can lead to the development and amplification of drug resistance, is well documented, but there is no accurate estimate of the scale of the problem. International quality standards have been developed but are often ignored, and an insufficient number of manufacturers have been approved under the WHO Prequalification Programme.

To effectively prevent and manage MDR tuberculosis, countries need to secure affordable, quality-assured, anti-tuberculosis drugs through national procurement mechanisms. Affordable and quality-assured, second-line anti-tuberculosis drugs can also be accessed through the WHO Green Light Committee, which ensures management of MDR tuberculosis that is in line with international quality standards in 70 countries. However, of particular concern for efforts to increase the scale of MDR tuberculosis management is the insufficient supply of quality-assured, second-line anti-tuberculosis drugs. As of April 2010, only two manufacturers that produce three of the seven second-line anti-tuberculosis drugs on the WHO Model List of Essential Medicines had been approved by the WHO Prequalification Programme. Building up a reliable market of second-line anti-tuberculosis drugs, with manufacturers investing in increased volumes and improved quality, requires more accurate forecasting of demand. In addition, national authorities need to expedite the enrollment of many more patients under proper management conditions.

**RESTRICTING DRUG AVAILABILITY**

Anti-tuberculosis drugs are widely available over the counter in retail pharmacies in many countries. This encourages self-treatment and the purchase of inadequate quantities and combinations of medicines. Even when the drugs are prescribed, those prescribing the drugs outside national tuberculosis programs may not abide by recommended regimens, and some patients may purchase only part of the prescription because of financial constraints. Prescription and dispensing of medicines in general, and of antibiotics in particular, are poorly monitored and regulated in most countries. Even when regulations exist, their enforcement is often insufficient.

An essential step toward improved prevention
of MDR tuberculosis is to encourage the engagement of private and public providers with national tuberculosis programs on a voluntary basis. A more forceful approach would be to restrict the right to prescribe and dispense the drugs to the national tuberculosis program itself or to providers that have been accredited by the program. Either approach would require a combination of new government policy and dialogue with care providers, including pharmacists, and the pharmaceutical industry. Such measures undertaken by national tuberculosis programs to optimize drug management and supply have been successful in some countries, including Brazil, Ghana, Syria, and Tanzania. Consumers also need to be aware of the risks of poor prescribing practices and, as discussed above, the clinical and public health threats posed by substandard medicines. Demand-driven efforts to push for more accountability and enforcement of regulations by national authorities may be highly effective. Further advances in social responsibility and improved marketing practices on the part of drug manufacturers are also essential, along with supportive government measures.

PRIORITY CONTROL OF TUBERCULOSIS INFECTION

As a result of inadequate measures of infection control, there is ongoing transmission of MDR tuberculosis and XDR tuberculosis in health care facilities and congregate settings (e.g., prisons). To date, virtually no country with a high burden of tuberculosis has implemented systematic measures to reduce the risk of tuberculosis transmission in health facilities. Health care workers, especially those working in tuberculosis hospitals and in resource-limited settings, are at substantially higher risk of contracting tuberculosis and MDR tuberculosis than the general population.

All health care facilities that admit patients with tuberculosis or patients suspected of having tuberculosis should implement tuberculosis-control measures that complement general measures of infection control, especially those which target other airborne infections. Home-based and community treatment of MDR tuberculosis should be promoted. To curb the increased risk of nosocomial tuberculosis and MDR tuberculosis among health care workers, some countries have added tuberculosis to the list of recognized occupational hazards. Infection control requires engagement with a wide range of stakeholders across the health care system, including hospital administrators, architects, engineers, doctors, nurses, and laboratory staff. On the policy level, infection control requires collaborative action among those concerned with infections with airborne potential, such as influenza.

THE URGENT NEED FOR ACTION

Critical weaknesses in current approaches to the treatment and control of MDR tuberculosis and XDR tuberculosis have been identified and are being addressed at the global level. In 2009, the Beijing Call for Action and the passage of World Health Assembly Resolution 62.15 signaled a major step forward in coordinated planning for the treatment and control of MDR tuberculosis and in the commitment to achieve universal access to diagnosis and treatment by 2015 for patients who have the disease. Resolutions, however, are useful only insofar as they stimulate the appropriate policymakers in governments to act on them. By October 2009, 20 of the 27 countries with the highest burden of MDR tuberculosis were updating their national tuberculosis-control plans to include a component addressing MDR tuberculosis, in compliance with the World Health Assembly resolution. Furthermore, for the countries that have received grants from the Global Fund in its ninth round of grants, funding requested for the management of MDR tuberculosis was by far the largest requested for all aspects of tuberculosis control: more than $500 million (in U.S. dollars) was requested for the management of MDR tuberculosis in 28 countries over a period of 5 years.

Every one of the recommendations in this article for improving the treatment and control of MDR tuberculosis requires action beyond national tuberculosis control programs, sometimes in the political environment outside the health care system. This is a highly ambitious but necessary agenda for health authorities in the affected countries and for the global health community. The steps involved in controlling MDR tuberculosis are also important steps toward strengthening health care systems, including progress in achieving universal health care coverage. If this
policy agenda is not pursued with urgency. The human and financial costs to societies will be profound.

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References

35. Cox HS, Kalon S, Allamaturova S, et al. Multidrug-resistant tuberculosis treatment...
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Clinical Evaluation of the Knee

Teresa L. Schraeder, M.D., Richard M. Terek, M.D., and C. Christopher Smith, M.D.

The knee is one of the most complex joints in the body. Not surprisingly, knee problems are one of the most common musculoskeletal symptoms evaluated by the primary care physician.1

ANATOMY

The knee joint consists of three bones — the femur, tibia, and patella — with three areas of articulation. The important soft-tissue structures of the knee include the four major ligaments — the anterior cruciate, posterior cruciate, and medial and lateral collateral ligaments — the joint capsule, the medial and lateral menisci, the quadriceps tendon, and the patellar tendon. The menisci are fibrocartilaginous structures located between the tibiofemoral articulations; they increase stability and distribute contact forces on the articular cartilage (Fig. 1 and 2).

COMMON KNEE INJURIES

All the bones and soft tissues of the knee are subject to injury. The most common problems that are reported in a physician’s office are related to soft-tissue inflammation, injury, or arthritis. Injuries to soft tissue and injuries resulting from overuse are often caused by reproducible mechanisms of physical trauma or forces. Fractures are less common and include fractures of the tibial plateau, the femoral condyles, or the patella.

Knowledge of the mechanisms of knee injury can be essential to making an accurate diagnosis. An injury caused by valgus stress to the knee can result in medial collateral ligament strain or rupture, and an injury caused by varus stress can result in lateral collateral ligament strain or rupture. Abrupt noncontact deceleration or twisting and pivoting with simultaneous valgus stress to the knee can cause rupture of the anterior cruciate ligament, whereas abrupt posterior translation of the tibia can result in rupture of the posterior cruciate ligament. Twisting and pivoting of the knee while it is bearing weight can cause a meniscal tear.

Overuse injuries are often manifested as pain in the structure subject to repetitive stress. For example, repetitive jumping can lead to patellar tendonitis, also called jumper’s knee, whereas repeated application of direct pressure to the patella through kneeling can cause prepatellar bursitis, sometimes referred to as housemaid’s knee.

HISTORY

Obtaining a complete history is the first step in determining the cause of knee pain. The key elements include location and characterization of pain, mechanism of injury, sound of a “pop” at the time of injury (which can indicate a ligamentous tear or fracture), immediate or delayed swelling, recent infections, ability to bear weight, locking sensation or instability (or incidents of subluxation), and prior injuries to the joint.
To assess nontraumatic causes of subacute or chronic knee pain (in addition to questions about location and characterization of pain), the clinician should inquire about fever, morning stiffness, pain after exercise, tick bites (to assess risk of Lyme disease), infections (including sexually transmitted diseases, such as gonorrhea), history of gout or psoriasis, and activities contributing to long-term overuse.

GENERAL EXAMINATION OF THE KNEE

Gait is an important element of the physical examination of the knee. The clinician should always evaluate the patient's gait and weight-bearing abilities, since the findings can help distinguish knee pathology from pain referred from the hip, lower back, or foot.

When clinically appropriate, a useful part of the clinical evaluation of knee pain is observing the patient execute a duckwalk, which requires the patient to squat and attempt to walk in that position. The duckwalk requires an intact ligamentous system and a knee free of significant meniscal pathology, effusions, and bony abnormalities, such as arthritis. Thus, if a patient can perform a duckwalk, he or she probably has no ligamentous instability, large effusions, or meniscal tears.

The alignment of the knees should also be evaluated, with the patient standing with feet together. Look for a varus (bow-legged) or valgus (knock-kneed) deformity. Such deformities can predispose the patient to osteoarthritis or indicate the presence of significant osteoarthritis. Quadriceps atrophy can indicate disuse after an injury. If there is any suspicion of quadriceps atrophy the circumference of each thigh should be measured to confirm or rule out any changes to the underlying musculature.

It is also important to carefully assess the skin around the knee. Abnormalities such as hematoma, rash (e.g., psoriasis), abrasions or lacerations, and cellulitis provide important diagnostic clues.

PALPATION OF THE KNEE

Always examine both knees, beginning with the unaffected knee. This approach will reassure the patient and limit any apprehension about the examination, and it will also establish a baseline against which the affected knee can be compared.

Using the back of the hand, assess for warmth as an indicator of inflammation. Next, with the knee at a 90-degree angle, palpate the knee, beginning with the anterior structures. Start by placing your thumbs on the tibial tuberosity and move superiorly. As you move superiorly, palpate the patellar tendon and its insertion at the inferior pole of the patella; pain in this area, especially in an athlete, might indicate patellar tendonitis.

In a patient with a direct trauma to the knee, carefully palpate for areas of tenderness that might indicate a fracture. In such patients, five specific findings or factors should prompt consideration of radiographic imaging to rule out a traumatic fracture: an age of 55 years or older, tenderness at the head of the fibula, isolated patellar tenderness, inability to flex the knee to 90 degrees, or inability to bear weight and complete at least four steps. These five factors constitute the Ottawa knee rules, a validated decision-making tool with a sensitivity of 100%. Radiography should also be considered if an injury to the anterior cruciate ligament is suspected; such an injury can be associated with avulsion fractures of the lateral tibial plateau.

In a patient with focal tenderness, erythema, and warmth and swelling anterior to the patella, acute prepatellar bursitis should be considered. Patients with this condition, which can be septic and may require aspiration or drainage, typically have a history of recurrent kneeling or of direct trauma.
Pain, swelling, and a palpable defect at the insertion of the quadriceps tendon into the superior aspect of the patella suggests rupture of a quadriceps tendon. This injury may be accompanied by a “pop” when it occurs, followed by diminished or complete absence of extensor strength.

The clinician should identify the inferior pole of the patella and move medially to examine the medial joint line. Pain along the medial joint line might represent medial compartment osteoarthritis, injury to the medial collateral ligament, or a medial meniscal tear.

Tenderness at the midpoint between the anterior aspect of the medial joint line and the tibial tuberosity may indicate pes anserine bursitis (located at the insertion of the hamstring tendons into the tibia). Pes anserine bursitis is often found in runners with tight hamstrings and in patients with valgus deformity; in the latter case, it is often associated with osteoarthritis of the knee.

The clinician should also examine the lateral joint line for tenderness, which can be caused by lateral compartment osteoarthritis, injury to the lateral collateral ligament, or a lateral meniscal tear. Focal pain at the lateral femoral condyle is suggestive of iliotibial band syndrome.

Palpation of the popliteal fossa can reveal a tender, fluid-filled mass called a Baker’s cyst. This results from a posterior extension of knee-joint effusions and often accompanies osteoarthritis.

ASSESSMENT OF EFFUSION

The absence of the normal indentations on the peripatellar grooves on either side of the patella may indicate the presence of a large intraarticular effusion. Two maneuvers can help confirm the presence of an intraarticular effusion.

In the first maneuver, with the knee extended, use the nondominant hand to squeeze the intraarticular fluid from the suprapatellar region into the space between the patella and femur. With the dominant hand, exert pressure superiorly from the tibia while using your index finger to push the patella against the patellofemoral groove. When an effusion is present, you can easily ballot the patella.

The second maneuver used to assess for an effusion should also be performed with the knee in extension. Gently milk the fluid into the suprapatellar pouch by moving your hand proximally along the medial aspect of the patella. Next milk or compress the fluid from the suprapatellar pouch to the medial knee by moving your hand from the superior lateral region to the inferior lateral region; if there is an effusion, compressing the lateral regions will cause a bulge to appear medial to the patella in the areas that are naturally concave.

Comparison with the unaffected knee is essential. If an effusion is present, arthrocentesis may be necessary for diagnostic or therapeutic reasons.

RANGE OF MOTION

Both active and passive range of motion of the knee should be tested. The normal range of extension is 0 to −10 degrees, and the normal range of flexion is 130 to 150 degrees. The location and movement of the patella should be noted: watch for any signs of abnormal tracking, crepitus, or pain. If retropatellar pain and crepitus occur while the patella is being compressed against the trochlea during active extension, patellofemoral syndrome or patellofemoral arthritis (chondromalacia) should be considered. Pain with active range of motion but painfree passive range of motion suggest a soft-tissue disorder such as tendinitis. Pain that is equal on both passive and active range of motion is more likely to suggest an intraarticular process.
ASSESSMENT OF THE MEDIAL COLLATERAL AND LATERAL COLLATERAL LIGAMENTS

Injury to the medial or lateral collateral ligaments typically involves direct trauma to the contralateral side of the knee — for example, a direct blow to the lateral side results in valgus stress and injury to the medial collateral ligament. To assess the medial collateral ligament, apply valgus stress to the knee. With the knee flexed to 25 degrees, place one hand on the outer aspect of the knee to apply medial pressure, and the other hand on the inner aspect of the distal tibia to apply lateral pressure; you are testing for tenderness or laxity along the medial collateral ligament.6,7 Similarly, the lateral collateral ligament can be tested by applying lateral pressure to the inner knee and medial pressure to the outer ankle or lower leg, which causes varus stress to the knee.

When assessing the medial or lateral collateral ligaments, tenderness along the ligament, but less than 5 mm of laxity and a solid end point, indicates a first-degree sprain. In a second-degree sprain, a solid end point is maintained but there is increased laxity when the knee is tested at 25 degrees of flexion and no laxity in full extension. In a third-degree sprain or a complete tear of the ligament, there will be a soft end point and more than 10 mm of laxity when the knee is at 25 degrees of flexion; if there is also laxity with full extension, there may be additional damage to the cruciate ligament.6

ASSESSMENT OF THE ANTERIOR CRUCIATE LIGAMENT

The anterior drawer test and the Lachman test provide information about the integrity of the anterior cruciate ligament.

In the anterior drawer test, the patient should be supine, with the knee flexed to 90 degrees and the foot placed flat on the table. Stabilize the foot (you can sit on the end of the patient’s foot) and place your thumbs on the tibial plateau and your fingers around the calf, relaxing the hamstrings; pull forward to test the anterior cruciate ligament. If the ligament is intact, it should abruptly stop the anterior motion of the tibia with a solid end point. The affected and unaffected legs should have similar degrees of anterior translation.

The Lachman test is a more sensitive and specific test for assessment of the anterior cruciate ligament.7,8 In this maneuver, the patient is supine and asked to relax the hamstrings. Use one hand to stabilize the femur while placing the knee at 20 degrees of flexion. With the other hand, grasp the proximal tibia and briskly pull the tibia forward. If there is more than 6 to 8 mm of laxity, more laxity than in the unaffected knee, or a soft end point, the ligament may be torn.9 If you are unable to firmly grasp and stabilize the femur, you can modify the Lachman maneuver by placing your knee under the patient’s knee, firmly pressing down on the distal femur with one hand, and pulling the tibia anteriorly with your other hand.

A large hemorrhagic effusion of rapid onset frequently accompanies anterior cruciate ligament tears and bony fractures and contributes to the patient’s discomfort. Arthrocentesis can be of both diagnostic and therapeutic benefit and can also facilitate a more accurate examination.

ASSESSMENT OF THE POSTERIOR CRUCIATE LIGAMENT

To test the integrity of the posterior cruciate ligament, perform the posterior drawer test and assess for evidence of a tibial sag.

As in the anterior drawer test, the patient should be supine and the knee flexed to 90 degrees. The foot should be flat on the table. Stabilize the foot (you can sit on the end of the patient’s foot) and place your thumbs on the tibial tubercle and your fingers around the calf, then briskly push the tibia posteriorly to test the posterior cruciate ligament. If the ligament is intact, there should be a solid end point and little posterior translation of the tibia.
The tibial sag test is another test of the integrity of this ligament.6 Have the patient flex both knees at 90 degrees and place both feet flat on the table; then observe the alignment of the tibial plateau. Normally, the tibial plateau extends 1 cm beyond the femoral condyle. If the affected tibia is displaced posteriorly on the femur, or sags, as compared with the unaffected tibial plateau, the posterior cruciate ligament may be ruptured.

**ASSESSMENT OF THE MENISCUS**

Patients with meniscal injuries may report clicking, catching, or locking of the knee. In addition, they frequently have an effusion of delayed onset, appearing hours or even days after the injury.

In addition to assessment of the knee for joint-line tenderness, there are two common maneuvers that can be used to assess for possible meniscal tears. In the McMurray test, the patient is supine. To test the medial meniscus, place one hand over the anterior aspect of the knee, with fingers and thumb on the medial and lateral joint lines. Grasp the patient’s heel with the other hand and externally rotate the tibia, using the first hand to apply valgus force at the knee during passive flexion and extension. The maneuver is repeated when applying internal rotation and varus stress to test the lateral meniscus. Clicking, catching, or popping at the joint line during early extension or midextension may indicate a meniscal tear.10

In the Apley compression test, or grind test, the patient lies prone and the knee is flexed to 90 degrees. Stabilize the thigh by placing your knee or hand firmly on top of the patient’s posterior thigh. Grasp the foot and apply a downward compressive force while rotating the tibia internally and externally. Pain on compression is considered positive for a meniscal tear.7,11

Suspicion of a meniscal tear should prompt a careful assessment of the anterior cruciate ligament; likewise, suspicion of a torn anterior cruciate ligament should prompt a careful assessment of the meniscus. Injuries to these two structures often occur together.

**SUMMARY**

In summary, a thorough history and physical examination are the first steps in evaluating knee pain and making an accurate diagnosis, after which decisions about imaging studies (radiography, magnetic resonance imaging, and ultrasonography), treatment, and referral to specialists can be made.

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

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**REFERENCES**


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Lying Low

John J. Ross, M.D., Anand Vaidya, M.D., and Ursula B. Kaiser, M.D.

An 88-year-old woman presented to the emergency room with confusion. She began having transient episodes of confusion, dizziness, tremors, and anxiety a year earlier. These episodes were unpredictable, lasting for minutes and then abating spontaneously, and had been increasing in frequency since they began. The patient felt well between episodes and reported no abnormal sensation . . .

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