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# CLINICAL PRACTICE

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Caren Solomon • Jeffrey Drazen

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JOURNAL *of* MEDICINE

*Clinical Practice*



EDITED BY  
CAREN G. SOLOMON, M.D., M.P.H.,  
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# *Clinical Practice*

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## CLINICAL PRACTICE

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## Preface

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The Clinical Practice series was introduced in the *New England Journal of Medicine* in 2001 to help meet the information needs of clinicians who want to remain up to date on a wide variety of problems commonly encountered in practice. Articles in this biweekly series review clinical problems at the interface of primary and specialty care in a concise, easily recognized format. Each article begins with a brief case vignette to highlight the major clinical question or questions to be covered. Subsequent sections include: "The Clinical Problem" (Who is at risk? How common is the condition?), "Strategies and Evidence" (What are the data to support particular approaches?), "Areas of Uncertainty" (What are major gaps in our current knowledge?), "Guidelines" (What do professional organizations recommend?), and finally, "Summary and Conclusions" (What would the author(s) recommend with respect to the diagnosis or treatment of the patient outlined in the vignette?). Simply put, each article is a structured "curbside consult" about a patient with a well-defined clinical problem.

Recognizing that data are lacking to guide the "optimal" approach to many clinical problems that physicians must manage, the experts who author these articles are asked to not only make clear where rigorous data are or are not available, but also to provide recommendations based on their assessment of the literature and their personal experience where rigorous data are lacking.

This book includes selected Clinical Practice articles previously published in the *New England Journal of Medicine*. Topics covered include those in cardiology, pulmonary medicine, dermatology, women's health, psychiatry, infectious disease, allergy-immunology, and gastroenterology. In cases where there have been clinically meaningful changes in the area covered by the article since publication, authors have provided a short update to their article.

We have created this collection to provide an easy way to access this clinical resource. We anticipate that once you have scanned the book, you will use it as a reference as you encounter problems similar to the ones outlined in the chapters. We hope that you will find the material of value in your care of patients.

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# *Subclinical Hyperthyroidism*

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ANTHONY D. TOFT, M.D.

**A 67-year-old woman presents with palpitations and is found to be in atrial fibrillation at a rate of 120 beats per minute. The only other finding on physical examination is a goiter, which is known to be long-standing. Echocardiography shows neither valvular disease nor left ventricular systolic dysfunction. The serum thyrotropin concentration is less than 0.05 mU per liter, and the serum total triiodothyronine and free thyroxine concentrations are in the normal range. Should the thyroid dysfunction be treated?**

## THE CLINICAL PROBLEM

**T**he combination of an undetectable serum thyrotropin concentration, as measured by an assay with a threshold of detection that is 0.1 mU per liter or less, and normal serum triiodothyronine and thyroxine concentrations (usually at the upper end of the normal range) is known as subclinical hyperthyroidism. This condition reflects the fact that before clinical features of thyrotoxicosis are apparent, the thyrotrophs usually respond to minor increments in thyroid hormone concentrations, which remain within the normal range, by switching off the production and secretion of thyrotropin.<sup>1</sup> An absence of symptoms was once part of the definition of subclinical hyperthyroidism, but we now understand that subtle symptoms or signs of thyrotoxicosis may be present. Subclinical hyperthyroidism is classified as endogenous in patients with thyroid hormone production associated with nodular thyroid disease or underlying Graves' disease; it is classified as exogenous in those with undetectable serum thyrotropin concentrations as a result of treatment with levothyroxine. Not all patients with undetectable serum thyrotropin concentrations and normal thyroxine and triiodothyronine concentrations have subclinical hyperthyroidism, and this combination of findings can be associated with various other conditions (Table 1).

Multinodular goiter is usually palpable, if not visible, and may be sufficiently large to cause compressive complications. Imaging with technetium-99m pertechnetate or iodine-123 generally shows "hot" (functioning) nodules and is particularly useful for detecting a single, impalpable, autonomously functioning adenoma. Most patients who present with

Table 1. Patterns of Thyroid Function Associated with a Suppressed Serum Thyrotropin Concentration and a Thyroid Hormone Concentration That May Be Normal.

Condition or Factor	Triiodothyronine		Thyroxine	
	Free	Total	Free	Total
Endogenous subclinical hyperthyroidism (associated with Graves' disease or nodular goiter)*	Upper end of normal range	Upper end of normal range	Upper end of normal range	Upper end of normal range
Exogenous subclinical hyperthyroidism (associated with levothyroxine therapy)	Normal	Normal	Upper end of normal range or elevated	Upper end of normal range or elevated
Nonthyroidal illness	Normal, low, or elevated†	Normal or low	Normal, low, or elevated‡	Normal, low, or elevated§
Drug therapy¶				
Dopamine	Normal	Normal	Normal	Normal
Corticosteroids	Normal	Normal	Normal	Normal
Amiodarone	Normal	Normal	Usually elevated but may be at upper end of normal range	Usually elevated but may be at upper end of normal range
Central hypothyroidism	Normal or low	Normal or low	Low end of normal range or low	Low end of normal range or low

\* Subclinical hyperthyroidism may also be noted during the hyperthyroid phase of subacute, silent, or postpartum thyroiditis.

† In patients with nonthyroidal illness, the concentration of free triiodothyronine may be found to be elevated if a particular commercial assay system (Vitros ECi, Ortho Clinical Diagnostics) is used.

‡ The value depends on both the severity of the illness and the method of measurement used.

§ The value depends on the type and severity of the illness.

¶ Thyroid-function test results in patients with nonthyroidal illness may be influenced by concomitant drug therapy.

multinodular goiter have been aware of thyroid enlargement for several years, and they may have undergone partial thyroidectomy. The so-called simple, diffuse goiter observed in patients in their late teens and 20s tends to progress to a more obvious, multinodular goiter at around 40 years of age. As the goiter increases in size and as the autonomous nodules become larger and more numerous, subclinical or overt hyperthyroidism is increasingly present.<sup>2</sup>

Underlying Graves' disease may be present if a patient has a family history of the disorder or has other organ-specific autoimmune diseases, such as type 1 diabetes mellitus, vitiligo, pernicious anemia, myasthenia gravis, or Addison's disease, or if the patient has diffuse goiter, ophthalmopathy, or pretibial myxedema. Thyroid imaging with isotope methods shows an even distribution, and the results in patients with early-stage Graves' disease are likely to be similar to those in normal persons. The presence of thyrotropin-receptor antibodies in serum is diagnostic of Graves' disease, irrespective of the clinical findings, but the antibodies are absent in approximately 5 to 20 percent of patients with hyperthyroid Graves' disease, depending on the assay used,<sup>3</sup> and almost certainly in a greater proportion of those with subclinical hyperthyroidism.

## STRATEGIES AND EVIDENCE

The issue of screening for thyroid disease in patients with few or no symptoms was discussed in a recent article in the *Journal*.<sup>4</sup> In view of the relatively high prevalence of unrecognized hypothyroidism in older adults, especially women, an expert panel of the American Thyroid Association has recommended routine screening of adults for thyroid disease by measurement of serum thyrotropin.<sup>5</sup> In hospital practice, thyroid-function testing has become almost routine. Such screening will inevitably identify patients with undetectable serum thyrotropin concentrations but normal thyroxine and triiodothyronine concentrations, although the prevalence of such findings is low. In one study, for example, involving 1210 patients over the age of 60 years who were seen at a single general practice in the United Kingdom and who were not taking thyroxine, serum thyrotropin concentrations were undetectable in 16 patients (1.3 percent).<sup>6</sup> During one year of follow-up, thyrotoxicosis developed in only one patient, and serum thyrotropin concentrations returned to normal in two patients. In some patients, the thyrotropin concentration may have been undetectable because of a transient nonthyroidal disorder or because of drug therapy for such a disorder.

The estimated rate of progression from subclinical to overt hyperthyroidism in patients with multinodular goiter is 5 percent each year,<sup>7</sup> and it may be significantly higher with the administration of iodine as a dietary supplement in areas where goiter is endemic, or with the use of the antiarrhythmic drug amiodarone, which contains iodine. Progression to prolonged overt hyperthyroidism in patients with underlying Graves' disease is probably less common, given the relapsing and remitting nature of Graves' disease and the eventual development of hypothyroidism in some patients.

If screening or the investigation of goiter shows that a patient has subclinical hyperthyroidism, should it be treated? Other than regular monitoring, the options for managing subclinical hyperthyroidism are the same as those for managing overt hyperthyroidism: the administration of antithyroid drugs (in patients with Graves' disease only) or iodine-131. Although iodine-131 uptake is likely to be lower in patients with subclinical hyperthyroidism than in those with overt hyperthyroidism, there is no evidence that a dose that is therapeutic in the second group is less effective in the first. Partial thyroidectomy would be indicated for a large multinodular goiter that caused mediastinal compression. One reason to treat subclinical hyperthyroidism is to prevent the development of overt hyperthyroidism. Prevention of atrial fibrillation and prevention of osteoporosis are the other chief potential benefits of treatment, but how good is the evidence of these preventive effects?

### Atrial Fibrillation

The best evidence that subclinical hyperthyroidism is a risk factor for the development of atrial fibrillation comes from the Framingham Study.<sup>8</sup> A cohort of 2007 persons 60 years of age or older was followed for 10 years, and the development of atrial fibrillation was analyzed in relation to the initial concentration of serum thyrotropin. Among the 61 subjects with a thyrotropin concentration of less than 0.1 mU per liter and a normal serum thyroxine concentration at the outset, atrial fibrillation developed in 13, of whom an unspecified number were taking thyroxine. The relative risk of atrial fibrillation in this group of 61 subjects was 3.1 as compared with those who had a normal serum thyrotropin concentration (0.4 to 5.0 mU per liter); the risk was similar when the patients who were taking thyroxine were excluded from the analysis. A low but detectable serum thyrotropin concentration (0.1 to 0.4 mU per liter) was not associated with an increased risk of atrial fibrillation.

Assuming that antithyroid therapy would reduce the risk of dysrhythmia to that in the general population, 4.2 cases of subclinical hyperthyroidism would need to be treated to prevent 1 case of atrial fibrillation over a period of 10 years.<sup>9</sup> There is only limited evidence that established atrial fibrillation in patients with subclinical hyperthyroidism reverts spontaneously or after cardioversion once the serum thyrotropin concentration has been normalized with antithyroid therapy.<sup>10</sup>

Thyrotoxic atrial fibrillation is commonly considered a risk factor for systemic embolism, but the reported risk has ranged from negligible to 40 percent — extremes that do not reflect clinical experience. Even a risk of 10 percent probably represents an overestimate, since it is based on data obtained at a time when accurate tests of thyroid function were not widely available<sup>11</sup> and when an early diagnosis of hyperthyroidism was less likely than it is now. However, the available data suggest that among patients with atrial fibrillation that is unrelated to rheumatic heart disease, those with thyrotoxicosis have a higher rate of embolism than do patients without the condition. The risk of systemic embolism in patients with atrial fibrillation complicating subclinical hyperthyroidism is not known.

### Osteoporosis

Frank hyperthyroidism is a recognized risk factor for osteoporosis, but the effects of subclinical hyperthyroidism on bone mineral density are less well defined. The increased bone turnover that is characteristic of Graves' disease persists during treatment with antithyroid drugs if serum thyrotropin concentrations remain suppressed, despite normal concentrations of thyroid hormones.<sup>12</sup> In two cross-sectional studies of patients

with subclinical hyperthyroidism due to multinodular goiter, there was statistically and clinically significantly lower bone mineral density at the femoral neck and radius than in age-matched controls.<sup>13,14</sup> Whether these changes are associated with an increased rate of fracture is not known. More impressive are the reports that postmenopausal women with subclinical hyperthyroidism due to multinodular goiter have a 2 percent loss of bone mineral density each year, which can be reversed by treatment that restores serum thyrotropin concentrations to the normal range.<sup>15,16</sup>

A large meta-analysis of patients with exogenous subclinical hyperthyroidism showed that bone loss was greater among postmenopausal women with this condition than among those without it.<sup>17</sup> However, the validity of these results is questionable, since the study also found increased bone loss in premenopausal women who were receiving levothyroxine replacement therapy and who had normal serum thyrotropin concentrations. Furthermore, the increased risk of fracture reported in older women taking thyroid hormones disappears when those with a history of hyperthyroidism are excluded.<sup>18</sup> The evidence that exogenous subclinical hyperthyroidism is a risk factor for osteoporosis is therefore inconclusive.<sup>19,20</sup>

### Other Considerations

Other abnormalities have been linked to both endogenous and exogenous subclinical hyperthyroidism. There is evidence that patients with subclinical hyperthyroidism due to multinodular goiter have increased left ventricular mass, increased systolic function, and impaired diastolic function, but the clinical significance of these observations is not known.<sup>21</sup> Impairment of the quality of life, as assessed with the use of a questionnaire, was also reported in these patients.<sup>21</sup> Whether normalization of the serum thyrotropin concentration improves these measures is uncertain. An increased risk of dementia and Alzheimer's disease was recently reported among patients with endogenous subclinical hyperthyroidism who were 55 years of age or older, particularly if antibodies against thyroid peroxidase were present<sup>22</sup>; this finding requires confirmation.

Patients receiving long-term suppressive therapy with levothyroxine have been reported to have diminished cardiac reserve and exertional capacity.<sup>23</sup> However, similar abnormalities were abolished by reducing the dose of levothyroxine to a level that was still associated with subclinical hyperthyroidism.<sup>24</sup> Short-term studies of small numbers of patients with exogenous subclinical hyperthyroidism have found changes in target-organ function — e.g., an increase in the nocturnal heart rate and an altered ratio of diurnal urinary sodium excretion to nocturnal excretion. These changes are similar to but less marked than those in overt hyperthyroidism<sup>25</sup> but may not be sustained in the long term.<sup>26</sup>

### AREAS OF UNCERTAINTY

The natural history of subclinical hyperthyroidism remains unclear. Furthermore, the evidence that endogenous or exogenous subclinical hyperthyroidism is a risk factor for osteoporosis and atrial fibrillation is not definitive. However, it would be surprising if the complications of overt hyperthyroidism were not seen, albeit at a reduced frequency, in a condition that is effectively the mildest form of thyrotoxicosis; such complications are more likely to occur in patients with multinodular goiter, since the biochemical abnormality is persistent and the age of affected persons puts them at increased risk for bone loss or ischemic or structural heart disease.

The issue is further complicated by confusion over the meaning of subclinical hyperthyroidism, which is sometimes used to describe elevated serum thyroxine concentrations in patients who are taking thyroxine as replacement therapy. The inclusion of patients with wide ranges of thyroid-function test results and ratios of thyroxine to triiodothyronine may explain, at least in part, the disparate results of studies of target-organ function.

### GUIDELINES

In its 1995 consensus statement on the treatment of patients with hyperthyroidism and hypothyroidism, the American Thyroid Association does not mention subclinical hyperthyroidism.<sup>27</sup> However, the association does state that in patients taking levothyroxine as replacement therapy, the dose should be adjusted to achieve clinical euthyroidism, with normal serum concentrations of both thyroxine and thyrotropin.<sup>28</sup> In statements issued in 1996 and 1998, respectively, the Royal College of Physicians of London<sup>29</sup> and the American College of Physicians<sup>9</sup> concluded that there is no agreement about the benefits of detecting and treating endogenous subclinical hyperthyroidism or about whether it causes excess morbidity. The statement of the American College of Physicians was based on a meta-analysis of available data. In contrast, the American Association of Clinical Endocrinologists<sup>30</sup> concluded that subclinical hyperthyroidism associated with goiter requires treatment in most cases.

### RECOMMENDATIONS

In the absence of clinical signs of thyroid disease, and even after additional investigations such as isotope uptake and imaging and measurement of the thyrotropin-receptor antibody concentration, it may be difficult to decide whether the pattern seen on thyroid-function tests is a consequence of nonthyroidal illness and concomitant medication, underlying autonomous thyroid function, or the initial phase of thyroiditis. In such



circumstances, thyroid-function tests should be repeated after eight weeks; a normal or elevated serum thyrotropin concentration at this time suggests recovery from nonthyroidal illness or the hypothyroid phase of thyroiditis. If the initial pattern persists, the choice should be made between a trial of antithyroid drugs and close clinical follow-up.

### Exogenous Subclinical Hyperthyroidism

The dose of thyroxine should normally be reduced in patients with exogenous subclinical hyperthyroidism, excluding those with prior thyroid cancer, in whom thyrotropin suppression may be desired. The dose can usually be reduced abruptly to a more appropriate level. For example, in a symptomatic patient who has a markedly elevated serum free thyroxine concentration and a triiodothyronine concentration at the high end of the normal range while taking 250 µg of levothyroxine daily, it would be appropriate to reduce the dose to 150 µg daily and to retest thyroid function at a follow-up visit. The thyrotropin concentration may remain suppressed for six to eight weeks or more in patients with previous overreplacement of levothyroxine.

Although most patients feel well when thyroid function is normalized, a minority of patients have a sense of well-being only when taking a suppressive dose of levothyroxine.<sup>31</sup> In the absence of apparent complications of excess thyroid hormone, which would clearly warrant a dose reduction (Table 2), I would consider a slightly suprathreshold dose acceptable as long as the serum triiodothyronine concentration remained well within the normal range.<sup>29</sup>

### Endogenous Subclinical Hyperthyroidism

In many patients with endogenous subclinical hyperthyroidism who do not have nodular thyroid disease or complications of excess thyroid hormone, treatment is unnecessary, but thyroid-function tests should be performed every six months, with the recognition that the serum triiodothyronine concentration may become elevated before the serum thyrox-

Table 2. Indications for Reducing the Dose of Thyroxine in Patients with Exogenous Subclinical Hyperthyroidism.

New atrial fibrillation, angina, or cardiac failure
Accelerated loss of bone density
Oligomenorrhea, amenorrhea, or infertility
Nonspecific symptoms such as tiredness, hyperreflexia, and palpitations
Burdenline high serum triiodothyronine concentration

ine concentration does. In patients with questionable symptoms, such as fatigue, I would use the empirical approach of a six-month trial with an antithyroid drug at a low dose, such as methimazole at a daily dose of 5 to 10 mg initially, and if this approach was effective, I would consider ablative therapy with iodine-131. To treat a woman who wanted to become pregnant, propylthiouracil at a dose of 50 mg twice a day would be more appropriate, because aplasia cutis congenita, a rare scalp defect, has been linked to the use of methimazole during pregnancy. The management of hyperthyroidism during pregnancy is beyond the scope of this review, but it would require extremely close monitoring and use of the lowest possible dose of propylthiouracil.<sup>32</sup> In older patients with atrial fibrillation or osteoporosis that could have been caused or exacerbated by the mild excess of thyroid hormone, ablative therapy with iodine-131 is the best initial option.

Treatment of patients with subclinical hyperthyroidism due to nodular thyroid disease is more routinely justified, given the expected progression to overt hyperthyroidism. The patient described in the vignette has both goiter and atrial fibrillation, two findings that warrant therapy. In the case of atrial fibrillation, I would first administer an antithyroid drug such as methimazole in order to restore the serum thyrotropin concentration to a normal value as quickly as possible. I would also administer warfarin because of the risk of systemic embolism, even though there are no data from controlled studies of anticoagulant therapy in patients with thyrotoxic atrial fibrillation. Careful monitoring of the dose is essential, since patients with overt hyperthyroidism and, presumably to a lesser degree, those with subclinical hyperthyroidism are more sensitive than euthyroid patients to the anticoagulant effects of warfarin. If sinus rhythm is not restored within four months after the normalization of the serum thyrotropin concentration, cardioversion should be performed.<sup>33</sup> The definitive treatment would be an ablative dose of iodine-131. In the case described, and in similar cases, this approach is warranted for several reasons: the potential contribution of subclinical hyperthyroidism to the development of osteoporosis, the low incidence of hypothyroidism after iodine-131 therapy in patients with multinodular goiter (6 percent at one year at my institution, as compared with 75 percent in patients with Graves' disease), the possibility of loss to follow-up and the attendant worsening of symptoms if treatment is withheld in favor of continued observation, and the likely cosmetic benefit of up to a 50 percent reduction in the size of the goiter at one to two years.<sup>34,35</sup>

*This article first appeared in the August 16, 2001, issue of the New England Journal of Medicine.*

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# *Treatment of Tobacco Use and Dependence*

NANCY A. RIGOTTI, M.D.

**A 66-year-old woman with stable angina and a history of depression smokes 25 cigarettes daily. She would like to stop smoking but is concerned about weight gain. She has tried to quit several times on her own without success. What should her physician recommend?**

## THE CLINICAL PROBLEM

**T**obacco use is the leading preventable cause of death in the United States, responsible for more than 400,000 deaths annually, or 1 of every 5 deaths.<sup>1</sup> Half of regular smokers die prematurely of a tobacco-related disease.<sup>1</sup> The potential health benefits of smoking cessation are substantial. Cessation reduces the risk of tobacco-related diseases, slows the progression of established tobacco-related diseases, and increases life expectancy, even when smokers stop smoking after the age of 65 years or after the development of a tobacco-related disease.<sup>2</sup>

An estimated 70 percent of smokers see a physician each year, providing physicians with substantial opportunity to influence smoking behavior.<sup>3</sup> However, that opportunity presents challenges, as the case vignette illustrates. Many patients continue to smoke despite knowing about or experiencing the health consequences of tobacco use. Some who try to quit repeatedly fail. Most mistakenly believe that stopping smoking requires only willpower and are unaware that effective treatments are available. To help smokers, physicians must be familiar with the spectrum of effective therapies. They must also appreciate that tobacco use has complex physiological and psychological determinants and understand that changing any behavior is a gradual process. Smoking is best regarded as a chronic disease that requires a long-term management strategy, rather than a quick fix.<sup>3</sup>

Currently, 23.5 percent of U.S. adults (25.7 percent of men and 21.5 percent of women) smoke cigarettes.<sup>4</sup> Nearly all smokers acknowledge that tobacco use is harmful to health but underestimate the magnitude of their own risk. Few know the full spectrum of health risks.<sup>2,5</sup> For many smokers, the risk of future disease does not outweigh the current perceived benefits of smoking or barriers to cessation. Yet 70 percent of smokers report that

they want to quit.<sup>2</sup> Approximately one third of smokers try to stop smoking each year, but only 20 percent of them seek help.<sup>2,6</sup> Fewer than 10 percent of smokers who attempt to quit on their own are successful over the long term.<sup>2,3</sup> Smokers have a higher rate of success when they seek help with quitting.<sup>6</sup> Even then, several attempts are often required before long-term abstinence is achieved.<sup>2</sup>

The chief physiological obstacle to quitting is the addictive nature of nicotine. Nicotine causes tolerance and physical dependence. When tobacco use is stopped, there is a withdrawal syndrome characterized by irritability, anger, impatience, restlessness, difficulty concentrating, insomnia, increased appetite, anxiety, and depressed mood.<sup>7</sup> Symptoms of nicotine withdrawal are nonspecific, vary widely in intensity and duration, and are not correctly identified by smokers. Symptoms begin a few hours after the last cigarette, peak two to three days later, and wane over a period of several weeks or months.

Psychological factors also contribute to the difficulties that smokers have when they try to quit. Tobacco use is a learned behavior. Cigarettes become part of a smoker's daily routine, associated with events, such as finishing a meal, that become cues that trigger the desire to smoke. Smokers also use cigarettes to handle stress and negative emotions such as anger or anxiety. To stop smoking, a smoker must learn new coping skills and break old patterns, an incremental process in which attempts to quit often end in the resumption of smoking until abstinence is achieved.

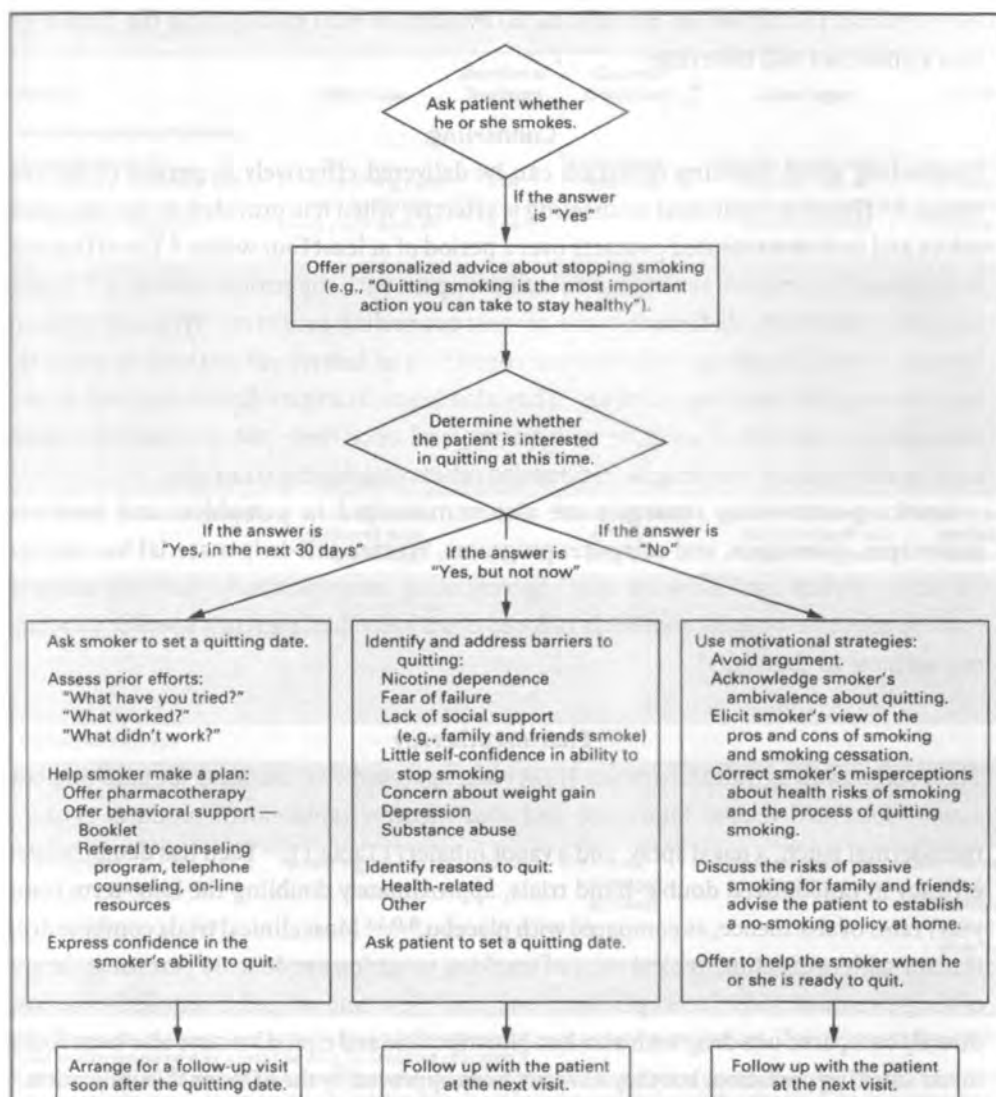
#### STRATEGIES AND EVIDENCE

Two approaches have strong evidence of efficacy for smoking cessation: pharmacotherapy and counseling.<sup>3,8,9</sup> Each is effective by itself, but the two in combination achieve the highest rates of smoking cessation. The efficacy of a treatment correlates with its intensity, but even brief interventions by physicians during an office visit promote smoking cessation.

##### Interventions by Physicians

Randomized, controlled trials conducted in primary care practices demonstrate that a physician's advice to stop smoking increases the rates of smoking cessation among patients by approximately 30 percent.<sup>8</sup> Providing a brief period of counseling (three minutes or less) is more effective than simply advising the patient to quit and doubles the cessation rate, as compared with no intervention. Effective interventions have a common approach<sup>3</sup> (Figure 1). Optimal implementation requires support from the health care system to bolster the efforts of individual physicians.<sup>8,10</sup> Office-based systems that document every patient's smoking status before the patient sees the physician and remind





**Figure 1. Smoking-Cessation Strategy for Physicians.**

This strategy uses the five steps (the "five A's") recommended in Public Health Service guidelines<sup>1</sup>: ask, advise, assess, assist, and arrange follow-up.

the physician to address the use of tobacco by patients who smoke triple the likelihood that a physician will intervene.<sup>8</sup>

### Counseling

Counseling about smoking cessation can be delivered effectively in person or by telephone.<sup>8,9</sup> Group or individual counseling is effective when it is provided by trained counselors and includes repeated contacts over a period of at least four weeks.<sup>8</sup> The efficacy of this approach increases as the amount of time spent with the patient increases.<sup>8</sup> Cognitive behavioral methods form the core of most counseling programs. Typically, smokers learn to identify smoking cues, then use cognitive and behavioral methods to break the link between the cues and smoking. They also learn strategies for coping with stress, managing symptoms of nicotine withdrawal, and once they quit, preventing relapse, such as anticipating tempting situations and rehearsing coping strategies.

Smoking-counseling strategies are also summarized in pamphlets and booklets, audiotapes, videotapes, and computer programs. Written self-help material has negligible efficacy when used alone but may augment other interventions.<sup>8,9</sup> Self-help material is more effective when its content is tailored to an individual patient's specific concerns or readiness to change.<sup>8,9</sup>

### Pharmacotherapy

The Food and Drug Administration (FDA) has approved five products for smoking cessation: sustained-release bupropion and four nicotine-replacement products (gum, a transdermal patch, a nasal spray, and a vapor inhaler) (Table 1).<sup>11</sup> Each has demonstrated efficacy in randomized double-blind trials, approximately doubling the long-term (one-year) rates of abstinence, as compared with placebo.<sup>8,9,11</sup> Most clinical trials combine drug therapy with counseling; typical rates of smoking cessation are 40 to 60 percent at the end of drug treatment and 25 to 30 percent at one year.<sup>8</sup> Few randomized, controlled trials have directly compared one drug with another. Nortriptyline and clonidine have also been found to aid smoking cessation, but they have not been approved by the FDA for this indication.<sup>8</sup>

**Nicotine-Replacement Therapy** Nicotine-replacement therapy provides an alternative form of nicotine to relieve symptoms of withdrawal in a smoker who is abstaining from tobacco use. The pharmacokinetic properties of available products differ, but none deliver nicotine to the circulation as fast as does inhaling cigarette smoke<sup>11</sup> (Figure 2). The patch provides a relatively stable, fixed dose of nicotine over a period of 16 or 24 hours. The other products have a more rapid onset and a shorter duration of action, allowing

Table 1. Drugs Used for Smoking Cessation.

Product	Daily Dose	Duration of Treatment	Common Side Effects	Advantages	Disadvantages
<b>Nicotine-replacement therapy</b>					
Transdermal patch*					
24 hr (e.g., Nicoderm CQ)	7-, 14-, or 21-mg patch worn for 24 hr†	8 wk	Skin irritation, insomnia	Provides steady level of nicotine; easy to use; unobtrusive; available without prescription	User cannot adjust dose if craving occurs; nicotine released more slowly than in other products
16 hr (e.g., Nicotrol)	15-mg patch worn for 16 hr	8 wk			
Nicotine polacrilex gum (Nicorette)*	1 piece/hr (<24 pieces/day)	8–12 wk	Mouth irritation, sore jaw, dyspepsia, hiccups	User controls dose; oral substitute for cigarettes; available without prescription	Proper chewing technique needed to avoid side effects and achieve efficacy; user cannot eat or drink while chewing the gum; can damage dental work; difficult for denture wearers to use
2 mg (<25 cigarettes/day)					
4 mg (≥25 cigarettes/day)					
Vapor inhaler (Nicotrol Inhaler)*	6–16 cartridges/day (delivered dose, 4 mg/cartridge)	3–6 mo	Mouth and throat irritation, cough	User controls dose; hand-to-mouth substitute for cigarettes	Frequent puffing needed; device visible when used
Nasal spray (Nicotrol NS)*	1–2 doses/hr (1 mg total; 0.5 mg in each nostril) (maximum, 40 mg/day)	3–6 mo	Nasal irritation; sneezing, cough, teary eyes	User controls dose; offers most rapid delivery of nicotine and the highest nicotine levels of all nicotine-replacement products	Most irritating nicotine-replacement product to use; device visible when used
<b>Non-nicotine therapy</b>					
Sustained-release bupropion (Zyban or Wellbutrin SR)†	150 mg/day for 3 days, then 150 mg twice a day‡	7–12 wk (up to 6 mo to maintain abstinence)	Insomnia, dry mouth, agitation	Easy to use (pill), no exposure to nicotine	Increases risk of seizure (≤0.1 percent)
Nortriptyline§	75–100 mg/day**	12 wk	Dry mouth, sedation, dizziness	Easy to use (pill), no exposure to nicotine	Side effects common; should be used cautiously in patients with coronary heart disease
Clonidine	0.1–0.3 mg twice a day	3–10 wk	Dry mouth, sedation, dizziness	No exposure to nicotine	Side effects limit use

\* This product has been approved by the Food and Drug Administration as a smoking-cessation aid. The Public Health Service clinical guidelines also recommend it as a first-line drug for smoking cessation.<sup>8</sup>

† The starting dose is 21 mg per day unless the smoker weighs less than 45.5 kg (100 lb) or smokes fewer than 10 cigarettes per day, in which case the starting dose is 14 mg per day. The starting dose should be maintained for four weeks, after which the dose should be decreased every week until it is stopped.

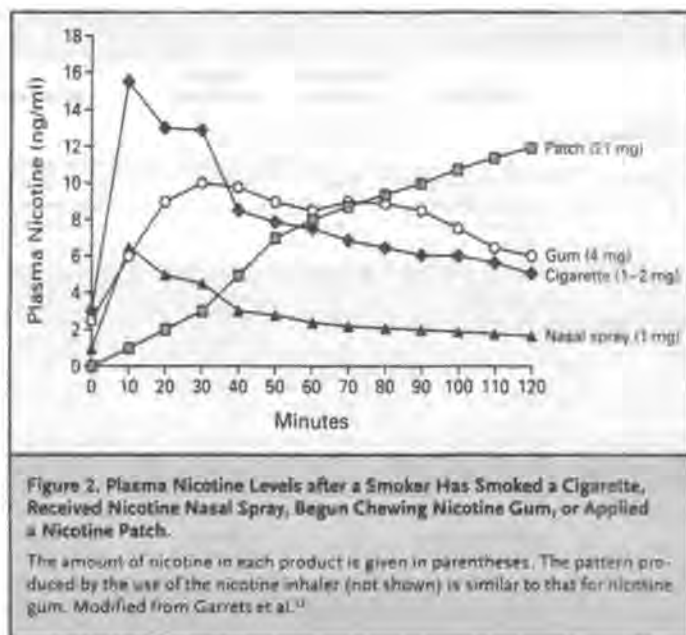
‡ The user should chew the gum slowly until he or she experiences a distinct taste, indicating that nicotine is being released. The user should then place the gum between cheek and gum until the taste disappears to allow the nicotine to be absorbed through oral mucosa. The sequence should be repeated for 30 minutes before the gum is discarded. Acidic beverages (such as coffee and soft drinks) reduce the absorption of nicotine and should be avoided for 30 minutes before and during chewing.

§ Tolerance develops to local side effects during the first week of use.

|| Treatment should be started one week before the quitting date.

|| This agent has not been approved by the Food and Drug Administration as a smoking-cessation aid. The Public Health Service clinical guidelines recommend it as a second-line drug for smoking cessation.<sup>8</sup>

\*\*Treatment should be started 10 to 28 days before the quitting date at a dose of 25 mg per day, and the dose should be increased as tolerated.



the user to adjust the dose of nicotine. Blood nicotine levels peak 5 to 10 minutes after the administration of nicotine nasal spray, 20 minutes after the user begins chewing nicotine gum or uses a vapor inhaler, and 2 to 4 hours after the application of a nicotine patch. The nicotine gum and the inhaler have similar pharmacokinetic properties since in both the nicotine is absorbed through the oral mucosa.

The use of all nicotine-replacement products increases the long-term rates of smoking cessation and relieves cravings for nicotine and the symptoms of nicotine withdrawal. In meta-analyses of placebo-controlled trials, the nicotine patch doubled the long-term smoking-cessation rate. The use of nicotine gum increases cessation rates by 50 to 70 percent.<sup>8,9</sup> For heavy smokers (those who smoke at least 25 cigarettes per day), the gum that contains 4 mg of nicotine per piece is more effective than that containing 2 mg per piece. Fewer studies have assessed the nasal spray and the vapor inhaler, but in meta-analyses both products doubled the cessation rates, as compared with placebo inhaler.

One randomized, controlled trial directly compared the four nicotine-replacement products.<sup>13</sup> The efficacy of each product was similar at week 12 of follow-up, but the rates of compliance varied, being highest for the patch, intermediate for the gum, and lowest for the vapor inhaler and the nasal spray. Studies consistently report higher rates of smoking cessation when nicotine-replacement therapy is combined with counseling, although the

former is effective even when used alone.<sup>8,9,11</sup> Different nicotine-replacement products can be combined safely. In some studies, combining the nicotine patch with gum, inhaler, or nasal spray was more efficacious than the use of any of these products alone.<sup>8,9,14</sup>

The safety of nicotine-replacement products is underscored by the fact that the patch and gum, initially sold only by prescription, are now available without a prescription. Although nicotine's hemodynamic effects increase the myocardial workload, nicotine-replacement therapy is safe in patients with cardiovascular disease, including stable angina.<sup>15,16</sup> The safety of nicotine-replacement therapy has not been studied in patients with unstable angina or in those who have had a myocardial infarction within two weeks before treatment, but the risk of cardiac complications should be lower than with smoking. Unlike smoking, nicotine-replacement therapy does not increase the coagulability of blood or expose a patient to carbon monoxide or oxidizing gases that damage endothelium.<sup>17</sup> The side effects of these products vary according to the manner in which nicotine is administered (Table 1).

**Non-Nicotine Therapy** Bupropion, an antidepressant with dopaminergic and noradrenergic activity, was efficacious for smoking cessation when combined with counseling in randomized, controlled trials.<sup>18,19</sup> The efficacy of bupropion when accompanied by minimal levels of psychosocial support, as occurs in medical practice, is unknown. Like nicotine-replacement therapy, treatment with bupropion doubles smoking-cessation rates as compared with placebo treatment.<sup>8,9,11</sup> Bupropion lowers the threshold for seizure and is contraindicated in patients who are at risk for seizures. The risk of seizure associated with the use of bupropion is 0.1 percent or less.<sup>8,9</sup> In one randomized, placebo-controlled trial that directly compared bupropion alone or in combination with the nicotine patch,<sup>19</sup> bupropion produced a significantly higher rate of abstinence at one year than either the nicotine patch or placebo. Treatment with both bupropion and the nicotine patch was safe but did not lead to significantly higher cessation rates than did treatment with bupropion alone (36 percent and 30 percent, respectively). Nonetheless, many clinicians use the combination for smokers who are very dependent on nicotine.

Nortriptyline was effective for smoking cessation in two small studies that used 75 to 100 mg daily for three months, starting 10 to 28 days before the quitting date.<sup>20,21</sup> No other antidepressant has had demonstrated efficacy for use in smoking cessation in a published trial,<sup>8,9</sup> nor are there data to support the use of anxiolytic agents for smoking cessation.<sup>8,9</sup> Treatment with clonidine reduces the symptoms of nicotine withdrawal and has been effective for smoking cessation, but the high frequency of adverse effects limits its use.<sup>8,9</sup>

### Other Methods

Hypnosis and acupuncture have also been suggested as therapies for smoking cessation. However, few controlled trials of hypnosis have been conducted,<sup>8,9</sup> and acupuncture was found to be ineffective in randomized trials.<sup>8,9</sup>

### Weight Gain after Smoking Cessation

Weight gain averages 2.3 to 4.5 kg (5 to 10 lb) after smoking cessation and is thus a concern for many smokers who are contemplating quitting, especially women.<sup>2,22</sup> Large weight gains (more than 13 kg [29 lb]) are uncommon, but are more likely in women, nonwhites, and heavy smokers than in other groups.<sup>23</sup> A large weight gain does not negate the benefits of smoking cessation, but this point rarely comforts smokers who are concerned about their weight. In one study, a weight-management program did not avert post-cessation weight gain.<sup>24</sup> Vigorous exercise reduced weight gain and increased abstinence rates in one trial.<sup>25</sup> Whether moderate physical activity has similar benefits is unknown, but exercise has sufficient merits on its own to be recommended routinely. Bupropion and, in some studies, nicotine gum (but not the nicotine patch) temporarily reduced weight gain after smoking cessation, but only while the drug was being administered.<sup>17,22</sup>

### AREAS OF UNCERTAINTY

Most treatment studies have been conducted in healthy adults who were motivated to stop smoking. Effective treatment for adolescent smokers, for smokers who are not interested in quitting smoking, or for those who repeatedly fail to quit is unclear. For smokers who are reluctant to attempt cessation, experts recommend "motivational interviewing," a counseling technique developed to help people prepare for a change in behavior.<sup>26</sup> The counselor builds empathy by acknowledging a smoker's ambivalence about stopping smoking, supports the smoker's autonomy with respect to making a responsible decision, and bolsters a smoker's self-confidence so that he or she can make a change. The technique is promising and reasonable, but it has not yet been proved to increase cessation rates.

Characteristics associated with a low rate of successful treatment include coexisting psychiatric conditions (current or past depression or schizophrenia), alcohol or substance abuse, strong nicotine dependence, lack of social support for quitting (e.g., a spouse who smokes), and a low level of confidence in one's ability to quit.<sup>8,9</sup> The optimal treatment for such persons is also not known. Most experts advise the use of more intensive treatments for longer periods.

Current and past major depression are more common in smokers than nonsmokers.<sup>27</sup> Smokers with a history of depression who attempt to quit smoking not only have lower



rates of success but also have more depressive symptoms during nicotine withdrawal and a greater risk of recurrent depression after cessation than do smokers with no history of depression.<sup>28</sup> The optimal treatment for smokers with current or past depression is uncertain, but they may require longer and more intensive treatment.<sup>9</sup> Bupropion and nortriptyline are effective in smokers with a history of depression.<sup>8,9</sup> Nicotine-replacement therapy may also be effective in such patients.<sup>29,30</sup> Psychological support appears to be important.<sup>31</sup>

### GUIDELINES

Two sets of clinical-practice guidelines based on independent, systematic reviews of the evidence were released in 2000. The Public Health Service's *Treating Tobacco Use and Dependence* (available at <http://www.surgeongeneral.gov/tobacco>)<sup>8</sup> updated a 1996 clinical-practice guideline issued by the Agency for Health Care Policy and Research.<sup>32</sup> The guidelines issued by Britain's Health Education Authority draw on systematic reviews by the Cochrane Collaboration's Tobacco Addiction Review group (available at <http://www.cochrane.org/cochrane/revabstr>).<sup>9,33,34</sup> The 1996 guidelines of the Preventive Services Task Force are consistent with newer guidelines except that they do not address newer types of pharmacotherapy (available at <http://www.odphp.osophs.dhhs.gov/pubs/guidecps>).<sup>35</sup> In 2001, the Task Force on Community Preventive Services of the Centers for Disease Control and Prevention released evidence-based guidelines for interventions at the level of the health care system (available at <http://www.thecommunityguide.org>).<sup>10</sup> The rate at which physicians provide advice on smoking cessation to their patients is now a standard measure for assessing the quality of care delivered by U.S. health plans.<sup>36</sup>

Guidelines consistently recommend that physicians assess and record patients' smoking status; advise smokers to quit; assess their readiness to do so; and assist smokers by offering support, pharmacotherapy (a nicotine-replacement product or bupropion), and referrals to cessation resources. Health care delivery systems (including hospitals) are directed to identify patients' smoking status, offer smoking-cessation services, and document these actions. The Public Health Service guidelines urge health insurers to cover all recommended treatments, including counseling and pharmacotherapy.<sup>8</sup>

### CONCLUSIONS AND RECOMMENDATIONS

There is broad agreement, based on strong evidence, about what constitutes effective treatment of tobacco use and dependence. Physicians should routinely identify patients' smoking status and readiness to quit, advise and assist smokers to quit, and offer pharmacotherapy to help them quit (Figure 1).<sup>8</sup> There is insufficient evidence to determine

whether nicotine-replacement products or bupropion is superior. Current guidelines and most experts regard them as roughly equivalent.<sup>8,9,11</sup> The choice of pharmacotherapy (Table 1) should take the patient's preferences and past experiences into consideration, unless one agent is contraindicated. A general approach is to start with a single agent and add a second if the smoker has severe withdrawal symptoms, cravings, or difficulty maintaining abstinence. Nicotine-replacement products can safely be combined with one another and with bupropion. Drugs are most effective when accompanied by counseling, whether delivered in person or by telephone. The addition of pharmacotherapy to counseling doubles the cessation rate.<sup>11</sup> Counseling is also effective by itself and should not be neglected.

The case vignette highlights common challenges facing physicians who treat smokers. The patient has repeatedly failed to quit smoking on her own, she has coexisting medical and psychiatric conditions, and she is concerned about gaining weight if she does quit smoking.<sup>37</sup> Often, smokers who repeatedly fail to quit have never received effective treatments (especially counseling) or have used pharmacotherapy incorrectly. Such patients may also have coexisting psychiatric conditions or substance abuse. When a smoker has a history of depression, careful screening for symptoms of depression is warranted before and during treatment.

In the case of the woman described in the clinical vignette, intensive treatment combining counseling with one or more drugs is warranted; bupropion may be a good choice, since it has proved effective in depressed patients. Strong symptoms of nicotine withdrawal should be expected but can be relieved by pharmacotherapy. The use of two or more products may be necessary. Even though she has stable angina, the patient can safely use either nicotine-replacement therapy or bupropion. She may reduce her risk of weight gain after smoking cessation by participating in a program of moderate exercise and by using bupropion, nicotine gum, or both.

Smoking is a chronic problem, like hypertension or hyperlipidemia, that requires long-term management.<sup>3</sup> Assistance with smoking cessation is a cost-effective intervention that is underused by physicians and inadequately covered by many health insurers.<sup>38,39</sup> For physicians and health care systems alike, the challenge is implementing effective treatment in routine medical practice.

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# Aortic Stenosis

BLASE A. CARABELLO, M.D.

A 60-year-old man is evaluated for a heart murmur. He jogs 3 mi (5 km) per day and is asymptomatic. Physical examination reveals a delayed carotid upstroke, a 3/6 late-peaking systolic ejection murmur that radiates to the neck, and a single  $S_2$ . An echocardiogram shows normal systolic function and a heavily calcified aortic valve. The patient's peak Doppler transvalvular gradient is 64 mm Hg, with a mean gradient of 50 mm Hg. His calculated valve area is  $0.7 \text{ cm}^2$ . How should this patient be treated?

## THE CLINICAL PROBLEM

**A**ortic stenosis is the most common cardiac-valve lesion in the United States. Two factors account for its common occurrence: approximately 1 to 2 percent of the population is born with a bicuspid aortic valve, which is prone to stenosis; and aortic stenosis develops with age, and the population is aging.

The clinician is usually first alerted to the presence of aortic stenosis by the finding of a systolic ejection murmur at the right upper sternal border that radiates to the neck. Clues that the disease is at least moderate in severity are peaking of the murmur late in systole, palpable delay of the carotid upstroke, and a soft single second heart sound, because the aortic component of  $S_2$  disappears when the valve no longer opens or closes well.

Although once thought of as a degenerative lesion, calcific aortic stenosis has many features in common with coronary disease.<sup>1</sup> Both conditions are more common in men, older persons, and patients with hypercholesterolemia, and both derive in part from an active inflammatory process.<sup>2</sup>

Aortic stenosis is distinguished from aortic sclerosis by the degree of valve impairment. In aortic sclerosis, the valve leaflets are abnormally thickened, but obstruction to outflow is minimal, whereas in aortic stenosis, the functional area of the valve has decreased enough to cause measurable obstruction of outflow. Little hemodynamic disturbance occurs as the valve area is reduced from the normal 3 to 4  $\text{cm}^2$  to 1.5 to 2  $\text{cm}^2$ . However, as shown in Table 1, an additional reduction in the valve area from half its normal size to

Table 1. Relation of the Aortic-Valve Area to the Mean Gradient.\*

Aortic-Valve Area cm <sup>2</sup>	Mean Gradient mm Hg
4	1.2
3	2.9
2	8.6
1	26
0.9	37
0.8	41
0.7	51
0.6	71
0.5	100

\*Data were derived with the Gorlin formula: aortic-valve area =

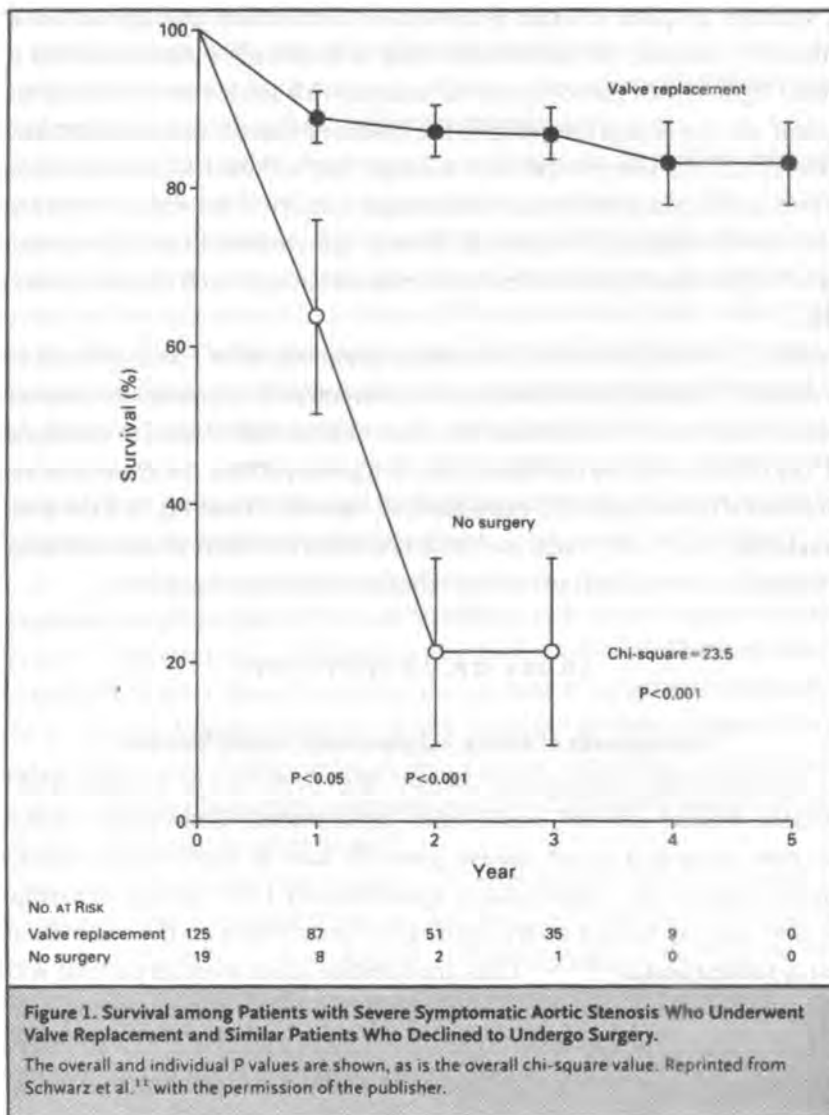
$$\frac{\text{cardiac output}}{44.3 \sqrt{\text{mean gradient}}}$$

where the cardiac output was assumed to be 6 liters per minute, the systolic ejection period was assumed to be 0.33 second, and the heart rate was assumed to be 80 beats per minute.

one quarter of its normal size produces severe obstruction to flow and a progressive pressure overload on the left ventricle. The concentric hypertrophy that develops in response to this overload is both adaptive and maladaptive. Whereas the increased muscle mass allows the ventricle to generate the increased force necessary to propel blood past the obstruction, the hypertrophied myocardium has decreased coronary blood flow reserve<sup>3</sup> (even in the presence of normal epicardial coronary arteries) and can also cause both diastolic and systolic left ventricular dysfunction, producing the symptoms of congestive heart failure.<sup>4,5</sup> The obvious question for the physician is when is the optimal time for clinical intervention? Although aortic stenosis often coexists with other valvular diseases, this review focuses on isolated aortic stenosis.

#### STRATEGIES AND EVIDENCE

There is no effective medical therapy for severe aortic stenosis; aortic stenosis is a mechanical obstruction to blood flow that requires mechanical correction. In children with congenital aortic stenosis, the valve leaflets are merely fused, and balloon valvotomy may offer substantial benefit.<sup>6</sup> In adults with calcified valves, however, balloon valvot-



omy only temporarily relieves symptoms and does not prolong survival.<sup>7</sup> Thus, the intervention required in adults, other than standard prophylactic antibiotics against infective endocarditis,<sup>8</sup> is the replacement of the valve. The risks of replacing that valve must be weighed against the risks of delaying the procedure. The procedure can usually be delayed until symptoms develop.<sup>9,10</sup> Studies of aortic stenosis uniformly demonstrate that once

angina, syncope, dyspnea, or other symptoms of heart failure develop and are found to be due to aortic stenosis, the patient's life span is drastically shortened unless the valve is replaced (Figure 1). Of the 35 percent of patients with aortic stenosis who present with angina, half will die within five years in the absence of aortic-valve replacement. Of the 15 percent of patients who present with syncope, half will die within three years, and of the 50 percent of patients who present with dyspnea, half will die within two years, unless the aortic valve is replaced. In contrast, 10-year age-corrected rates of survival among patients who have undergone aortic-valve replacement approach the rate in the normal population.<sup>11,12</sup>

The striking contrast between the excellent prognosis after aortic-valve replacement and the dismal prognosis in the absence of replacement in symptomatic patients makes the presence or absence of symptoms the crucial factor with respect to management. In general, the clinician can be confident that, in a given patient, the symptoms are due to aortic stenosis if the mean aortic-valve gradient exceeds 50 mm Hg or if the aortic-valve area is no larger than 1 cm<sup>2</sup>. I will use these as criteria for severe disease, although there is no universally accepted definition that relies on valve area or gradient.

## AREAS OF UNCERTAINTY

### Management of Severe Asymptomatic Aortic Stenosis

There is overwhelming evidence that patients with severe aortic stenosis who become symptomatic require prompt aortic-valve replacement. Conversely, asymptomatic patients, even those with severe disease, generally have an excellent prognosis without aortic-valve replacement. Unfortunately, approximately 1 to 2 percent of asymptomatic patients die suddenly or have a very rapid rate of progression to the symptomatic state and then to sudden death.<sup>9,10,13,14</sup> Thus, the question arises whether patients with severe asymptomatic aortic stenosis should undergo aortic-valve replacement to protect them from sudden death. Although some experts advocate this approach, this strategy exposes the entire group of asymptomatic patients with severe aortic stenosis to the risk of perioperative and valve-related complications and death. Even in the best of circumstances, the surgical mortality rate is approximately 1 percent and the risk of a valve-related complication (including thromboembolism; bleeding during therapy with anticoagulants; deterioration of the prosthetic valve, requiring reoperation; and infective endocarditis) is 1 percent per year.<sup>15</sup>

Echocardiography and exercise testing may identify asymptomatic patients who are likely to benefit from surgery. Otto et al.<sup>16</sup> found that patients with asymptomatic aor-



severe stenosis whose peak transaortic blood flow velocity exceeded 4 m per second (a peak gradient of 64 mm Hg) had a risk of becoming symptomatic and requiring aortic-valve replacement of 70 percent within two years. None of the patients in this moderate-sized series died suddenly, and all underwent exercise testing.

Although exercise testing is unwarranted and dangerous in patients with symptomatic aortic stenosis, it has proved safe in patients with moderate-to-severe asymptomatic aortic stenosis.<sup>16,17</sup> A preliminary report suggests that exercise testing may identify some patients with latent symptoms or exercise-induced hemodynamic instability, facilitating timely aortic-valve replacement. In a study of 58 asymptomatic patients,<sup>18</sup> 21 had symptoms for the first time during the exercise test. Most likely, these patients had failed to recognize the symptoms previously or had not engaged in activities that would have precipitated symptoms. Although patients with asymptomatic aortic stenosis can exercise safely under a physician's scrutiny, it seems most unwise to permit patients with moderate-to-severe aortic stenosis to engage in vigorous, unmonitored exercise in view of the limitations imposed by left ventricular hypertrophy on coronary blood flow.

#### **Treatment of the Patient with a Low Gradient and Reduced Ejection Fraction**

In patients with left ventricular dysfunction who have a substantial transvalvular gradient (a mean gradient of more than 40 mm Hg), the outcome of surgery is excellent despite the presence of a reduced ejection fraction preoperatively.<sup>19</sup> In these patients, the excessive afterload generated by the obstructing valve is a prime contributor to the left ventricular dysfunction. Once the obstruction is removed and the afterload is reduced, left ventricular function returns to or approaches normal.

Patients with a reduced ejection fraction and a small transvalvular gradient (less than 30 mm Hg)<sup>19,20</sup> have a high operative risk, and only half such patients are alive three to four years after surgery.<sup>21</sup> The poor outcome in these patients is related to the presence of both severely depressed myocardial contractility and the excessive afterload.<sup>19</sup>

Although the overall prognosis for this group of patients is poor, some patients in this category, presumably those with severe valve obstruction, benefit from surgery.<sup>21,22</sup> In other patients, the calculated valve area may be severely reduced because cardiomyopathy inhibits the left ventricle from completely opening a mildly but not a severely stenotic valve. The presence of low output may lead clinicians to the false conclusion that the valve is severely stenotic (aortic pseudostenosis).<sup>23-25</sup> The best method for distinguishing these two conditions is to increase cardiac output during Doppler echocardiography or cardiac catheterization and to use the new data to recalculate the valve area. In the case of pseudostenosis, increased output causes a large increase in the calculated valve area, often to

more than 1 cm<sup>2</sup>. In this group of patients, valve replacement is unlikely to be beneficial. Conversely, patients in whom increased cardiac output produces a substantial increase in gradient have a true outflow obstruction and may benefit from surgery. Patients with a low gradient who have no response to inotropic stimulation have a poor outcome, presumably because the myocardial damage is so far advanced.<sup>26</sup>

#### **Safety of Cardiac Surgery in Patients with Mild-to-Moderate Aortic Stenosis**

Controversy also exists regarding the optimal approach to patients with mild-to-moderate aortic stenosis (as indicated by a transvalvular gradient in the range of 10 to 30 mm Hg and a valve area of more than 1 cm<sup>2</sup>) who require cardiac surgery for some other cause, usually coronary revascularization. Concomitant aortic-valve replacement increases the risk of both perioperative death and complications related to the prosthetic valve. However, if the native valve is left in place, aortic stenosis may progress so rapidly that another cardiac surgery is required despite the fact that the bypass grafts are functioning normally.<sup>27</sup> Unfortunately, there is wide individual variability in the rate of disease progression,<sup>27-29</sup> virtually precluding prognostication of the course of a given patient. Concomitant aortic-valve replacement is considered unwise if it is likely to increase the gradient even further.

#### **Safety of Noncardiac Surgery in Patients with Severe Asymptomatic Aortic Stenosis**

On the basis of a small number of adverse events, one study indicated that noncardiac surgery posed an increased risk among patients with aortic stenosis.<sup>30</sup> However, O'Keefe et al. examined the course of 48 patients with severe aortic stenosis who underwent noncardiac surgery<sup>31</sup> and found that there were no complications in the 25 patients who had local anesthesia and only one complication in the 23 patients who received general anesthesia. Thus, although intraoperative hemodynamics must be closely monitored during noncardiac surgery in patients with asymptomatic aortic stenosis, there is no apparent need for concomitant aortic-valve intervention.

#### **Ability to Slow or Halt Progression of the Valve Lesion**

As noted above, the lesion of aortic stenosis shares many features with coronary disease. Although recent data suggest that hydroxymethylglutaryl coenzyme A reductase inhibitors (referred to as "statins") can retard the progression of aortic stenosis,<sup>32</sup> in my opinion it is a bit too early to begin prescribing statins for this purpose.

Table 2. Recommendations for the Use of Aortic-Valve Replacement in Patients with Aortic Stenosis.
<b>Aortic-valve replacement indicated</b>
Patients with severe aortic stenosis and any of the classic symptoms (angina, syncope, or dyspnea)
Patients with severe aortic stenosis who are undergoing coronary-artery bypass surgery
Patients with severe aortic stenosis who are undergoing surgery on the aorta or other heart valves
<b>Aortic-valve replacement possibly indicated</b>
Patients with only moderate aortic stenosis who require coronary-artery bypass surgery or surgery on the aorta or other heart valves
Asymptomatic patients with severe aortic stenosis and at least one of the following: an ejection fraction of no more than 0.50, hemodynamic instability during exercise (e.g., hypotension), or ventricular tachycardia

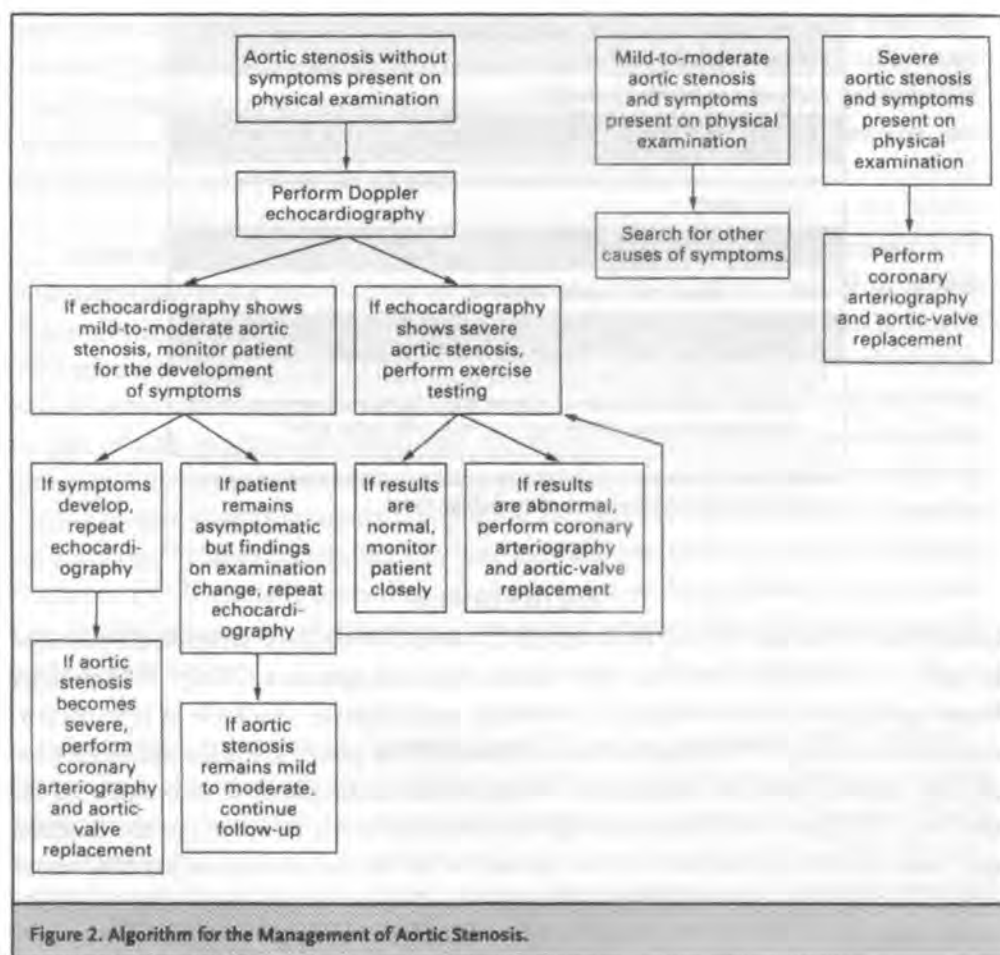
\* Aortic-valve replacement is not indicated to prevent sudden death in asymptomatic patients who have none of the findings listed.

### GUIDELINES

Guidelines for the use of valve replacement in patients with aortic stenosis are provided in Table 2. In 1998 the American Heart Association and American College of Cardiology issued guidelines for the treatment of valvular heart disease (available at <http://www.americanheart.org>).<sup>8</sup> These guidelines recommend the use of standard antibiotic prophylaxis against infective endocarditis. Doppler echocardiography is recommended for the initial diagnosis and assessment of the severity of aortic stenosis and the function and hemodynamics of the left ventricle, as well as for the reevaluation of patients whose symptoms and signs are changing and of patients known to have severe asymptomatic aortic stenosis.

### CONCLUSIONS AND RECOMMENDATIONS

Doppler echocardiography is indicated for the initial evaluation in all patients suspected of having aortic stenosis, as well as in patients with established disease if symptoms develop or physical signs change. The development of angina, syncope, or dyspnea in a patient with severe aortic stenosis constitutes a grave medical condition, requiring prompt aortic-valve replacement. For patients with severe asymptomatic disease, such as the patient described in the clinical vignette, the presence of an aortic-jet velocity of at least 4 m per second on Doppler echocardiography indicates the need for close scrutiny. I routinely recommend exercise



testing in this group (but never in symptomatic patients), since it may help identify which of these patients are at high enough risk to warrant undergoing surgery (Figure 2).

The postoperative prognosis of patients with a reduced ejection fraction is good if the mean transvalvular pressure gradient exceeds 40 mm Hg. Thus, a low ejection fraction alone should never be an absolute contraindication to surgery. However, the prognosis of patients with a low gradient and a low ejection fraction is worse. For such patients I recommend hemodynamic manipulation in the catheterization or echocardiographic laboratory to help determine which patients are more likely to benefit from surgery.

Preliminary evidence indicates that patients who have moderate aortic stenosis (as indicated by a gradient of more than 20 mm Hg and a valve area of less than 1.2 cm<sup>2</sup>) but who require heart surgery for other diseases should probably undergo concomitant aortic-valve replacement. Further study of this approach is required.

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### ADDENDUM

Since publication of this article, additional data from newly added, prospectively enrolled patients with aortic stenosis, low ejection fractions (less than 0.30), and low transvalvular gradients (less than 30 mm Hg) have indicated that those patients with inotropic reserve (i.e., those who are able to increase their forward output by at least 20 percent) benefit more from aortic-valve replacement than do similar patients treated medically, and that these patients have a much better outcome after surgery than do patients without inotropic reserve.<sup>1</sup>

In addition, a recent analysis<sup>2</sup> demonstrated that among patients under 70 years of age with mild-to-moderate aortic stenosis undergoing coronary-artery bypass graft surgery, survival was better in those who also underwent concomitant aortic-valve replacement, provided that they had a transvalvular gradient of more than 25 mm Hg.

The threshold transvalvular gradient at which valve replacement was associated with improved survival increased by 1 to 2 mm Hg per year, so that by the age of 80, the transvalvular gradient above which combined aortic and coronary surgery appeared warranted was 40 mm Hg.

A recently published randomized trial of patients with mild-to-moderate aortic stenosis found no benefit of statins in retarding disease progression.<sup>3</sup>

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# Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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**A 68-year-old former heavy smoker with a history of chronic obstructive pulmonary disease (COPD) presents to the emergency room with a two-day history of worsened dyspnea and increased purulence and volume of phlegm. Chest radiography shows hyperinflation and no acute infiltrates. Measurement of arterial blood gases while the patient is breathing room air shows acute respiratory acidosis. How should this patient be treated?**

## THE CLINICAL PROBLEM

**C**OPD, which is characterized by a fixed obstruction of the airway caused by emphysema, chronic bronchitis, or both, is a common and growing clinical problem that is responsible for a substantial worldwide health burden.<sup>1-6</sup> COPD affects 16.4 million persons in the United States and at least 52 million worldwide, and it accounted for 2.74 million deaths in 2000.<sup>2,3</sup> In the United States, COPD is now the fourth leading cause of death<sup>2-4</sup> and is the only leading cause of death for which the mortality rate is currently increasing. COPD has been estimated to account for more than 16 million office visits and 500,000 hospitalizations annually in the United States. Costs attributable to this condition totaled \$30.4 billion in 1995, with \$14.7 billion spent directly on health care.<sup>2,3,7</sup>

Acute exacerbations of COPD are variously defined but are characterized by worsened dyspnea and increased volume of phlegm, purulence of phlegm, or both. They are often accompanied by hypoxemia and worsened hypercapnia.<sup>8-10</sup> Available series data suggest that patients have such exacerbations regularly (e.g., median rates of 2.4 and 3 episodes per year in two recent series<sup>10,11</sup>). Furthermore, active smokers have more frequent exacerbations than nonsmokers; stopping smoking can reduce the frequency by approximately one third.<sup>12</sup> Data reported in 1996 on 1016 patients who were hospitalized for acute exacerbations,<sup>13</sup> half of whom required intensive care, demonstrated an in-hospital mortality rate of 11 percent, and six-month and one-year mortality rates of 33 percent and 43 per-



cent, respectively. Those who survived the first hospitalization had a 50 percent rate of rehospitalization within six months after discharge.

## STRATEGIES AND EVIDENCE

### Overview

The optimal treatment of an outpatient with an acute exacerbation of COPD involves diagnostic assessment and use of bronchodilators, systemic corticosteroids, and antibi-

Table 1. Some Commonly Used Medications for Acute Exacerbations of Chronic Obstructive Pulmonary Disease.

Drug	Mode of Delivery	Dose	Frequency
Bronchodilators			
Beta-adrenergic agonist Albuterol	Metered-dose inhaler	100–200 µg	4 times daily
	Nebulizer	0.5–2.0 mg	4 times daily
	Pill	4 mg	Twice daily
Fenoterol	Metered-dose inhaler	12–24 µg	Twice daily
Metaproterenol	Nebulizer	0.1–0.2 mg	4 times daily
	Pill	10–20 mg	3 to 4 times daily
Terbutaline	Metered-dose inhaler	400 µg	4 times daily
	Subcutaneous injection	0.2–0.25 mg	Every 15–30 min (maximum, two times)
	Pill	2.5–5 mg	4 times daily
Anticholinergic agent Ipratropium bromide*	Metered-dose inhaler	18–36 µg	4 times daily
	Nebulizer	0.5 mg	4 times daily
Methylxanthines			
Aminophylline†	Intravenous	0.9 mg/kg of body weight/hr	Infusion
Theophylline	Pill (sustained-release preparations)	150–450 mg‡	Twice daily
Corticosteroids			
Methylprednisolone succinate (for inpatients)§	Infusion, then	125 mg	Every 6 hours for 3 days, then
	Pill	60 mg	Daily for 4 days
		40 mg	Daily for 4 days
		20 mg	Daily for 4 days
Prednisone (for outpatients)	Pill	30–60 mg	Daily for 5 to 10 days, for example,
		40 mg	Daily for 2 days
		30 mg	Daily for 2 days
		20 mg	Daily for 2 days and
		10 mg	Daily for 2 days
Limited-spectrum antibiotics¶			
Trimethoprim-sulfamethoxazole	Pill	160 mg and 800 mg	Twice daily for 5 to 10 days
Amoxicillin	Pill	250 mg	4 times daily for 5 to 10 days
Doxycycline	Pill	100 mg	2 tablets first day, then 1 tablet/day for 5 to 10 days

\* Quaternary ammonium anticholinergic agents (e.g., ipratropium, glycopyrrolate) are preferred to tertiary ammonium compounds (e.g., atropine) because they have fewer side effects.

† Aminophylline is sometimes administered after a loading dose; the dose should be determined on the basis of serum levels of theophylline.

‡ The dose varies among and within patients.

§ Recommendations are according to Saint et al.<sup>14</sup>

¶ According to Anthonisen et al.,<sup>8</sup> all should be 10-day courses.

tics; for patients who are sick enough to be hospitalized, oxygen and mechanical ventilation may also be used. The types and dosages of some commonly used medications for an acute exacerbation of COPD are presented in Table 1.

### Diagnostic Assessment

For patients assessed in the emergency department or hospital, chest radiography is recommended because it reveals abnormalities that prompt a change in short-term treatment in 16 percent<sup>15</sup> to 21 percent<sup>16</sup> of cases. Spirometry is infrequently performed in hospitalized patients with acute exacerbations of COPD,<sup>13</sup> although observational studies of patients in the emergency department suggest that a forced expiratory volume in one second (FEV<sub>1</sub>) that is less than 40 percent of the predicted value has a sensitivity of 96 percent for predicting relapse or the need for hospitalization<sup>17</sup>; hypercapnia is unlikely when the FEV<sub>1</sub> exceeds 35 percent of the predicted value.<sup>18</sup>

### Oxygen

Although it has been relatively unstudied (perhaps because of its evident benefit), supplemental oxygen should be included in the initial therapy for a flare of COPD associated with hypoxemia; oxygen is usually administered by nasal cannula or through a face mask equipped to control the inspired oxygen fraction. Target oxygen saturation values are 90 to 92 percent, with corresponding target values for partial pressure of arterial oxygen (PaO<sub>2</sub>) of 60 to 65 mm Hg. These targets ensure near-maximal hemoglobin saturation while lessening the likelihood of the hypercapnia that can accompany the use of supplemental oxygen.<sup>19</sup> Although the cause of such hypercapnia can be multifactorial, increased inhomogeneity of ventilation and perfusion accompanied by increased dead-space ventilation appears to be more important than decreased alveolar ventilation caused by the suppression of the hypoxic drive.

### Bronchodilators

Substantial evidence shows that both inhaled beta-adrenergic agonists (for example, albuterol, fenoterol, metaproterenol, and terbutaline) and anticholinergic agents (including ipratropium bromide and glycopyrrolate) can improve airflow during acute exacerbations of COPD. Specifically, the administration of a bronchodilator can increase the FEV<sub>1</sub> and the forced vital capacity (FVC) by 15 to 29 percent over a period of 60 to 120 minutes.<sup>20-23</sup> Beta-adrenergic agonists have not been shown to be superior to anticholinergic agents.<sup>7,20-23</sup> Factors such as the time to peak effect (which is slightly more rapid with beta-adrenergic agonists) and the frequency of adverse effects (which are generally

fewer and milder with ipratropium bromide) may influence the choice of agent for a given patient.

Data from randomized clinical trials have not shown a benefit of the combined use of beta-adrenergic agonists and anticholinergic agents over therapy with either class alone. A recent meta-analysis<sup>22</sup> supports a strategy of initial use of an inhaled anticholinergic agent, with subsequent addition of a beta-adrenergic agonist only if it is needed despite the use of maximal doses of the anticholinergic medication. However, this approach remains controversial.

The benefits of using a methylxanthine drug such as aminophylline as an additional bronchodilator remain unclear. In three randomized, controlled trials,<sup>7,20,24-26</sup> the addition of intravenous aminophylline did not result in improvements on tests of pulmonary function, produce apparent clinical benefit, or reduce the likelihood of a return to the emergency department during the succeeding week. Furthermore, aminophylline was associated with an increased rate of adverse effects, especially nausea and vomiting.<sup>25</sup> However, in one study, patients treated with aminophylline in the emergency department had a hospitalization rate that was 70 percent lower than that in a control group.<sup>24</sup>

Equivalent bronchodilation appears to be achieved with the use of metered-dose inhalers or nebulizers.<sup>27</sup> Because metered-dose inhalers cost less than nebulizers, but are frequently ineffective during respiratory distress, it is reasonable to initiate therapy with nebulizers and then switch to metered-dose inhalers when clinically feasible.<sup>7,28</sup>

### Antibiotics

Bacterial infection may contribute to acute exacerbations of COPD. Two recent meta-analyses of 11 randomized, placebo-controlled trials of antibiotics for acute exacerbations of COPD support their use when there is purulent sputum.<sup>14,20</sup> Pooled data from six trials that evaluated peak expiratory flow rates showed a mean increase in the peak expiratory flow rate of 10.75 liters per minute, in contrast to the decrease in peak expiratory flow rate that has been observed during an acute flare.<sup>11</sup> In the largest trial from which the results are available, symptoms resolved within 21 days in 68 percent of the patients who received antibiotics, as compared with 55 percent of those given placebo.<sup>8</sup>

Antibiotics appear to be most useful in patients with severe exacerbations. For example, in a randomized trial involving 173 patients who were assigned to a 10-day course of doxycycline, trimethoprim-sulfamethoxazole, or amoxicillin,<sup>8</sup> patients with more severe exacerbations (as assessed in terms of worsened dyspnea and the purulence and volume of phlegm) received greater benefit from treatment than those with milder exacerbations.

Although concern about resistant flora has prompted some to advocate the initial use of broader-spectrum antibiotics, there have been no definitive studies supporting the first-line use of newer, more expensive antibiotics. Gram's staining of sputum has generally not been useful,<sup>8</sup> and sputum culture has generally been reserved for patients with no response to initial empirical therapy directed at the common causal pathogens (e.g., *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*). Without definitive data regarding the optimal duration of therapy, most clinicians prescribe courses of 5 to 10 days.

### Corticosteroids

Several randomized, placebo-controlled trials<sup>7,19</sup> have demonstrated that systemic corticosteroids accelerate improvement in airflow, gas exchange, and symptoms and reduce the rate of treatment failure. In the largest of these trials,<sup>29</sup> 271 hospitalized veterans were randomly assigned to receive a 3-day course of intravenous methylprednisolone (125 mg every six hours) or placebo, and the recipients of corticosteroids were further assigned to have the dose of oral prednisone tapered over the course of either 15 days or 8 weeks. Patients who received corticosteroids had an FEV<sub>1</sub> that was slightly but significantly higher (by 0.1 liter) than that in the placebo group on day 1. Other benefits associated with corticosteroid use were a lower rate of treatment failure at 30 and 90 days and a shorter hospital stay. The difference in FEV<sub>1</sub> between the corticosteroid group and the placebo group was no longer significant at 2 weeks, and outcomes were no better with an 8-week course of corticosteroids than with a 15-day course.

The optimal duration of corticosteroid therapy for an acute exacerbation of COPD remains uncertain, but recent data support a course of 5 to 10 days.<sup>30-32</sup> Specifically, in a randomized trial comparing oral prednisolone (a two-week regimen of 30 mg per day) with placebo, the FEV<sub>1</sub> improved through day 5 more in the corticosteroid group than in the placebo group.<sup>30</sup> In a more recent study comparing a 3-day regimen with a 10-day regimen of intravenous methylprednisolone in hospitalized patients,<sup>31</sup> improvements in FEV<sub>1</sub> and PaO<sub>2</sub> were evident after 3 days of therapy, but the 10-day course was associated with greater improvement in FEV<sub>1</sub>, FVC, and PaO<sub>2</sub>, as well as with more rapid resolution of symptoms. No difference was observed in the rate of recurrence at six months.

### Noninvasive Positive-Pressure Ventilation

Enhancing ventilation by unloading fatigued ventilatory muscles is an important treatment goal in the case of an acute exacerbation of COPD that is complicated by respiratory failure. In six of seven randomized, controlled trials of positive-pressure ventilation without intubation, patients who received this type of therapy had better outcomes than those who did

Table 2. Recommendations by Professional Societies Regarding the Management of Acute Exacerbations of Chronic Obstructive Pulmonary

Variable	British Thoracic Society <sup>a</sup>	American College of Chest Physicians and American College of Physicians-American Society of Internal Medicine <sup>18,20</sup>
Date of statement	1997	2001
Type of statement	Consensus	Evidence-based systematic review
Diagnostic testing	Recommended for patients being admitted: chest radiography, arterial blood gases, complete blood count, electrolytes, blood urea nitrogen, electrocardiography, and FEV <sub>1</sub> , peak flow, or both; sputum culture and sensitivity	Recommended for patients admitted from emergency department: chest radiography Not recommended: spirometry
Bronchodilator therapy	Recommended: For outpatients: beta-adrenergic agonists, anticholinergic agents, or both For inpatients: beta-adrenergic agonists and anticholinergic agents; add IV aminophylline if no response	Recommended: anticholinergic agent in maximal dose as first-line agent; then add beta-adrenergic agonist Not recommended: methylxanthines
Bronchodilator delivery	For outpatients: metered-dose inhaler (with instruction) For inpatients: nebulizer	Insufficient evidence for a preferred delivery device
Antibiotics	Recommended for moderate or severe exacerbations: oral route; "common" antibiotic (e.g., tetracycline, amoxicillin) as first-line agent; broader-spectrum cephalosporin or macrolide if no response	Optimal duration of therapy unclear
Corticosteroids	Not recommended for outpatients unless already receiving, known response, or failure to achieve response to increased bronchodilator dose Recommended for inpatients: e.g., 30 mg of prednisone daily for 7 to 14 days	Recommended for patients not receiving long-term oral corticosteroids: systemic corticosteroids for up to 2 wk
Supplemental oxygen	Recommended: to achieve PaO <sub>2</sub> ≥50 mm Hg without pH <7.26; initial treatment with face mask with FIO <sub>2</sub> ≤0.28	Recommended
Chest physiotherapy and clearance of secretions	Not recommended	Not recommended
Mucokinetic drugs	Not recommended	Not recommended
Mechanical ventilation	Recommended: when pH <7.26 and no response to other treatment; initial trial of NIPPV, IV doxapram, or both	Recommended: NIPPV in severe exacerbations
Other	Diuretics for raised jugular venous pressure and peripheral edema	

<sup>a</sup>GOLD denotes the Global Initiative for Chronic Obstructive Lung Disease (a joint panel of the National Heart, Lung, and Blood Institute and the World Health Organization). FEV<sub>1</sub>, forced expiratory volume in one second, IV intravenous, PaO<sub>2</sub>, partial pressure of arterial oxygen, FIO<sub>2</sub>, fraction of inspired oxygen, PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide, SaO<sub>2</sub>, arterial oxygen saturation, and NIPPV noninvasive positive pressure ventilation.

Disease <sup>a</sup>		
European Respiratory Society <sup>b</sup>	American Thoracic Society <sup>c</sup>	GOLD <sup>d</sup>
1995	1995	2001
<b>Consensus</b>	<b>Consensus</b>	<b>Evidence-based review</b>
Recommended for hospitalized patients: FEV <sub>1</sub> , arterial blood gases, chest radiography, complete blood count, sputum Gram's stain and culture, electrolytes, electrocardiography	Recommended: determine the cause of exacerbation; sputum culture in severe exacerbations, if condition has worsened despite use of antibiotics, or for residents of a nursing home	Recommended: chest radiography, electrocardiography, arterial blood gases, sputum culture and sensitivity testing (if no response to initial antibiotics), electrolytes, hematocrit
Recommended: beta-adrenergic agonists, anticholinergic agents, or both in increased dose or frequency; consider IV aminophylline in severe exacerbations	Recommended: beta-adrenergic agonist as first-line agent, possibly in combination with anticholinergic agent; IV aminophylline if aerosol therapy cannot be given or proves inadequate	Recommended: beta-adrenergic agonist as first-line agent; add anticholinergic agent if prompt response not evident; consider oral or IV methylxanthine in severe exacerbation
Metered-dose inhaler can generally achieve good response; some patients prefer nebulizer during exacerbations	No preference	Not discussed
Recommended: 7-to-14-day course of inexpensive antibiotic (e.g., amoxicillin or tetracycline)	Recommended for abnormal mucus: "simple" antibiotic (e.g., doxycycline or amoxicillin) unless severe exacerbation, in which case consider extended-spectrum penicillin or cephalosporin	Recommended with increased sputum volume and purulence: choice should reflect local sensitivity for <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , and <i>Moraxella catarrhalis</i>
Recommended: 0.4–0.6 mg/kg/day of oral corticosteroids for outpatients; IV for severe exacerbation in hospitalized patients	Recommended: reassess use after 1–2 wk	Recommended: 30–40 mg of oral or IV prednisolone per day for 10–14 days
Recommended: to raise PaO <sub>2</sub> ≥60 mm Hg without raising PaCO <sub>2</sub> by ≥10 mm Hg	Recommended: to raise PaO <sub>2</sub> just above 60 mm Hg	Recommended: target PaO <sub>2</sub> >60 mm Hg or SaO <sub>2</sub> >90%; measure arterial blood gases 30 min after the initiation of oxygen
Recommended: coughing to clear sputum; physiotherapy at home	Recommended for hospitalized patients with ≥25 ml of sputum/day	Manual or mechanical chest percussion and postural drainage possibly beneficial for patients with lobar atelectasis or >25 ml of sputum/day; facilitate sputum clearance by stimulating coughing
Mucokinetic drugs	Not recommended	Not discussed
Mechanical ventilation	Recommended: when criteria met (e.g., ample experience, adequate staffing, hemodynamic stability, patient awake without copious secretions)	Recommended when ≥2 of the following present: severe dyspnea with accessory muscle use or paradoxical abdominal motion; pH, 7.30–7.35; and PaCO <sub>2</sub> 45–60 mm Hg; respiratory rate >25
Other		Diet; low-molecular-weight heparin; fluids

not.<sup>33-35</sup> Benefits included lower rates of intubation, lower in-hospital mortality rates, accelerated symptomatic and physiological improvement, and shorter hospital stays.

Noninvasive positive-pressure ventilation<sup>33,36-38</sup> should be considered when there is a need for ventilatory assistance, as indicated by such symptoms as worsened dyspnea, acute respiratory acidosis, and worsened oxygenation (e.g., a ratio of  $\text{PaO}_2$  to the fraction of inspired oxygen of less than 200). Patients unlikely to benefit from noninvasive positive-pressure ventilation include those with respiratory arrest, medical instability (e.g., hypotensive shock or uncontrolled cardiac ischemia), an inability to protect the airway, excessive secretions, agitation or uncooperativeness, or conditions that preclude the placement of a mask or the achievement of a proper fit. Although there has been some concern to the contrary, management of noninvasive positive-pressure ventilation does not require more of health care providers' time and does not cost more than the treatment of intubated patients.<sup>36-40</sup>

#### AREAS OF UNCERTAINTY

Better methods are needed to encourage smoking cessation, since smoking is a key causative factor in COPD. More attention to detecting and treating  $\alpha_1$ -antitrypsin deficiency is also needed.<sup>41</sup> In addition, standards are needed for the definition of an acute exacerbation of COPD and for the stratification of risk. The optimal bronchodilator regimen and route of delivery remain uncertain, especially with the advent of new drugs (e.g., tiotropium). The role of broader-spectrum antibiotics and guidelines for their use, and the indications for noninvasive positive-pressure ventilation, especially outside the intensive care unit, remain to be defined.

#### GUIDELINES

Five sets of guidelines for managing acute exacerbations of COPD have been issued by five widely recognized professional societies and health organizations since 1994: the European Respiratory Society,<sup>5</sup> the British Thoracic Society,<sup>6</sup> the American Thoracic Society,<sup>1</sup> a joint panel of the American College of Chest Physicians and the American College of Physicians–American Society of Internal Medicine,<sup>20-22</sup> and a joint panel of the National Heart, Lung, and Blood Institute and the World Health Organization (known as the Global Initiative for Chronic Obstructive Lung Disease, or GOLD).<sup>2</sup> These guidelines, summarized in Table 2, are similar in many respects; most (including those proposed by GOLD) endorse a short course of systemic corticosteroids and antibiotics for severe exacerbations and the use of noninvasive ventilation for exacerbations complicated by acute ventilatory

failure. Unlike some of the guidelines, those from GOLD favor beta-adrenergic agonists as first-line bronchodilator therapy, recommend adding an anticholinergic agent if there is no response to the beta-adrenergic agonist, and endorse consideration of a methylxanthine drug.

#### SUMMARY AND RECOMMENDATIONS

My approach to treating the patient with an acute exacerbation of COPD is as follows. For patients who present to the emergency department or who are deemed sick enough to be hospitalized, diagnostic assessment includes chest radiography and, if the patient's distress or somnolence prompts concern about acute respiratory acidemia, measurement of arterial blood gases. Initial therapy includes supplemental oxygen, usually through a face mask to ensure an oxyhemoglobin saturation, measured by pulse oximetry, of 90 to 92 percent. For both inpatients and outpatients, combined bronchodilator therapy should be used, with ipratropium bromide and albuterol administered every four to six hours initially; nebulizers are recommended whenever the patient's distress level raises doubt about the effective use of a metered-dose inhaler. As the condition improves and the distress level is reduced, metered-dose inhalers can be used in place of nebulizers. Since many patients do not use their inhalers appropriately, spacer devices should be prescribed and appropriate techniques should be reviewed.

On the basis of data from a randomized trial,<sup>8</sup> a 10-day course of a narrow-spectrum antibiotic (e.g., trimethoprim-sulfamethoxazole, doxycycline, or amoxicillin) should be prescribed when there is increased dyspnea and increased purulence and volume of phlegm. Sputum staining and cultures are reserved for cases that are refractory to antibiotic therapy. Oral systemic corticosteroids are prescribed both for outpatients (tapering over the course of eight days, beginning with 40 mg per day and decreasing the dose by 10 mg every other day) and for inpatients (Table 1).<sup>29</sup> Given the lack of evidence to support the usefulness of chest physiotherapy or mucokinetic drugs, neither of these should be routinely prescribed.

For eligible patients with acute respiratory acidemia, bilevel noninvasive positive-pressure ventilation should be implemented for multiple-hour stretches, with occasional interruption, during the first several days of hospitalization. Such ventilation is initially administered in the intensive care unit to ensure close monitoring and ready access to intubation and mechanical ventilation, should the trial of noninvasive positive-pressure ventilation fail.

For patients who present for the first time with an exacerbation of underlying COPD, recovery from the acute episode provides an opportunity to discuss smoking cessation, to



explore the possibility of  $\alpha_1$ -antitrypsin deficiency, to vaccinate the patient against pneumococcus and influenza, and to consider referral to a pulmonary rehabilitation program. For patients who require hospitalization, an outpatient follow-up visit should be scheduled for four to eight weeks after hospital discharge. Spirometry should be performed after the administration of a bronchodilator, and the patient's need for supplemental oxygen both while at rest and during activity should be reassessed. Bronchodilator therapy should be continued over the long term, with the addition of an inhaled corticosteroid reserved for patients in whom the obstruction of airflow has been demonstrated to be reversible (e.g., those who have an increase of at least 12 percent and 200 ml in the FEV<sub>1</sub> after the use of a bronchodilator) and patients who have frequent exacerbations.

Given this approach, the short-term treatment of the patient described in the vignette should include admission to the hospital because of acute respiratory acidemia, and the administration of a combination of bronchodilators, a limited-spectrum antibiotic, and intravenous corticosteroids. Unless there is rapid reversal of acidemia, bilevel noninvasive positive-pressure ventilation should be initiated.

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## ADDENDUM

Since publication of this article, data have been published supporting the benefits of early treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD).<sup>1</sup> In an observational study of 128 patients with COPD and a history of frequent exacerbations, earlier initiation of therapy with oral antibiotics, systemic corticosteroids, or both was associated with faster recovery. Moreover, patients who did not seek treatment for acute exacerbations, as compared with patients who did seek treatment, had poorer recovery health-related quality of life and were more likely to be hospitalized. Although these results could be confounded by unknown factors influencing patients' care-seeking behavior, they support early initiation of therapy for acute exacerbations of COPD.

Another important observation is that use of the long-acting anticholinergic drug tiotropium lessens the risk of having an acute exacerbation of COPD or of being hos-

pitalized for it.<sup>2-4</sup> Specifically, in three different randomized, controlled trials comparing tiotropium with placebo,<sup>2</sup> ipratropium,<sup>3</sup> and salmeterol,<sup>4</sup> treatment with tiotropium improved outcomes. As compared with placebo, tiotropium reduced the proportion of patients having one or more acute exacerbations of COPD in a year, the yearly incidence of exacerbations, the number of hospitalizations for exacerbations, and the time from initiation of treatment to the first exacerbation.<sup>2</sup> As compared with ipratropium, tiotropium reduced the likelihood of having an acute exacerbation of COPD and the number of exacerbations.<sup>3</sup> Finally, as compared with salmeterol, tiotropium reduced the number of hospitalizations for acute exacerbations of COPD, although there was no significant difference in the number of exacerbations.<sup>4</sup>

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# *Peanut Allergy*

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**A 19-year-old woman is brought to the emergency room because of the acute onset of dyspnea, wheezing, vomiting, and generalized flushing. She has well-controlled asthma as well as a history of atopic dermatitis as an infant and urticaria after ingesting peanut butter at the age of five years. According to friends she ate a chocolate-chip cookie from a vending machine in her college dormitory just before the symptoms developed. The list of ingredients on the cookie wrapper does not include peanuts. Nevertheless, how should this patient's condition be treated?**

## THE CLINICAL PROBLEM

**I**n a patient with asthma, the acute onset of severe bronchospasm in the absence of earlier signs of asthma must always raise the suspicion of anaphylaxis. Food allergy affects about 6 to 8 percent of children younger than four years of age and about 2 percent of the U.S. population beyond the first decade of life.<sup>1</sup> Food allergy is the leading cause of anaphylaxis treated in hospital emergency departments in the United States and many westernized countries. Food allergy accounts for about 30,000 anaphylactic reactions, 2000 hospitalizations, and 200 deaths each year in the United States.<sup>2</sup> Allergies to peanuts and tree nuts account for the majority of fatal and near-fatal anaphylactic reactions.<sup>3,4</sup> A national survey indicated that about 1.1 percent of Americans, or 3 million people, are allergic to peanuts, tree nuts, or both.<sup>5</sup> Ironically, despite an increasing public awareness of food allergy, most patients are ill prepared to deal with anaphylactic reactions.<sup>6</sup> In a recent series, over 80 percent of patients who died from allergic reactions to food were not given appropriate information to avoid accidental food-induced reactions or self-injectable epinephrine to manage them.<sup>4</sup>

Food-induced anaphylaxis is primarily a clinical diagnosis and is often mistaken for severe status asthmaticus or an acute cardiovascular event. People who have life-threatening reactions usually have asthma and frequently have a history of atopy, including atopic dermatitis and food allergy as young children.<sup>7</sup> Symptoms may develop within minutes to

a few hours after ingestion of the food, and in life-threatening cases, symptoms include severe bronchospasm. Although similar to anaphylaxis due to other causes, early symptoms of food-induced anaphylaxis often include oral pruritus and "tingling," pharyngeal pruritus and a sensation of tightening of the airways, colicky abdominal pain, nausea and vomiting, and cutaneous flushing, urticaria, and angioedema. Progressive respiratory symptoms, hypotension, and dysrhythmias typically develop in fatal and near-fatal cases. Obstructive laryngeal edema is uncommon, and cutaneous symptoms may be absent in severe cases. Surveys of fatal and near-fatal reactions suggest that a delay in the initiation of therapy such as injectable epinephrine is associated with a poorer prognosis, although about 10 percent of patients who receive epinephrine early still die.<sup>3,4</sup> Biphasic reactions have been noted in up to one third of patients with fatal or near-fatal reactions. These patients seem to have fully recovered when severe bronchospasm suddenly recurs; the recurrence is typically more refractory to standard therapy and often requires intubation and mechanical ventilation. The mechanism underlying this phenomenon is unknown, but it appears to be more common when therapy is initiated late and symptoms at presentation are more severe. Secondary pneumothoraxes are a fairly common consequence of the high airway pressures generally required to overcome the obstruction.

Although the relative epidemic of peanut allergy appears to be a phenomenon of the past two decades, peanuts were first cultivated in South America about 2000 to 3000 B.C., and the practice has spread throughout the world.<sup>8</sup> After the Civil War, peanuts became increasingly popular throughout the United States. America now ranks third only to China and India in peanut production, with over 40 percent of the U.S. peanut crop consumed as peanut butter. Whereas the per capita consumption of peanuts in China is similar to that of the United States,<sup>9</sup> peanut allergy is extremely rare in China.<sup>10</sup> In addition, the prevalence of peanut allergy appears to be rising in the United States and other westernized countries. In a population-based study of three-year-olds in the United Kingdom, the prevalence of sensitization to peanuts increased from 1.3 percent to 3.2 percent from 1989 to 1995.<sup>11</sup> In a cohort of American children referred for the evaluation of moderate-to-severe atopic dermatitis between 1990 and 1994, the prevalence of allergic reactivity to peanuts was nearly twice as high as that in a similar group evaluated between 1980 and 1984.<sup>12</sup> Data from the third National Health and Nutrition Examination Survey (collected from 1988 to 1994) indicated that about 6 percent of Americans have serologic evidence of sensitivity to peanuts (i.e., the presence of IgE antibodies specific for peanut proteins),<sup>13</sup> although the majority of these people will not have an allergic reaction when they eat peanuts.

There appears to be something unique about the peanut that is not shared by other members of the legume family or most other food proteins. The three major allergenic

Table 1. Approach to Patients with Peanut Allergy.

**Patient education**

Avoidance of peanut proteins

Recognition of early signs of anaphylaxis

Early treatment of allergic symptoms (anaphylaxis) with injectable epinephrine (EpiPen Autoinjector) and oral liquid diphenhydramine (the most easily absorbed form)

**Treatment of acute reaction\*****By patient and family members**

Injection of epinephrine, depending on patient's history and symptoms

Administration of oral liquid diphenhydramine (1 mg/kg of body weight; maximum, 75 mg)

Transport to emergency facility

**By emergency personnel**

Administration of supplemental oxygen and airway management

Administration of intramuscular epinephrine (0.01 ml of a 1:1000 dilution/kg every 10 to 20 minutes as needed; maximum, 0.3 to 0.5 ml) or intravenous epinephrine in patients with severe hypotension (0.5 to 5  $\mu$ g/min to maintain blood pressure)

Administration of intravenous fluids

Administration of oral, intramuscular, or intravenous H<sub>1</sub>-receptor antagonist (e.g., diphenhydramine, 1 mg/kg; maximum, 75 mg)

Treatment with oral prednisone (1 to 2 mg/kg; maximum, 75 mg) or intravenous methylprednisolone (2 mg/kg; maximum, 250 mg)

Administration of nebulized albuterol (1.25 to 2.5 mg every 20 minutes as needed or continuously with monitoring)

Use of H<sub>2</sub>-receptor antagonist (e.g., for adults: 4 to 5 mg of ranitidine/kg orally; maximum, 300 mg; 50 mg intramuscularly or intravenously every 6 to 8 hr; for children: 1.5 mg/kg intramuscularly or intravenously; maximum, 50 mg)

**Follow-up**

Treatment with oral H<sub>1</sub>-receptor antagonist for 3 days: cetirizine (patients weighing less than 30 kg, 5 mg/day; patients weighing at least 30 kg, 10 mg/day), fexofenadine (patients younger than 12 years of age, 30 mg twice a day; patients at least 12 years of age, 60 mg twice a day), or loratadine (patients younger than 6 years of age, 5 mg/day; patients at least 6 years of age, 10 mg/day)

Treatment with oral prednisone (1 mg/kg/day; maximum, 75 mg) for 3 days

Referral for evaluation by allergist if patient has not previously been evaluated

\* Treatment varies depending on the patient's symptoms.

proteins in peanuts are Ara h 1, 2, and 3.<sup>14</sup> Although other legumes contain similar proteins and most patients with peanut allergy have IgE antibodies against these proteins, fewer than 15 percent of such patients react to other members of the legume family.<sup>15</sup> In addition, other legumes rarely provoke severe anaphylactic reactions or result in a lifelong allergy. However, in 25 to 35 percent of patients with peanut allergy, an allergic reaction to tree nuts (such as walnuts, cashews, and pistachios) will develop even though tree nuts are from a different botanical family.<sup>16</sup>

## STRATEGIES AND EVIDENCE

### Diagnosis

A physician who knows about food allergies should evaluate any person who is thought to have had an adverse reaction to peanuts. The evaluation should include a careful history-

taking, skin-prick tests, radioallergosorbent tests, and possibly, an oral food challenge. Patients who have had unequivocal symptoms of allergy after the isolated ingestion of a peanut product (especially if they occur on more than one occasion) and who have evidence of peanut-specific IgE antibodies (a positive skin-prick test or radioallergosorbent test) do not usually need to undergo oral peanut challenges to establish the diagnosis. The use of a radioallergosorbent test to quantify the level of peanut-specific serum IgE antibodies can be diagnostic, since patients with peanut-specific serum IgE levels of at least 15 kU per liter have a likelihood of an allergic reaction of 95 percent or greater if they ingest peanuts.<sup>17</sup> In the absence of a conflicting history, these patients may be given a diagnosis of peanut allergy and do not need to undergo a food challenge. In persons who have peanut-specific serum IgE antibody levels of less than 15 kU per liter and no clear-cut history of peanut-induced symptoms, a physician-supervised food challenge is necessary to make a definitive diagnosis. The double-blind, placebo-controlled challenge is considered the gold standard for diagnosing food allergy, but less rigorous challenges are often adequate if they are performed by a physician with experience in food allergies and the treatment of anaphylaxis. Such challenges may lead to severe anaphylactic symptoms and so should be conducted only in a hospital setting by an experienced specialist.

Peanut allergy generally develops at an early age and, unlike many other food allergies in children, is often a lifelong disorder. In a registry of 4685 patients with peanut allergy, the first reaction to peanuts occurred at a median age of 14 months.<sup>18</sup> Infants who have peanut allergy tend to have more severe allergic reactions as they get older. However, recent studies suggest that about 20 percent of young infants who have allergic reactions to peanuts will outgrow their allergy, especially if they have low levels of peanut-specific serum IgE antibodies in infancy (less than 5 kU per liter).<sup>19</sup> Therefore, children with low levels of peanut-specific IgE antibodies should be reevaluated periodically to determine whether they have outgrown their allergy. A conversion of the skin-prick test from positive to negative generally indicates that a patient has outgrown his or her peanut allergy. However, skin-prick tests often remain positive for many years in children who have outgrown their peanut allergy and are therefore not as useful as the measurement of peanut-specific IgE antibodies for assessing clinical reactivity.

The diagnosis of an acute allergic reaction is based on clinical symptoms and a history of exposure to an allergen. Laboratory studies are not helpful in distinguishing food-induced anaphylaxis from severe asthma, since serum  $\beta$ -tryptase levels, a hallmark of mast-cell activation that is associated with anaphylactic reactions, usually remain normal in patients with food-induced anaphylaxis.<sup>3,20</sup>



### Management

Currently, treatment of peanut allergy consists of teaching patients and their families how to avoid the accidental ingestion of peanuts, how to recognize early symptoms of an allergic reaction, and how to manage the early stages of an anaphylactic reaction (Table 1).<sup>21</sup> Patients must learn to check all food labels for the presence of peanuts and to avoid high-risk situations, such as foods served in buffets and ice-cream parlors and unlabeled candies and desserts. Although most patients with peanut allergy avoid ingesting peanut oil, highly processed oils — acid-extracted, heat-distilled oils — do not contain peanut protein and can be safely consumed by such patients.<sup>22</sup> However, cold-pressed or extruded peanut oils contain peanut protein and many induce allergic reactions.

Although considerable educational material is available through organizations such as the Food Allergy and Anaphylaxis Network (telephone number, 1-800-929-4040; Web site, <http://www.foodallergy.org>), inadvertent exposure as a result of peanut contamination of equipment used in the manufacture of various products, inadequate food labeling, cross-contamination of food during cooking in restaurants (e.g., the use of the same pan to cook foods containing peanuts and foods without peanuts),<sup>23</sup> and unanticipated exposures (e.g., the inhalation of peanut dust in airplanes<sup>24</sup>) result in an allergic reaction every three to five years in the average patient with peanut allergy.<sup>16</sup> Consequently, such patients must be given a written emergency plan (one is available at the Food Allergy and Anaphylaxis Network Web site) and appropriate doses of liquid diphenhydramine and self-injectable epinephrine (e.g., EpiPen Autoinjector, Dey) so that therapy can be initiated in case they accidentally eat peanuts. Patients who have an allergic reaction to peanuts that requires the use of epinephrine should always go to a local emergency room for follow-up in case they have persistent refractory symptoms or a biphasic response.

Patients who have an anaphylactic reaction to peanuts should be treated aggressively with intramuscular epinephrine<sup>25</sup>; oral, intramuscular, or intravenous histamine H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists; oxygen; inhaled albuterol; and systemic corticosteroids. Because over 90 percent of biphasic responses occur within four hours after the initial reaction, patients should be observed for at least four hours before being discharged from the emergency department.<sup>3</sup> The administration of corticosteroids does not appear to reduce the risk of a biphasic response. A subsequent three-day course of oral prednisone (1 mg per kilogram of body weight per day; maximum, 75 mg per day) and an antihistamine is often recommended, although there are no studies demonstrating that this practice decreases the risk of recurrent symptoms.

## AREAS OF UNCERTAINTY

**Cause of the Increasing Prevalence of Peanut Allergy**

The cause of the rising prevalence of peanut allergy and the reasons this increase appears to be confined to westernized countries remain uncertain. In addition to theories regarding the general increase in the prevalence of allergic disease worldwide over the past several decades,<sup>26</sup> a number of factors have been suggested to account for the apparent increase in prevalence. The growing demand for highly nutritional, "quick-energy" foods has made the peanut a staple of the American diet. Breast-feeding is increasingly common, and peanut products have increasingly been promoted as excellent nutritional sources for pregnant and lactating women. In one registry of patients with peanut allergy, about 85 percent had been breast-fed and more than 70 percent had had their first allergic reaction after their first apparent contact with peanuts. Since reactions require previous exposure for sensitization and since IgE antibodies do not cross the placenta, these findings suggest that peanut protein was encountered in utero or through breast milk.<sup>24,27</sup> In a French study of 54 infants who were less than 11 days of age and 71 who were 17 days to 4 months of age, 8 percent had a positive skin-prick test for peanuts.<sup>10</sup> Another study found that mothers of children with peanut allergy ate more peanuts during pregnancy, but not during lactation, than mothers of children with an allergy to milk or eggs.<sup>28</sup>

Given the immaturity of the immune system at birth, food allergies are more likely to develop during the first few years of life.<sup>1</sup> The majority of American children are exposed to peanuts (e.g., peanut butter) in the first year of life, and virtually all have been exposed by their second birthday.<sup>29</sup> In countries where peanut butter is rarely eaten, such as Denmark and Norway, peanut allergy is much less common.

Differences in the way peanuts are prepared may also contribute to the increasing prevalence of peanut allergy as well as to variations in the rates of peanut allergy among countries. Most peanuts in the United States are dry-roasted, including peanuts that are made into peanut butter, whereas peanuts in China are typically boiled or fried. The higher temperatures required for dry-roasting increase the allergenicity of the three major peanut proteins more than do the lower temperatures used for boiling or frying.<sup>9</sup> Although genetics plays a part in the development of peanut allergy,<sup>30</sup> the prevalence of peanut allergy is similar among the children of Chinese immigrants to the United States and the children of native-born Americans.

### Therapy for Peanut Allergy

Unlike traditional immunotherapy for allergic reactions to inhalants and bee stings, injections of peanut extracts have an unacceptable risk–benefit ratio.<sup>31</sup> However, novel therapeutic agents are being investigated for the treatment of peanut allergy.<sup>32</sup> One approach being evaluated in phase 1 and 2 trials is monthly injections of humanized recombinant anti-IgE antibodies, which may reduce the levels of IgE bound to mast cells and basophils sufficiently to prevent the activation of allergic responses, at least to small amounts of peanut protein. Another approach uses engineered (mutant) recombinant peanut proteins, in which substitutions of critical amino acids within the IgE-binding epitopes prevent the activation of IgE-mediated reactions, for traditional desensitizing immunotherapy. Both engineered recombinant proteins and a series of overlapping peptides comprising T-cell epitopes of peanut reversed sensitivity to peanuts in a murine model of peanut-induced anaphylaxis without triggering IgE-mediated acute reactions.<sup>32</sup> However, the clinical usefulness of these approaches has not been established.

### GUIDELINES

Both the American Academy of Asthma, Allergy and Immunology and the American Academy of Pediatrics have published guidelines on the management of food-induced anaphylaxis.<sup>33,34</sup> Patients, as well as the parents and caregivers of children with peanut allergy, must be educated to avoid accidentally ingesting peanuts, learn to recognize early signs of an allergic reaction, and learn to medicate themselves as soon as symptoms develop. All patients with peanut allergy should be given a written emergency plan and adequate doses of liquid diphenhydramine and self-injectable epinephrine for use in case they accidentally ingest peanuts. School and day-care personnel must also be educated to provide a safe environment for children with peanut allergy<sup>35</sup> and to recognize and treat food-induced reactions. In the event of an allergic reaction to peanuts, especially if epinephrine is used, patients should be taken to the nearest emergency room where they can be treated further and observed for at least four hours.

Whether peanut allergy can be prevented remains in question. Nonetheless, the Department of Health in the United Kingdom (and many allergists in the United States) recommends that mothers from “high-risk” families (those with a history of atopy) avoid eating peanuts during pregnancy and lactation and that they not give their infants peanut products for the first three years of life.<sup>36</sup>

### CONCLUSIONS AND RECOMMENDATIONS

Food allergy — and peanut allergy in particular — has become a major health concern in the United States and many other westernized countries. Pending further information, it is probably wise to encourage mothers from families with a history of atopy to avoid eating peanuts during pregnancy and lactation and to avoid introducing peanut proteins to their offspring for the first three years of life. Children in whom an allergy to milk or eggs develops during the first year of life should also avoid peanuts, since other food allergies will develop in about one third of them. Any person suspected of having had an allergic reaction to peanuts should be evaluated by a specialist knowledgeable in this area. Since about one third of patients with peanut allergy are also allergic to at least one tree nut,<sup>16</sup> patients who have had an anaphylactic reaction to peanuts should be evaluated for nut allergy. Children younger than five years of age who are allergic to peanuts should avoid all nuts because of the risk of developing new nut sensitivities and the difficulty children in this age group have accurately identifying peanut-containing products. Physicians must teach their patients appropriate avoidance strategies and to recognize early signs of an allergic reaction and provide them with emergency plans and appropriate medications in case of an accidental peanut ingestion. Child-care facilities and schools must develop appropriate plans to protect children with peanut allergy and initiate treatment in case of an accidental ingestion. Restaurants and other public eating establishments and airlines need to be more cognizant of the needs of people with peanut allergy. Mandatory food-labeling laws and manufacturing practices should be enacted to prevent the inadvertent ingestion of mislabeled or contaminated products.<sup>37</sup>

If an accidental ingestion occurs, as apparently occurred in the patient described in the clinical vignette, intramuscular epinephrine and liquid diphenhydramine should be given immediately (Table 1). The patient should be brought to an emergency department as quickly as possible and treated with epinephrine, antihistamines, supplemental oxygen, intravenous fluids, nebulized albuterol, and corticosteroids, as appropriate. Because of the risk of a biphasic reaction, the patient should be observed for at least four hours before being discharged and should then be given a short course of prednisone and an antihistamine.

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#### ADDENDUM

Since publication of this article, there has been further investigation of novel therapeutic agents for the treatment of peanut allergy.<sup>1</sup> One approach is to administer monthly injections of humanized recombinant anti-IgE antibodies, which may reduce mast-cell- and basophil-bound IgE sufficiently to prevent the activation of allergic responses, at least to small amounts of peanut protein. My colleagues and I conducted a double-blind, randomized, dose-ranging trial of anti-IgE (TNX-901) administered subcutaneously on a monthly basis in patients with a history of immediate hypersensitivity to peanut.<sup>2</sup> Peanut allergy was confirmed, and the threshold dose of defatted peanut flour was established by a double-blind, placebo-controlled oral food challenge. We found that the highest monthly dose (450 mg) of TNX-901 significantly increased the threshold of sensitivity to peanut by oral challenge from a level of roughly half a peanut (178 mg) to almost nine peanuts (2805 mg) — an effect that should provide protection from most unintended ingestions. A decision was made not to go forward with TNX-901, but phase II trials have since been initiated with omalizumab (Xolair) to determine its efficacy in treating peanut-allergic patients.

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# *Carpal Tunnel Syndrome*

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A 64-year-old, right-handed, retired woman presents with intermittent numbness, tingling, and burning pain in the three radial digits of both hands. She has had these symptoms for three months, and they awaken her several times each night. She has no atrophy of the thenar muscles. Sensation to light touch is intact. How should she be evaluated and treated?

## THE CLINICAL PROBLEM

Hand, finger, or wrist symptoms account for 2.7 million office visits to physicians for new problems per year in the United States.<sup>1</sup> The differential diagnosis of discomfort of the hand and wrist includes entrapments of the nerves (such as carpal tunnel syndrome, entrapment of the ulnar nerve, and cervical radiculopathy), tendon disorders, overuse of muscles, nonspecific pain syndromes, and less common disorders. The prevalence of electrophysiologically confirmed, symptomatic carpal tunnel syndrome is about 3 percent among women and 2 percent among men, with peak prevalence in women older than 55 years of age.<sup>2</sup>

The carpal tunnel (Figure 1) is located at the base of the palm, just distal to the distal wrist crease. It is bounded on three sides by the carpal bones, which create an arch, and on the palmar side by the fibrous flexor retinaculum, or transverse carpal ligament. Nine flexor tendons (two extending to each finger and one to the thumb) traverse the carpal tunnel, along with the median nerve.

Carpal tunnel syndrome is caused by elevated pressure in the carpal tunnel<sup>3</sup>; this increased pressure produces ischemia of the median nerve, resulting in impaired nerve conduction and attendant paresthesia and pain. Early in the course, no morphologic changes are observable in the median nerve, neurologic findings are reversible, and symptoms are intermittent. Prolonged or frequent episodes of elevated pressure in the carpal tunnel may result in segmental demyelination and more constant and severe symptoms, occasionally with weakness. When there is prolonged ischemia, axonal injury ensues, and nerve dysfunction may be irreversible.<sup>3,4</sup>

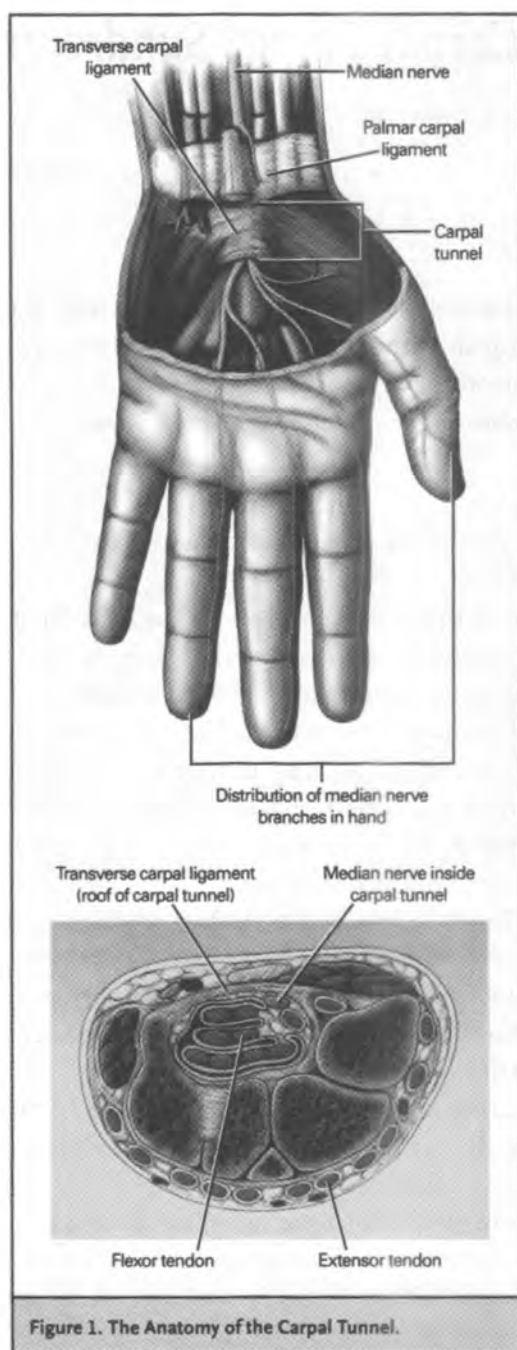


Figure 1. The Anatomy of the Carpal Tunnel.



A variety of conditions may be associated with carpal tunnel syndrome. These include pregnancy, inflammatory arthritis, Colles' fracture, amyloidosis, hypothyroidism, diabetes mellitus, acromegaly, and use of corticosteroids and estrogens.<sup>5,6</sup> Up to one third of cases of carpal tunnel syndrome occur in association with such medical conditions<sup>7</sup>; about 6 percent of patients have diabetes.<sup>6</sup> Carpal tunnel syndrome is also associated with repetitive activities of the hand and wrist, particularly with a combination of forceful and repetitive activities.<sup>8-10</sup> Occupations associated with a high incidence of carpal tunnel syndrome include food processing, manufacturing, logging, and construction work.<sup>8,11</sup>

The natural history of carpal tunnel syndrome is variable. One 11-year study of workers with carpal tunnel syndrome showed that, although abnormalities of nerve conduction tend to worsen over time, the prevalence of carpal-tunnel symptoms diminishes.<sup>12</sup>

## STRATEGIES AND EVIDENCE

### Diagnosis

A combination of electrodiagnostic studies (nerve-conduction studies and electromyography) and knowledge of the location and type of symptoms permits the most accurate diagnosis of carpal tunnel syndrome.<sup>13</sup> Symptoms consistent with carpal tunnel syndrome occur in up to 15 percent of the population,<sup>2</sup> and false negative<sup>14</sup> and false positive<sup>15,16</sup> results on electrodiagnostic testing have been well documented. Hence, both symptoms and electrodiagnostic studies must be interpreted carefully. Electrodiagnostic studies are most useful for confirming the diagnosis in suspected cases and ruling out neuropathy and other nerve entrapments.

**History** Carpal tunnel syndrome generally produces pain, tingling, burning, numbness, or some combination of these symptoms on the palmar aspect of the thumb, index finger, middle finger, and radial half of the ring finger. Patients often report only on detailed questioning that no such symptoms affect the fifth finger. A diagram of symptoms in the hand can help patients to localize symptoms. A diagram of symptoms rated as classic or probable carpal tunnel syndrome according to a standard rating system had a sensitivity of 61 percent and a specificity of 71 percent for the diagnosis of carpal tunnel syndrome in a clinic-based sample.<sup>17</sup> The sensitivity was lower and the specificity higher when the diagram was used to screen workers for carpal tunnel syndrome.<sup>18</sup> A history of nocturnal symptoms has moderate sensitivity (51 to 77 percent) and specificity (27 to 68 percent).<sup>19</sup> Often, patients report that they shake the symptomatic hand or hands when symptoms are at their worst. This response, the "flick sign," had both a sensitivity and a specificity that exceeded 90 percent in one study,<sup>20</sup> but it has not been evaluated further.

**Physical Examination** Loss of two-point discrimination in the median-nerve distribution (inability to distinguish between one sharp point on the fingertip and two) as well as thenar atrophy occur late in the course of carpal tunnel syndrome. These signs have low sensitivity and high specificity.<sup>17,19</sup> Tests of the patient's ability to perceive varying degrees of vibratory stimulation<sup>21</sup> and direct pressure on the pulp of the finger<sup>22</sup> in the median-nerve distribution are technically demanding and have moderate sensitivity and specificity.

Several provocative tests may assist in the diagnosis. In Phalen's maneuver, the patient reports whether flexion of the wrist for 60 seconds elicits pain or paresthesia in the median-nerve distribution.<sup>23</sup> Studies of Phalen's maneuver report a wide range of values for sensitivity and specificity, from 40 to 80 percent.<sup>17,19,21,22,24</sup> Tinel's sign is judged to be present if tapping lightly over the volar surface of the wrist causes radiating paresthesia in the digits innervated by the median nerve.<sup>22,23</sup> The sensitivity of Tinel's sign ranges from 25 to 60 percent, although its specificity is higher (67 to 87 percent).<sup>17,19,21,22,24</sup> In the pressure provocation test,<sup>25</sup> the examiner's thumb is pressed over the carpal tunnel for 30 seconds. In the tourniquet test, a blood-pressure cuff is inflated around the arm to above systolic pressure for 60 seconds. Both tests are deemed positive if they elicit radiating paresthesia in the median-nerve distribution. Estimates of sensitivity and specificity for both of these tests vary widely.<sup>20,26</sup>

Since findings on physical examination and the history have limited diagnostic value, they are most useful when there is a reasonable clinical suspicion of carpal tunnel syndrome (as when a patient presents with hand symptoms). The history and physical examination have poor predictive value when the likelihood of carpal tunnel syndrome is low (as it is among participants in population-based or workplace screening programs).<sup>17</sup>

### Treatment

**Treating Associated Conditions** When carpal tunnel syndrome arises from rheumatoid arthritis or other types of inflammatory arthritis, treatment of the underlying condition generally relieves carpal-tunnel symptoms. Treatment of other associated conditions (such as hypothyroidism or diabetes mellitus) is also appropriate, although data are lacking on whether such treatment alleviates carpal tunnel syndrome. Similarly, it is not known whether stopping medications associated with carpal tunnel syndrome (such as corticosteroids or estrogen) leads to improvement, although taking such a step is also reasonable in the absence of contraindications.

**Splinting** More than 80 percent of patients with carpal tunnel syndrome report that a wrist splint alleviates symptoms,<sup>27</sup> generally within days. Splinting also reduces senso-

ty latency,<sup>28</sup> suggesting that the intervention may alter the underlying course of carpal tunnel syndrome. Splints are more effective if they maintain the wrist in neutral posture rather than in extension.<sup>27</sup> Commercially available splints are acceptable, provided that they maintain such a neutral position.

**Medications** Nonsteroidal antiinflammatory medications, diuretics, and pyridoxine (vitamin B<sub>6</sub>) have each been studied in small, randomized trials, with no evidence of efficacy. One four-week randomized trial involving 91 patients had four treatment groups; one group received placebo, one received nonsteroidal antiinflammatory medication, one received a diuretic, and one received 20 mg of prednisolone daily for two weeks followed by 10 mg daily for another two weeks. The prednisolone group had a substantial reduction in symptoms, whereas the outcomes in the other medication groups did not differ from those in the placebo group.<sup>29</sup> In this small study, patients were not followed after the four-week course of treatment ended, nor did the study address the dose of corticosteroids needed to maintain a response. There were essentially no toxic effects of corticosteroids in this short-term trial, although risks including weight gain, hypertension, and hyperglycemia are recognized even with short-term treatment. Apart from this small, short-term study, there have been no other placebo-controlled trials of nonsteroidal antiinflammatory medications.

**Local Corticosteroid Injection** Patients who remain symptomatic after modification of their activities and splinting are candidates for injection of corticosteroids into the carpal tunnel. A 25-gauge needle may be used to inject 1 ml of 1 percent lidocaine just to the ulnar side of the palmaris longus tendon, proximal to the wrist crease. The needle is aimed toward the carpal tunnel at a 30-degree angle of entry. If there is no paresthesia on injection of a small amount of lidocaine, the rest of the lidocaine is injected followed by the depot corticosteroid.

Injection of corticosteroids is superior to injection of placebo,<sup>30,31</sup> improving symptoms in more than 75 percent of patients.<sup>30,32-34</sup> Local injection of corticosteroids is also associated with improvement in median-nerve conduction.<sup>30,33,34</sup> Symptoms generally recur within one year.<sup>30,32</sup> Risk factors for recurrence include severe abnormalities on electrodiagnostic testing, constant numbness, impaired sensibility, and weakness or thenar muscular atrophy.<sup>30,32,34</sup> The risks of infection and nerve damage resulting from corticosteroid injection are considered to be low but have not been formally studied. Many clinicians limit the number of injections into the carpal tunnel (as they would for other sites) to about three per year in order to minimize local complications (such as rupture of

tendons and irritation of the nerves) and the possibility of systemic toxic effects (such as hyperglycemia or hypertension). The optimal number of injections per year has not been studied. Preliminary data suggest that iontophoresis with corticosteroid cream (a method that involves the use of an electrical current to deliver medication to deeper structures) may provide an alternative to corticosteroid injection.<sup>35</sup>

In general, conservative treatment is more successful in patients with mild nerve impairment. In one study,<sup>32</sup> 89 percent of patients with severe carpal tunnel syndrome (constant numbness with weakness, atrophy, or sensory loss) had recurrence of the syndrome within one year after a conservative program that included splinting and injection of corticosteroids into the carpal tunnel. Among patients with mild carpal tunnel syndrome (intermittent numbness and normal sensory and motor findings on physical examination), 60 percent had recurrence of symptoms after such conservative treatment.

**Surgery** In general, the decision about whether to proceed with carpal-tunnel-release surgery should be driven by the preference of the patient. However, if a patient has symptoms and signs that are suggestive of axonal loss — constant numbness, symptoms for more than one year, loss of sensibility, and thenar muscular atrophy or weakness — surgery should be seriously considered.

There are several surgical approaches to carpal-tunnel release. In the traditional open procedure, the surgeon makes an incision 5 to 6 cm long, extending distally from the distal wrist crease, and releases the transverse carpal ligament under direct visualization. For endoscopic release, a device with either two portals<sup>36</sup> or one portal<sup>37</sup> is used to release the transverse carpal ligament. The endoscopic techniques carry a higher risk than open carpal-tunnel release of injury to the median nerve.<sup>37-39</sup> Relief of symptoms is similar with the open and the endoscopic procedures,<sup>37,38</sup> and many studies report that patients return to work earlier after the endoscopic surgery.<sup>37-39</sup>

In recent years, many surgeons have adopted a “mini”-open release that uses an incision of 2.0 to 2.5 cm to release the transverse carpal ligament under direct visualization. This approach is used in an attempt to achieve earlier recovery while avoiding the complications associated with the endoscopic approach.<sup>40</sup> The efficacies of the “mini”-open, endoscopic, and traditional open techniques have not been compared in an adequately powered randomized trial.

More than 70 percent of patients report being completely satisfied or very satisfied with the results of carpal-tunnel surgery (irrespective of whether they have undergone open or endoscopic surgery).<sup>41</sup> Similarly, 70 to 90 percent of subjects report being free of nocturnal pain after surgery.<sup>38,41</sup> There have been no randomized controlled trials comparing

carpal-tunnel release with conservative therapy. After surgery, pain relief occurs within days, but hand strength does not reach preoperative levels for several months.<sup>42</sup> Tenderness of the surgical scar may also persist for up to a year after open release.<sup>41</sup> Patients with better general functional status and mental health have more favorable outcomes after carpal-tunnel release.<sup>41,43</sup>

Among workers undergoing carpal-tunnel release, involvement of an attorney (generally to dispute a decision about a workers' compensation claim) is associated with a worse surgical outcome.<sup>43</sup> Also, workers with less striking abnormalities on electrodiagnostic testing have worse outcomes.<sup>44</sup> This somewhat paradoxical finding may reflect the inclusion of cases in which symptoms arise from other disorders of the arm or hand, underscoring the importance of careful selection of patients for surgery.

**Alternative Therapies** Acupuncture for carpal tunnel syndrome has not been evaluated in controlled studies. In a randomized trial, an intervention involving yoga-based stretching, strengthening, and relaxation in patients with carpal tunnel syndrome resulted in greater improvement in grip strength and reduction of pain than did splinting.<sup>45</sup> In one study, chiropractic therapy for carpal tunnel syndrome was as effective for pain as splints and medication,<sup>46</sup> but data are limited.

#### AREAS OF UNCERTAINTY

The benefit of modifying the patient's activities remains uncertain. It is reasonable to suggest that patients minimize forceful hand and wrist activities at home and work, since these activities increase carpal-tunnel pressure in patients with carpal tunnel syndrome,<sup>47</sup> and that patients minimize any activities that exacerbate their symptoms. The effects of ergonomically designed equipment and frequent rest breaks on the incidence and course of carpal tunnel syndrome have not been studied rigorously. Rigorous studies are also needed to define the effectiveness of various medications, acupuncture, dietary supplements, chiropractic, and yoga, as well as the optimal timing of carpal-tunnel surgery and the results of carpal-tunnel release with a "mini"-open incision.

#### GUIDELINES

The "Clinical Guideline on Wrist Pain" from the American Academy of Orthopedic Surgeons recommends that patients with suspected carpal tunnel syndrome modify their activities for two to six weeks while they are treated with wrist splints and nonsteroidal antiinflammatory medication. If these therapies are ineffective, or if the patient has

thenar-muscle atrophy or weakness, the guidelines recommend referral to a specialist for consideration of injection or surgery.<sup>48</sup> The practice guidelines of the American College of Occupational and Environmental Medicine<sup>49</sup> suggest a similar approach and emphasize the importance of avoiding occupational activities that cause bothersome symptoms.

### CONCLUSIONS AND RECOMMENDATIONS

Patients with discomfort of the hand and wrist, such as the woman described in the vignette, should be evaluated with a detailed history of symptoms (which can be facilitated with a diagram of hand pain) and a physical examination that includes tests of sensory and motor-nerve function and provocative maneuvers. Findings on such examination have limited diagnostic value, however, and will not establish the diagnosis with certainty. If carpal tunnel syndrome seems likely, conservative management with splinting should be initiated. If splinting causes discomfort during the performance of some hand-intensive tasks, it is advisable either to avoid the activity or to perform it without the splint. We suggest that patients reduce activities at home and work that exacerbate symptoms. Although the effects of nonsteroidal antiinflammatory medications on carpal tunnel syndrome have not been well studied, we generally suggest a trial of these agents if there are no contraindications. We do not recommend use of vitamin B<sub>6</sub> (because there is no evidence of efficacy) or oral corticosteroids (given the potential for toxic effects). We generally screen for and treat common underlying disorders — specifically, diabetes and hypothyroidism.

If the condition fails to improve, we recommend referral to a specialist with expertise in the diagnosis and management of carpal tunnel syndrome. If the diagnosis appears secure, the clinician should discuss the options of corticosteroid injection and surgical therapy with the patient. Injection is especially effective if there is no loss of sensibility or thenar-muscle atrophy and weakness and if symptoms are intermittent rather than constant. We perform electrodiagnostic studies if the diagnosis is uncertain, particularly if surgery is contemplated. For surgically treated patients, we favor the limited open incision for carpal-tunnel release.

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# Postpartum Depression

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A woman visits the doctor for her six-week postpartum evaluation. She reports that she cannot sleep even if her baby sleeps. She cries daily and worries constantly. She does not feel hungry and is not eating regularly. Making decisions is overwhelming. She says she is not herself. How should this new mother be evaluated and treated?

## THE CLINICAL PROBLEM

Postpartum depression, the most common complication of childbearing, occurs in 13 percent of women (one of every eight) after delivery.<sup>1</sup> Given that there are nearly 4 million births in the United States annually, a half-million women have this disorder every year.

## STRATEGIES AND EVIDENCE

### Definitions

Major depression is defined by the presence of five of the symptoms listed in Table 1, one of which must be either depressed mood or decreased interest or pleasure in activities. The symptoms reflect the physiologic dysregulation (disturbance of sleep, appetite, and cognition) that is characteristic of depression and must be present for most of the day nearly every day for two weeks or more. According to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),<sup>2</sup> an episode of depression is considered to have postpartum onset if it begins within four weeks after delivery. However, onset within three months after delivery is the time frame commonly used by investigators on the basis of epidemiologic studies.<sup>3</sup> The patterns of symptoms in women with postpartum depression are similar to those in women who have episodes unrelated to childbirth.<sup>4</sup> Difficulties in the interactions between caretakers who are under stress and infants increase the risk of insecure attachment and cognitive and behavioral problems in children. The conse-

Table 1. Symptoms of Major Depression with Postpartum Onset.\*

Major depression is defined by the presence of five of the following symptoms, one of which must be either depressed mood or decreased interest or pleasure†:

- Depressed mood, often accompanied or overshadowed by severe anxiety
- Markedly diminished interest or pleasure in activities
- Appetite disturbance—usually loss of appetite with weight loss
- Sleep disturbance—most often insomnia and fragmented sleep, even when the baby sleeps
- Physical agitation (most commonly) or psychomotor slowing
- Fatigue, decreased energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Decreased concentration or ability to make decisions
- Recurrent thoughts of death or suicidal ideation

\* From the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).<sup>3</sup> Postpartum depression is defined in the DSM-IV as that which begins within four weeks after delivery.

† Symptoms must be present most of the day nearly every day for two weeks. A diagnosis of major depression also requires a decline from the woman's previous level of functioning and substantial impairment.

quences of parental mental illness, such as family discord, loss of income, and placement of children outside of the home, also affect child development.

### Causes

The rapid decline in the levels of reproductive hormones that occurs after delivery is believed to contribute to the development of depression in susceptible women. In one study, such a decline after delivery was simulated in nonpregnant women with the use of leuprolide to induce a hypogonadal state, followed by treatment with supraphysiologic doses of estradiol and progesterone, and finally the withdrawal of both steroids under double-blind conditions.<sup>5</sup> Five of eight women with a history of postpartum depression, but none of eight women without previous depression, had mood changes. Women with a history of postpartum depression appear differentially sensitive to the effects on mood of the withdrawal of gonadal steroids.

Although it is tempting to attribute postpartum depression to hormonal decline, several other factors may predispose women to this condition. Stressful life events,<sup>6</sup> past episodes of depression (not necessarily related to childbearing), and a family history of mood disorders,<sup>1,7</sup> all recognized predictors of major depression in women,<sup>6</sup> are also predictors of postpartum depression. The likelihood of postpartum depression does not appear to

be related to a woman's educational level, the sex of her infant, whether or not she breast-feeds, the mode of delivery, or whether or not the pregnancy was planned.<sup>7</sup>

### Screening

The Edinburgh Postnatal Depression Scale (Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>),<sup>8</sup> a 10-item questionnaire that is easy to administer, is an effective screening tool. One example of an item on the questionnaire is the following statement: "I have looked forward with enjoyment to things," to which responses are scored from 0, for "as much as I ever did," to 3, for "hardly at all." A cutoff score of 9 or 10 has been recommended in the United Kingdom for first-stage screening<sup>9</sup> and is a reliable indicator of the presence of postpartum depression in women in the United States as well.<sup>10</sup> If a woman has a total score on the Edinburgh Postnatal Depression Scale of 10 or higher or indicates that "the thought of harming myself has occurred to me" either "sometimes" (a score of 2) or "quite often" (a score of 3), a brief clinical interview to review symptoms and establish the diagnosis of depression is warranted.

An alternative to the Edinburgh Postnatal Depression Scale is to frame the required criterion for the diagnosis of depression as a screening question<sup>2</sup>: "Have you had depressed mood or decreased interest or pleasure in activities most of the day nearly every day for the past two weeks?" If the woman answers in the affirmative, the clinician can next determine whether at least five of the symptoms listed in Table 1 are present. The level of impairment and distress can be explored with the question "Has the depression made it hard for you to do your work, take care of things at home, or get along with people?"<sup>2</sup>

### Evaluation and Differential Diagnosis

If the patient has considered a plan to act on suicidal thoughts or has thoughts about harming her infant, provisions for safety and urgent referral for psychiatric care are recommended. Women who have major functional impairment (as evidenced by the avoidance of family or friends, an inability to attend to hygiene, or an inability to care adequately for the infant) and those with coexisting substance abuse are also candidates for rapid referral. Women who report depressive symptoms without suicidal ideation or major functional impairment (or score between 5 and 9 on the Edinburgh Postnatal Depression Scale) should be evaluated again two to four weeks later in order to determine whether an episode of depression has evolved or whether symptoms have subsided.

A careful history taking and a physical examination are warranted in all women with postpartum depression. Thyroid function should be assessed, since both hypothyroidism and hyperthyroidism are more frequent during the postpartum period and may contribute

to mood changes. However, in women with hyperthyroidism or hypothyroidism, treatment of both thyroid and depressive disorders is usually required.<sup>7</sup>

Postpartum depression must be distinguished from the “baby blues,” which occur in the majority of new mothers. In this syndrome, symptoms such as weeping, sadness, irritability, anxiety, and confusion occur, peaking around the fourth day after delivery, and resolving by the tenth day. This transient mood disturbance does not consistently affect the woman’s ability to function.

Postpartum psychosis represents a psychiatric emergency that requires immediate intervention because of the risk of infanticide and suicide. Onset usually occurs within the first two weeks after delivery. This disorder differs from other psychotic episodes because it usually involves extreme disorganization of thought, bizarre behavior, unusual hallucinations (which may be visual, olfactory, or tactile), and delusions, all of which suggest an organic cause.<sup>4</sup> Treatments for postpartum psychosis have been discussed in detail elsewhere.<sup>11</sup>

Postpartum psychosis is usually a manifestation of bipolar disorder.<sup>12</sup> A depressive episode (with or without psychotic features) can occur during the course of bipolar disorder. Therefore, all patients with postpartum depression should be screened with the following questions<sup>2</sup>: “Have you ever had four continuous days when you were feeling so good, high, excited, or ‘hyper’ that other people thought you were not your normal self or you got into trouble?” and “Have you experienced four continuous days when you were so irritable that you found yourself shouting at people or starting fights or arguments?” Positive responses to these questions necessitate psychiatric referral.

### Antidepressant Treatment

For women who are given a diagnosis of major depression with postpartum onset, treatment with antidepressant drugs is appropriate. A selective serotonin-reuptake inhibitor should be tried initially because such agents are associated with a low risk of toxic effects in patients taking an overdose, as well as with ease of administration. However, if the patient has previously had a positive response to a specific drug from any class of antidepressants, that agent should be strongly considered.

The efficacy of antidepressant drugs for depression unrelated to childbearing supports their use for postpartum depression, and the available data confirm the assumption that they are effective against postpartum depression. Information about drugs used to treat depression<sup>13-18</sup> is presented in Table 2. However, only one placebo-controlled trial and three open trials that specifically addressed postpartum depression have been published. The selective serotonin-reuptake inhibitor fluoxetine was compared with psychotherapy,

Table 2. Pharmacotherapy for Postpartum Depression.

Drug	Recommended Range of Doses (mg/day) <sup>a</sup>	Side Effects	Implications for Use during Breast-Feeding
<b>Selective serotonin-reuptake inhibitors</b>			
Sertraline	50–200	Nausea, loose stools, tremors, insomnia, sexual dysfunction, possible drug interactions†	Drug and weakly active metabolite generally not detectable in infants; no reports of adverse events
Paroxetine	20–60	Nausea, drowsiness, fatigue, dizziness, sexual dysfunction, possible drug interactions†	No active metabolite; levels not detectable in infants; no reports of adverse events
Fluvoxamine	50–200	Nausea, drowsiness, anorexia, anxiety, sexual dysfunction, possible drug interactions†	No active metabolite; levels not detectable in infants; no reports of adverse events
Citalopram	20–40	Nausea, insomnia, dizziness, somnolence	One infant with a measurable level had colic; other infants had no problems and serum levels that were undetectable or just above the limit of detection
Fluoxetine	20–60	Nausea, drowsiness, anorexia, anxiety, sexual dysfunction, possible drug interactions†	Drug and active metabolite have comparatively long half-lives; serum levels similar to those in adults reported in some symptomatic infants; prenatal exposure adds to serum levels in breast-fed infants
<b>Tricyclic antidepressants</b>			
Nortriptyline	50–150	Sedation, weight gain, dry mouth, constipation, orthostatic hypotension, possible drug interactions†; base-line ECG recommended‡	Drug and metabolites generally below or slightly above limit of detectability; no reports of adverse events in infants
Desipramine	100–300	Sedation, weight gain, dry mouth, constipation, orthostatic hypotension, possible drug interactions†; base-line ECG recommended‡	Drug and metabolites below quantifiable level; no adverse effects
<b>Serotonin-norepinephrine reuptake inhibitor</b>			
Venlafaxine	75–300	Nausea, sweating, dry mouth, dizziness, insomnia, somnolence, sexual dysfunction	Undetectable or low serum levels of drug; metabolite usually measurable and levels similar to those in adults observed in some infants; drug level greater in breast milk than in maternal serum
<b>Other</b>			
Bupropion	300–450	Dizziness, headache, dry mouth, sweating, tremor, agitation, rare seizures, possible drug interactions†	Unknown
Nefazodone	300–600	Dry mouth, somnolence, nausea, dizziness, possible drug interactions†	No published data on serum levels in infants; sedation and poor feeding in a premature infant described
Mirtazapine	15–45	Somnolence, nausea, weight gain, dizziness	Unknown

<sup>a</sup>Treatment with any of these agents should be initiated at half of the lowest recommended therapeutic dose. Dosages are from the *Physicians' Desk Reference*, 55th ed.<sup>13</sup>

†Drug interactions are possible because of the drug's inhibition of the following cytochrome P450 (CYP) enzyme systems<sup>17,18</sup>: for sertraline, 2D6, 2C, and 3A4; for paroxetine, nortriptyline, desipramine, and bupropion, 2D6; for fluvoxamine, 1A2, 2C, and 3A4; for fluoxetine, 2D6, 2C, and 3A4; for nefazodone, 3A4.

‡If the electrocardiogram (ECG) shows conduction defects, consider a non-tricyclic antidepressant.

and both treatments were similarly effective.<sup>18</sup> Fluoxetine was significantly more effective than placebo.<sup>18</sup> Sertraline,<sup>19</sup> venlafaxine,<sup>20</sup> and drugs grouped according to class (selective serotonin-reuptake inhibitors and tricyclic antidepressants<sup>21</sup>) were effective in open trials. Women with postpartum depression may be more likely to have a response to serotonergic agents, such as selective serotonin-reuptake inhibitors and venlafaxine, than to nonserotonergic tricyclic antidepressants.<sup>19-21</sup>

Because women who have recently given birth are often sensitive to the side effects of medications,<sup>22</sup> treatment should be initiated at half the recommended starting doses listed in Table 2 (e.g., 25 mg of sertraline per day or 10 mg of paroxetine per day) for four days, and doses should be increased by small increments (e.g., 25 mg of sertraline per week or 10 mg of paroxetine per week) as tolerated, until full remission is achieved. Slow increases in the dose are helpful in managing side effects. If the patient has a response to an initial trial of medication lasting six to eight weeks, the same dose should be continued for a minimum of six months after a full remission has been achieved, in order to prevent relapse.<sup>23</sup> If there is no improvement after six weeks of drug therapy, or if the patient has a response but then has a relapse, referral to a psychiatrist should be considered. The average duration of a postpartum episode of depression (without treatment) is seven months.<sup>24</sup> Fifty to 85 percent of patients with a single episode of major depression will have at least one more episode after the discontinuation of medication, and the risk increases with the number of previous episodes.<sup>23</sup> Therefore, long-term treatment for the prevention of recurrence should be considered for women who have had three or more episodes of severe depression.

### **Breast-Feeding**

All antidepressants are excreted in breast milk. Optimal clinical management dictates the use of the lowest effective dose of antidepressants in a lactating mother. Observation of the infant's behavior before the mother is treated permits clinicians to avoid misinterpreting typical behavior as potentially drug-related.

The serum levels of antidepressants in infants of breast-feeding mothers have been evaluated in multiple studies.<sup>25-41</sup> The selective serotonin-reuptake inhibitor sertraline has been recommended as the first-line treatment for breast-feeding mothers on the basis of multiple case series by several investigators that suggest that this agent may be used with little risk.<sup>42</sup> Epperson and colleagues<sup>27</sup> evaluated the functional effects of very low levels of sertraline in breast-fed infants by assessing the platelet serotonin level. In humans, platelet and central neuronal serotonin transporters are identical. The expected marked decline in serotonin levels was observed in mothers after treatment, but there was

minimal change in the infants who were exposed to small amounts of sertraline through breast milk. No reports of adverse effects in breast-fed infants whose mothers were treated with sertraline, paroxetine, or fluvoxamine have been published.

Colic has been reported in three infants who were breast-fed by mothers taking fluoxetine; when tested, the infants were shown to have serum levels of fluoxetine and norfluoxetine (the active metabolite of fluoxetine) that were in the therapeutic range for adults.<sup>31,32</sup> Chambers et al.<sup>43</sup> reported that breast-fed infants of fluoxetine-treated mothers gained significantly less weight after birth, although the mothers did not report unusual behavior in these infants. Unlike most antidepressants, fluoxetine has a highly active metabolite (norfluoxetine), and both agents have very long half-lives (84 and 146 hours, respectively).<sup>41</sup> Continuous exposure to fluoxetine through breast milk is more likely than exposure to other selective serotonin-reuptake inhibitors to lead to measurable serum levels of the antidepressant agent.<sup>41</sup> Prenatal exposure to fluoxetine may also contribute to measurable serum levels in infants of mothers who take this medication. In one report, "uneasy sleep" was described in an infant with a measurable serum level of citalopram, a selective serotonin-reuptake inhibitor with a shorter half-life<sup>35</sup>; however, this report is inconsistent with data on other selective serotonin-reuptake inhibitors that have similar half-lives. An unusually high level of sertraline was reported in one infant,<sup>25</sup> although the authors believed it to be a spurious finding. However, some infants may have particularly poor metabolism of antidepressants.<sup>41</sup>

Tricyclic antidepressants are not typically found in measurable amounts in nursing infants.<sup>41</sup> Since these agents are not first-line drugs for depression, only the representative drugs nortriptyline and desipramine (which have fewer side effects than others in the class) are listed in Table 2. Of the drugs in this class, nortriptyline has been studied the most as a treatment for breast-feeding women. The only adverse outcome reported with any tricyclic antidepressant, respiratory depression and sedation, occurred in an infant whose mother was taking doxepin.<sup>41</sup> Data are lacking on other classes of antidepressants.

Children who were exposed to tricyclic antidepressants through breast milk have been followed through preschool and compared with children who were not exposed to such drugs, and no developmental problems have been found.<sup>44</sup> However, there are no published long-term evaluations of infants exposed to selective serotonin-reuptake inhibitors through breast milk, and effects of antidepressants on developing neurotransmitter systems cannot be ruled out. Although substantial data have been published on antidepressant levels in infants exposed through breast milk, they reflect effects in full-term infants. Close clinical monitoring and measurement of serum levels are warranted for

premature or sick newborns. In the cases of women who have a response only to drugs for which data are unavailable, decisions regarding treatment during breast-feeding must take into account this uncertainty. The importance of caretaking by capable parents, which is compromised by depression, and the benefits of breast-feeding should also be weighed in the decision-making process.

### **Prophylactic Treatment**

Women who have a history of depression are justifiably concerned about recurrence after childbirth. After one postpartum episode, the risk of recurrence (defined as a return of symptoms that fulfill the DSM-IV criteria for major depression) is 25 percent.<sup>10</sup> Preventive therapy after delivery should be considered for women with any previous episode of depression.<sup>10</sup> The drug to which the patient previously had a response or a selective serotonin-reuptake inhibitor are reasonable choices; the tricyclic antidepressant nortriptyline did not confer protection, as compared with placebo.<sup>10</sup> At a minimum, postpartum management should include monitoring for recurrence, with a plan for rapid intervention if indicated.

### **Psychotherapy**

In a study involving 120 women who had recently given birth, interpersonal psychotherapy, a 12-session treatment that focuses on changing roles and important relationships, was effective for the relief of depressive symptoms and improvement in psychosocial functioning in treated women as compared with controls who were on the waiting list for such therapy.<sup>24</sup> A group intervention based on interpersonal psychotherapy and delivered during pregnancy prevented postpartum depression in 35 economically disadvantaged women.<sup>45</sup> However, psychotherapy in addition to fluoxetine did not improve outcomes more than fluoxetine alone.<sup>13</sup>

### **Hormonal Therapy**

Estradiol<sup>46</sup> has been evaluated as a treatment for postpartum depression. In a study comparing transdermal 17 $\beta$ -estradiol (200  $\mu$ g per day) with placebo, the estradiol-treated group had a significant reduction in depression scores during the first month. However, nearly half the women also were treated with antidepressants, so the effect of estradiol alone remains uncertain. Prophylactic administration of a progestogen after delivery increased the risk of postpartum depression as compared with placebo.<sup>47</sup>



### AREAS OF UNCERTAINTY

Antidepressants are effective for postpartum depression; however, it is not certain whether specific antidepressants or classes of antidepressants are more beneficial than others. The optimal approach to prophylaxis in high-risk patients is also unclear. The role of psychotherapy for patients with a partial response or no response to medication has not been explored. More data are needed on predictors of the response to therapy so that patients may be systematically matched with therapies. The role of gonadal steroids in causing postpartum depression remains unclear. In addition, data are needed about long-term physical and mental development in infants exposed to antidepressants through breastfeeding as well as prenatally.

### GUIDELINES

To our knowledge, there are no treatment guidelines available that are specific to postpartum depression. Clinical-practice guidelines developed by the American Psychiatric Association for major depression in adults apply<sup>23</sup> (they are available at <http://www.psych.org>). The severity of symptoms, the preferences of the patient, and the response to treatment during previous episodes influence the recommendations for psychotherapy, antidepressants, or electroconvulsive therapy.

### CONCLUSIONS AND RECOMMENDATIONS

Physicians must expect that one out of eight new mothers will have postpartum depression. In women with previous episodes of postpartum depression, the risk of recurrence is one in four. Since identification of postpartum depression is the first step, we recommend that women be screened after delivery with the Edinburgh Postnatal Depression Scale, which is brief, is highly acceptable to patients, and reliably detects the presence of postpartum depression (indicated by a score of 10 or higher).<sup>8</sup> Alternatively, women should be asked about depressed mood and other associated symptoms. Once depression has been identified, rapid implementation of treatment is advisable, because episodes may be long and the number and severity of sequelae increase with the duration of the episode. Depressed women should be asked about any intention to harm themselves or their children, which necessitates urgent referral for psychiatric care.

A selective serotonin-reuptake inhibitor should be the first-line drug because such agents carry a low risk of toxic effects in patients who take an overdose, are easy to administer, and have been used relatively frequently in breast-feeding women. Any drug should be initiated at half the usual starting dose. We administer medication for at least six months after full

remission in order to prevent relapse,<sup>23</sup> and we consider long-term maintenance therapy for women with three or more episodes or episodes that featured serious disability. Women with postpartum depression may also respond to interpersonal psychotherapy. The goal of treatment is complete normalization of mood and physiologic and social functioning.

Women with this disorder need not feel alone in their suffering. They may find useful information in Marie Osmond's book *Behind the Smile: My Journey Out of Postpartum Depression*<sup>48</sup> and on the Web sites of the National Women's Health Information Center (<http://www.4woman.gov>) and groups such as Postpartum Support International (<http://www.chss.iup.edu/postpartum>) and Depression after Delivery (<http://www.depressionafterdelivery.com>).

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## ADDENDUM

Since the publication of this article, authors of a meta-analysis have identified the incidence of postpartum depression to be 14.5 percent (one in seven new mothers) in the first three postpartum months.<sup>1</sup> A pooled analysis of studies of antidepressant levels in lactating mothers, breast milk, and nursing infants<sup>2</sup> indicated that maternal treatment with nortriptyline, paroxetine, and sertraline usually results in nonquantifiable serum levels in breast-fed infants, and it concluded that these are drugs of choice for the breast-feeding woman; however, established efficacy of another drug in a given patient must be considered in the decision-making process.

A small placebo-controlled randomized trial of non-depressed women with a history of postpartum depression suggested that sertraline might prevent recurrence. As com-

pared with the placebo group, women randomized to a six-month course of sertraline immediately postpartum were significantly less likely to experience a postpartum major depression.<sup>3</sup>

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# Preventing Falls in Elderly Persons

MARY E. TINETTI, M.D.

A 79-year-old woman with a history of congestive heart failure, arthritis, depression, and difficulty sleeping presents for a follow-up visit. She takes several prescription medications, including an antidepressant, a diuretic, an angiotensin-converting-enzyme inhibitor, and a beta-blocker, as well as over-the-counter sleep and allergy medications. Her chronic conditions appear to be stable. Her daughter reports that the patient has fallen twice during the past six months. What can be done to prevent future falls?

## THE CLINICAL PROBLEM

More than one third of persons 65 years of age or older fall each year, and in half of such cases the falls are recurrent.<sup>1,2</sup> Approximately 1 in 10 falls results in a serious injury, such as hip fracture, other fracture, subdural hematoma, other serious soft-tissue injury, or head injury.<sup>3-5</sup> Falls account for approximately 10 percent of visits to the emergency department and 6 percent of urgent hospitalizations among elderly persons.<sup>4,6</sup> Independently of other health conditions, falls are associated with restricted mobility; a decline in the ability to carry out activities such as dressing, bathing, shopping, or housekeeping; and an increased risk of placement in a nursing home.<sup>7-9</sup>

Although a few falls have a single cause, the majority result from interactions between long-term or short-term predisposing factors and short-term precipitating factors in a person's environment.<sup>1-5</sup> Each of the following conditions has been shown to increase the subsequent risk of falling in two or more observational studies: arthritis; depressive symptoms; orthostasis; impairment in cognition, vision, balance, gait, or muscle strength; and the use of four or more prescription medications. Furthermore, the risk of falling consistently increases as the number of these risk factors increases.<sup>1,2</sup> The risk of falling increased in a cohort of elderly persons living in the community, for example, from 1 percent among those with no risk factors to 78 percent among those with four or more risk factors.<sup>1</sup>

Although there is a clear relation between falling and the use of a higher number of medications, the risks associated with individual classes of drugs have been more vari-

able.<sup>10,11</sup> To date, serotonin-reuptake inhibitors, tricyclic antidepressants, neuroleptic agents, benzodiazapines, anticonvulsants, and class IA antiarrhythmic medications have been shown to have the strongest link to an increased risk of falling.<sup>10-12</sup>

During the month after hospital discharge, the risk of falling is high, particularly among elderly persons frail enough to require home health care.<sup>13</sup> Other periods of high risk include those in which there are episodes of acute illness or exacerbations of chronic illness.

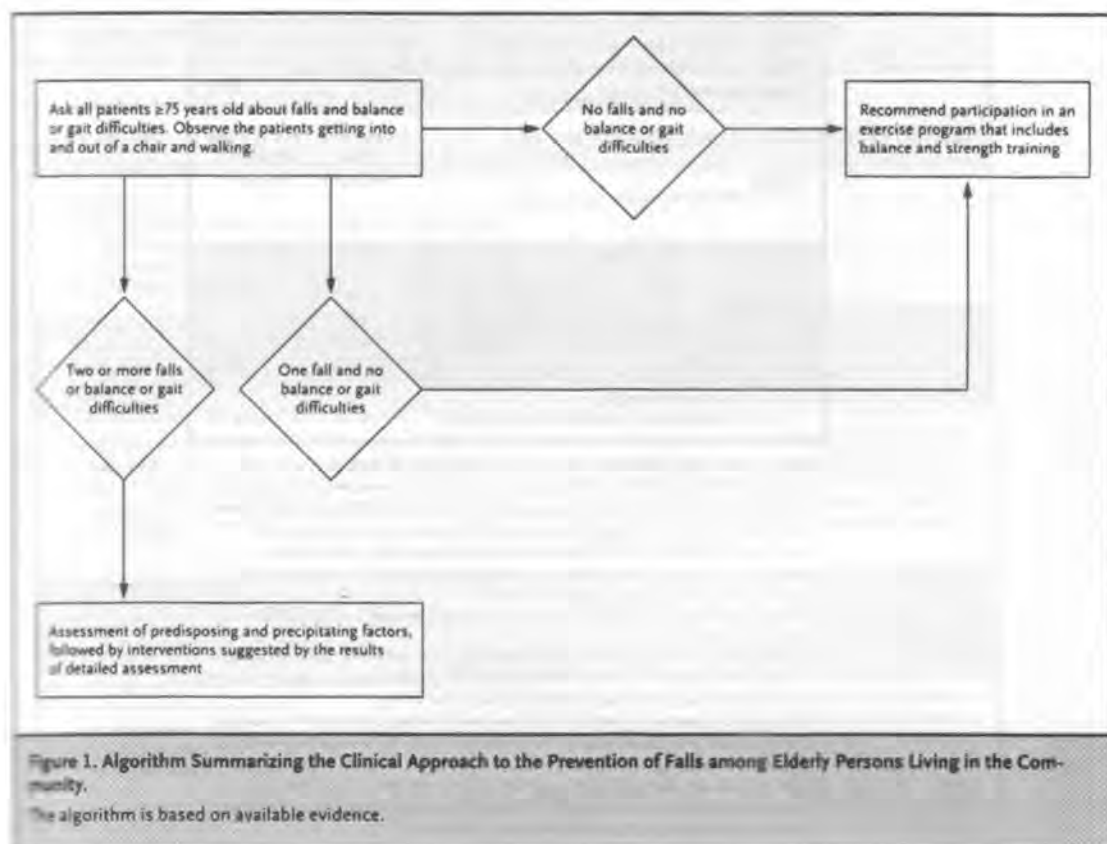
As discussed in the next section of this article, several single and multifactorial health care–based strategies have proved effective in reducing the rate of falling in clinical trials.<sup>14-21</sup> However, implementation of these approaches for the prevention of falling may be complicated, for at least two reasons. First, clinicians are more experienced at managing discrete diseases than at managing multifactorial conditions, such as falling. Second, although many components of an effective fall-prevention strategy are relatively straightforward, others require tradeoffs and the weighing of risks and benefits. Perhaps the most complicated component of a strategy to prevent falls involves reduction in the use of medications. Medications may be appropriately recommended for the treatment of a disease, but they also have adverse effects; falling is one of the most common adverse events related to drugs.<sup>22-24</sup> Many elderly patients have several chronic conditions for which multiple medications are prescribed, further increasing the associated risks, including falling.

## STRATEGIES AND EVIDENCE

### Assessment and Intervention

Because falls result from various combinations of factors, an effective and efficient clinical strategy for risk assessment and management must address many predisposing and precipitating factors. However, a clinically sensible strategy can be extrapolated from the available clinical-trial data, augmented by observational data from well-designed studies.<sup>1-5,10-21</sup>

A rational approach to the prevention of falls is presented in Figure 1. Because elderly persons may not volunteer the information, physicians should, on at least a yearly basis, ask their elderly patients about any falls and ask about and look for any difficulties with balance or gait. Brief screens such as the “Get-Up and Go” test, which involves looking for unsteadiness as the patient gets up from a chair without using his or her arms, walks a few meters, and returns, is easily incorporated into short clinical encounters.<sup>25,26</sup> Other assessments provide more specific information about balance and gait abnormalities.<sup>27</sup>



Although there is no consensus about the optimal time to initiate screening, the rate of falling and the prevalence of risk factors for falling increase steeply after the age of 70 years.<sup>1-4</sup>

Single-intervention strategies that have proved effective among elderly persons deemed at risk for falling, either because of the presence of a known risk factor or because of a history of falls, include professionally supervised balance and gait training and muscle-strengthening exercise; gradual discontinuation of psychotropic medications; and modification of hazards in the home after hospital discharge (Table 1).<sup>14-21</sup> In one study, tapering and discontinuation of psychotropic medications, including benzodiazepines, other sleep medications, neuroleptic agents, and antidepressants, over a 14-week period were associated with a 39 percent reduction in the rate of falling.<sup>17</sup> Although nonspecific advice about modification of home hazards directed at untargeted groups of elderly persons has not proved effective, standardized assessment of home hazards by an occupational thera-



Table 1. Strategies Shown in Randomized Clinical Trials to Be Effective in Reducing the Occurrence of Falls among Elderly Persons Living in the Community.\*

Strategy	Estimated Risk Reduction	No. of Trials with Positive Results†
%		
Health care–based strategy‡		
Balance and gait training and strengthening exercise	14–27	2 of 3
Reduction in home hazards after hospitalization	18	1 of 1
Discontinuation of psychotropic medication	39	1 of 1
Multifactorial risk assessment with targeted management§	25–39	3 of 3
Community-based strategy¶		
Specific balance or strength exercise programs	29–40	2 of 2

\* The trials are those reported in the Cochrane review<sup>14</sup> that included at least six months of follow-up and involved persons living in the community. Among the strategies that have not been shown to be effective are multifactorial risk assessment without targeted management (none of three trials with positive results<sup>28–30</sup>), low-intensity general exercise programs (none of seven trials with positive results<sup>31–37</sup>), and cognitive-behavioral, educational, and self-management programs (one of six trials with positive results<sup>38–43</sup>).

† Positive results were defined as relative risks with 95 percent confidence intervals that did not include 1.<sup>15,16,19–21</sup>

‡ Participants were recruited from clinical settings, and interventions were carried out by health care professionals. Participants had reported previous falls or balance or gait difficulties or had one or more risk factors for falling.

§ The specific assessments and interventions varied among the trials. The trial personnel directed or carried out specific interventions on the basis of the results of the assessments.

¶ Participants were recruited from community sites, and interventions were not carried out by health care professionals. Participants were not recruited on the basis of previous falls, balance or gait difficulties, or risk factors.<sup>44,45</sup>

pist, along with specific recommendations and follow-up after hospital discharge, was associated with a 20 percent reduction in the risk of falling.<sup>14,18</sup> The most commonly recommended modifications in that study were the removal of rugs, a change to safer footwear, the use of nonslip bathmats, the use of lighting at night, and the addition of stair rails. Adherence to the recommended interventions ranged from 19 percent for the installation of stair rails to 75 percent for the use of bathmats.<sup>18</sup>

Whereas multifactorial assessments not linked to targeted interventions have been ineffective in preventing falls,<sup>14,28–30</sup> the most consistently successful approach to prevention has been multifactorial assessment, followed by interventions targeting the identified risk factors.<sup>19–21</sup> Such targeted assessment and management strategies have been shown to reduce the occurrence of falling by 25 to 39 percent (Table 1). Successful components of these interventions include review and possible reduction of medications; balance

Table 2. Recommended Components of Clinical Assessment and Management for Older Persons Living in the Community Who Are at Risk for Falling.

Assessment and Risk Factor	Management
Circumstances of previous falls*	Changes in environment and activity to reduce the likelihood of recurrent falls
Medication use High-risk medications (e.g., benzodiazepines, other sleeping medications, neuroleptics, antidepressants, anti-convulsants, or class IA antiarrhythmics)*†‡ Four or more medications‡	Review and reduction of medications
Vision* Acuity <20/60 Decreased depth perception Decreased contrast sensitivity Cataracts	Ample lighting without glare; avoidance of multifocal glasses while walking; referral to an ophthalmologist
Postural blood pressure (after ≥5 min in a supine position, immediately after standing, and 2 min after standing)‡ ≥20 mm Hg (or ≥20%) drop in systolic pressure, with or without symptoms, either immediately or after 2 min of standing	Diagnosis and treatment of underlying cause, if possible; review and reduction of medications; modification of salt restriction; adequate hydration <sup>46</sup> ; compensatory strategies (e.g., elevation of head of bed, rising slowly, or dorsiflexion exercises); pressure stockings; pharmacologic therapy if the above strategies fail
Balance and gait†‡ Patient's report or observation of unsteadiness Impairment on brief assessment (e.g., the Get-Up and Go test <sup>25,26</sup> or performance-oriented assessment of mobility <sup>27</sup> )	Diagnosis and treatment of underlying cause, if possible; reduction of medications that impair balance; environmental interventions; referral to physical therapist for assistive devices and for gait and progressive balance training
Targeted neurologic examination Impaired proprioception* Impaired cognition* Decreased muscle strength†‡	Diagnosis and treatment of underlying cause, if possible; increase in proprioceptive input (with an assistive device or appropriate footwear that encases the foot and has a low heel and thin sole); reduction of medications that impede cognition; awareness on the part of caregivers of cognitive deficits; reduction of environmental risk factors; referral to physical therapist for gait, balance, and strength training
Targeted musculoskeletal examination: examination of legs (joints and range of motion) and examination of feet*	Diagnosis and treatment of the underlying cause, if possible; referral to physical therapist for strength, range-of-motion, and gait and balance training and for assistive devices; use of appropriate footwear; referral to podiatrist
Targeted cardiovascular examination† Syncope Arrhythmia (if there is known cardiac disease, an abnormal electrocardiogram, and syncope)	Referral to cardiologist; carotid-sinus massage (in the case of syncope)
Home-hazard evaluation after hospital discharge†‡	Removal of loose rugs and use of nightlights, nonslip bath mats, and stair rails; other interventions as necessary

\* Recommendation of this assessment is based on observational data that the finding is associated with an increased risk of falling.

† Recommendation of this assessment is based on one or more randomized controlled trials of a single intervention.

‡ Recommendation of this assessment is based on one or more randomized controlled trials of a multifactorial intervention strategy that included this component.

and gait training, muscle-strengthening exercise; evaluation of postural blood pressure, followed by strategies to reduce any decreases in postural blood pressure; home-hazard modifications; and targeted medical and cardiovascular assessments and treatments. Ascertainment of the circumstances surrounding previous falls may reveal precipitating factors, such as environmental hazards, risks associated with the activity at the time of the fall, and acute host factors, such as acute illness or immediate effects of medication, that may be amenable to intervention.

Specific recommendations for assessment and intervention are summarized in Table 2. The assessments can be performed either by the patient's usual physician or by a geriatric specialist. All medications, including over-the-counter medications, should be thoroughly reviewed and considered for possible elimination or dose reduction; the goal should be to maximize the overall health and functional benefits of the medications while minimizing their adverse effects, such as falls. Psychotropic medications warrant particular attention, since there is very strong evidence that use of these medications is linked to the occurrence of falls.<sup>10,11,17</sup> Reducing the total number of medications to four or fewer, if feasible, has also been demonstrated to reduce the risk of falling.<sup>47</sup>

When assessed appropriately, clinically significant postural hypotension is detected in up to 30 percent of elderly persons.<sup>46,48</sup> Moreover, some elderly persons with postural hypotension do not report symptoms, such as dizziness or lightheadedness.<sup>46</sup> Evidence from trials of single and multifactorial interventions suggests that all elderly persons who have any abnormalities on balance and gait testing should be referred to physical therapy for a comprehensive evaluation as well as rehabilitation.<sup>15,16,19-21</sup>

In addition to direct observation of the elderly person while he or she stands from a sitting position and walks, a targeted neurologic examination may reveal potentially treatable causes of balance or gait impairment. Proprioceptive impairment due to a neuropathy, for example, is a common cause of balance impairment in elderly persons. A decreased sensation of vibration, a frequent but abnormal finding in this population, is a more sensitive marker of neuropathy than a decrease in the sensation of position. A gait that worsens when the eyes are closed and improves when minor support is given by the examiner is a further clue to proprioceptive problems.

Persons who have fallen should be asked about loss of consciousness. Given recent evidence that some elderly persons are unaware of episodes of loss of consciousness, syncope should also be considered in those who report "just going down."<sup>49</sup>

### Laboratory Tests and Imaging

The role of laboratory and ancillary testing in the prevention of falls has not been well studied. Laboratory tests that might reasonably be performed in all persons at risk for

falling include a complete blood count; measurement of serum electrolytes, blood urea nitrogen, creatinine, glucose, and vitamin B<sub>12</sub>; and assessment of thyroid function. These tests are relatively inexpensive, and abnormal results, which are likely to be prevalent, suggest the presence of a treatable entity. Other tests should be reserved for persons in whom the presence of an abnormality is suggested by the history and results of physical examination. Neuroimaging is indicated only if there is a head injury or new, focal neurologic findings on the physical examination or if a central nervous system process is suspected on the basis of the history or examination results. Electroencephalography is rarely helpful and is indicated only if there is a high degree of clinical suspicion of seizure. Similarly, ambulatory cardiac monitoring is helpful only rarely; in elderly persons, this technique is associated with frequent false positives and false negatives.<sup>50</sup> An evaluation for arrhythmia is warranted only if there is clinical evidence of this diagnosis, such as a known history of cardiac events or an abnormal electrocardiogram.

### Education and Other Measures

Though repeatedly shown to be ineffective as a sole intervention,<sup>38-43</sup> education is an important component of strategies to manage the risk of falling. The person at risk and his or her family members should be educated about the multifactorial nature of most falls, about the specific risk factors for falling that are present, and about recommended interventions. Persons at risk for falling who live alone or who spend large amounts of time alone should be taught what to do if they fall and cannot get up, and they should have a personal emergency-response system or a telephone that is accessible from the floor.

For healthy elderly persons who have not fallen and who do not report or show balance or gait difficulties, the available evidence suggests that community-based exercise programs not supervised by health care professionals that include progressive balance-training and strengthening components may reduce the likelihood of a fall (Table 1).<sup>14,44,45</sup> Nonspecific, general exercise programs,<sup>31-37</sup> self-management and cognitive-behavioral approaches,<sup>38-43</sup> and home-hazard modifications for older persons without a history of falling or recent hospitalization have not proved effective.<sup>14,38,51</sup>

Low bone density increases the risk of hip and other fractures and should be identified and treated. The guidelines of the National Osteoporosis Foundation recommend that all women 65 years of age or older and women less than 65 years of age who are postmenopausal and who have additional risk factors for osteoporotic fractures (such as a lean habitus, a history of fractures, or a history of cigarette smoking) should undergo bone mineral density measurement to assess the risk of fractures and to ascertain whether pharmacologic or nonpharmacologic treatment would be appropriate.<sup>52</sup> A discussion of the preven-

tion and treatment of osteoporosis is beyond the scope of this article, but information is available from the National Osteoporosis Foundation (<http://www.nof.org/physguide>).<sup>52</sup> In addition to other therapies, hip protectors appear to reduce the risk of hip fracture among persons at high risk.<sup>53</sup>

#### AREAS OF UNCERTAINTY

It remains to be determined whether the strategies that have proved effective in reducing the occurrence of falls are equally effective in reducing the most serious injuries that occur as a result of falling, such as fractures and head injuries. Observational data suggest that the risk factors for falls and for serious injuries due to falls are similar<sup>3-5</sup>; trials of fall-prevention strategies to date, however, have not had sufficient power to detect whether they have an effect on the incidence of serious injury.<sup>14</sup>

The exercise programs found to be effective have been short term, usually lasting one year or less. Since most of the benefits of exercise are maintained only as long as the exercise regimen is maintained, methods for enhancing long-term adherence are needed. The optimal intensity, frequency, and type of exercise needed to minimize the risk of falling and of incurring injury while maximizing mobility remain to be determined.

Studies suggest that the number of medications prescribed can be reduced safely and effectively.<sup>14,47,54</sup> However, practical methods are needed to balance the benefits of medications for the treatment of specific diseases with the risk of adverse events, including falls, in elderly persons.

There may be an overlap between falling and the presence of syncope: preliminary data suggest that patients who have had recurrent, unexplained falls and who have bradycardia in response to carotid-sinus stimulation have fewer falls with cardiac pacing.<sup>49</sup> Until these findings are confirmed in clinical trials, however, pacemaker therapy for the prevention of unexplained falls cannot be recommended.

#### GUIDELINES

The U.S. Preventive Services Task Force recommends that all persons 75 years of age or older, as well as those 70 to 74 years of age who have a known risk factor, be counseled about specific measures to prevent falls.<sup>55</sup> It also recommends that elderly persons at high risk for falling receive individualized, multifactorial interventions in settings where adequate resources to deliver such services are available.

The American Geriatrics Society, the British Geriatrics Society, and the American Academy of Orthopaedic Surgeons have released joint, evidence-based guidelines for the pre-

vention of falls.<sup>56</sup> They recommend that all elderly patients be asked about any falls that have occurred during the previous year and that they undergo a quick test of gait and balance. The age at which screening should begin is not stipulated in the guidelines. A more comprehensive assessment, followed by a multifactorial intervention strategy, is recommended for patients who report recurrent falls, who present after a fall, or who have difficulties with balance or gait.

#### CONCLUSIONS AND RECOMMENDATIONS

All patients 75 years of age or older (or 70 years of age or older, if they are known to be at increased risk for falling) should be asked whether they have a history of falls and, if they do, should be carefully questioned about the circumstances of the falls and examined for potential risk factors. Strategies involving multifactorial assessment and intervention effectively reduce the rate of falling.

In the case of the patient described in the vignette, a review of the circumstances of her previous falls may identify high-risk activities that should be discontinued, such as carrying laundry up and down stairs. Her depressive symptoms should be reviewed to assess the tradeoff between the amelioration of depression and the risk of falling associated with her use of antidepressant medication. Efforts should be made to encourage the patient to eliminate over-the-counter sleep and allergy medications, both of which have anticholinergic effects and thus probably contribute to her risk of falling. Because her congestive heart failure is stable, it may be possible to reduce the dose of her diuretic or her cardiac medications. Any evidence of postural hypotension would further support an attempt to reduce the dose of her cardiac medications. Adequate hydration should be ensured, while avoiding fluid overload or serious hyponatremia.<sup>57</sup> If, as is likely, she has any balance or gait problems, she should be referred to a physical therapist who will train her in the use of an appropriate assistive device, such as a cane or walker, and who will prescribe a progressive program of balance and gait training and muscle strengthening. If her bone mineral density is low, I would advise her to wear hip protectors and to take calcium and vitamin D supplements, along with a bisphosphonate. These interventions will reduce by one third her risk of falling and of sustaining a hip fracture.

Additional information on the prevention of falls, including educational material for patients, can be obtained from the National Institute on Aging (<http://www.nia.nih.gov>), the Centers for Disease Control and Prevention (<http://www.cdc.gov>), and the American Geriatrics Society (<http://www.americangeriatrics.org/education/forum>).

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# Suspected Appendicitis

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A 22-year-old woman comes to the emergency department with acute abdominal pain of 18 hours' duration in the right lower quadrant. On physical examination, she is afebrile, with tenderness on deep palpation in the right lower quadrant, and has no peritoneal signs. Pelvic examination reveals tenderness in the right adnexa without a mass. How should this patient be further evaluated?

## THE CLINICAL PROBLEM

Approximately 3.4 million patients with abdominal pain seek medical care at emergency departments in the United States annually.<sup>1</sup> The various underlying causes of the pain range from benign processes to acute life-threatening disorders. Timely diagnosis and treatment of conditions for which a delay in care may have grave consequences remain a challenge.

More than 250,000 appendectomies are performed in the United States each year, making it the most common abdominal operation performed on an emergency basis.<sup>2</sup> Although the diagnosis of appendicitis in young men who have abdominal pain is usually straightforward,<sup>3</sup> the diagnostic considerations are broader for premenopausal women with the same clinical presentation. In addition, abdominal pain in patients at the extremes of age often presents a diagnostic challenge because of delays in seeking medical care or difficulty obtaining a history and performing an accurate physical examination. Since delayed diagnosis and treatment of appendicitis are associated with an increased rate of perforation, with resulting increases in morbidity and mortality rates,<sup>4-6</sup> timely intervention is crucial.

To minimize the risk of appendiceal perforation while patients await treatment, surgeons have traditionally favored early laparotomy, even in the absence of a definitive diagnosis. In approximately 20 percent of patients who undergo exploratory laparotomy because of suspected appendicitis, the appendix is normal. When advanced age or female sex confounds the usual signs and symptoms of appendicitis, the error rate in managing pain in the right lower quadrant can approach 40 percent.<sup>7</sup> In an effort to improve

Table 1. Sensitivity and Specificity of Clinical Findings for the Diagnosis of Acute Appendicitis.

Finding	Sensitivity	Specificity	Study
	percent		
Signs			
Fever	37	59	Wagner et al. <sup>8</sup>
Guarding	76-78	57-84	Wagner et al. <sup>8</sup> Jahn et al. <sup>9</sup>
Rebound tenderness	67	69	Wagner et al. <sup>8</sup>
Indirect tenderness (Royston's sign)	52	58	Jahn et al. <sup>9</sup>
Rock sign	16	85	Wagner et al. <sup>8</sup>
Symptoms			
Right-lower-quadrant pain	34	90	Wagner et al. <sup>8</sup>
Nausea	53-68	37-49	Wagner et al. <sup>8</sup> Jahn et al. <sup>9</sup>
Vomiting	49-51	45-69	Wagner et al. <sup>8</sup> Jahn et al. <sup>9</sup>
Onset of pain before vomiting	100	64	Wagner et al. <sup>8</sup>
Anorexia	88	76	Wagner et al. <sup>8</sup>

diagnostic accuracy, observation of the patient, laparoscopy, and diagnostic imaging have been used when the clinical presentation is equivocal.

## STRATEGIES AND EVIDENCE

### History and Physical Examination

The history taking and physical examination remain the diagnostic cornerstone in evaluating pain in the right lower quadrant. Although no single aspect of the clinical presentation accurately predicts the presence of the disease, a combination of various signs and symptoms may support the diagnosis. The specificity and sensitivity of common signs and symptoms of appendicitis are presented in Table 1. The three signs and symptoms that are most predictive of acute appendicitis are pain in the right lower quadrant, abdominal rigidity, and migration of pain from the periumbilical region to the right lower quadrant.<sup>8</sup> The duration of pain, defined as the time from the onset of symptoms to presentation, has also been shown to be an important predictor, since patients with appendicitis have a significantly shorter duration of pain than do patients with other disorders.<sup>10</sup>

For women with appendicitis, the most common misdiagnoses include pelvic inflammatory disease, gastroenteritis, abdominal pain of unknown origin, urinary tract infection, ruptured ovarian follicle, and ectopic pregnancy.<sup>11</sup> In a retrospective study of signs and symptoms that differentiated appendicitis from pelvic inflammatory disease in

Women with abdominal pain who were seen in the emergency department,<sup>12</sup> the findings that were most predictive of pelvic inflammatory disease included a history of the disorder, a history of vaginal discharge, vaginal discharge on examination, urinary symptoms, abnormalities on urinalysis, tenderness outside the right lower quadrant, and cervical-motion tenderness. A history of anorexia was not helpful in differentiating appendicitis from pelvic inflammatory disease.<sup>12</sup>

### Laboratory Testing

Laboratory tests are performed as part of the initial evaluation of right-lower-quadrant pain in order to rule out or confirm specific disorders. In all women of reproductive age who present with acute abdominal pain, the serum  $\beta$ -human chorionic gonadotropin level should be measured to rule out uterine or ectopic pregnancy. Although approximately 70 to 90 percent of patients with acute appendicitis have an elevated leukocyte count, leukocytosis is also characteristic of several other acute abdominal and pelvic diseases and thus has poor specificity for the diagnosis of acute appendicitis.<sup>13-17</sup> Use of the leukocyte count alone to make management decisions in cases of suspected appendicitis may result in missed diagnoses or unnecessary surgery.

Approximately 10 percent of patients with abdominal pain who are seen in the emergency department have urinary tract disease.<sup>18</sup> A urinalysis may confirm or rule out urologic causes of abdominal pain. Although the inflammatory process of acute appendicitis may cause pyuria, hematuria, or bacteriuria in as many as 40 percent of patients,<sup>19</sup> urinary erythrocyte counts exceeding 30 cells per high-power field or leukocyte counts exceeding 20 cells per high-power field suggest a urinary tract disorder.

### Observation and Laparoscopy

When the history and findings on physical examination are consistent with the diagnosis of appendicitis, appendectomy is often performed without further evaluation. If the initial clinical presentation does not suggest the need for immediate surgery, the patient may be observed for 6 to 10 hours in order to clarify the diagnosis.<sup>20,21</sup> This practice may reduce the rate of unnecessary laparotomy without increasing the rate of appendiceal perforation.<sup>22-24</sup> However, with the improved diagnostic accuracy of computed tomography (CT), early use of CT may result in lower overall costs and use of hospital resources<sup>25</sup> than the observation strategy.

Diagnostic laparoscopy has been advocated to clarify the diagnosis in equivocal cases and has been shown to reduce the rate of unnecessary appendectomy.<sup>26</sup> It is most effective for female patients, since a gynecologic cause of pain is identified in approximately 10 to



Figure 1. Endovaginal Ultrasonogram in a 46-Year-Old Premenopausal Woman with Right-Lower-Quadrant Pain, Adnexal Tenderness, and an Elevated White-Cell Count.

A carefully performed ultrasonographic examination of the right lower quadrant failed to show the appendix or the cause of pain. Endovaginal ultrasonographic examination of the right adnexa shows a fluid-filled, dilated, tubular structure (arrows), which is consistent with the presence of a hydrosalpinx or pyosalpinx. The patient underwent exploratory laparotomy, and a pyosalpinx was identified. Salpingo-oophorectomy was performed, and the patient had an uneventful recovery.

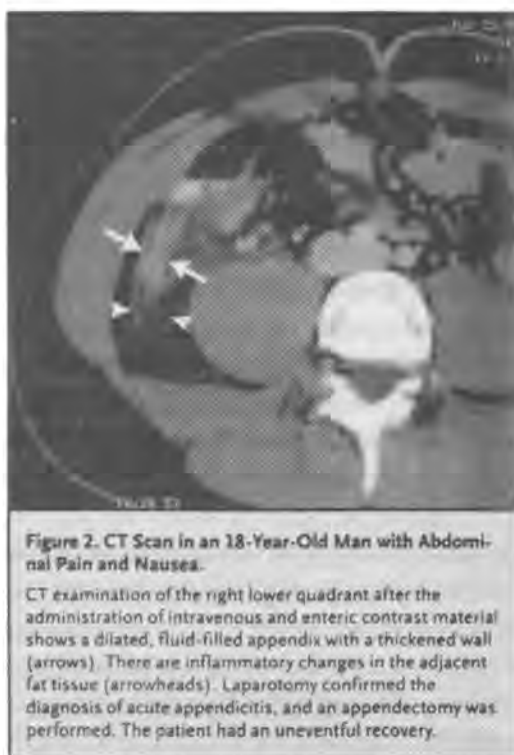
20 percent of such patients.<sup>27,28</sup> However, diagnostic laparoscopy is an invasive procedure with approximately a 5 percent rate of complications, which in most cases are associated with the use of a general anesthetic.<sup>27</sup>

### Conventional Radiography

Abdominal radiography has low sensitivity and specificity for the diagnosis of acute appendicitis.<sup>29,30</sup> Similarly, contrast-enema examination has a low accuracy. In the era of cross-sectional imaging, neither test has a role in the diagnosis of acute appendicitis.<sup>29-31</sup>

### Ultrasonography

A carefully performed ultrasonographic study has a sensitivity of 75 to 90 percent, a specificity of 86 to 100 percent, and a positive predictive value of 89 to 93 percent for the diagnosis of acute appendicitis,<sup>32-37</sup> with an overall accuracy of 90 to 94 percent.<sup>9</sup> In addition, ultrasonography may identify alternative diagnoses, such as pyosalpinx or ovarian torsion, in as many as 33 percent of female patients with suspected appendicitis<sup>38,39</sup> (Figure 1). Although appendicitis may be ruled out if the appearance of the appendix is normal on ultrasonography, a normal appendix is seen in less than 5 percent of patients.<sup>33,35,40</sup>



Most physicians hesitate to make clinical decisions about appendicitis when the appendix itself is not seen on imaging studies. Therefore, the failure to see the appendix, whether it is diseased or normal, fundamentally limits the usefulness of ultrasonography for the diagnosis of appendicitis.

### Computed Tomography

With improvements in CT, including multislice spiral CT, the entire abdomen can be scanned with high resolution in thin slices during a single period of breath-holding. Such scanning virtually eliminates motion and misregistration artifacts and routinely results in high-quality, high-resolution images of the appendix and periappendiceal tissue. For patients with suspected appendicitis, spiral CT has a sensitivity of 90 to 100 percent, a specificity of 91 to 100 percent, a positive predictive value of 95 to 97 percent, and an accuracy of 94 to 100 percent.<sup>33,41-49</sup> In a retrospective review of 650 consecutive adults with clinical findings suggestive of acute appendicitis, CT had a sensitivity of 97 percent, a specificity of 98 percent, and an accuracy of 98 percent; alternative disorders were diagnosed in 66 percent of patients.<sup>50</sup>

CT has also proved to be accurate in patients in whom the diagnosis is uncertain. In one study, 107 consecutive patients in the emergency department who had pain in the right lower quadrant but equivocal clinical or physical findings were evaluated by means of contrast-enhanced CT.<sup>45</sup> All the patients underwent appendectomy, and the histologic diagnosis was compared with the CT diagnosis. CT had a sensitivity of 92 percent, a specificity of 85 percent, a positive predictive value of 75 percent, a negative predictive value of 95 percent, and an overall accuracy of 90 percent.

CT findings that are diagnostic of appendicitis, such as a distended appendix, a thickened appendiceal wall, and periappendiceal inflammation, are shown in Figure 2. Since CT provides a view of the entire abdomen and pelvis, alternative diagnoses may be readily identified.<sup>38,39</sup> Alternative diagnoses include, but are not limited to, colitis, diverticulitis, small-bowel obstruction, inflammatory bowel disease, adnexal cysts, acute cholecystitis, acute pancreatitis, and ureteral obstruction.<sup>50</sup>

### Computed Tomography versus Ultrasonography

Two prospective studies directly comparing the efficacy of CT with that of ultrasonography in adults have shown the superiority of CT in diagnosing appendicitis.<sup>38,39</sup> In one study, 100 consecutive patients with suspected appendicitis underwent imaging, regardless of the degree of diagnostic certainty on the basis of the history and physical examination.<sup>38</sup> As compared with ultrasonography, CT had greater sensitivity (96 percent vs. 76 percent), greater accuracy (94 percent vs. 83 percent), and a higher negative predictive value (95 percent vs. 76 percent). There were smaller differences in specificity (89 percent for CT and 91 percent for ultrasonography) and the positive predictive value (96 percent and 95 percent, respectively). Among patients who did not have appendicitis, an alternative diagnosis was detected more frequently with CT than with ultrasonography. In cases in which there were conflicting interpretations of the CT and ultrasonographic findings, the CT findings were more frequently correct. Abscesses and phlegmons were also more likely to be detected by CT.<sup>38</sup>

Similar findings were reported in a prospective trial of 120 patients with an equivocal clinical presentation of appendicitis.<sup>39</sup> CT and ultrasonography had a sensitivity of 95 percent and 87 percent, specificity of 89 percent and 74 percent, positive predictive value of 97 percent and 92 percent, and negative predictive value of 83 percent and 63 percent, respectively. Among patients who did not have acute appendicitis, the correct alternative diagnosis was based on CT studies more frequently than on ultrasonographic studies. CT detected an abscess in 15 percent of patients, whereas ultrasonography detected an abscess in 9 percent of patients. There was no difference in diagnostic accuracy between men and women with the use of either CT or ultrasonography.<sup>39</sup>

### Effect of Imaging on Outcome

Although CT has been shown to be sensitive and specific for the diagnosis of acute appendicitis, retrospective studies of its effects on management decisions and rates of unnecessary appendectomy have had conflicting results.<sup>51,52</sup> However, prospective studies have directly addressed these questions.<sup>24,53</sup> One study prospectively evaluated CT in 100 consecutive patients with suspected appendicitis for whom the initial management plan was either immediate surgery or admission for observation.<sup>25</sup> The initial plan was compared with the actual care received after CT studies had been performed. The accuracy of CT in diagnosing appendicitis was 98 percent, and it led to a change in management in 59 patients, including avoidance of an unnecessary appendectomy, avoidance of admission for observation (on the basis of normal CT findings), prompt surgery (on the basis of CT evidence of appendicitis), and identification of an alternative disease process. Taking into account the costs of an unnecessary appendectomy, one day of inpatient observation, and the CT scan, the use of CT resulted in an average cost savings of \$447 per patient.<sup>25</sup>

Another study included 99 patients for whom a surgical consultation was obtained because of suspected appendicitis.<sup>53</sup> After the initial management plan had been established, all patients underwent CT and ultrasonographic studies of the right lower quadrant. Approximately two hours later, each patient was reevaluated clinically, and the treating physicians were informed of the imaging results. The surgical team then developed a final plan, using all the available information. Forty-four patients were initially scheduled for appendectomy, 49 were to be admitted for observation, and 6 were to be discharged. Among the 44 patients originally scheduled for surgery, CT combined with repeated clinical examination led to cancellation of the planned surgery for 6 patients, none of whom were found to have appendicitis; all 6 were women. Overall, of the 18 women initially assigned to surgery, 9 (50 percent) had appendicitis. Six of the 9 women who did not have appendicitis were spared unnecessary surgery by the use of CT, with the rate of unnecessary appendectomy reduced from 50 percent (9 of 18) to 17 percent (3 of 18), a difference that was statistically significant. The fact that only 50 percent of the women initially designated to have surgery actually had appendicitis emphasizes the difficulty of establishing the correct diagnosis in women.

In contrast, of the 26 men initially assigned to surgery, 24 (92 percent) had appendicitis and 2 (8 percent) did not. The addition of CT did not influence the decision to operate in any of these men. There were no men or women in whom the use of ultrasonography alone led to the cancellation of a planned surgery.

Among the 49 patients for whom observation was planned, the CT findings, combined with repeated clinical examination, led to the discharge of 13 patients from the hospital and immediate appendectomy in 10 patients. Given the costs of observation in the hospital, CT,

and appendectomy (both in patients who had appendicitis and in those who did not), the authors calculated that this approach resulted in an average cost savings of \$206 per patient.

#### AREAS OF UNCERTAINTY

Whether CT should be performed with the use of intravenous iodinated contrast material or enteric contrast material is a controversial matter.<sup>33,41,42,47</sup> Recent work indicates that intravenous contrast material improves the delineation of a thickened appendiceal wall, as well as the detection of inflammation within and surrounding the appendix, leading to improved diagnostic accuracy.<sup>49</sup> The primary purpose of using enteric contrast material is to permit definitive identification of the terminal ileum and cecum, since terminal ileitis can mimic appendicitis both clinically and radiographically.<sup>33</sup> The enteric contrast material can be delivered orally or rectally. Some suggest scanning solely in the region of the appendix<sup>48</sup>; others suggest scanning the entire abdomen and pelvis.<sup>44,49,50</sup> The spiral CT technique with slice thicknesses of no more than 5 mm is critical for accurate imaging of acute appendicitis.<sup>32,33,46</sup> In addition to the scanning technique, the skill and experience of the radiologist influence the usefulness of the examination.

#### GUIDELINES

To our knowledge, no major medical organization has proposed specific guidelines for the evaluation of patients with acute pain in the right lower quadrant.

#### CONCLUSIONS AND RECOMMENDATIONS

The evaluation of acute pain in the right lower quadrant is a common clinical problem. The diagnosis relies heavily on an accurate history and physical examination. Figure 3 shows our proposed approach. A patient, male or female, who presents with acute abdominal pain that has migrated from the umbilicus to the right lower quadrant and that is associated with tenderness in the right lower quadrant should be taken directly to the operating room for an appendectomy. The expected diagnostic accuracy in these circumstances approaches 95 percent and is probably not improved by imaging. If the clinical presentation is equivocal or if there is the suspicion of a mass or perforation with abscess formation, we advocate CT imaging to help establish the diagnosis, as in the patient described in the clinical vignette. CT has demonstrated superiority over transabdominal ultrasonography for identifying appendicitis, associated abscess, and alternative diagnoses. We reserve the use of ultrasonography for the evaluation of women who are pregnant and women in whom there is a high degree of suspicion of gynecologic disease.



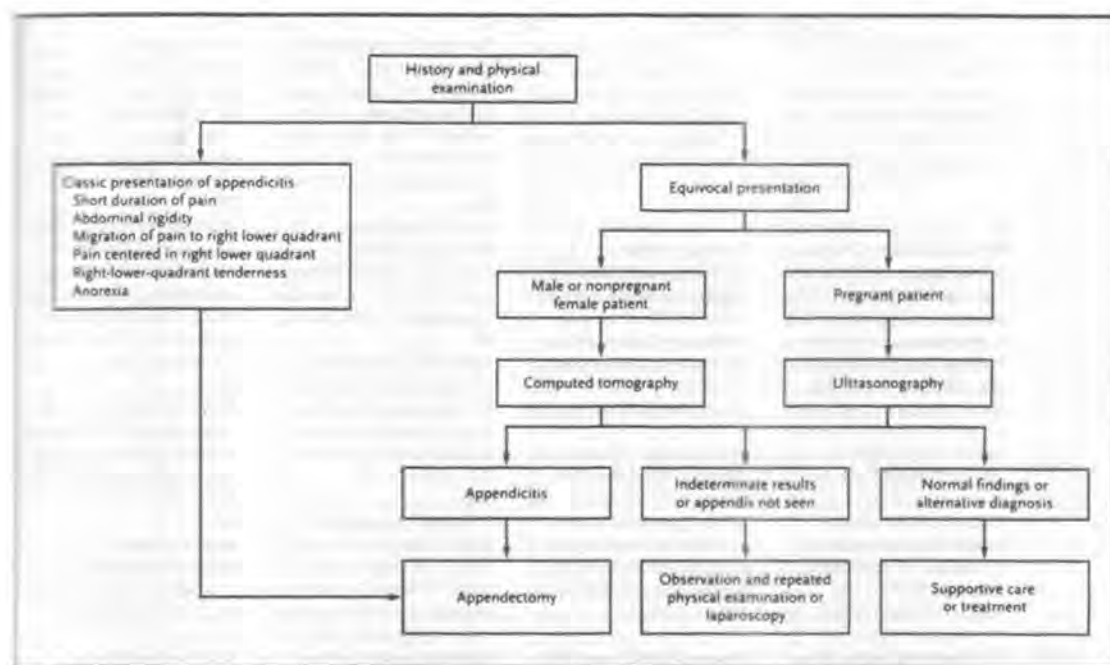


Figure 3. Clinical Algorithm for the Evaluation of Pain in the Right Lower Quadrant.

The algorithm is for suspected cases of acute appendicitis. If gynecologic disease is suspected, a pelvic and endovaginal ultrasonographic examination should be considered.

The results of imaging can be broadly classified as positive for appendicitis, indeterminate, or negative for appendicitis. If imaging suggests the presence of appendicitis, we recommend that an appendectomy be performed without further delay. If the appendix is not seen or if the results of imaging are otherwise indeterminate, we suggest further clinical observation and repeated physical examination or laparoscopy, with appropriate intervention. Finally, if CT studies show the presence of another disorder or an absence of abnormalities, there is no need for appendectomy, and supportive care or appropriate alternative treatment can be provided. This strategy can reduce the cost of observation, since a normal CT scan rules out appendicitis with a high degree of accuracy. We believe that adherence to these guidelines will increase diagnostic accuracy, leading to timely intervention, while reducing the rate of unnecessary appendectomy, and largely eliminating the costs of unnecessary imaging or observation.

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# Mammographic Screening for Breast Cancer

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A 44-year-old woman who is a new patient has no known current health problems and no family history of breast or ovarian cancer. Eighteen months ago, she had a normal screening mammogram. She recently read that mammograms may not help to prevent death from breast cancer and that “the patient should decide.” But she does not think she knows enough. She worries that there is a breast-cancer epidemic. What should her physician advise?

## THE CLINICAL PROBLEM

In 1990, for the first time in 25 years, mortality from breast cancer in the United States began dropping; by 1999, the age-adjusted mortality rate was at its lowest level (27.0 per 100,000 population) since 1973.<sup>1</sup> Meanwhile, by 1997, 71 percent of women in the United States who were 40 years of age or older reported having undergone mammography during the previous two years — an increase from 54 percent in 1989.<sup>2</sup> Ironically, just as screening (or better treatment or both) seemed to be lowering mortality from breast cancer nationally, questions were raised about the validity of the studies that had led to widespread screening. For more than two decades, expert groups uniformly agreed that screening mammography reduces mortality from breast cancer among women in their 50s and 60s, even though they disagreed about other age groups.<sup>3</sup> However, questions were raised in 2000, when two Danish investigators concluded that only three of eight randomized trials were of sufficient quality to determine the effectiveness of mammography and that the combined results of these three trials showed no benefit. This report led to confusion about the usefulness of screening mammography.

## STRATEGIES, EVIDENCE, AND AREAS OF UNCERTAINTY

Women are interested in knowing about breast cancer and want information from their doctors.<sup>4,5</sup> When women and their physicians are making decisions about screening, they need information about the underlying risk of the condition being screened for, the

Table 1. Chances of the Development of and Death from Breast Cancer within the Next 10 Years.<sup>6,7</sup>

Age	Cases of Invasive Breast Cancer	Death from Breast Cancer	Death from Any Cause
no./1000 women			
40 Yr	15	2	23
50 Yr	28	5	55
60 Yr	37	7	126
70 Yr	43	9	309
80 Yr	35	11	670

\* Rates for breast cancer and death from breast cancer were calculated on the basis of data from Feuer and Wun<sup>6</sup>; rates of death from any cause were calculated on the basis of data from Anderson and DeTurk.<sup>7</sup>

effectiveness of the procedure in preventing an untoward outcome such as death, and the potential ill effects of screening, such as false positive tests. (For policymakers and payers, cost-effectiveness is an important factor in decisions about the allocation of finite resources.) Clinical information about each of these issues with regard to breast cancer and mammography is summarized below.

### The Risk of Development of and Death from Breast Cancer

The average 10-year risk of the development of and death from breast cancer is shown in Table 1, along with the 10-year risk of death from any cause (in order to provide context).<sup>6,7</sup> A computerized tool for calculating an individual woman's risk of breast cancer, the Breast Cancer Risk Assessment Tool (available at <http://bcra.nci.nih.gov/brc/>), can be used to calculate the five-year risk and the lifetime risk. The tool uses the woman's age, history of first-degree relatives with breast cancer (up to two relatives), number of previous breast biopsies (and whether any revealed atypical hyperplasia), age at menarche, and age at first delivery. It assumes regular screening and no history of breast cancer and does not include several known risk factors and several known protective factors (see Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>).<sup>8</sup> Overall, the tool has been found to predict breast cancer well, but its ability to discriminate at the individual level was not much better than that of predictions that would have occurred by chance,<sup>9</sup> so its usefulness is similar to that of Table 1. For women with

a strong family history of breast cancer, ovarian cancer, or both, a program that can be used to estimate the risk of genetic mutations in the *BRCA1* and *BRCA2* genes is available at <http://astor.som.jhmi.edu/brcapro/>. The program has been found to be effective in predicting risk on an individual level.<sup>10</sup>

### **Mammography and Mortality from Breast Cancer**

There have been eight randomized trials of the effectiveness of mammography: four trials in Sweden comparing mammography with no screening; one in Edinburgh, Scotland, one in New York, and one in Canada comparing the combination of mammography and clinical breast examination with no screening; and one in Canada evaluating the effect of the addition of mammography to a standardized, 10-to-15-minute clinical breast examination. The studies differed with respect to the years in which they were conducted, the type of mammography used, the interval between mammographic examinations, the method of assigning women to the screened and unscreened groups, the number of screening visits, the age of the women who were included, and the methods of analysis.<sup>3,11</sup> For women between 50 and 69 years of age, all reports of studies comparing screening with no screening showed protective effects of screening, and meta-analyses that included all trials demonstrated statistically significant 20 to 35 percent reductions in mortality from breast cancer.

A widely cited meta-analysis published in 2000<sup>12</sup> (updated in 2001<sup>13</sup>) by Gotzsche and Olsen raised questions about the efficacy of mammography. The authors concluded that the methods used in five of the eight studies were so flawed that they had to be excluded from the meta-analysis. Appropriate randomization should lead to very similar groups, but for five of the studies (and part of a sixth, the Malmö II Trial), there were significant differences between the screened group and the control group in some of the characteristics; Gotzsche and Olsen suggested that these differences might bias the trial results. Also, numbers varied among different reports on the same trials. Finally, according to a combined analysis of the four Swedish studies, mortality from breast cancer, but not overall mortality, decreased in the screened group, raising the possibility of bias in determining the cause of death, as well as the possibility that treatments resulting from findings in screening could be dangerous. A meta-analysis of the remaining three studies showed no protective effect of mammography.

The investigators defended their trials. Several trials included some subjects who were later determined to be ineligible, and reports sometimes used the woman's age instead of the date of birth, accounting for differing numbers. The cluster randomization that was used in several trials probably led to small, unimportant base-line differences between groups.<sup>14,15</sup> In an updated analysis of the four Swedish studies published after the cri-

tique, unadjusted overall mortality was lower in the screened group (relative risk, 0.94 [95 percent confidence interval, 0.96 to 1.00]).<sup>16</sup> (Detailed responses to the criticisms of Gotzsche and Olsen are reviewed in Supplementary Appendix 2, available with the full text of this article at <http://www.nejm.org>.) In addition, Gotzsche and Olsen were criticized for not considering other methodologic aspects, such as the age of participants (one of the trials included only women in their 40s); the number, type, and quality of screening and the intervals between them; compliance with the assigned strategy; and contamination (the degree to which women in control groups underwent screening mammography).<sup>14,15,17,18</sup> Finally, they included a study that compared two methods of screening and had no unscreened control group.

In summary, criticisms of all but one of the trials excluded from the meta-analysis have been answered. In-depth independent reviews of the criticisms concluded that they do not negate the effectiveness of mammography, especially for women older than 50 years of age.<sup>3,18,20</sup>

### Women in Their 40s

For many years, there has been controversy over the use of screening mammography for women in their 40s.<sup>21</sup> In general, the effect of screening younger women has been slower to appear and less dramatic than the effect among women older than 50 years of age. These differences may result from mammographically denser breasts in younger women (leading to reduced sensitivity of mammography), faster spread of some cancers in younger women, or both. Meta-analyses show that screening in this age group decreased 15-year mortality from breast cancer by about 20 percent.<sup>3,22</sup>

Because trial results are presented according to women's ages at the time of entry into the studies, some women who entered in their late 40s received a diagnosis of breast cancer in their 50s; therefore, some of the benefit ascribed to the screening of women in their 40s would have occurred if the women had waited until 50 years of age to be screened.<sup>23,24</sup> Also, although analyses are usually presented according to the decade of life, it is likely that a gradual change occurs as a woman ages. The latest analysis of the four Swedish trials — the first to examine screening effects according to five-year age increments — found that screening was most effective after 55 years of age.<sup>16</sup>

### Mammography in Women Older than 70 Years of Age

Too few women older than 70 years of age participated in randomized trials to permit conclusions to be drawn about the effects of mammographic screening in this age group. One case-control study in the Netherlands found that screening women between 65 and

74 years of age led to a 55 percent decrease in mortality from breast cancer (relative risk of death from breast cancer, 0.45 [95 percent confidence interval, 0.20 to 1.02]).<sup>25</sup>

### Risks Associated with Mammography

**False Positive Mammograms** Because most women do not have breast cancer at the time of screening, there is potential to do harm with false positive results that necessitate further investigation before a woman can be declared to be free of disease. Nationally, an average of 11 percent of screening mammograms are read as abnormal and necessitate further diagnostic evaluation<sup>26</sup>; breast cancer is found in about 3 percent of women with an abnormal mammogram (representing 0.3 percent of all mammograms). Therefore, on average, a woman has about a 10.7 percent chance of a false positive result with each mammogram. Because women are screened repeatedly, a woman's risk of having a false positive mammogram increases over time. One study estimated that after 10 mammograms, about half of women (49 percent [95 percent confidence interval, 40 to 64]) will have had a false positive result, which will have led to a needle biopsy or an open biopsy in 19 percent (95 percent confidence interval, 10 to 41).<sup>27</sup>

False positive mammograms increase patients' anxiety; the degree of anxiety is related to the intensity of the additional diagnostic procedures and the recency of the screening mammogram.<sup>20</sup> One study found that in the 12 months after a false positive mammogram, women initiated more health care visits for both breast-related and non-breast-related problems.<sup>28</sup> However, false positive mammograms increase women's adherence to further screening.<sup>29-31</sup>

The risk of a false positive mammogram varies according to characteristics of the woman and radiologic factors: a younger age, an increasing number of breast biopsies, a positive family history of breast cancer, estrogen use, an increasing interval between screenings, the lack of comparison with previous mammograms, and a tendency by the radiologist to consider mammograms abnormal (as determined by the percentage of mammograms read as abnormal) were independent risk factors for a false positive result in one study.<sup>32</sup> Having mammographically dense breasts also increases the risk of false positive (or false negative) mammograms.<sup>33-35</sup> Many characteristics of patients are immutable, but obtaining mammograms during the luteal phase of the menstrual cycle may decrease mammographic sensitivity.<sup>36</sup> Also, a preliminary investigation found that stopping hormone-replacement therapy 10 to 30 days before a repeated mammogram eliminated or reduced mammographic abnormalities.<sup>37</sup>

Lowering the recall rate (the percentage of mammograms that result in recommendations for further tests) is likely to reduce the risk of false positive mammograms. Because



of the trade-off between sensitivity and specificity, it is important not to lower the radiographic threshold for recall so much that cancers are missed. The Agency for Health Care Policy and Research recommends that the false positive rate be no more than 10 percent.<sup>38</sup> The malpractice climate in this country may work against the lowering of the threshold, since failure to diagnose breast cancer is the leading reason for malpractice suits.<sup>39</sup> Comparison of current and previous mammograms decreases the false positive rate, as does the use of screening intervals of 18 months or less.

*Possible Overdiagnosis — Ductal Carcinoma in Situ* Ductal carcinoma in situ was a relatively rare diagnosis before the introduction of mammography. In 1973, the incidence in the United States was 2.4 cases per 100,000 women; by 1998, it was 30.7 per 100,000 women, accounting for approximately 14 percent of all breast cancers diagnosed.<sup>1</sup> With treatment, the prognosis is excellent. In one study, women given a diagnosis of ductal carcinoma in situ had a 9-year survival rate that was the same as or better than that in the general population,<sup>40</sup> and in another study, the risk of death from breast cancer within 10 years after the diagnosis of ductal carcinoma in situ was 1.9 percent.<sup>41</sup>

Such an excellent prognosis could be attributable to the detection of lesions before they become invasive cancers, which could save lives. However, if ductal carcinoma in situ were the usual precursor to early invasive cancer, the incidence of early-stage invasive breast cancer should decrease as the incidence of in situ cancer increases, but the opposite is happening. Also, autopsy studies in women who died from causes unrelated to breast cancer have shown a substantial “reservoir” of ductal carcinoma in situ in such women.<sup>42</sup> Therefore, detection of ductal carcinoma in situ may be an example of overdiagnosis — finding early neoplasms, many of which will never become invasive breast cancer.

Unfortunately, ductal carcinoma in situ can progress to invasive cancer. The eight-year rate of recurrence in one study of treatment with only surgical excision was 27 percent, and half the recurrences were invasive cancers.<sup>43</sup> It is not clear who is at risk for recurrence and whether survival results would be the same if surgery were undertaken only after early invasive cancer had been diagnosed. In sum, women who undergo screening mammography are more likely than other women to be given a diagnosis of ductal carcinoma in situ. Whether finding it saves lives or merely increases the number of women who receive a diagnosis of breast cancer is not yet clear.

*Other Risks* Many women have pain during mammography, but few report that pain deters them from obtaining subsequent mammograms.<sup>44-48</sup> The risks associated with radiation are small. It has been estimated that 10 years' worth of annual mammographic

Table 2. North American Recommendations for Routine Mammographic Screening in Women at Average Risk Who Are 40 Years of Age or Older.<sup>a</sup>

Group (Date)	Frequency of Screening  yr	Initiation of Screening		
		40–49 Yr of Age	50–69 Yr of Age	≥70 Yr of Age
<b>Government-sponsored and private groups</b>				
U.S. Preventive Services Task Force (2002) <sup>†</sup>	1–2	Yes	Yes	Yes <sup>‡</sup>
Canadian Task Force on Preventive Health Care (1998, 1999, 2001)	1–2	No	Yes	No
National Institutes of Health consensus conference (1997)		No <sup>§</sup>	—	—
American Cancer Society (1997)	1	Yes	Yes	Yes
National Cancer Institute (2002)	1–2	Yes	Yes	Yes
<b>Medical societies</b>				
American College of Obstetricians and Gynecologists (2000)	1–2 if 40–49 yr old 1 yr if ≥50 yr old	Yes	Yes	Yes
American Medical Association (1999)	1	Yes	Yes	Yes
American College of Radiology (1998)	1	Yes	Yes	Yes
American College of Preventive Medicine (1996)	1–2	No <sup>¶</sup>	Yes	Yes
American Academy of Family Physicians (2001)	1–2	No <sup>¶¶</sup>	Yes	No
American Geriatrics Society (1999)	1–2	—	—	Yes <sup>‡</sup>
<b>Advocacy groups</b>				
National Breast Cancer Coalition (2000)		No	— <sup>§</sup>	No
National Alliance of Breast Cancer Organizations (2002)	1	Yes	Yes	Yes
Susan B. Komen Foundation (2002)	1	Yes	Yes	Yes

Adapted from the U.S. Preventive Services Task Force.<sup>3</sup> A “no” recommendation may be a statement that there is insufficient evidence for a positive recommendation.

• Recommendations are for mammography with or without clinical breast examination.

• There is an explicit recommendation to screen women older than 70 years of age.

• Recommendations note that women should be counseled about the risks and benefits of mammography.

¶ Recommendations note that women at high risk should be screened beginning at 40 years of age.

Screenings in 10,000 women will cause one additional breast cancer.<sup>49</sup> False negative interpretations are possible and are more common in younger women and in those with dense breasts.<sup>50–52</sup>

## GUIDELINES

Recommendations from several leading groups regarding mammographic screening are summarized in Table 2.<sup>3</sup> After the analysis by Gotzsche and Olsen, some, but not all, reconsidered and changed their recommendations. For example, the editorial board of the Physician Data Query data base of the National Cancer Institute (which does not issue recommendations, as such) backed away from concluding that mammography is effective; instead, the board now concludes that mammography “may” decrease mortality.<sup>23</sup> The U.S. Preventive Services Task Force moved in the opposite direction and extended its recommendations for the use of screening to include women ranging from 40 years of age to more than 70 years of age.<sup>3</sup>

Recommendations from expert groups with regard to screening women in their 40s have long varied, but over time, more groups have moved toward endorsing the same approach for this age group as for older women. Most groups have not issued explicit recommendations for women older than 70 years and merely recommend that screening begin at a certain age. More groups have begun calling for shared decision making about breast-cancer screening, but the information to be shared has not been specified.

## CONCLUSIONS AND RECOMMENDATIONS

### General Conclusions

Breast cancer is common, but when viewed over a 10-year period, the risk for the average woman is relatively small. During the past few years, scientific controversy about the benefits of screening mammography has increased. As with most screening tests, there are hazards — primarily, risks of false positive mammograms, with associated anxiety and unnecessary biopsies, and perhaps a risk of overdiagnosis.

When the benefits of medical interventions are controversial and when hazards exist, shared decision making is needed, with the clinician providing facts and the patient assessing her situation from the vantage point of her personal values. In addition, the climate in the United States with regard to malpractice makes discussions between clinician and patient about breast-cancer screening essential for all women beginning at 40 years of age. To save time, information can be provided by handouts and an office practice that is organized to address the concerns of patients.

Women vary in terms of how much they want to participate in decisions about screening. In one survey of women younger than 50 years of age, 49 percent wanted to share in decision making, 44 percent wanted to make the decision themselves, and 7 percent wanted the physician to decide.<sup>5</sup> However, 79 percent wanted information from the doctor. Because of varying

Table 3. Recommendations Regarding Breast-Cancer Screening in Women.

Age	Recommendations
Any	Ask about family history of breast cancer, ovarian cancer, or both on both maternal and paternal sides. Consider referral or counseling for possible genetic testing if risk of a BRCA1 or BRCA2 gene mutation is at least 10 percent (to calculate risk, see <a href="http://astor.som.jhmi.edu/bcapro/">http://astor.som.jhmi.edu/bcapro/</a> ) or the patient has one of the following: a first-degree relative with a known deleterious mutation for breast cancer; $\geq 2$ relatives given a diagnosis of breast cancer before 50 yr of age; $\geq 1$ of them a first-degree relative; $\geq 3$ relatives given a diagnosis of breast cancer; $\geq 1$ of them before 50 yr of age; $\geq 2$ relatives given a diagnosis of ovarian cancer; $\geq 1$ relative given a diagnosis of breast cancer and $\geq 1$ relative given a diagnosis of ovarian cancer.
40–70 Yr	Begin discussions about breast-cancer screening at 40 yr of age. Recommend screening mammography every 1–2 yr between 50 and 69 yr of age. Use information on the chances of development of or death from breast cancer within the next 5 yr (as given in the National Cancer Institute Breast Cancer Assessment Tool) or 10 yr.* Also give information on benefits and hazards of mammography.† Emphasize the increasing risk of breast cancer, increasing benefit of screening, and decreased harms associated with screening with increasing age. Record decision about screening in the medical record.
$\geq 70$ Yr	For women with life expectancy of $\geq 10$ yr, consider screening as above, making clear that risks of breast cancer are known, but less is known about the benefits and harms of screening. Record decision about screening in the medical record.

\* This information is presented in Table 1.

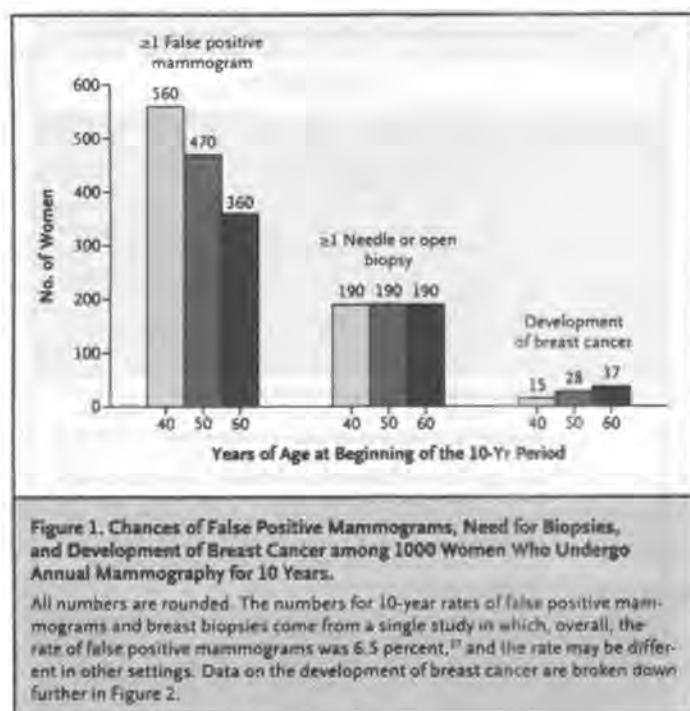
† This information is shown in Figures 1 and 2.

individual values, and because women have a good deal of fear about breast cancer,<sup>53</sup> physicians should be prepared for a decision different from the one they would recommend.

A woman needs some knowledge of her risk of breast cancer and the benefits and hazards of screening — specifically, her risks of the development of and death from breast cancer and her chances of successful treatment with screening and without screening, of having a false positive mammogram or an invasive breast procedure, and of having ductal carcinoma in situ diagnosed. Numerical risks may be best explained with the use of pictures or graphs, with discussion of absolute as well as relative risks (occurring over meaningful periods), and through comparisons with other risks.<sup>54</sup>

### Specific Recommendations

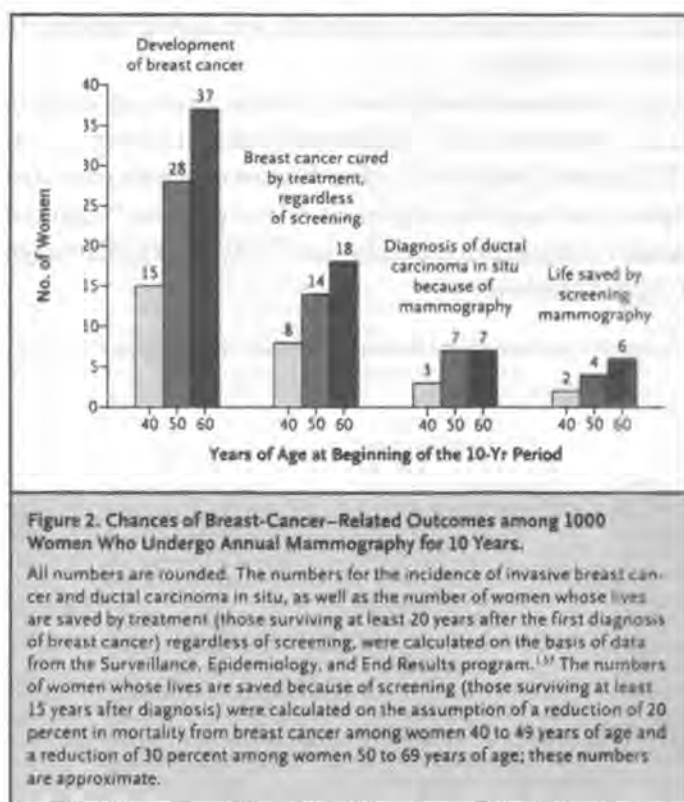
All women, regardless of age, should be asked whether they have a family history of breast cancer, ovarian cancer, or both (Table 3).<sup>55,56</sup> For women without strong family histories, discussions about breast-cancer screening should begin at 40 years of age and continue



until life expectancy is less than 10 years. Evidence supporting the usefulness of mammographic screening is strongest for women between 50 and 69 years of age, and screening should be routinely recommended for women in this age group. For women 40 to 49 years of age (such as the patient described in the vignette), shared decision making is especially important, because the absolute benefit of screening is smaller and the risks associated with it are greater. Screening should be routinely discussed, and the patient and clinician should decide together according to the woman's values.

For women who want more information, Table 1, the Breast Cancer Risk Assessment Tool, or both can be used to estimate the individual risk of breast cancer. Women should be reminded that the risk of breast cancer increases with age and that the one-in-eight risk is a lifetime risk for a newborn who lives for 90 years.

The chances of being helped or harmed by screening mammography are summarized in Figure 1 and Figure 2, which contain information that may be useful to patients. These figures show the chances that yearly screening mammography in women of different ages will result in a false positive mammogram, an invasive breast procedure, or a diagnosis of



ductal carcinoma in situ or invasive breast cancer. Women should be made aware that at least half the patients given a diagnosis of breast cancer survive regardless of the use or nonuse of screening — a fact that many women do not understand.<sup>57,58</sup> Recently, survival rates have been improving, but how much of this improvement is attributable to treatment itself and how much to earlier diagnosis due to screening are difficult to determine. The number of women “saved” is calculated according to the estimates that screening of women in their 40s reduces mortality from breast cancer by about 20 percent and screening of women in their 50s or 60s reduces it by about 30 percent. It should be emphasized that these numbers may vary, depending on the efficacy of mammography in reducing mortality. Individual women will interpret these numbers differently depending on their own values.

To decrease the risk of false positive results, patients should be referred to experienced mammographers with recall rates of no more than 10 percent. They should be encouraged

to obtain previous mammograms for comparison and should undergo screening more frequently than every 18 months.

Women often are unaware of the difference between screening and diagnostic examinations to evaluate a breast symptom or abnormal finding. In one study, cancer was diagnosed in about 10 percent of women older than 40 years of age who reported a breast mass and in almost 5 percent of those with any breast-related problem.<sup>59</sup> Clinicians and women should not be falsely reassured by a previously normal screening mammogram in the case of a new breast-related problem.

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# Emergency Contraception

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A healthy 19-year-old woman comes in for a routine appointment. She is sexually active in a monogamous relationship. Pregnancy is not currently desired. Her partner uses condoms most of the time. She is uncertain of the date of her last menstrual period but has had sexual intercourse several times since her last menses, including unprotected intercourse four days earlier. A high-sensitivity urine test for pregnancy is negative. Should emergency contraception be prescribed?

## THE CLINICAL PROBLEM

About 3 million unintended pregnancies occur each year in the United States.<sup>1</sup> Most of these result from the nonuse of contraception or from a noticeable contraceptive failure, such as a broken condom,<sup>2</sup> and could be prevented with the use of emergency contraception.

A fertile couple has a 25 percent chance of pregnancy with repeated unprotected intercourse during a single menstrual cycle. In a large, prospective study of couples seeking pregnancy, a single act of unprotected intercourse occurring about one to two days before ovulation was associated with a 24 percent probability that conception would lead to successful pregnancy.<sup>3,4</sup> However, among women 19 to 26 years of age (the age group in which fertility is greatest), the chance of pregnancy may be as high as 50 percent when unprotected intercourse occurs during this interval.<sup>5</sup>

Because sperm can survive in the female genital tract for five to six days, fertilization may occur days after sexual activity. Even the most sensitive pregnancy test will not be positive until after the implantation of a fertilized egg in the uterus, an event that occurs about seven days after fertilization.<sup>6</sup>

## STRATEGIES AND EVIDENCE

Immediate use of an emergency contraceptive will reduce a woman's risk of pregnancy to 1 to 2 percent. The effectiveness depends on the regimen used and on the time between

Table 1. Types of Emergency Contraception.		
Class	Dose	Brands Available in the United States
Combined oral contraceptives	100 $\mu$ g of ethinyl estradiol and 0.5 mg of levonorgestrel twice 12 hr apart	Previen (Gynetics) Oneal (Wyeth)
Progestin-only oral contraceptives	1.5 mg of levonorgestrel once or 0.75 mg twice 12 hr apart	Plan B (Women's Capital Corporation)
Copper T intrauterine device	—	ParaGard T 380A (Gynco-McNeil)
Antiprogestins	10 mg of mifepristone	None at this dose

\* Other hormonal contraceptives that are effective for emergency contraception, along with the doses and instructions for use, are listed at <http://www.not-2-late.com>.

unprotected intercourse and treatment. Table 1 lists the main types of emergency contraception.

### The Yuzpe Regimen

An approach first studied in the 1970s by Yuzpe et al. is the use of two doses of a combination oral contraceptive containing 100  $\mu$ g of ethinyl estradiol and 1.0 mg of the progestin norgestrel.<sup>7</sup> This treatment has been approved by the Food and Drug Administration (FDA) and is available by prescription (Previen, Gynetics); two tablets are given twice, 12 hours apart (a total of four tablets).<sup>8</sup> A similar approach with the same efficacy is to use pills from a package of combination birth-control pills that contain the progestin norgestrel; each dose must contain 1.0 mg of norgestrel or 0.5 mg of its active isomer levonorgestrel, along with 100  $\mu$ g of ethinyl estradiol. Depending on the brand of pill, two to five pills are required per dose. This treatment reduces the risk of pregnancy to about 2 percent, as compared with about 8 percent in the absence of treatment.<sup>9</sup> The main side effects are nausea (in at least 50 percent of women) and vomiting (in about 20 percent), which can be minimized or prevented by prior or concomitant treatment with an antiemetic (e.g., 10 mg of metoclopramide).<sup>10</sup> The next menses after treatment will usually occur within one week before or after the expected date; if menses do not occur within three to four weeks after treatment, then a pregnancy test is indicated.

### Progestin-Only Regimen

A newer, more effective approach to emergency contraception is the use of progestin-only contraceptive tablets. An FDA-approved product (Plan B, Women's Capital Corporation) is available in the United States and consists of 0.75-mg tablets of levonorgestrel, to be taken within 72 hours after unprotected intercourse in two doses separated by 12 hours.<sup>11</sup>

Clinical trials directly comparing a progestin-only regimen with a combined estrogen-progestin regimen indicate that the progestin-only approach is more effective, reducing the risk of pregnancy to 1 percent and the incidence of nausea and vomiting to 22 percent and 8 percent, respectively.<sup>12</sup> Recent data indicate that the levonorgestrel-only treatment can be given once in a single dose, rather than twice in a divided dose, with the same efficacy.<sup>13</sup> In contrast, a single dose of combination hormonal contraceptive pills (including 20 µg of ethinyl estradiol) cannot be recommended, given the lack of data regarding its effectiveness and the likelihood of more severe side effects.

### Timing of Use

Both the combination and the progestin-only regimens of emergency contraception were originally studied for use up to three days after a single unprotected act of intercourse. Data from a large, randomized clinical trial demonstrated that pregnancy rates were low when emergency contraception was initiated within 12 hours after unprotected intercourse, with a monotonic decrement in effectiveness as the interval between unprotected intercourse and treatment increased. The pregnancy rate was less than 1 percent when treatment was given within 12 hours, as compared with over 3 percent when treatment was given 61 to 72 hours after intercourse.<sup>13,14</sup> Other studies, however, have not shown a strong relation between the timing of therapy and efficacy.<sup>15</sup> Two observational studies indicate that treatment 72 to 120 hours after intercourse results in pregnancy rates similar to those in studies of earlier treatment.<sup>16,17</sup> Emergency contraception should thus be offered for any act of unprotected intercourse that has occurred in the preceding five days, even if the patient has had other unprotected acts earlier in the same menstrual cycle. Because the length of the menstrual cycle varies and the day of ovulation is generally unknown even in women who report having regular cycles,<sup>18</sup> treatment is indicated regardless of the cycle day on which unprotected intercourse occurred.

### Other Approaches

Other strategies for postcoital contraception are either less well studied or less available than progestin-only or combination regimens. Combination oral contraceptives that contain other progestins may be similar in effectiveness to pills containing levonorgestrel. In a randomized clinical trial that included nearly 1200 women, the pregnancy rate after two doses of a norethindrone-containing oral contraceptive (2.0 mg per dose) did not differ significantly from the rate after two doses of a levonorgestrel-containing pill (the Yuzpe regimen) (2.7 percent and 2.0 percent, respectively).<sup>19</sup>

Insertion of a copper-containing intrauterine device (IUD) up to five days after unprotected intercourse also reduces the risk of pregnancy. This approach is supported by pub-

lished case series that included 879 insertions of an IUD after intercourse, with only one pregnancy.<sup>20</sup> A randomized clinical trial compared the use of two different copper-bearing IUDs among 192 women requesting emergency contraception, most of whom were nulliparous. Follow-up data were available for 98 percent of the women at six weeks; there were no pregnancies and no cases of pelvic inflammatory disease.<sup>21</sup> However, the number of pregnancies that would have been expected without treatment was not clear.

An important benefit of IUD insertion is that it provides continued contraception; 81 percent of the trial participants continued using the IUD after completion of the study.<sup>21</sup> In other studies of hormonal emergency contraception, pregnancies occurred in women who had additional acts of unprotected intercourse later in the same cycle,<sup>19</sup> indicating the importance of providing ongoing contraception immediately. An IUD is more expensive than hormonal emergency contraception but is cost effective for women who choose to use it long-term.<sup>22</sup> The copper IUD is approved by the FDA for use for up to 10 years, and clinical data indicate that its effectiveness lasts for at least 12 years.

Mifepristone, a progesterone-receptor antagonist used for medical abortion, is another alternative. Randomized clinical trials show that a single 10-mg dose of mifepristone is as effective as the levonorgestrel-containing regimens,<sup>13</sup> with an even lower incidence of nausea and vomiting. However, the 10-mg dose is not commercially available in the United States. The 200-mg tablet that is used for medical abortion is available in the United States only to physicians who establish an account with the distributor, severely limiting access. In addition, mifepristone is more expensive than other hormonal therapies. New antiprogestins are being studied for this indication and may have similar effectiveness.<sup>23</sup>

### Safety of Emergency Contraception

A theoretical concern is that the use of combined oral contraceptives for emergency contraception might increase the risk of thrombotic events, such as venous thromboembolism or stroke, that are associated with long-term use of these products.<sup>24,25</sup> Such adverse events did not occur in the clinical trials evaluating these agents; however, the studies lacked power to detect rare events. A Medline search for reports of thrombotic events that occurred in association with hormonal emergency contraception yielded four case reports of cerebrovascular complications<sup>26-29</sup> — all of which followed the use of combination hormonal therapy. No case reports of cerebrovascular events were identified in association with the use of progestin-only emergency contraceptives, nor were there reports of deep-vein thrombosis or pulmonary embolism after either type of hormonal contraception.

Population-based or case-control studies of cerebral thrombosis after emergency contraception have not been performed. A population-based retrospective cohort study<sup>30</sup> assessed the risk of venous thromboembolism among users of combination hormonal

emergency contraception, on the basis of data from the General Practice Research Database in the United Kingdom. The analysis included 73,302 women who received 100,615 prescriptions for postcoital contraception between 1989 and 1996; of these women, 19 had a deep-vein thrombosis or a pulmonary embolus during follow-up. There were no venous thromboembolic events during the 45 days after the receipt of any prescription for emergency contraception. In contrast, the risk of venous thromboembolism was increased during pregnancy and with ongoing use of oral contraceptives — observations that support the validity of the analysis.

There are no absolute contraindications to the use of hormonal emergency contraception. Even for women who have contraindications to the long-term use of combination hormonal contraception (such as liver disease or a history of thromboembolism),<sup>31</sup> the balance of risks and benefits may favor the brief hormonal exposure resulting from emergency contraception over the possibility of a high-risk pregnancy. Progestin-only emergency contraception or the insertion of an IUD should be considered first in women with these or other medical contraindications to combination oral contraceptives, especially given the effectiveness of these approaches and the low rate of side effects. Insertion of an IUD for emergency contraception should be performed according to the regular guidelines for IUD use.<sup>32</sup> This approach should be avoided, for instance, in women with active, recent, or recurrent pelvic infections.

### Outcomes of Pregnancy after Emergency Contraception

Pregnancies can be established, but not diagnosed, at the time of emergency contraceptive use or can be associated with the failure of the emergency contraceptive. Although case reports have described ectopic pregnancy after the use of emergency contraception, there is no good evidence of an increased risk of this outcome.<sup>33,34</sup> In a large World Health Organization trial, only 42 pregnancies were identified after nearly 2000 treatments,<sup>12</sup> and none were ectopic. Five of these pregnancies were continued, with normal outcomes. No studies have been large enough to quantify the teratogenic risk among the very small number of pregnancies that follow the use of emergency contraception. However, observations that there is no increase in birth defects among pregnancies exposed to daily use of combined oral contraceptives are reassuring.<sup>35</sup>

Patients who had a recent menstrual period at the usual time and with the usual flow do not need a pregnancy test before using emergency contraception.<sup>36</sup> If the patient's menstrual history is either vague or unusual, then a pretreatment pregnancy test may allow earlier diagnosis of a pregnancy that is already established, facilitating earlier prenatal care,<sup>37</sup> or an earlier abortion. A physical examination is unnecessary before treatment.<sup>38</sup>

### Advance Prescribing

Emergency contraception is currently available by prescription only; therefore, there may be a substantial delay between the time women identify the need for treatment and the time they receive it.<sup>39</sup> Clinicians can help prevent this problem by providing emergency contraception in advance of need. Several clinical trials, three of them randomized, have compared the effects of advance provision of emergency contraception with the effects of education alone.<sup>40-44</sup> All these trials found that advance provision increased the use of emergency contraception, that the use was appropriate, that women did not abandon or decrease the use of their regular contraceptives, and that advance provision led to a reduction in the number of unintended pregnancies. These studies were too small, however, to identify a significant difference in the pregnancy rate. No serious adverse events were observed.

### Possible Over-the-Counter Status

The FDA is currently evaluating an application for a switch to over-the-counter status for the levonorgestrel-only formulation of emergency contraceptive. Hormonal emergency contraception is highly suitable for such a switch. The dose is the same for everyone, there are no contraindications to its use, adverse events are rare, and there is no potential for addiction.<sup>45</sup> Repeated use is safe and reasonably effective but is unlikely to replace long-term contraception, owing to the expense and side effects such as menstrual changes.<sup>46</sup>

### AREAS OF UNCERTAINTY

The mechanism of action of emergency contraception is incompletely understood. It does not interfere with an established, postimplantation pregnancy. The use of emergency contraception can delay ovulation and decrease the probability of fertilization after ovulation<sup>47</sup>; at least some of its effect appears to occur after ovulation.<sup>48</sup>

Immediate initiation of long-term contraception is desirable to reduce the risk of pregnancy after treatment. A small, nonrandomized study in which the use of oral contraceptives was initiated on the same day as a levonorgestrel-only emergency contraceptive found that this approach was highly acceptable to patients<sup>49</sup> and was associated with higher rates of continuation of the oral contraceptive than was waiting to start long-term contraception. Whether immediate initiation of oral contraceptives influences the effectiveness of therapy or increases the rate of side effects has not been studied.

### GUIDELINES

Both the American Medical Association and the American College of Obstetricians and Gynecologists (ACOG) encourage physicians and other professionals to discuss emer-



gency contraception as part of routine family planning and contraceptive counseling and promote efforts to expand access to such treatment, including making it available in physicians' offices.<sup>50,51</sup> ACOG recommends both combination and progestin-only hormonal methods but advises that the progestin-only approach be considered first. ACOG also specifically supports efforts to make emergency oral contraception available to women over the counter in a designated product.<sup>52</sup>

#### CONCLUSIONS AND RECOMMENDATIONS

The patient described in the clinical vignette, who had had unprotected intercourse four days earlier, should receive emergency contraception as soon as possible. The preferred regimen is the levonorgestrel-only product at a dose of 1.5 mg, since this is highly effective and generally well tolerated. If supplies are not available in the physician's office, the physician should be able to identify a local pharmacy that stocks this product. In addition, the physician should provide refills of this prescription or provide a separate prescription that the patient can use in case she has unprotected intercourse again. Having emergency contraception readily available does not lead to the abandonment of other forms of contraception.

The use of regular contraception should also be emphasized, along with condom use to reduce the transmission of sexually transmitted diseases. If hormonal contraception is chosen, it should be initiated immediately, rather than waiting for the patient's next menstrual period. Some pregnancies in clinical trials resulted from additional acts of unprotected intercourse later in the same menstrual cycle. Ample refills should be provided, since running out of pills is a major reason for unintended pregnancy among users of oral contraceptives.<sup>2</sup> A need for emergency contraception should prompt consideration of screening for sexually transmitted diseases, such as chlamydia.<sup>53</sup> A follow-up pregnancy test is indicated if the patient does not have withdrawal bleeding after finishing her first pack of oral contraceptives or, for those who do not immediately begin taking oral contraceptives, if menses do not occur within three to four weeks after treatment.

Until a dedicated product is widely available over the counter, emergency contraception should routinely be provided in advance of need. Eligible women should include those who are not currently sexually active, since they are unlikely to have an ongoing method of contraception and are at risk if they become sexually active.

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## ADDENDUM

Since publication of this article in 2003, the FDA received an application for a switch to over-the-counter status for emergency contraception (Plan B). There was scientific agreement among, and strong guidance from, the FDA advisory panel favoring the switch.

The FDA continues to defer action on the matter; thus, emergency contraception remains available only by prescription. The prolonged FDA inaction on this application lacks scientific or clinical justification.<sup>1,2</sup>

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Preven, one manufacturer's formulation of combined oral contraceptives mentioned in Table 1, is no longer available.

# Dysplastic Nevi

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**A 26-year-old man comes to establish primary care. Physical examination reveals multiple moles on his body, which he describes as “funny-looking.” There is no family history of melanoma. He thinks that one of his two brothers (15 years of age) and his father have the same kind of moles. How should this case be managed?**

## THE CLINICAL PROBLEM

Various names are used in the literature for dysplastic nevi, including BK moles (after the initials of the first two patients in whom these lesions were described),<sup>1</sup> Clark's nevi, and atypical moles or nevi. All these terms refer to lesions with specific clinicopathological characteristics associated with an increased risk of melanoma.

A dysplastic nevus is typically a macular lesion that is 5 mm or more in diameter, usually with irregular, fuzzy borders (Figure 1).<sup>2</sup> Under oblique or lateral illumination, most lesions are slightly elevated and have a smooth or pebbled surface. Some have a central papule surrounded by a macular pigmented rim, creating a “fried-egg” appearance. Their pigmentation is variegated shades of tan and brown. Some lesions have a characteristic reddish hue and blanch with pressure under a glass microscope slide. Dysplastic nevi may be present anywhere on the skin, including the so-called doubly protected areas (breasts and buttocks) and the scalp, but they are most common on the trunk, especially on the upper back.<sup>3</sup> In preadolescent children who are members of a family with dysplastic nevus-melanoma syndrome, dysplastic nevi may first appear on the scalp.<sup>4</sup>

Dysplastic nevi usually become clinically apparent at puberty or adolescence, but true dysplastic nevi have been described in prepubertal children.<sup>1,4</sup> The dysplastic nevi continue to appear throughout life. Their number may vary greatly, from one to hundreds. In patients with multiple lesions, there is marked heterogeneity among lesions, resulting in a highly characteristic clinical phenotype (Figure 2). Counts of dysplastic nevi are highly correlated with total nevus counts (increasing as the total count increases), independent of a personal or family history of melanoma.<sup>5</sup>

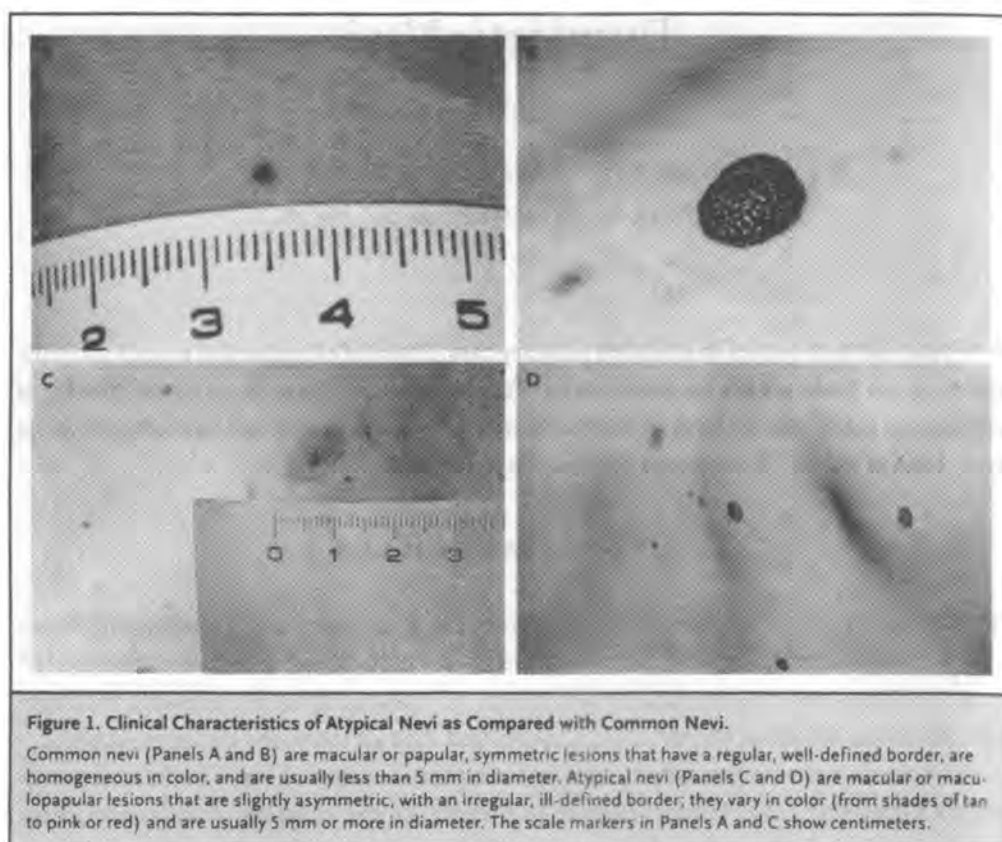


Figure 1. Clinical Characteristics of Atypical Nevi as Compared with Common Nevi.

Common nevi (Panels A and B) are macular or papular, symmetric lesions that have a regular, well-defined border, are homogeneous in color, and are usually less than 5 mm in diameter. Atypical nevi (Panels C and D) are macular or maculopapular lesions that are slightly asymmetric, with an irregular, ill-defined border; they vary in color (from shades of tan to pink or red) and are usually 5 mm or more in diameter. The scale markers in Panels A and C show centimeters.

The term "dysplastic nevus syndrome" is used arbitrarily. Some clinicians use it to describe patients with only one atypical nevus,<sup>6</sup> although the "classic" dysplastic nevus syndrome refers to patients who have the triad of 100 or more nevi, at least 1 nevus 8 mm or larger in diameter, and at least 1 nevus with clinically atypical features.<sup>7</sup> The syndrome can occur sporadically or in a familial setting. To diagnose sporadic dysplastic nevus syndrome with certainty, clinical examination of first-degree relatives is necessary.<sup>8</sup> Although there has been concern that nonspecialists might not reliably recognize the clinical phenotype, a recent study showed that identification of the phenotype with the use of a specific scoring system was a skill that could be easily learned by health care professionals who are not specialists.<sup>9</sup>

#### Pathological Diagnosis of Dysplastic Nevi

The pathological diagnosis of a dysplastic nevus requires the identification of both specific cytologic and architectural abnormalities (Figure 3). Interobserver agreement in the



Figure 2. A 26-Year-Old Man with Atypical Nevi.

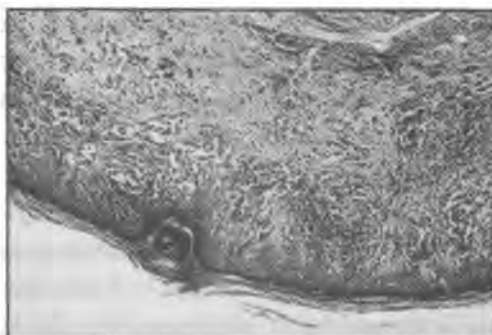


Figure 3. Pathological Appearance of a Dysplastic Nevus.

The pathological diagnosis is based on the presence of two major criteria and at least two minor criteria. The major criteria are basilar proliferation of atypical nevomelanocytes, extending three rete ridges beyond a dermal melanocytic component (if present), and intraepidermal melanocytic proliferation (lentiginous or epithelioid). The minor criteria are concentric eosinophilic fibrosis enveloping the rete ridges or lamellar fibroplasia beneath the tips of the rete ridges, neovascularization, a dermal inflammatory response, and fusion of the rete ridges due to the confluence of adjacent melanocytic nests. In the lesion shown, all the criteria are met.

Pathological diagnosis of melanocytic dysplasia is hampered by the lack of universally accepted diagnostic criteria. In studies that use preset criteria for diagnosis, interobserver agreement is moderate to good.<sup>10-12</sup> Reproducibility in grading atypia remains poor to moderate because of the nonuniform criteria used.<sup>11-13</sup>

### Clinicopathological Correlations

The presence or absence of atypical clinical features correlates, imperfectly, with the presence or absence of histologic dysplasia. In a study involving 101 patients with a history of sporadic melanoma in whom the most clinically atypical nevus was removed, the likelihood of histologic dysplasia ranged from 7 percent among lesions with no or only one clinically atypical feature (a diameter of 5 mm or more, an ill-defined or irregular border, or color variation) to 23 percent in cases with two atypical features and 62 percent in cases with three atypical features.<sup>14</sup> Among nevi without histologic dysplasia, only 4 percent had all three clinically atypical features.<sup>14</sup> In another study, roughly 30 percent of common (nondysplastic) nevi met the histologic criteria for dysplasia (architectural atypia, cytologic atypia, and a dermal host response), albeit minimally.<sup>15</sup>

In a population-based study, histologic findings of melanocytic dysplasia were associated with higher total nevus counts. Among subjects from whom biopsy specimens were

obtained from the two most clinically atypical nevi, the histologic concordance between the biopsy results was higher than would be expected on the basis of chance alone, suggesting that melanocytic dysplasia is not randomly distributed but, rather, that some persons appear to have a predisposition to melanocytic dysplasia.<sup>16</sup>

### Epidemiologic Characteristics

The estimated prevalence of clinically atypical nevi ranges from 7 percent to 18 percent in population-based samples,<sup>17,18</sup> and the prevalence of histologic melanocytic dysplasia is approximately 10 percent.<sup>19,20</sup> The reported frequency of clinically atypical nevi among patients with a history of melanoma is higher, ranging from 34 percent to 59 percent.<sup>18,21-24</sup> The variations in the estimates of prevalence probably reflect, at least in part, the use of different diagnostic criteria in different studies. However, differences among populations in sun exposure could also play a part.<sup>25</sup> Dysplastic nevi also appear to be more prevalent in younger populations (those less than 30 to 40 years of age) than in older groups.<sup>5,8</sup>

Clinically atypical nevi may evolve from normal-appearing nevi or may be dysplastic from their first appearance.<sup>26</sup> As dynamic lesions, dysplastic nevi can become progressively more or progressively less clinically atypical, but the majority either remain stable or regress over time.<sup>5,27</sup> New dysplastic nevi may develop after the age of 30 years.<sup>5</sup>

The predilection of atypical nevi for intermittently sun-exposed areas (especially the trunk), their positive association with a history of painful sunburn (in which the pain lasts more than two days) or blistering sunburn, and the finding that persons with clinically atypical nevi often have sun-sensitive skin types suggest that the development of dysplastic nevi could relate to acute, intense sun exposure.<sup>3,18</sup> Genetic factors also appear to be important; an autosomal dominant mode of inheritance has been reported in families with the dysplastic nevus-melanoma syndrome.<sup>8</sup>

### Clinical Significance of Dysplastic Nevi

The clinical importance of dysplastic nevi lies in their association with the risk of melanoma. This has been demonstrated in several cohort and case-control studies.<sup>17-24,27-35</sup> In most of these studies, dysplastic nevi were defined according to clinical criteria, without histologic confirmation.<sup>21-24,27,28,30-34</sup> In some studies, the presence of large nevi without other atypical features was also found to be associated with an increased risk of melanoma.<sup>22,24,35</sup> The age-adjusted incidence of melanoma is approximately 15 times as high among patients with dysplastic nevi as among members of the general population (154 vs. 10 per 100,000 person-years, standardized to the population of Pennsylvania in 1985).<sup>31</sup>

The risk of melanoma in persons with dysplastic nevi increases with an increasing number of nevi and in the presence of a personal or family history of melanoma.<sup>29-32,34</sup> There is a 100-fold increase in the incidence of melanoma in patients who have previously had melanoma, a 200-fold increase in those with at least two family members with melanoma, and a more than 1200-fold increase in those with both a personal and family history of melanoma.<sup>31</sup> In persons with a family history of melanoma, the incidence of melanoma is highly concentrated in family members with dysplastic nevi, although melanoma may occur in those without this phenotype.<sup>28</sup> The presence of dysplastic nevi is an independent risk factor for the development of multiple primary melanomas.<sup>28,36</sup>

Melanoma has been shown to occur both in and separate from preexisting nevi (common or dysplastic). In cohort studies of persons with dysplastic nevi, melanoma appears to arise in contiguity with dysplastic nevi in 44 to 80 percent of subjects,<sup>27,29,31,37</sup> a rate much higher than that for melanoma in the general population.<sup>38,39</sup> Currently, there are no published data on the extent to which the presence of histologic melanocytic dysplasia predicts melanoma independently of other risk factors for melanoma, such as clinically atypical nevi and the total number of nevi.

Dysplastic nevi may be confused with melanoma, both clinically and histologically. In one study, lesions histologically diagnosed as dysplastic nevi by an expert panel were diagnosed by other pathologists as melanoma in 21 percent of the readings (in situ in 86 percent of the cases), and thin or in situ melanomas were misdiagnosed as dysplastic nevi in 12 percent of the readings.<sup>40</sup>

## STRATEGIES AND EVIDENCE

### Prophylactic Excision

According to the available evidence, the clinical diagnosis of dysplastic nevi (or dysplastic nevus syndrome) does not need to be confirmed histologically.<sup>21-24,27,28,30-34</sup> Despite the recognized association between dysplastic nevi and the risk of melanoma, the majority of dysplastic nevi will never progress to melanoma.<sup>26</sup> The relatively low absolute risk that a single dysplastic nevus will develop into melanoma is indicated by the following calculations: in a population of 10 million inhabitants in which the incidence of melanoma is 10 per 100,000 inhabitants per year, about 1 million people (10 percent of the population) will have one or more dysplastic nevi (with a mean of two such nevi). On the assumption that 20 percent of melanomas develop in contiguity with a dysplastic nevus, this calculation implies that only 1 in 10,000 dysplastic nevi per year will progress to melanoma. These



estimates underscore the argument that prophylactic excision of dysplastic nevi is unlikely to be cost effective and might, in addition, give patients a false sense of security, since an increased risk of melanoma may remain after these nevi have been removed. Some have advocated the excision of dysplastic nevi that are difficult to follow because of their location; however, data are lacking to support this approach.<sup>2</sup>

### Follow-up of Patients with Dysplastic Nevi

Melanoma of the skin offers the theoretical advantage of early detection by simple, noninvasive investigation (examination of the skin), and therefore regular dermatologic examinations are commonly recommended for persons with dysplastic nevi. In several studies monitoring by trained dermatologists, with follow-up schedules ranging from once every three months to once a year, has been associated with high proportions of thin melanomas with a good prognosis,<sup>27,29,31,32,37</sup> although those studies did not include contemporaneous control groups. Serial photographs have also been proposed as a method of documenting changes in existing lesions or the development of new lesions.<sup>29,31,32,41</sup> In a historical, uncontrolled cohort study of patients with dysplastic nevi, 6 of 11 melanomas were excised because of change, relative to base line, in a preexisting nevus (in 5 cases or development of a new lesion (in 1 case) on serial photographs; only 2 of the 11 lesions were diagnosed clinically as melanoma at the time of excision.<sup>31</sup>

Although close follow-up seems reasonable, it remains possible that close surveillance may preferentially detect slow-growing tumors with a good prognosis. In addition, it is uncertain whether the *in situ* melanomas (Clark level I) detected by such surveillance would have progressed to invasive melanoma if left in place. There are no prospective cohort studies comparing the survival of patients who are being closely monitored with those who are not. Proposed benefits of close surveillance include the opportunity to teach patients to identify suspicious lesions and possible improvements in the quality of life resulting from the reassurance of regular expert skin examinations; however, there are currently no data to support these possibilities.

Prospective studies have demonstrated that the risk of melanoma in members of families affected by the dysplastic nevus-melanoma syndrome is considerable, with an estimated cumulative risk of 49 percent for persons 10 to 50 years of age and 82 percent by the age of 72 years<sup>27</sup>; the benefit of close surveillance is likely to be higher among such persons than among those with one or more dysplastic nevi but no family history of melanoma (which is the more frequent scenario). No studies have assessed the cost effectiveness of surveillance programs for dysplastic nevi.

**Self-Examination** No randomized, controlled trials have assessed the value of self-examination of the skin. One study, which included 650 patients with melanoma, suggested a survival benefit in patients who had performed self-examination of the skin, as compared with those who had not, although the investigators emphasized that longer follow-up was needed to confirm a beneficial effect of self-examinations.<sup>42</sup> In a survey of 816 patients with melanoma, the habit of skin self-examination was associated with thinner melanomas.<sup>43</sup> Since self-examination is relatively simple and inexpensive, it is routinely recommended, despite the limited supporting data.

**Ocular Examination** Patients with dysplastic nevi may have an increased risk of ocular melanoma.<sup>44</sup> In a case-control study involving 211 patients with ocular melanoma, 16 percent had one or more dysplastic nevi, as compared with 7 percent of the controls (odds ratio, 24.1 [95 percent confidence interval, 4.8 to 119.8] among patients with four or more atypical nevi).<sup>44</sup> The estimated cumulative lifetime risk of eye melanoma in patients with the dysplastic nevus phenotype is 1 in 200.<sup>44</sup> A yearly ocular examination of patients with the dysplastic nevus syndrome has been recommended by some experts<sup>45</sup> but not by others.<sup>46</sup>

### Genetic Screening

Germ-line *CDKN2A* mutations (on chromosome 9p21) have been found in 20 to 40 percent of families in which at least three first-degree relatives are affected by melanoma.<sup>47</sup> These germ-line mutations were three times as likely to be found in family members affected by the dysplastic nevus syndrome as in relatives who were unaffected; however, the presence or absence of the syndrome was not perfectly correlated with gene-carrier status.<sup>48</sup> Thus, a consortium recommended in a consensus statement that DNA testing not be performed in persons with the dysplastic nevus syndrome (familial or not) unless it is in the context of a defined research program, since the implications for management are currently unclear.<sup>47</sup>

## AREAS OF UNCERTAINTY

### Use of Sunscreens

Total nevus counts have been found to be higher in children protected by sunscreens than in those protected by clothing,<sup>49</sup> and a recent study<sup>50</sup> indicated that the use of broad-spectrum sunscreens was effective in reducing the development of nevi in white children with freckles. However, data are lacking on the relation between the use of sunscreens and dysplastic nevi, and it is not known whether the use of sunscreens reduces the risk of mela-

Table 1. Published Guidelines for the Management of Dysplastic Nevus.

Organization	Patient Characteristics	Surveillance	Self-Examination	Other Advice	Source
Melanoma Working Group, the Netherlands	History of melanoma in at least two of the following and a history of dysplastic nevus in at least one of the following: patient, children, parents, brothers, sisters, uncles, or aunts	At least once a year, starting at age 10 yr (absolute indication)	No recommendation	Oral and written information about alarming signs and sun protection should be offered	Bergman et al.
	At least three dysplastic nevi and a family history of melanoma	Once a year (relative indication)	No recommendations	Oral and written information about alarming signs and sun protection should be offered	
	At least three dysplastic nevi and no family history of melanoma	Not recommended	No recommendations	Oral and written information about alarming signs and sun protection should be offered	
National Institutes of Health	Large numbers of moles (often more than 50), some of which are atypical and have certain distinct histologic features; family history of melanoma (in a first- or second-degree relative)	Intensive surveillance, initially at intervals of 4 to 6 mo; total-body photographs and dermoscopy in some cases	Once a month	Sun protection	NIH Consensus Conference <sup>50</sup>

noma.<sup>50,51</sup> A real concern is that sunscreen use may lead to increased sun exposure, which could increase the risk of melanoma. Patients should thus be advised to avoid sun exposure during the hours of peak intensity of ultraviolet (UV) B radiation (noon to 4 p.m.) and to use physical protection, such as clothing, in addition to a broad-spectrum sunscreen (sun protection factor [SPF] 15 or higher) on uncovered areas.

### Dermoscopy

Dermoscopy, or dermatoscopy (epiluminescence or incident-light microscopy), is a non-invasive technique in which oil immersion and optical magnification are used to make the epidermis translucent and to allow the visualization of structures not visible to the naked eye. The use of this technique has been proposed as a means of distinguishing melanocytic from nonmelanocytic pigmented lesions and of differentiating benign, suspicious and malignant melanocytic lesions.<sup>52-56</sup> Studies of images of skin lesions (including dysplastic nevi and early melanomas) extracted from image data bases have suggested that this technique improves the number of correct diagnoses over that achieved by clinical examination,<sup>53</sup> but its influence on the rate of excision of benign lesions or other clinical outcomes has not been studied.

## GUIDELINES

Table 1 summarizes recommendations for the management of dysplastic nevi according to two published sets of guidelines.<sup>57,58</sup>

## CONCLUSIONS AND RECOMMENDATIONS

When encountering a patient with clinically dysplastic nevi, as in the case described in the vignette, the physician should take a detailed personal history, including information on any history of skin or other cancer, prior excisions of nevi, episodes of sunburn, and UV-radiation exposure (e.g., during childhood while residing in a sunny region) and should ask whether any family members have or have had melanoma or dysplastic nevi. All first-degree relatives should be encouraged to undergo a skin examination. During the complete examination of the skin at base line (which should include examination of the doubly protected areas and the scalp), the total number of nevi should be evaluated and the presence or absence of atypical nevi assessed.

Although the role of dermoscopy remains controversial, we use this technique to evaluate lesions that look suspicious clinically, in particular to rule out the presence of non-melanocytic pigmented lesions. A lesion should be excised if, after careful examination, the dermatologist believes that melanoma cannot be ruled out; in such cases, we excise the lesion with a 2-mm margin. Prophylactic excision is not warranted for lesions diagnosed clinically as dysplastic nevi, since the probability that a single lesion will develop into melanoma is very low and since excision does not clearly reduce the overall risk of melanoma.

Patients should be educated about the risk of melanoma and should be advised to watch for alarming signs (changes in a mole or findings according to the "ABCD" rule for melanoma detection [asymmetry, border irregularity, color variation, or a diameter greater than 6 mm]). Avoidance of sun exposure during the hours of peak UV intensity (noon to 4 p.m.) and routine use of sun-protective clothing, sunglasses, and broad-spectrum sunscreens (SPF 15 or higher) should be routinely advised.

Although data to guide follow-up are lacking, we follow patients with the use of serial, standardized (digital), total-body photographs and close-up photographs of prominent atypical nevi (with a ruler placed next to the nevus). We recommend reevaluation six months after the base-line examination and then once a year, or more frequent follow-up if there is a personal history of melanoma. Patients should be advised to request an earlier visit if they judge a newly appearing lesion to be suspicious or a change in an existing lesion to be suspicious, according to the information they have received.

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# Genital Chlamydial Infections

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A 19-year-old woman visits her primary care provider for counseling about contraception. She became sexually active one year previously and has had a new sexual partner for the past three months. Her partner currently uses a condom intermittently for contraception, and she inquires about oral contraceptives. She reports no medical problems and is in good health. Her physical examination is unremarkable. Is testing for *Chlamydia trachomatis* indicated?

## THE CLINICAL PROBLEM

*Chlamydia trachomatis* is the most common bacterial cause of sexually transmitted infections in the United States, responsible for an estimated 3 million new infections each year.<sup>1,2</sup> The cost of care for untreated chlamydial infections and their complications is estimated to exceed \$2 billion annually.<sup>3</sup>

### Clinical Presentation

As many as 85 to 90 percent of *C. trachomatis* infections in men and women are asymptomatic.<sup>4,5</sup> Asymptomatic infections can persist for several months.<sup>5</sup> Despite the frequent absence of symptoms, at least one third of women have local signs of infection on examination.<sup>5</sup> The two most commonly reported signs are mucopurulent discharge from the cervix and hypertrophic cervical ectopy (Figure 1). Signs and symptoms in men include urethral discharge of mucopurulent or purulent material, dysuria, or urethral pruritus.

Clinical manifestations of *C. trachomatis* infections in women include acute urethral syndrome, urethritis, Bartholinitis, cervicitis, upper genital tract infection (endometritis, salpingo-oophoritis, or pelvic inflammatory disease), perihepatitis (Fitz-Hugh-Curtis syndrome), and reactive arthritis.<sup>5</sup> Symptoms depend on the site of infection. Infection of the urethra and lower genital tract may cause dysuria, abnormal vaginal discharge, or post-coital bleeding, whereas infection of the upper genital tract (e.g., endometritis or salpingitis) may be manifested as irregular uterine bleeding and abdominal or pelvic discomfort.





Figure 1. Cervical Ectropion (White Arrow) with Mucopurulent Cervicitis (Black Arrow).

Photograph courtesy of Dr. Marc Steben.

In women, untreated chlamydial infection can lead to severe reproductive complications. *C. trachomatis* is an important causal agent in pelvic inflammatory disease, with sequelae including infertility, ectopic pregnancy, and chronic pelvic pain.<sup>6</sup> Up to two thirds of cases of tubal-factor infertility and one third of cases of ectopic pregnancy may be attributable to *C. trachomatis* infection.<sup>7</sup> Chlamydial infection during pregnancy is associated with a number of adverse outcomes of pregnancy including preterm labor, premature rupture of the membranes, low birth weight, neonatal death, and postpartum endometritis.<sup>8,9</sup>

Chlamydial infection during pregnancy may be transmitted to the infant during delivery.<sup>10</sup> An infant born to a mother with active infection has a risk of acquiring infection at any anatomical site of 50 to 75 percent. Approximately 30 to 50 percent of infants born to chlamydia-positive mothers will have conjunctivitis, and at least 50 percent of infants with chlamydial conjunctivitis will also have nasopharyngeal infection. Chlamydial pneumonia develops in about 30 percent of infants with nasopharyngeal infection.<sup>5</sup>

In men, the most common clinical manifestation of *C. trachomatis* infection is nongonococcal urethritis. In fact, *C. trachomatis* causes approximately 35 to 50 percent of all cases of nongonococcal urethritis in heterosexual men. Symptoms of nongonococcal urethritis may develop after an incubation period of 7 to 21 days and include dysuria and mild-to-moderate whitish or clear urethral discharge. In most cases, physical examination reveals no abnormalities other than the discharge. Other clinical syndromes in men include acute epididymitis, acute proctitis, acute proctocolitis, conjunctivitis, and Reiter's syndrome.<sup>7</sup> Male infertility, chronic prostatitis, and urethral strictures are possible results of infection.

Both Reiter's syndrome (urethritis, conjunctivitis, arthritis, and mucocutaneous lesions) and reactive tenosynovitis or arthritis (without the other components of Reiter's syndrome) have been associated with genital *C. trachomatis* infection.<sup>5</sup> Infection with *C. trachomatis* is also believed to be a cofactor for the transmission of human immunodeficiency virus in both men and women.<sup>11</sup>

### Epidemiology of Chlamydial Infections

The prevalence of chlamydia depends on the characteristics of the population studied. Reported prevalence rates in the United States have ranged from 2 to 7 percent among female college students and 4 to 12 percent among women attending a family planning clinic to 6 to 20 percent among men and women attending a clinic for sexually transmitted diseases or persons entering correctional facilities.<sup>5,12</sup> In the United Kingdom, recent data suggest that the rate of infection among young women exceeds 10 percent.<sup>13</sup> The prevalence of *C. trachomatis* infection is highest in groups of persons who are the least likely to see a clinician. Prevalence rates have declined in geographic areas where screening programs have been implemented.<sup>14</sup>

Risk factors for chlamydial infection in sexually active women include a young age (less than 25 years and, in particular, less than 20 years), intercourse at an early age, having more than one sexual partner, involvement with a new sexual partner, being unmarried, black race, a history of or coexistent sexually transmitted infection, cervical ectopy, and inconsistent use of barrier contraceptive methods.<sup>15,16</sup> Young age is the factor that is most strongly associated with infection (relative risk among women younger than 25 years as compared with older women, 2.0 to 3.5).<sup>17</sup> This association is largely attributable to the higher level of sexual activity among younger women. Also, in younger women, the squamocolumnar junction of the cervix often lies well out on the ectocervix, forming a bright red central zone of ectopic columnar epithelium called an ectropion (Figure 1); this ectopy provides a larger target area for chlamydial infection than is present in older women.<sup>18</sup>

## STRATEGIES AND EVIDENCE

### Screening

**Screening in Women** There is good evidence that screening women who are at risk for *C. trachomatis* infection can prevent reproductive sequelae by reducing the rate of pelvic inflammatory disease.<sup>15</sup> The strongest evidence supporting screening in women comes from a large randomized trial of screening and treatment at a health maintenance organization in Seattle.<sup>19</sup> Participants were unmarried, asymptomatic women (18 to 34 years

of age) who were considered to have a high risk of *C. trachomatis* infection on the basis of a scoring system that included as risk factors a young age (less than 25 years), black race, nulligravidity, douching, and two or more sexual partners during the previous 12 months. By the end of the follow-up period, there were 9 verified cases of pelvic inflammatory disease in the screened group (8 per 10,000 woman-months of follow-up) and 33 cases in the usual-care group (18 per 10,000 woman-months; relative risk in the screened group, 0.44; 95 percent confidence interval, 0.20 to 0.90). Long-term adverse outcomes of chlamydial infection were not addressed in this study.

In addition, two ecologic studies (studies evaluating associations between types of exposure and outcomes in populations rather than individual persons), conducted in Sweden, showed that the rates of both ectopic pregnancies and pelvic inflammatory disease were reduced in communities after screening for chlamydial infection was adopted.<sup>20,21</sup> However, it is possible that the lower prevalence of adverse outcomes in these studies was due to factors other than screening, such as increased use of barrier contraceptives and reductions in risk-taking behavior.

Although data from randomized trials of screening for chlamydial infection during pregnancy are lacking, there is some evidence that screening high-risk women for *C. trachomatis* during pregnancy can reduce the rate of adverse outcomes of pregnancy. Two observational studies showed associations between the treatment of chlamydial infections during pregnancy and improved outcomes of pregnancy, including lower rates of premature rupture of the membranes, low birth weight, births of infants who were small for their gestational age, and neonatal death.<sup>22,23</sup>

**Screening in Men** The U.S. Preventive Services Task Force found no direct evidence to determine whether screening asymptomatic men is effective for reducing the incidence of new infections in women, and it could not determine the balance of the harms and benefits of screening men.<sup>15</sup>

**Testing Methods** The gold standard for the diagnosis of *C. trachomatis* infection was traditionally a culture of a swab from the endocervix in women or the urethra in men. However, the methodologic challenges of culturing this organism led to the development of non-culture-based tests. Whereas early non-culture-based tests, including antigen-detection tests and nonamplified nucleic acid hybridization, were limited by their failure to detect a substantial proportion of infections,<sup>24</sup> newer tests that amplify and detect *C. trachomatis*-specific DNA or RNA sequences<sup>25</sup> (including polymerase chain reaction, ligase chain reaction, and transcription-mediated amplification of RNA) are substantially more sensitive than the first-generation non-culture-based tests (80 to 91 percent, depending

Table 1. Common Clinical Syndromes and Their Treatment.

Syndrome	Recommended Regimens
<b>Men</b>	
Acute nongonococcal urethritis	Azithromycin, 1 g orally (single dose), or doxycycline, 100 mg orally 2 times a day for 7 days
Recurrent or persistent urethritis	Metronidazole, 2 g orally (single dose), plus erythromycin base, 500 mg orally 4 times a day for 7 days, or erythromycin ethylsuccinate, 800 mg orally 4 times a day for 7 days
Epididymitis	Ceftriaxone, 250 mg intramuscularly (single dose), plus doxycycline, 100 mg orally 2 times a day for 10 days
<b>Women</b>	
Acute nongonococcal cervicitis	Azithromycin, 1 g orally (single dose), or doxycycline, 100 mg orally 2 times a day for 7 days
Chlamydia during pregnancy	Erythromycin base, 500 mg orally 4 times a day for 7 days, or amoxicillin, 500 mg orally 3 times a day for 7 days, or azithromycin, 1 g orally (single dose)
<b>Pelvic inflammatory disease<sup>1</sup></b>	
Outpatient	Ofloxacin, 400 mg orally 2 times a day for 14 days, or levofloxacin, 500 mg orally once a day for 14 days, with or without metronidazole, 500 mg orally 2 times a day for 14 days; otherwise, ceftriaxone, 250 mg intramuscularly (single dose), or cefoxitin, 2 g intramuscularly (single dose), plus probenecid, 1 g orally, plus doxycycline, 100 mg orally 2 times a day for 14 days, with or without metronidazole, 500 mg orally 2 times a day for 14 days
Inpatient	Cefotetan, 2 g intravenously every 12 hours, or cefoxitin, 2 g intravenously every 6 hours, plus doxycycline, 100 mg orally or intravenously every 12 hours; otherwise, clindamycin, 900 mg intravenously every 8 hours, plus gentamicin, 2 mg per kg of body weight loading dose intravenously, then 1.5 mg per kg every 8 hours; daily administration of a single dose may be substituted

<sup>1</sup>Therapy for pelvic inflammatory disease should be continued for 24 to 48 hours after clinical improvement occurs and should consist of continuous oral therapy with doxycycline, 100 mg orally twice a day, or clindamycin, 450 mg orally 4 times a day, for a total of 14 days.

from the site from which the specimen is obtained, vs. 62 to 75 percent), when culture is used as the gold standard.<sup>25</sup> The sensitivity is slightly lower when these newer tests are performed on urine specimens rather than endocervical specimens, but the specificity is high for all types of specimens (range, 94 to nearly 100 percent).<sup>25</sup> The majority of nucleic acid–amplification tests have been approved by the Food and Drug Administration for the detection of *C. trachomatis* (and *Neisseria gonorrhoeae*) in urine from both men and women, providing a noninvasive testing method.<sup>25</sup> Limitations of nucleic acid–amplification tests include their relatively high cost and the requirement for a suitable laboratory.<sup>25</sup>

The most recent addition to the testing armamentarium is the use of specimens collected by patients.<sup>26,27</sup> Amplification testing of vaginal or urethral swab specimens collected by patients has a sensitivity and specificity similar to those of amplification testing of specimens collected by clinicians, and studies indicate that patients prefer this method to the standard collection methods.<sup>28,29</sup>

### Treatment

The treatment of chlamydial infection depends on the clinical syndrome (Table 1).<sup>2</sup> Effective and low-cost treatments for genital chlamydial infection are available for the most

common clinical syndromes (nongonococcal urethritis in men and mucopurulent cervicitis in women). In a randomized trial, the efficacy of a seven-day course of doxycycline was equivalent to that of a single dose of azithromycin; both resulted in cure rates of more than 95 percent among men and nonpregnant women.<sup>30</sup> Sexual partners should be notified, examined, and treated for chlamydia and any other identified or suspected sexually transmitted disease. Patients and their partners should be instructed to refrain from sexual intercourse until therapy is completed (specifically, until seven days after a single-dose regimen or until the completion of a seven-day regimen).<sup>2</sup>

**Infection during Pregnancy** A Cochrane review of 11 randomized trials for the treatment of chlamydia during pregnancy concluded that amoxicillin was as effective as oral erythromycin.<sup>31</sup> Several small trials comparing oral azithromycin with these therapies have shown similar cure rates and acceptability for azithromycin.<sup>32,33</sup>

**Pelvic Inflammatory Disease** Although pelvic inflammatory disease is thought to be a polymicrobial infection, *C. trachomatis* is one of the more common pathogens involved. The minimal criteria for a diagnosis of pelvic inflammatory disease include uterine–adnexal tenderness or cervical-motion tenderness.<sup>2</sup> Some studies suggest that atypical presentations of pelvic inflammatory disease, including discomfort without appreciable tenderness, abnormal uterine bleeding, and abnormal vaginal discharge, are often associated with infection and inflammation in the upper genital tract (i.e., endometritis and salpingitis).<sup>34,35</sup> Chlamydial pelvic inflammatory disease tends to have a more insidious onset than pelvic inflammatory disease caused by *N. gonorrhoeae* or other more virulent organisms. However, the damage to the fallopian tube can be as great or greater with chlamydia, especially with repeated infections.<sup>36</sup>

Because of the risks of infertility and other sequelae of pelvic inflammatory disease, clinicians should have a low threshold for the prompt institution of treatment in women who are at risk for chlamydial infection. The delay of antibiotic therapy is associated with an increased risk of adverse outcomes.<sup>37</sup> The PID [Pelvic Inflammatory Disease] Evaluation and Clinical Health (PEACH) study, a randomized trial comparing inpatient therapy consisting of cefoxitin and doxycycline with similar outpatient therapy, demonstrated that outpatient therapy for uncomplicated pelvic inflammatory disease (without tubo-ovarian abscess or severe illness) was as effective as intravenous inpatient therapy in terms of fertility and other long-term health outcomes, including the prevention of ectopic pregnancy and chronic pelvic pain.<sup>38</sup>

## AREAS OF UNCERTAINTY

There continues to be uncertainty regarding whom to screen and how frequently to do so. There is little evidence of the effectiveness of screening in asymptomatic women who are not in high-risk groups.<sup>15</sup> Screening on the basis of age (less than 25 years) appears to be effective even in areas where the prevalence of chlamydial infection is low to moderate (3 to 6 percent). In a longitudinal cohort study of screening in 3202 high-risk, inner-city young women, chlamydial infection was detected in 24.1 percent; the median time to new infection was slightly more than 7 months, and the median time to a repeated positive test was 6.3 months. On the basis of these results, it was recommended that all young, sexually active women be screened every six months.<sup>39</sup> It is unclear, however, whether these findings can be generalized to populations with a lower prevalence of infection.

Level I evidence (from randomized trials) is also lacking regarding the effectiveness of the screening and treatment of pregnant women in populations with a low prevalence of chlamydial infection. In addition, the balance of benefits and harms (including false-positive test results and the inappropriate use of antibiotics) has not been assessed.<sup>15</sup>

Given the high prevalence of asymptomatic infections in the population, some experts advocate for the routine screening of young men as the next important step toward reduced rates of infections and complications.<sup>40,41</sup> Although there is strong evidence that treatment can eradicate *C. trachomatis* infection in men, there are no studies demonstrating that the screening of asymptomatic men can reduce the rates of acute infection and adverse outcomes in men or in women. Cost-effectiveness analyses have suggested that there is an economic benefit to society of screening for *C. trachomatis*, as compared with not screening, in high-risk women.<sup>42,43</sup> However, the cost effectiveness of the screening of men and low-risk women is debatable and will depend on the prevalence of infections, the ease and cost of specimen collection, the cost of testing, the characteristics of the diagnostic tests (e.g., their sensitivity and specificity), and the short- and long-term adverse outcomes that are prevented. Additional research is needed to determine the optimal interval between screenings and to compare the universal screening of all sexually active women younger than 25 years of age with screening based on the presence of additional risk factors in populations with a range of prevalence rates.

It remains uncertain whether the routine use of urine specimens or specimens collected by patients would improve compliance with testing and treatment. Also, it is unclear whether the empirical treatment of the sexual partners of patients with chlamydial infections is preferable to the screening of these partners. Some experts suggest that providing patients with prescriptions for empirical treatment to deliver to their sexual partners will reduce the rate of reinfection,<sup>44</sup> but this hypothesis remains unproven. In a recent trial in

which patients were randomly assigned to either patient-delivered treatment for partners (patients were asked to deliver a dose of azithromycin to each of their sexual partners) or self-referral (patients were asked to refer their sexual partners for treatment), the risk of reinfection was nonsignificantly lower in the group assigned to patient-delivered treatment (odds ratio for reinfection, 0.8; 95 percent confidence interval, 0.6 to 1.1).<sup>45</sup>

### GUIDELINES

Guidelines from several professional societies, the Centers for Disease Control and Prevention, and the U.S. Preventive Services Task Force are summarized in Table 2.<sup>46-50</sup>

Table 2. Guidelines from Professional Societies and Federal Agencies.

Organization	Who Should Be Screened	Timing or Frequency of Screening
American Academy of Pediatrics <sup>46</sup>	All young, sexually active women	Perform annually
American College of Obstetricians and Gynecologists <sup>47</sup>	All young sexually active women and other women at high risk for infection	Perform routinely (interval not specified)
American College of Preventive Medicine <sup>48</sup>	All sexually active women with risk factors (age $\leq 25$ yr, new male sexual partner or two or more sexual partners in previous year, inconsistent use of barrier contraceptives, history of sexually transmitted disease, black race, cervical ectopy)	Perform annually
	Pregnant women	Perform during first trimester in all women, third trimester if risk factors present
American Medical Association <sup>49</sup>	All young, sexually active women	Perform annually
Canadian Task Force on Preventive Health Care <sup>50</sup>	Persons in high-risk groups (sexually active women $< 25$ yr of age, men and women with a new sexual partner or more than one partner in the previous year, women who use nonbarrier contraceptive methods)	Not specified
	Pregnant women	Perform during first trimester in all women
Centers for Disease Control and Prevention <sup>46</sup>	All sexually active women $< 20$ yr of age; women 20–24 yr of age if one of the following risk factors is present: inconsistent use of barrier contraceptives or a new sexual partner or multiple sexual partners during the previous 3 mo; women $> 24$ yr of age if both risk factors are present	Perform annually
	Pregnant women	Perform during first prenatal visit in all women, third trimester if high risk ( $< 25$ yr of age or other risk factors)
U.S. Preventive Services Task Force <sup>13†</sup>	All sexually active women $\leq 25$ yr of age and other asymptomatic women at increased risk for infection	Perform routinely, optimal interval uncertain
	All asymptomatic pregnant women $\leq 25$ yr of age and others at increased risk for infection	Perform routinely, optimal interval uncertain

\* The guidelines of the Centers for Disease Control and Prevention are available at <http://www.cdc.gov/std/treatment/rr5106.pdf>.

† The guidelines of the U.S. Preventive Services Task Force are available at <http://www.ahrq.gov/clinic/uspstf/uspstfchl.htm>. The task force recommends routine screening in the groups listed and notes that there is insufficient evidence to make a recommendation for or against screening in asymptomatic men.

All groups suggest that clinicians screen routinely for *C. trachomatis* in all sexually active women less than 25 years of age and in other asymptomatic women who are at increased risk for infection.

#### CONCLUSIONS AND RECOMMENDATIONS

Screening for *C. trachomatis* infection is indicated in sexually active women with risk factors for this infection, including an age of less than 25 years, inconsistent use of barrier contraceptives, a new sexual partner, more than one sexual partner, cervical ectopy, and a history of or coexisting sexually transmitted disease. The patient described in the vignette has some of these risk factors. Electing not to screen her would place her at risk for adverse outcomes, including ascending infection (pelvic inflammatory disease) and infertility, chronic pelvic pain, and ectopic pregnancy. Annual screening is reasonable, although more frequent testing may be indicated in areas of high prevalence or in women with several risk factors. Information on prevalence (the rates of positive tests) can often be obtained from microbiology laboratories. The use of barrier contraception (e.g., condoms) as a method of prevention should be discussed with all patients. If a screening test is positive for *C. trachomatis*, I would treat the patient with doxycycline or azithromycin. Retesting (a "test of cure") after treatment with recommended regimens is not indicated unless compliance is in question, symptoms are present, or reinfection is suspected.<sup>2</sup> Rescreening for chlamydia is recommended when patients present for care within 12 months after a positive test.<sup>2</sup>

The timely treatment of the patient's sexual partners is also essential in order to reduce the risk of reinfection. The sexual partners should be evaluated, tested, and treated if they have had sexual contact with the patient during the 60 days preceding the diagnosis. Treatment for sexual partners that is delivered by the patient for the prevention of repeated infection has efficacy similar to that of self-referral and is a reasonable approach.

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## *Prevention of Hepatitis A with the Hepatitis A Vaccine*

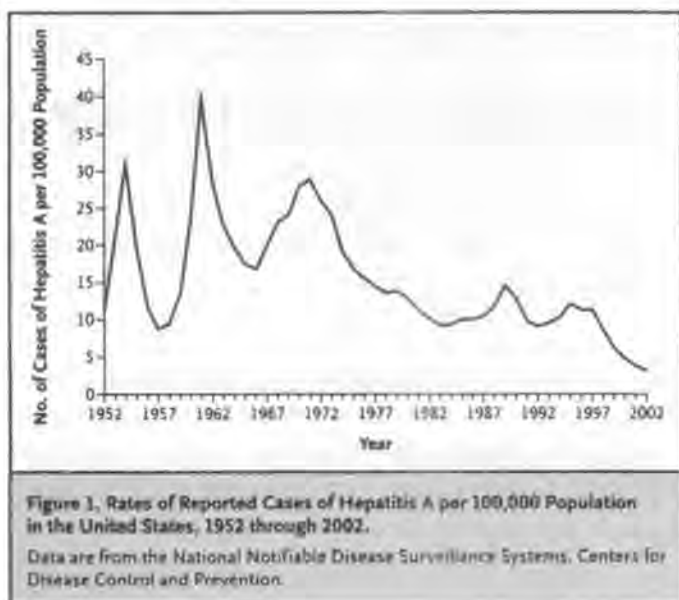
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A 34-year-old man presented to the emergency department two weeks after returning from a trip to India, reporting a six-day history of anorexia, vomiting, malaise, fatigue, and dark urine. His alanine aminotransferase level was 7330 U per liter, the bilirubin level was 8 mg per deciliter (137  $\mu$ mol per liter), and a test of the serum for hepatitis A IgM antibodies was positive. He was admitted for observation and hydration. Should he have been vaccinated against hepatitis A before his departure, and should his household contacts receive vaccine?

### THE CLINICAL AND PUBLIC HEALTH PROBLEMS

The hepatitis A virus occurs throughout the world, and humans are thought to be its principal host.<sup>1</sup> The virus replicates in the liver and is transported through the bile to the stool, where it is shed beginning one to three weeks before the onset of illness and continuing for a week or more after the onset of jaundice. The virus is transmitted from person to person through the fecal-oral route and through the ingestion of contaminated food or drink. Although more than 75 percent of adults with hepatitis A infection have symptoms,<sup>2</sup> 70 percent of infections in children younger than six years of age are asymptomatic. These biologic characteristics contribute to the stealthy and efficient spread of the virus. The virus is spread easily from asymptomatic young children to other young children and to adult contacts. Young children are thus considered to be a principal reservoir and the dominant source of transmission in the community. The virus may also be transmitted by adults before symptoms occur, given that the virus appears in the stool substantially before the onset of illness. Thus, the source of a patient's infection often remains unknown.

After an average incubation period of 28 days (range, 15 to 50), an illness characterized by nausea, abdominal pain, fever, fatigue, dark urine, and jaundice occurs. Although



most patients recover completely and uneventfully, the potential seriousness of hepatitis A in adults is generally underappreciated.<sup>3</sup> Coagulopathy, encephalopathy, renal failure, a prolonged duration of disease, and occasional relapses are among its complications. Overall, 13 percent of patients require hospitalization, with a range from 7 percent of children younger than 15 years of age to 27 percent of adults 45 years of age or older.<sup>4</sup> Each year, approximately 100 deaths in the United States are attributed to fulminant hepatitis A infection.

Enhanced surveillance for hepatitis, conducted since 1981 by the Centers for Disease Control and Prevention (CDC) in four sentinel counties, has demonstrated that the epidemiology of hepatitis A in the United States is heterogeneous.<sup>4</sup> The CDC surveillance program showed that 52 percent of patients could not identify the source of their infection. Household or sexual contact with a person with hepatitis A (in 12 percent of patients) and a history of injection-drug use within the six months before the onset of illness (in 14 percent of patients) were the two most commonly recognized risk factors. Whether the latter risk factor reflected actual transmission through the sharing of blood-contaminated needles<sup>5</sup> or simply close contact could not be ascertained. Other reported risk factors included attendance or employment at a day-care center (in 11 percent of patients), a history of male homosexual activity within the previous six months (in 7 percent), and recent international travel to countries where hepatitis A is endemic (in 4 percent). Contrary to

common belief, outbreaks of hepatitis A associated with restaurants are infrequent<sup>6</sup>; their notoriety probably stems from the extensive publicity surrounding these events.

There have been cyclic communitywide outbreaks of hepatitis A every 5 to 10 years in the United States for decades. More than 10,000 cases were reported in this country in 2001.<sup>7</sup> The actual number of cases of hepatitis A was probably 5 times that reported, and the number of new asymptomatic infections was probably 10 times the number of reported symptomatic cases. The incidence is highest in the western states and among persons 5 to 39 years of age.<sup>8</sup> One third of the U.S. population has serologic evidence of previous hepatitis A infection, with a prevalence ranging from 9 percent among children 6 to 11 years of age to 75 percent among persons 70 years of age or older.<sup>6</sup>

Periodic community epidemics notwithstanding, the rates of hepatitis A infection in the United States have been decreasing gradually during the past several decades (Figure 1). This decrease probably reflects advances in hygiene, including improved water supplies, enhanced sewage disposal, reduced crowding, augmented food safety, and other factors. The use of hepatitis A vaccine since 1995 in many communities where the rate of infection had been high has most likely accelerated this downward trend. Rates of hepatitis A infection are similar in Europe and in most developed countries. In developing countries, nearly all people have had hepatitis A infection by early adulthood.<sup>9</sup>

#### STRATEGIES AND EVIDENCE

Two biologic products, hepatitis A vaccine and immune globulin, have been used successfully to prevent hepatitis A infection.

##### Hepatitis A Vaccine

In the mid-1990s two formalin-inactivated hepatitis A virus vaccines were licensed by the Food and Drug Administration (FDA) for use in preventing disease in persons two years of age or older. Both vaccines are highly immunogenic; neutralizing antibodies are present in more than 94 percent of vaccinees one month after the first dose has been given, and essentially all recipients have a response after the second dose.<sup>10-12</sup> Two large efficacy trials were conducted, one in Thai villages and the other in a religious community in New York, all of which had sustained high rates of transmission of hepatitis A. Vaccination efficacy rates of 94 to 100 percent were recorded in these challenging circumstances.<sup>13,14</sup> The available data suggest that the vaccine is less immunogenic in patients with chronic liver disease (seroconversion rate, 93 percent),<sup>15,16</sup> immunocompromised persons (88 percent),<sup>17</sup> and transplant recipients (26 percent).<sup>18</sup> The immunogenicity also appears to be lower in the elderly (65 percent).<sup>19</sup>

Table 1. Recommended Doses of Hepatitis A Vaccine and Immune Globulin.*			
Agent and Age Group	Dose	Volume ml	Dose Schedule
Havrix	2-18 Yr	720 ELISA units	0.5
	>18 Yr	1440 ELISA units	1.0
Vaqta	2-18 Yr	25 U	0.5
	>18 Yr	50 U	1.0
Twinrix (>17 yr)†	720 ELISA units	1.0	3 doses, at 0, 1, and 6 mo
Immune globulin (any age)	—	0.02 per kg of body weight	1 dose

\* ELISA denotes enzyme-linked immunosorbent assay.

† Twinrix is a combination hepatitis A-hepatitis B vaccine.

Hepatitis A vaccine is not approved for use in children younger than two years of age because of concern that children who have passively acquired maternal antibody will have a diminished response to the vaccine.<sup>20,21</sup> In spite of a lower antibody response, an anamnestic response occurred in children who were vaccinated at two, four, and six months of age and then revaccinated several years later.<sup>20</sup>

The vaccine is considered to be very safe. Reported adverse events have included soreness at the injection site in 18 to 39 percent of persons, headache (in 15 percent), and fever (in less than 10 percent).<sup>10-14,22</sup> By 1999, more than 65 million doses of hepatitis A vaccine had been administered worldwide; investigators who reviewed data from multiple sources could not identify any serious adverse events that could be attributed to the vaccines with certainty.<sup>6,23</sup> The only contraindication to vaccination is a previous allergic reaction to either of the vaccines or sensitivity to any vaccine component. Although the vaccines have not been studied in pregnant women, it is likely that they would be safe during pregnancy, given their inactivated formulation. Both vaccines are classified in pregnancy category C (studies in animals and humans have not been conducted). Pregnant women who are at risk for hepatitis A, such as those traveling to developing countries, should be vaccinated only if there is a clear indication; immune globulin (discussed below) is a reasonable alternative for such women.

A two-dose schedule is recommended for both vaccines, with the second dose given 6 to 18 months after the first (Table 1). If the second dose is delayed, it can still be given without the need to repeat the primary dose.<sup>24</sup> Because of the high rate of seroconversion,

Table 2. Persons Currently Considered to Have an Indication for Hepatitis A Vaccine or Immune Globulin.

**Hepatitis A vaccine**

Children at least 2 years of age living in a state (Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah, or Washington) or a county with a high rate of infection ( $\geq 20$  cases per 100,000 population from 1987 through 1997)<sup>\*</sup>

Travelers at least 2 years of age to countries with high or intermediate rates of disease<sup>†</sup>

Men who have sex with men

Users of illicit drugs

Persons who have chronic liver disease or who have received or will receive a liver transplant

Persons who use clotting-factor concentrates

Laboratory personnel who work with the hepatitis A virus or with nonhuman primates that are infected with hepatitis A

**Immune globulin**

Persons who will be traveling to countries with high or intermediate rates of disease within the next 2 weeks

Children younger than 2 years of age who will be traveling to countries with high rates of disease

For postexposure prophylaxis, within 14 days after exposure: persons who have been exposed to food that was handled by someone with acute hepatitis A who had either poor hygiene or diarrhea or persons exposed to a family member with acute hepatitis A

\* Further information is available at <http://www.cdc.gov/ncidod/diseases/hepatitis/a/vax/index.htm>.

† Further information is available at <http://www.cdc.gov/ncidod/diseases/hepatitis/a/prevalence.htm>.

testing for antibodies after vaccination is not required. Pediatric and adult formulations are available for both vaccines. The vaccines are given in the deltoid muscle and can be administered concurrently with other vaccines. They can also be given with immune globulin, at different anatomical sites, if immediate protection is required. The two brands of vaccine are considered to be interchangeable; if necessary, the two doses of vaccine can be of two different brands.<sup>6</sup> Serologic testing for hepatitis A before vaccination is likely to be cost effective only among persons who have a high likelihood of previous infection. Three additional hepatitis A vaccines have been licensed for use in Europe, Latin America, and other parts of the world. Routine vaccination programs are in place in Israel<sup>25</sup> and in regions of Italy and Spain.

Recently, a combination hepatitis A–hepatitis B vaccine was licensed in the United States for use in persons older than 17 years of age. This vaccine appears to be both as safe and as effective as individual vaccines for the two viruses given separately.<sup>26</sup> The 1-ml

dose is given in a three-dose schedule at 0, 1, and 6 months (Table 1). Studies suggest that the combination vaccine is highly immunogenic in children 1 to 15 years of age.<sup>27</sup>

### Strategies for the Use of Hepatitis A Vaccine

One strategy is to immunize people who are recognized to be at high risk for hepatitis A, in order to protect them. Vaccination should be offered to all high-risk persons two years of age or older (Table 2).<sup>6</sup> Such an approach, however, would be expected to have only a marginal effect on the occurrence of disease nationwide, because most persons who become infected with hepatitis A do not have identifiable risk factors.<sup>4</sup>

In addition to protecting the individual vaccinee, immunization has the public health goal of protecting the entire community. The achievement of this goal requires interruption of the transmission of the hepatitis A virus, which extends protection to immunocompromised persons (who have an insufficient response to the vaccine and who may be at particular risk for severe disease) and to persons who, for whatever reason, have not been immunized. The effectiveness of immunization strategies is also influenced by practical realities, such as the acceptance of the vaccine by the public and providers, competing priorities, and costs.

An initial approach to protecting the community involved the use of hepatitis A vaccine during large community outbreaks. Although small outbreaks in rural communities could be aborted by use of hepatitis A vaccine,<sup>28</sup> the strategy was less successful for epidemics occurring in larger urban centers,<sup>29-31</sup> reflecting the difficulty of attaining high rates of vaccine coverage in the target population. Moreover, by the time mass vaccination campaigns were initiated in urban centers, the outbreaks had begun to wane.

These experiences led to a shift in strategy to classic preexposure prevention: the areas of the country with the highest rates of cases were identified, and routine childhood immunization against hepatitis A was recommended in the identified communities. The intent was to reduce the rates of hepatitis A infection and disease among immunized children and — because children had been the primary sources of the spread of hepatitis A virus in these settings — to curtail the transmission of the virus and the incidence of disease among older children and adults through a herd-immunity effect. The introduction of routine immunization of young children in selected areas with high rates of infection, including a California county,<sup>32</sup> a community in New York,<sup>33</sup> and Indian reservations,<sup>34</sup> has demonstrated that universal childhood immunization against hepatitis A is feasible and that it can be sustained. Furthermore, after the introduction of hepatitis A vaccine in these communities, the incidence of disease rapidly decreased to rates that were similar to the national average or even lower. As anticipated, the rates of disease were also reduced among older persons who were not targeted for immunization.<sup>35</sup> It is likely that a



Sustained reduction in the national incidence of hepatitis A will require universal routine immunization, just as the elimination of measles and other diseases has been achieved by means of childhood vaccination.

### **Immune Globulin for Passive Immunoprophylaxis**

Immune globulin is a preparation of concentrated antibodies derived from pooled human plasma. In 1945, Stokes and Neefe demonstrated that immune globulin provided protection against illness among children at a summer camp who had been exposed to hepatitis A.<sup>36</sup> Since then, immune globulin has been used widely for postexposure prophylaxis. The administration of a dose of 0.02 ml per kilogram of body weight intramuscularly in the gluteus within the first two weeks after exposure prevents disease in more than 85 percent of persons.<sup>37</sup> Prophylaxis given later during the incubation period may not prevent disease entirely but does result in reductions in the severity of symptoms and the duration of illness.<sup>36</sup> There is no need to perform serologic testing for antibody against hepatitis A before administering immune globulin.

Immune globulin remains an effective intervention for preventing the transmission of hepatitis A to family members and other close contacts of patients who have recently become ill. Immune globulin has also been used widely for preexposure prophylaxis in persons planning short-term or long-term travel to developing countries, as well as in persons exposed to food prepared by someone who was infected with hepatitis A. The use of immune globulin in travelers has been largely superseded by the use of hepatitis A vaccine, except when the traveler's departure is imminent and immediate protection must be provided or the traveler is younger than two years of age (Table 2), or possibly when the traveler is pregnant. The most common adverse event is pain at the injection site.

### **AREAS OF UNCERTAINTY**

Although experience has been limited, hepatitis A vaccination appears likely to provide long-term protection. Follow-up five to six years after vaccination has demonstrated protective levels of antibody,<sup>33</sup> and clinical efficacy has been maintained for seven to nine years.<sup>38,39</sup> Models based on the kinetics of antibody against hepatitis A virus suggest that immunity will persist for at least 20 years, without the need for periodic boosters.<sup>38-42</sup>

The question of whether hepatitis A vaccine can be used for postexposure prophylaxis is unresolved. One study suggests that it may be effective when given after exposure,<sup>43</sup> but this study was small and did not involve a comparison with immune globulin, and its observations remain unconfirmed.

Fulminant infection may develop in patients with chronic liver disease if they are exposed to hepatitis A virus. There has been some debate about the cost effectiveness of hepatitis A vaccination in this population.<sup>44-47</sup> We believe that hepatitis A vaccine should be given to persons who have evidence of chronic liver disease and those who are awaiting or have received a liver transplant; these groups are at high risk for complications from a superimposed insult to the liver.

Although the FDA has approved these vaccines only for use one month or more before international travel, the vaccine is protective in most persons two weeks after the administration of the first dose, and many travel clinics administer it up to two weeks before departure.<sup>48</sup>

### GUIDELINES

The Advisory Committee on Immunization Practices of the CDC<sup>6</sup> recommends the vaccination of high-risk persons two years of age or older, as outlined in Table 2. The advisory committee also recommends the routine immunization of all children in states or counties with high rates of infection, beginning at two years of age. The cases of hepatitis A reported in the 11 states that have high infection rates, most of which are in the West, accounted for half the total number of cases in the United States between 1987 and 1997, yet these states contained only 22 percent of the U.S. population (Table 2).<sup>6</sup>

### CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette clearly should have been vaccinated when he was planning his journey to a country that is known to have a high rate of hepatitis A. His family members should now receive immune globulin as postexposure prophylaxis against infection. The new combination hepatitis A–hepatitis B vaccine is an option for adults who are at risk for either infection and have not previously been vaccinated.

Routine vaccination is currently recommended for all young children in states with high rates of hepatitis A infection. Nevertheless, large community-wide outbreaks of hepatitis A continue to occur throughout the United States, with consequent disruption, hospitalizations, and deaths. Although it is not current policy, we propose that the universal vaccination of children for hepatitis A be extended to the entire United States, starting at two years of age, with catch-up immunization for all older children through adolescence.<sup>49,50</sup>

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# Cellulitis

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**An otherwise healthy 40-year-old man felt feverish and noted pain and redness over the dorsum of his foot. Tender edema and erythema extended up the pretibial area. Fissures were present between the toes. What diagnostic procedures and treatment are indicated?**

## THE CLINICAL PROBLEM

**C**ellulitis is an acute, spreading pyogenic inflammation of the dermis and subcutaneous tissue, usually complicating a wound, ulcer, or dermatosis. The area, usually on the leg, is tender, warm, erythematous, and swollen. It lacks sharp demarcation from uninvolved skin. Erysipelas is a superficial cellulitis with prominent lymphatic involvement, presenting with an indurated, "peau d'orange" appearance with a raised border that is demarcated from normal skin. The distinctive features, including the anatomical location of cellulitis and the patient's medical and exposure history, should guide appropriate antibiotic therapy (Table 1).

## Anatomical Features

Periorbital cellulitis involves the eyelid and periocular tissues anterior to the orbital septum. Periorbital cellulitis should be distinguished from orbital cellulitis because of the potential complications of the latter: decreased ocular motility, decreased visual acuity, and cavernous-sinus thrombosis.

Before young children began to be immunized with conjugated *Haemophilus influenzae* type b vaccine, buccal cellulitis due to *H. influenzae* type b was responsible for up to 25 percent of cases of facial cellulitis in children 3 to 24 months of age; now such cellulitis is rare. Infection originates in the upper respiratory tract.

Perianal cellulitis occurs mainly in young children and is generally caused by group A streptococci.<sup>1</sup> Manifestations include perianal pruritus and erythema, anal fissures, purulent secretions, and rectal bleeding.

### Types of Exposure That Predispose Patients to Cellulitis

Severe bacterial cellulitis has been known to occur as a complication of liposuction. The subcutaneous injection of illicit drugs ("skin popping") can result in cellulitis due to unusual bacterial species.<sup>2,3</sup>

A distinctive form of cellulitis, sometimes recurrent, may occur weeks to months after breast surgery for cancer. Cellulitis in the ipsilateral arm has been well described after radical mastectomy,<sup>4</sup> where it occurs because of associated lymphedema; cellulitis in the ipsilateral breast is more common now, occurring after breast-conservation therapy.<sup>5</sup> Local lymphedema from the combination of partial mastectomy, axillary lymph-node dissection, and breast irradiation is a predisposing factor.

Cellulitis also occurs in the legs of patients whose saphenous veins have been harvested for coronary-artery bypass.<sup>7</sup> Lymphatic disruption and edema occur on the removal of the vein.

### Unusual Manifestations of Cellulitis

Crepitant cellulitis is produced by either clostridia or non-spore-forming anaerobes (bacteroides species, peptostreptococci, and peptococci) — either alone or mixed with facultative bacteria, particularly *Escherichia coli*, *Klebsiella*, and *Aeromonas*.

Table 1. Specific Anatomical Variants of Cellulitis and Causes of Predisposition to the Condition.

Anatomical Variant or Cause of Predisposition	Location	Likely Bacterial Cause
Periorbital cellulitis	Periorbital	<i>Staphylococcus aureus</i> , pneumococcus, group A streptococcus
Buccal cellulitis	Cheek	<i>Haemophilus influenzae</i>
Cellulitis complicating body piercing	Ear, nose, umbilicus	<i>S. aureus</i> , group A streptococcus
Mastectomy (with axillary-node dissection) for breast cancer	Ipsilateral arm	Non-group A hemolytic streptococcus
Lumpectomy (with limited axillary-node dissection, breast radiotherapy)	Ipsilateral breast	Non-group A hemolytic streptococcus
Harvest of saphenous vein for coronary-artery bypass	Ipsilateral leg	Group A or non-group A hemolytic streptococcus
Liposuction	Thigh, abdominal wall	Group A streptococcus, peptostreptococcus
Postoperative (very early) wound infection	Abdomen, chest, hip	Group A streptococcus
Injection-drug use ("skin popping")	Extremities, neck	<i>S. aureus</i> , streptococci (groups A, C, F, G) <sup>*</sup>
Perianal cellulitis	Perineum	Group A streptococcus
Crepitant cellulitis	Trunk, extremities	See text
Gangrenous cellulitis	Trunk, extremities	See text
Erythema migrans (bright red, circular lesion at initial sites; secondary annular lesions may develop elsewhere several days later because of hematogenous spread)	Extremities, trunk	<i>Borrelia burgdorferi</i> (agent of Lyme disease)

\* Other bacteria to consider on the basis of isolation from skin or abscesses in this setting include *Enterococcus faecalis*, viridans-group streptococci, coagulase-negative staphylococci, anaerobes (including bacteroides and clostridium species), and Enterobacteriaceae.



Figure 1. Cellulitis Due to *Pasteurella multocida* after a Cat Bite.

Bite marks are evident, as are adjacent swelling and edema.



Figure 2. Cellulitis Due to Group A Beta-Hemolytic Streptococci in Leg (Previously Mildly Edematous) of a Patient with Paraplegia.

Some of the superficial skin is eroded. The initiating event was an abrasion on the lower leg.

Gangrenous cellulitis produces necrosis of the subcutaneous tissues and overlying skin. Skin necrosis may complicate conventional cellulitis or may occur with distinctive clinical features (including necrotizing cutaneous mucormycosis in immunocompromised patients).

#### Initiating Sources of Infection

Identifying the source of cellulitis — whether it is cutaneous, subjacent, or bacteremic — can provide clues as to the causative microorganism and the identity of a process that requires additional intervention. Most commonly, the source is skin trauma or an underlying lesion (an ulcer or fissured toe webs, for example). Animal or human bites can cause cellulitis due to the skin flora of the recipient of the bite or the oral flora of the biter (Figure 1). Specific pathogens are suggested when infection follows exposure to seawater (*Vibrio vulnificus*), fresh water (*Aeromonas hydrophila*), or aquacultured fish (*Streptococcus iniae*).

Edema predisposes patients to cellulitis (Figure 2). Some lymphedema persists after recovery from cellulitis or erysipelas and predisposes patients to recurrences,<sup>8</sup> which may be of longer duration than the initial inflammation.<sup>9</sup>

Occasionally, cellulitis may be caused by the spread of subjacent osteomyelitis. Rarely, infection may emerge as apparent cellulitis, sometimes distant from the initial site. Crepitant cellulitis on the left thigh, for instance, might be a manifestation of a colonic diverticular abscess.

Cellulitis infrequently occurs as a result of bacteremia. Uncommonly, pneumococcal cellulitis occurs on the face or limbs in patients with diabetes mellitus, alcohol abuse,

systemic lupus erythematosus, the nephrotic syndrome, or a hematologic cancer.<sup>10</sup> Meningococcal cellulitis occurs rarely, although it can affect both children (periorbital cellulitis) and adults (cellulitis on an extremity).<sup>11</sup> Bacteremic cellulitis due to *V. vulnificans*, with prominent hemorrhagic bullae may follow the ingestion of raw oysters by patients with cirrhosis, hemochromatosis, or thalassemia.<sup>12,13</sup> Cellulitis caused by other gram-negative organisms (e.g., *E. coli*) usually occurs through a cutaneous source in an immunocompromised patient but can also develop through bacteremia<sup>14</sup>; it sometimes follows

Table 2. Important Processes to Be Distinguished from Cellulitis.

Process	Clinical Clues to Diagnosis
<b>Infectious</b>	
Necrotizing fasciitis	
Type I (mixed infection of anaerobes plus facultative species such as streptococci or Enterobacteriaceae)	Acute, rapidly developing infection of deep fascia; marked pain, tenderness, swelling, and often crepitus; bullae and necrosis of underlying skin
Type II (infection with group A streptococci)	Acute infection, often accompanied by toxic shock syndrome; rapid progression of marked edema to violaceous bullae and necrosis of subcutaneous tissue; absence of crepitus
Anaerobic myonecrosis (gas gangrene, due to <i>Clostridium perfringens</i> )	Rapidly progressive toxemic infection of previously injured muscle, producing marked edema, crepitus, and brown bullae (showing large, gram-positive bacilli with scant polymorphonuclear cells); on radiography, extensive gaseous dissection of muscle and fascial planes; bacteremic spread of <i>C. septicum</i> from occult colonic cancer can produce myonecrosis without penetrating trauma
Cutaneous anthrax	Gelatinous edema surrounding eschar of anthrax lesion may be mistaken for cellulitis; anthrax lesion is painless or pruritic; epidemiologic factors are of paramount importance
Vaccinia vaccination	Erythema and induration around vaccination site reaches peak at 10–12 days (more slowly than cellulitis); little toxicity; represents cellular response to vaccinia
<b>Inflammatory and neoplastic</b>	
Insect bite (hypersensitivity response)	History of insect bite, local pruritus; absence of fever, toxicity, or leukocytosis
Acute gout	Involvement of foot (podagra); joint pain; repeated attacks; increase in serum uric acid level
Deep venous thrombophlebitis	Involvement of leg; sentinel venous cord and linear extent
Familial Mediterranean fever-associated cellulitis-like erythema <sup>18</sup>	Occurs in Sephardic Jews and persons from the Middle East who have had previous episodes of recurrent fevers with or without episodes of acute abdominal pain
Fixed drug reaction	Skin erythema does not spread as rapidly as cellulitis; fever low, if present; history of medication use
Pyoderma gangrenosa (particularly lesions starting in subcutaneous fat as acute panniculitis)	Lesions become nodular or bullous and ulcerate; occurs particularly in patients with inflammatory bowel disease or collagen vascular syndromes
Sweet's syndrome (acute febrile neutrophilic dermatosis) <sup>19</sup>	Acute, tender erythematous pseudovesiculated plaques, fever, and neutrophilic leukocytosis; often associated with cancer (commonly hematologic); on face, may resemble erysipelas or periorbital cellulitis; corticosteroid-responsive
Kawasaki's disease <sup>20</sup>	Fever, conjunctivitis, acute cervical lymphadenopathy, oropharyngeal erythema; dermatitis of palms and soles; facial appearance may suggest periorbital cellulitis; occurs mainly in infancy and childhood
Wells' syndrome	Urticaria-like lesions with central clearing; lesions progress slowly and persist for weeks or months; histologically, infiltration with eosinophils; peripheral eosinophilia
Carcinoma erysipeloides <sup>21,22</sup>	A form of metastatic carcinoma with lymphatic involvement; occurs most often on anterior chest wall with cancer of the breast but may also occur at sites of distant metastases; absence of fever; slower progression than cellulitis



*Pseudomonas aeruginosa* bacteremia in patients with neutropenia. In immunocompromised persons, less common opportunistic pathogens (e.g., *Helicobacter cinaedi* in patients with human immunodeficiency virus infection; *Cryptococcus neoformans*; and *fusarium*, *proteus*, and *pseudomonas* species) have also been associated with bloodborne cellulitis.<sup>15-17</sup>

### Differential Diagnosis

The differential diagnosis of cellulitis is summarized in Table 2. Soft-tissue infections that resemble cellulitis must be distinguished from it, since the management of necrotizing fasciitis or gas gangrene requires extensive débridement. The diagnosis of necrotizing fasciitis can be established definitively only by direct examination on surgery or by biopsy with frozen section.<sup>23,24</sup>

## STRATEGIES AND EVIDENCE

### Diagnostic Studies

**Cultures of Aspirates and Lesions** The diagnosis of cellulitis is generally based on the morphologic features of the lesion and the clinical setting. Culture of needle aspirates is not indicated in routine care. However, data from five series using needle aspiration have elucidated common pathogens. Among 284 patients, a likely pathogen was identified in 29 percent.<sup>25-30</sup> Of 86 isolates, only 3 represented mixed cultures. Gram-positive microorganisms (mainly *Staphylococcus aureus*, group A or B streptococci, viridans streptococci, and *Enterococcus faecalis*) accounted for 79 percent of cases; the remainder were caused by gram-negative bacilli (Enterobacteriaceae, *H. influenzae*, *Pasteurella multocida*, *P. aeruginosa*, and acinetobacter species). A small study in children demonstrated higher yields when needle aspirates were obtained from the point of maximal inflammation than when they were obtained from the leading edge.<sup>30</sup>

In two small studies, the yield of punch biopsies was slightly better than that of needle aspirates,<sup>27,29</sup> and the biopsies revealed the presence of gram-positive bacteria in all but one case (*S. aureus* alone in 50 percent of cases, and either group A streptococci alone or *S. aureus* with other gram-positive organisms in most of the remainder). Cultures of ulcers and abrasions in areas contiguous to those with cellulitis have similarly revealed the presence of *S. aureus*, group A streptococci, or both in the majority of cases.<sup>28</sup> These data indicate that antimicrobial therapy for cellulitis in immunocompetent hosts should be focused primarily on gram-positive cocci.

Broader coverage is warranted in patients with diabetes. Among 96 leg-threatening foot infections (including cellulitis) in patients with diabetes, the main potential patho-

gens recovered from deep wounds or débrided tissue were gram-positive aerobes including *S. aureus*, enterococci, and streptococci (in 56 percent of cases); gram-negative aerobes including proteus, *E. coli*, klebsiella, enterobacter, acinetobacter, and *P. aeruginosa* (in 22 percent); and anaerobes including bacteroides and peptococcus (in 22 percent).<sup>31</sup> This broad range of microorganisms should also be considered as potential pathogens in cellulitis that occurs as a complication of decubitus ulcers.

**Blood Cultures** Bacteremia is uncommon in cellulitis: among 272 patients, initial blood cultures were positive in 4 percent.<sup>25,26,28-30</sup> Two thirds of the isolates were either group A streptococci or *S. aureus*, and the remainder were either *H. influenzae* or *P. multocida*. A retrospective study of blood cultures in 553 patients with community-acquired cellulitis

Table 3. Initial Treatment for Cellulitis at Specific Sites or with Particular Exposures.

Variable	Bacterial Species to Consider*	Standard Antimicrobial Therapy†	Alternative Antimicrobial Agents
Buccal cellulitis	<i>H. influenzae</i>	Ceftriaxone (1–2 g/day intravenously)	Meropenem or imipenem-cilastatin
Limb-threatening diabetic foot ulcer	Aerobic gram-negative bacilli (Enterobacteriaceae, <i>P. aeruginosa</i> , acinetobacter); anaerobes (bacteroides, peptococcus)	Ampicillin-sulbactam (3 g intravenously every 6 hr)	Meropenem or imipenem-cilastatin; clindamycin plus a broad-spectrum fluoroquinolone (ciprofloxacin or levofloxacin); metronidazole plus a fluoroquinolone or ceftriaxone
Human bites	Oral anaerobes (bacteroides species, peptostreptococci); <i>Eikenella corrodens</i> , viridans streptococci; <i>S. aureus</i>	Amoxicillin-clavulanate (500 mg orally every 8 hr)	Penicillin plus a cephalosporin
Dog and cat bites	<i>P. multocida</i> and other pasteurella species; <i>S. aureus</i> , <i>S. intermedius</i> , <i>Neisseria canis</i> , <i>Haemophilus felix</i> , <i>Capnocytophaga canimorsus</i> ; anaerobes	Amoxicillin-clavulanate (500 mg orally every 8 hr)	Moxifloxacin plus clindamycin
Exposure to salt water at site of abrasion or laceration	<i>Vibrio vulnificans</i>	Doxycycline (200 mg intravenously initially, followed by 100–200 mg intravenously per day in 2 divided doses)‡	Cefotaxime; ciprofloxacin
Exposure to fresh water at site of abrasion or laceration or after the therapeutic use of leeches	<i>Aeromonas</i> species	Ciprofloxacin (400 mg intravenously every 12 hr) or ceftazidime plus gentamicin‡	Meropenem or imipenem-cilastatin
Working as a butcher, fish or clam handler, veterinarian	<i>Erysipelothrix rhusiopathiae</i>	Amoxicillin (500 mg orally every 8 hr) for mild skin infections; penicillin G (12 million–20 million units intravenously daily) for bacteremic infections or endocarditis	Ciprofloxacin or cefotaxime or imipenem-cilastatin

\* These bacterial species should be considered in addition to the common pathogens.

† Doses given are for adults with normal renal function; the duration of treatment should be 7 to 15 days or longer, depending on the clinical response.

‡ Treatment is to be given along with antimicrobial agents targeted to the common pathogens.

is found a relevant isolate, mainly group A or group G streptococci (but also *S. aureus* and *S. pyogenes*), in only 2 percent,<sup>32</sup> indicating that blood cultures were not likely to be cost effective for most patients with cellulitis.

In contrast, blood cultures are indicated in patients who have cellulitis superimposed on lymphedema. In a study involving 10 such patients, 3 had positive blood cultures (all group A streptococci).<sup>9</sup> This high prevalence of bacteremia may be attributable to the preexisting lymphedema and the infecting bacterial species. Blood cultures are also warranted in patients with buccal or periorbital cellulitis, in patients in whom a salt-water or fresh-water source of infection is likely (Table 3), and in patients with chills and high fever, which suggest bacteremia.

**Radiology** Radiologic examination is unnecessary in most cases of cellulitis. Plain-film radiography and computed tomography (CT) are of value, however, when the clinical setting suggests a subjacent osteomyelitis. When it is difficult to differentiate cellulitis from necrotizing fasciitis, magnetic resonance imaging (MRI) may be helpful, although surgical exploration for a definitive diagnosis should not be delayed when the latter condition is suspected.<sup>24</sup> In a study involving 17 patients with suspected necrotizing fasciitis, 11 cases were ultimately confirmed to be necrotizing fasciitis (at surgery or, in 1 case, on autopsy), and 6 were confirmed to be cellulitis on the basis of the clinical course<sup>33</sup>; on MRI, all 11 cases of necrotizing fasciitis were identified (100 percent sensitivity), but 1 of the 6 cases of cellulitis was misdiagnosed (for a specificity of 86 percent). The criteria for identifying necrotizing fasciitis on MRI include the involvement of deep fasciae, as evidenced by fluid collection, thickening, and enhancement with contrast material.

Ultrasonography and CT are of less value in distinguishing necrotizing fasciitis from cellulitis, but ultrasonography can be helpful in detecting the subcutaneous accumulation of pus as a complication of cellulitis and can aid in guiding aspiration.<sup>34</sup> Gallium-67 scintillography may aid in the detection of cellulitis superimposed on recently increasing, chronic lymphedema of a limb.<sup>35</sup>

### Antimicrobial Treatment

Because most cases of cellulitis are caused by streptococci and *S. aureus*, beta-lactam antibiotics with activity against penicillinase-producing *S. aureus* are the usual drugs of choice. Initial treatment should be given by the intravenous route in the hospital if the lesion is spreading rapidly, if the systemic response is prominent (e.g., chills and a fever, with temperatures of 100.5°F [37.8°C] or higher), or if there are clinically significant coexisting conditions (such as immunocompromise, neutropenia, asplenia, preexisting edema, cir-

rhosis, cardiac failure, or renal insufficiency) (Table 4). Specially tailored treatment for other bacterial causes is warranted when cellulitis occurs after an unusual exposure (human or animal bite or exposure to salt or fresh water), in patients with certain underlying conditions (neutropenia, splenectomy, or immunocompromise), or in the presence of bullae (Table 3). Diabetic foot infections involve multiple potential pathogens, and broad antimicrobial coverage is required.<sup>31</sup> Ampicillin-sulbactam and imipenem-cilastatin were shown in a randomized, double-blind trial to have similar cure rates in this setting (81 percent vs. 85 percent), but the former combination was more cost effective.<sup>38</sup>

Several trials have evaluated newer antibiotics. In a multicenter, double-blind trial involving 461 patients, oral ciprofloxacin (750 mg every 12 hours) was as safe and effective as parenteral cefotaxime (overall failure rate, 2 percent vs. 8 percent;  $P=0.008$ ) in the treatment of various skin and skin-structure infections.<sup>39</sup> The evaluation of these results must be tempered by the facts that most of the skin infections studied were infected ulcers

Table 4. Antimicrobial Treatment for a Usual Case of Cellulitis.\*

Initial Treatment	Subsequent Treatment
Cefazolin, 1.0 g intravenously every 6–8 hr	Dicloxacillin, 0.5 g orally every 6 hr or Cephadrine, 0.5 g orally every 6 hr or Cephalexin, 0.5 g orally every 6 hr or Cefadroxil, 0.5–1.0 g orally every 12–24 hr
or	
Nafcillin, 1.0 or 1.5 g intravenously every 4–6 hr	Same as above
or	
Ceftriaxone, 1.0 g intravenously every 24 hr†	Same as above
or	
Cefazolin, 2.0 g intravenously once daily, plus probenecid (1.0 g orally once daily)‡	Same as above
If methicillin-resistant <i>S. aureus</i> is suspected or patient is highly allergic to penicillin	
Vancomycin, 1.0–2.0 g intravenously daily	Linezolid, 0.6 g orally every 12 hr
or	
Linezolid, 0.6 g intravenously every 12 hr	Same as above

\* Doses given are for adults; patients should be switched to oral therapy when they are afebrile and skin findings begin to resolve (after approximately three to five days). The total duration of treatment should be 7 to 14 days or longer, depending on the rate of response. Treatment should last longer in cases with associated abscesses, tissue necrosis, or underlying skin process (e.g., infected ulcer).

† Ceftriaxone has the advantage of allowing early discharge home with intravenous doses of 1.0 g daily.<sup>36</sup>

‡ Cefazolin-probenecid is given as a substitute for a once-daily parenteral third-generation cephalosporin. It has been shown to be similar in efficacy to ceftriaxone (1.0 g intravenously once daily) in home-based therapy for moderate-to-severe cellulitis in adults.<sup>37</sup>

and abscesses rather than cellulitis and that, since the time of the study, the fluoroquinolone resistance of *S. aureus*, the predominant pathogen isolated, has increased. More recently, oral moxifloxacin (400 mg once daily) has been shown to be as effective (84 percent) as oral cephalexin (500 mg three times a day) in the treatment of uncomplicated skin and soft-tissue infections.<sup>40</sup>

In a randomized, open-label trial of treatment of "complicated" skin and skin-structure infections in which high-dose levofloxacin (750 mg intravenously once daily) was compared with ticarcillin-clavulanate (3.1 g intravenously every four to six hours), therapeutic equivalence was demonstrated (success rates of 84 percent and 80 percent, respectively).<sup>41</sup> However, cellulitis (as a complication of preexisting skin lesions, immunosuppression, or vascular insufficiency) accounted for only 7 percent of the 399 skin infections. Linezolid (600 mg intravenously every 12 hours) has been compared with oxacillin (2 g intravenously every 6 hours) in a randomized, double-blind trial of treatment of complicated skin and soft-tissue infections in 819 hospitalized adults,<sup>42</sup> 44 percent of whom had cellulitis. The cure rates were 89 percent for linezolid and 86 percent for oxacillin. Clinically relevant pathogens isolated from contiguous sites included *S. aureus* (in 35 percent), group A streptococci (in 11 percent), and group B streptococci (in 27 percent), but infections due to methicillin-resistant *S. aureus* were excluded. A trial comparing linezolid and vancomycin in the treatment of adults with methicillin-resistant *S. aureus* infections, including 175 skin and soft-tissue infections,<sup>43</sup> found similar cure rates (79 percent with linezolid and 73 percent with vancomycin), but cellulitis accounted for only 13 percent of these infections.

### Ancillary Measures

The local care of cellulitis involves the elevation and immobilization of the involved limb to reduce swelling and cool sterile saline dressings to remove purulence from any open lesion. Interdigital dermatophytic infections should be treated with a topical antifungal agent until they have been cleared. Such lesions may provide ingress for infecting bacteria. Several classes of topical antifungal agents are effective in clearing up fungal infection when applied one to two times daily; these include imidazoles (clotrimazole and miconazole), allylamines (terbinafine), and substituted pyridones (ciclopirox olamine).<sup>44</sup> Observational data suggest that after the successful treatment of such dermatophytic infections, the subsequent prompt use of topical antifungal agents at the earliest evidence of recurrence (or prophylactic application once or twice per week) will reduce the risk of recurrences of cellulitis.

Patients with peripheral edema are predisposed to recurrent cellulitis. Support stockings, good skin hygiene, and prompt treatment of tinea pedis can prevent recurrences.

In patients who, despite these measures, continue to have frequent episodes of cellulitis or erysipelas, the prophylactic use of penicillin G (250 to 500 mg orally twice daily) may prevent additional episodes; if the patient is allergic to penicillin, erythromycin (250 mg orally once or twice daily) may be used.

#### AREAS OF UNCERTAINTY

A variety of antimicrobial agents have been used to treat cellulitis because of their spectrum of action against likely causative organisms and have been approved by the Food and Drug Administration for use in skin and soft-tissue infections. However, such approval is often based on clinical studies of heterogeneous collections of cutaneous infections (including infected ulcers, abscesses, and wound infections); in some studies, cellulitis accounts for a minority of the infections.<sup>39,43</sup>

Most studies of cellulitis have involved patients with serious infections. Studies are needed to determine specific criteria that define the types of mild cases that are highly likely to respond to oral antibiotics administered at home. Penicillinase-resistant penicillins and cephalosporins have been used because most community-acquired pathogens causing cellulitis (streptococci and *S. aureus*) are susceptible to methicillin. However, the rate of community-acquired methicillin-resistant *S. aureus* infections in patients without identified risk factors appears to be increasing. In a rural Native American community, 55 percent of 112 isolates of *S. aureus* were methicillin-resistant, and 74 percent of these cases were community-acquired; the risk factors did not differ from those in patients with community-acquired methicillin-susceptible strains.<sup>45</sup> It remains uncertain how this change in resistance patterns will affect the management of cellulitis.<sup>46</sup>

Although there is a rationale for the empirical prophylactic use of penicillin to prevent recurrences of cellulitis in patients with multiple previous episodes, the results of efficacy studies have been conflicting. In a study of prophylaxis with monthly intramuscular doses of penicillin G benzathine (1.2 million units) after treatment for an acute episode of streptococcal cellulitis in the lower leg, such prophylaxis reduced the rate of recurrence from 17 percent to 0 (0 of 11) among patients who did not have predisposing factors, but it failed to prevent recurrence in those who had such predisposing factors as lymphedema (4 of 20 cases).<sup>47</sup> Whether it would be more effective to shorten the interval between doses to two or three weeks or to increase the dose is not known. Long-term erythromycin therapy (250 mg orally twice daily for 18 months) has been used to prevent recurrences in patients with a history of two or more episodes of cellulitis or erysipelas.<sup>48</sup> Episodes did not occur in 16 treated patients, whereas 8 of 16 controls had one or more recurrences.

## GUIDELINES

Guidelines for the treatment of skin and soft-tissue infections (including cellulitis) are being prepared by the Infectious Diseases Society of America.

### SUMMARY AND RECOMMENDATIONS

Cellulitis is a clinical diagnosis based on the spreading involvement of skin and subcutaneous tissues with erythema, swelling, and local tenderness, accompanied by fever and malaise. The approach to therapy involves the identification of the likely source as either local (secondary to abrasion or ulcer or due to another exposure, such as an animal bite or seawater, which implicates particular bacterial species — *P. multocida* and *V. vulnificus*, respectively) or an uncommon bacteremic spread of infection. Distinctive features of the patient (such as the presence of diabetes or immunocompromise) or anatomical sites should also be considered in treatment decisions. Streptococci (groups A, G, and B) and *S. aureus* are the most frequently isolated bacterial species.

Initial empirical antimicrobial treatment for moderate or severe cellulitis in a patient such as the one described in the vignette would thus consist of an intravenous cephalosporin (cefazolin or ceftriaxone) or nafcillin (vancomycin in patients with an allergy to penicillin), followed by dicloxacillin or an oral cephalosporin, generally for a course of 7 to 14 days. In patients with recurrent cellulitis of the leg, any fissures in the interdigital spaces caused by epidermophytosis should be treated with topical antifungal agents in order to prevent recurrences. Daily prophylaxis with oral penicillin G (or amoxicillin) should be considered for patients who have had more than two episodes of cellulitis at the same site.

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## ADDENDUM

Since publication of this article, the role of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in skin and soft tissue infections, noted in the section entitled "Areas of Uncertainty," has increased in prominence. Outbreaks of skin infec-

tions due to CA-MRSA have occurred among prison inmates, members of football teams, children in daycare centers, users of parenteral illicit drugs, and the homeless.<sup>1-3</sup> In addition, CA-MRSA has been recognized as a cause of necrotizing fasciitis in Los Angeles.<sup>4</sup> In surveillance in three areas (Baltimore, Atlanta, and 12 hospitals in Minnesota), 8 to 21 percent of all MRSA isolates from infections were CA-MRSA, and 77 percent of those were from skin and soft-tissue infections.<sup>5</sup> Antimicrobial susceptibilities of these isolates differed from those of hospital-associated methicillin-resistant *S. aureus* (HA-MRSA) that had been carried into the community; community-acquired isolates were more often susceptible to commonly used antimicrobials than HA-MRSA isolates: community-acquired isolates were susceptible to clindamycin (87 percent), rifampin (98 percent), trimethoprim-sulfamethoxazole (97 percent), tetracycline (88 percent), ciprofloxacin (65 percent), vancomycin (100 percent), and linezolid (96 percent).

Initial antimicrobial treatment for the usual case of community-acquired cellulitis typically remains a drug like cefazolin since the microbial etiology still is likely to be streptococcal or a methicillin-susceptible *S. aureus* strain. However, the presence of CA-MRSA in an associated skin lesion (infected ulcer, abscess) might furnish a rationale for use of an antimicrobial such as clindamycin or trimethoprim-sulfamethoxazole, provided the severity of the process does not warrant use of vancomycin or linezolid. If clindamycin is used, the *S. aureus* strain should be tested for inducible clindamycin resistance.

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# Asymptomatic Primary Hyperparathyroidism

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A 60-year-old woman is noted incidentally to have a calcium level of 10.8 mg per deciliter (2.70 mmol per liter; normal range, 8.4 to 10.2 mg per deciliter [2.10 to 2.55 mmol per liter]). The parathyroid hormone level, as measured on immunoradiometric assay, is 84 pg per milliliter (normal range, 10 to 65). She has never had a kidney stone or a fracture, and she feels well. Her urinary calcium excretion is normal. Her bone density is within 0.5 SD of the peak bone mass at the lumbar spine and the hip and is 1.0 SD below the peak bone mass at the forearm. How should her case be managed?

## THE CLINICAL PROBLEM

For the first 40 years after its recognition as a clinical entity, primary hyperparathyroidism was a symptomatic disorder in which kidney stones and bone disease were common.<sup>1,2</sup> Management was straightforward, since parathyroidectomy was always indicated. The advent of a multichannel biochemical screening test in the early 1970s ushered in the era of asymptomatic primary hyperparathyroidism, and the incidence of this disorder increased by a factor of four to five.<sup>3,4</sup>

In patients with asymptomatic primary hyperparathyroidism, the serum calcium concentration is elevated, but usually only to within 1 mg per deciliter above the upper limit of normal (10.2 mg per deciliter). The parathyroid hormone level, measured by means of immunoradiometric assay, is usually 1.5 to 2.0 times the upper limit of normal (65 pg per milliliter), although it may be inappropriately "normal." Hypophosphatemia and hyperchloremia, which were common among patients with symptomatic disease, are uncommon among patients with asymptomatic disease. The 24-hour urinary calcium excretion tends to be near the upper limit of normal.

Although radiography almost never shows skeletal involvement, bone densitometry typically does. As measured on dual-energy x-ray absorptiometry, the greatest reduction in bone density is at the distal third of the radius, a site composed predominantly of cortical bone that is vulnerable to the catabolic actions of parathyroid hormone. The hip and

the lumbar spine, sites where bone becomes progressively more cancellous, show smaller reductions.<sup>5</sup> This pattern of bone loss differs from the usual pattern of the early postmenopausal years, when cancellous bone of the lumbar spine is lost preferentially. But in estrogen-deficient postmenopausal women with primary hyperparathyroidism, bone density at the lumbar spine is generally well preserved, emphasizing a protective effect of parathyroid hormone against the loss of cancellous bone. Recent trials showing improved bone density at the lumbar spine in postmenopausal women with osteoporosis who were treated with intermittent low-dose parathyroid hormone have confirmed its anabolic potential.<sup>6</sup> However, occasionally, patients with primary hyperparathyroidism do have bone loss at the lumbar spine.<sup>7-9</sup>

Approximately 20 percent of patients are symptomatic, with kidney stones, overt bone disease, or proximal neuromuscular weakness.<sup>10,11</sup> Some patients do report weakness, easy fatigability, intellectual weariness, and even depression.<sup>12,13</sup> Since these symptoms are nonspecific and are hard to attribute to primary hyperparathyroidism in particular, they do not enter prominently into decisions regarding surgery, nor do they necessarily define patients as symptomatic. When the calcium level exceeds 12 mg per deciliter (3.0 mmol per liter), such nonspecific problems are more likely to be related to primary hyperparathyroidism.

A less common presentation of asymptomatic primary hyperparathyroidism is characterized by a normal serum calcium level but an elevated parathyroid hormone level. This condition is typically identified during an evaluation of skeletal health. The diagnosis is made when there is no apparent cause of secondary elevations of the parathyroid hormone level and the serum 25-hydroxyvitamin D level is not below the lower limit of the physiologically normal range (i.e., is above 20 ng per milliliter). This normocalcemic variant may represent the earliest manifestation of primary hyperparathyroidism.<sup>14</sup>

Although asymptomatic primary hyperparathyroidism commonly occurs in countries that use multichannel screening tests, symptomatic disease is common in other geographic areas, such as India, northeastern Brazil, and China, where access to multichannel screening is limited.<sup>15</sup> In addition, the high prevalence of vitamin D deficiency in these countries may fuel the processes associated with overactivity of the parathyroid glands, leading to more cases of symptomatic disease.

## STRATEGIES AND EVIDENCE

## Diagnosis

Although there are clear advantages to measuring the concentration of ionized calcium rather than the total calcium concentration, most experts in the United States use the total serum calcium concentration, corrected for the patient's albumin concentration (by adding 0.8 mg per deciliter to the total serum calcium value for every 1 g per deciliter below a serum albumin concentration of 4 g per deciliter). The corrected total serum calcium concentration is used because of the technical challenges involved in the accurate measurement of ionized calcium. The diagnosis of primary hyperparathyroidism is made on the basis of the combination of an elevated total serum calcium concentration and an elevated or inappropriately normal parathyroid hormone level.<sup>16</sup>

There are many causes of hypercalcemia, but few are associated with elevated levels of parathyroid hormone, and thus the differential diagnosis of hypercalcemia does not usually present difficulties. A newly introduced immunoradiometric assay for parathyroid hormone detects only the intact, full-length 84-amino-acid molecule.<sup>17</sup> This more specific assay has the potential to be more clinically useful than the established immunoradiometric assay for parathyroid hormone, in which large fragments truncated at the N-terminal end are measured along with the full-length molecule.<sup>18</sup>

When the parathyroid hormone level is elevated in a patient with hypercalcemia, the differential diagnosis includes hyperparathyroidism due to thiazide diuretics or lithium, familial hypocalciuric hypercalcemia, and the tertiary hyperparathyroidism associated with end-stage renal disease. If the patient is taking a thiazide diuretic or lithium and it is considered to be safe to discontinue the use of the medication, then it should be withdrawn and the patient retested three months later. If the serum calcium concentration continues to be elevated, it can be concluded that the hypercalcemia is due to primary hyperparathyroidism. Familial hypocalciuric hypercalcemia is distinguished from primary hyperparathyroidism by a family history of mild hypercalcemia, a usual onset in young adulthood, and a ratio of urinary calcium to urinary creatinine of less than 0.01.<sup>19</sup> Humoral hypercalcemia of malignancy should not be a consideration when the parathyroid hormone level is high, because the hypercalcemic agent in this condition, parathyroid hormone-related protein, is not detected by the immunoradiometric assay for parathyroid hormone. If the parathyroid hormone level is high in a patient with humoral hypercalcemia of malignancy, he or she is more likely to have concomitant primary hyperparathyroidism and cancer than to have a cancer that has produced authentic parathyroid hormone (a situation that is reported rarely).

### **Natural History of Asymptomatic Primary Hyperparathyroidism without Surgery**

Management decisions about asymptomatic primary hyperparathyroidism require knowledge of its natural history. Most patients who do not meet the criteria for surgery (listed below) do well, with no evidence of progressive disease.<sup>20</sup> In most patients who are followed without surgery, the average serum levels of calcium and parathyroid hormone do not change over a 10-year period. Average bone mass as measured by dual-energy x-ray absorptiometry is typically stable, and hypercalciuria does not worsen. The microarchitecture of cancellous bone appears to be maintained. However, approximately 25 percent of patients have evidence of progressive disease, including worsening hypercalcemia, hypercalciuria, and reduction in bone mass. Only age appears to be predictive of progression; younger patients (younger than 50 years of age) are approximately three times as likely to have worsening disease.<sup>21</sup> Therefore, despite the generally benign natural history of primary hyperparathyroidism, patients who are not candidates for surgery should be monitored.

Surgery is routinely warranted in patients with a history of nephrolithiasis. Over a 10-year follow-up period, all patients with such a history who did not undergo parathyroidectomy had progressive disease.

### **Outcomes after Parathyroid Surgery**

Most adults with primary hyperparathyroidism (80 to 85 percent) have a single benign adenoma, whereas 15 to 20 percent have hyperplasia of all four parathyroid glands. Parathyroid cancer is exceedingly rare (found in less than 0.5 percent of patients with hyperparathyroidism).

Although the standard surgical approach is the exploration of all four parathyroid glands with the use of general anesthesia,<sup>22</sup> an alternative approach is to perform the same four-gland operation with the use of local anesthesia. Another strategy is a unilateral operation in which the other gland on the side that harbors the adenoma is ascertained to be normal. Since multiple parathyroid adenomas are unusual, the presence of one normal parathyroid gland is considered by some to be sufficient evidence of single-gland disease.

When performed by an expert parathyroid surgeon, these approaches are successful more than 90 percent of the time. However, since not all surgeons are experts and the parathyroid glands are notoriously variable in their location, preoperative localization has become popular in recent years.<sup>23,24</sup> Imaging with technetium-labeled sestamibi, with or without single-photon-emission computed tomography, is a preferred method, although there are other approaches to localization (ultrasonography, computed tomography, and magnetic resonance imaging). Most experts consider preoperative imaging to be manda-

tory for patients who have had previous neck surgery, but its use in patients without such a history remains controversial.

Preoperative parathyroid imaging is required for all patients who are to undergo minimally invasive parathyroidectomy, a procedure that is directed only at the site where the abnormal parathyroid gland has been visualized.<sup>25</sup> After the removal of the parathyroid gland that is presumed to be abnormal, a sample of peripheral blood is obtained intraoperatively for a rapid parathyroid hormone assay. If the level decreases by more than 50 percent after resection, the gland that has been removed is considered to be the sole source of overactive parathyroid tissue, and the operation is terminated. If the parathyroid hormone level does not decrease by more than 50 percent, the operation is extended to a more traditional one in a search for other overactive parathyroid tissue. There is controversy over the use of minimally invasive parathyroidectomy, since it may miss another overactive gland (a second adenoma or four-gland hyperplasia) whose activity is relatively suppressed when a larger, more dominant gland is present.<sup>26,27</sup>

Complications of parathyroidectomy include injury to the recurrent laryngeal nerve or hypoparathyroidism, both of which are very uncommon if the procedure is performed by an expert parathyroid surgeon. Symptomatic hypocalcemia may occur in the postoperative period in patients with more severe primary hyperparathyroidism (termed "hungry bone syndrome"), but it is rare in patients with mild disease.

After the removal of the parathyroid adenoma or multiple overactive glands, the serum and urinary calcium concentrations return to normal. The rate of recurrence of kidney stones has been reduced by more than 90 percent after parathyroid surgery in some series.<sup>10</sup> Over a period of three to four years, bone density improves, with the lumbar spine and hip regions typically showing increases of 12 to 14 percent without the need to resort to antiresorptive therapy.<sup>20</sup> In patients with vertebral osteopenia, increases in bone density at these sites can approach 20 percent.<sup>7</sup> The density of the distal third of the radius changes little, if at all. Although some reports have suggested that patients feel better in terms of a number of subjective variables after surgery,<sup>13,28</sup> more rigorous quantitative assessment of quality-of-life measures after surgery is still needed.

## AREAS OF UNCERTAINTY

### Long-Term Risks

The long-term risks associated with living with chronic hypercalcemia are unknown. In a population-based study from the United States, mild, asymptomatic primary hyperparathyroidism was not associated with increased overall mortality, although mortality

was increased among patients in the highest quartile of serum calcium concentrations.<sup>22</sup> Whereas classic primary hyperparathyroidism has been linked to cardiovascular disorders (hypertension), gastrointestinal disorders (peptic ulcer disease), and metabolic disorders (diabetes mellitus), it is not clear whether these individual associations are causal.<sup>23</sup> Studies from Europe, however, indicate that patients with primary hyperparathyroidism may have increased cardiovascular risk, rates of lipid disorders, rates of glucose intolerance, and mortality.<sup>30-34</sup>

The incidence of fracture among patients with primary hyperparathyroidism is unknown. Although the risk of fracture has been reported to be increased at all sites,<sup>35</sup> an increased risk of vertebral fracture is a surprising finding, since most patients have relatively well preserved vertebral bone density. An increased incidence of forearm fractures is more consistent with the finding of reduced bone density at that site. However, even this risk is uncertain, because it is now known that parathyroid hormone may increase the cross-sectional area of bone and therefore strengthen it, even if the bone density appears to be reduced.<sup>36</sup>

### Medical Therapy

There is considerable interest in the development of a safe, medical approach to asymptomatic primary hyperparathyroidism. The use of estrogen therapy in postmenopausal women with primary hyperparathyroidism is associated with small reductions (of 0.5 to 1 mg per deciliter) in the serum calcium concentration and increases in bone density, along with stable parathyroid hormone levels.<sup>37</sup> However, risks associated with estrogen use have been well publicized recently.<sup>38</sup> In addition, doses higher than the current standard have been most consistently associated with beneficial effects in primary hyperparathyroidism, although some positive studies have used lower doses.<sup>39</sup> Raloxifene, a selective estrogen-receptor modulator, is a potential alternative. In a short-term (eight-week) trial involving 18 postmenopausal women, raloxifene was associated with a statistically significant, although small (0.5 mg per deciliter), reduction in the serum calcium concentration and in the levels of markers of bone turnover.<sup>40</sup>

Since primary hyperparathyroidism is characterized by high bone turnover, potent bisphosphonates are another therapeutic option. In recent clinical trials involving small numbers of patients with primary hyperparathyroidism, the use of alendronate has resulted in significant increases (of 4 to 6 percent) in vertebral bone density.<sup>41,42</sup> Serum calcium and parathyroid hormone levels do not change significantly.

The calcimimetic drug cinacalcet has been investigated in patients with primary hyperparathyroidism.<sup>43</sup> By increasing the affinity of the parathyroid-cell calcium receptor for



Table 1. Comparison of Old and New Criteria for Parathyroid Surgery in Patients with Asymptomatic Primary Hyperparathyroidism.<sup>a</sup>

Variable	1990 Guidelines	2002 Guidelines
Serum calcium concentration	1.0–1.6 mg/dl above upper limit of normal	1.0 mg/dl above upper limit of normal
24-Hr urinary calcium excretion	>400 mg	>400 mg
Reduction in creatinine clearance	30%	30%
Bone mineral density	Z score below -2.0 in the forearm	T score below -2.5 at any site
Age	<50 Yr	<50 Yr

\* Data are from Bilezikian et al.<sup>46</sup>

Table 2. Comparison of Old and New Management Guidelines for Monitoring Patients with Asymptomatic Primary Hyperparathyroidism Who Do Not Undergo Parathyroid Surgery.<sup>a</sup>

Variable	Recommended Monitoring	
	1990 Guidelines	2002 Guidelines
Serum calcium level	Every 6 mo	Every 6 mo
24-Hr urinary calcium excretion	Annual	Not recommended
Creatinine clearance	Annual	Not recommended
Serum creatinine concentration	Annual	Annual
Bone density	Annual	Annual; at all 3 sites
Abdominal radiography	Annual	Not recommended

\* Data are from Bilezikian et al.<sup>46</sup>

extracellular calcium, this agent leads to an increase in intracellular calcium and a subsequent reduction in parathyroid hormone secretion. This action, in turn, reduces the serum calcium level. Clinical trials have demonstrated prolonged normalization (lasting up to three years) of the serum calcium level<sup>44</sup> but no change in bone density as measured on dual-energy x-ray absorptiometry. There are no data regarding the incidence of fractures with this agent or any other medical therapy in patients with primary hyperparathyroidism. More information is required about all these potential medical approaches to asymptomatic primary hyperparathyroidism before evidence-based recommendations can be made regarding their use in this disorder.

### Calcium and Vitamin D Intake

Although it is prudent for patients to refrain from the ingestion of more calcium than is recommended for adults (1200 to 1500 mg per day), it is also important not to restrict calcium intake too much (to less than 750 mg per day). Calcium-poor diets may fuel processes associated with excessive secretion of parathyroid hormone. Many patients with asymptomatic primary hyperparathyroidism have levels of 25-hydroxyvitamin D that are at the lower end of the normal range or frankly low,<sup>45</sup> and a low level of supplementation, achievable with a multivitamin (400 IU of vitamin D daily), is reasonable. Patients should be advised to be cautious about using higher doses of vitamin D, because hypercalcemia and hypercalciuria can develop and worsen quickly. They should also be advised to maintain adequate fluid intake, because dehydration can exacerbate hypercalcemia.

### Other Uncertainties

Data are lacking regarding the natural history of the recently recognized normocalcemic variant of primary hyperparathyroidism. In addition, more research is needed on possible neuropsychological, cardiovascular, and metabolic manifestations of mild hyperparathyroidism. The roles of newer assays for parathyroid hormone, newer imaging methods, and different surgical approaches require further study.

### GUIDELINES

In 2002, the National Institutes of Health (NIH) Workshop on Asymptomatic Primary Hyperparathyroidism<sup>46</sup> revisited key issues related to the management of this condition that had previously been addressed in the 1990 NIH Consensus Development Conference.<sup>4</sup> A panel convened after the workshop recommended new management guidelines that relate specifically to the asymptomatic form of the disease. The current guidelines for surgery are compared with the 1990 guidelines in Table 1. In the new guidelines, the serum calcium concentration above which surgery is recommended has been lowered to 1 mg per deciliter above the upper limit of normal, because the panel judged that levels that are consistently higher than this are associated with greater risks of complications. The recommendation that bone densitometry be performed at three sites (the lumbar spine, the hip, and the distal third of the radius) reflects the fact that this disease can affect all bones and that the radius is particularly vulnerable. The use of the T score for bone mineral density and the guideline recommending surgery if the T score is less than -2.5 are consistent with the definition of osteoporosis established by the World Health Organization.

Some patients with asymptomatic primary hyperparathyroidism do not meet any of these criteria for surgery. For these patients, a conservative approach including monitoring (as outlined in Table 2) is considered to be an appropriate and safe alternative.

#### CONCLUSIONS AND RECOMMENDATIONS

Many patients with asymptomatic primary hyperparathyroidism will not require surgery. On the basis of long-term follow-up in patients as well as expert opinion, accepted indications for surgery include a serum calcium concentration that is at least 1 mg per deciliter above the upper limit of normal, marked hypercalciuria (urinary calcium excretion of more than 400 mg per day), reduced bone density (a T score of less than -2.5 at any site), and an age of less than 50 years. For patients who do not meet any of these criteria, such as the patient described in the vignette, monitoring with semiannual measurement of serum calcium and annual measurement of bone mass is recommended. Patients should be encouraged to maintain an active lifestyle, with normal intakes of calcium and vitamin D.

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# Treatment of Deep-Vein Thrombosis

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**A 52-year-old-woman with no history of venous thromboembolism presents with a four-day history of discomfort in her left calf. Proximal deep-vein thrombosis is diagnosed by compression ultrasonography. How should her case be managed?**

## THE CLINICAL PROBLEM

The annual incidence of venous thromboembolism is approximately 0.1 percent; the rate increases from 0.01 percent among persons in early adulthood to nearly 1 percent among those who are at least 60 years old.<sup>1,2</sup> More than half of these events involve deep-vein thrombosis. To minimize the risk of fatal pulmonary embolism, accurate diagnosis and prompt therapy are crucial.<sup>3</sup> Long-term complications include the post-thrombotic syndrome<sup>4-6</sup> and recurrent thromboembolism.<sup>4,7-13</sup>

The pathogenesis of venous thrombosis involves three factors, which are referred to as Virchow's triad. Those factors are damage to the vessel wall, venous stasis, and hypercoagulability. Damage to the vessel wall prevents the endothelium from inhibiting coagulation and initiating local fibrinolysis. Venous stasis due to immobilization or venous obstruction inhibits the clearance and dilution of activated coagulation factors. Finally, congenital or acquired thrombophilia promotes coagulation. Venous thromboembolism is multifactorial and often results from a combination of risk factors (Table 1).<sup>14,15</sup>

Deep-vein thrombosis typically originates in the venous sinuses of the calf muscles<sup>16</sup> but occasionally originates in the proximal veins, usually in response to trauma or surgery.<sup>17</sup> Signs and symptoms result from venous outflow obstruction and from inflammation of the vessel wall and perivascular tissue. Calf-vein thrombi often spontaneously lyse and rarely lead to symptomatic pulmonary embolism.<sup>16,18</sup> Approximately 25 percent of untreated calf thrombi extend into the proximal veins, usually within a week after presentation.<sup>19</sup> The risk of pulmonary embolism (either symptomatic or asymptomatic) with

Table 1. Risk Factors for Venous Thromboembolism.*	
Risk Factor	Estimated Relative Risk
<b>Inherited conditions†</b>	
Antithrombin deficiency	25
Protein C deficiency	10
Protein S deficiency	10
Factor V Leiden mutation	
Heterozygous	5
Homozygous	50
G20210A prothrombin-gene mutation (heterozygous)	2.5
Dysfibrinogenemia	18
<b>Acquired conditions</b>	
Major surgery or major trauma	5–200‡
History of venous thromboembolism	50
Antiphospholipid antibodies	
Elevated anticardiolipin antibody level	2
Nonspecific inhibitor (e.g., lupus anticoagulant)	10
Cancer	5
Major medical illness with hospitalization	5
Age	
>50 years	5
>70 years	10
Pregnancy	7
Estrogen therapy	
Oral contraceptives	5
Hormone-replacement therapy	2
Selective estrogen-receptor modulators	
Tamoxifen	5
Raloxifene	3
Obesity	1–3
<b>Hereditary, environmental, or idiopathic conditions</b>	
Hyperhomocysteinemia§	3
Elevated levels of factor VIII (>90th percentile)	3
Elevated levels of factor IX (>90th percentile)	2.3
Elevated levels of factor XI (>90th percentile)	2.2

\* Data are from Rosendaal<sup>14</sup> and Kearon.<sup>15</sup> Relative risks are for patients with the specified risk factor, as compared with those without the risk factor.

† The definition of deficiency of antithrombin, protein C, or protein S varies among studies; it is usually defined as a functional or immunologic value that is less than the 5th percentile of values in the control population.

‡ The risk varies greatly, depending on the type of surgery, the use and type of prophylaxis, and the method of diagnosis.

§ The definition of hyperhomocysteinemia varies among studies; it is usually defined as a persistent elevation of fasting plasma homocysteine levels or plasma homocysteine levels after methionine loading that are greater than the 95th percentile of the control population or more than 2 SD above the mean for the control population.

Table 2. Contraindications to Anticoagulant Therapy.\*

**Absolute contraindications**

Active bleeding

Severe bleeding diathesis or platelet count  $\leq 20,000/\text{mm}^3$ 

Neurosurgery, ocular surgery, or intracranial bleeding within the past 10 days

**Relative contraindications**

Mild-to-moderate bleeding diathesis or thrombocytopenia†

Brain metastases

Recent major trauma

Major abdominal surgery within the past 7 days

Gastrointestinal or genitourinary bleeding within the past 14 days

Endocarditis

Severe hypertension (i.e., systolic blood pressure  $>200$  mm Hg, diastolic blood pressure  $>120$  mm Hg, or both) at presentation\* Data are from Abrams et al.<sup>25</sup>

† Mild-to-moderate thrombocytopenia is defined as a platelet count that is less than normal but greater than 20,000 per cubic millimeter.

proximal-vein thrombosis is approximately 50 percent,<sup>20</sup> and most fatal emboli probably arise from proximal thrombi.<sup>21</sup> Rarely, thrombosis is massive, causing vascular compromise of the leg (i.e., phlegmasia cerulea dolens).

## STRATEGIES AND EVIDENCE

### Diagnosis

Because clinical diagnosis is unreliable, accurate diagnostic tests are required when deep-vein thrombosis is suspected. The failure of a proximal deep vein to flatten when compressed with an ultrasound probe or the finding of a persistent intraluminal filling defect in any deep vein on venography provides a definitive diagnosis.<sup>22</sup> Venography is often not used clinically because of its invasive nature, its technical demands, its costs, and its potential risks, such as allergic reactions and renal dysfunction. Therefore, compression ultrasonography is the diagnostic test of choice when deep-vein thrombosis is suspected. The sensitivity and specificity of compression ultrasonography for proximal deep-vein thrombosis are more than 95 percent.<sup>23</sup> However, for isolated deep-vein thrombosis in the calf, the sensitivity of ultrasonography is lower (approximately 70 percent), and its positive predictive value is only 80 percent.<sup>23</sup> Therefore, imaging of the calf veins



is not routinely performed. Consequently, follow-up ultrasonography one week after a normal test result has been obtained is recommended to detect the possible extension of a deep-vein thrombosis from the calf into the proximal veins; if the test is negative at this time, subsequent extension is unlikely. Venography may be useful to confirm the diagnosis when ultrasonography suggests isolated distal thrombosis<sup>23</sup> and when patients are unable to return for serial ultrasonography or have highly suggestive clinical signs or symptoms but negative results on ultrasonography.

### Initial Therapy

Once deep-vein thrombosis is diagnosed, the goals of treatment are relief of symptoms and prevention of embolization and recurrence. The cornerstone of initial therapy is either unfractionated or low-molecular-weight heparin, followed by an oral anticoagulant drug.<sup>3,19,22,24</sup> Table 2 lists the contraindications to anticoagulant therapy.<sup>25</sup>

Table 1. Options for the Initial Treatment of Deep-Vein Thrombosis with Anticoagulant Agents.

Drug	Method of Administration	Dose*	Reported Risks	
			Risk of Heparin-Induced Thrombocytopenia†	Risk of Major Bleeding‡
			no./total no. (%)	
Unfractionated heparin	Intravenous	Leading dose, 5000 U, or 80 U/kg of body weight with infusion adjusted to maintain activated partial thromboplastin time within the therapeutic range§	9/332 (2.7)	15/1853 (1.9)
Low-molecular-weight heparin			0/333 (0)	20/1821 (1.1)
Dalteparin	Subcutaneous	100 U/kg every 12 hr or 200 U/kg daily; maximum, 18,000 U/day		
Enoxaparin	Subcutaneous	1 mg/kg every 12 hr or 1.5 mg/kg daily; maximum, 180 mg/day		
Tinzaparin	Subcutaneous	175 U/kg daily; maximum, 18,000 U/day		
Nadroparin	Subcutaneous	86 U/kg every 12 hr or 171 U/kg daily; maximum, 17,100 U/day		

\* Doses vary in patients who are obese or who have renal dysfunction. Monitoring of anti-factor Xa levels has been suggested for these patients, with dose adjustment to a target range of 0.6 to 1.0 U per milliliter four hours after injection for twice-daily administration or 1.0 to 2.0 U per milliliter for once-daily administration. Even though there are few supporting data, most manufacturers recommend capping the dose for obese patients at that for a 90-kg patient.

† Data are from Warkentin et al.<sup>29</sup> and are based on the incidence in patients who had undergone orthopedic surgery and were receiving prophylactic doses of unfractionated heparin or low-molecular-weight heparin (i.e., enoxaparin).

‡ Data are from Gould et al.<sup>30</sup>

§ The therapeutic range of activated partial-thromboplastin time corresponds to heparin levels of 0.3 to 0.7 U per milliliter, as determined by anti-factor Xa assay. High levels of heparin-binding proteins and factor VIII may result in so-called heparin resistance. In patients requiring more than 40,000 U per day to attain a therapeutic activated partial-thromboplastin time, the dosage can be adjusted on the basis of plasma heparin levels.<sup>31</sup>

**Unfractionated Heparin** Unfractionated heparin is usually given intravenously by continuous infusion after a loading dose has been administered.<sup>26</sup> The anticoagulant response varies among patients, because this drug binds nonspecifically to plasma and cellular proteins. Laboratory monitoring, with assessment of the activated partial-thromboplastin time, is required, with adjustment of the dose to achieve the target therapeutic range. This range depends on which reagent and coagulometer are used to measure the activated partial-thromboplastin time. Although the use of a fixed ratio of 1.5 to 2.5 between the patient's value and the control value is commonly suggested, this strategy results in variable (and usually subtherapeutic) degrees of anticoagulation, because of the differing degrees of responsiveness among the available reagents. Ideally, the therapeutic range of activated partial-thromboplastin times for each reagent should correspond to *ex vivo* plasma levels of activity against activated factor X (anti-factor Xa) of 0.3 to 0.7 U per milliliter.<sup>26</sup> Weight-based heparin nomograms facilitate the achievement of a therapeutic anticoagulant effect.

Hemorrhage occurs in up to 7 percent of patients during initial treatment; the risk is affected by the heparin dose, the patient's age, and concomitant use or nonuse of thrombolytic and antiplatelet agents. Long-term use of heparin (i.e., longer than one month) can cause osteoporosis.<sup>26-28</sup> Heparin-induced thrombocytopenia is immune-mediated and in 30 to 50 percent of cases is associated with venous or arterial thrombosis.<sup>26</sup> Patients with previous heparin-induced thrombocytopenia should receive alternative anticoagulant agents, such as danaparoid, lepirudin, or argatroban.<sup>26</sup>

**Low-Molecular-Weight Heparins** Meta-analyses suggest that low-molecular-weight heparins are as effective as unfractionated heparin in preventing recurrent venous thromboembolism, and they cause less bleeding (Table 3).<sup>30</sup> These heparin products — which show less nonspecific binding, have improved bioavailability, and elicit more predictable dose responses than unfractionated heparin — are administered subcutaneously once or twice daily in weight-adjusted doses,<sup>26</sup> generally without monitoring.

Although heparin-induced thrombocytopenia develops less frequently with low-molecular-weight heparins than it does with unfractionated heparin,<sup>26,29</sup> these agents often cross-react with the antibody that causes heparin-induced thrombocytopenia and are therefore contraindicated in patients with a history of this condition. Low-molecular-weight heparins also cause less osteoporosis than does unfractionated heparin.<sup>27,28</sup> In a randomized study comparing prophylactic regimens during pregnancy and the puerperium, 2 of 23 women who received unfractionated heparin were given a diagnosis of osteoporosis on the basis of postpartum studies of bone mineral density, whereas none of

the 21 women who received low-molecular-weight heparin (dalteparin) had osteoporosis.<sup>27</sup> In another study, symptomatic vertebral fractures occurred in 6 of 40 patients with contraindications to warfarin therapy who received three to six months of unfractionated heparin (10,000 U subcutaneously twice daily), as compared with 1 of 40 patients who received dalteparin (5000 U subcutaneously twice daily) for the same length of time.<sup>28</sup>

Outpatient therapy with low-molecular-weight heparins is safe and effective.<sup>32,33</sup> If there is a system in place for administering the medication (or for teaching patients or caregivers to administer it) and for monitoring, more than 80 percent of patients can be treated without hospitalization.<sup>26</sup> However, outpatient treatment is unsuitable for patients with massive thrombosis, serious coexisting illnesses, or a high risk of hemorrhage (e.g., patients who are very old, have recently undergone surgery, or have a history of bleeding or renal or liver disease). Low-molecular-weight heparins are more expensive than is unfractionated heparin, but they cut costs by reducing the frequency of hospital admissions and the need for laboratory monitoring.<sup>34</sup> Reductions in nursing time also make low-molecular-weight heparins cost effective for inpatients.

**Thrombolytic Therapy** Thrombolytic agents dissolve fresh clots and restore venous patency more rapidly than do anticoagulants.<sup>35</sup> They are given systemically or by regional catheter-directed infusion, which results in a higher local concentration of the drug than does systemic administration. Theoretically, catheter-directed infusion should result in improved efficacy, but this hypothesis remains untested. Both routes of administration cause substantially more bleeding than does heparin,<sup>35</sup> and it is unclear whether either agent reduces the incidence of the post-thrombotic syndrome. Consequently, thrombolytic therapy is generally reserved for patients who have limb-threatening thrombosis, who have had symptoms for less than one week, and who have a low risk of bleeding.<sup>36</sup>

### Long-Term Therapy

Warfarin (or another coumarin) at a dose that is titrated to achieve an international normalized ratio (INR) of 2.0 to 3.0 is used for secondary prophylaxis and, as compared with placebo, reduces the risk of recurrence by 90 percent among patients who have received four weeks to three months of therapy.<sup>36,37</sup> Because the antithrombotic effect of warfarin is delayed for 72 to 96 hours, heparin therapy is overlapped with initiation of warfarin. When therapy with the two drugs is started on the same day, heparin can be discontinued after five days, provided the INR has been at a therapeutic level for two consecutive days. Patients with massive thrombosis often receive an extended course (i.e., 7 to 14 days) of heparin. The use of oral anticoagulant therapy was reviewed recently in the *Journal*.<sup>38</sup>

Patients with cancer who have venous thromboembolism have a substantial risk of a recurrent event when they are treated with warfarin. A randomized study involving such patients showed that after standard initial therapy with low-molecular-weight heparin, patients who were taking the drug on a long-term basis had half as many recurrent events as those who were taking coumarin derivatives.<sup>39</sup> Bleeding rates were similar with both medications, and daily injections were acceptable to the patients. Therefore, this therapy should be considered for all patients with cancer who also have deep-vein thrombosis.

For other patients, the role of long-term therapy with low-molecular-weight heparin is less clear. In a systematic review of randomized, controlled trials in which low-molecular-weight heparin was compared with warfarin for secondary prophylaxis, the rates of recurrent thrombosis and major bleeding were similar with the two regimens.<sup>40</sup> Although low-molecular-weight heparin has advantages over warfarin, its cost, the need for daily injections, and the risk of osteoporosis with long-term therapy make it unsuitable for routine secondary prophylaxis.

Inferior vena cava filters are useful in patients who have a contraindication to anticoagulation or those in whom treatment has failed (Table 2).<sup>36</sup> In a randomized trial of 400 patients with proximal-vein thrombosis who received anticoagulants either alone or with a filter, the incidence of early pulmonary embolism by day 12 was significantly lower among patients treated with filters.<sup>41</sup> However, this difference did not persist; at two years, the reduction in symptomatic pulmonary embolism in the filter-treated patients was not significant, and mortality was similar in the two groups. The approximate doubling of the risk of recurrent deep-vein thrombosis in patients treated with filters suggests that anticoagulant therapy should be started if it is safe to do so. It remains a matter of controversy whether filters can be used to prevent embolization of "free-floating" iliofemoral thrombi to avert pulmonary embolism in patients who have deep-vein thrombosis and a reduced cardiopulmonary reserve and to treat venous thromboembolism in patients with cancer.<sup>36</sup>

### Duration of Anticoagulation

Patients should receive anticoagulant therapy for at least three months. The optimal duration of treatment should be determined so as to balance the risks of recurrence and bleeding. When anticoagulation is adjusted to achieve an INR of 2.0 to 3.0, the annual risk of major bleeding is approximately 3 percent.<sup>42</sup> In patients whose thrombosis is associated with a major transient risk factor, the risk of recurrence after three months of anticoagulation is also approximately 3 percent per year.<sup>36</sup> Case fatality rates of 5 percent for recurrence<sup>43</sup> and 10 percent for major bleeding<sup>42</sup> have been reported. After three months, the risk of a fatal recurrence among patients who are not receiving treatment is lower than the

Table 4. Recommendations for the Duration of Anticoagulant Therapy for Patients with Deep-Vein Thrombosis.\*

Characteristics of Patient†	Risk of Recurrence in the Year after Discontinuation (%)	Duration of Therapy
Major transient risk factor	3	3 mo
Minor risk factor; no thrombophilia	<10 (if risk factor avoided) >10 (if risk factor persistent)	6 mo (or, 3 factors/less)
Idiopathic event; no thrombophilia or low-risk thrombophilia	<10	6 mo‡
Idiopathic event; high-risk thrombophilia	>10	indefinite
More than one idiopathic event	>10	indefinite
Cancer (or other ongoing risk factor)	>10	indefinite

\* Data are from Hirsh and Hoak,<sup>22</sup> Hyers et al.,<sup>36</sup> and Kearon.<sup>44</sup>

† Examples of major transient risk factors are major surgery, a major medical illness, and leg casting. Examples of minor transient risk factors are the use of an oral contraceptive and hormone-replacement therapy. Examples of low-risk thrombophilias are heterozygosity for the factor V Leiden and G20210A prothrombin-gene mutations. Examples of high-risk thrombophilias are antithrombin, protein C, and protein S deficiencies; homozygosity for the factor V Leiden or prothrombin-gene mutation or heterozygosity for both; and the presence of antiphospholipid antibodies.

‡ Therapy may be prolonged if the patient prefers to prolong it or if the risk of bleeding is low.

risk of fatal hemorrhage among patients taking warfarin (i.e., approximately 0.15 percent vs. 0.3 percent per year); therefore, therapy of three months' duration is generally sufficient for patients whose thrombosis is associated with a major transient risk factor.<sup>36</sup>

The optimal duration of therapy for patients who have had idiopathic events or who have continuing risk factors remains controversial.<sup>7-13,36,44</sup> Patients with idiopathic deep-vein thrombosis who are treated for approximately three months have a 10 to 27 percent risk of recurrence during the year after they discontinue anticoagulants.<sup>8-12</sup> With six months of treatment, the risk of recurrence is approximately 10 percent in the year after anticoagulation is stopped<sup>12,13</sup>; patients whose initial events occur in association with a minor transient risk factor probably have a lower risk of recurrence. Extending therapy beyond six months does not substantially reduce the risk of recurrence after discontinuation of treatment.<sup>11</sup> Although continuing treatment prevents recurrences, it also exposes the patient to the risk of anticoagulant-induced bleeding. On the basis of the rates of recurrent venous thromboembolism and major bleeding that are cited above, extended anticoagulant therapy should be considered for patients with idiopathic deep-vein thrombosis whose estimated risk of major bleeding is less than 5 percent per year. However, therapy for six months or less may be more appropriate for patients at higher risk of bleeding or those in whom thrombosis occurred in association with a minor transient risk factor (Table 4).

Table 5. Prevalence of Thrombophilic Abnormalities and the Associated Risk of Recurrent Venous Thromboembolism after the Cessation of Anticoagulant Therapy.<sup>a</sup>

Risk Factor <sup>b</sup>	Estimated Prevalence (%) <sup>c</sup>	Estimated Relative Risk of Recurrence
Antithrombin deficiency	1	1.5-3
Protein C deficiency	3	1.5-3
Protein S deficiency	3	1.5-3
Factor V Leiden mutation		
Heterozygous	20	1-4
Homozygous	2	About 4
G20210A prothrombin gene mutation (heterozygous)	5	1-3
Dysfibrinogenemia	<1	NA
Factor V Leiden and G20210A prothrombin gene mutations	2	2-5
Antiphospholipid antibodies	5	2-4
Elevated factor VIII levels	10-30	1-3
Elevated factor IX levels	10-50	1-5
Hyperhomocysteinemia	10-25	1-3

<sup>a</sup> Data are from Kearon,<sup>44</sup> Christiansen et al.,<sup>50</sup> Baglin et al.,<sup>51</sup> Margaglione et al.,<sup>52</sup> and Kyrle et al.<sup>53</sup> Relative risks are for patients with the risk factor in question, as compared with those without the risk factor.

<sup>b</sup> The definition of deficiency of antithrombin, protein C, or protein S varies; it is usually defined as a functional or immunologic value that is less than the 5th percentile of values in the control population.

<sup>c</sup> Prevalence and relative risk depend on the definitions of hyperhomocysteinemia and elevations in levels of factor VIII and factor IX and on the reference group.

## AREAS OF UNCERTAINTY

### The Role of Reduced-Intensity Anticoagulation

The role of reduced-intensity anticoagulation (that is, anticoagulant therapy targeted to achieve an INR of 1.5 to 1.9) after three months of conventional therapy has been examined in two randomized, controlled trials. One of the studies suggested that, as compared with placebo, low-intensity warfarin is highly effective and safe when used to prevent recurrences.<sup>45</sup> The other study suggested that low-intensity warfarin was less effective and not safer than conventional-intensity warfarin for extended treatment after idiopathic venous thromboembolism.<sup>46</sup> In both studies, the small number of major bleeding events probably precludes an accurate assessment of the true risk of major hemorrhage with either regimen.

### New Anticoagulants

The limitations of traditional anticoagulants have prompted the development of new agents. Drugs that are in an advanced stage of development but have not yet received approval from the Food and Drug Administration include parenteral synthetic pentasac-

charide analogues (e.g., fondaparinux and idraparinux) and oral direct thrombin inhibitors (e.g., ximelagatran). In a large randomized trial comparing fondaparinux with enoxaparin for the initial treatment of deep-vein thrombosis, rates of symptomatic, recurrent venous thromboembolism and major bleeding were not statistically different between the two groups.<sup>47</sup> Similar results were obtained in a randomized trial involving 2489 patients with acute deep-vein thrombosis (with or without pulmonary embolism) that compared six months of ximelagatran monotherapy with six months of therapy consisting of enoxaparin followed by warfarin.<sup>48</sup>

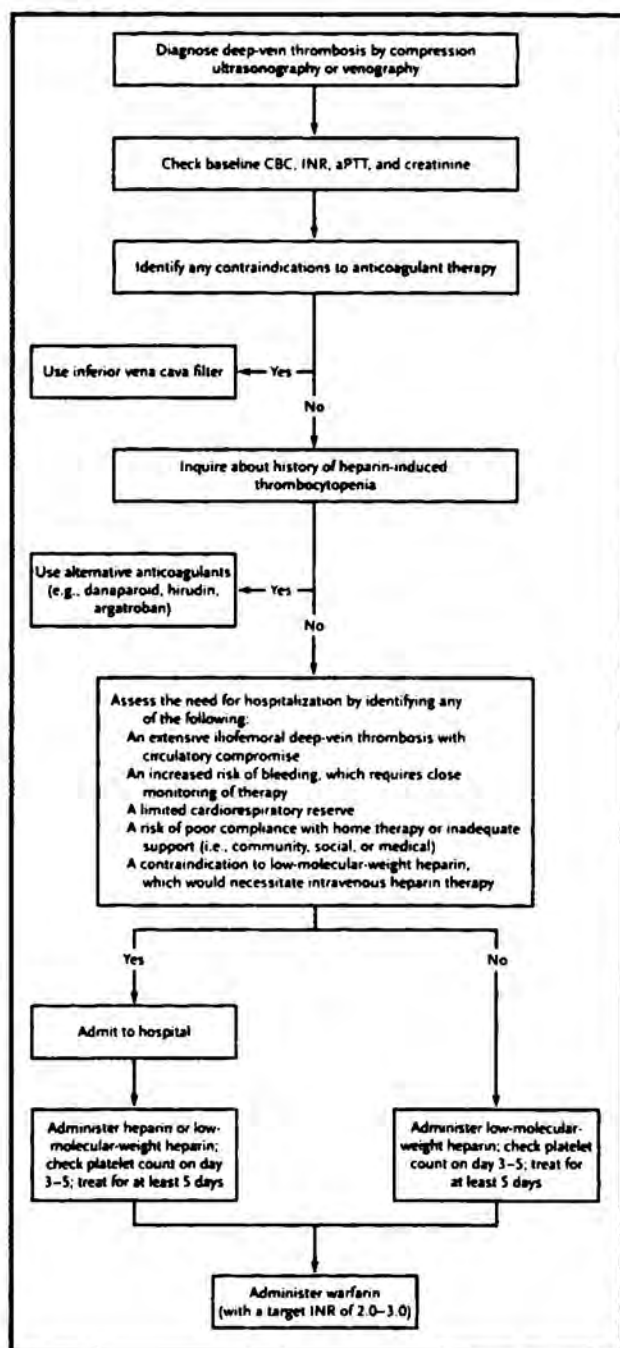
A placebo-controlled trial showed that ximelagatran reduced the risk of recurrent venous thromboembolism without increasing the risk of major hemorrhage in patients who had already completed six months of standard treatment.<sup>49</sup> In contrast to warfarin, ximelagatran does not require monitoring of the degree of anticoagulation. However, ximelagatran has potential limitations, including the occurrence of elevations in liver enzyme levels (specifically, alanine aminotransferase) in 5 to 10 percent of patients receiving long-term therapy. To date, such elevations are not usually associated with symptoms and are reversible, even if the medication is continued. Further studies are required to define the appropriate role of these new agents.

### Testing for Thrombophilia

At least one third of patients with idiopathic venous thromboembolism have an identifiable thrombophilia on laboratory testing.<sup>15,44</sup> Although testing for hypercoagulable states is costly, the procedure is routine in many centers for patients who have had a single episode of thrombosis. However, there is no clear evidence that modifying treatment because a hypercoagulable state has been found improves outcome or that more intensive therapy is required in patients with laboratory evidence of thrombophilia. Although it is assumed that the presence of a thrombophilic abnormality increases the risk of recurrence and, consequently, justifies prolonged therapy, the available data are inconsistent, and these assumptions remain unproved (Table 5).<sup>15,44,50-52</sup> The effectiveness of testing asymptomatic relatives and its potential consequences — including anxiety, avoidance of effective hormonal contraception, unnecessary exposure to anticoagulants in patients with a positive test, and possibly false reassurance from a negative test — have not been formally assessed. Thus, there are no unequivocal indications for testing for the presence of thrombophilic abnormalities in either patients or their relatives.

**Figure 1. Management of Uncomplicated Deep-Vein Thrombosis.**

For patients with limb-threatening iliofemoral thrombosis, symptoms for less than one week, and a low risk of bleeding, thrombolysis should be considered. Absolute contraindications to thrombolysis include suspected aortic dissection, acute pericarditis, active bleeding, cerebral neoplasm, intracranial vascular lesion, and previous central nervous system hemorrhage. The following are relative contraindications to thrombolysis: head trauma, major surgery, organ biopsy, major trauma, prolonged cardiopulmonary resuscitation with resultant chest trauma, or puncture of a noncompressible vessel within the past two to four weeks; severe hypertension at presentation (i.e., systolic blood pressure above 200 mm Hg, diastolic blood pressure above 120 mm Hg, or both); nonhemorrhagic stroke within the past six months; endocarditis; pregnancy; cancer; bleeding diathesis; and hepatic dysfunction.<sup>25</sup> For patients with cancer, long-term therapy with low-molecular-weight heparin should be considered. CBC denotes complete blood count, INR international normalized ratio, and aPTT activated partial-thromboplastin time.





### Prevention of the Post-Thrombotic Syndrome

In an unblinded, randomized trial, daytime use of knee-length, graduated compression stockings for at least two years starting two to three weeks after the diagnosis of proximal deep-vein thrombosis reduced the frequency of the post-thrombotic syndrome by 50 percent.<sup>5</sup> However, in a placebo-controlled trial in which the definition of the post-thrombotic syndrome focused on the quality of life (i.e., the presence of chronic pain and swelling six months or more after deep-vein thrombosis), compression stockings worn "as much as possible" during waking hours did not prevent the condition.<sup>6</sup> Although the role of compression stockings in preventing the post-thrombotic syndrome remains uncertain, they are widely used to control symptoms in patients with established disease. Thrombolytic therapy has the potential to prevent the post-thrombotic syndrome by preventing damage to venous valves and subsequent venous hypertension, but outcome data supporting such an effect are lacking.

### GUIDELINES

Guidelines for the treatment of deep-vein thrombosis have been published by the American College of Chest Physicians<sup>36</sup> and the American Heart Association<sup>22</sup> and are consistent with the approach outlined in this article.

### RECOMMENDATIONS

For most patients with deep-vein thrombosis, such as the patient described in the vignette, low-molecular-weight heparin administered on an outpatient basis is appropriate as initial therapy. If patients or family members cannot administer injections, home care should be arranged. Hospital admission is still warranted for some patients (Figure 1). Thrombolytic therapy should be considered for patients less than 60 years of age who have limb-threatening circulatory compromise. Inferior vena cava filters should be inserted in patients with contraindications to anticoagulation (Table 2) and in those who require urgent surgery that precludes anticoagulation. Temporary filters should be used if anticoagulation is likely to be safe within 14 days after the bleeding event.

Oral anticoagulation should generally be started on the first day of treatment. Heparin should be given for a minimum of five days and not stopped until the patient's INR has been 2.0 or higher for two consecutive days. A platelet count should be obtained three to five days after initiating heparin administration. The INR should be measured after three to four days of warfarin treatment and the dose adjusted to maintain a target INR of 2.5. Twice-weekly monitoring of the INR is usually required for the first one to two weeks,

followed by weekly monitoring until the INR is stable. Thereafter, the INR can be measured every two to four weeks, or more frequently if there are changes in medications or health status. Patients with cancer should receive long-term maintenance therapy with low-molecular-weight heparin, if that is practical.

Although the indications for testing for thrombophilia remain controversial, we test for the presence of thrombophilic states — the factor V Leiden mutation, the G20210A prothrombin-gene mutation, hyperhomocysteinemia, antiphospholipid antibodies, and deficiencies of antithrombin, protein C, and protein S — if patients have clinical features suggestive of these abnormalities. These features include a family history of venous thromboembolism, venous thromboembolism before the age of 45 years, recurrent venous thromboembolism, thrombosis in an unusual site (e.g., in mesenteric, renal, hepatic, or cerebral veins), idiopathic venous thromboembolism or thromboembolism after minimal provocation, heparin resistance (in the case of antithrombin deficiency), warfarin-induced skin necrosis (in the case of protein C or protein S deficiency), and neonatal purpura fulminans (in the case of homozygous protein C or protein S deficiency). We also offer the test if identifying a thrombophilic mutation will alter the care of patients or their relatives or if a patient requests it. Testing for dysfibrinogenemia is often not undertaken, given its low yield. We do not routinely test for elevated levels of factor VIII or IX, given the concern about the variability of this assay, the variation in factor levels among patients, and the most appropriate cutoff values.

We treat patients with a major transient risk factor for three months and those with a first episode of idiopathic thrombosis for at least six months. We recommend indefinite therapy for patients with a high-risk thrombophilia (e.g., a deficiency of antithrombin, protein C, or protein S; persistent antiphospholipid antibodies; or homozygosity for factor V Leiden or the prothrombin-gene mutation or heterozygosity for both), a continuing risk factor (e.g., advanced cancer), or recurrent episodes of idiopathic venous thrombosis, provided the risk of bleeding is not high. Although it has recently been suggested that the risk of recurrent venous thromboembolism is significantly higher in men than it is in women,<sup>53</sup> more data are required before these findings can be incorporated into routine recommendations regarding the duration of treatment.

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## ADDENDUM

Since publication of this article in July 2004, fondaparinux has been approved by the Food and Drug Administration for the initial treatment of venous thromboembolism. However, citing concerns about hepatic toxicity, both the Food and Drug Administration and the French Regulatory Authority (acting as the Reference Member State for the European Mutual Recognition Procedure) have declined to approve ximelagatran for the treatment of venous thrombosis.

A randomized trial evaluating the efficacy of early application of below-knee elastic stockings after the diagnosis of venous thrombosis was published shortly after our paper.<sup>1</sup> The authors concluded that compression stockings reduce the risk of post-thrombotic syndrome by 50 percent. However, given the unblinded design of the study and the lack of specificity and subjective nature of the scale used to diagnose post-thrombotic syndrome, the role of routine stocking therapy remains controversial.

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## Bell's Palsy

DONALD H. GILDEN, M.D.

A healthy 50-year-old man notices that his face is drooping on the right side. On examination, facial asymmetry is evident, and some saliva has accumulated on the right side of the patient's mouth. When the patient attempts to close his eyes, his right eye does not close, although it rolls upward, and he is unable to show his teeth or inflate his cheek on the right. How should the patient be evaluated? Does he need immediate treatment?

### THE CLINICAL PROBLEM

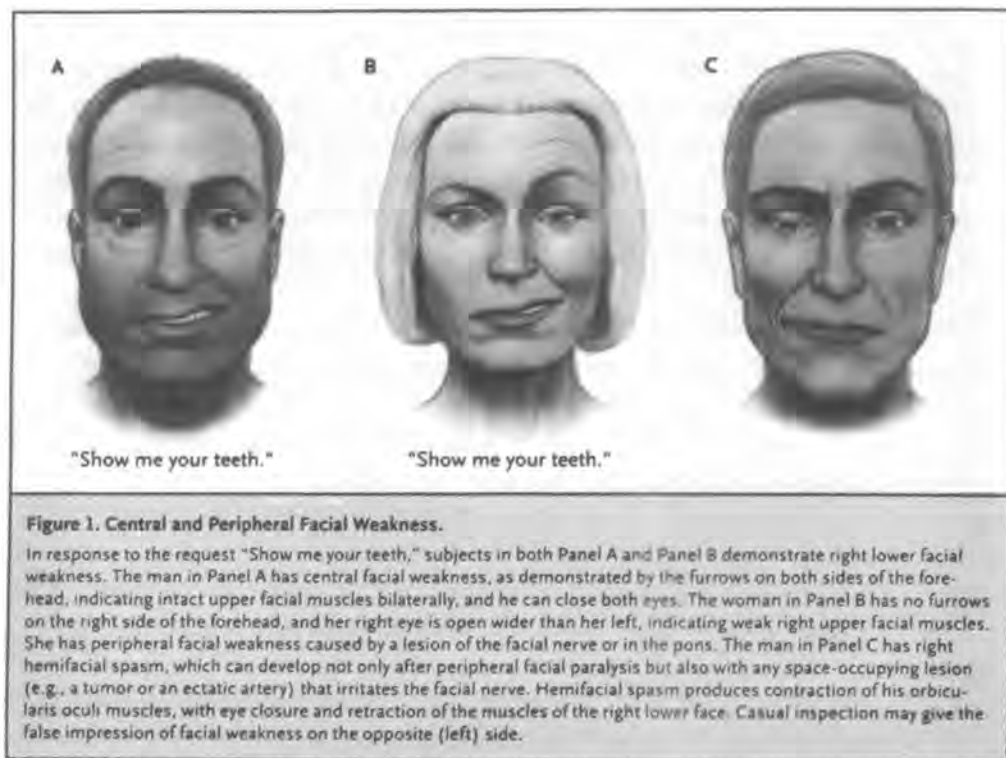
The most common causes of the abrupt onset of unilateral facial weakness are stroke and Bell's palsy. The patient's history and neurologic examination will determine whether facial weakness is central or peripheral. If weakness is central, brain magnetic resonance imaging (MRI) is required to evaluate the patient for ischemia and for infectious and inflammatory diseases. Other tests — such as examination of the cerebrospinal fluid, sedimentation rate, and glucose level; a blood count; and serologic studies to identify syphilis, the human immunodeficiency virus (HIV), and vasculitis — may be necessary.

If facial weakness is peripheral, no apparent cause will be found in most instances (in the case of Bell's palsy), and no tests are immediately indicated. The incidence of Bell's palsy is 20 to 30 cases per 100,000 people per year<sup>1</sup>; it accounts for 60 to 75 percent of all cases of unilateral facial paralysis.<sup>2</sup> The sexes are affected equally. The median age at onset is 40 years, but the disease may occur at any age.<sup>3</sup> The incidence is lowest in children under 10 years old, increases from the ages of 10 to 29, remains stable at the ages of 30 to 69, and is highest in people over the age of 70. The left and right sides of the face are involved with equal frequency. Most patients recover completely, although some have permanent disfiguring facial weakness.<sup>4</sup> Poor prognostic factors include older age,<sup>1</sup> hypertension,<sup>5</sup> impairment of taste,<sup>6</sup> pain other than in the ear, and complete facial weakness.<sup>7</sup> In the first three days, electrical studies reveal no changes in involved facial muscles, whereas a steady decline in electrical activity is often noted on days 4 to 10. When excitability is

retained, 90 percent of patients recover completely; in the absence of excitability, only 21 percent of patients recover completely.<sup>8,9</sup>

Other causes of acquired peripheral facial weakness are much less common. Associated conditions include diabetes mellitus, hypertension, HIV infection, Lyme disease, the Ramsay Hunt syndrome (facial palsy with zoster oticus caused by varicella-zoster virus), sarcoidosis, Sjögren's syndrome, parotid-nerve tumors, eclampsia, and amyloidosis. Peripheral-facial-nerve palsy has also been reported among recipients of inactivated intranasal influenza vaccine.<sup>10</sup>

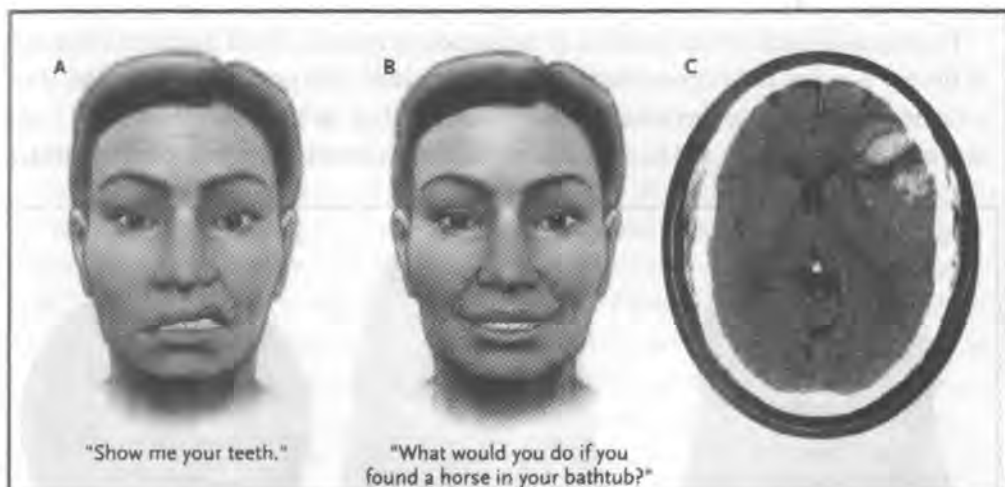
Bell's palsy rarely recurs. Recurrent or bilateral facial palsy should prompt consideration of myasthenia gravis or lesions at the base of the brain, where the facial nerve exits the pons: such types of palsy occur in lymphoma, sarcoidosis, and Lyme disease.<sup>11</sup> In rare cases, patients with inflammatory demyelinating polyneuropathy (the Guillain-Barré syndrome) present with bilateral facial palsy but relatively little weakness of the extremities. In immunocompetent people, the Ramsay Hunt syndrome is neither recurrent nor bilateral.



## STRATEGIES AND EVIDENCE

## Diagnosis

The first step in diagnosis is to determine whether facial weakness is due to a problem in the central nervous system or one in the peripheral nervous system. This is done rapidly with observation and a few questions (Figure 1, Figure 2, Figure 3, and Table 1). Central weakness of the unilateral lower facial area (Figure 1A), which is always due to a lesion above the level of the facial nucleus in the pons of the contralateral hemisphere, is explained by the fact that cells of the facial nucleus that innervate the lower face receive corticobulbar fibers primarily from the contralateral cerebral hemisphere. In contrast, cells of the facial nucleus that innervate the upper face receive corticobulbar fibers originating from both cerebral hemispheres. Thus, a unilateral lesion in the cortex or underlying corticobulbar



**Figure 2. Voluntary Central Facial Weakness That Is Greater Than Mimetic (Involuntary) Central Facial Weakness.**

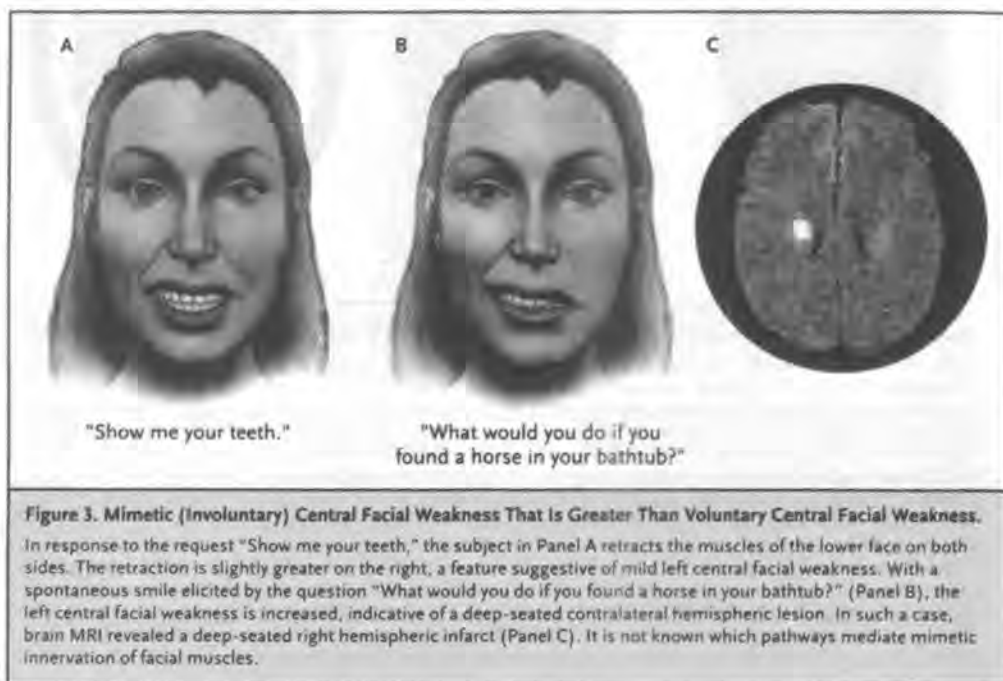
Central facial weakness can be voluntary, mimetic (involuntary), or both. If it is both, it is due to an extensive contralateral hemispheric lesion. When facial weakness is either mostly voluntary or mostly mimetic, the brain site involved can be determined on the basis of the patient's response to a simple request such as "Show me your teeth" (which requires a voluntary response) or a question such as "What would you do if you found a horse in your bathtub?" (which usually elicits a spontaneous smile — i.e., a mimetic response). The examiner should not ask the patient to smile, since that usually elicits a voluntary response. Weakness that is greater during a voluntary contraction than after an involuntary response (i.e., spontaneous laughter) indicates either cortical involvement of the contralateral lower third of the precentral gyrus or subcortical involvement of motor fibers that project from the cortex to the facial nucleus. In response to the request "Show me your teeth," the subject in Panel A shows right lower (central) facial weakness. With a spontaneous smile elicited by the question "What would you do if you found a horse in your bathtub?" (Panel B), no facial weakness is evident; even in the presence of a voluntary central facial palsy, muscles of the lower face contract symmetrically after an involuntary emotional response. In such a case, axial computed tomography of the brain revealed a left hemispheric infarct involving cortical and subcortical structures (Panel C). Because voluntary central facial weakness is greater than mimetic central facial weakness, the cerebral cortex is functionally more damaged than are subcortical structures.



fibers usually produces contralateral voluntary central-type facial paralysis and a contralateral hemiplegia but does not affect salivary and lacrimal secretions or the sense of taste (Table 2).

Peripheral facial palsy, or a weakness or paralysis of all muscles of facial expression (Figure 1B), is usually due to a lesion of the ipsilateral facial nerve but can also be produced by a lesion of the ipsilateral facial nucleus or facial nerve in the pons. Although it appears paradoxical that a "central" lesion in the pons produces peripheral facial weakness, the nomenclature is not likely to change. Facial weakness is best demonstrated by the patient's response to the requests "Close your eyes" (for testing the upper facial area) and "Show me your teeth" (for testing the lower facial area). Denervation of the orbicularis oculi muscles will result in the inability of the patient to close the eyelids effectively and denervation of the risorius muscle will result in limited retraction of the angle of the mouth (Figure 1B).

Hyperacusis results from paralysis of the stapedius muscle, which dampens vibrations of the ear ossicles and causes sounds to be abnormally loud on the affected side; there is no hearing loss. Also, because the nervus intermedius carries parasympathetic fibers that stimulate salivation and lacrimation, patients with lesions proximal to the geniculate



**Table 1. Diagnosis of Peripheral or Central Facial Weakness and Site of Injury.**

Characteristic	Peripheral*	Central†	
		Voluntary	Mimetic
Weakness in the upper facial area	Yes	No	No
Weakness in the lower facial area	Yes	Yes‡	Yes§
Site of injury¶	Peripheral nerve, pons	Contralateral hemisphere	

\* The lesion is ipsilateral to the facial weakness.

† The lesion is contralateral to the weakness in the lower facial area.

‡ The weakness in the lower facial area is greater when the patient responds to the request "Show me your teeth" than when the patient smiles spontaneously.

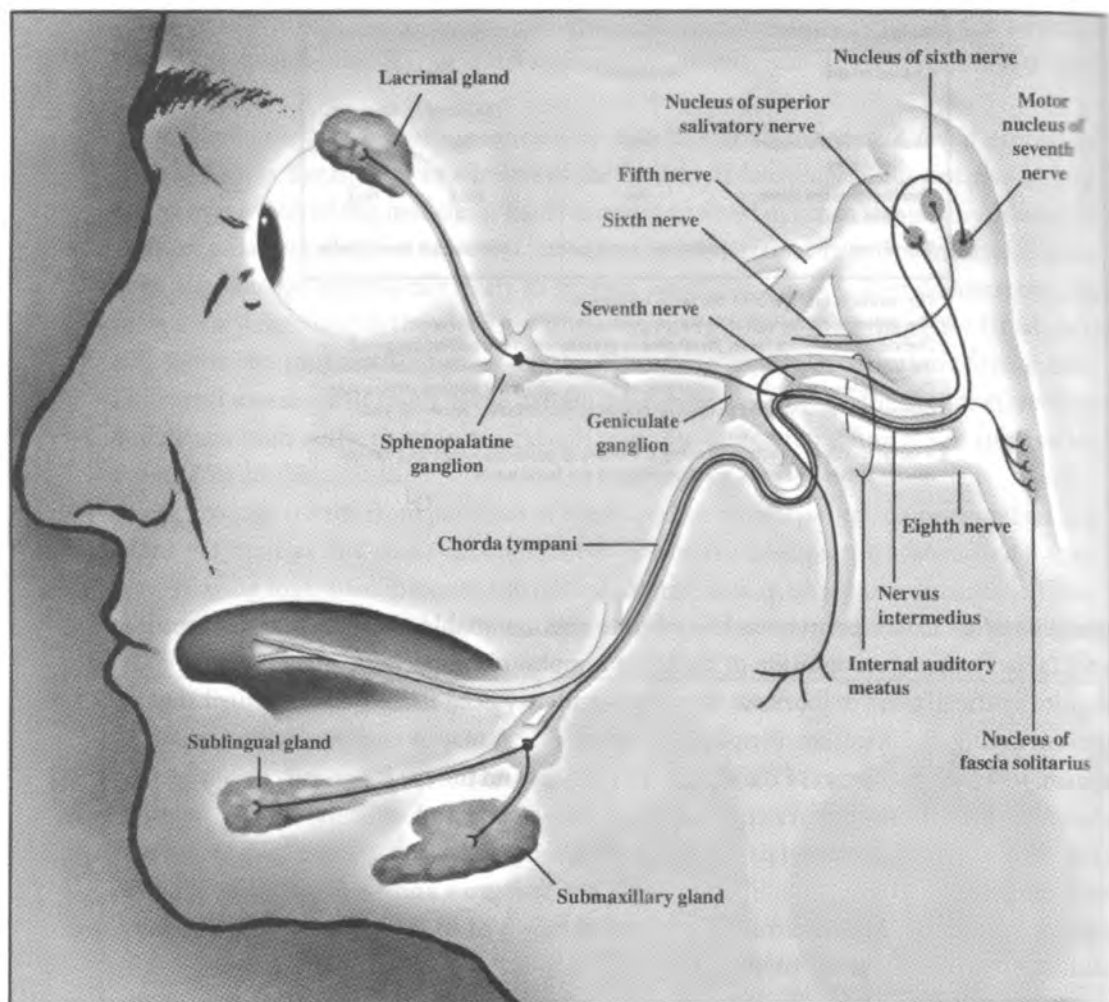
§ The weakness in the lower facial area is greater when the patient smiles spontaneously than when the patient responds to the request "Show me your teeth."

¶ A facial twitch or spasm preceding the onset of paralysis suggests a tumor, usually outside the pons, that has irritated the facial nerve.

ganglion often have a permanent loss of taste and are unable to produce tears (Figure 4 and Table 2). Rapid recognition of the latter symptom is important, since these patients require artificial tears to lubricate the cornea and may need to have the eye taped shut to prevent drying and infection. Peripheral facial weakness may be confused with hemifacial spasm, in which the corner of the mouth is drawn up and the eye is partially or completely closed because of involuntary contraction of the risorius and orbicularis oculi muscles (Figure 1C). After acute facial paralysis, preganglionic parasympathetic fibers that previously projected to the submandibular ganglion may regrow and enter the major superficial petrosal nerve. Such aberrant regeneration may lead to lacrimation after a salivary stimulus (the syndrome of crocodile tears).

### Brain MRI

Brain MRI is not routinely indicated, but if it is performed, the most common abnormality seen is contrast enhancement of the distal intracanalicular and labyrinthine segments of the facial nerve; the geniculate ganglion, as well as the proximal and distal tympanic and mastoid portions of the facial nerve, may also be involved (Figure 5A).<sup>12</sup> A central pontine lesion (e.g., an infarct, as shown in Figure 5B) may also produce facial weakness and is often associated with additional neurologic symptoms and signs.



**Figure 4. Functional Anatomy of the Facial Nerve and Diagnosis of Peripheral Facial Weakness.**

Although the facial nerve has a long, circuitous path, the site of involvement can be deduced from the patient's clinical deficit. The facial, or seventh cranial, nerve is predominantly motor in function. Its nucleus is in the caudal pons. The facial nerve courses dorso-medially and encircles the nucleus of the abducens (sixth) cranial nerve. After bending around the abducens nucleus, the facial nerve lies close to the sixth nerve. The facial nerve exits the pons in the cerebellopontine angle close to the fifth, sixth, and eighth cranial nerves. The eighth nerve, the motor root of the seventh nerve, and the nervus intermedius (the sensory and parasympathetic root of the facial nerve) enter the internal auditory meatus. Sensory cells located in the geniculate ganglion continue distally as the chorda tympani nerve, which carries taste fibers. Peripheral fibers of the nervus intermedius portion of the facial nerve initiate salivary, lacrimal, and mucous secretion.

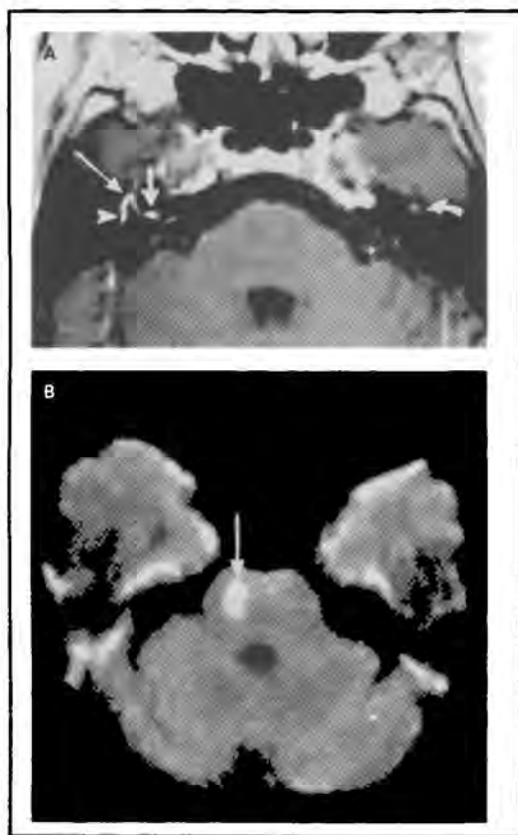
### Electrodiagnostic Studies

Incomplete return of facial motor function and synkinesis (involuntary movement of facial muscles accompanying voluntary facial movement) are long-term sequelae in some patients. These sequelae are predicted by a lack of early clinical improvement in complete facial paralysis and by results of electroneurography; such testing may be clinically useful in patients with complete paralysis. Electroneurography uses a maximal electrically evoked stimulus and recording technique to measure the amplitude of the compound action potential of the facial muscle<sup>13</sup>; the extent of nerve degeneration can be determined by comparing the paralyzed side of the face with the normal side. After facial-nerve compression or complete transection by trauma, axonal degeneration is not evident for a few days. Thus, electrical testing should not be performed until three days after the onset of complete paralysis.

Among patients who do not have 90 percent degeneration within the first three weeks, 80 to 100 percent regain excellent function, with a grade of either 1 (normal strength) or 2 (minimal facial weakness) on the House–Brackmann scale. Among patients who have 90 percent or more degeneration within the first three weeks, only 50 percent have a good recovery of facial function.<sup>14</sup> The rate of degeneration also predicts prognosis; for example, patients with 90 percent degeneration on day 5 have a worse prognosis than

**Table 1. Clinical and Anatomic Features of Facial-Nerve Damage.**

Site of Damage	Facial-Nerve Signs	Common Associated Features	Common Causes
Cortex, subcortical region	Contralateral central facial weakness; lacrimation, salivation, and taste intact	Contralateral hemiparesis and spasticity	Cortical or subcortical infarct
Pons	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste intact	Contralateral hemiparesis, sensory loss, ataxia, nystagmus, ipsilateral abducens palsy, ophthalmoparesis	Pontine infarction, glioma, multiple sclerosis
Cerebellopontine angle	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste usually intact	Tinnitus, facial numbness, ataxia, nystagmus	Acoustic or facial neuroma, meningioma, cholesteatoma, lymphoma, aneurysm, sarcoidosis
Facial nerve in internal auditory canal proximal to or involving geniculate ganglion	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste likely to be involved	Tinnitus, nystagmus, hearing loss	Bell's palsy, the Ramsay Hunt syndrome, acoustic or facial neuroma
Facial nerve distal to internal auditory canal and geniculate ganglion	Ipsilateral peripheral facial weakness; lacrimation intact but salivation and taste impaired	Tinnitus, nystagmus, hearing loss	Bell's palsy, temporal-bone fracture, cholesteatoma or glomus tumor, middle-ear infection
Facial nerve in stylomastoid foramen	Ipsilateral peripheral facial weakness; lacrimation, salivation, and taste intact	Head injury, parotid mass	Head injury, parotid tumor



**Figure 5. Brain MRIs Contrasting Bell's Palsy with a Central Pontine Infarct.**

A T<sub>1</sub>-weighted gadolinium-enhanced axial image (Panel A) shows the temporal bones at the level of the facial nerve in a patient with Bell's palsy on the right side. There is enhancement in the geniculate ganglion (long arrow) as well as in the intracanalicular segment (short arrow) and the tympanic segment (arrowhead) of the facial nerve on the right. There is minimal physiologic enhancement of the left geniculate ganglion (curved arrow). Panel B shows a central pontine infarct (arrow) that produced not only ipsilateral peripheral facial weakness and ataxia, but also ophthalmoparesis and contralateral hemisensory loss. (Image showing Bell's palsy courtesy of Dr. Enrique Palacios, Department of Radiology, Louisiana State University Health Science Center, New Orleans.)

those with 90 percent degeneration on day 14. Electroneurography is most useful when performed within two weeks after a complete loss of voluntary facial function.

#### Medical Treatment

Any evaluation must consider that 71 percent of untreated patients recover completely and 84 percent achieve near-normal function.<sup>5</sup> Thus, the 20 to 30 percent who do not recover fully remain the focus of treatment. Various findings provide a rationale for early and aggressive treatment. First, for more than half a century, surgeons who perform decompression operations on patients with Bell's palsy have described facial-nerve swelling,<sup>15</sup> a finding confirmed by MRI. Second, the detection of herpes simplex virus (HSV) in endoneurial fluid in patients with Bell's palsy<sup>16</sup> has implicated the virus in the pathogenesis of the disease.

Numerous studies of patients with Bell's palsy have compared treatment with glucocorticoids with treatment with acyclovir or placebo; studies comparing antiviral treatment with no treatment have not been performed. One large observational study compared 194 patients treated with prednisone for 12 days (40 mg for 4 days tapered to 8 mg daily by day 12) with 110 untreated patients in a historical control group; complete facial paralysis was observed at follow-up in no patient in the treated group as compared with 10 percent of patients in the untreated group.<sup>17</sup> A later randomized, double-blind, placebo-controlled trial demonstrated a higher rate of recovery of facial function (as assessed by the House–Brackmann grading system) among 35 patients treated with prednisone (30 mg twice daily for five days tapered to 5 mg daily by day 10), as compared with 41 patients given placebo; all the patients in the study were treated within five days after the onset of paralysis.<sup>18</sup> In diabetic patients with complete Bell's palsy who were treated with prednisolone (200 mg for two days tapered to 70 mg by day 7), the rate of cure (i.e., a return to normal facial function) was 97 percent, as compared with 58 percent in untreated patients ( $P < 0.01$ ).<sup>19</sup>

Meta-analyses have also been performed comparing glucocorticoids with placebo. One such analysis, which combined findings from four published studies (one of which was neither blinded nor placebo-controlled), showed significant improvement of facial weakness with glucocorticoid therapy.<sup>20</sup> A second meta-analysis (including only randomized, controlled trials) showed that treatment with glucocorticoids that was started within seven days after the onset of complete facial paralysis increased the likelihood of complete facial recovery by 17 percent ( $P = 0.005$ ), as compared with placebo.<sup>21</sup>

However, not all studies have shown a benefit to glucocorticoid therapy. In one controlled, double-blind trial, rates of recovery were not significantly different between the prednisone and placebo groups after six months<sup>22</sup>; this finding was considered to be potentially attributable to a small sample as well as to a high percentage of patients with initially severe weakness. Another study of 239 patients with Bell's palsy who were randomly assigned to receive either prednisone or placebo showed complete recovery of facial strength in 88 percent of glucocorticoid-treated patients and in 80 percent of the patients in the control group, a difference that was not statistically significant,<sup>23</sup> which is perhaps explained by the fact that patients were followed until complete recovery or for one year.

One randomized trial with no placebo group included 101 patients and compared oral prednisone (1 mg per kilogram of body weight for 10 days tapered to 0 by day 16) with acyclovir (800 mg three times daily for 10 days); the administration of both study drugs was initiated within 4 days after the onset of facial weakness. This study indicated that at three months or later, facial-muscle strength was better after treatment with prednisone than

it was after treatment with acyclovir.<sup>24</sup> In another randomized, double-blind trial that included 99 patients, a combination of prednisone and acyclovir (the latter at a dose of 400 mg five times daily) was superior to a combination of prednisone and placebo in restoring the function of voluntary facial muscles ( $P=0.02$ ) and in preventing partial nerve degeneration ( $P=0.05$ ).<sup>25</sup> Overall, the data suggest that glucocorticoids decrease the incidence of permanent facial paralysis, although more studies are required to determine whether antiviral therapy confers additional benefit.

### Surgical Decompression

Some patients with Bell's palsy may be candidates for surgery. The facial nerve may be compressed (and its conduction blocked) at its narrowest point, the entrance to the meatal foramen, occupied by the labyrinthine segment and geniculate ganglion. Among 12 patients with facial-nerve paralysis who underwent decompression surgery, bulbous swelling of the facial nerve was seen proximal to the geniculate ganglion in 11, and intra-operative evoked-potential electromyography performed in 3 documented conduction block proximal to the geniculate ganglion.<sup>26</sup>

The role of surgical decompression in management remains controversial. In a prospective observational study of 31 patients with complete paralysis and 90 percent or more nerve degeneration as determined by electroneurography, 91 percent of those who underwent decompression had a good outcome (i.e., a grade 1 or 2 on the House–Brackmann scale) by the seventh month, as compared with 42 percent of those who were treated with glucocorticoids.<sup>27</sup> Other observational studies comparing outcomes at 6 to 36 months after prednisone treatment with outcomes after decompression<sup>28–31</sup> have not confirmed a benefit of surgery, however. Data from randomized trials are lacking to compare surgery with medical therapy, and available data are limited by small samples, possible bias in the selection of patients for surgery, the use of varying surgical approaches and systems to assess facial function, and a lack of blinding in studies assessing functional outcomes.

After decompression surgery, permanent unilateral deafness may occur, with estimates ranging from less than 1 percent<sup>27</sup> to 15 percent<sup>29</sup> of patients. Because severe degeneration of the facial nerve is probably irreversible after 2 to 3 weeks,<sup>32</sup> decompression should not be performed 14 days or more after the onset of paralysis.

## AREAS OF UNCERTAINTY

### Cause of Bell's Palsy

Some cases of Bell's palsy have been attributed to ischemia from diabetes and arteriosclerosis, which helps to explain the increased incidence of Bell's palsy in elderly patients; the disorder is analogous to ischemic mononeuropathy of other cranial nerves in patients with diabetes.<sup>33,34</sup> However, HSV type 1 (HSV-1) is probably the cause of most cases of Bell's palsy. Virologic analysis of endoneurial fluid obtained during decompression surgery<sup>16</sup> revealed HSV-1 DNA in 11 of 14 patients with Bell's palsy. HSV-1 DNA appeared to be specific to Bell's palsy, since it was not found in anyone with the Ramsay Hunt syndrome or other neurologic diseases. The rising incidence of Bell's palsy with increasing age parallels seroconversion to HSV-1.<sup>35</sup> Because seropositivity to HSV is well established by adult life, when Bell's palsy is most common, the disease probably reflects virus reactivation from latency in the geniculate ganglion,<sup>36</sup> rather than primary infection. How the virus damages the facial nerve is uncertain.

### Treatment

Large randomized, double-blind trials are needed to better assess the effectiveness of glucocorticoids, antiviral agents, or both as compared with placebo, as well as to assess the benefit of surgical decompression among patients considered to be at high risk for permanent paralysis.<sup>37</sup> In particular, studies are needed to determine the time after which medical treatment or surgery is of no value. Furthermore, additional data are needed to determine whether a combination of antiviral and corticosteroid therapy is better than treatment with corticosteroids alone. Of note is the recent observation that long-term recovery of peripheral vestibular function in patients with vestibular neuritis, a condition also attributed to HSV infection, is significantly improved by treatment with corticosteroids but not with valacyclovir.<sup>38</sup>

## GUIDELINES

The Quality Standards Subcommittee of the American Academy of Neurology states that early treatment with oral corticosteroids is probably effective in improving facial-function outcomes in Bell's palsy, that the addition of acyclovir to prednisone is possibly effective, and that insufficient evidence exists to recommend facial-nerve decompression.<sup>37</sup>



## SUMMARY AND RECOMMENDATIONS

The first step in evaluating patients with acute facial paralysis is to determine whether the paralysis is central or peripheral. If it is peripheral without any apparent cause (and is thus Bell's palsy), and is diagnosed within one week after the onset of symptoms, as in the patient described in the vignette, no tests are indicated unless other cranial-nerve deficits develop (indicating more widespread disease). There is no recovery three to six weeks after the onset of symptoms, or a facial twitch or spasm preceded Bell's palsy (indicating continuous facial-nerve irritation suggestive of a tumor). The collective findings of facial-nerve swelling, MRI changes consistent with inflammation, and available data regarding clinical outcomes support the use of a short course of prednisone within 2 to 14 days after the onset of symptoms. Because Bell's palsy is associated with HSV infection, antiviral treatment may help, although data are lacking to show that such treatment speeds recovery or leads to a better long-term outcome. In the case described in the vignette, I would treat the patient with oral valacyclovir (1 g twice daily for seven days) or famciclovir (750 mg three times daily) and oral prednisone (1 mg per kilogram per day for seven days). Prednisone should be used cautiously in patients with diabetes, peptic ulcer disease, renal or hepatic dysfunction, or severe hypertension. Either valacyclovir or famciclovir is preferable to acyclovir because adherence to treatment is better than with acyclovir, which requires five daily doses of 800 mg. In children, the dose of prednisone and antiviral agents must be adjusted for weight. The same treatment can be given during pregnancy, although the safety of antiviral agents in pregnancy has not been established. There is no need to taper the dose of prednisone after only one week of treatment.

If complete facial paralysis is still present after one week of medical treatment, electroneurography should be performed. If electroneurography documents 90 percent nerve degeneration, decompression may be considered, although there are no data from clinical trials to support its use.<sup>27</sup> If decompression is performed, timing is critical. The destiny of the facial nerve in Bell's palsy is probably decided within the first two to three weeks after the onset of symptoms.<sup>32</sup> Finally, for patients with permanent facial paralysis, various surgical procedures exist for dynamic reconstruction of the facial nerve.<sup>39</sup>

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# The Thyroid Nodule

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**A 42-year-old woman presents with a palpable mass on the left side of her neck. She has no neck pain and no symptoms of thyroid dysfunction. Physical examination reveals a solitary, mobile thyroid nodule, 2 cm by 3 cm, without lymphadenopathy. The patient has no family history of thyroid disease and no history of external irradiation. Which investigations should be performed? Assuming that the nodule is benign, which, if any, treatment should be recommended?**

## THE CLINICAL PROBLEM

**I**n the United States, 4 to 7 percent of the adult population have a palpable thyroid nodule.<sup>1</sup> However, only 1 of 20 clinically identified nodules is malignant. This corresponds to approximately 2 to 4 per 100,000 people per year, constituting only 1 percent of all cancers and 0.5 percent of all cancer deaths.<sup>2</sup> Nodules are more common in women and increase in frequency with age and with decreasing iodine intake. The prevalence is much greater with the inclusion of nodules that are detected by ultrasonography or at autopsy. By the latter assessment, approximately 50 percent of 60-year-old persons have thyroid nodules.<sup>3</sup>

The clinical spectrum ranges from the incidental, asymptomatic, small, solitary nodule, in which the exclusion of cancer is the major concern, to the large, partly intrathoracic nodule that causes pressure symptoms, for which treatment is warranted regardless of cause.<sup>3</sup> The most common diagnoses and their approximate distributions are colloid nodules, cysts, and thyroiditis (in 80 percent of cases); benign follicular neoplasms (in 10 to 15 percent); and thyroid carcinoma (in 5 percent).

The management of a solitary thyroid nodule remains controversial.<sup>3-5</sup> This review will focus on the management of a solitary thyroid nodule that is detected on physical examination, regardless of the finding of additional nodules by radionuclide scanning or ultrasonography, since such a finding does not alter the risk of cancer.<sup>3</sup>

**Table 1. Clinical Findings Suggesting the Diagnosis of Thyroid Carcinoma in a Euthyroid Patient with a Solitary Nodule, According to the Degree of Suspicion.**

**High suspicion**

Family history of medullary thyroid carcinoma or multiple endocrine neoplasia  
Rapid tumor growth, especially during levothyroxine therapy  
A nodule that is very firm or hard  
Fixation of the nodule to adjacent structures  
Paralysis of vocal cords  
Regional lymphadenopathy  
Distant metastases

**Moderate suspicion**

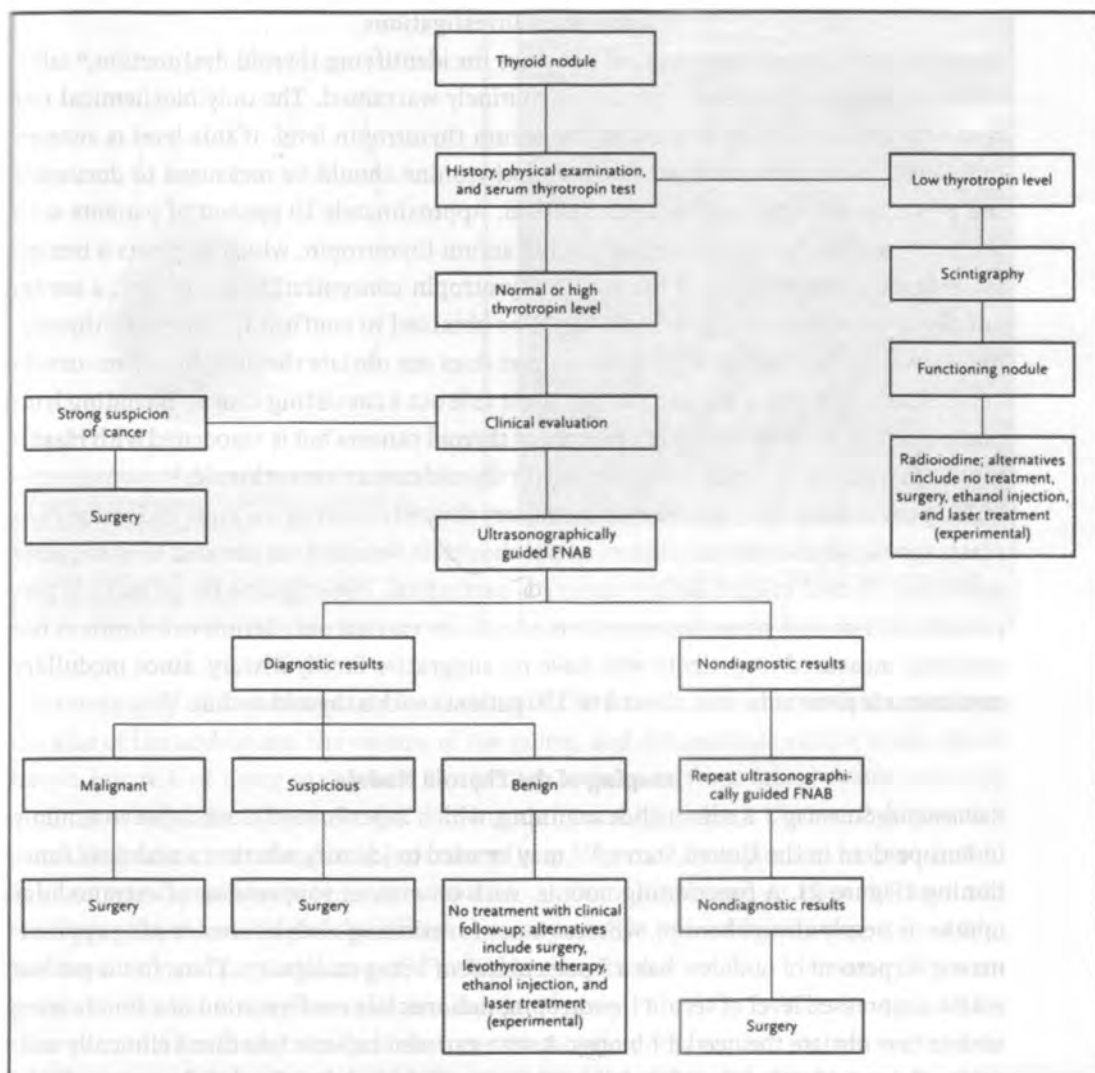
Age of either <20 years or >70 years  
Male sex  
History of head and neck irradiation  
A nodule >4 cm in diameter or partially cystic  
Symptoms of compression, including dysphagia, dysphonia, hoarseness, dyspnea, and cough

## STRATEGIES AND EVIDENCE

### History and Physical Examination

The history and physical examination remain the diagnostic cornerstones in evaluating the patient with a thyroid nodule and may be suggestive of thyroid carcinoma (Table 1). However, a minority of patients with malignant nodules have suggestive findings, which often also occur in patients with benign thyroid disorders. There is also substantial variation among practitioners in evaluating nodules,<sup>2,6</sup> a finding that may explain why an increasing number of thyroid specialists use imaging as part of the evaluation.<sup>4,5</sup>

The risk of thyroid cancer seems nearly as high in incidental nodules (<10 mm), the majority of which escape detection by palpation, as in larger nodules.<sup>7</sup> However, the vast majority of these microcarcinomas do not grow during long-term follow-up and do not cause clinically significant thyroid cancer.<sup>8</sup> The fact that ultrasonography detects nodules (a third of which are more than 20 mm in diameter) in up to 50 percent of patients with a normal neck examination underscores the low specificity and sensitivity of clinical examination.<sup>9</sup> When two or more risk factors that indicate a high clinical suspicion are present, the likelihood of cancer approaches 100 percent.<sup>10</sup> In such cases, biopsy is still useful to guide the type of surgery<sup>1,2</sup> (Figure 1).



**Figure 1. Algorithm for the Cost-Effective Evaluation and Treatment of a Clinically Detectable Solitary Thyroid Nodule.**

In the case of a strong clinical suspicion of cancer, surgery is recommended, regardless of the results of fine-needle aspiration biopsy (FNAB). In the case of a suppressed level of serum thyrotropin, thyroid scintigraphy should be performed, since a functioning nodule almost invariably rules out cancer. In the case of a nondiagnostic FNAB, a repeated biopsy yields a satisfactory aspirate in 50 percent of cases. If ultrasonography reveals additional nodules that are more than 10 mm in diameter, FNAB could be performed on one other nodule, in addition to the one that is clinically detectable. The therapeutic options shown cover both solid and cystic nodules. In the case of a recurrent cyst, the possibilities of treatment are repeated FNAB, surgery, and ethanol injection. I do not recommend levothyroxine therapy for the thyroid nodule.

### Laboratory Investigations

Because clinical examination is not sensitive for identifying thyroid dysfunction,<sup>6</sup> laboratory evaluation of thyroid function is routinely warranted. The only biochemical test routinely needed is measurement of the serum thyrotropin level. If this level is subnormal, levels of free thyroxine or free triiodothyronine should be measured to document the presence and degree of hyperthyroidism. Approximately 10 percent of patients with a solitary nodule have a suppressed level of serum thyrotropin, which suggests a benign hyperfunctioning nodule.<sup>2</sup> If the serum thyrotropin concentration is elevated, a serum antithyroperoxidase antibody level should be obtained to confirm Hashimoto's thyroiditis. However, the finding of an elevated level does not obviate the need for a fine-needle aspiration biopsy, since the practitioner must rule out a coexisting cancer, including lymphoma, which accounts for only 5 percent of thyroid cancers but is associated with Hashimoto's thyroiditis.<sup>11</sup> Nearly all patients with thyroid cancer are euthyroid.<sup>1</sup>

If a patient has a family history of medullary thyroid cancer or multiple endocrine neoplasia type 2, a basal serum calcitonin level should be obtained; an elevated level suggests medullary thyroid cancer. Before surgery is performed, investigation for primary hyperparathyroidism and pheochromocytoma should be carried out. Serum calcitonin is not routinely measured in patients who have no suggestive family history, since medullary carcinoma is present in only about 1 of 250 patients with a thyroid nodule.<sup>12</sup>

### Imaging of the Thyroid Nodule

**Radionuclide Scanning** Radionuclide scanning, which is performed much more commonly in Europe than in the United States,<sup>3-5</sup> may be used to identify whether a nodule is functioning (Figure 2). A functioning nodule, with or without suppression of extranodular uptake, is nearly always benign, whereas a nonfunctioning nodule, constituting approximately 90 percent of nodules, has a 5 percent risk of being malignant. Thus, in the patient with a suppressed level of serum thyrotropin, radionuclide confirmation of a functioning nodule may obviate the need for biopsy. A scan can also indicate whether a clinically solitary nodule is a dominant nodule in an otherwise multinodular gland and can reveal substernal extension of the thyroid. A scan can be performed with iodine-123, iodine-131, or technetium-99m-labeled pertechnetate. Iodine isotopes, which are both trapped and bound organically in the thyroid, are preferred, since 3 to 8 percent of nodules that appear functioning on pertechnetate scanning may appear nonfunctioning on radioiodine scanning, and a few of those nodules may be thyroid cancers.<sup>13</sup> A scan cannot be used to measure the size of a nodule accurately.

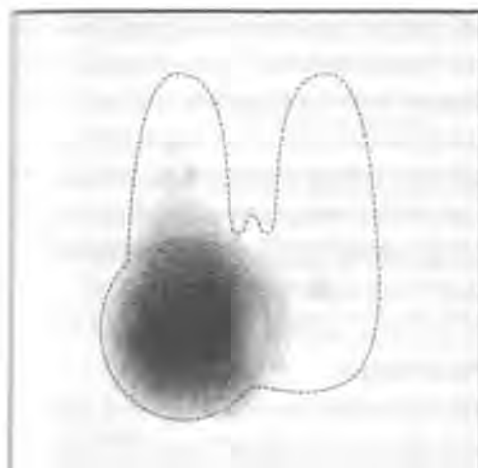


Figure 2. Scintigram of a Solitary Functioning Nodule in the Right Thyroid Lobe.

Scintigraphy that was performed with the use of technetium-99m-labeled pertechnetate shows suppression of extranodular uptake in thyroid tissue.



Figure 3. Cross-Sectional Ultrasonogram Showing a Solid, Hypoechoic Nodule (Dark Gray) in the Right Thyroid Lobe.

**Ultrasonography** Ultrasonography can accurately detect nonpalpable nodules, estimate the size of the nodule and the volume of the goiter, and differentiate simple cysts, which have a low risk of being malignant, from solid nodules or from mixed cystic and solid nodules, which have a 5 percent risk of being malignant (Figure 3). Ultrasonography also provides guidance for diagnostic procedures (e.g., fine-needle aspiration biopsy) as well as therapeutic procedures (e.g., cyst aspiration, ethanol injection, or laser therapy) and facilitates the monitoring of the effects of treatment.<sup>9</sup> In one study, among patients who had been referred for evaluation of a palpable thyroid abnormality, ultrasonography altered the clinical management in two thirds of cases,<sup>14</sup> mainly by identifying nodules that were smaller than 1 cm (which were not considered to require further evaluation) in 20 percent of the patients and by discovering additional nodules (which required biopsy) in 24 percent of the patients. Characteristics revealed by ultrasonography — such as hypoechogenicity, microcalcifications, irregular margins, increased nodular flow visualized by Doppler, and, especially, the evidence of invasion or regional lymphadenopathy — are associated with an increased risk of cancer; however, sonographic findings cannot reliably distinguish between benign and cancerous lesions.<sup>9</sup>



**Other Methods** Computed tomography (CT) and magnetic resonance imaging also cannot reliably differentiate between malignant and benign nodules. These tests are rarely indicated in the evaluation of a nodule. An exception is in the diagnosis and evaluation of substernal goiters, since these imaging techniques can assess the extent of the goiter more precisely than can other techniques and can evaluate tracheal compression.<sup>3,15</sup> Evaluation of glucose metabolism by positron-emission tomography using fludeoxyglucose (fluorodeoxyglucose) F 18 may help in distinguishing benign from malignant nodules, but its use is limited by cost and accessibility<sup>16</sup> and it cannot replace biopsy.

### Fine-Needle Aspiration Biopsy

Independent of morphology, fine-needle aspiration provides the most direct and specific information about a thyroid nodule. It is performed on an outpatient basis,<sup>1,4,5</sup> is relatively inexpensive, and is easy to learn. Complications are rare and primarily involve local discomfort. The use of anticoagulants or salicylates does not preclude biopsy. In centers with experience in fine-needle aspiration, the use of this technique has been estimated to reduce the number of thyroidectomies by approximately 50 percent, to roughly double the surgical confirmation of carcinoma, and to reduce the overall cost of medical care by 25 percent,<sup>17</sup> as compared with surgery performed on the basis of clinical findings alone.

Fine-needle aspiration has diagnostically useful results in about 80 percent of cases,<sup>18</sup> typically with two to four passes of the needle. The number of cases in which sufficient samples are obtained increases if aspiration is guided by ultrasonography, especially in nodules that are partly cystic, and repeated biopsy reduces by half the rate of insufficient samples (to about 10 percent).<sup>19,20</sup> The diagnostic accuracy of fine-needle aspiration depends on the way in which suspicious lesions are handled. Viewing them as "positive" increases sensitivity (rate of false negative results, 1 percent), but decreases specificity.<sup>21</sup> If fine-needle aspiration reveals a follicular neoplasm (which occurs in approximately 15 percent of nodules, of which only 20 percent turn out to be malignant), radionuclide scanning should be performed.<sup>1-3</sup> If such scanning shows a functioning nodule with or without complete suppression of the rest of the thyroid, surgery can be avoided, since the risk of cancer is negligible.<sup>17</sup> In a cystic lesion or one that is a mixture of cystic and solid components, fine-needle aspiration of a possible solid component should be performed, since the risk of cancer is the same as that for a solid nonfunctioning nodule.<sup>2,20,21</sup> With the exception of calcitonin immunostaining for medullary carcinoma, there are no reliable immunohistologic or molecular tests for distinguishing between benign and malignant nodules.<sup>3</sup>

Table 2. Treatment of the Single Nonmalignant Thyroid Nodule.

Treatment Type	Advantages	Disadvantages
Surgery	Nodule ablation, complete relief of symptoms, definite histologic diagnosis	Need for hospitalization, high cost, risks associated with surgery, vocal-cord paralysis (approximately 1% of patients), hypoparathyroidism (<1%), hypothyroidism (approximately 1%)
Levothyroxine	No need for hospitalization, low cost, may slow nodule growth, may prevent new nodule formation	Low efficacy, need for lifelong treatment, regrowth of nodule after cessation of treatment, cardiac tachyarrhythmias, reduced bone density, not feasible when thyrotropin level is suppressed
Radioiodine <sup>131</sup> I	No need for hospitalization, low cost, few subjective side effects, nodule reduced by 40% in 1 yr	Use of contraceptives needed in fertile women, only gradual reduction of the nodule, hypothyroidism within 5 yr (10% of patients), risk of radiation thyroiditis and thyrotoxicosis
Ethanol injection	No need for hospitalization, relatively low cost, no hypothyroidism, nodule reduced by 45% in 6 mo	Limited experience with treatment, decreasing efficacy with increasing nodule size, success dependent on operator's skill, painful (reducing compliance), risk of thyrotoxicosis and vocal-cord paralysis (approximately 1-2%), seepage of ethanol, interpretation of cytologic and histologic findings impeded in treated nodules
Laser therapy <sup>1</sup>		

• This risk applies only to the case of hemithyroidectomy.

<sup>1</sup> This treatment is used only for the functioning thyroid nodule.

Side effects due to the seepage of ethanol outside the nodule, which are rare (occurring in about 1 percent of patients), comprise nerve damage, perinodular or periglandular fibrosis jeopardizing subsequent surgery, thrombosis of the jugular vein, and neck hematomas.

Laser therapy is still experimental, and experience with it is limited. The advantages are the same as those of ethanol injection, but side effects are probably more limited because the higher degree of control with laser therapy limits the risk of extranodular damage.

### Treatment of the Solitary Thyroid Nodule

The natural history of solitary thyroid nodules is poorly understood, mainly because nodules that are suspicious for cancer, cause pressure, or prompt reports of cosmetic problems are rarely left untreated. With this reservation, it seems that the majority of benign non-functioning nodules grow, particularly those that are solid.<sup>22-24</sup> In one study, 89 percent of nodules that were followed for five years increased by 15 percent or more in volume.<sup>24</sup> The annual rate of evolution of a solitary functioning nodule into a hyperfunctioning nodule is as high as 6 percent; the risk is positively related to the size of the nodule and negatively related to the serum thyrotropin level.<sup>25,26</sup> There is controversy as to whether a solitary nodule should be treated and, if so, how.<sup>4,5</sup> Table 2 summarizes the advantages and disadvantages of potential treatment options. Figure 1 shows a management algorithm.

**Levothyroxine** Treatment with levothyroxine at a dose sufficient to keep the serum thyrotropin at a level below 0.3 mU per liter has been suggested as a way to prevent growth of an apparently benign nodule. However, this approach has clear limitations. A recent meta-analysis showed no significant difference in the size of nodules after 6 to 12 months of suppressive therapy with levothyroxine, as compared with no treatment, although the size of the nodules decreased by more than 50 percent in a larger proportion of levothyroxine-

treated patients than in patients who had no treatment.<sup>27</sup> The likelihood of such shrinkage is greater when serum thyrotropin is suppressed to a level below 0.1 mU per liter than it is when the level is below 0.3 mU.<sup>27-29</sup> In a five-year, randomized trial, suppression to below 0.1 mU per liter significantly reduced the frequency with which new nodules developed (i.e., 8 percent of patients who were treated with levothyroxine as compared with 25 percent of untreated patients).<sup>29</sup> However, therapy with levothyroxine to reduce thyrotropin levels below 0.1 mU per liter is associated with an increased risk of atrial fibrillation, other cardiac abnormalities,<sup>30,31</sup> and reduced bone density.<sup>32</sup> Regrowth of nodules occurs after cessation of therapy. Levothyroxine has no effect on the recurrence of thyroid cysts after aspiration.<sup>33</sup>

**Surgery** The main indications for surgery are clinical or cytologic features suggestive of cancer or symptoms due to the nodule (Table 1).<sup>4,5</sup> If preoperative cytology suggests a benign lesion, hemithyroidectomy is generally preferred.<sup>4,5,18</sup> Postoperative administration of levothyroxine is indicated only in cases of hypothyroidism.<sup>34</sup> When surgery is performed by a specialist, the incidence of complications is low (i.e., postoperative hypoparathyroidism in 1 percent of cases and injuries to the recurrent laryngeal nerve in about 1 percent), but the complication rate is higher for less experienced surgeons and those without special training.<sup>35</sup>

**Radioiodine** Radioiodine is an option for treatment of a functioning nodule, with or without biochemical hyperthyroidism. It is contraindicated in pregnant and breast-feeding women. Normalization of the results of thyroid radionuclide scanning and the serum thyrotropin level (often referred to as a "cure") is achieved in 75 percent of patients, and thyroid volume is reduced an average of 40 percent, after a single dose of iodine-131 aiming at a level of 100 Gy, independent of pretreatment thyroid function.<sup>36,37</sup> The main side effect is hypothyroidism, which occurs in approximately 10 percent of patients within five years after treatment and increases in frequency over time. This risk is unrelated to dose but is greater in patients with thyroid peroxidase antibodies and with iodine uptake in extranodular thyroid tissue.<sup>36,37</sup> Most nodules do not disappear after radioiodine therapy but may become harder on palpation and may reveal unusual cytologic features as a result of irradiation. Thyroid function should be checked regularly during the first year and yearly thereafter in order to detect hypothyroidism. Nodules are unlikely to grow after radioiodine therapy, but if growth occurs, a biopsy may be warranted.

**Percutaneous Ethanol Injection** A number of studies have suggested a benefit of ultrasonographically guided ethanol injection in the treatment of benign functioning and nonfunctioning solid thyroid nodules as well as cystic nodules.<sup>38-40</sup> The mechanism of effect involves coagulative necrosis and small-vessel thrombosis. The procedure requires prior documentation of benign cytology, skill, and experience<sup>3,9</sup>; drawbacks include local pain and a potential risk of serious side effects (Table 2). There are few data from controlled trials to support this approach.

Available data suggest that multiple injections of ethanol (a median of four) can achieve a complete cure (i.e., a normalization of results of radionuclide scanning and serum thyrotropin measures) in two thirds of patients with hyperfunctioning nodules and three quarters of patients with functioning nodules without hyperthyroidism.<sup>38,39</sup> In solid nonfunctioning nodules that are solitary and cytologically benign, a single ethanol injection has been shown to reduce the volume of nodules by approximately 50 percent.<sup>3,23</sup> Additional ethanol injections have only a limited effect.<sup>41,42</sup> Recently, data from a preliminary study suggested that the use of laser photocoagulation may be as effective as ethanol injection, with fewer adverse effects.<sup>43</sup> However, controlled trials are needed.

In thyroid cysts, the recurrence rate after aspiration is high. Tetracycline, a sclerosing agent, had no effect in a randomized study.<sup>44</sup> Uncontrolled studies have suggested that ethanol injection may prevent the recurrence of cysts.<sup>39,40</sup> A recent randomized, double-blind study<sup>45</sup> involving a six-month follow-up period reported that 21 of 33 patients (64 percent) who were treated with ethanol were cured after one session, as compared with 6 of 33 patients (18 percent) who were treated with saline.

#### AREAS OF UNCERTAINTY

There are no data from studies comparing the outcome and cost-effectiveness of various strategies of evaluating a nodule (e.g., using radionuclide imaging and ultrasonographic guidance for fine-needle aspiration). There are also insufficient data comparing the outcome (including quality of life) of various management approaches in the absence of cancer.

#### GUIDELINES FROM PROFESSIONAL SOCIETIES

Clinical-practice guidelines were published in 1996 by the American Thyroid Association<sup>1</sup> (<http://www.thyroid.org/professionals/publications/guidelines.html>) and the American Association of Clinical Endocrinologists<sup>46</sup> ([http://www.aace.com/clin/guidelines/thyroid\\_nodules.pdf](http://www.aace.com/clin/guidelines/thyroid_nodules.pdf)). The recommendations of both organizations correspond with those provided here. Radionuclide scanning is not routinely recommended, but it is advo-

cated in the case of a suppressed level of serum thyrotropin or the finding of follicular neoplasia with the use of fine-needle aspiration. Thyroid ultrasonography is recommended to guide fine-needle aspiration, especially in nodules that are small and incidental or are partly cystic or from which primary fine-needle aspiration has yielded insufficient material. Fine-needle biopsy of all possibly malignant nodules (which are not defined in the guidelines) is advocated. If the cytology is benign, repeated biopsy is seldom indicated.

In the case of a benign nodule, periodic lifelong follow-up every 6 to 24 months (including measurement of serum thyrotropin levels, neck palpation, and fine-needle aspiration in case of growth or other suspicious signs) is recommended. For a functioning benign nodule, iodine-131 is considered the treatment of choice, with surgery as an alternative, especially if the nodule is very large or partly cystic or if the patient is young; treatment is more strongly recommended if the serum thyrotropin level is decreased or overt hyperthyroidism is present, because of adverse effects on bone and the cardiovascular system. For a nonfunctional benign nodule, there is no clear recommendation on the use of levothyroxine, although this therapy is considered contraindicated when the serum thyrotropin level is suppressed, in patients more than 60 years old, and in postmenopausal women. If levothyroxine therapy is used, regular reassessment (the interval is not defined in the guidelines) is recommended, with monitoring of serum thyrotropin levels, which should be subnormal but measurable. The guidelines do not address ethanol injection and laser therapy.

#### CONCLUSIONS AND RECOMMENDATIONS

For the patient who presents with a nodule, as in the case described in the vignette, the main concern is to exclude the possibility of thyroid cancer, even though the vast majority of nodules are benign (Figure 1). The initial evaluation should include measurement of the serum thyrotropin level and a fine-needle aspiration, preferably guided by ultrasonography. If the patient has a family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, the serum calcitonin level should also be checked. If the thyrotropin level is suppressed, radionuclide scanning should be performed. In patients less than 20 years old, and in the case of a high clinical suspicion for cancer (e.g., follicular neoplasia as diagnosed by fine-needle aspiration and a nonfunctioning nodule revealed on scanning), the patient should be offered hemithyroidectomy regardless of the results of fine-needle aspiration.

In the case of a functioning benign nodule, iodine-131 is generally the therapy of choice, independent of concomitant hyperthyroidism. For nonfunctioning cystic nodules, aspiration and ethanol injection therapy may be considered, and ethanol injection

or laser therapy if the nodules are solid, but data to support the use of these therapies are limited. My usual approach after documenting benign cytology is to follow the patient yearly with neck palpation and measurement of the serum thyrotropin level, with repeated ultrasonography and fine-needle aspiration if there is evidence of growth of the nodule. I do not recommend levothyroxine therapy to shrink or prevent growth of benign nodules because of the drug's low efficacy and potential side effects.

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# *Hypersensitivity to Hymenoptera Stings*

THEODORE M. FREEMAN, M.D.

A 29-year-old man reported that he was stung by a flying hymenopteran — he does not know what type — outside his door, where he had previously noted a nest. Skin itching, diffuse hives, swelling of his arms and legs, tightness in his throat, dizziness, and difficulty talking developed immediately, and he was taken to a local clinic where he received epinephrine and antihistamines. He was observed for two hours, and all symptoms resolved. How should his case be managed subsequently?

## THE CLINICAL PROBLEM

Insects of the order Hymenoptera, which includes ants, bees, hornets, wasps, and yellow jackets, have a stinging apparatus at the tail end of their abdominal segment and are capable of delivering between 100 ng (fire ants)<sup>1</sup> and 50  $\mu$ g (bees)<sup>2</sup> of venom (Table 1 and Figure 1). Although the venoms have various peptide and protein components, some of which are capable of inducing toxic or vasoactive responses, it has been estimated that about 1500 stings would be required to deliver a lethal dose of hymenoptera venom for a nonallergic adult who weighs 70 kg.<sup>5</sup> Despite this estimate, about 40 deaths a year are attributed to hymenoptera stings<sup>6</sup>; these deaths are ascribed to anaphylaxis occurring in persons with a history of prior stings in whom specific IgE antibodies developed to various venom components. Due to the vasoactive components of the venoms, most people experience a local reaction to hymenoptera stings consisting of redness, swelling, tenderness, and pain at the site of the sting. This reaction is self-limited and will resolve within hours. If the sting occurs near or within the oral cavity, there is a potential for respiratory compromise.

Fire-ant venom is composed primarily of a transpiperidine alkaloid that causes tissue necrosis. Most fire-ant stings produce a blister within 24 hours, which often fills with necrotic material, giving the appearance of a pustule (Figure 2). Despite their appearance, these blisters are not infected and should be left intact.

Occasionally, persons will have swelling from a hymenoptera sting that may involve a large area and persist for up to a week. These large local reactions are not life threatening

Table 1. Characteristics of Hymenoptera.

Common Name	Taxonomic Classification	Size	Nesting Habits	Feeding Habits	Aggressiveness	Venom Protein per Sting*	Avoidance Techniques
Honeybee	Family Apidae <i>Apis mellifera</i>	15–20 mm	Man-made hives	Nectar and pollen	Nonaggressive	50 µg	Avoid flower-print clothing Avoid flowery scents Wear shoes and socks outdoors
Africanized honeybee†	Family Apidae <i>Apis mellifera scutellata</i>	15–20 mm	Natural hives	Nectar and pollen	Aggressive	Approximately 50 µg	Avoid flower-print clothing Avoid flowery scents Wear shoes and socks outdoors Remove nests near homes
Fire ant	Family Formicidae <i>Solenopsis invicta</i>	4–6 mm	Mounds in disturbed soil	Omnivorous	Aggressive in defense of mounds	10–100 ng	Wear shoes and socks outdoors Wear gloves and pants when gardening Remove mounds near homes
Paper wasp	Family Vespidae Subfamily Polistinae Polistes species	20–25 mm	Single layer hanging from eaves, porches	Nectar and arthropods	Aggressive in defense of nests	NA	Avoid flower-print clothing Avoid flowery scents Remove nests near homes
Yellow jacket	Family Vespidae Subfamily Vespinae Vespula species	15–20 mm	Multilayered, usually underground	Scavengers	Very aggressive	2–20 µg	Avoid open food sources, picnic areas, garbage Remove nests near homes
White-faced or bald-faced hornet	Family Vespidae Subfamily Vespinae Dolichovespula species	25–35 mm	Multilayered, usually in open areas	Nectar and arthropods	Aggressive in defense of nests	NA	Avoid flower-print clothing Avoid flowery scents Remove nests near homes
European hornet	Family Vespidae Subfamily Vespinae Vespa species	25–35 mm	Multilayered, usually in open areas	Nectar and arthropods	Aggressive in defense of nests	NA	Avoid flower-print clothing Avoid flowery scents Remove nests near homes

\* NA denotes that data are not available.

† The subspecies of honeybee called "Africanized" is more aggressive than the parent species and has caused some clinical problems in South and Central America and in south Texas. The venom is similar to honeybee venom, which may therefore be used in testing and treating patients who have had anaphylaxis after being stung by this subspecies.<sup>3,4</sup>

unless they involve the airway. They may result in considerable morbidity because of a temporary loss of function, such as occurs when the sting involves a foot or hand or is near an eye. Secondary infections can frequently complicate fire-ant stings when the pseudopustule is opened, and they can sometimes complicate other hymenoptera stings. Although it may be difficult in some cases to distinguish a secondary infection from a large local reaction, in the latter event the swelling usually peaks within 48 hours, whereas progression of swelling for more than two days, accompanied by fever or lymphadenitis, suggests secondary infection.

The reactions that lead to anaphylaxis, however, are of more concern than secondary infections. Some anaphylactic events are restricted to cutaneous findings (pruritus, urticaria, and angioedema). Others have a broader effect, with systemic symptoms that may involve the gastrointestinal tract (metallic taste, nausea, vomiting, diarrhea, and abdominal cramping), genitourinary tract (uterine cramps), or nervous system (sense of impending

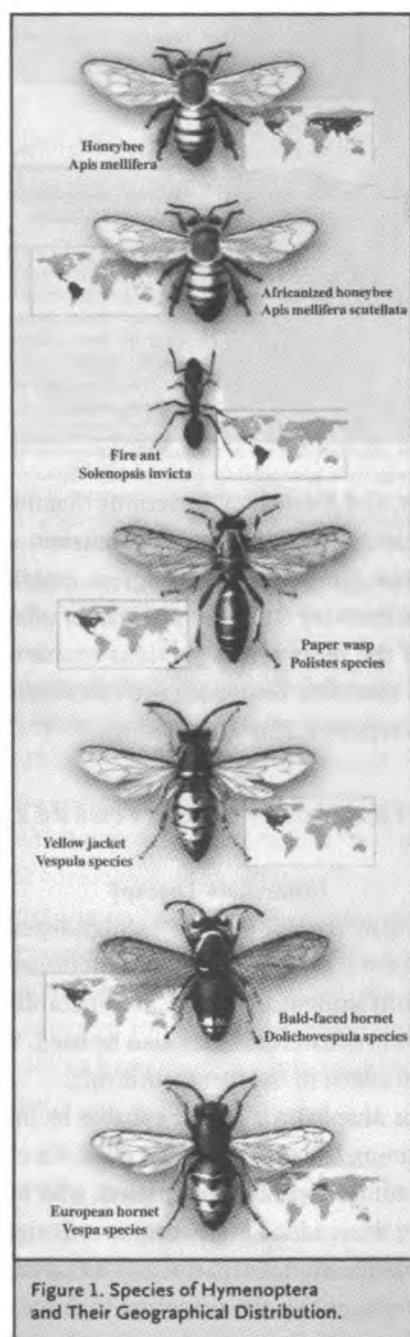




Figure 2. Stings from a Fire Ant on an Ankle, Showing the Pseudopustule.

The clustering of the stings (white arrow) contrasts with the single sting (black arrow) in the photograph, which was taken 24 hours after the event. This pattern is typical of fire-ant stings, as one ant will often inflict multiple stings in a semicircular arc if given time to do so. Also, the pseudopustule is typical of fire-ant stings; it is not a pustule. The stings occurred just above the level of the ankle sock the patient was wearing on the day of the event.

ing doom, light-headedness, and dizziness). Reactions that involve the cardiopulmonary system (breathing difficulties, bronchospasm, hypotension, and arrhythmia) pose the greatest risk. Initial subjective symptoms may progress rapidly (in seconds to minutes) to life-threatening cardiopulmonary collapse. The risk of anaphylaxis with any event is dependent on the nature of the most severe previous reaction experienced by a patient (Table 2). Neuropathic and vasculitic responses and reactions that resemble serum sickness have in rare cases been reported after insect stings.<sup>15,16</sup>

## STRATEGIES AND EVIDENCE

### Immediate Therapy

The optimal choice of immediate therapy for insect stings depends on the type of reaction. Strategies are based on anecdotal evidence. Local reactions are best treated symptomatically with nonsteroidal antiinflammatory agents, antihistamines, and cold compresses. Topical antihistamines and corticosteroids may also be used. When large local reactions occur, oral steroids are often added to the therapeutic mix.

The definitive therapy for anaphylaxis is epinephrine by injection (0.01 mg per kilogram of body weight; maximum, 0.3 and 0.5 mg per dose, for children and adults, respectively), and this should be administered to any patient who has more than a cutaneous reaction. Antihistamines are often added to treat cutaneous signs and symptoms. Supplemental oxygen, beta-agonists for bronchospasm, and intravenous fluids for hypotension are sometimes indicated. Occasionally, for a reaction that does not respond to the initial dose of epinephrine, steroids (oral or intravenous) are added, although definitive support for their addition is lacking.

Table 2. Risk of Anaphylactic Reactions to Hymenoptera Stings after an Initial Event.

Patient History*	Approximate Risk of Anaphylaxis (%)†	Immunotherapy if Skin Test or In Vitro Test Is Positive for Antibodies
Unknown history	3	No
Large local reactions	10	No
Cutaneous anaphylaxis in child	10	No
Systemic anaphylaxis in child	50-60	Yes
Anaphylaxis in adult	30-60	Yes
Receiving immunotherapy	2	Not applicable

\* The risk in the general population refers to the risk in adults; the risk may be lower in children. Large local reactions are defined as persistent swelling of up to a week's duration; cutaneous anaphylaxis in a child is characterized by pruritus, urticaria, or angioedema. The risk of anaphylaxis for adults with cutaneous reactions only may be as low as it is for children, but this is yet to be determined.

† The data in this table are from Golden,<sup>7</sup> Settiple and Boyd,<sup>8</sup> Chaffee,<sup>9</sup> Golden et al.,<sup>10</sup> Graft et al.,<sup>11</sup> Schuberth et al.,<sup>12</sup> Hunt et al.,<sup>13</sup> and Golden et al.<sup>14</sup>

There is a distressing tendency by both patients and physicians to treat anaphylaxis without using epinephrine,<sup>17,18</sup> perhaps because of concern about adverse effects of epinephrine on the heart. However, anaphylaxis itself has been associated with coronary vasospasm.<sup>19-22</sup> The fact that available data suggest that a failure or delay in administering epinephrine increases the chance of a fatal outcome in anaphylaxis<sup>23</sup> underscores the prevailing opinion that epinephrine must be considered the definitive therapy for anaphylaxis.

Epinephrine auto-injectors should be prescribed for any patient who has had an anaphylactic reaction to a hymenoptera sting. The instructions for use are printed on the side of each injector, but these should be reviewed with the patient when prescribing the medication. Patients should be educated to use epinephrine if signs or symptoms beyond a cutaneous reaction develop after a hymenoptera sting, and always to seek additional medical care after using an injector.

### Long-Term Therapy

**Avoidance** The long-term goal is to prevent future systemic anaphylactic events. The optimal approach to prevent IgE-mediated disease is avoidance of the antigen, but this may not be feasible in practice. Current recommendations for avoidance are summarized in Table 1. The proximity of the habitats of wasps and fire ants to those of humans makes these insects the most likely members of the order to cause anaphylaxis.<sup>24</sup>

**Immunotherapy** If avoidance of hymenoptera cannot be ensured, the next step is to minimize the potential for anaphylaxis if a sting should occur. Immunotherapy with hymenoptera venom has been shown to reduce the potential risk of anaphylaxis with subsequent stings significantly<sup>13,14</sup> (Table 2). Although the administration of whole-body extracts is no more effective than placebo therapy for treating the stings of flying hymenoptera,<sup>23</sup> whole-body extracts of fire ants appear to be as useful in preventing future reactions as is venom immunotherapy for flying hymenoptera,<sup>25</sup> perhaps because whole-body extracts of fire ants (in contrast to those of flying hymenoptera) contain adequate amounts of venom.<sup>26</sup> Whole-body extract therapy for fire ants has not been compared directly with fire-ant venom immunotherapy.

**Evaluation** The evaluation of patients for whom immunotherapy is considered begins with a review of the history of stings and reactions. The circumstances of the sting may suggest a particular agent (Table 1). The presence of a stinger or a venom sac at the site of a sting suggests, but is not definitive of, a honeybee sting, as occasionally other hymenoptera may leave a stinger in place. Fire ants are usually easy to identify since they do not fly away and will grasp victims with their mandibles and inflict multiple stings if allowed (Figure 2).

The clinical course is also reviewed to verify the diagnosis of anaphylaxis. It is sometimes difficult to separate anxiety symptoms from true anaphylaxis in the setting of a sting. This is especially true if there are no documented objective findings, such as urticaria, hypotension, or air-flow reduction. However, when patients are concerned enough to seek an evaluation even with an unclear or remote history, it is appropriate to test them for specific IgE antibodies. If the results of these tests are negative, patients can be reassured; if they are positive, immunotherapy should be offered. Age is also important. Studies have shown that in children under the age of 16 years who have cutaneous anaphylaxis (urticaria, angioedema, or both), the risk of systemic (in addition to cutaneous) anaphylaxis in response to future stings is only slightly greater than the risk in the general population<sup>6</sup> (Table 2). It is uncertain whether the same is true in adults.

Subsequent evaluation involves testing for the presence of specific IgE antibodies.<sup>27,28</sup> Initial testing is usually delayed for four to six weeks after the sting event to eliminate the possibility of a false negative result caused by a depletion of mediators in the setting of anaphylaxis. If the particular agent is known, then testing includes only that insect. It is often unclear which insect was the perpetrator, in which case testing of sensitivity to each of the flying hymenoptera is warranted.

Typically, testing involves *in vivo* skin testing for specific IgE antibodies; this is more sensitive than *in vitro* methods, which are an alternative. The prick method (a needle

pricks the skin through a drop of the antigen) is used as the first step (a dilution of 1:1000 weight/volume [wt/vol] for fire-ant venom; 1  $\mu\text{g}$  per milliliter for venom from other hymenoptera). If the result of this test is negative, testing proceeds with an intradermal method (antigen is injected into the dermis), usually using about 0.001  $\mu\text{g}$  per milliliter (1:1,000,000 wt/vol for fire-ant venom) and increases sequentially by 10 times the previous amount to 1.0  $\mu\text{g}$  per milliliter (1:1000 wt/vol for fire-ant venom); above these concentrations, false positive test results may occur. Testing is stopped when the skin test is positive (the reaction is equivalent to or greater than a histamine control). If the maximal intradermal dose is reached without a positive response, the test result is considered negative. If a false negative result is suspected (on the basis of a history suggestive of anaphylaxis), or for patients who cannot be skin-tested (those who have severe dermatitis or who are receiving medications that suppress the histamine response), *in vitro* methods are reasonable alternatives. Immunotherapy is then offered to anyone who has both a history consistent with anaphylaxis after a sting and specific IgE antibodies to the potential agent, as demonstrated by positive results on skin testing or *in vitro* testing.

Whereas there may be extensive cross-reactivity between some venom components, such as antigen 5 (one of the more potent vespid antigens), there are enough highly specific components of the venoms (including differences between molecules common to all the venoms, such as phospholipases)<sup>29</sup> to support the recommendation that all venoms for which skin testing yields positive results should be used in treatment. Treatment with more than one venom can be administered concurrently, but this generally requires multiple injections per visit; an exception is the commercial preparation that is a mixture of venoms from the yellow jacket, white-faced hornet, and yellow hornet (maximal dose, 100  $\mu\text{g}$  of each species' venom).

**Therapy** Immunotherapy starts at 0.1  $\mu\text{g}$  per milliliter for most hymenoptera venoms (1:100,000 wt/vol for fire-ant venom). Each subsequent dose increases the amount of venom delivered to the patient, generally until a dose of 100  $\mu\text{g}$  per milliliter for the venom of flying hymenoptera (0.5 ml of 1:100 wt/vol for fire-ant venom) is reached; 100  $\mu\text{g}$  is twice the dose to which a patient would be exposed in a routine sting, and it is the dose used in initial studies showing the effectiveness of venom immunotherapy. Usually the doses are delivered once a week. This means there is a three-to-six-month period required to reach the maintenance dose. So-called rush protocols have been published,<sup>30-32</sup> in which a shorter dosing interval is used to reach maintenance doses in weeks or even days, and they appear to provide good protection from sting challenges. These are particularly useful when the risk of exposure is high and ongoing, as may occur with patients who must work or play outdoors.<sup>33</sup> These protocols have not been compared directly with standard

immunotherapy protocols in randomized controlled trials, but they have been found to give reasonably equivalent protection against direct sting challenges.

When a maintenance level is reached, the interval between injections is often expanded to one month. Some observational data suggest that the interval may be expanded to 8 or even 12 weeks without losing protection.<sup>34,35</sup> The maintenance dose and interval may be adjusted on the basis of clinical criteria. For instance, if a patient receives a sting that results in symptoms while receiving maintenance immunotherapy, the dose interval may be shortened or the dose increased to more than 100  $\mu$ g.<sup>36</sup>

Protection after a course of immunotherapy appears to last a long time. In a recent report involving a follow-up evaluation of children 10 to 20 years after they had received immunotherapy, only 5 percent of the children with a history of a moderate-to-severe sting reactions who reported a subsequent sting had had a recurrent systemic reaction, as compared with 32 percent of untreated children with a similar history.<sup>37</sup>

The risks associated with hymenoptera immunotherapy are the same as for other allergen immunotherapy. The risk of anaphylaxis after an immunotherapy injection is low (fewer than 1.6 reactions per 100 injections).<sup>13</sup> The majority (88 percent) of patients complete an immunotherapy course without reactions, and most reactions that occur are mild.<sup>38</sup> Rarely, more severe reactions occur, including death (about 1 in 5 million injections for all types of immunotherapy).<sup>39</sup> Therefore, immunotherapy should be administered only in a medical setting by trained personnel capable of recognizing and treating anaphylaxis.

#### AREAS OF UNCERTAINTY

An important unanswered question relates to the optimal duration of maintenance immunotherapy. The package insert that comes with the venom immunotherapy recommends indefinite use, whereas current clinical guidelines recommend discontinuing immunotherapy after three to five years of the maintenance-level dose,<sup>40,41</sup> especially if the patient no longer has specific IgE antibodies (as evaluated by repeated skin testing).<sup>42,43</sup> However, data from patients who have not received immunotherapy indicate that the loss of these antibodies is no guarantee that anaphylaxis will not occur. In one report, 98 patients (including patients with and patients without a history of anaphylaxis) who had positive tests for specific IgE antibodies at baseline slowly lost their positive responses over time. However, the risk of anaphylaxis was not eliminated; at a mean of four years after initial evaluation, approximately 17 percent of patients (11 of 65) who had subsequent stings had anaphylactic reactions, despite the presumed loss of specific IgE antibodies.<sup>44</sup> Other reports have documented reactions to hymenoptera stings after discontinuing immunotherapy.<sup>37,45</sup> Given these data, some allergists extend venom immunotherapy longer than



the suggested three to five years. Consideration of an extended course may be warranted particularly for patients who have had a severe reaction (for such patients, some allergists might continue immunotherapy indefinitely).

Another area that requires additional research is the treatment of patients who have a history of a reaction suggestive of anaphylaxis but in whom testing for specific IgE antibodies yields negative results. One potential explanation is that the earlier reaction was not to hymenoptera; the stings or bites of other insects (mosquitoes, biting flies, and reduvids) and arthropods (spiders, scorpions, and ticks) may also result in anaphylaxis. In rare cases, people with mastocytosis may have an anaphylactoid response to hymenoptera stings without actually having specific IgE antibodies.<sup>46</sup> A more common explanation is the imperfect sensitivity of tests for specific IgE antibodies.<sup>10,47,48</sup> Twenty percent of patients with negative in vitro tests will have positive results on skin testing, and 10 percent of patients whose skin test is negative will have positive results on in vitro testing.<sup>49</sup> In cases in which the suspicion of hymenoptera hypersensitivity is high, and initial tests are negative, it has been recommended that repeated testing be undertaken with both in vivo and in vitro methods.<sup>50,51</sup>

#### GUIDELINES

Under the joint auspices of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology, the *Journal of Allergy and Clinical Immunology* published the newest set of guidelines for insect hypersensitivity in 2004.<sup>52</sup> In general, the recommendations presented here are consistent with these guidelines.

#### SUMMARY AND CONCLUSIONS

For patients with a clear history of anaphylaxis, such as the one described in the vignette, information should be provided on avoidance and on the use of emergency treatment with epinephrine auto-injectors. Patients should be advised to carry an auto-injector and to wear a medical alert bracelet. Referral to an allergist is warranted, and skin testing should be performed for sensitivity to honeybees, wasps, white-faced hornets, yellow hornets, and yellow jackets. Venom immunotherapy should be administered for all venoms for which testing results are positive. The protective benefit is expected from the immunotherapy by the time maintenance dose is reached, usually by three to six months with standard protocols. A rush protocol would be recommended if the patient's risk of being stung again before standard immunotherapy could work were considered high. Although immunotherapy is often administered by allergists, it may be delivered by any practitioner who is willing to observe the patient and to treat anaphylaxis if it should occur.

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# Newly Diagnosed Atrial Fibrillation

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

## THE CLINICAL PROBLEM

Atrial fibrillation is the most common arrhythmia that requires treatment, with an estimated prevalence in the United States of 2.3 million patients in 2001.<sup>1</sup> The prevalence increases with age — atrial fibrillation occurs in 3.8 percent of people 60 years of age and older and in 9.0 percent of those 80 years of age and older.<sup>1</sup>

### Risk of Stroke and Death

The most devastating consequence of atrial fibrillation is stroke as a result of thromboembolism typically emanating from the left atrial appendage.<sup>2</sup> The rate of stroke varies but may range from 5.0 percent to 9.6 percent per year among patients at high risk who are taking aspirin (but not warfarin).<sup>3,4</sup>

Patients with paroxysmal (i.e., self-terminating) and persistent atrial fibrillation (i.e., that lasts more than seven days or requires cardioversion) appear to have a risk of stroke that is similar to that of patients with permanent atrial fibrillation.<sup>5</sup> In the Stroke Prevention in Atrial Fibrillation studies of patients with atrial fibrillation, the risk of stroke among those with sinus rhythm that had been documented within the 12 months before enrollment (3.2 percent per year) was similar to that among those with permanent atrial fibrillation (3.3 percent per year).<sup>5</sup> The duration of episodes of atrial fibrillation and the overall time spent in atrial fibrillation (i.e., burden) have not been established as deter-

mining the risk of stroke. Atrial fibrillation is associated with an increase in the relative risk of death ranging from 1.3 to twice that value, independent of other risk factors.<sup>6</sup> This risk may be greater for women than for men.<sup>7</sup>

### **Associated Diseases and Predisposing Conditions**

In most cases, atrial fibrillation is associated with cardiovascular disease, in particular: hypertension, coronary artery disease, cardiomyopathy, and valvular disease (primarily mitral); it also occurs after cardiac surgery and in the presence of myocarditis or pericarditis. When atrial fibrillation complicates severe mitral regurgitation, valve repair or replacement is indicated.<sup>8</sup> In some cases, atrial fibrillation results from another supraventricular tachycardia. When it is associated with the Wolff–Parkinson–White syndrome, rapid conduction down the accessory pathway may result in hemodynamic collapse.<sup>9</sup>

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

### **Evaluation**

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

### **Symptoms and Hemodynamic Consequences**

Patients with atrial fibrillation may have palpitations, dyspnea, fatigue, light-headedness, and syncope. These symptoms are usually related to the elevated heart rate and, in most

patients, can be mitigated with the use of drugs to control the heart rate. Exceptions are due, presumably, to an irregular ventricular response or a reduction of cardiac output.

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

A chronically elevated heart rate of 130 beats per minute or more may result in secondary cardiomyopathy,<sup>15</sup> a type of left ventricular dysfunction that may largely be reversed when control of the ventricular rate is achieved.<sup>15,16</sup> A report by Hsu et al.<sup>17</sup> indicates that, in patients with atrial fibrillation, heart-rate control and rhythm control with the use of radiofrequency catheter ablation improve left ventricular function in both those with and those without congestive heart failure.

### Asymptomatic Atrial Fibrillation

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

## STRATEGIES AND EVIDENCE

**Anticoagulant Therapy**

The need for anticoagulation to reduce the risk of stroke among patients with atrial fibrillation due to mitral stenosis is well recognized.<sup>11</sup> Several randomized, prospective trials involving patients with nonvalvular atrial fibrillation<sup>26-32</sup> have confirmed a significant reduction in the risk of stroke with warfarin. These studies defined the patients at greatest risk as the elderly, variably defined as those older than 60, 65, and 75 years of age, and those with a history of thromboembolism, diabetes mellitus, coronary artery disease, hypertension, heart failure, and thyrotoxicosis.<sup>11,33</sup> These trials have provided a basis for two important guidelines for the use of warfarin in such patients<sup>11,33,34</sup> (Table 1). Recently, an index based on the assignment of points for five risk factors (i.e., congestive heart failure, hypertension, age, diabetes, and transient ischemic attack or stroke) was reported to be accurate in predicting stroke when it was used to evaluate the risk among patients in the Medicare database<sup>4</sup>; it is the basis for yet another guideline for antithrombotic therapy in atrial fibrillation<sup>35</sup> (Table 1). In addition, complex aortic plaques detected by transesophageal echocardiography that are associated with an increased risk of stroke in patients with atrial fibrillation also warrant the institution of anticoagulant therapy.<sup>36</sup>

An international normalized ratio (INR) value in the range of 2.0 to 3.0 is recommended. The risk of stroke doubles when the INR falls to 1.7, although values up to 3.5 do not convey an increased risk of bleeding complications.<sup>37</sup> INR values of 2.0 or greater are associated with a reduced severity of stroke and, if stroke occurs, a lower likelihood that it will result in death.<sup>38</sup>

Certain patients are at relatively low risk for a thromboembolic event and do not require intensive anticoagulant therapy<sup>11,33,35</sup> (Table 1). Aspirin is often recommended for these patients, although their risk is so low that even aspirin may not be necessary. Alternative antiplatelet agents, such as clopidogrel, have not been tested adequately in this clinical situation.

The duration of atrial fibrillation becomes important when cardioversion (with the use of electric or pharmacologic means) is being considered. It is generally accepted that patients who have had an episode of atrial fibrillation lasting less than 48 hours may safely undergo cardioversion without anticoagulant therapy, although the data supporting this practice are scant.<sup>11</sup> For episodes lasting longer than 48 hours, adequate anticoagulant therapy is warranted, both before cardioversion and for four weeks afterward. A recent report concluded that a strategy of initiating anticoagulant therapy and ruling out left atrial thrombus with the use of transesophageal echocardiography was a possible alternative to the usual strategy of anticoagulant therapy for three weeks before cardioversion.<sup>39</sup>

Table 1. Guidelines for Antithrombotic Therapy in Atrial Fibrillation.

Characteristic	Therapy Recommended by the ACC-AHA and ESC	Differences in ACCP Guidelines
<b>Age</b>		
<60 yr, no heart disease	Aspirin at a dose of 325 mg per day, or no therapy	Aspirin at a dose of 325 mg for patients <65 yr of age with no risk factor†
<60 yr, with heart disease but no risk factors*	Aspirin at a dose of 325 mg per day	No divergence
≥60–75 yr, no risk factors*	Aspirin at a dose of 325 mg per day	Option of aspirin at a dose of 325 mg per day or warfarin (INR, 2.0–3.0) for patients 65–75 yr of age
≥60 yr, with diabetes mellitus or coronary artery disease	Warfarin (INR, 2.0–3.0), aspirin optional in addition (at a dose of 81–162 mg per day)	Option of aspirin at a dose of 325 mg per day or warfarin (INR, 2.0–3.0) for patients with diabetes alone or coronary artery disease alone who are <65 yr of age
>75 yr, especially among women	Warfarin (INR, approximately 2.0; target INR, 1.6–2.5)	Warfarin (INR, 2.0–3.0), but no recommendation for INR value <2.0
Heart failure, left ventricular ejection fraction ≤0.35, thyrotoxicosis, and hypertension	Warfarin (INR, 2.0–3.0)	No divergence
Rheumatic heart disease (mitral stenosis)	Warfarin (INR, 2.5–3.5 or higher) may be appropriate	Other than for patients with mechanical valves, no INR recommended above target, 2.5 (range, 2.0–3.0)
Previous thromboembolism	Warfarin (INR, 2.5–3.5 or higher) may be appropriate	Other than for patients with mechanical valves, no INR recommended above target, 2.5 (range, 2.0–3.0)
Persistent atrial thrombus on transesophageal echocardiography	Warfarin (INR, 2.5–3.5 or higher) may be appropriate	Other than for patients with mechanical valves, no INR recommended above target, 2.5 (range, 2.0–3.0)
Prosthetic heart valves	Warfarin (INR, 2.5–3.5 or higher) may be appropriate	Depending on the type of prosthetic valve, warfarin (INR, 2.5 [range, 2.0–3.0] or INR, 3.0 [range, 2.5 to 3.5]) with or without additional aspirin, at a dose of 80 to 100 mg <sup>34</sup>
Warfarin recommended but contraindicated or refused	Aspirin at a dose of 325 mg per day	No divergence

\* According to the guidelines of the American College of Cardiology and American Heart Association (ACC-AHA) Task Force on Practice and the European Society of Cardiology (ESC) Committee for Practice, the risk factors for thromboembolism include heart failure, a left ventricular ejection fraction of less than 35 percent, and a history of hypertension.<sup>11</sup> INR denotes international normalized ratio.

† According to the American College of Chest Physicians (ACCP), moderate risk factors include an age of 65 to 75 years, diabetes mellitus, and coronary artery disease with preserved left ventricular function; high risk factors include previous stroke, transient ischemic attack, or systemic embolus; a history of hypertension; poor left ventricular systolic function; an age of 75 years or older; rheumatic mitral-valve disease; and the presence of a prosthetic heart valve.<sup>33</sup>



Table 2. Pharmacologic Agents to Control Heart Rate and Rhythm.\*

Drug (Class)†	Purpose	Usual Maintenance Dose	Adverse Effects	Cautions and Contraindications
Metoprolol (II)	Rate control (rhythm in some cases)	50–200 mg daily, divided doses or sustained-release formulation	Hypotension, heart block, bradycardia, asthma, congestive heart failure	—
Propranolol (II)	Rate control (rhythm in some cases)	80–240 mg daily, divided doses or sustained-release formulation	Hypotension, heart block, bradycardia, asthma, congestive heart failure	—
Diltiazem (IV)	Rate control	120–360 mg daily, divided doses or sustained-release formulation	Hypotension, heart block, congestive heart failure	—
Verapamil (IV)	Rate control	120–360 mg daily, divided doses or sustained-release formulation	Hypotension, heart block, congestive heart failure, interaction with digoxin	—
Digoxin	Rate control	0.125–0.375 mg daily	Toxic effects of digitalis, heart block, bradycardia	—
Amiodarone (III)	Rhythm control (rate in some cases)	100–400 mg daily	Pulmonary toxic effects, skin discoloration, hypothyroidism, gastrointestinal upset, hepatic toxic effects, corneal deposits, optic neuropathy, interaction with warfarin, torsades de pointes (rare)	—
Quinidine (IA)	Rhythm control	600–1500 mg daily, divided doses	Torsades de pointes, gastrointestinal upset, enhanced atrioventricular nodal conduction	Prolongs QT interval; avoid with left ventricular wall thickness $\geq 1.4$ cm
Procainamide (IA)	Rhythm control	1000–4000 mg daily, divided doses	Torsades de pointes, lupus-like syndrome, gastrointestinal symptoms	Prolongs QT interval; avoid with left ventricular wall thickness $\geq 1.4$ cm
Disopyramide (IA)	Rhythm control	400–750 mg daily, divided doses	Torsades de pointes, congestive heart failure, glaucoma, urinary retention, dry mouth	Prolongs QT interval; avoid with left ventricular wall thickness $\geq 1.4$ cm
Flecainide (IC)	Rhythm control	200–300 mg daily, divided doses	Ventricular tachycardia, congestive heart failure, enhanced atrioventricular nodal conduction (conversion to atrial flutter)	Contraindicated in patients with ischemic and structural heart disease
Propafenone (IC)	Rhythm control	450–900 mg daily, divided doses	Ventricular tachycardia, congestive heart failure, enhanced atrioventricular nodal conduction (conversion to atrial flutter)	Contraindicated in patients with ischemic and structural heart disease
Sotalol (III)	Rhythm control	240–320 mg daily, divided doses	Torsades de pointes, congestive heart failure, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease	Prolongs QT interval; avoid with left ventricular wall thickness $\geq 1.4$ cm
Dofetilide (III)	Rhythm control	500–1000 $\mu$ g daily, divided doses	Torsades de pointes	Prolongs QT interval; avoid with left ventricular wall thickness $\geq 1.4$ cm

\* The information in the table is adapted from Fuster et al.<sup>11</sup>

† The Vaughn Williams class of antiarrhythmic drugs is given for those classified. Digoxin is not classified in this system.

Table 3. Choice of Antiarrhythmic Agent According to the Underlying Cardiac Disorder.\*

Underlying Disorder	Rate Control†	Rhythm Control		
		First Choice	Second Choice	Third Choice
Minimal or no heart disease	$\beta$ -adrenergic blocker or calcium-channel blocker	Flecainide, propafenone, sotalol	Amiodarone, dofetilide	Disopyramide, procainamide, quinidine (or nonpharmacologic options)
Adrenergic atrial fibrillation with minimal or no heart disease	$\beta$ -adrenergic blocker	$\beta$ -adrenergic blocker or sotalol	Amiodarone, dofetilide	—
Heart failure	$\beta$ -adrenergic blocker, if tolerated; digoxin	Amiodarone, dofetilide	—	—
Coronary artery disease	$\beta$ -adrenergic blocker	Sotalol	Amiodarone, dofetilide	Disopyramide, procainamide, quinidine
Hypertension with LVH but wall thickness $<1.4$ cm	$\beta$ -adrenergic blocker or calcium-channel blocker	Flecainide, propafenone	Amiodarone, dofetilide, sotalol	Disopyramide, procainamide, quinidine
Hypertension with LVH and wall thickness $\geq 1.4$ cm	$\beta$ -adrenergic blocker or calcium-channel blocker	Amiodarone	—	—

\* LVH denotes left ventricular hypertrophy. The information in this table is adapted from Fuster et al.<sup>11</sup>

†  $\beta$ -adrenergic blockers include metoprolol and propranolol; calcium-channel blockers includes diltiazem and verapamil.

### Rate Control

Current guidelines recommend a ventricular rate during atrial fibrillation of 60 to 80 beats per minute at rest and 90 to 115 beats per minute during exercise.<sup>11</sup> A number of pharmacologic agents are available to control the heart rate and rhythm (Tables 2 and 3). Digoxin has been replaced as first-line therapy for rate control by  $\beta$ -adrenergic blockers and calcium-channel blockers, largely owing to improved rate control during exertion with the use of these alternative agents.<sup>11</sup> In one study, during peak exercise, the mean heart rate was 175 beats per minute in patients receiving digoxin, as compared with 130 in those receiving a  $\beta$ -adrenergic blocker and 151 in those receiving a calcium-channel blocker.<sup>40</sup> Digoxin is useful in combination with other agents<sup>40</sup> or when  $\beta$ -adrenergic-blocking agents and calcium-channel blockers are not tolerated. In some patients, particularly the elderly, the ventricular rate during atrial fibrillation may be intrinsically controlled, so that no atrioventricular nodal-blocking agent is required. Among patients with a pause that causes symptoms after the spontaneous conversion of atrial fibrillation, or those whose symptoms are due to low heart rates in spite of their having high heart rates at other times, a pacemaker may be necessary to permit therapy with atrioventricular nodal-blocking agents (as in the "tachy-brady" or the sick sinus syndrome).

### Rhythm Control

A number of agents may maintain sinus rhythm (Tables 2 and 3). The use of  $\beta$ -adrenergic agents may be effective in adrenergically mediated and paroxysmal atrial fibrillation<sup>43</sup> (although the effects may be related to the conversion of symptomatic atrial fibrillation into asymptomatic atrial fibrillation).<sup>24</sup> With the exception of the  $\beta$ -adrenergic-blocking agents, most antiarrhythmic drugs carry a risk of serious adverse effects. Antiarrhythmic therapy should be chosen on the basis of the patient's underlying cardiac condition (Table 3).<sup>11</sup> Antiarrhythmic agents classified according to the Vaughn Williams system as class IC are reserved to treat patients without a structural cardiac abnormality, and as described elsewhere,<sup>42</sup> may be prescribed for outpatients with acute conversion of paroxysmal atrial fibrillation (i.e., the so-called pill-in-the-pocket approach). Agents in classes IA and III should be avoided by patients with prolongation of the QT interval or left ventricular hypertrophy because of the potential for torsades de pointes. On the one hand, amiodarone, which has a low risk of proarrhythmia (less than 1 percent per year),<sup>43</sup> causes substantial noncardiac toxic effects and is therefore generally reserved for second-line therapy except in the treatment of patients with severe cardiomyopathy. On the other hand, it is the most effective antifibrillatory agent; in one trial, 65 percent of patients treated with amiodarone were free from recurrence after 16 months of therapy (as compared with 37 percent of those who were treated with propafenone or sotalol).<sup>44</sup>

### Rate Control versus Rhythm Control

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

lation — rate control versus rhythm control — does not have a substantial effect on the quality of life or on cardiovascular end points, including death.

Nonetheless, some questions remain. All three of these trials compared strategies with the use of an intention-to-treat analysis. The success rate for maintaining sinus rhythm was as low as 39 percent after 2.3 years of treatment<sup>46</sup> and as high as 73 percent at 3 years.<sup>47</sup> A secondary analysis of the data from the RACE trial showed that for patients with symptoms related to atrial fibrillation and those who were in sinus mechanism at the end of the follow-up period, regardless of the treatment randomly assigned, the quality of life had improved.<sup>48</sup> All three studies enrolled only patients for whom rhythm control was considered to be an option by both the patient and the physician; in highly symptomatic patients, rhythm control may still be preferable. For patients who have minimal symptoms or when sinus rhythm cannot be maintained, however, a strategy of rate control is safe and appropriate. Anticoagulant therapy should be continued, irrespective of the strategy used.

### Ablation

In the past decade, ablation for atrial fibrillation has become a therapeutic option. The initial efforts involved the creation of radiofrequency lines of conduction block, rather than surgical incisions.<sup>49</sup> The subsequent discovery that paroxysmal atrial fibrillation primarily emanates from the pulmonary veins<sup>50</sup> led to the use of focal-vein ablation and then to techniques to isolate the firing foci with the use of circumferential or segmental ablation near the ostia of the pulmonary veins.<sup>51</sup>

Recently, the use of anatomical ablation with lesions placed circumferentially around the right and left veins, with or without additional left atrial linear lesions, has been successful in patients with paroxysmal atrial fibrillation and those with persistent atrial fibrillation. In an observational study of 1171 patients, those who underwent ablation had significantly lower rates of recurrence after one year (16 percent) than those receiving antiarrhythmic drugs (39 percent)<sup>52</sup>; among the patients who underwent ablation, mortality and morbidity also were lower and the quality of life was better.

However, data are needed from a randomized trial to establish whether these differences are attributable to the therapy or to other factors. Early series primarily enrolled patients with normal left ventricular function, but in a recent study of 377 patients, one quarter had an ejection fraction below 40 percent,<sup>53</sup> and 73 percent of this group had no recurrence during a follow-up period of 14 months (as compared with 87 percent of the patients with a left ventricular ejection fraction of 40 percent or greater).<sup>53</sup>

Although new techniques and increased experience are associated with lower complication rates, concern persists about potential stroke and tamponade (events that are estimated to occur in 1 percent of cases among experienced physicians).<sup>54</sup> Furthermore, pulmonary-vein stenosis may occur in 5 to 6 percent of patients,<sup>55,56</sup> even when techniques to minimize the risk are used.<sup>57</sup> When a pulmonary-vein stenosis occurs, conservative management may be appropriate, but dilation with or without stenting may be necessary.<sup>55,56</sup>

#### AREAS OF UNCERTAINTY

Approaches to prevent the development of atrial fibrillation warrant further attention. Recent randomized trials involving patients with left ventricular dysfunction suggest that angiotensin-converting-enzyme inhibitors reduce the risk of atrial fibrillation.<sup>58,59</sup> These data emphasize the importance of treatment for hypertension and cardiovascular disease in such patients.

The role of ablation, as compared with antiarrhythmic therapy, remains uncertain; its use may increase as tools and techniques are improved. The role of new oral anticoagulant agents that are currently in development, which might obviate the need for dose adjustment and the measurement of INR values, needs to be determined. The direct thrombin inhibitor ximelagatran appears to be as effective as warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation.<sup>60</sup> However, clinical use of ximelagatran may be limited by its hepatic toxicity; the elevation of levels of alanine aminotransferase to more than three times the upper limit of normal occurred in 6 percent of the patients taking ximelagatran, as compared with 1 percent of those taking warfarin, and hepatic failure leading to death has been reported with the use of ximelagatran.<sup>61</sup>

#### GUIDELINES

The American College of Cardiology and American Heart Association (ACC-AHA) Task Force on Practice and the European Society of Cardiology (ESC) Committee for Practice have published guidelines for the management of atrial fibrillation<sup>11</sup> that recommend the "minimum evaluation" of newly discovered atrial fibrillation, mentioned earlier, and advise on the use of antiarrhythmic agents (Tables 2 and 3).<sup>11</sup> These guidelines suggest that there is "no clear advantage"<sup>11</sup> to a strategy of rate control as compared with rhythm control. Their recommendations for antithrombotic therapy are similar to, but not identical with, those published by the American College of Chest Physicians (ACCP)<sup>33,34</sup> (Table 1). A third set of guidelines, proposed by the American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP),<sup>35</sup> recommend less aggressive

anticoagulant therapy with warfarin. This set of guidelines defines patients who have no history of stroke or transient ischemic attack and have only a single risk factor for stroke (e.g., an age of 75 years or older, congestive heart failure, hypertension, or diabetes)<sup>35</sup> as at low risk (i.e., not in need of warfarin therapy).

#### RECOMMENDATIONS

The patient described in the vignette presented with atrial fibrillation that was asymptomatic and may have been present for months (as suggested by the failure of the treadmill monitor to measure her heart rate). The evaluation should include testing with electrocardiography, echocardiography, and chest radiography and measurement of the serum thyrotropin level. On the basis of data from randomized trials, her survival would not be improved by the use of strategies aimed at conversion and the maintenance of sinus rhythm, and no strategy could improve her symptoms since she has none. Thus, I would continue heart-rate-control therapy with the use of her current  $\beta$ -adrenergic-blocking agent. Her age and hypertension place her at elevated risk for thromboembolism, and anticoagulant therapy with warfarin is indicated, with a target INR of 2.0 to 3.0. Because atrial fibrillation represents a marker of risk for atherosclerotic disease and stroke,<sup>62</sup> I would also assess the patient for and aggressively treat other risk factors for cardiovascular disease, including her hypertension.

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

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## ADDENDUM

Since publication of this article, atrio-esophageal fistula has been reported as an additional rare complication of percutaneous transcatheter ablation of atrial fibrillation.<sup>1</sup>

1. Pappone C, Oral H, Santinelli V, et al. Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. *Circulation* 2004;109:2724-6.

# *Prophylaxis against Rabies*

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A six-month-old girl presents for a “well-baby” appointment in New Jersey. The mother is concerned about a dead bat she found in the child’s bedroom.

A Virginia businessman relaxing on his patio after work pulls a toy from his puppy’s mouth. He notices a dead raccoon within his fenced yard, where his puppy has been playing, and telephones you for advice.

You receive e-mail from a South American colleague, who has been bitten by a stray dog while jogging. She solicits your medical opinion.

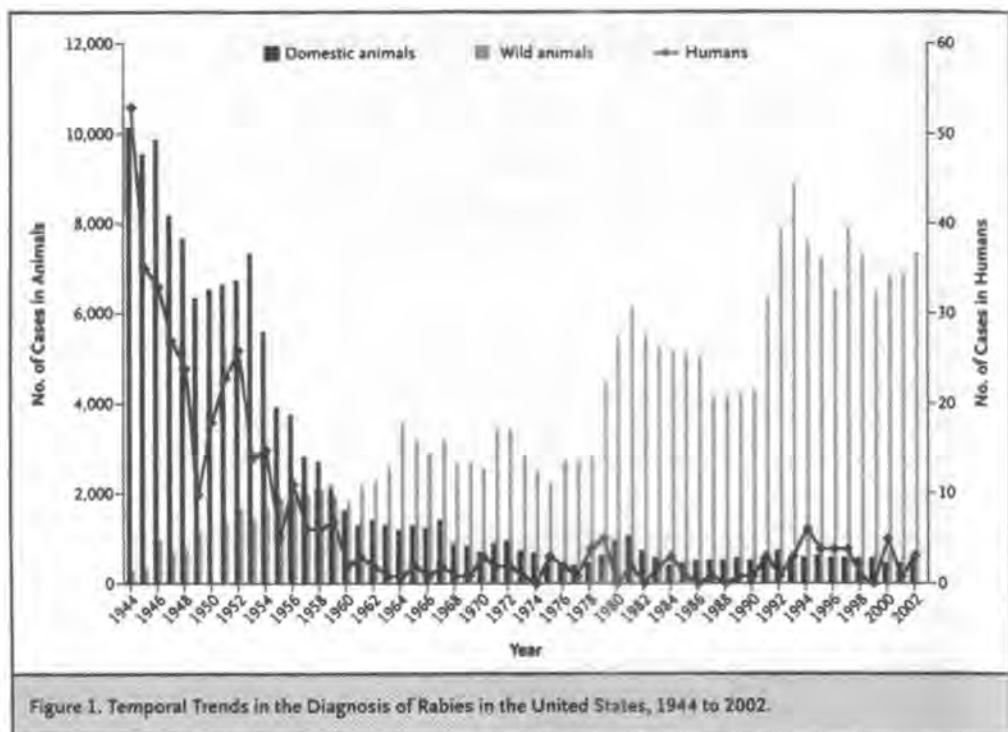
How would you manage these situations?

## THE CLINICAL PROBLEM

**H**uman rabies is uncommon in developed nations.<sup>1-5</sup> In the United States, scores of deaths from rabies were documented annually in the early 20th century. Now, fewer than three deaths are reported each year, most without a documented exposure (Figure 1 and Table 1). Still, this zoonosis exerts a disproportionate influence on health resources because of the necessity for prophylactic measures, including the administration of biologic agents. Continued apprehension is rooted in ancient superstitions, the dramatic manifestation of hydrophobia, and the extreme case fatality ratio. Cases of the disease in humans are preventable, but enzootic foci are plentiful and are not eliminated easily. The public may not appreciate that their surroundings are a veritable sea of rabies, maintained by common animals (Table 2).

Globally, dogs are the major reservoirs. Bites from rabid dogs cause tens of thousands of deaths per year and prompt prophylactic treatment in millions of persons.<sup>4,5</sup> Recent assessments illustrate that the magnitude of rabies in developing countries is grossly underestimated.<sup>6</sup> Exposures may occur as single events, or one rabid animal may expose multiple people.<sup>7</sup> In the United States, 15,000 to 40,000 people receive prophylaxis annually.<sup>8</sup>

Prophylaxis is effective and safe, but it is expensive and is often used inappropriately.<sup>9,10</sup> As with any pharmaceutical agent, minimal considerations when prophylactic measures



are used include proper training, storage, handling, administration, infection-control precautions, and sterile technique.

#### Nature of the Infection

Rabies is an acute progressive encephalitis caused by RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus*.<sup>11-14</sup> Rabies virus is the only known lyssavirus in the New World. Some locations are considered rabies-free: among them are Hawaii and many islands in the Pacific Ocean and the Caribbean (except Cuba, the Dominican Republic, Haiti, Grenada, and Puerto Rico).<sup>15</sup> However, their continued freedom from rabies depends on effective methods to prevent introduction of the virus and depends on active laboratory-based surveillance.

All mammals are susceptible and can transmit rabies virus, but true reservoirs, which are responsible for ultimate long-term disease maintenance, persist only among *Carnivora* (mainly carnivorous mammals) and *Chiroptera* (bats).<sup>15</sup> Specific viruses are adapted to these hosts and typically perpetuate infection within a species before the hosts die. In North America, raccoons, skunks, bats, and foxes are the primary reservoirs responsible

Table 1. Sources of Human Exposure to Rabies in the United States.

Year	Domestic Animal <sup>a</sup>	Wildlife	Other Sources <sup>b</sup>	Unknown <sup>c</sup>	Total No. of Cases
<i>number of cases (percent)</i>					
1946-1955	86 (72)	3 (7)	0	26 (22)	115
1956-1965	21 (55)	7 (18)	0	10 (26)	38
1966-1975	6 (38)	7 (44)	1 (6)	2 (12)	16
1976-1985	6 (30)	1 (5)	2 (10)	11 (55)	20
1986-1995	2 (12)	1 (6)	0	14 (82)	17
1996-2003	4 (19)	2 (10)	0	15 (71)	21

\* After 1979, there were no cases involving documented exposure to a domestic animal known to be rabid or probably rabid. Thereafter, all cases originated in countries where canine rabies was endemic.

† Other sources of exposure included laboratory aerosol (in 1972 and 1977) and corneal transplantation (in 1978).

‡ If a definitive source of exposure was not identified in the patient's history, the source of exposure was considered to be unknown, regardless of the source suspected on the basis of antigenic or genetic characterization.

for transmission (Table 2). Unvaccinated domestic animals and humans become rabid after exposure to such reservoirs. By definition, all reservoirs are capable of transmitting infection, but not all potential vectors are reservoirs. For example, livestock die of the disease without effective prolonged transmission. Cats (usually infected by dogs or wild animals) are effective vectors but do not sustain the disease.

In developed countries, the incidence of human exposure to rabid domestic animals has decreased as a result of improved canine vaccination.<sup>16</sup> Whereas more than 9000 rabid dogs were reported in the United States in 1944, fewer than 100 were reported in 2002.<sup>15</sup> Because cats are popular but less well supervised and less often vaccinated than dogs, rabid cats now outnumber rabid dogs. Rabies in small mammals (such as mice and squirrels) is rare, and transmission from them to humans remains undocumented.<sup>17</sup> Larger rodents, like woodchucks, are more frequently reported to be rabid (Table 2).

### Transmission

In nature, the rabies virus is labile; is inactivated by sunlight, heat, desiccation, and other environmental factors; and is not viable outside the host. Exposure occurs when there is penetration of the skin by teeth or direct transdermal or mucosal contact with infectious material, such as brain tissue or saliva. Almost all cases are caused by bites from infected mammals.

Table 2. Cases of Animal Rabies in the United States.

Animal*	Average No. of Cases, 1998–2002	Geographic Focus†
Raccoon	2162	Eastern United States
Skunk	2257	California, upper and lower Midwest, eastern United States
Bat	1175	Entire United States, except Hawaii
Fox	443	Alaska, Texas, southwestern United States
Cat	276	Entire United States, except Hawaii
Cattle	106	Entire United States, except Hawaii
Dog	105	Entire United States, except Hawaii
Horse or mule	62	Entire United States, except Hawaii
Mongoose	58	Puerto Rico
Woodchuck	50	Eastern United States
Bobcat	30	Entire United States, except Hawaii
Sheep or goat	9	Entire United States, except Hawaii
Other wild animal	24	Entire United States, except Hawaii
Other domestic animal	3	Entire United States, except Hawaii

\* All mammals are considered to be susceptible to rabies, and incidental (or spillover) infection from wild-animal reservoirs may occur in any species.

† Rabies may occur in an exposed animal in any location; the geographic foci listed here are based on current epidemiologic trends. No cases of rabies have been reported in Hawaii or in American Samoa, the Commonwealth of the Northern Mariana Islands, Guam, or the U.S. Virgin Islands.

Lyssaviruses are highly neurotropic and travel by retrograde axoplasmic flow from the periphery to the central nervous system.<sup>18</sup> Replication occurs primarily in neurons. There is passive, centrifugal movement from the brain to other organs or glands, such as the salivary glands. The virus is excreted abundantly in saliva. Excretion is concomitant with the development of clinical signs but may begin several days beforehand. The virus may be detected in practically any tissue.

According to experimental data and epidemiologic observations, some domestic species may be observed for signs of rabies. A healthy dog, cat, or ferret that exposes a person may be observed for 10 days.<sup>16</sup> If the animal remains healthy, the patient does not need prophylaxis; only wound care is needed. If the animal sickens with signs compatible with rabies, it should be euthanized and the brain should immediately be examined. If infection is confirmed within 24 to 48 hours after the animal is euthanized, there is adequate

Table 3. Biologic Agents Licensed in the United States for Human Rabies Prevention \*

Product	Dose	Route	Indications
<b>Vaccines†</b>			
AbAvert (Chiron Behring)‡	1 ml	Intramuscular	Preexposure or postexposure§
Rabies vaccine adsorbed (BioPort)¶	1 ml	Intramuscular	Preexposure or postexposure§
Imovax Rabies (Aventis Pasteur)‡	1 ml	Intramuscular	Preexposure or postexposure§
<b>Human rabies immune globulins**</b>			
BayRab (Bayer)	70 IU/kg	Local††	Postexposure only
Imogam Rabies-HT (Aventis Pasteur)	20 IU/kg	Local††	Postexposure only

\* Adverse reactions include pain, erythema, swelling, or induration (in 15 to 74 percent of recipients); itching or local lymphadenopathy; headache, malaise, myalgia, or dizziness (10 to 25 percent); gastrointestinal symptoms (in less than 10 percent); allergic reactions during primary vaccination (in 0.1 percent [less than 10 percent of whom have anaphylactic reactions]); type III hypersensitivity reactions (in 6 to 10 percent after booster doses of human diploid cell vaccine and in fewer during primary vaccination).<sup>23-26</sup> Precautions should be taken if a serious allergic reaction has been documented after previous administration of a product or component.

† The vaccines are inactivated with beta-propiolactone. Additives (e.g., polygeline) or residual substances used during the manufacturing process (e.g., antibiotics) may be present.

‡ This vaccine is a lyophilized preparation.

§ For postexposure prophylaxis, the vaccine is administered on days 0, 3, 7, 14, and 28 in patients who have not previously been vaccinated and on days 0 and 3 in patients who have been previously vaccinated; for preexposure prophylaxis, the vaccine is administered on days 0, 7, and 21 or 28.

¶ This vaccine is currently not available.

‡ Imovax Rabies I.D., given by the intradermal route, is no longer available in the United States.

\*\* Human rabies immune globulins are purified from the serum of vaccinated donors. Historically, licensed human rabies immune globulins in the United States have been safe. No human infection with adventitious agents has been documented.

†† As much of the product as is anatomically feasible is infiltrated into and around the wound, and any remainder is administered intramuscularly, in the deltoid or quadriceps (at a location other than that used for vaccine inoculation, to minimize potential interference).

time to begin prophylaxis. After exposure to wildlife in which rabies is suspected, prophylaxis is warranted in most circumstances. Vaccination is discontinued if tests of the animal's brain tissue are negative for infection.

## STRATEGIES AND EVIDENCE

### Prophylaxis

Decisions regarding prophylaxis are complex: they depend on local epidemiology, the nature of the animal involved and its behavior, the degree of contact, and (when possible) the results of diagnostic testing. Procedures include treatment of the patient after exposure as well as vaccination of those at risk for exposure. Efficacy data for prophylaxis are generated by experiments in animals as well as clinical trials.<sup>19</sup>

Postexposure prophylaxis consists of three primary elements: wound care, infiltration of rabies immune globulin, and vaccine administration.<sup>20</sup> Immediate and thorough washing of wounds with a soap solution may considerably reduce the risk of contracting rabies.<sup>21</sup> Other measures, such as the use of tetanus toxoid or antibiotics, are applied as needed.<sup>22</sup> Decisions are urgent, because delays may affect the outcome. Postexposure prophylaxis is highly effective if applied appropriately. In the United States, no failures have been reported since 1979.<sup>1-3</sup>

### Vaccines

Three rabies vaccines are licensed in the United States. Table 3 summarizes their uses and potential adverse effects, which are generally minor.<sup>20,27-31</sup> Serious reactions are infrequent<sup>32</sup> and are less common with current cell-culture vaccines than with products derived from nerve tissue.<sup>33</sup> Although associations have been reported between current vaccines and cases of neurologic illness, causality has not been established.<sup>34-39</sup>

When possible, the same product is used for an entire vaccine series. Switching to another product is reasonable if sensitivity to a vaccine or its components develops between doses, although follow-up data are limited.<sup>20,40</sup> Prophylaxis should not be discontinued after the development of local or mild systemic signs.

Modern cell-culture vaccines are potent, but the immunity they afford eventually wanes. After primary vaccination, additional doses are needed after known exposures or as part of routine maintenance of the antibody titer in persons deemed at risk (as discussed below). When booster doses of vaccine are given, complex anamnestic responses occur: they include the stimulation and deployment of existing memory T cells, the differentiation of memory B cells into antibody-secreting cells, elicitation of additional memory B cells, and replenishment of antigen depots at lymphoid germinal centers.

### Human Rabies Immune Globulin

Passive administration of virus-neutralizing antibodies, before a patient mounts an active immune response from vaccination, is an important part of postexposure prophylaxis.<sup>20</sup> For patients who have not been vaccinated, human rabies immune globulin is administered only once, concomitantly with vaccine. When there is a visible wound, as much of the dose as is feasible is infiltrated directly into the wound (Table 3). The expense and limited distribution of human rabies immune globulin, however, are problems in the developing world.<sup>4</sup> Equine rabies immune globulin may be an alternative. Multisite intradermal vaccination is another possible strategy to accelerate the immune response.

As compared with unpurified or heterologous serum, modern commercial preparations of human rabies immune globulin are highly safe and are not associated with the acquisition of disease. Human blood products can contain antibodies to other agents and may inhibit immune responses to noninactivated viral vaccines. Interference depends on the amount of specific antibody. Administration of vaccines such as measles and varicella vaccines should be delayed for at least four months after postexposure prophylaxis to allow the degradation of human rabies immune globulin.<sup>41,42</sup> If the interval is shorter, additional vaccination may be necessary, unless serologic testing indicates that the immunologic response has been appropriate.

### **Preexposure Vaccination**

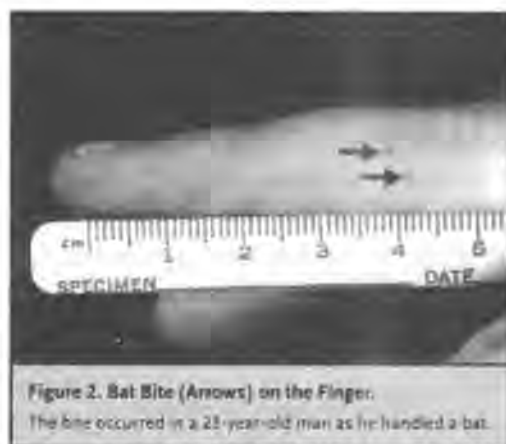
It is recommended that vaccination be provided to persons at risk (laboratory workers, diagnosticians, veterinarians and their staff, animal-control officers, rabies researchers, and some travelers to areas where rabies is prevalent) before exposure.<sup>20</sup> This strategy simplifies the management of a subsequent exposure because fewer doses are needed and because human rabies immune globulin is not required (Table 3). To avoid injury to sciatic nerves and lessen the delivery to adipose depots, it is recommended that the gluteal region not be used for administration.<sup>41</sup> Routine serologic analysis for verification of the presence of virus-neutralizing antibody is unnecessary after primary vaccination, unless major interruptions in the schedule occur or questions arise about immune competence. Thereafter, the need for routine booster vaccination may be monitored by serologic testing performed every six months to two years as long as a person remains at risk. If titers fall below a minimal acceptable level (i.e., complete neutralization at a serum dilution of 1:5), a single vaccine booster is administered. Healthy adults maintain adequate titers for years. No absolute protective level exists, and two booster doses are administered as part of postexposure prophylaxis, regardless of titer. Antibodies are important but are only one means of preventing a productive viral infection. More short-lived immune functions, such as cytokine responses, are reinvigorated in response to vaccination.

## **AREAS OF UNCERTAINTY**

### **Bats and Rabies**

"Cryptic" human cases, in which there is no history of exposure to a rabid animal, are now the norm in the United States (Table 1). Molecular characterization has determined that the majority of these cases are associated with bat rabies viruses.<sup>43</sup> Bat bites are not dramatic and may not be appreciated when they occur or when the patient is examined





(Figure 2). In other cases, people may recognize that a bite has occurred but may not comprehend its implications<sup>44</sup> or may believe that the risk of rabies is exceedingly low.<sup>45</sup> Certain persons, such as young children or persons with disabilities, may be unable to provide an accurate history of a bite. When in doubt, attempts should be made to capture animals safely for submission to a laboratory.

Rabies is not commonly reported in free-ranging bats (estimated frequency, less than 1 percent, according to field surveillance) and is diagnosed in approximately 5 to 15 percent of bats submitted for public health evaluation. If test results are negative, postexposure prophylaxis is unnecessary. As with wild-carnivore bites, prophylaxis should begin if the bat is unavailable for examination.<sup>20</sup> Once the risks have been explained, many patients without a definitive exposure (such as healthy adults who are light sleepers or who had body parts covered and would have detected a bat bite) may elect to forgo postexposure prophylaxis.

#### Exposures Other Than Bites

Since 1960, exposures other than bites have resulted in fewer than 35 well-documented human cases.<sup>46</sup> Most of the reported cases were due to poorly inactivated vaccine (in 18 instances) or transplantation (in 12). Although extremely uncommon, transplantation of tissue from a donor with rabies will have disastrous consequences for the transplant recipient, as has recently been described.<sup>47</sup> No cases in humans after indirect, nonbite exposure, such as touching a pet that may have been exposed to a rabid animal, have been reported. Theoretically, human-to-human transmission is possible, but no cases have been documented among health care workers. Barrier procedures and personal-protection equipment minimize the risk of true exposure.

Many circumstances, though fueled by fear, are not indications for prophylaxis. The medical care of a patient with rabies can cause anxiety on the part of the clinician because of the voluminous production of saliva and the opportunity for unnoticed exposure. Often, postexposure prophylaxis is entertained because the threat of disease is erroneously considered to be greater than unanticipated risks of vaccination. *Primum non nocere*: if the benefits do not outweigh the risks, postexposure prophylaxis should not be performed.

### Schedules and Delays

Clinicians should adhere to prophylaxis schedules. Deviations of a few days are unimportant, but the effect of lapses lasting weeks or months is unknown. Most deviations will not require complete reinitiation of vaccination.<sup>41</sup> For example, if a patient who had begun postexposure prophylaxis missed the dose scheduled for day 14 and attended a clinic visit on day 21, vaccination may be continued with administration of doses at intervals as if the patient had been on schedule. When in doubt, the patient's immune status may be monitored by serologic testing 7 to 14 days after the final dose is given.<sup>20</sup>

Prophylaxis should be instituted whenever exposure is suspected, and it is warranted regardless of the interval between exposure and presentation. Delays in initiating prophylaxis are associated with treatment failure.<sup>48</sup> Typical incubation periods are between one and three months<sup>1-3</sup>; in rare cases, incubation periods are less than two weeks or exceed one year.<sup>49,50</sup> The extent of delay that renders postexposure prophylaxis ineffective is not known.<sup>51</sup>

### Travel

Rabies vaccination is not warranted for most routine international travel.<sup>52</sup> Business ventures lasting several days are unlikely to pose a substantive risk. If an exposure does occur, timely access to proper care can be sought on the traveler's return. Concerns related to the rise in ecotourism are minimized by careful planning, tempered with common sense. Minimally, all travelers should receive education about rabies and refrain from contact with animals. Modern biologic agents are not readily available in developing countries. Regardless of the duration of travel, if the location and activity are such that contact with animals is probable but opportunities for intervention are unlikely (especially in the case of travel to a remote region where rabies is endemic), preexposure vaccination should be encouraged.<sup>20</sup> Guidelines related to travel are available from the Centers for Disease Control and Prevention (<http://www.cdc.gov/travel/diseases/rabies.htm>).

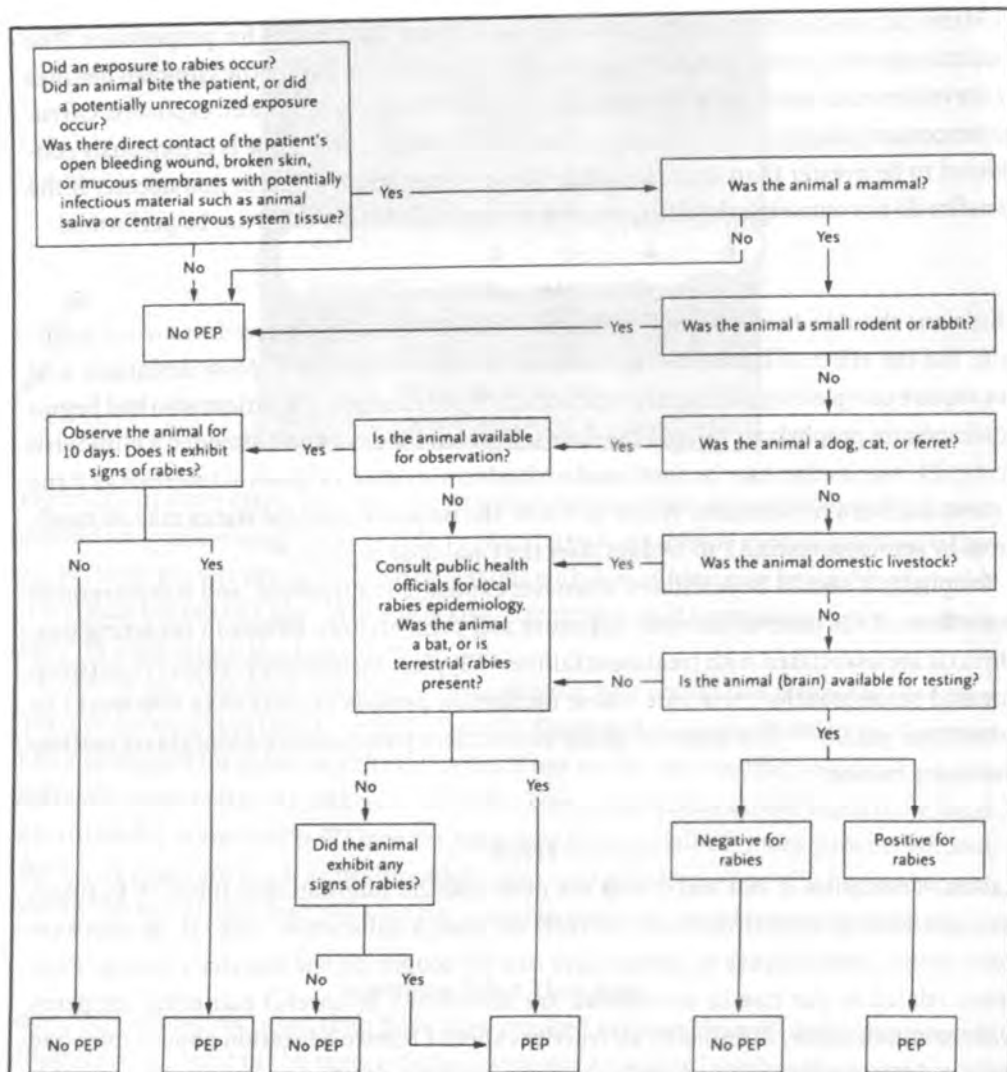


Figure 3. General Guidelines for Prophylaxis against Rabies in the United States.

Bites from bats and high-risk wild carnivores such as raccoons, skunks, foxes, bobcats, coyotes, and mongoose are of great concern and warrant consideration of immediate postexposure prophylaxis (PEP). In the case of direct contact between a human and a bat, the possibility of a bite should be considered unless the exposed person can be reasonably certain that a bite did not occur. PEP should be considered for persons who were in the same room as a bat and who might be unaware, or unable to communicate, that a bite had occurred. Rabies has been reported in large rodents (e.g., woodchucks and beavers) in areas where terrestrial rabies is enzootic. Rabies has rarely been diagnosed in small mammals such as rabbits and small rodents (e.g., squirrels, chipmunks, rats, hamsters, gerbils, guinea pigs, and mice).

(continued on next page)

### Pregnancy

Specific testing of reproductive outcomes has not been performed, but pregnancy is not a contraindication to postexposure prophylaxis against rabies. Vaccination has not been associated with adverse outcomes.<sup>53</sup> Prophylaxis is appropriate after exposure to protect the life of the mother and the fetus. Exposure, or the diagnosis of rabies in the mother, is not an indication for termination of the pregnancy.

### Treatment

Once symptoms begin, treatment is largely futile. Patients usually die within days to weeks after presentation. Historically, five patients who survived represent unusual occurrences and received some form of prophylaxis before onset. Diagnosis by detection of virus, antigen, antibodies, or nucleic acid in the patient's saliva, tissues, serum, or cerebrospinal fluid warrants attempts to treat,<sup>54</sup> although management is essentially palliative. Experimental trials have included rabies immune globulin, interferon, and ribavirin, without beneficial effect.<sup>45</sup>

### GUIDELINES

The Advisory Committee on Immunization Practices (ACIP) publishes routine protocols for prevention of human rabies in the United States (<http://www.cdc.gov/nip/publications/acip-list.htm>).<sup>20</sup> The information presented in this article is consistent with the ACIP guidelines. The recommendations of the American Academy of Pediatrics are in accord

(continued from previous page)

There has never been a documented case of transmission from these small mammals to a human. PEP may be considered for the latter in unusual circumstances (e.g., a bite from a small mammal with a history and clinical signs compatible with rabies), unless the animal is available for testing and is negative. An apparently healthy dog, cat, or ferret that bites a person should be confined and observed daily for 10 days. (The determination of whether a bite was provoked is necessarily subjective. For domestic animals, territorial-defense-related aggression and bites that occur when the animal is surprised, startled, or manipulated are generally viewed as provoked.) The animal should not receive a rabies vaccine during the observation period. A veterinarian should evaluate the animal at the first sign of illness. Management of animals other than dogs, cats, and ferrets depends on the species, the circumstances of the bite, the local rabies epidemiology, and the biting animal's history, current health status, and potential for exposure to rabies. Because prior vaccination of an animal may not be 100 percent effective, current vaccination does not preclude the necessity of a 10-day observation period or, as warranted, euthanasia and testing. State and local authorities should be informed of biting incidents involving cats, dogs, and ferrets. If the animal exhibits signs of rabies during the 10-day observation period, the patient should immediately begin to receive prophylaxis, and the animal should be euthanized and its brain tissue tested for rabies. If the animal is confirmed to have been rabid, PEP should be completed; if test results are negative, PEP can cease. Diagnostic testing of brain tissue should be completed within 24 to 48 hours so that a decision about starting PEP can be made. If the diagnosis cannot be completed within this period, prophylaxis should be started, pending the results of testing. Incubation periods of less than one week have been reported after severe bites on the face, head, and neck. The initiation of PEP should be considered in persons with such exposures before the results of laboratory testing become available.

with those of the ACIP; vaccine doses during postexposure prophylaxis are equivalent in adults and children.<sup>55</sup> The National Association of State Public Health Veterinarians regularly issues a compendium of recommendations for the prevention and control of rabies in animals.<sup>16</sup> As a barrier to human infection, pets and other animals should be vaccinated and receive regular booster doses. Exposed, currently vaccinated animals should receive immediate booster doses, whereas unvaccinated animals should either be euthanized or quarantined. The World Health Organization maintains information on the global distribution of rabies and recommendations for postexposure prophylaxis, including alternative vaccines, schedules, and routes, on its Web site (<http://www.who.int/emc-documents/rabies/whocdscsreph200210.html>).<sup>5,56</sup> Booster doses of vaccine are suggested when the antibody titer in a patient at risk falls below 0.5 IU per milliliter.

#### SUMMARY AND RECOMMENDATIONS

Once symptoms develop, rabies is almost invariably fatal. The overarching public health goals are to educate the public about the disease, prevent exposures, offer vaccination to those at increased risk, and administer postexposure prophylaxis appropriately. Figure 3 provides general guidance for the most common circumstances encountered in the United States.

The child described in the first vignette should be examined thoroughly for any evidence of a small lesion compatible with a bite wound. If the bat is available, the carcass should be sent to a diagnostic facility. Postexposure prophylaxis is unnecessary if test results in the bat are negative. However, prophylaxis is needed if the bat is found to have been rabid. If the bat is unavailable, consultation with the local or state health department is appropriate, and prophylaxis should be considered if it is likely that the child was exposed.

In the second vignette, the owner has not been exposed, even if his puppy had contact with the raccoon sometime that morning. Actions should focus on diagnostic testing of the raccoon and pet management, depending on the results and depending on the immune status of the puppy.

In the last vignette, the action to be taken depends on the specific circumstances. If the suspicion of rabies is low (i.e., the dog appeared healthy; the attack was provoked; the woman was bitten on an ankle through her clothing; there were only minor abrasions, which were washed well; and the episode occurred in a major city free of canine rabies in recent years, such as Rio de Janeiro or Montevideo, Uruguay) or if the dog is found alive, prophylaxis is not indicated. If the bite occurred in an area where canine rabies is endemic,

**immediate postexposure prophylaxis is warranted, either with locally produced biologic agents or those obtained from the closest major urban area or country.**

The views expressed in this article are those of the authors and do not necessarily represent the official policies of the Centers for Disease Control and Prevention, the Department of the Army, or the Department of Defense.

Use of trade names does not constitute government endorsement.

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### ADDENDUM

Rabies remains a major global health problem and a consuming medical challenge. Recently, recovery was reported of a patient with rabies after the induction of coma and use of antiviral drugs.<sup>1</sup> Such treatment strategies offer hope but require confirmation in other cases.

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# Attention Deficit–Hyperactivity Disorder

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MARSHA D. RAPPLEY, M.D.

A mother brings in her eight-year-old son for evaluation after he is suspended from riding the school bus for jumping out of his seat, teasing other children, and not following directions. He spends two to three hours a night with homework that he never successfully completes. His mother wants to know whether he has attention deficit–hyperactivity disorder. How should he be evaluated and treated?

## THE CLINICAL PROBLEM

Attention deficit–hyperactivity disorder (ADHD) is characterized by the inability to marshal and sustain attention, modulate activity level, and moderate impulsive actions. The result is maladaptive behaviors that are inconsistent with age and developmental level. Evidence from neuropsychological, pharmacologic, and brain-imaging studies implicates dopamine and norepinephrine neurotransmitter systems in frontostriatal circuitry in the pathophysiology of the disorder. Genetic factors appear to play an important role.<sup>1–3</sup> Extremely low birth weight (less than 1000 g)<sup>4</sup> and environmental conditions, such as head trauma and exposure to lead, are also associated with symptoms of ADHD.

The diagnosis of ADHD requires the identification of specific behaviors that meet the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, revised (DSM-IV-R)<sup>5</sup> (Table 1). Three types of ADHD are diagnosed: combined inattentive, hyperactive, and impulsive (about 80 percent of patients); predominantly inattentive (about 10 to 15 percent); and predominantly hyperactive and impulsive (about 5 percent).

The prevalence of ADHD is estimated at 3 to 7 percent of all children. Boys are more often affected than girls (the ratio ranges, according to the population studied, from 9 to 1 to 2.5 to 1), but increasingly, cases involving girls are being identified.<sup>5,6</sup> ADHD is a chronic condition with symptoms experienced over a lifetime.<sup>7</sup> This review focuses on ADHD in children and adolescents.

Table 1. Criteria for the Diagnosis of ADHD.\*

The diagnosis requires evidence of inattention or hyperactivity and impulsivity or both

**Inattention**

Six or more of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:

- Often fails to give close attention to details and makes careless mistakes.
- Often has difficulty sustaining attention
- Often does not seem to listen
- Often does not seem to follow through
- Often has difficulty organizing tasks
- Often avoids tasks that require sustained attention
- Often loses things necessary for activities
- Often is easily distracted
- Often is forgetful

**Hyperactivity and impulsivity**

Six or more of the following symptoms of hyperactivity and impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:

- Often fidgets
- Often leaves seat
- Often runs about or climbs excessively
- Often has difficulty with quiet leisure activities
- Often is "on the go" or "driven by a motor"
- Often talks excessively
- Often blurts out answers
- Often has difficulty awaiting turn
- Often interrupts or intrudes

**Symptoms that cause impairment:**

- Are present before 7 years of age
- Are present in two or more settings (e.g., home, school, or work)
- Do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or another psychotic disorder
- Are not better accounted for by another mental disorder (e.g., a mood disorder or an anxiety disorder)

\* The criteria are adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, revised.<sup>5</sup>

## STRATEGIES AND EVIDENCE

### Diagnosis

The abilities to focus attention, regulate activity, and control impulses emerge for all children in a developmental process. Thus, the diagnosis of ADHD is based on a comprehensive history that elicits symptoms specific to the diagnosis, the context in which these symptoms occur, and the degree to which these are inconsistent with age and persist to cause impairment.<sup>8</sup>

Evidence of symptoms is obtained directly from the child, the parents, and the teachers. The National Initiative for Children's Healthcare Quality Vanderbilt Assessment Scale

Table 2. Mental Health Conditions That Mimic or Coexist with ADHD.

Disorder	Symptoms Overlapping with ADHD	Features Not Characteristic of ADHD	Diagnostic Problem
Learning disorders	Underachievement in school Disruptive behavior during academic activity Refusal to engage in academic tasks and use academic materials	Underachievement and disruptive behavior in academic work, rather than in multiple settings and activities	It can be difficult to determine which to evaluate first — a learning disorder or ADHD (follow the preponderance of symptoms)
Oppositional defiant disorder	Disruptive behavior, especially regarding rules Failure to follow directions	Defiance, rather than unsuccessful attempts to cooperate	Defiant behavior is often associated with a high level of activity It is difficult to determine the child's effort to comply in instances of a negative parent-child or teacher-child relationship
Conduct disorder	Disruptive behavior Encounters with law-enforcement and legal systems	Lack of remorse Intent to harm or do wrong Aggression and hostility Antisocial behavior	Fighting or running away may be reasonable reactions to adverse social circumstances
Anxiety, obsessive-compulsive disorder, or post-traumatic stress disorder	Poor attention Fidgetiness Difficulty with transitions Physical reactivity to stimuli	Excessive worries Fearfulness Obsessions or compulsions Nightmares Reexperiences of trauma	Anxiety may be a source of high activity and inattention
Depression	Irritability Reactive impulsivity Demoralization	Pervasive and persistent feelings of irritability or sadness	It may be difficult to distinguish depression from a reaction to repeated failure, which is associated with ADHD
Bipolar disorder	Poor attention Hyperactivity Impulsivity Irritability	Expansive mood Grandiosity Manic quality	It is difficult to distinguish severe ADHD from early-onset bipolar disorder
Tic disorder	Poor attention Impulsive verbal or motor actions Disruptive activity	Repetitive vocal or motor movements	Tics may not be apparent to the patient, the family, or a casual observer
Adjustment disorder	Poor attention Hyperactivity Disruptive behavior Impulsivity Poor academic performance	Recent onset Precipitating event	Chronic stressors, such as having a sibling with mental illness, or attachment-and-loss issues may produce symptoms of anxiety and depression

for parents and teachers consists of checklists of behaviors that can help the primary care physician assess the child with ADHD.<sup>9</sup> Parents and teachers rate the child's symptoms on a scale of "never" to "very often" on items derived from the DSM-IV-R criteria for ADHD. They also rate the child's school performance and interpersonal relationships. The scores indicate whether impairment meets the diagnostic criteria for ADHD. Although the checklists reflect subjective impressions, they allow a comparison of the patient with children of the same age and are the best available tool to discern behavior that exceeds normal variation.

Behaviors of ADHD may overlap or coexist with other mental health conditions (Table 2). The most common conditions are learning and language disorders, oppositional defiant disorder, conduct disorder, anxiety, and depression, as well as bipolar, post-traumatic stress, tic, and adjustment disorders.<sup>10</sup>

Table 3. Guidelines for the Diagnosis and Treatment of Patients with ADHD.\*

## Diagnosis

- Comprehensive developmental, social, and family history
- Standardized checklists to assess behaviors<sup>9,10</sup>
- Consideration of coexisting mental health disorders
- Physical examination, not to diagnose ADHD but to assess genetic and other conditions

## Treatment

- Management of ADHD as a chronic health condition
- Establishment of treatment goals agreed on by the child, the family, and school personnel
- Medication with stimulants to manage symptoms (monotherapy)†
- Behavioral therapy for parent-child discord and persistent oppositional behavior

## Desired outcomes of treatment

- Improved relationships with family, teachers, and peers
- Decreased frequency of disruptive behavior
- Improved quality of and efficiency in completing academic work, and increased quantity of work completed
- Increased independence in caring for self and carrying out age-appropriate activities
- Improved self-esteem
- Enhanced safety (e.g., care in crossing streets, staying with an adult in public places, and reduced risk-taking behavior)

\* This information has been compiled from the guidelines of the American Academy of Pediatrics,<sup>7,13</sup> the American Academy of Child and Adolescent Psychiatry,<sup>15,16</sup> the European Society for Child and Adolescent Psychiatry,<sup>17</sup> and the Scottish Intercollegiate Guidelines Network.<sup>18</sup>

† Atomoxetine is recommended by the American Academy of Child and Adolescent Psychiatry as a possible alternative to stimulant medication.<sup>20</sup>

A careful history is warranted of the development of motor, social, and language skills, as well as of temperament, sleep habits, school achievement, moods, worries, and relationships. Furthermore, the primary care physician should be informed about prenatal and birth events, including prematurity and prenatal exposure to substances associated with behavioral and learning problems, such as tobacco and cocaine.<sup>11</sup> The assessment should include circumstances that might influence behavior and school performance, such as frequent moves or bitter custody disputes.<sup>12</sup> It is also important to determine whether there is a family history of ADHD, depression, bipolar disorder, anxiety disorders, or tic disorders. Genetic disorders that may have symptoms similar to those of ADHD (such as the fragile X syndrome) should be considered.

No physical findings are diagnostic of ADHD. Laboratory studies are not routinely obtained. Testing for achievement, intelligence, and specific learning disabilities may aid the differential diagnosis and help with planning for school services; such testing may be

obtained through school-based assessment or by referral to a psychologist. Computerized or manual performance tests of attention and impulsivity are not diagnostic of ADHD.<sup>13</sup>

### Treatment of the Patient

Treatment of the patient with ADHD focuses on control of the symptoms (which vary with the patient's development), classroom education, interpersonal relationships, and the transition to adult life.<sup>14</sup> Therapy is guided by measurable target outcomes, such as the number of calls in a week from the teacher to report disciplinary action, the amount of time spent on homework assignments, or participation in other activities without disruption (Table 3).<sup>7</sup>

## THERAPY

### Pharmacologic Interventions

*Methylphenidate and Dextroamphetamine* There is strong evidence to support the use of stimulant medication for the management of inattention, impulsivity, and hyperactivity in school-age children.<sup>21</sup> Methylphenidate and dextroamphetamine have consistently shown efficacy and safety when compared with placebo in randomized, controlled trials.<sup>22</sup> Two studies are particularly informative. The Multimodal Treatment Study of ADHD involved 597 children at six centers who were followed for 24 months, including a 14-month treatment phase.<sup>23</sup> The study by Abikoff et al. involved 103 children at two centers who were randomly assigned to 24 months of treatment.<sup>24</sup> The two studies included children seven to nine years of age and involved randomized pharmacologic and psychological interventions. Both studies assessed behavioral outcomes in the settings of the home and the school. Consistent with previous smaller studies, these trials showed that 68 to 80 percent of children treated with stimulants had improvements in behavior such that at the end of the treatment phase the children no longer met the criteria for a diagnosis of ADHD. The benefit of treatment was reduced in the Multimodal Treatment Study of ADHD after the children completed the active-study phase, whereas the benefit was sustained in the study by Abikoff et al. during the 24 months of treatment.

Randomized trials directly comparing methylphenidate and dextroamphetamine have shown similar benefits from the two medications but more frequent mild side effects with dextroamphetamine.<sup>25,26</sup> Evidence supports either medication as a first choice; 70 to 80 percent of children show improved attention with the use of one or the other.<sup>22</sup> Preparations are available as short-, intermediate-, and long-acting, with a duration of 3 to 10

Table 4. Recommended Medications for ADHD.

Medication*	Initial Dose	Usual Dose	Doses per Day	Side Effects	Contraindications
mg					
Methylphenidate†					
Ritalin, Methylin	5-10	10-20	2-3	Appetite suppression, stomachaches, headaches, irritability, weight loss, deceleration in rate of growth, exacerbation of psychosis, exacerbation of tics, mild increase in blood pressure and pulse	Marked anxiety, tension, agitation, glaucoma, use of monoamine oxidase inhibitors, seizures, tics
Concerta	18-27	27-54	1		
Metadate ER, Metadate CD, Methylin ER	10	10-20	1		
Ritalin LA	20	20-40	1		
Focalin‡	2.5-5	2.5-10	2-3		
MethyPach§					
Dextroamphetamine (sulfate alone and in combination with amphetamine salts)†					
Dexedrine	5	5-20	2-3	Appetite suppression, weight loss, stomachaches, headaches, irritability, possible growth inhibition, exacerbation of psychosis, exacerbation of tics, mild increase in blood pressure and pulse	Cardiovascular disease, hypertension, hyperthyroidism, glaucoma, drug dependence, use of monoamine oxidase inhibitors
Dexedrine Spansule	5-10	5-15	1-2		
Adderall	5-10	5-30	1-2		
Adderall XR	5-10	10-30	1		
Atomoxetine¶					
Strattera	10-25	18-60	1	Appetite suppression, nausea, vomiting, fatigue, weight loss, deceleration in rate of growth, mild increase in blood pressure and pulse	Jaundice or other clinical or laboratory evidence of liver injury, use of monoamine oxidase inhibitors, narrow-angle glaucoma
Bupropion					
Wellbutrin SR	100-150	150	1-2	Weight loss, insomnia, agitation, anxiety, dry mouth, seizures, others	Seizures, bulimia, anorexia nervosa, abrupt discontinuation of alcohol or benzodiazepines, use of monoamine oxidase inhibitors or other bupropion products (e.g., Zyban)
Wellbutrin XL	150	150-300	1		

\* For each category the generic drug is given and dosing information for each named marketed drug.

† The manufacturer states that seizures and tic disorder are contraindications; research supports the use of stimulants in children with seizures that have stabilized with the use of anticonvulsants and in children with tic disorder or Tourette's disorder.<sup>27,28</sup> With use of a long-acting methylphenidate or dextroamphetamine product, a short-acting product may be added at 4 p.m. to 6 p.m. for homework or special activities; appetite and sleep onset are then carefully monitored.

‡ Focalin is a dextro isomer of methylphenidate that is given at a lower dose.

§ The MethyPach is a sustained-action transdermal patch that is not yet available.

¶ Younger children may need two doses a day.

|| Bupropion has not been approved by the Food and Drug Administration for pediatric use. Only sustained release (twice daily) or extended release (once daily) are recommended for adolescents. There is a higher incidence of side effects with the immediate-release preparation.

hours and similar efficacy (Table 4). The administration of short-acting medications can be timed to correspond to certain of the child's activities. Long-acting medications obviate the need for doses during the school day.

*Dosages of methylphenidate and dextroamphetamine* are not weight-based. Guidelines consistently recommend starting with lower doses and titrating to an effective dose that does not cause side effects (Table 4).<sup>7,15</sup> Side effects are generally mild and managed by attention to dose and timing. The most common side effects are appetite suppression, stomachache, and headache, leading to discontinuation of the medication in approximately 1 percent to 4 percent of children.<sup>25,29</sup> Delayed onset of sleep, previously thought to be associated with treatment, may be associated with the underlying disorder.<sup>30</sup> In a 24-month follow-up, the Multimodal Treatment Study of ADHD showed a deceleration in growth of approximately 1 cm per year with the use of stimulant medication.<sup>31</sup> However, growth remained within the normal curve for most children, except those at the lowest percentiles of height for age. It is not known whether this effect is cumulative or can be ameliorated by summers off medication, allowing time for growth to catch up.

Follow-up visits in the Multimodal Treatment Study of ADHD<sup>23</sup> and the study by Abikoff et al.<sup>24</sup> were monthly. In general practice, however, once a stable dose of medication has been established, visits every three to four months are reasonable to monitor the effectiveness and potential side effects of the medication. Blood pressure, pulse, height, and weight are followed, given the potential for the medication to affect these measures (Table 4).

*Other Medications* Two other medications are effective with core symptoms of ADHD. Atomoxetine, a norepinephrine-reuptake inhibitor, is not classified as a stimulant. Randomized trials including more than 1000 children and adults showed that 58 to 64 percent of children treated during a 6-to-12-week period achieved 25 to 30 percent or greater improvement in symptoms.<sup>32,33</sup> Two recent reports of severe liver injury (which apparently reversed after drug cessation) have led to the addition of a bolded warning to the label indicating that atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury.<sup>34</sup> Side effects such as appetite suppression and weight loss are reported at a frequency similar to that for side effects seen with methylphenidate.<sup>32,35</sup> A study conducted in several countries showed a treatment benefit that was sustained over nine months.<sup>36</sup> Seizures and prolonged QT intervals corrected for heart rate are reported with overdoses of atomoxetine, but not with therapeutic doses.<sup>37</sup> Cases of tics developing during treatment with atomoxetine were recently reported<sup>38</sup> but were not described in randomized trials.



Bupropion, an aminoketone antidepressant, is also effective for inattention and impulsivity, but has not been approved by the Food and Drug Administration for use in children. Two randomized trials comparing bupropion with methylphenidate reported a smaller treatment effect and more side effects with bupropion among a total of 124 children and adolescents (Table 4).<sup>39,40</sup> Atomoxetine and bupropion might be effective for children who require control of symptoms 24 hours a day and for those who do not respond to methylphenidate or dextroamphetamine.<sup>32</sup>

The tricyclic antidepressants imipramine and desipramine, and the alpha-adrenergic agonist clonidine, are not often used in the treatment of ADHD because of concerns about cardiac effects and the availability of safe, effective medications described above. The stimulant pemoline remains available but is no longer recommended owing to reports of fatal hepatotoxicity.

A single medication is generally all that is needed to treat uncomplicated ADHD. Combinations of psychotropic medications have not been well studied and are reserved for very severe ADHD and coexisting mental health disorders.

### Nonpharmacologic Interventions

**Behavioral Therapy** Behavioral therapy is not routinely recommended as first-line treatment for uncomplicated ADHD in school-age children. Large randomized trials directly compared behavioral therapy with pharmacologic therapy. The trials showed that behavioral therapy alone was less effective than pharmacologic therapy alone, and they showed mixed results for behavioral therapy in combination with medication.

The behavioral-treatment group of the Multimodal Treatment Study of ADHD involved 35 individual and group sessions over 14 months and focused on behavior-management techniques, a summer treatment program, consultation with each child's teacher, and the presence of a behavioral aide in the child's classroom for 12 weeks.<sup>41</sup> This intensive behavioral therapy alone was not as effective as medication alone for improving attention. However, the combination was more effective for oppositional behavior and parent-child discord, among other outcomes, than either of the treatments alone.

The study by Abikoff et al.<sup>24</sup> examined psychosocial treatment, not as the sole treatment, but in addition to medication. The sessions were weekly in the first year and monthly in the second year and included parent training, family therapy, organizational-skills training, individual tutoring, social-skills training, and individual psychotherapy. No benefit was found for adding psychosocial treatment to treatment with medication.

Behavioral treatment that is generally available in communities and schools usually involves 8-to-12-week group sessions with children and parents, provided by psychologists or social workers. Sessions focus on improving the understanding of ADHD, teach-

ing parents skills such as effective use of rewards and disincentives, and modifying the physical and social environment to change the child's behavior, such as structuring daily routines.<sup>7</sup> Behavioral therapy is added to medication for specific indications, such as persistent oppositional behavior and parent–child discord. Psychological treatment is indicated for coexisting mental health conditions, such as depression and anxiety.

*Other Interventions* Physicians cannot prescribe an educational assessment, but they can support a parent's request for an assessment when it is indicated by persistent academic problems. In the United States, children with ADHD are entitled to interventions within the school setting if the parents and school officials determine that the child's behavior or condition interferes with his or her ability to participate in the educational process. The interventions might be simple, such as seating the child near the teacher to minimize classroom distractions, or they might involve assigning specific staff members to review daily assignments with the child.<sup>42</sup> Collaboration among the doctor, the parents, and the teacher can be facilitated with very brief lists of target behaviors, rated by the teacher, and taken by parents to appointments; these can be useful in gauging the effectiveness of treatment (Table 3).<sup>7,9</sup>

Other treatment interventions, such as physical exercises, neurofeedback, chelation therapy, systemic antifungal treatment, and vitamins, are often promoted at substantial expense to families. Little evidence supports a role for these interventions in the treatment of ADHD. Diets, including those involving the reduced consumption of sugar, were studied and found to affect behavior in no more than 1 percent of children.<sup>43–45</sup>

Reasons to refer to a specialist such as a developmental or behavioral pediatrician or a child psychiatrist include coexisting mental health conditions, adverse social circumstances that warrant team management, and treatment failure.<sup>7</sup>

### Special Populations

Children less than five years of age may demonstrate severely disruptive behaviors; these are probably associated with other chronic physical and mental health conditions.<sup>46,47</sup> Randomized trials show that training parents improves symptoms in preschoolers. In one trial, parents of 87 three-year-olds were randomly assigned to a control group or to 10 to 12 sessions in which they were taught to set consistent limits and positively interact with their preschooler. Children of parents in the intervention group were significantly more likely to achieve at least a 30 percent reduction in negative behaviors than were children of parents in the control group (62 percent vs. 28 percent), and 80 percent of the children in the intervention group showed improvement at one year of follow-up (there was no

comparison group at that time).<sup>48</sup> An 8-week randomized trial involving parents of three-year-olds showed that training the parents had a significant benefit on the children, and improvement was sustained 15 weeks after the intervention.<sup>49</sup>

A short-term study (three to four weeks) involving 28 children with ADHD, who were 4 to 5.9 years of age, showed normalization of behavior for 25 children who received stimulant medication as compared with 3 who received a placebo. Irritability and decreased appetite were frequent side effects.<sup>50</sup> Although approximately 1 percent of children two to four years of age may be treated with psychotropic medications, there is little evidence to support or guide this treatment,<sup>51,52</sup> and the overuse of medication is a particular concern in this group.

Children with mental retardation may have symptoms that meet the criteria for a separate diagnosis of ADHD. However, according to DSM-IV-R criteria, symptomatic behaviors should not be diagnosed as ADHD if they can be better explained by another diagnosis.<sup>5</sup> Randomized, controlled trials support the use of stimulant medication to treat children and adults who have symptoms of ADHD and mental retardation.<sup>53,54</sup>

ADHD affects 4 percent of adults; as many as 60 to 80 percent of children continue to have problems in adulthood with inattention and impulsivity, which adversely affect achievement and interpersonal relationships. The diagnosis of ADHD in adults, as in children and adolescents, is established through DSM-IV-R criteria, and coexisting mental health disorders must be considered in the diagnosis and treatment. Short-term studies have indicated improvement in attention and impulsivity with the use of stimulants and atomoxetine, but long-term data are lacking.<sup>55</sup> A detailed discussion of adult ADHD is beyond the scope of this article.

#### AREAS OF UNCERTAINTY

The subjective nature of judging behavior contributes to concern that ADHD is overdiagnosed and overtreated. Epidemiologic studies consistently show either underdiagnosis or overdiagnosis, with wide geographic and demographic variation.<sup>56,57</sup> Data are not yet available to assess the long-term benefits and risks of medication. Although a concern has been raised regarding a risk of substance abuse in patients treated with stimulant medication, studies indicate that children with ADHD who are treated have a lower risk of substance abuse later in life than children with ADHD who are not treated.<sup>58,59</sup>

### GUIDELINES

Guidelines for diagnosing and treating ADHD have been issued by several organizations representing pediatrics and child psychiatry (Table 3). These are consistent, and taken together, establish the standard of care for ADHD.

### CONCLUSIONS AND RECOMMENDATIONS

The evaluation of a child for ADHD involves taking a careful history, including the use of a standardized checklist to assess behaviors, and paying attention to the possibility of other mental health conditions or adverse social circumstances causing or exacerbating symptoms (Table 2). If the evaluation reveals behaviors meeting DSM-IV-R criteria for the diagnosis of ADHD (Table 1), a plan for care should take into consideration that ADHD is a chronic health condition and should involve the parents, the child, and the teacher in identifying behaviors to which therapy is targeted (Table 3).

In school-age children such as the one described in the vignette, I begin treatment with methylphenidate, because it is the treatment best supported by research. I prescribe a long-acting preparation, typically a low dose (10 to 18 mg) for a child less than 10 years of age and a midrange dose (20 to 36 mg) for older children or teenagers. A higher starting dose (30 to 54 mg) is reasonable for patients with severe symptoms. If medication is ineffective at the maximal dose or causes intolerable side effects, I try prescribing two to four daily doses of short-acting medication or switching to a long-acting preparation of dextroamphetamine; an alternative is atomoxetine. I see the child and his or her parents every month initially and every three months once a stable dose has been reached, to assess effectiveness and side effects. I recommend behavioral therapy for children and families experiencing conflict with one another and for children with a coexisting mental health condition.

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#### ADDENDUM

On February 9, 2005, Health Canada, the Canadian drug regulatory agency, removed Adderall XR from the Canadian market because of concerns about sudden death, which was reported in 20 patients taking this medication.<sup>1</sup> Other Adderall products had not been previously marketed in Canada. On the same day, the U.S. Food and Drug Administration (FDA) announced that it had reviewed the same postmarketing reports that were reviewed by Health Canada, described 12 pediatric deaths, and concluded that Adderall products should not be removed from the U.S. market.<sup>2</sup> Among these 12 deaths, 5 occurred in children with structural heart defects, and the remaining cases had complicating circumstances of heat exhaustion, dehydration, near drowning, and toxic levels, among others. The FDA also concluded that the number of sudden deaths was not greater than that expected among this population, given the approximately 30 million prescriptions written during the time of these reports (1999 to 2003). The FDA instituted a labeling change for Adderall XR in August 2004 to include a warning that patients with heart disease should not ordinarily be treated with Adderall products. A recent multicenter trial assessing the tolerability and effectiveness of Adderall XR was conducted for 24 months among 273 children 6 to 12 years of age who had been treated for 24 months or longer. The only serious adverse events (defined as events that resulted in death or hospitalization or that were life-threatening or medically significant) reported by this study were two occurrences of seizure.<sup>3</sup>

1. Health Canada suspends the market authorization of Adderall XR®, a drug prescribed for Attention Deficit Hyperactivity Disorder (ADHD) in children. Ottawa, Ont., Canada: Health Canada, 2005. (Accessed January 31, 2006, at [www.hc-sc.gc.ca/english/protection/warnings/2005/2005\\_01.html](http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_01.html).)

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2. Public health advisory for Adderall and Adderall XR. Rockville, Md.: U.S. Food and Drug Administration, 2005. (Accessed January 31, 2006, at [www.fda.gov/cder/drug/advisory/adderall.htm](http://www.fda.gov/cder/drug/advisory/adderall.htm).)
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## Hypercalcemia Associated with Cancer

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A 47-year-old woman with a history of breast cancer presents with confusion and dehydration. The serum calcium level is 18.0 mg per deciliter (4.5 mmol per liter). She has postural hypotension and low central venous pressure on examination of the jugular veins. The serum phosphorus level is 5.0 mg per deciliter (1.6 mmol per liter), the blood urea nitrogen level is 80.0 mg per deciliter (28.6 mmol per liter), the serum creatinine level is 2.0 mg per deciliter (177 mmol per liter), and the albumin level is 3.3 g per deciliter. A bone scintigraphic scan reveals no evidence of skeletal involvement by the tumor. How should she be treated?

### THE CLINICAL PROBLEM

Hypercalcemia has been reported to occur in up to 20 to 30 percent of patients with cancer at some time during the course of their disease.<sup>1-4</sup> This incidence may be falling owing to the wide use of bisphosphonates in patients with either multiple myeloma or breast cancer, although data are lacking. Hypercalcemia leads to progressive mental impairment, including coma, as well as renal failure. These complications are particularly common terminal events among patients with cancer. The detection of hypercalcemia in a patient with cancer signifies a very poor prognosis; approximately 50 percent of such patients die within 30 days.<sup>5</sup>

Hypercalcemia associated with cancer can be classified into four types (Table 1).<sup>1-4</sup> In patients with local osteolytic hypercalcemia, the hypercalcemia results from the marked increase in osteoclastic bone resorption in areas surrounding the malignant cells within the marrow space.<sup>3,4,6</sup> The condition known as humoral hypercalcemia of malignancy (HHM) is caused by systemic secretion of parathyroid hormone (PTH)-related protein (PTHrP) by malignant tumors.<sup>1,2,7,8</sup> PTHrP causes increased bone resorption<sup>1,2,7,8</sup> and enhances renal retention of calcium.<sup>9,10</sup> The tumors that most commonly cause HHM are listed in Table 1, but essentially any tumor may cause this syndrome. Some lymphomas secrete the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), causing hypercalcemia as a result of the combination of enhanced osteoclastic bone resorption

Table 1. Types of Hypercalcemia Associated with Cancer.\*

Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP	Breast cancer, multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer
1,25(OH) <sub>2</sub> D-secreting lymphomas	<1	Variable	1,25(OH) <sub>2</sub> D	Lymphoma (all types)
Ectopic hyperparathyroidism	<1	Variable	PTH	Variable

\* PTH denotes parathyroid hormone, PTHrP PTH-related protein, 1,25(OH)<sub>2</sub>D 1,25-dihydroxyvitamin D, and HTLV human T-cell lymphotropic virus.

and enhanced intestinal absorption of calcium.<sup>1,2,11</sup> Finally, ectopic secretion of authentic PTH is a rare cause of hypercalcemia, having been well documented in only eight patients to date.<sup>1,2,12</sup>

## STRATEGIES AND EVIDENCE

### Diagnosis

Although clinical laboratories generally measure the total serum calcium level, it is occasionally valuable to measure the serum level of ionized calcium, because increases or decreases in the albumin level may cause misleading increases or decreases, respectively, in the total serum calcium level. In addition, in rare patients with myeloma in whom calcium-binding immunoglobulins are produced,<sup>13</sup> measurement of total serum calcium may substantially overestimate the serum ionized calcium level. There are formulas with which to calculate the serum ionized calcium level or to "correct" the total calcium level (e.g., add 0.8 mg per deciliter to the total calcium level for every 1.0 g per deciliter of serum albumin below the level of 3.5 g per deciliter), but they are not precise or always reliable.<sup>14</sup> Thus, measurement of serum ionized calcium should be considered whenever there is doubt about the validity of the measurement of total calcium. The test can be performed rapidly in most hospital laboratories or neonatal intensive care units.

If the calcium level is elevated, a further evaluation should consider not only the mechanisms that are potentially related to the cancer but also causes of the elevation of the cal-

cium level that are unrelated to the cancer (e.g., primary hyperparathyroidism, the use of thiazide diuretics, and granulomatous disease, among other causes).<sup>15-18</sup> The tumors present in hypercalcemia associated with malignant disease are generally large and readily apparent<sup>1-4</sup>; notable exceptions are small neuroendocrine tumors (such as islet tumors and pheochromocytomas). The levels of intact PTH should be measured routinely. Although ectopic hyperparathyroidism is extremely rare in hypercalcemia associated with cancer, concomitant primary hyperparathyroidism is not (we found that in 8 of 133 patients with cancer and hypercalcemia, primary hyperparathyroidism was the cause).<sup>18</sup> Although most patients with typical HHM (Table 1) have increased levels of circulating PTHrP, the diagnosis is usually obvious on clinical grounds; PTHrP should therefore be measured in the occasional cases in which the diagnosis of HHM cannot be made on clinical grounds or when the cause of hypercalcemia is obscure. Plasma  $1,25(\text{OH})_2\text{D}$  should be measured when sarcoidosis, other granulomatous disorders, or the  $1,25(\text{OH})_2\text{D}$  lymphoma syndrome is considered in the differential diagnosis. A bone scan (or a skeletal survey, in the case of myeloma) is useful to assess the skeletal tumor burden in patients with cancer and hypercalcemia, if the test was not previously performed for tumor staging.

### Therapeutic Considerations

In planning therapy for patients with hypercalcemia associated with malignant disease, antihypercalcemic therapy should be considered an interim measure, one with no ultimate effect on survival.<sup>5</sup> Thus, it is imperative that antitumor therapy be implemented promptly: control of the serum calcium level merely buys time in which such therapy can work. Another critical point is that when all the available therapies have failed, withholding antihypercalcemic therapy (which will eventually result in coma and death) may be an appropriate and humane approach. In cases in which treatment is considered appropriate, an assessment of the severity of the hypercalcemia is needed to guide therapy.

Although there are no formal guidelines, I consider mild hypercalcemia to be a serum calcium level of 10.5 to 11.9 mg per deciliter (2.6 to 2.9 mmol per liter), moderate hypercalcemia a level of 12.0 to 13.9 mg per deciliter (3.0 to 3.4 mmol per liter), and severe hypercalcemia a level of 14.0 mg per deciliter (3.5 mmol per liter) or greater. In general, the neurologic and renal complications of hypercalcemia worsen with increasing severity of hypercalcemia, but other factors also influence the response to hypercalcemia. For example, the rate of the ascent of the serum calcium level is important — a rapid increase to moderate hypercalcemia frequently results in marked neurologic dysfunction, whereas chronic severe hypercalcemia may cause only minimal neurologic symptoms. Similarly, older patients with preexisting neurologic or cognitive dysfunction may become severely

obtunded in the presence of mild hypercalcemia, whereas younger patients with moderate-to-severe hypercalcemia may remain alert. Finally, the concomitant administration of sedatives or narcotics may worsen the neurologic response to hypercalcemia.

The optimal therapy for hypercalcemia associated with cancer is one that is tailored both to the degree of hypercalcemia and to its underlying cause. True hypercalcemia (i.e., an elevated serum level of ionized calcium) occurs through three basic mechanisms: enhanced osteoclastic bone resorption (in local osteolytic hypercalcemia, HHM,  $1,25(\text{OH})_2\text{D}$ -secreting lymphomas, and the rare case of ectopic hyperparathyroidism); enhanced renal tubular reabsorption of calcium (in HHM and ectopic hyperparathyroidism); and enhanced intestinal absorption of calcium (in  $1,25(\text{OH})_2\text{D}$ -secreting lymphomas and possibly ectopic hyperparathyroidism). Therapy should be targeted accordingly.

### General Supportive Measures

The important general supportive measures include the removal of calcium from parenteral feeding solutions (a measure often overlooked); discontinuation of the use of oral calcium supplements in enteral feeding solutions or as calcium tablets; discontinuation of medications that may independently lead to hypercalcemia (e.g., lithium, calcitriol, vitamin D, and thiazides); an increase in the weight-bearing mobility of the patient, if possible; and discontinuation of the use of sedative drugs, including analgesic drugs, if possible, to enhance the patient's mental clarity and promote weight-bearing ambulation.

Hypophosphatemia develops in most patients with hypercalcemia associated with cancer at some point during the course of the disease, regardless of the underlying cause, because of decreased food intake, saline diuresis, the use of loop diuretics, the phosphaturic effects of PTHrP, the hypercalcemia itself, and treatment with calcitonin or antacids. In general, the presence of hypophosphatemia increases the difficulty of treating the hypercalcemia, and in animal models hypophosphatemia has been shown to cause hypercalcemia.<sup>19</sup> Phosphorus should be replaced orally or administered through a nasogastric tube as neutral phosphate.<sup>20</sup> The serum phosphorus and creatinine levels should be followed closely, in an effort to keep the phosphorus level in the range of 2.5 to 3.0 mg per deciliter (0.98 to 1.0 mmol per liter), the serum creatinine level in the normal range, and the calcium-phosphorus product below 40, ideally in the range of 30 (when both are expressed in milligrams per deciliter). Intravenous phosphorus replacement should not be given except in dire circumstances, when oral or nasogastric administration is impossible, because its use can result in severe hypocalcemia, seizures, and acute renal failure.<sup>21</sup> These general support measures alone may be sufficient to treat patients with mild hypercalcemia.

Table 2. Pharmacologic Therapy for Hypercalcemia Associated with Cancer.\*

Intervention	Dose	Adverse Effect
Hydration or calciuresis		
Intravenous saline	200–500 ml/hr, depending on the cardiovascular and renal status of the patient	Congestive heart failure
Furosemide	20–40 mg intravenously, after rehydration has been achieved	Dehydration, hypokalemia
Phosphate repletion		
Oral phosphorus (if serum phosphorus $\leq 3.0$ mg/dl)†	For example, 250 mg Neutraphos orally, four times daily until serum phosphorus level $> 3.0$ mg/dl or until serum creatinine level increases	Renal failure, hypocalcemia, seizures, abnormalities of cardiac conduction, diarrhea
First-line medications		
Intravenous bisphosphonates‡		
Pamidronate	60–90 mg intravenously over a 2-hr period in a solution of 50–200 ml of saline or 5% dextrose in water§	Renal failure, transient flu-like syndrome with aches, chills, and fever
Zoledronate	4 mg intravenously over a 15-min period in a solution of 50 ml of saline or 5% dextrose in water	Renal failure, transient flu-like syndrome with aches, chills, and fever
Second-line medications		
Glucocorticoids¶	For example, prednisone, 60 mg orally daily for 10 days	Potential interference with chemotherapy; hypokalemia, hyperglycemia, hypertension, Cushing's syndrome, immunosuppression
Mithramycin	A single dose of 25 µg/kg of body weight over a 4-to-6-hour period in saline	Thrombocytopenia, platelet-aggregation defect, anemia, leukopenia, hepatitis, renal failure
Calcitonin	4–8 IU per kilogram subcutaneously or intramuscularly every 12 hr	Flushing, nausea
Gallium nitrate	100–200 mg/m <sup>2</sup> of body surface area intravenously given continuously over a 24-hr period for five days	Renal failure

\* Many of the recommendations in this table are based on historical precedent and common practice rather than on randomized clinical trials. There are data from randomized trials comparing bisphosphonates to the other agents listed and to one another.

† The use of intravenous phosphorus should be avoided except in the presence of severe hypophosphatemia (serum phosphorus level  $< 1.5$  mg per deciliter [0.48 mmol per liter]) and when oral phosphorus cannot be administered. If intravenous phosphorus is used, it should be used with extreme caution and with careful observation of the levels of serum phosphorus and creatinine.<sup>20,21</sup> To convert values for phosphorus to millimoles per liter, multiply by 0.3229.

‡ Pamidronate and zoledronate are approved by the Food and Drug Administration. Ibandronate and clodronate are available in continental Europe, the United Kingdom, and elsewhere. Bisphosphonates should be used with caution if at all when the serum creatinine level exceeds 2.5 to 3.0 mg per deciliter (221.0 to 265.2 µmol per liter).

§ Pamidronate is generally used at a dose of 90 mg, but the 60-mg dose may be used to treat patients of small stature or those with renal impairment or mild hypercalcemia.

¶ These drugs have a slow onset of action, as compared with the bisphosphonates; approximately 4 to 10 days are required for a response.

|| These effects have been reported in association with higher-dose regimens used to treat testicular cancer (50 µg per kilogram of body weight per day over a period of five days) and in patients receiving multiple doses of 25 µg per kilogram; they are not expected to occur with a single dose of 25 µg per kilogram unless preexisting liver, kidney, or hematologic disease is present.

### Saline Hydration and Calciuresis

Patients with hypercalcemia associated with cancer are substantially dehydrated as a result of a renal water-concentrating defect (nephrogenic diabetes insipidus) induced by hypercalcemia and by decreased oral hydration resulting from anorexia and nausea, vomiting, or both. The dehydration leads to a reduction in the glomerular filtration rate that further reduces the ability of the kidney to excrete the excess serum calcium. First, therefore, parenteral volume expansion should be initiated, with the administration of normal saline. Although there are no randomized clinical trials to guide this therapy, in general practice normal saline is administered at a rate of 200 to 500 ml per hour, depending on the baseline level of dehydration and renal function, the patient's cardiovascular status, the degree of mental impairment, and the severity of the hypercalcemia. These factors must be assessed with the use of careful clinical monitoring for physical findings that are consistent with fluid overload. The goals of treatment are to increase the glomerular filtration rate, thus increasing the filtered load of calcium that passes through the glomerulus into the tubular lumen, and to inhibit calcium reabsorption in the proximal nephron (because saline itself is calciuretic). Increasing the glomerular filtration rate to or above the normal range (within safe limits) also permits the use of loop diuretics (Table 2) to increase the renal excretion of calcium (loop diuretics block calcium reabsorption in the loop of Henle and make possible increased administration of saline, which induces further calcium excretion). Loop diuretics should not be administered until after full hydration has been achieved, because these agents can cause or worsen dehydration, leading to a decline in the glomerular filtration rate and the filtered load of calcium. In contrast to loop diuretics, thiazide diuretics should not be administered, since they stimulate, rather than inhibit, renal calcium reabsorption.

### Medications

Intravenous bisphosphonates are by far the best studied, safest, and most effective agents for use in patients with hypercalcemia associated with cancer. These drugs work by blocking osteoclastic bone resorption.<sup>22-33</sup> Because they are poorly absorbed when given orally (approximately 1 to 2 percent of an oral dose is absorbed), only intravenously administered bisphosphonates are used for this indication. In the United States, the two drugs that are approved by the Food and Drug Administration (FDA) and are currently considered the agents of choice in the treatment of mild-to-severe hypercalcemia associated with cancer are pamidronate<sup>22,24,25</sup> and zoledronate.<sup>22,23,26,27</sup> In continental Europe, the United Kingdom, and other countries, ibandronate<sup>22,28,29</sup> and clodronate<sup>22,30-32</sup> are also widely used. Etidronate, which was the first to be used for this indication,<sup>22</sup> has been replaced by these

more potent bisphosphonates. A number of randomized clinical trials comparing bisphosphonates to saline and diuretics alone, to other bisphosphonates, and to other antiresorptive agents such as calcitonin have confirmed the superiority of bisphosphonates.<sup>22,27,28,33</sup>

Bisphosphonate therapy should be initiated as soon as hypercalcemia is discovered, because a response requires two to four days, and the nadir in serum calcium generally occurs within four to seven days after therapy is initiated.<sup>22-33</sup> Approximately 60 to 90 percent of patients have normal serum calcium levels within four to seven days, and responses last for one to three weeks.<sup>22-33</sup> As compared with pamidronate, zoledronate has the advantage of rapid and simpler administration (15 minutes vs. 2 hours for infusion), whereas pamidronate is less expensive. Although a direct comparison of the two drugs in a randomized clinical trial showed a statistically significant increase in the efficacy of zoledronate,<sup>27</sup> the difference in control of calcemia was small (mean nadir serum calcium level, 9.8 mg per deciliter [2.4 mmol per liter] with zoledronate and 10.5 mg per deciliter [2.6 mmol per liter] with pamidronate; the proportion of patients in whom a corrected serum calcium level of 10.8 mg per deciliter [2.7 mmol per liter] was achieved by day 10 was 88 percent and 70 percent, respectively). Thus, the differences are of arguable clinical importance, and the choice is largely one between convenience and cost. Either pamidronate or zoledronate is acceptable therapy.

In animal models, bisphosphonates have been associated with azotemia<sup>22,23</sup> and thus, their use in patients with renal failure is a potential concern. However, because hypercalcemia is a frequent cause of renal dysfunction in patients with hypercalcemia associated with cancer, effective treatment of the hypercalcemia associated with cancer often improves renal function.<sup>25,34</sup> The manufacturer and the American Society of Clinical Oncology<sup>35</sup> do not recommend the use of a reduced dose of pamidronate or zoledronate for patients with serum creatinine values of less than 3.0 mg per deciliter (265.2  $\mu$ mol per liter), but they do advise that the recommended duration of the infusion not be shortened. Pamidronate and zoledronate have been reported to cause or exacerbate renal failure, but this effect has generally occurred in patients receiving multiple doses.<sup>36</sup> In patients whose condition fails to respond to a low initial dose of bisphosphonates, the use of a second, larger dose (an approach that has not been approved by the FDA) or a second-line agent may be considered.

### Other Pharmacologic Agents

Several agents commonly used before the advent of bisphosphonates are now used infrequently, usually when bisphosphonates are ineffective or contraindicated (Table 2). Glucocorticoids<sup>37,38</sup> may still have a role in the treatment of some patients, such as those with

lymphomas resulting in elevated levels of 1,25(OH)<sub>2</sub> vitamin D. Calcitonin may result in a more rapid reduction in serum calcium levels than do other agents (the maximal response occurs within 12 to 24 hours), but its value is questionable because the reductions are small (approximately 1.0 mg per deciliter [0.25 mmol per liter]) and transient.<sup>37,39</sup> Mithramycin, which was the mainstay of therapy for hypercalcemia associated with cancer before the bisphosphonates became available,<sup>40</sup> remains effective, but its use is limited by potential adverse effects (Table 2). Gallium nitrate is also approved for treatment,<sup>41</sup> but the need for continuous intravenous administration over a period of five days limits its use.

### Dialysis

In patients who have cancers that are likely to respond to therapy but in whom acute or chronic renal failure is present, aggressive saline infusion is not possible, and other therapies such as bisphosphonates should be used with caution, if at all. In these circumstances, dialysis against a dialysate containing little or no calcium is a reasonable and highly effective option for selected patients.<sup>42,43</sup> There are no specific guidelines with regard to how low the glomerular filtration rate must be for dialysis to be a rational choice in treating hypercalcemia, but in general, when the rate falls below 10 to 20 ml per minute, or when the presence of congestive heart failure contraindicates an adequate administration of saline, or both, dialysis should be considered.

### AREAS OF UNCERTAINTY

The receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) system is the molecular pathway that leads to osteoclast recruitment and differentiation and bone resorption in hypercalcemia associated with cancer. Agents that interfere with the system, such as recombinant osteoprotegerin (a decoy receptor for RANKL) or monoclonal antibodies directed against RANKL, have been proposed as novel treatments for hypercalcemia associated with malignant disease, as have monoclonal antibodies, which neutralize PTHrP. Preliminary data from studies in animals or small studies involving women with osteoporosis indicate reductions in bone resorption with these approaches.<sup>44-46</sup> Whether these agents will prove to be safe and effective in humans with hypercalcemia associated with cancer, whether they can be produced commercially at a cost competitive with that of bisphosphonates, and whether they can reverse hypercalcemia more effectively than the potent bisphosphonates remain unknown.



### GUIDELINES

No guidelines are available from the major professional societies for the treatment of hypercalcemia associated with cancer.

### RECOMMENDATIONS

The patient described in the vignette, who has breast cancer and a large, obvious tumor burden, is typical of patients with hypercalcemia associated with cancer in general and with HHM in particular. As in all cases of hypercalcemia in patients with cancer, other causes of the hypercalcemia need to be carefully considered. Coexisting primary hyperparathyroidism should routinely be ruled out by measurement of the level of immunoreactive parathyroid hormone. In the patient described, HHM is the most likely cause of the hypercalcemia; thus, immunoreactive parathyroid hormone would be suppressed and circulating PTHrP would be elevated (however, I do not routinely measure PTHrP unless the diagnosis is uncertain).

When a patient presents with hypercalcemia associated with cancer, the physician should first consider whether treatment is appropriate according to an assessment of the overall prognosis. The cornerstones of successful antihypercalcemic therapy are vigorous rehydration (with the use of normal saline at 200 to 500 ml per hour, depending on the patient's cardiovascular status and renal function); aggressive calciuresis with the use of loop diuretics, after normovolemia has been restored; and inhibition of bone resorption with the use of intravenous bisphosphonates (in the United States, the administration of either pamidronate [an infusion of 60 to 90 mg over a 2-hour period] or zoledronate [4 mg over a 15-minute period]). Pamidronate is at present less expensive, whereas zoledronate is more convenient to use and results in slightly greater mean reductions in the serum calcium level, although the differences are small. The expectation with the use of either regimen is that the serum calcium level will begin to fall within 12 hours after the therapy is initiated and will reach the nadir within approximately four to seven days. The serum calcium level generally will remain in the normal or near-normal range for one to three weeks, allowing time to institute other treatments for the malignant disease responsible for the hypercalcemia.

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# Rosacea

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**A 47-year-old white woman reports facial redness and flushing. Her eyes are itchy and irritated. She thinks she may have rosacea and is worried that she will have a “whiskey nose.” On examination, multiple erythematous papules, pustules, and telangiectasias are observed on a background of erythema of the central portion of her face. How should her case be managed?**

## THE CLINICAL PROBLEM

A constellation of clinical symptoms and signs are included under the broad rubric of rosacea. These consist of facial flushing, the appearance of telangiectatic vessels and persistent redness of the face, eruption of inflammatory papules and pustules on the central facial convexities, and hypertrophy of the sebaceous glands of the nose, with fibrosis (rhinophyma).<sup>1</sup> Ocular changes are present in more than 50 percent of patients and range from mild dryness and irritation with blepharitis and conjunctivitis (common symptoms) to sight-threatening keratitis (rare).<sup>2</sup> Patients with rosacea may report increased sensitivity of the facial skin<sup>3</sup> and may have dry, flaking facial dermatitis, edema of the upper face,<sup>4</sup> or persistent granulomatous papulonodules.<sup>5</sup> There is often an overlapping of clinical features, but in the majority of patients, a particular manifestation of rosacea dominates the clinical picture. As a useful approach to the guidance of therapy, the disease can thus be classified into four subtypes — erythematotelangiectatic (subtype 1), papulopustular (2), phymatous (3), and ocular (4)<sup>6</sup> — with the severity of each subtype graded as 1 (mild), 2 (moderate), or 3 (severe).<sup>7</sup> The psychological, social, and occupational effects of the disease on the patient should also be assessed and factored into treatment decisions.

The onset of rosacea usually occurs between the ages of 30 and 50 years.<sup>8</sup> The course of the disease is typically chronic, with remissions and relapses. Some patients identify exacerbating factors, particularly in regard to flushing, such as heat, alcohol, sunlight, hot beverages, stress, menstruation, certain medications, and certain foods.<sup>9</sup> Rosacea is

Table 1. Classification, Features, and Treatment of Rosacea.\*

Subtype	Clinical Features	Severity†	
		Grade	Features
Erythematotelangiectatic (subtype 1)	Persistent erythema of the central face. Flushing; telangiectasias often present; easily irritated facial skin. Patient may report stinging or burning of the face and have symptoms of ocular rosacea. Rhinophyma occasionally coexists.	1	Occasional mild flushing; faint persistent erythema; occasional telangiectasias.
		2	Frequent troublesome flushing; moderate persistent erythema; several distinct telangiectasias.
		3	Frequent severe flushing; pronounced persistent erythema; possible edema; many prominent telangiectasias.
Papulopustular (subtype 2)	Persistent erythema of the central face; dome-shaped erythematous papules; small pustules surmount some papules. Flushing, telangiectasias, ocular inflammation, and phymatous skin changes may be present.	1	Few papules or pustules; mild persistent erythema; no plaques.
		2	Several papules or pustules; moderate persistent erythema; no plaques.
		3	Many or extensive papules or pustules; pronounced persistent erythema; inflammatory plaques or edema may be present.
Phymatous (subtype 3)	Thickened skin with prominent pores. May affect nose (rhinophyma — most common type), chin (gnathophyma), forehead (metophyma), ears (otophyma), and eyelids (blepharophyma). May occur in isolation or with other skin changes of rosacea (flushing, erythema, edema, telangiectasias, papules, pustules in a nasal or central-facial distribution) or with ocular rosacea.	1	For rhinophyma: slight puffiness of nose; slight prominence of follicular orifices (patulous follicles); no clinically apparent hypertrophy of connective tissue or sebaceous glands; no change in nasal contour.
		2	For rhinophyma: bulbous nasal swelling; moderately dilated patulous follicles; clinically apparent mild hypertrophy of the sebaceous glands or connective tissue, with change in nasal contour but without nodular component.
		3	For rhinophyma: marked nasal swelling; large dilated follicles; distortion of nasal contour due to hypertrophy of the sebaceous glands or connective tissue, with nodular component.
Ocular (subtype 4)	Sensation of foreign body in the eye; telangiectasia and erythema of lid margins, often with scaling. Conjunctival injection; recurrent chalazion or hordeolum. Keratitis, episcleritis or scleritis, and iritis may occur, though rarely. May precede, follow, or occur simultaneously with cutaneous changes. Both eyes are usually affected.	1	Mild itch, dryness, or grittiness of eyes; fine scaling of lid margins; telangiectasia and erythema of lid margins; mild conjunctival injection (mild congestion of conjunctival vessels).
		2	Burning or stinging of eyes; crusting or irregularity of lid margins, with erythema and edema; definite conjunctival hyperemia or injection; formation of chalazion or hordeolum.
		3	Pain, photosensitivity, or blurred vision; severe lid changes, with loss of lashes; severe conjunctival inflammation; corneal changes, with potential loss of vision; episcleritis or scleritis; iritis.

\*Adapted from Wilkin et al.<sup>4,7</sup>

†In general, 1 denotes mild disease, 2 moderate disease, and 3 severe disease, but grades of severity are not always clearly defined. Patients may have more than one subtype, and the grade of severity should be assessed in each of these. Patients should also be asked to grade the psychological, social, and occupational effects of their disease on a similar scale. For example, in grade 1 (mild), the patient is conscious of the condition, but it does not cause embarrassment or inhibit social functioning; in grade 2 (moderate), the patient is constantly aware of the rosacea during social situations and it regularly causes embarrassment; in grade 3 (severe), the patient is constantly thinking about the condition and avoids social interaction because of it. Such grading on the part of the patient facilitates evaluation of the overall effect of the disease on him or her and guides assessment of the efficacy of therapy.

Therapeutic Approach	Comments
Reduce flushing and redness and minimize skin irritation. Topical medications recommended for papulopustular rosacea are not indicated and may cause irritation. Systemic treatments used for papulopustular rosacea may reduce erythema if significant inflammation is present. Ablative therapy of prominent vessels for grade-2-to-3 disease.	Difficult to treat satisfactorily.
Topical or systemic medications for grade-1-to-2 disease; systemic medications for grade 3.	Response to treatment is usually good. Maintenance therapy is usually required to maintain remission.
Rhinophyma (grades 2 and 3) may respond well to surgical or laser therapy. Other phymatous skin changes are very difficult to treat but may improve with treatment of inflammatory skin lesions, if present.	All phymatous skin changes are rare. The most common form (rhinophyma) occurs predominantly in men.
Topical medication for grade 1; systemic medication for grade 2. Refer patients with persistent grade 1 or 2 disease or suspected grade 3 disease to ophthalmologist.	May occur in the majority of rosacea cases, but not often diagnosed. Vision-threatening ocular inflammation is rare.

Table 2. General Nonpharmacologic Guidelines for the Management of Rosacea.

<p>Reassure patients about the benign nature of the disorder and the rarity of rhinophyma (particularly in women).</p> <p>Direct patients to Web sites such as those of the National Rosacea Society (<a href="http://www.rosacea.org">www.rosacea.org</a>) and the American Academy of Dermatology (<a href="http://www.aad.org">www.aad.org</a>), where patient-related information can be accessed.</p> <p>Advise patients to keep a daily diary to identify precipitating or exacerbating factors.</p> <p>Suggest a daily application of combined ultraviolet A-protective and ultraviolet B-protective sunscreen (with a sun-protection factor of 15 or greater). Sunscreen may be incorporated into moisturizer or topical medication. Vehicle formulations with dimethicone and cyclomethicone may be less irritating than others. Sun-blocking creams containing titanium dioxide and zinc oxide are usually well tolerated.</p> <p>Suggest a daily application of soap-free cleansers, silicone facial foundations, and liquid film-forming moisturizers.</p> <p>Suggest cosmetic coverage of excess redness with brush application; matte-finish, water-soluble facial powder containing inert green pigment helps neutralize erythema.</p> <p>Advise patients to avoid potentially exacerbating factors:</p> <ul style="list-style-type: none"> <li>Overly strenuous exercise, hot and humid atmosphere, emotional upset, alcohol, hot beverages, spicy foods, and large hot meals.</li> <li>Exposure to sun or to intense cold or harsh winds.</li> <li>Perfumed sunscreens or those containing insect repellents.</li> <li>Astringents and scented products containing hydroalcoholic extracts or sorbic acid.</li> <li>Cleansers containing acetone or alcohol.</li> <li>Abrasive or exfoliant preparations.</li> <li>Vigorous rubbing of the skin.</li> <li>Toners or moisturizers containing glycolic acid.</li> </ul> <p>If possible, medications that may exacerbate flushing (e.g., vasodilative drugs, nicotinic acid and amyl nitrite, calcium-channel-blocking agents, and opiates).</p>
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more common in women than in men, but men with rosacea are more prone to the development of thickening and distorting phymatous skin changes. Rosacea has been anecdotally reported to be associated with seborrheic dermatitis (this association is likely), with migraine headaches in women<sup>10</sup> (possible), and with *Helicobacter pylori* infection<sup>11</sup> (controversial). A rosacea-like eruption can be induced by the topical application of fluorinated corticosteroids<sup>12</sup> and tacrolimus ointment<sup>13</sup> to the face. In two European population studies, the prevalence of rosacea was reported to be 1.5 percent<sup>14</sup> and 10 percent,<sup>15</sup> but estimates are complicated by the difficulty of distinguishing between chronic actinic damage and erythematotelangiectatic rosacea. Although rosacea can occur in all racial and ethnic groups, white persons of Celtic origin are thought to be particularly prone to the disorder,<sup>16</sup> and it is uncommon in persons with dark skin. Up to 30 percent of patients report a family history of rosacea.<sup>17</sup> The common misconception that both the facial red-



Figure 1. Erythematotelangiectatic (Subtype I) Rosacea.

Prominent telangiectasias and erythema of the medial cheek are evident in this example of grade 2 disease. As the erythema subsides, the telangiectasias often become more evident. This patient, who has fair skin and works outside, reported sensitive, easily irritated skin and frequent flushing.

ness and the rhinophyma associated with rosacea are due to excessive alcohol consumption makes rosacea a socially stigmatizing condition for many patients.

#### STRATEGIES AND EVIDENCE

The diagnosis of rosacea is a clinical one. There is no confirmatory laboratory test. Biopsy is warranted only to rule out alternative diagnoses, since histopathological findings are not diagnostic.<sup>18</sup>

The differential diagnosis and therapy vary according to subtype (Table 1). Rosacea that is manifested predominantly by flushing is difficult to treat, but the condition may improve with the management of other manifestations and the avoidance of provoking or triggering factors. Inflammatory changes in the skin are usually responsive to medical therapies and heal without scarring, whereas telangiectasias and phymatous changes often require laser or surgical intervention. Ocular rosacea is usually mild and responsive to lid hygiene, tear replacement, and topical or systemic antibiotics, but patients with persistent or severe ocular disease should be referred to an ophthalmologist. All patients should be advised in regard to protection from climatic influences (both heat and cold), avoidance of factors that trigger or exacerbate flushing or that irritate the often-sensitive skin, appropriate care of the facial skin (Table 2), and a strategy for maintenance of remission when the





**Figure 2. Papulopustular (Subtype 2) and Ocular (Subtype 4) Rosacea of Moderate Severity.**

In this example of grade-2-to-3 disease, the typical distribution of papules and pustules on a background of inflammatory erythema is seen over the convexities of the central portion of the face, with sparing of the periocular area. Grade-1-to-2 ocular rosacea (erythema and edema of the upper eyelids) is also present.



**Figure 3. Severe Papulopustular Rosacea with Moderate Ocular Involvement.**

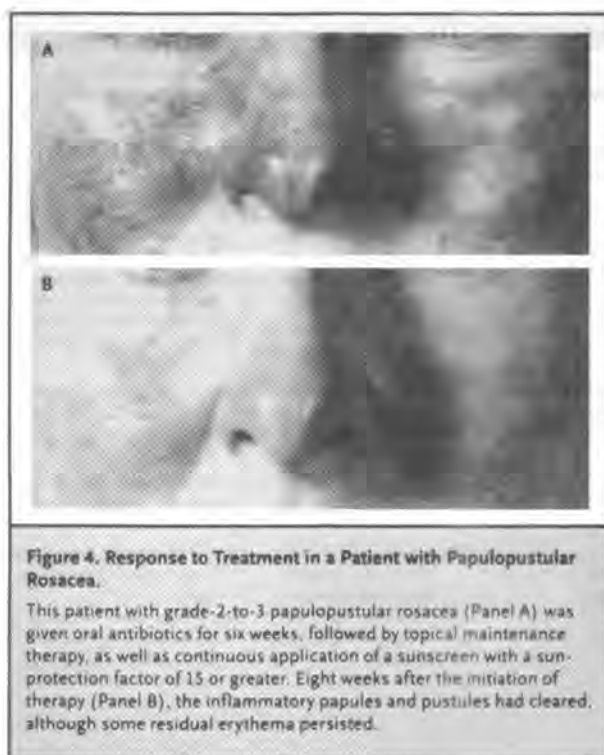
In this patient with grade 3 papulopustular disease, inflammatory lesions have coalesced into an erythematous plaque below the eye. Note the multiple small, studded pustules on the surface of the plaque and the inflammatory lesions on the lower eyelid (grade 2 ocular rosacea).

condition improves. The choice of medications, dosages, and duration of therapy is often based on clinical experience. Off-label prescription-drug use is common.<sup>19</sup>

### Subtype 1

Flushing, with persistent central facial erythema (erythematotelangiectatic rosacea), is probably the most common presentation of rosacea.<sup>6</sup> Although it has been suggested that rosacea is essentially a cutaneous vascular disorder,<sup>20</sup> facial flushing is not always a feature; patients who report flushing as their only symptom should not receive a diagnosis of "preroseacea," since, in many such patients, rosacea never develops. Common causes of flushing (e.g., psychosocial factors or anxiety, food, alcohol or drugs, or menopause) should become apparent when a medical history is taken. Prolonged episodes of severe flushing accompanied by sweating, flushing that is not limited to the face, and, especially, systemic symptoms such as diarrhea, wheezing, headache, palpitations, or weakness indicate the need for investigations to rule out rare conditions that may be characterized by flushing (e.g., the carcinoid syndrome, pheochromocytoma, or mastocytosis).<sup>21</sup>

Telangiectatic vessels are usually prominent on the cheeks and nose in grades 2 and 3 of subtype 1 rosacea (Figure 1) and contribute to the facial erythema. Erythematotelangiectatic



**Figure 4. Response to Treatment in a Patient with Papulopustular Rosacea.**

This patient with grade-2-to-3 papulopustular rosacea (Panel A) was given oral antibiotics for six weeks, followed by topical maintenance therapy, as well as continuous application of a sunscreen with a sun-protection factor of 15 or greater. Eight weeks after the initiation of therapy (Panel B), the inflammatory papules and pustules had cleared, although some residual erythema persisted.

tatic rosacea is difficult to distinguish from the effects of chronic actinic damage, which may coexist. Since the management of the two conditions is similar, this distinction is not essential for patient care. Erythematotelangiectatic rosacea may occasionally mimic facial contact dermatitis, the "butterfly rash" of lupus erythematosus, or photosensitivity; if the diagnosis is uncertain, skin biopsies, serologic screening for antinuclear and anticytoplasmic autoantibodies, or other investigations may be indicated.

Subtype 1 rosacea is poorly responsive to treatment. The measures outlined in Table 2 are particularly relevant for patients with subtype 1, who often have sensitive, easily irritated skin. There are few studies of the effectiveness of medical treatments for flushing in patients with rosacea. Beta-blockers in low doses (e.g., nadolol, 20 to 40 mg daily)<sup>22</sup> as well as clonidine and spironolactone have been used to treat flushing in patients with rosacea, but evidence from randomized trials is lacking to support the effectiveness of these agents. Endoscopic transthoracic sympathectomy has been used successfully to treat socially disabling blushing<sup>23</sup>; however, its use as a treatment for rosacea is not

Table 3. Treatment of Papulopustular Rosacea.\*

Medication	Properties and Actions	Dosage and Duration†	Contraindications and Side Effects‡	Comments
<b>Topical</b>				
Metronidazole (0.75% gel or cream; 1% cream)	Antibacterial; antiinflammatory.	Applied once or twice daily. Can be used as initial treatment to clear inflammatory lesions or as indefinite maintenance therapy after clearance with systemic therapy.	Contraindications: women of childbearing age not on oral contraception should use with caution because of possibility of absorption and mutagenic effects. Side effects: gel preparation may be irritating to skin. Transient watering of eyes may occur when applied to periorcular skin.	Gel and cream and both concentrations appear to be equally effective.
Azelaic acid (20% cream; 15% gel)	Antibacterial; anti-inflammatory.	Applied twice daily. Can be used as initial or indefinite maintenance therapy.	Side effects: may cause mild burning or stinging sensation when applied initially. Pruritus, dryness, or scaling can occur. Rarely, contact dermatitis or facial edema may occur.	May be used in women of childbearing age and during pregnancy.
10% Sodium sulfacetamide and 5% sulfur in cream or lotion. Preparations may include 10% urea; sunscreen; green tint.	Antibacterial; keratolytic (sulfur); hydrating (urea).	Applied twice daily. Can be used as initial or indefinite maintenance therapy. Cleanser preparation available.	Contraindications: hypersensitivity to sulphonamide or sulfur. Side effects: rarely, systemic hypersensitivity reactions. May cause redness, peeling, and dryness of skin.	Sulfur component may help accompanying seborrheic dermatitis. Sunscreen or tinted preparations may reduce number of topical preparations needed.
Erythromycin (2% solution)	Antibacterial; anti-inflammatory.	Applied twice daily. Can be used as initial or indefinite maintenance therapy.	Side effects: local irritation or dryness.	May be used in pregnancy. Alcohol in solution may reduce tolerance.
Tretinoin (0.025% cream or lotion; 0.01% gel)	Alters epidermal keratinization. May improve photoaging changes.	Applied at night. Can be used as initial or indefinite maintenance therapy.	Contraindications: teratogenic; women of childbearing age not on oral contraceptives should use with caution. Side effects: Irritating and poorly tolerated by some patients. May cause photosensitivity. Use on damaged skin and contact with eyes should be avoided.	Theoretically useful for actinically damaged skin (common in rosacea).
<b>Systemic</b>				
Oxytetracycline	Antibacterial; antiinflammatory.	250 to 500 mg twice daily for 6 to 12 weeks to achieve remission. Intermittent low-dose therapy may prevent relapse.	Contraindications: should be avoided by women who are pregnant, contemplating pregnancy, or lactating and by persons with impaired renal or hepatic function. Side effects: gastrointestinal upset; candida; photosensitivity; benign intracranial hypertension. May reduce effectiveness of oral contraceptives. May cause tooth discoloration or enamel hypoplasia. Poor absorption if taken with food, milk, or some medications.	

Table 3. (Continued.)<sup>10</sup>

Medication	Properties and Actions	Dosage and Duration <sup>†</sup>	Contraindications and Side Effects <sup>‡</sup>	Comments
Doxycycline	Antibacterial; antiinflammatory.	50 to 100 mg once or twice daily for 6 to 12 weeks.	Same as for oxytetracycline.	May be taken with food.
Minocycline	Antibacterial; antiinflammatory.	50 to 100 mg twice daily or sustained-action formulation once daily for 6 to 12 weeks.	Contraindications: pregnancy or lactation. Persons with hepatic impairment should use with caution. Side effects: gastrointestinal upset (but less than with tetracycline); allergic reactions. Hyperpigmentation of the skin may occur. Long-term use should be avoided (hepatic damage or systemic-lupus-erythematosus-like syndrome may be induced). Drug interactions with antacids, mineral supplements, anti-coagulants.	Randomized, clinical trials to support its use in rosacea are lacking, but clinical impression is of equal efficacy to oxytetracycline. Unlike oxytetracycline, can be taken with food.
Erythromycin	Antibacterial; antiinflammatory.	250 to 500 mg once or twice daily for 6 to 12 weeks.	Contraindications: severe hepatic impairment. Side effects: gastrointestinal upset; headache or rash. Drug interactions (many).	Alternative to oxytetracycline or minocycline as first-line systemic treatment. Useful if systemic therapy necessary in oxytetracycline-intolerant or pregnant or lactating patients.
Metronidazole	Antibacterial; antiinflammatory.	200 mg once or twice daily for 4 to 6 weeks.	Contraindications: pregnant or lactating women should use with caution. Side effects: gastrointestinal upset; leukopenia; neurologic effect (seizures or peripheral neuropathy). Drug interactions with alcohol, anticoagulants, or phenobarbital.	Side-effect profile limits its use to resistant cases for short periods.

\* Topical treatment alone is usually effective for mild-to-moderate (grade 1-to-2) papulopustular rosacea. Topical metronidazole, combination 10 percent sodium sulfacetamide and 5 percent sulfur, and 15 percent azelaic acid have been approved by the Food and Drug Administration for the treatment of rosacea; however, several other topical medications are used off label. For patients with moderate-to-severe papulopustular rosacea (grade 2 to 3), oral medication is usually indicated. These patients may not tolerate topical medications initially, owing to inflamed skin, but topical therapy may be added as the inflammation subsides and is used to maintain remission after cessation of oral therapy.

† Dosage ranges relate to published reports and reflect the lack of uniformity in the approach to the treatment of papulopustular rosacea.

‡ Contraindications and side effects are selected examples rather than a comprehensive summary.

recommended, owing to rare but serious complications such as pneumothorax and pulmonary embolism, as well as postoperative increases in episodes of abnormal sweating.

If the telangiectatic component is prominent, as it is in grade-2-to-3 disease, ablation of vessels by laser can be helpful. A nonblinded, uncontrolled study of 16 patients who had erythematotelangiectatic rosacea and were treated with pulsed-dye-laser therapy showed a significant improvement in erythema and quality of life after treatment.<sup>24</sup> Although topical and systemic therapies, as outlined for papulopustular rosacea below, are often used to treat patients with erythematotelangiectatic rosacea, there is little evidence of the efficacy of these agents. In addition, topical therapy may irritate the sensitive skin of patients with subtype 1 rosacea.

### Subtype 2

Small, dome-shaped erythematous papules, some of which have tiny surmounting pustules, on the convexities of the central portion of the face, with background erythema (Figure 2), typify papulopustular rosacea.<sup>6</sup> In grade 3 disease, plaques can form from the coalescence of inflammatory lesions (Figure 3). Telangiectatic vessels, varying degrees of edema, ocular inflammation, and a tendency to flush are present in some patients. The differential diagnosis includes acne vulgaris, perioral dermatitis, and seborrheic dermatitis. Patients with acne vulgaris have less erythema, are often younger, and have oily skin with blackheads and whiteheads (comedones), larger pustules and nodulocystic lesions, and a tendency to scarring. In patients with perioral dermatitis, micropustules and microvesicles around the mouth or eyes and dry, sensitive skin may follow the inappropriate use of topical corticosteroids. Seborrheic dermatitis may accompany rosacea and contribute to the facial erythema, but it is distinguished from rosacea by a prominence of yellowish scaling around the eyebrows and alae nasi, together with troublesome dandruff.

**Management** Systemic or topical antibiotics, or both, are the mainstays of therapy for subtype 2 rosacea (Table 3), and the response is often satisfactory (Figures 4A and 4B). Moderate-to-severe (i.e., grade 2 or 3) papulopustular rosacea may require systemic therapy to achieve clearance of inflammatory skin lesions, whereas milder (grade 1 and some cases of grade 2) disease can often be treated with topical medications alone.<sup>25</sup> Although data are lacking to support the combined use of topical and systemic therapies, many clinicians recommend such a combination for the treatment of moderate-to-severe disease.<sup>20,25</sup>

On the basis of an analysis that pooled data from two randomized trials, van Zuuren and colleagues concluded that there was strong evidence of the efficacy of topical metronidazole and azelaic acid cream.<sup>26</sup> Sixty-eight of 90 patients (76 percent) treated with topical metronidazole for eight or nine weeks considered their rosacea to be improved, as



Figure 5. Advanced Rhinophyma (Subtype 3).

In grade 3 rhinophyma, enlargement and distortion of the nose occur, with prominent pores and thickened skin due to hyperplasia of the sebaceous glands and fibrosis of the connective tissue. There is follicular prominence and a distorted nodular appearance. In this patient, the rhinophyma was accompanied by mild papulopustular rosacea, which responded well to topical medications.

compared with 32 of 84 patients (38 percent) in the placebo group.<sup>26</sup> Significant reductions in the number of inflammatory lesions and in erythema were reported in two large placebo-controlled, double-blind studies of a 15 percent azelaic acid gel applied twice daily.<sup>27</sup> A double-blind, randomized, parallel-group trial involving 251 patients with papulopustular rosacea<sup>28</sup> demonstrated the superiority of 15 percent azelaic acid gel over 0.75 percent metronidazole gel applied twice daily for 15 weeks. In a double-blind study of 103 patients, a lotion containing 10 percent sodium sulfacetamide and 5 percent sulfur reduced inflammatory lesions by 78 percent, as compared with a reduction of 36 percent in the placebo group.<sup>29</sup> An investigator-blinded study involving 63 patients that compared the combination of 10 percent sodium sulfacetamide and 5 percent sulfur lotion with 0.75 percent metronidazole showed a significantly greater clearance of lesions among the patients treated with sodium sulfacetamide and sulfur.<sup>30</sup> An uncontrolled study showed a reduction in erythema, papules, and pustules in 13 of 15 patients (87 percent) who were treated with topical erythromycin applied twice daily for four weeks.<sup>31</sup>

Evidence of the efficacy of oral metronidazole and tetracycline was also reported by van Zuuren et al.<sup>26</sup> Of 73 patients who were treated with tetracycline for four to six weeks, 56 (77 percent) were considered to have improvement, as compared with 28 of 79 (35 percent) in

the placebo group.<sup>26</sup> Among 14 patients treated with 200 mg of metronidazole twice daily for six weeks, 10 were considered to have improvement, as compared with 2 of 13 patients (15 percent) who received placebo pills.<sup>32</sup> A double-blind trial that compared 200 mg of metronidazole twice daily with 250 mg of tetracycline twice daily for 12 weeks among 40 patients showed that the two agents were equally effective.<sup>33</sup> Although both minocycline and erythromycin are frequently used in the systemic treatment of rosacea, there are few data available on the effectiveness of these agents. On the basis of clinical experience, some investigators have suggested that intermittent low-dose antibiotic treatment (250 mg of tetracycline on alternate days) may be as effective as multiple daily doses.<sup>34</sup> An uncontrolled study of 10 patients with moderate or severe rosacea that had responded poorly to treatment were prescribed 250 mg of azithromycin three times per week; moderate or marked improvement was observed in all patients after four weeks of therapy.<sup>35</sup>

Oral isotretinoin in low doses has been reported to be effective in the control of rosacea that was otherwise resistant to treatment, but the ocular and cutaneous drying effects of this agent are poorly tolerated, and its potential for serious adverse effects (including teratogenic effects) contradicts its use in routine care. Topical tretinoin has been reported to be as effective as oral isotretinoin after 16 weeks of treatment<sup>36</sup> and may be helpful in the treatment of patients with papulopustular rosacea who also have oily skin.<sup>37</sup>

Anecdotal reports have suggested that *Cucumis sativus* (cucumber), applied in a cooled yogurt paste, is helpful in reducing facial edema of rosacea that is otherwise resistant to treatment<sup>38</sup> and that facial massage involving rotatory movements of the fingers from the central to the peripheral face may improve papulopustular and edematous skin changes.<sup>39</sup> However, data that support the effectiveness of either of these treatments are lacking.

**Maintenance Therapy** Because relapse occurs in about one quarter of patients within weeks after the cessation of systemic therapy,<sup>40</sup> topical therapy is usually used in an effort to maintain remission.<sup>41</sup> The required duration of maintenance therapy is unknown, but a period of six months is generally advised.<sup>42</sup> After this time, some patients report that they can keep their skin free of papulopustular lesions with topical therapy applied on alternate days or twice weekly, whereas others require repeated courses of systemic medication.

### Subtype 3

Phymatous rosacea is uncommon. The most frequent phymatous manifestation is rhinophyma (known familiarly as "whiskey nose" or "rum blossom"). In its severe forms (grade 3), rhinophyma is a disfiguring condition of the nose resulting from hyperplasia of both the sebaceous glands and the connective tissue (Figure 5). Rhinophyma occurs much

more often in men than in women (approximate ratio, 20:1),<sup>43</sup> and a number of clinico-pathologic variants have been described.<sup>44</sup> Although rhinophyma is often referred to as “end-stage rosacea,” it may occur in patients with few or no other features of rosacea. The diagnosis is usually made on a clinical basis, but a biopsy may be necessary to distinguish atypical, or nodular, rhinophyma from lupus pernio (sarcoidosis of the nose); basal-cell, squamous-cell, and sebaceous carcinomas; angiosarcoma; and even nasal lymphoma.<sup>45</sup>

Data from randomized trials of therapies for rhinophyma and long-term follow-up studies of recurrence rates are lacking. Clinical experience suggests that grades 2 and 3 rhinophyma respond well, at least initially, to surgical excision, electrosurgery, or carbon dioxide–laser therapy. A case series of 30 patients who were treated with carbon dioxide lasers and followed for one to three years showed good cosmetic results in almost all the patients.<sup>46</sup>

#### Subtype 4

Ocular rosacea is common but often not recognized by the clinician.<sup>47</sup> It may precede, follow, or occur simultaneously with the skin changes typical of rosacea. In the absence of accompanying skin changes, ocular rosacea can be difficult to diagnose, and there is no test that will confirm the diagnosis. Patients usually have mild, nonspecific symptoms, such as burning or stinging of the eyes. A sensation of dryness is common, and tear secretion is frequently decreased.<sup>48</sup> Mild-to-moderate ocular rosacea (including blepharoconjunctivitis, chalazia, and hordeola) occurs frequently, whereas serious (grade 3) disease with the potential for visual loss, such as that which results from keratitis, occurs rarely.

Artificial tears, eyelid hygiene (i.e., cleaning the lids with warm water twice daily), fucidic acid, and metronidazole gel applied to lid margins are treatments that are frequently used to treat mild ocular rosacea. Systemic antibiotics are often additionally required for grade-2-to-3 disease, although limited data are available to support these approaches. In a double-blind, placebo-controlled trial, 35 patients with ocular rosacea who received 250 mg of oxytetracycline twice daily for six weeks had a significantly higher rate of remission than did patients who received a placebo (65 percent vs. 28 percent).<sup>49</sup> In an uncontrolled study of 39 patients with cutaneous rosacea (28 with ocular symptoms), 100 mg of doxycycline daily for 12 weeks improved symptoms of dryness, itching, blurred vision, and photosensitivity.<sup>50</sup> After ocular symptoms subside, the maintenance of lid hygiene and the use of artificial tears are usually recommended. However, such treatment may be inadequate for moderate-to-severe ocular rosacea, and patients with persistent or potentially serious ocular symptoms should be referred to an ophthalmologist.



### AREAS OF UNCERTAINTY

The causes and pathogenesis of rosacea remain poorly understood.<sup>4,51</sup> Data from randomized, clinical trials on the efficacy and optimal duration of many of the therapies, including complementary therapies that are frequently used by patients,<sup>52</sup> are lacking. The possibility of emergence and carriage on the skin of resistant organisms is a concern with regard to the prolonged use of topical and systemic antibiotics.

### GUIDELINES

There are no specific guidelines for the management of rosacea.

### SUMMARY OF RECOMMENDATIONS

“Rosacea” is a diagnostic term applied to a spectrum of changes in the skin and eyes. Until the causes and pathogenesis are better understood, the classification of rosacea by its predominant features and grading according to severity (Table 1) are recommended to guide management. The emotional effect of rosacea on the patient must also be considered in the management of this condition, and advice on improving the cosmetic appearance of the skin is an important aspect of overall care.

The woman described in the vignette should be reassured that inflammatory papules and pustules usually respond to therapy and resolve without scarring and that rhinophyma rarely develops in women. She should be advised to apply a sunscreen daily that provides protection against both ultraviolet A and ultraviolet B irradiation and to avoid using irritating topical products. Treatment should be initiated with 100 mg of doxycycline or 100 mg of minocycline daily for a period of 6 to 12 weeks. This should be followed by maintenance therapy with azelaic acid, topical metronidazole, or a sodium sulfacetamide–sulfur preparation applied twice daily for six months and then gradually discontinued, as outlined above. Laser therapy should be considered for residual, prominent telangiectatic vessels. The oral antibiotic is likely to help the patient’s ocular symptoms, and she should also be advised to clean her eyelids with warm water twice daily and to use artificial tears. Referral to an ophthalmologist should be considered if her ocular symptoms persist.

Dr. Powell reports having received speaking fees from Galderma Laboratories, Bradley Pharmaceuticals, and Dermik Laboratories.

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# *Pertussis — Not Just for Kids*

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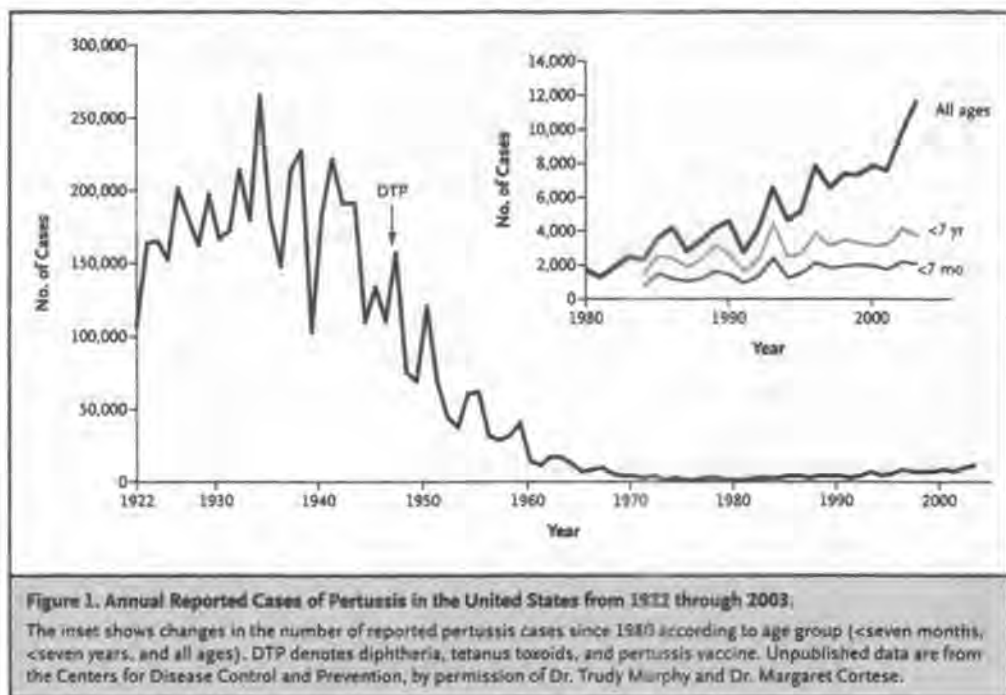
Six weeks ago, a 45-year-old woman noticed a scratchy feeling in her throat that has now progressed to more than 20 episodes of severe, spasmodic coughing per day. Her coughing spells are worse at night and are sometimes associated with gagging and vomiting. Her adolescent son and several of his friends, who received all of their childhood immunizations on schedule, had similar illnesses involving cough several weeks before the onset of her symptoms, and they continue to cough. How should the patient be assessed for possible pertussis? Should she be treated and, if so, how? Could this illness have been prevented?

## THE CLINICAL PROBLEM

**D**espite rates of immunization for pertussis of more than 80 percent among young children, the number of cases of pertussis reported annually in the United States has increased by a factor of six since 1980, with 11,647 cases reported in 2003 (Figure 1). The reported incidence rates probably substantially underestimate the true burden of disease because of incomplete reporting and a lack of recognition of the illness on the part of physicians.<sup>1-4</sup> The diagnosis of pertussis is frequently missed, often because of misconceptions that whooping cough is solely a pediatric illness that has been controlled by routine childhood immunizations and that immunity resulting from pertussis disease or immunization is lifelong. In addition, residual immunity from prior vaccination may modify the clinical presentation of pertussis in adolescents and adults and make the diagnosis even more difficult.

## Clinical Presentation and Complications

Anyone who has heard the frightening paroxysmal cough of a child with classic pertussis would question how the diagnosis of pertussis could be overlooked. The illness begins, however, less dramatically, with the catarrhal phase, which consists of nonspecific symptoms such as coryza, conjunctival irritation, and, occasionally, a slight cough, none of



which suggest pertussis as the primary diagnosis. After 7 to 10 days, the characteristic cough heralds the onset of the paroxysmal phase. After several weeks, the intensity and frequency of the cough may begin to decrease, but the convalescent phase, which can include episodes of exacerbated paroxysmal coughing brought on by unrelated upper airway infections, can last for weeks to months.

The typical paroxysmal cough in a child who is not immunized consists of a series of rapid, forced expirations, followed by gasping inhalation, which can result in the typical whooping sound. Post-tussive vomiting is common. These symptoms often occur in the absence of fever. Asymptomatic intervals occur between coughing spells. Very young infants may present with apnea or cyanosis in the absence of cough and are at greater risk than are older children for death or severe complications, including pneumonia (*Bordetella pertussis* infection or infection with another pathogen), pneumothorax, severe pulmonary hypertension, seizures, or encephalopathy.<sup>5-9</sup>

The current pertussis-related mortality rate among infants in the United States is 2.4 deaths per 1 million, and fatal cases in infants account for more than 90 percent of all deaths from pertussis. These numbers highlight the need for new approaches to protect infants, who are too young to be immunized according to the current vaccination schedule.<sup>2,10,11</sup>

Among immunized patients, especially adolescents and adults, a prolonged cough may be the only manifestation of pertussis.<sup>3</sup> A number of studies have documented that between 13 and 32 percent of adolescents and adults with an illness involving a cough of six days' duration or longer have serologic evidence of infection with *B. pertussis*.<sup>12-17</sup> The symptoms and complications of pertussis infection reported in these studies are often quite different from those seen in children.<sup>14-18</sup> For example, scratchy throat and other pharyngeal symptoms occur in about one third of adults with pertussis, and episodes of sweating are reported by 40 to 50 percent of persons over the age of 30 years. Although 70 to 99 percent of adolescents and adults with pertussis are reported to have paroxysmal cough, the reported frequencies of other symptoms are more variable, with whoop in 8 to 82 percent and post-tussive vomiting in 17 to 50 percent.<sup>6</sup> Because adolescents and adults often do not seek medical care until several weeks after the onset of their illness, the differential diagnosis includes other causes of chronic cough, such as asthma, gastroesophageal reflux disease, postviral bronchospasm, chronic sinusitis with postnasal drip, tuberculosis, chlamydia or mycoplasma infections, other chronic lung diseases, and malignant conditions. Almost 80 percent of adults with confirmed pertussis have an illness involving a cough of at least 3 weeks' duration, and 27 percent still had a cough after 90 days.<sup>18,19</sup> Complications of pertussis, which are similar in adolescents and adults, include pneumonia (in 2.1 to 3.5 percent of patients), seizures (0.3 to 0.6 percent), and encephalopathy (0.1 percent). Some complications, such as cough-induced urinary incontinence, increase with age. Unusual complications that have been reported anecdotally in older patients include a herniated intervertebral disc, the sudden onset of hearing loss, angina, and carotid-artery dissection.<sup>6,18-24</sup>

### **Epidemiology, Incidence, and Burden of Disease**

Although multiple reports have highlighted the role of pertussis as an important cause of persistent cough in adolescents and adults, the actual burden of disease in these groups is difficult to determine.<sup>4,6,12-25</sup> This seemingly simple task is complicated by the biology of *B. pertussis* and the difficulty in detecting the organism.<sup>4</sup> Most pathogens of the respiratory tract have short incubation periods, are easy to culture, cause illness for a relatively short period, and are rapidly eliminated. *B. pertussis* is different in that the incubation period is measured in days to weeks, the organism exhibits fastidious behavior in culture, and it has the ability to cause, as the Chinese term it, a "cough of 100 days." The organism can be recovered from patients only during the first three to four weeks of illness and is particularly difficult to isolate in previously immunized persons.<sup>25</sup> These factors result in outbreaks that span months and that can be difficult to track epidemiologically.<sup>26</sup>

Table 1. Recommended Immunization Schedules for Pertussis in Canada, France, Germany, and the United States.

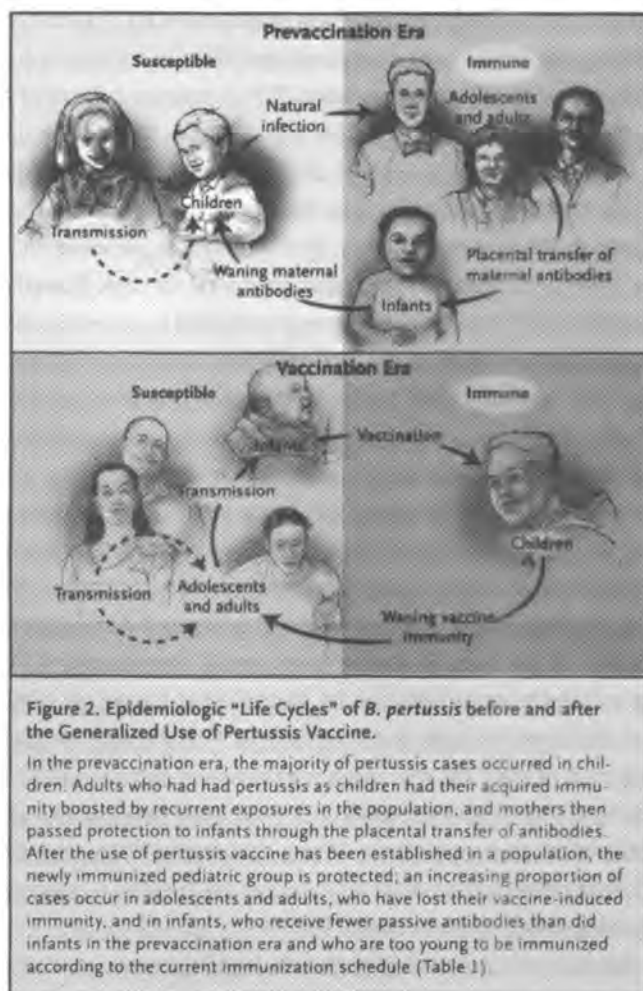
Country	Type of Vaccine <sup>a</sup>	Ages at Vaccination	Ages at Booster <sup>†</sup>
Canada	DTaP <sup>‡</sup>	2, 4, and 6 mo	18 mo; 4–6 yr and 14–16 yr
France	DTP <sup>‡</sup>	2, 3, and 4 mo	
	DTaP		15–18 mo; 11–13 yr
Germany	DTaP	3, 4, and 5 mo	11–14 mo; 9–17 yr
United States	DTaP	2, 4, and 6 mo	18 mo; 4–6 yr

\* DTaP denotes diphtheria, tetanus toxoids, and acellular pertussis vaccine. There are multiple formulations of this vaccine, with each formulation containing one to four antigens, and multiple manufacturers; therefore, no two vaccines are identical. Commonly recognized side effects include swelling, redness, and tenderness at the site of injection; fever; and secondary febrile convulsions.

† Canada, France, and Germany have initiated the use of a booster dose in adolescents at the ages indicated. In France, a DTaP booster is used after the primary series with DTP. In Canada and Germany, the adolescent booster is dTap, reflecting a reduced dose of diphtheria and acellular pertussis.

‡ DTP denotes diphtheria, tetanus toxoids, and pertussis vaccine. Side effects include anaphylaxis; swelling, redness, and tenderness at the site of injection; prolonged or inconsolable crying; fever; and secondary febrile convulsions.

Before vaccination was available, pertussis was responsible for more than 270,000 cases of severe illness involving cough and 10,000 deaths annually in the United States.<sup>27</sup> The introduction of whole-cell pertussis vaccine into the general population during the 1940s was associated with a 99 percent reduction in the incidence of the disease, with a nadir of 1010 reported cases in 1976. Since that time, the absolute number of reported cases has increased, with the 11,647 cases in 2003 approaching the highest total since 1964 (Figure 1).<sup>1</sup> The routine immunization of young children in the United States according to the schedule shown in Table 1 has markedly reduced the rates of reported pertussis in children. However, striking increases in rates of disease have been seen among adolescents and adults during the past 10 years (Figures 1 and 2). In the United States, from 1997 to 2000 there were 8273 cases of pertussis reported in patients 10 to 19 years of age and 5745 cases in those older than 19 years.<sup>1</sup> There are probably multiple reasons for this increase, and they include the increased recognition of the disease (with the use of serologic testing for diagnosis) and the limited duration of protection from vaccine.<sup>28</sup>



### STRATEGIES AND EVIDENCE

The critical elements involved in the diagnosis and treatment of pertussis, as with other infectious diseases, are its inclusion in the differential diagnosis, the availability of reliable and rapid laboratory tests for confirmation, and the prompt and appropriate use of the resultant information.

#### Diagnostic Methods

Three laboratory tests have been used to detect *B. pertussis* or related bordetella species in the respiratory secretions of patients suspected of having pertussis: direct fluorescent antibody



staining, bacterial culture, and polymerase chain reaction (PCR).<sup>29</sup> Because the direct fluorescent antibody technique has low sensitivity and specificity in comparison with culture and PCR, this method is not currently recommended.<sup>29,30</sup> A positive culture of nasopharyngeal secretions (preferably an aspirate) on selective Regan–Lowe medium is the gold standard for the diagnosis of pertussis. The sensitivity of culture is limited by the fastidious nature of *B. pertussis* and the loss of viability between the site of collection and the clinical laboratory. The yield is lower from dilute specimens, specimens from patients who have had a long duration of illness, and specimens obtained after antibiotic therapy. Nonetheless, when carried out appropriately, culture continues to be recommended in patients who present within three weeks after the onset of cough. Although antibiotic resistance is rare, isolation of the causative organism, as recommended by the Centers for Disease Control and Prevention (CDC), allows for characterization of antigenic variation and antibiotic sensitivity.<sup>31</sup>

The use of PCR-based diagnostic assays with one or more primers, available in many health departments and clinical laboratories, is an alternative approach. These assays have been reported to detect fewer than 10 organisms, which do not need to be viable to be detected, and thus the tests have significantly greater sensitivity than does culture.<sup>29,32</sup> PCR assays with multiple primers can be used to identify and distinguish among several *bordetella* species (i.e., *B. pertussis*, *B. parapertussis*, and *B. bronchiseptica*).<sup>29,33,34</sup> Although the period during which the organism can be identified is longer with PCR than for culture, false positive PCR results have been a problem.<sup>35</sup> For these reasons, the National Immunization Program of the CDC recommends the use of culture and PCR assays during the period in which patients could be infectious — at least three weeks after the onset of cough or four weeks after the appearance of any symptoms.<sup>36</sup> Standardized procedures and reagents and rigid quality control of PCR assays are needed to ensure accurate diagnoses and to minimize false positive results.<sup>35,37,38</sup>

An alternative method of diagnosing pertussis in adolescents and adults is the measurement of antibody to specific components of *B. pertussis* with the use of enzyme-linked immunosorbent assays. Since the diagnosis of pertussis is often not considered during the period when organisms can still be detected, the demonstration of increased antibody titers between the acute phase of illness (i.e., in serum obtained within the first week after the onset of symptoms) and the convalescent phase (in serum collected four to six weeks later) may be necessary. Alternatively, a single serum antibody titer (that exceeds a diagnostic cutoff point for the level of IgG against pertussis toxin or another antigen) obtained at least three weeks into the illness may be required to confirm the diagnosis.<sup>29,38–40</sup> However, the lack of a widely available serologic test with an established cutoff point, the limited diagnostic value of commercial tests, and the delay in obtaining results limit the usefulness of

serologic testing in practice.<sup>6,41</sup> As a result, the CDC recommends that combinations of diagnostic tests be used to identify persons with pertussis more effectively.<sup>29,38</sup> Within the first four weeks after the onset of symptoms (when cough has been present for three weeks), the use of culture and PCR is appropriate for diagnosis; when cough has been present for three to four weeks, PCR and serologic tests can both be used; and after four weeks of cough, serologic tests alone are most likely to provide a diagnosis.

### Treatment

Antibiotics should be administered to patients with pertussis to hasten clearance of the organism and to limit transmission to susceptible contacts. Although controversial, it appears that treatment can sometimes reduce the duration or severity of symptoms, or both, but a benefit is unlikely when treatment is initiated after the first week of symptoms.<sup>36</sup> Adolescents and adults with sporadic cases frequently present during the paroxysmal phase, which occurs at least a week after the onset of symptoms, and in such cases, antibiotics rarely affect the course of the disease. However, viable organisms can be recovered from untreated patients for three weeks after the onset of the cough. Thus, the routine administration of antibiotics during the first four weeks of illness is justified. For patients who are likely to be in contact with high-risk persons, such as infants, women in the third trimester of pregnancy (who might continue to be infectious after delivery), and health care workers, treatment is recommended even six to eight weeks after the onset of illness.<sup>36</sup>

The National Immunization Program recommends erythromycin for the treatment of pertussis.<sup>42</sup> However, the newer macrolides azithromycin and clarithromycin have been demonstrated in head-to-head trials to be similar in efficacy to erythromycin, with fewer side effects and more convenient administration.<sup>43-45</sup> Dosages, common side effects, and contraindications are summarized in Table 2.<sup>46,47</sup> An alternative treatment for patients who cannot tolerate macrolides is trimethoprim-sulfamethoxazole. Although *B. pertussis* strains are sensitive in vitro to fluoroquinolones and ketolides, there are no clinical data to support the use of these agents.<sup>48</sup>

Treatment also involves supportive care, which is most important for infants and small children, since they are vulnerable to dehydration and malnutrition from post-tussive vomiting and an inability to eat. None of the pharmacologic or immunologic interventions that have been tested, such as corticosteroids, salbutamol, diphenhydramine, and pertussis immune globulin, have been documented to be effective in reducing the symptoms or controlling the cough of pertussis.<sup>49</sup>

Table 2. Choice of Antibiotic Agents for the Treatment of Pertussis.

Drug	Dosage	Regimen	Side Effects	Contraindications
Erythromycin	Children, 40–50 mg/kg/day Adults, 1–2 g/day	4 divided doses for 14 days*	Gastrointestinal irritation, abdominal cramps, nausea, vomiting; hypertrophic pyloric stenosis has been reported in infants	Known sensitivity to any macrolide antibiotic; should be used with caution in infants because of association with hypertrophic pyloric stenosis <sup>42</sup>
Azithromycin	10 mg/kg (maximum, 500 mg) as a single dose on day 1; 5 mg/kg (maximum, 250 mg) thereafter <sup>43,44</sup>	Lower dose once daily for 4 additional days	Allergic reaction and hepatic toxicity	Known sensitivity to any macrolide antibiotic
Clarithromycin	20 mg/kg/day (maximum, 3 g/day)	Two divided doses daily for 7 days	Allergic reaction and hepatic toxicity	Known sensitivity to any macrolide antibiotic
Trimethoprim-sulfamethoxazole†	Trimethoprim, 8 mg/kg/day (maximum, 320 mg/day); sulfamethoxazole, 40 mg/kg/day (maximum, 1600 mg/day)	Two divided doses daily for 7 days	Rash, kernicterus in newborns	Known allergy to sulfonamides or trimethoprim; should not be given to pregnant women shortly before delivery, breastfeeding mothers, or infants <2 mo old, because of the risk of kernicterus

\* A 7-day regimen has been shown to be similar in efficacy to a 14-day regimen.<sup>54</sup>

† Trimethoprim-sulfamethoxazole should be prescribed as an alternative to the macrolides in patients who cannot tolerate them.

‡ The 2003 Red Book recommendation is for 10 to 12 mg per kilogram per day once daily for five days.

### Prophylaxis after Exposure

The same agents and regimens used for the treatment of patients with established pertussis are recommended for chemoprophylaxis in contacts. These modes of treatment are expected to be effective in the protection of persons exposed to patients with active pertussis, when administered before the onset of symptoms in the contact. Because infectiousness declines with the increasing duration of illness, prophylaxis for contacts needs to be initiated only if the interval since the onset of cough in the index case is three weeks or less. Prophylaxis is generally recommended only if the contact was exposed within the previous three weeks,<sup>50</sup> but for persons at high risk or those who are likely to come into contact with high-risk persons, prophylaxis may be warranted for up to six to eight weeks after exposure.

### Prevention

The mainstay for control of pertussis is vaccination, and this is recommended routinely for infants and young children according to the schedules shown for several countries in Table 1. Whole-cell vaccines consisting of killed organisms are highly effective but have been associated with frequent local and systemic reactions.<sup>27</sup> In the 1980s and early 1990s, new acellular vaccines, which contain one or more purified pertussis components,

were demonstrated to be immunogenic, associated with fewer local and systemic reactions than whole-cell vaccines, and efficacious in the prevention of culture-confirmed pertussis disease in infants and young children.<sup>51</sup> These acellular vaccines have replaced whole-cell vaccines in the United States and elsewhere.

Given the recognition that immunity wanes after vaccination early in life, repeated vaccination in adolescence or adulthood has been proposed. A large, randomized clinical trial evaluated the efficacy of a three-component acellular pertussis vaccine (containing pertussis toxoids, filamentous hemagglutinin, and pertactin) in nearly 3000 healthy subjects 15 to 65 years of age. Active surveillance for pertussis was conducted every two weeks for two years. With the use of culture or PCR and serologically confirmed disease as end points, preliminary data from this study indicated that there was a 92 percent efficacy rate for the vaccine (95 percent confidence interval, 32 to 99 percent).<sup>52</sup>

A recently published cost-benefit analysis that assumed that the incidence of pertussis was the same as that observed in the above-mentioned trial led to the conclusion that an additional booster dose of pertussis vaccine would be cost-effective.<sup>53</sup> Of the scenarios considered in the analysis, vaccination of adolescents was considered to be the least expensive, the easiest to implement, and the most acceptable. In light of the greater recognition of disease in adolescents and adults, some countries, such as Germany, France, and Canada, now recommend the routine vaccination of adolescents with acellular pertussis vaccine boosters (Table 1). Although there are no formulations of pertussis vaccine currently licensed in the United States for use in persons over the age of six years, advisory groups are considering the routine use of acellular vaccines in this population once vaccines are approved and become available.

#### AREAS OF UNCERTAINTY

Despite extensive research on the toxins, adhesions, and other factors related to the virulence of *B. pertussis*, little is known about the mechanisms by which these factors cause the illness of pertussis. For example, although it is clear that pertussis toxin causes the characteristic lymphocytosis and other abnormalities associated with the disease, the mechanism responsible for the severe and prolonged cough remains unknown.

Vaccination of pregnant women has been proposed as a strategy to protect infants from pertussis passively before they receive active vaccination. The potential for such a strategy to work is based on observations that maternal antibody titers to pertussis antigens are low but that, when present, antibodies are actively transported in cord blood.<sup>55</sup> However, data to support the safety and efficacy of maternal vaccination are lacking. An alternative

or complementary approach would be the active immunization of newborns with acellular pertussis vaccines; such approaches are being studied.

#### GUIDELINES

The CDC recommends that for all patients with presumed pertussis, culture be performed to identify the etiologic agent during the time when patients are likely to be infectious, regardless of which other diagnostic tests are used.<sup>36</sup> The CDC and the Food and Drug Administration are currently working on standardization of PCR and serologic methods for the diagnosis of pertussis. Patients seen early in the course of their illness (i.e., during the first three weeks after cough begins) should be evaluated with the use of culture and PCR; PCR and serologic tests can be used when cough has been present for three to four weeks; and serologic tests should be used for patients who present with cough that has persisted for longer than four weeks.

The CDC also recommends the treatment of presumed or confirmed cases of pertussis with erythromycin but acknowledges the limitations of this treatment due to side effects. In cases in which the patient presents after the onset of paroxysmal cough, antibiotic treatment is unlikely to affect the clinical course but will preclude transmission to susceptible hosts beginning five days after the onset of therapy.

#### CONCLUSIONS AND RECOMMENDATIONS

For the patient described in the vignette, whose symptoms started six weeks ago, single-sample serologic testing is the only method that could yield the diagnosis. Given the duration of the symptoms, treatment with antibiotics would not affect the course of the patient's illness, and we would not recommend it at this point. If, however, the diagnosis of pertussis had been made two or more weeks earlier, it would have been appropriate to treat the patient in order to prevent further spread of the infection. If pertussis had been documented (by culture, PCR, or both) in the patient's son during the first three weeks of his illness, it would have been appropriate to consider her a contact and to treat her, whether or not she became symptomatic, with either azithromycin or clarithromycin, according to the regimen in Table 2. With this approach, even if her condition did progress to clinical pertussis, the antibiotic treatment would have the potential to reduce the duration and severity of her illness.

Pertussis vaccines are highly efficacious, but in many countries, including the United States, they are administered only to a small subgroup of the population — namely, children younger than six years of age. The control of pertussis requires an increase in the

immunity of all age groups. We believe that the vaccination of adolescents (with a suitable formulation of acellular pertussis vaccine) should be added to the current immunization schedule for pertussis in order to reduce the risk of the disease later in life as well as the transmission to infants.

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## ADDENDUM

The proceedings of a conference on the Global Pertussis Initiative, at which experts from 17 countries analyzed the status of pertussis disease worldwide and evaluated potential immunization strategies, have been published.<sup>1</sup> The recommendations included increased protection of infants and toddlers by immunization of groups at the highest risk of transmitting *Bordetella pertussis* to them; development of a better understanding of the epidemiology and transmission of pertussis; and improved surveillance, diagnosis, and education. A recently published multicenter placebo-controlled randomized trial in the United States involving subjects ages 15 to 65 years demonstrated that acellular pertussis vaccination conferred 92 percent protection (95 percent confidence interval, 32 to 99 percent) against pertussis infection.<sup>2</sup> Another recent study using a cost-benefit analysis of tetanus, diphtheria, and acellular pertussis (Tdap) booster immunization in the United States projected that vaccinating all adolescents (persons 10 to 19 years of age) would prevent 0.4 to 1.8 million cases of pertussis and save from \$0.3 to \$1.6 billion in medical care costs over 10 years.<sup>3</sup>

Since publication of our article, we have been informed that in addition to those countries noted in Table 1, Australia has added a booster dose of acellular pertussis vaccine for adolescents 15 to 17 years of age.<sup>4</sup> This dose replaces the 18-month booster and, on the basis of computer simulation, is anticipated to reduce the overall incidence of pertussis.<sup>5</sup>

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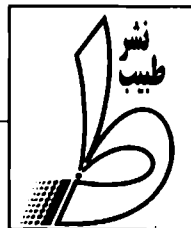
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