

# CLEVELAND CLINIC JOURNAL OF MEDICINE

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## MEDICAL UROLOGY FOR THE PRIMARY CARE PROVIDER

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SUPPLEMENT

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# CONTINUING MEDICAL EDUCATION INFORMATION

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## Content/Overview

Urologic complaints are common in the primary care setting. In recent years, understanding of common urologic disorders has improved and medical treatment options have expanded to the point that effective empiric therapy often can be initiated by primary care providers. This supplement reviews eight common urologic disorders or issues that can and should be identified in the primary care setting. The eight reviews aim to guide primary care providers in symptom identification, patient evaluation and differential diagnosis, initial management strategies, and when to refer patients for specialist evaluation and treatment.

## Statement of Need

Although many patients first report or present with urologic complaints in the primary care setting, primary care providers traditionally have received minimal training in identifying, evaluating, and treating urologic disease. Improved identification and evaluation of urologic disorders in the primary care setting should translate to earlier diagnosis and treatment of these disorders, reduced patient suffering, and better long-term outcomes for patients.

## Learning Objectives

Upon completing this activity, participants will be able to:

- Name and identify the presenting symptoms of the common urologic disorders discussed in this supplement
- Describe the evaluation and differential diagnosis of the common urologic disorders discussed in this supplement
- Identify red flags in the differential diagnosis of common urologic disorders and determine when referral to a specialist is warranted
- Describe evidence-supported treatments for specific urologic disorders and identify patients who are appropriate candidates for those therapies

## Intended Audience

This activity is intended for internists, family practitioners, and general practitioners.

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# The recognition of urologic disease is a primary care issue, whether we've known it or not

*When the facts change, I change my mind.  
What do you do, sir?*

—Sir John Maynard Keynes

Over the years, we have both made some observations about urologic disease that we believe are significant:

- There is a substantial burden of urologic disease that is going undiagnosed, which means patients are needlessly suffering.
- The average primary care provider (PCP) has had little to no training in identifying and evaluating—let alone treating—urologic disease.
- A significant portion of patients with urologic complaints can and should be identified, evaluated, and initially treated in the primary care setting.

Taken together, these observations signal that there is a tremendous need for primary education in urologic disease—not just any education, but education that the PCP can apply in his or her everyday practice.

In this supplement we are challenging the concept that genitourinary complaints are solely the responsibility of the urologist. Although the urologist will always remain a crucial part of the health care team for patients with genitourinary disorders, identification of these disorders must start with the PCP. In recent years, knowledge of many of these urologic diseases has improved so that empiric treatment can be initiated without much more than focused symptom identification, precise physical examination, and directed laboratory testing.

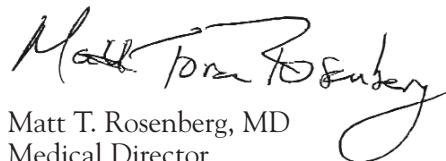
The opportunity to communicate how these changes can be integrated into primary care practice is the focus of this publication. The team approach has been enhanced by identifying those areas that require referral to the urologist. Hopefully the end result will be better care for the patient.

This supplement is unique in that it is written for primary care, by primary care. With the exception of coauthors on the malignancy screening and prostatitis articles, all of the authors of these papers are practicing PCPs. As they wrote their papers, and as we reviewed them, we all kept asking ourselves the same

key question: What does the average PCP need to know about this disease? This fundamental question guided our efforts to make this publication comprehensive yet practical enough to really help the busy PCP.

This project would not have been possible without the support of many people. The authors are experienced and dedicated primary care educators who understand how important it is to integrate urologic expertise into primary care. A special thank-you is extended by one of us (M.T.R.) to Dr. David Staskin, who has been a mentor since our years together in Boston. My love for medical education is directly related to his example and encouragement. Finally, this project could not have been possible without the efforts of Glenn Campbell and his staff at the *Cleveland Clinic Journal of Medicine*. A journal supplement on urologic disease for primary care, by primary care, has not been done before, but the *Journal* shared our belief that the time for it has come.

We hope you find this supplement both helpful and thought-provoking. Our aim is that some of the “pearls” shared in these pages will facilitate better care and improved quality of life for your patients. May you enjoy taking this educational journey as much as we have enjoyed preparing it.



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# Screening for urologic malignancies in primary care: Pros, cons, and recommendations

## ■ ABSTRACT

Interest in screening for urologic cancers has grown in recent years. This article considers the pros and cons of screening for four epidemiologically compelling urologic cancers: prostate, bladder, kidney, and testicular. Unfortunately, many of the urologic cancers do not meet the criteria for a successful cancer screening program—namely, high prevalence, availability of a sensitive and specific screening test, ability to detect clinically important cancers at an early stage, and cost-effectiveness. While age-based screening for prostate cancer should be offered to the general population after discussion of its benefits and risks, for the other three urologic malignancies the current consensus points more toward selective screening based on specific patient risk factors.

## ■ INTRODUCTION

The urologic cancers represent almost one quarter of all cancers in the human body and can be associated with substantial morbidity and mortality (Table 1).<sup>1</sup> Prostate and bladder cancer are two of the most prevalent cancers among American men, and public awareness of these and other urologic cancers has increased greatly over the past decade. The importance of hematuria as a warning sign for cancer, specifically bladder and kidney cancer, is becoming more ingrained in the public consciousness. As a result of these developments, interest in screening for these malignancies has grown among patients and physicians alike.

There are several general prerequisites for a successful cancer screening program:

- A highly prevalent cancer
- Availability of a sensitive and specific screening test with acceptable morbidity

- Ability of the test to detect clinically important cancers at an early stage and thereby improve outcomes
- Cost-effectiveness.

This article will review the utility of screening for four of the most epidemiologically compelling urologic cancers—prostate, bladder, kidney, and testicular—in the primary care setting.

## ■ PROSTATE CANCER

### Epidemiology

Prostate cancer is the most common noncutaneous malignancy in the United States; 232,000 new cases were estimated to have been diagnosed in 2006 (Table 1).<sup>1</sup> It is the third-leading cause of cancer deaths among American men, responsible for an estimated 32,000 deaths annually.<sup>1</sup> American men have a 17% lifetime risk of being diagnosed with prostate cancer and a 3.4% risk of dying from this disease.<sup>2</sup> Compared with other racial groups, African Americans are at increased risk of developing prostate cancer, tend to develop it at an earlier age, and tend to have more advanced disease at the time of diagnosis.

### Symptoms, presentation, and screening options

Since symptoms from prostate cancer usually do not develop until the disease is at an incurable stage, screening strategies cannot be symptom-based. Screening options, which consist of periodic serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE), are aimed at facilitating early diagnosis of prostate cancer, when it is still at a curable stage.

### Rationale and evidence for screening

Current evidence in support of screening for prostate cancer comes largely from national cancer trends and population-based studies. The PSA test was introduced in 1989, and age-adjusted death rates from prostate cancer subsequently declined by 4% per year (17.6% overall) from 1994 to 1998.<sup>3</sup> Population-based regional screening programs in Tyrol, Austria, and Olmsted County, Minnesota, have also shown

\* Drs. Stephenson and Campbell reported that they have no financial relationships that pose a potential conflict of interest with this article. Dr. Kuritzky reported that he has received honoraria from Pfizer, Eli Lilly, ICOS, Bayer, and GlaxoSmithKline for teaching/speaking.

**TABLE 1**  
US incidence and mortality rates for urologic cancers relative to other common malignancies\*

Cancer	Incidence (annual)	Mortality (annual)	% Mortality
Prostate	232,000	32,000	14%
Breast*	211,000	40,000	19%
Lung*	173,000	163,000	94%
Colorectal*	145,000	54,000	37%
Bladder	63,000	12,000	20%
Kidney	30,000	12,000	40%
Testicular	8,000	330	4%

\* The three most common nonurologic malignancies are included for comparison. Rates are estimates for 2006 based on Centers for Disease Control and Prevention data.<sup>1</sup>

substantial declines in prostate cancer mortality relative to national trends.<sup>4,5</sup> American prostate cancer mortality rates continue to decline, and in 2006 prostate cancer was overtaken by colorectal cancer as the second-leading cause of male cancer deaths.<sup>1</sup> Although some of the overall mortality reductions can be attributed to improvements in therapy, it is well recognized that currently the only way to significantly reduce prostate cancer death is treatment of localized disease, which requires early detection.

The only published randomized, prospective study of prostate cancer screening, conducted among 46,193 men in Québec, Canada, reported a 69% reduction in prostate cancer mortality among the 8,137 men who were screened compared with the 38,056 men who were not.<sup>6</sup> This study has been heavily criticized, however, as its data were not analyzed according to the intention-to-screen statistical methodology.

Opportunistic screening is driven by the logic that prostate cancer can be cured only when it is pathologically confined to the prostate and its environs and that screening increases the detection of clinically localized disease. In large screening studies, clinically confined cancers are detected in 85% to 99% of cases compared with 50% to 60% for cancers that are not discovered by screening.<sup>7,8</sup> Prostate cancer that is pathologically confined to the prostate is reported in up to 70% of patients in screening studies, and long-term cancer control rates of 90% are reported when these cancers are treated with radical prostatectomy.<sup>9</sup>

In light of the above, a strong rationale can be made for prostate cancer screening, and careful

**TABLE 2**  
Comparative cost-effectiveness of screening for prostate cancer and breast cancer\*

	Prostate cancer	Breast cancer
Age-adjusted deaths per 100,000 population	25.6	25.4
Mortality-to-incidence ratio	0.18	0.22
Sensitivity of screening test <sup>†</sup>	70%–80%	67.5%–80%
Positive predictive value of screening test <sup>†</sup>	30%–42%	9%–22%
Cost per quality-adjusted life-year gained from screening test <sup>†</sup>	\$8,700–\$145,000	\$232,000

\* Based on data from Wilson and Crawford.<sup>2</sup>

<sup>†</sup> Serum prostate-specific antigen (PSA) test for prostate cancer; mammography for breast cancer.

review of the data suggests that screening for this cancer compares favorably with screening for breast cancer, which is generally well accepted. Compared with screening mammography for breast cancer, screening for prostate cancer with the PSA test has a higher positive predictive value and is also more cost-effective (Table 2).<sup>2</sup>

In addition, screening with the PSA test is associated with minimal harm to the patient. Approximately 4% of screened men will undergo prostate biopsy during the course of screening; although the possible side effects of prostate biopsy include temporary pain, bleeding, and infection, hospital admission is required in only 0.3% to 0.5% of cases.<sup>10</sup>

Of course, the rationale for screening is based on the premise that prostate cancer-related morbidity and mortality will be improved as a result of early-stage treatment. Conclusive evidence on that score is now available, such as from a recent randomized trial demonstrating a 44% relative risk reduction in cancer-specific mortality with radical prostatectomy for early prostate cancer compared with watchful waiting.<sup>11</sup> However, conclusive evidence from randomized trials that prostate cancer screening reduces all-cause mortality is currently lacking. Two large ongoing screening studies should address this question: the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial, which is being conducted in the United States, and the European Randomized Study of Screening for Prostate Cancer (ERSPC). Their results are likely to be released in 2008.



**Arguments against screening**

A potential drawback to prostate cancer screening is that it will lead to the diagnosis and treatment of a large number of small, indolent tumors that would otherwise remain clinically covert until the patient died from other causes. The majority of screening-detected cancers are graded as 6 or less on the Gleason classification system for prostate cancer (scores range from 2 [least aggressive] to 10 [most aggressive]), and only an estimated 10% of patients with these cancers will die of prostate cancer within 10 years without treatment.<sup>12</sup> Estimates from the ERSPC suggest that annual screening programs for men aged 55 to 67 years lead to overdiagnosis (ie, detection of cancers that would not have been diagnosed in the absence of screening) in 56% of men diagnosed with prostate cancer.<sup>13</sup>

If these estimates are accurate, annual screening programs may introduce more harm (through treatment-related morbidity) than benefit in terms of reducing cancer-specific mortality. However, most data support the contention that current screening efforts using PSA testing do not detect substantial numbers of indolent prostate cancers. In most screening studies, the cancer detection rate ranges from 7% to 10%, which is substantially lower than the 50% to 70% incidence of indolent cancer in autopsy studies.<sup>7,8</sup> In a recent study, less than 10% of screening-detected cancers were classified as clinically insignificant.<sup>7</sup>

**Recommendations**

**Formal guidelines on screening.** Guidelines from professional societies and governmental organizations reflect the current uncertainty about the benefits of widespread prostate cancer screening. The American Cancer Society (ACS) and the American Urological Association (AUA) recommend annual screening with the PSA test and DRE beginning at age 50 years for men who have a life expectancy of 10 or more years.<sup>14,15</sup> Screening should begin earlier—at age 40 years—in men at high risk for developing prostate cancer on the basis of sub-Saharan African ancestry and/or the presence of an affected first-degree relative, particularly if the diagnosis in the relative was made before age 55.<sup>14,15</sup> However, mass prostate cancer screening is not endorsed by the United States Preventive Services Task Force (USPSTF), owing to the lack of definitive evidence that the benefits of screening outweigh the risks.<sup>16</sup> The USPSTF recommends that physicians discuss with patients the potential but uncertain benefits of screening and the possible risks before ordering a PSA test.

**Authors' recommendations on screening.** Despite a lack of conclusive evidence regarding the benefits of

prostate cancer screening and the conflicting recommendations, PSA testing is widely practiced in North America and in many parts of Europe. An estimated 57% of American men aged 50 years or older have undergone testing with serum PSA, and the vast majority of prostate cancers are now diagnosed as a result of opportunistic PSA screening.<sup>17,18</sup>

The controversy surrounding prostate cancer screening is unlikely to subside until results of the PLCO and ERSPC screening trials are available. Pending those results, we believe that prostate cancer screening using serum PSA level determinations and DRE should be offered to men 50 years of age or older who have a life expectancy of 10 years or more. Screening should be offered in conjunction with a discussion of its potential benefits and risks. Screening should always include serum PSA testing and DRE, as 25% or more of cancers will be detected in men with PSA levels less than 4.0 ng/mL. Men with risk factors for developing prostate cancer (sub-Saharan African ancestry, affected first-degree relative) should undergo PSA-based screening beginning at age 40 years (Table 3). The optimal screening interval has not been defined, but the ACS and the AUA recommend annual screening.<sup>14,15</sup>

**Recommendations for follow-up and referral.** An elevated serum PSA level or prostate abnormalities on DRE are indications for prostate biopsy. A total PSA level greater than 4.0 ng/mL has traditionally been the threshold for recommending prostate biopsy, although a lower threshold (2.0 ng/mL) may be considered in men younger than 60 years.<sup>19</sup> The probability of finding prostate cancer on biopsy when these indications are present is 20% to 30%.<sup>19</sup>

The PSA level may be elevated by conditions other than prostate cancer, such as benign prostate disease (benign prostatic hyperplasia and acute or chronic prostatitis), urinary retention, urethral instrumentation, DRE, and sexual activity. Before considering prostate biopsy for an isolated PSA elevation, the PSA level should be confirmed by a repeat measurement several weeks later, as 44% and 40% of men with an isolated PSA elevation greater than 4.0 ng/mL and 2.5 ng/mL, respectively, will have a normal PSA reading at one or more subsequent visits.<sup>20</sup>

Referral for prostate biopsy should also be made when there are abnormalities on DRE such as a palpable nodule, induration, or asymmetry. Normally the prostate should be symmetrical and should have the consistency of the thenar eminence.

In an analysis of patients enrolled in the Prostate Cancer Prevention Trial, the main predictors of

**TABLE 3**  
**Screening recommendations for urologic cancers**

Cancer	Screening options and their major limitations	Recommendations for general population	Target populations
Prostate	Prostate-specific antigen (PSA) test –Suboptimal specificity –May detect “insignificant” cancers Digital rectal examination (DRE) –Low sensitivity	No definitive evidence for reduction in prostate cancer mortality, but ample evidence supporting screening with PSA test and DRE for early diagnosis of prostate cancer  Annual screening starting at age 50 (age 40 in target populations), provided that patient has life expectancy > 10 years, is recommended by several professional societies and should be offered to and discussed with each patient	Men of sub-Saharan African ancestry Men with an affected first-degree relative
Bladder	Dipstick of urine –Hematuria is often intermittent –Incidence too low –Suboptimal specificity Cytology –Low sensitivity –Too expensive Tumor markers –Low sensitivity –Too expensive	Data do not justify generalized screening Focus should be on target populations; primarily use dipstick of urine to screen for hematuria in this setting Urologic referral indicated if microscopic or gross hematuria detected	Current or former tobacco users, especially older men Persons with occupational exposure in chemical, textile, or rubber industries Persons with past exposure to phenacetin, cyclophosphamide, or pelvic radiation therapy Patients with chronic UTIs or neurogenic bladder Patients with spinal cord injury with intermittent catheterization or indwelling catheter
Kidney (RCC)	Dipstick of urine –Incidence too low –May detect benign/indolent tumor –Hematuria often not present Ultrasonography –Too expensive –Yield too low to justify –Suboptimal specificity	Data do not justify generalized screening Focus should be on target populations; primarily use ultrasonography or computed tomography to screen for renal mass in this setting Urologic referral indicated if mass is found	Persons with history suggestive of familial RCC, such as von Hippel-Lindau disease Patients with end-stage renal failure (screen selectively)
Testicular	Physical exam and self-exam –Examiner-dependent	Data do not justify generalized screening Focus should be on target populations; primarily use clinical examination and selective ultrasonography for symptoms or signs in this setting	Patients with the following: –History of undescended testis –Atrophic testis –Male infertility –Personal or family history of testicular cancer –Microlithiasis on testicular ultrasonography

RCC = renal cell carcinoma; UTI = urinary tract infection

prostate cancer on biopsy were the total serum PSA level, a positive family history, an abnormal DRE, and the absence of a prior negative prostate biopsy.<sup>19</sup>

## ■ BLADDER CANCER

### Epidemiology and natural history

Bladder cancer is the fourth most common cancer in men and the eighth most common in women, and it represents a major source of morbidity and mortality

in the United States (Table 1).<sup>1,21</sup> Overall, this cancer is three to four times more common in men than women, and most cases are seen in the sixth through ninth decades of life.<sup>22,23</sup>

Bladder cancer is a prototype of the environmentally related cancer. Carcinogens filtered by the kidney bathe the lining of the bladder, leading to a field effect—ie, the entire urothelium is at risk. The pre-clinical phase is relatively short; bladder cancer is

rarely discovered at autopsy.<sup>22</sup> Multifocal disease is frequently found at presentation, and recurrence is common during longitudinal follow-up.<sup>23</sup>

Two clinical pathways predominate for bladder cancer. The first, which represents 50% to 60% of cases, is characterized by low-grade, noninvasive tumors that tend to recur but rarely progress.<sup>23</sup> The second pathway, on the other hand, is characterized by high-grade disease that not only can recur but also can progress to invasive disease.<sup>23</sup>

### Symptoms, presentation, and screening options

Bladder cancer commonly presents with painless hematuria, although about 10% to 20% of patients present primarily with irritative voiding symptoms.<sup>23</sup> Gross hematuria is a major warning sign of cancer and always mandates urologic evaluation, but microscopic hematuria is also commonly associated with bladder cancer.<sup>22</sup>

It is critical that distracting diagnoses not dissuade the clinician from pursuing an etiologic explanation for hematuria. For instance, a substantial minority of patients receiving warfarin who present with hematuria are subsequently determined to harbor urologic cancer—in other words, warfarin was *not* the culprit. Hence, just as we would not accept hemorrhoids as the cause of rectal bleeding in a middle-aged man until cancer had been ruled out, we must pursue clear delineation of the origin of hematuria in patients on anticoagulant therapy.

Dipstick urinalysis is the primary screening method for bladder cancer, although cytology has also been proposed, as has testing for molecular markers that detect tumor antigens and other abnormalities.

### Rationale for screening

The rationale for screening is to detect high-grade bladder tumors before they become invasive, when the likelihood of achieving a cure is still high. Once high-grade tumors become invasive, radical treatments are needed that often entail substantial morbidity. Even if treated in such an aggressive manner, about 50% of patients with high-grade invasive bladder cancer will die of disease progression.<sup>22,24</sup>

However, screening is not likely to have a substantial impact in patients with low-grade bladder tumors, who represent 50% to 60% of bladder cancer cases, as low-grade tumors are not life-threatening and the benefit of their early diagnosis is highly debatable.<sup>23</sup>

### Arguments against screening

The prospect of screening for bladder cancer poses inherent problems since the overall incidence of this cancer is low (about 20 per 100,000 population per

year<sup>1</sup>) and only a minority of patients—those with high-grade disease that has not yet become invasive—might benefit from screening. For these reasons, a screening test would need to be very inexpensive and highly specific to be considered cost-effective. In addition, hematuria, the main warning sign of bladder cancer, tends to be intermittent, so repetitive screening is required.<sup>22,24</sup>

The current literature supports these assertions. Most studies have focused on older men and have used urine dipstick analysis to screen for hematuria. In one large study using a single test to look for hematuria, no substantial change in the incidence of urologic cancers was found between screened and unscreened men.<sup>22</sup>

Studies using repetitive dipstick testing for hematuria have been more promising but remain inconclusive. In one such study of 2,356 asymptomatic men 60 years of age or older, bladder cancer was found in 17 subjects, and no tumors were muscle-invasive.<sup>25</sup> However, after 7 years of follow-up, 3 of the 9 subjects with high-grade tumors died of cancer progression, suggesting that the natural history of the disease cannot always be altered even if detected through screening.<sup>25</sup> In a landmark study, Messing et al screened 1,575 asymptomatic men 50 years of age or older with a urine dipstick and compared their outcomes with those of a control group of nonscreened subjects from a local cancer registry.<sup>24</sup> A total of 21 bladder cancers were screen-detected, and the incidence of invasive cancer was substantially lower in the screened population than in the control group (4.8% vs 23.9%, respectively).<sup>24</sup> Cancer-related mortality was also lower in the screened population (0% vs 16.4%).<sup>22,24</sup> Selection bias and biases in lead time or length time may have contributed to these results, however, and a randomized trial would be required to provide definitive data on the value of screening in this manner.

### Recommendations

Most authorities believe that screening the general population for bladder cancer is not likely to be cost-effective, and routine urinalysis has not been advocated as a part of routine preventive care by most major medical organizations. Rather, urinalysis is recommended for select patients with lower urinary tract symptoms, hypertension, diabetes, or other specific indicators of urologic or renal pathology (hematuria, flank pain, unexplained peripheral edema).<sup>26,27</sup>

Thus, a more rational approach is to focus on target populations that have an increased incidence of bladder cancer (**Table 3**), keeping in mind

the following risk factors:

**Tobacco use**, which is the single most common and most important predisposing factor, increasing the risk of bladder cancer twofold to fourfold.<sup>23</sup>

**Occupational exposure**, most notably in the chemical, textile, and rubber industries. Workers in these industries are at a 20-fold or greater increased risk of developing bladder cancer relative to the general population. The latency period is 15 to 20 years, on average.<sup>23</sup>

**Exposure to phenacetin or cyclophosphamide, or a history of pelvic radiation therapy.**<sup>23</sup>

**Chronic urinary tract infection or neurogenic bladder** (chronic inflammation is thought to be the etiology).<sup>22,23</sup>

**Spinal cord injury requiring intermittent catheterization or indwelling catheter.** Screening in this setting has been shown to be nonproductive, but all patients with gross hematuria should be evaluated.<sup>22,23</sup>

With the exception of the last subgroup, routine screening should include an occasional urinalysis; if this demonstrates 3 or more red blood cells per high-power field (40×), formal urologic evaluation should be pursued, including urine cytology, upper urinary tract imaging, and cystoscopy.<sup>27</sup> Formal biopsy should be obtained if cytology or cystoscopy reveal potentially suspicious findings.

Cytology has also been proposed as an intermediate screening tool to stratify patients with microhematuria into those who need further intensive evaluation and those who require only continued surveillance.<sup>22,27</sup> This approach has been advocated in patients with occupational exposure in an effort to reduce the number of invasive procedures, but its ultimate utility has not been determined. Urine cytology provides excellent specificity but suboptimal sensitivity: although it will reduce the number of required cystoscopies, it also will lead to a missed diagnosis in many patients.<sup>22,27</sup>

Molecular markers that can detect tumor antigens, nuclear matrix proteins, chromosomal changes, and other abnormalities associated with bladder cancer have also been studied and in general provide better sensitivity than does urine cytology.<sup>28</sup> Like cytology, however, most of these tests are too expensive to play a prominent role in generalized screening programs.

Actually, the patient group at highest risk for developing bladder cancer consists of those with a history of the disease.<sup>29</sup> More than 50% of cases will recur with time, and intensive surveillance with periodic urine cytology and cystoscopy has traditionally been recommended.<sup>29</sup> These patients should be followed by a urologist, although a subgroup of low-risk patients may be released back into the care of their

primary care physician after 5 years if they remain continuously cancer-free. The latter group should undergo a yearly urinalysis.<sup>28</sup>

## ■ KIDNEY CANCER

### Epidemiology

Kidney cancer, or renal cell carcinoma (RCC), has a relatively low incidence in the United States: 8.9 cases per 100,000 population per year.<sup>30</sup>

### Symptoms, presentation, and screening options

The classic symptoms of RCC, including gross hematuria, palpable mass, or flank pain, are now uncommon; today most patients present incidentally. This is decidedly fortunate, as all signs and symptoms related to RCC have negative prognostic implications.<sup>31</sup>

The screening modalities that have been studied for detection of RCC include dipstick urinalysis, ultrasonography, and computed tomography (CT).

### Rationale for screening

Several factors make screening for RCC appealing. Most important, RCC remains primarily a surgical disease requiring early diagnosis to optimize the opportunity for cure. Unfortunately, current systemic therapies for RCC have only modest efficacy, and our ability to salvage patients with more advanced disease remains limited, as reflected in the formidable mortality statistics in **Table 1**. As one might expect, several studies have demonstrated an apparent survival advantage to early or incidental diagnosis of RCC.<sup>31</sup> Early diagnosis can also facilitate nephron-sparing approaches and the use of less invasive modalities, such as thermal ablation.<sup>31</sup>

### Arguments against screening

The primary factor that limits widespread screening for RCC is its relatively low incidence in the general population, as noted above.<sup>30</sup> Any potential screening test would need to be almost 100% specific or it would lead to a multitude of unnecessary, expensive, and potentially harmful diagnostic or therapeutic procedures. In addition, even if the test were 100% sensitive and specific, the yield from screening the general population would be so low as to not be considered cost-effective. Even when one considers populations with established risk factors for RCC, such as male sex, advanced age, and heavy tobacco use, screening would be difficult to justify because the increase in relative risk associated with each of these factors is, at most, twofold to threefold.<sup>31</sup>

Another factor that argues against generalized screening for RCC is the prevalence of clinically

insignificant tumors such as renal adenomas, which have an autopsy incidence of 10% to 20%, and other benign or indolent tumors.<sup>31</sup>

The current literature on the use of dipstick urinalysis, ultrasonography, or CT for screening for RCC substantiates these concerns. Urinalysis for hematuria is simple and inexpensive, but its yield of RCC detection in clinical studies has been exceedingly low. Many small RCC tumors are not associated with hematuria, whether gross or microscopic, since this is a parenchymal-based, rather than urothelial-based, cancer.<sup>31</sup> The incidence of RCC in screening studies using ultrasonography or CT has ranged from 20 to 300 per 100,000 population, somewhat higher than expected given the clinical incidence of this cancer.<sup>32,33</sup> These rates are still relatively low, however, and such approaches are not likely to be considered cost-effective. Overall, the yield of RCC diagnoses in such studies is still more than an order of magnitude lower than the yield of prostate cancer diagnoses from PSA-based screening, and many of the same controversies about lead and length time biases in screening for other cancers also apply to RCC.<sup>31</sup> Some have argued that imaging-based screening could be broadened to look for other malignancies, abdominal aneurysms, and coronary artery disease in addition to RCC, which might increase the utility and cost-effectiveness of this approach. However, solid data in support of this argument are not currently available, and this remains a controversial topic.

### Recommendations

In light of the above, generalized screening for RCC is not indicated. The primary focus of screening for this cancer must be on well-defined target populations such as patients with familial RCC and those with end-stage renal failure (ESRF) or acquired renal cystic disease.<sup>31,34,35</sup>

About 2% to 4% of RCC cases are familial, and these comprise a number of well-characterized entities such as von Hippel-Lindau disease.<sup>34</sup> This disorder, which is transmitted in an autosomal dominant manner, can lead to hemangioblastomas of the central nervous system, retinal angiomas, renal cysts, pheochromocytoma, and RCC. RCC in von Hippel-Lindau disease tends to be early-onset and multifocal, and patients with other manifestations of this syndrome or with a family history suggestive of von Hippel-Lindau disease or other familial forms of RCC should undergo abdominal imaging to screen for RCC.<sup>34</sup>

Eighty percent of patients with ESRF eventually develop acquired renal cystic disease, and 1% to 2% of patients in this subgroup develop RCC.<sup>31,35</sup> Overall,

the relative risk of RCC appears to be about 5-fold to 20-fold higher in patients with ESRF than in the general population.<sup>31,35</sup> However, many patients with ESRF have a short life expectancy and RCC is typically not seen in the first few years after initiation of dialysis. A reasonable approach is to focus screening efforts on ESRF patients who do not have other major comorbidities, to delay screening until the third year on dialysis, and to start with ultrasonography and withhold CT until suspicious lesions are identified.<sup>31</sup>

## ■ TESTICULAR CANCER

### Epidemiology

Germ cell tumors of the testis (nonseminoma and seminoma) are the most common malignancy in males aged 15 to 35 years; the lifetime risk of testicular cancer is 1 in 500.<sup>1</sup> The typical age at diagnosis ranges from 15 to 50 years.

### Symptoms, presentation, and screening options

Symptoms related to the testicle are present in the vast majority of patients and typically include a history of a palpable testicular mass. Nevertheless, diagnostic delay is a well-recognized phenomenon of testicular cancer, and one to which both patients and physicians contribute. Patients may delay medical evaluation of a testicular mass out of embarrassment, fear, guilt, or ignorance. Additionally, physicians often may contribute to diagnostic delay through misdiagnosis or unnecessary diagnostic tests or interventions; up to one third of testicular tumors are initially misdiagnosed as epididymitis or hydrocele.<sup>36</sup> A relationship has been observed between the length of diagnostic delay and response to chemotherapy, with patients who are subject to delay presenting with more advanced disease that requires more intensive treatment regimens.<sup>37</sup>

The primary means of screening for testicular cancer is physical examination of the testicles, both by the patient himself and by his primary care provider as part of the periodic health examination. Careful testicular examination can usually differentiate pain or a mass arising from the epididymis from pain or a mass in the testicle. The presence of a hydrocele may prevent accurate assessment of the testicle, and ultrasonography of the scrotum is indicated if a patient has symptoms related to the testicle with an associated hydrocele.

### Recommendations

Thanks to the development of effective chemotherapy and the integration of chemotherapy and surgery, the overall cure rate associated with testicular cancer is 96%.<sup>38</sup> Given the relative rarity of this disease

(Table 1), its high cure rates, and the ease of detection by testicular self-examination, routine screening specifically for this disease (other than by self-examination) is not recommended and is unlikely to significantly affect the prognosis. However, patient education about regular testicular self-examination is recommended, as is the inclusion of routine testicular examination in periodic health examinations of postpubertal males until age 50.

Several risk factors for the development of testicular cancer have been identified,<sup>39</sup> as outlined in Table 3, and should prompt increased clinician vigilance in conducting testicular examinations:

**A history of cryptorchidism (undescended testis)** confers an 8-fold to 16-fold increased risk of developing testicular cancer.<sup>39</sup> Although it is controversial whether orchiopexy in early childhood reduces this risk, orchiopexy is still recommended to allow further development of the testis and to facilitate early diagnosis should a tumor occur. Periodic testicular examination should begin at puberty in these patients.

**Family or personal history.** Having an affected first- or second-degree relative also appears to increase risk, and patients with a personal history of testicular cancer have a 3% to 5% lifetime risk of developing a germ cell tumor in the contralateral testicle.<sup>39</sup>

**Microlithiasis, atrophic testis, infertility.** The presence of testicular microlithiasis identified on routine scrotal ultrasonography has been reported in 0.6% to 0.9% of the general male population and may be associated with a slightly increased risk of testicular cancer.<sup>40</sup> An increased incidence of testicular cancer has also been correlated with atrophic testis and male infertility, so patients with these conditions also merit careful scrutiny.

The potential association of the above conditions with development of testicular cancer should be conveyed to the postpubertal male patient younger than age 50, and the importance of testicular self-examination and routine clinical assessment should be emphasized. Equivocal or suspicious findings from a physical examination should prompt ultrasonographic examination of the testes, and urologic referral should be pursued if any intratesticular abnormalities are found.

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# Benign prostatic hyperplasia: When to 'watch and wait,' when and how to treat

## ■ ABSTRACT

Benign prostatic hyperplasia (BPH) is a clinical diagnosis. While BPH is a common cause of lower urinary tract symptoms (LUTS) in men, LUTS can signify a number of other disease states. For this reason, the patient evaluation, which includes a digital rectal examination, and careful differential diagnosis are crucial in men with LUTS. Many men with BPH are asymptomatic, and many others are not bothered by their symptoms; watchful waiting is appropriate management for these patients. When symptoms affect quality of life, pharmacologic therapy should be an option; choices include an alpha-blocker, a 5 alpha-reductase inhibitor, or, for men with larger prostates, a combination of the two. Surgical intervention is indicated when BPH leads to other medical complications, including urinary retention and renal insufficiency.

## ■ DEFINITION OF THE CONDITION

The term "benign prostatic hyperplasia" (BPH) carries one of three meanings:

- Microscopic detection of prostatic hyperplasia, which is the benign proliferation of the stroma and epithelium
- Palpable enlargement of the prostate, which can be detected by clinical or ultrasonographic examination
- The collection of urinary symptoms associated with prostatic hyperplasia, loosely defined as lower urinary tract symptoms (LUTS). These symptoms are categorized in **Table 1**<sup>1</sup> and will be discussed in detail later in this article.

The variation in definitions stems from the reality that prostate size does not always correlate well with symptoms. As a result of the interrelatedness of the microscopic, macroscopic, and clinical designations,

BPH is generally understood to imply one or more of these findings.

Classic BPH, the focus of this article, is the most common cause of LUTS in men, but if LUTS in a man does not respond to an appropriate course of BPH therapy, clinicians should consider other diagnoses that may cause LUTS, including overactive bladder, prostatitis, and interstitial cystitis, each of which is the subject of an article in this supplement.

## ■ PREVALENCE AND SOCIAL IMPLICATIONS

A 1995 population-based cross-sectional study concluded that approximately 5.6 million white men in the United States aged 50 to 79 years were appropriate candidates for discussion of treatment options for BPH based on guidelines for BPH diagnosis established by the Agency for Health Care Policy and Research.<sup>2</sup> The study projected that this figure of 5.6 million would double by 2020 with the aging of the US population.<sup>2</sup>

Population-based studies of prostate enlargement in Africans and African Americans are lacking. The most recent data, from the National Hospital Discharge Data Survey, indicate that the percentage of African American men undergoing prostatectomy for prostate enlargement is similar to the percentage of whites, when adjusted for age.<sup>3</sup> These data suggest that the prevalence of prostate enlargement in African American men is similar to that in white American men. However, the incidence of and the mortality from prostate cancer are approximately twice as high among African Americans compared with whites, and are lowest among Asians.<sup>4</sup>

## Histologic and clinical findings often inconsistent

Histologic BPH—microscopic nodular hyperplasia—increases linearly with age in all ethnic groups.<sup>5</sup> Prostate enlargement is identifiable in half of men at age 60 and in about 90% at age 85.<sup>5</sup> However, only 50% of men with microscopic nodular hyperplasia will develop clinical prostate enlargement as detected by digital rectal examination (DRE) or ultrasonogra-

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**TABLE 1**  
Lower urinary tract symptoms seen in benign prostatic hyperplasia

Storage	Voiding	Postmicturition
Urgency	Hesitancy	Terminal dribble
Frequency	Poor flow	Postvoid dribble
Nocturia	Intermittency	Incomplete emptying
Urge incontinence	Straining	
Stress incontinence	Dysuria	

Adapted from Abrams et al.<sup>1</sup>

phy.<sup>6</sup> The relationship between histologic and clinically assessed prostate enlargement is inconsistent: only about 30% to 50% of men with gland enlargement detected by DRE or ultrasonography manifest symptoms.<sup>7,8</sup>

A larger prostate gland predicts a greater degree of future growth than does a smaller gland. Fortunately, BPH progresses slowly.<sup>9</sup> Larger prostate volume and increased levels of prostate-specific antigen (PSA) are associated with an increased risk for acute urinary retention and other problems, such as bladder calculi, urinary tract infection (UTI), hydronephrosis, and LUTS.<sup>10</sup>

**Patients’ knowledge of disease progression is key**

Most cases of BPH are asymptomatic. Of men who develop symptoms, most live with them for long periods before seeking medical help. Although the symptoms of BPH can be remarkably problematic, BPH does not increase the incidence of prostate cancer. However, an age-independent association between BPH-related LUTS and impaired sexual function has been noted.<sup>11</sup> The mechanisms for this association are not clear, but it has been proposed that an excessive sensitivity to alpha tone could explain both LUTS and a decline in sexual function. Fortunately, symptomatic BPH can be managed effectively with currently available treatment.

In a patient with an enlarged prostate, increased PSA values, or both, it may be prudent to provide education about the potential for symptom progression. The patient will then be aware of the possible disease course and will thereby be participating in his own care. Otherwise, a patient might not communicate any symptom until he suffers one episode of urinary retention and renal insufficiency caused by an enlarged prostate. Disease awareness may potentially avert this outcome.

**■ PATHOGENESIS**

**The normal prostate at a glance**

BPH is caused by hypertrophy of the stromal cells of the transitional zone of the prostate. The adult prostate consists of two thirds glandular and one third fibromuscular components. The glandular portion comprises three zones—central, transitional, and peripheral—and has two primary components: the stroma, with its smooth muscle and connective tissues, and the epithelium, which contains glands. The transitional zone represents 5% to 10% by volume, the peripheral or outer zone represents 70% to 80%, and the central or innermost zone represents 20% to 25%. Functionally, the prostate reaches maturity at puberty.

After achieving adult size, the prostate remains essentially the same size for several decades. Then, in midlife and beyond, prostatic growth again occurs in the majority of men.

**Hyperplasia alters anatomic relationships**

With the development of hyperplasia, the anatomic relationships change. Hyperplastic growth occurs in concentric circles, primarily in the transitional zone, resulting in compression of the peripheral and central zones.

Histologically, BPH is associated not only with an increased number of both stromal and epithelial cells but also with a perturbed balance of these cells. For instance, in the healthy young adult prostate, the ratio of stroma to epithelium is approximately 2:1; with the development of BPH, this ratio increases to as high as 4:1 to 5:1. There is an apparent relationship between the increase in this ratio and symptoms. At lower levels of the stroma:epithelium ratio (< 2.8:1), most men remain asymptomatic; by the time higher ratios are attained (> 4.5:1), symptoms of BPH are increasingly likely.<sup>12</sup>

In addition to the histologic changes, macroscopic glandular enlargement of the transitional zone results in compression of the periurethral area, which is responsible for LUTS. In clinical trials, patients with untreated BPH developed urinary obstruction at a rate of 6 to 25 cases per 1,000 patients per year, or approximately one third higher than the rate in treated patients.<sup>13–15</sup>

Progressive prostatic hyperplasia most often compromises the lateral walls of the urethral lumen. Although there is no anatomically defined prostatic median lobe, a specific localized hypertrophy of the posterior transitional zone has been commonly known as “median lobe hypertrophy.” The hypertrophied prostatic projection intrudes upon the bladder wall and posterior urethra. This type of enlargement may not, however, be readily appreciated upon palpa-

tion, compared with the “typical” BPH that can be detected by palpation on DRE.

### The role of hormones

The etiology of BPH is thought to be hormonal. The testis is essential in the development of BPH. Eunuchoid patients, who lack testosterone, do not develop BPH, and neither do chemically castrated males, who lack the enzyme to aromatize testosterone. Additionally, estrogen plays a role in priming the androgen receptors.<sup>16</sup>

Testosterone itself is not the “culprit hormone” in the development of BPH. Rather, intraprostatic dihydrotestosterone (DHT) is responsible for pathologic hyperplasia. DHT is synthesized mainly in the prostate stromal cells from circulating testosterone by the action of the enzyme 5 alpha-reductase type 2.<sup>17</sup> In the serum, the testosterone level is higher than the DHT level (testosterone:DHT ratio is > 10). In prostate tissue, the ratio is reversed. In the prostate, DHT binds to androgen receptors more tightly than testosterone does, owing to high affinity. Testosterone levels decline during aging (whereas DHT levels in the prostate do not) and alter the androgen dynamics. The maintenance of prostatic DHT and 5 alpha-reductase type 2 levels leads to continued hyperplasia of the prostate.<sup>18</sup>

### Symptoms have anatomic and hormonal origins

The LUTS associated with BPH are both anatomic and neurohormonal in origin. A significant component of these symptoms is related to increased muscle tone and pressure of the smooth muscle in the urethra, prostatic stroma, and bladder neck, mediated through the alpha-1A adrenoceptors.

Other factors may contribute to the clinical symptoms. Anatomic changes can result from enlargement of prostatic stromal tissue. For instance, smooth muscle proliferation can result in urethral lengthening and exaggeration of the posterior urethral curve. Other potential contributors are adrenergic neurotransmitters and neuroendocrine cells that are present in the prostatic tissue (which develop from the urogenital sinus). One consequence of BPH is bladder wall trabeculation and hypertrophy of the detrusor musculature, which may also be accompanied by venous vascular dilation.

### PRESENTING SYMPTOMS

Table 1 presents the clusterings of LUTS that are frequently seen in patients with BPH. The symptoms of BPH are broadly categorized as involving problems of either bladder storage or bladder emptying (voiding and postmicturition). This categorization is intended to assist in attributing various symptoms to pathologic

changes in BPH. For instance, emptying problems, such as hesitancy in initiation of voiding, weak stream, dribbling, diminished stream caliber, stop-start urination, and urinary retention, are usually ascribed to the mechanical impact of an enlarged prostatic transitional zone. Similarly, irritative symptoms, such as frequency, urgency, urge incontinence, and nocturia, are thought of as storage problems. The cause of irritative symptoms is believed to be obstruction of the bladder by the hyperplastic prostate.

Patients are bothered by storage symptoms significantly more than by voiding symptoms.<sup>19</sup> Nocturia is one of the most common bothersome symptoms of BPH, after urgency and incontinence.<sup>20</sup> It produces sleep disturbances and significantly affects patients' quality of life.<sup>20-22</sup> Few patients will complain of less-interfering symptoms, such as urinary frequency and dribbling, and fewer still will require an emergency visit for acute urinary retention. Notably, however, acute urinary retention or a UTI may be the first presenting symptom.

Physicians who would like assistance in assessing LUTS can turn to standardized questionnaires such as the American Urological Association (AUA) Symptom Index for BPH<sup>23</sup> (Table 2) or the International Prostate Symptom Score, which includes an additional question that assesses the degree of bother caused by the patient's symptoms (see Table 2 footnote).<sup>24</sup> In the authors' experience, the AUA Symptom Index is very helpful in establishing a diagnosis, but a few simple questions that get at the same types of issues often can suffice to direct a clinician to the disease.

In some men, severe symptoms may actually subside with simple watchful waiting, whereas mild symptoms can progress in other men to require surgical interventions. Symptoms without bother do not merit intervention beyond watchful waiting. Since BPH is not a mortal disorder, treatment decisions are based on morbidity and quality-of-life issues. If symptoms do not negatively affect morbidity or quality of life, treatment is not required.

### EVALUATION

As with any other medical condition, a history and a physical examination are mandatory. For instance, relevant disorders such as diabetes or UTIs are of vital importance in the history of a patient presenting with LUTS, as is the use of antihypertensive or anticholinergic medications, in light of their side effects.

The DRE should include estimation of the size, shape, symmetry, and texture of the prostate. A DRE-based estimation of prostate size is clinician-dependent and often unreliable (usually an underestimate) but is

**TABLE 2**  
**American Urological Association Symptom Index for benign prostatic hyperplasia\***

**1. Incomplete emptying:** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Not at all	< 1 time in 5	< Half the time	About half the time	> Half the time	Almost always	Your score
0	1	2	3	4	5	

**2. Frequency:** Over the past month, how often have you had to urinate again < 2 hours after you finished urinating?

Not at all	< 1 time in 5	< Half the time	About half the time	> Half the time	Almost always	Your score
0	1	2	3	4	5	

**3. Intermittency:** Over the past month, how often have you found that you stopped and started again several times when you urinated?

Not at all	< 1 time in 5	< Half the time	About half the time	> Half the time	Almost always	Your score
0	1	2	3	4	5	

**4. Urgency:** Over the past month, how often have you found it difficult to postpone urination?

Not at all	< 1 time in 5	< Half the time	About half the time	> Half the time	Almost always	Your score
0	1	2	3	4	5	

**5. Weak stream:** Over the past month, how often have you had a weak stream?

Not at all	< 1 time in 5	< Half the time	About half the time	> Half the time	Almost always	Your score
0	1	2	3	4	5	

**6. Straining:** Over the past month, how often have you had to push or strain to begin?

Not at all	< 1 time in 5	< Half the time	About half the time	> Half the time	Almost always	Your score
0	1	2	3	4	5	

**7. Nocturia:** Over the past month or so, how many times did you get up to urinate from the time you went to bed until the time you got up in the morning?

None	1 time	2 times	3 times	4 times	5 or more times	Your score
0	1	2	3	4	5	

Add up scores for total symptom score<sup>†</sup> = \_\_\_\_

Adapted from Barry et al,<sup>23</sup> copyright 1992, with permission from American Urological Association.

\*The International Prostate Symptom Score uses the same seven questions with an additional disease-specific quality-of-life question (bother score) that uses a scale from 0 to 6 (delighted to terrible): "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?"<sup>24</sup>

<sup>†</sup>Total symptom score: 0 to 7 = mild symptoms; 8 to 19 = moderate symptoms; 20 to 35 = severe symptoms

essential for the management of BPH or for referral to a urologist based on nodularity or consistency.

Measuring the postvoid residual volume of urine can be helpful and may be appropriate in a patient whose symptoms do not respond to medications for BPH. Measurement of postvoid residual volume is not needed prior to therapy unless the patient has symptoms of incomplete emptying. There is considerable debate over the amount of postvoid residual urine that

should be of concern to the clinician. In the authors' view, any amount greater than 100 mL should prompt referral to a urologic surgeon.

A set of laboratory tests may be ordered after the history and physical exam and can include glucose, electrolytes, urinalysis, and (in appropriate patients) a PSA assay. (For further detail on screening for prostate and bladder cancer, see the article in this supplement on screening for urologic malignancies.)

## ■ DIFFERENTIAL DIAGNOSIS

LUTS in men is not always caused by BPH. Other conditions to consider in the differential diagnosis are overactive bladder, interstitial cystitis, prostatitis, urethral strictures, and prostate or bladder cancer.

## ■ TREATMENT

### Watchful waiting

Watchful waiting is an appropriate strategy for most men with BPH. We recommend it for men with BPH who are not bothered by their symptoms and have not developed complications of BPH (such as bladder outlet obstruction, hydronephrosis, hematuria, hydronephrosis, acute urinary retention, UTIs, bladder hypertrophy, and others). The serum PSA level and prostate size are helpful in predicting the risk of acute urinary retention and the need for surgery in men managed with watchful waiting. However, neither the PSA level nor prostate size should be used as the sole determinant of the need for active therapy. The overall risks and benefits of therapy must also be considered.

### Medical therapy

Alpha-1-adrenergic blockers (alpha-blockers) and androgen hormone inhibitors (5 alpha-reductase inhibitors) are the medications currently approved by the US Food and Drug Administration for treatment of BPH (Table 3).<sup>25</sup>

The alpha-blockers include alfuzosin, doxazosin, tamsulosin, and terazosin. They address the dynamic component of prostatic obstruction by decreasing muscle tone in the stroma and the prostate capsule, and provide the most rapid symptom relief. Alpha-blockers are considered the most effective monotherapy for improving LUTS in men with BPH.<sup>24</sup> Although there are slight differences in these four agents' side effects, they are believed to be equally clinically effective.<sup>24</sup>

The hormonal agents are the 5 alpha-reductase inhibitors finasteride and dutasteride, which address the static component of BPH by reducing the prostate mass.

There is some evidence that combination therapy with both an alpha-blocker and a 5 alpha-reductase inhibitor may be more effective than alpha-blocker therapy alone. Such combination therapy is an appropriate option for men with LUTS associated with demonstrable prostate enlargement.<sup>24</sup>

### Indications for surgery

Noninvasive therapy is recommended whenever possible, but surgical intervention is necessary in patients in whom benign prostatic obstruction causes renal insufficiency, urinary retention, recurrent UTIs, bladder cal-

**TABLE 3**  
Common drugs used to treat benign prostatic hyperplasia

	Dosage	Side effects
<b>Alpha-blockers</b>		
Alfuzosin	10 mg once daily	Fatigue, edema, rhinitis, headache, upper respiratory tract infection
Doxazosin	1 mg once daily to start; may increase up to 8 mg once daily	Orthostatic hypotension, fatigue, dyspnea
Tamsulosin	0.4 mg once daily	Dizziness, rhinitis, abnormal ejaculation
Terazosin	1 mg once daily to start; may increase up to 20 mg/day	Asthenia, hypotension, dizziness, somnolence
<b>5 alpha-reductase inhibitors</b>		
Dutasteride	0.5 mg once daily	Impotence, decreased libido, decreased semen quantity at ejaculation, decreased serum PSA, gynecomastia (rare)
Finasteride	5 mg once daily	Same as for dutasteride

Based on the drugs' package inserts.<sup>25</sup>  
PSA = prostate-specific antigen

culi, hydronephrosis, or large postvoid residual volume.

Surgical options for such patients include transurethral resection of the prostate, transurethral laser prostatectomy (which consists of resection, ablation, and vaporization), transurethral incision of the prostate, and open prostatectomy (usually when the prostate weight is > 100 g). Surgeries are associated with postoperative risks such as erectile dysfunction (4% to 10% incidence) and urinary incontinence (0.5% to 1.5%).<sup>26,27</sup> The 5-year recurrence rate of BPH following surgery is 2% to 10%.<sup>26</sup>

Minimally invasive procedures to correct BPH include transurethral needle ablation, transurethral microwave thermotherapy, water-induced thermotherapy, and intraprostatic stents.

## ■ APPROPRIATE FOLLOW-UP

For men receiving a 5 alpha-reductase inhibitor, the PSA level should be checked prior to initiating the medicine and, in the authors' opinion and practice, 6 months and again 18 months after initiation, at which time the

PSA level should have been reduced by one half. If it has not, consider referring the patient to a urologist for a possible prostate biopsy.

Follow-up visits can consist of a few appropriate questions about relevant symptoms and possible side effects.

If both an alpha-blocker and a 5 alpha-reductase inhibitor are being prescribed, consider discontinuing the alpha-blocker after 6 months.

If you refer a patient to a urologist for further evaluation, request that he be seen in your office afterwards. This practice will enhance the patient's rapport with you, his primary care provider, and will confirm that the patient has indeed seen the specialist. It also will give you and the patient the opportunity to discuss the implications of the urologic consultation, including any medical and sociopsychological implications of interventional procedures or new medications that may affect the patient's life or relations with his spouse or partner.

**■ WHEN TO REFER**

In addition to the referral recommendations already mentioned, referral to a urologist should be considered for a suspicious DRE, hematuria, pelvic or rectal pain, recurrent urologic infections, a palpable bladder, large postvoid residual volume, bladder stones, an elevated PSA level, or nonresponse to conservative treatment.

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# Overactive bladder: Recognition requires vigilance for symptoms

## ■ ABSTRACT

Overactive bladder (OAB) is a prevalent condition in both men and women that imposes significant burdens on the patient and his or her quality of life. Nevertheless, only a small percentage of patients with OAB receive diagnosis and treatment. The identification of OAB is well within the scope of the primary care provider, as it is symptom-based and does not generally require specialized testing. The treatment of OAB relies on behavioral modification and/or pharmacologic options, primarily antimuscarinic therapy. Better identification of OAB symptoms in the primary care setting should reduce the number of patients suffering from untreated OAB.

## ■ DEFINITION OF THE CONDITION

Overactive bladder (OAB) is defined by the International Continence Society as a symptom complex of urinary urgency (intense, sudden desire to void) with or without incontinence, urinary frequency (voiding eight or more times in a 24-hour period), or nocturia (awakening at night to void).<sup>1,2</sup> The symptoms of OAB are present in the absence of any pathologic or metabolic disorders that could cause them.

Although this paper deals primarily with OAB, it is important to recognize other types of lower urinary tract symptoms (LUTS) and dysfunctions that are

common in the primary care setting; for an overview, see the sidebar on the next page.

## ■ PREVALENCE AND SOCIAL IMPLICATIONS

Studies on OAB show that approximately 33 million US adults of all ages are affected.<sup>3</sup> Although OAB historically has been thought of as a disease diagnosed more frequently in women, its prevalence is nearly equal in both sexes, affecting 16.9% of US women and 16.0% of US men.<sup>4</sup> The major difference between the sexes is the frequency of accompanying urinary incontinence (UI) (see sidebar): 55% of women have OAB with UI versus only 16% of men.<sup>4</sup>

The prevalence of OAB increases with age: a multinational population-based survey in Europe showed prevalence rates of 31% and 42% among women and men, respectively, 75 years of age or older compared with rates of 17% and 16% among women and men 40 years of age or older.<sup>5</sup>

### Most cases go untreated

Despite the large number of both men and women with OAB, only 15% of all patients with symptoms of OAB receive treatment.<sup>6</sup> Kinchen and colleagues noted that only one of four women with symptoms of OAB with UI seeks clinical help.<sup>7</sup>

Patients want their primary care provider (PCP) to discuss the issue, yet there appears to be a communication gap.<sup>8</sup> A recent online survey of 1,228 women aged 40 to 65 years (898 of whom had symptoms of OAB) found that more than half of the women who discussed OAB with a health care provider (56%) waited longer than 1 year to seek treatment; many attempted self-management of their symptoms.<sup>9</sup> A contributing factor is the stigma surrounding bladder control problems and the many misconceptions that patients have about their condition that may prevent them from seeking care.<sup>10</sup>

### Social cost of OAB

OAB significantly affects many aspects of a patient's life, including self-esteem, sexual relations, family

\* **Dr. Rosenberg** reported that he has received consulting fees and honoraria from Indevus Pharmaceuticals/ESPRIT Pharma, Pfizer, and GlaxoSmithKline for consulting, teaching/speaking, and serving on advisory committees; honoraria and consulting fees from Verathon Medical for consulting and serving on advisory committees; honoraria from Eli Lilly and Auxilium Pharmaceuticals for teaching/speaking; a research grant from Sanofi-Aventis; and consulting fees and honoraria from Ortho-McNeil for consulting and teaching/speaking. **Ms. Newman** reported that she has received honoraria from Watson Pharmaceuticals, Pfizer, Astellas Pharma, GlaxoSmithKline, Novartis, and SCA Personal Care for teaching/speaking, as well as for serving on an advisory committee (for Watson) and for consulting (for SCA Personal Care). **Mr. Tallman and Ms. Page** reported that they have no financial relationships that pose a potential conflict of interest with this article.

## Lower urinary tract symptoms: Defining terms

Following are some common types of lower urinary tract symptoms (LUTS) and dysfunctions seen in the primary care setting that should be kept in mind when evaluating complaints suggestive of overactive bladder:

**Urge urinary incontinence** is involuntary leakage accompanied or immediately preceded by urgency, and is most commonly associated with overactive bladder.

**Stress urinary incontinence** is involuntary leakage associated with physical activities that increase intra-abdominal pressure, such as coughing, sneezing, or laughing, or upon effort or exertion, such as lifting objects or exercising. Stress urinary incontinence reflects a dysfunction of the bladder outlet, the urethral sphincter.

**Mixed urinary incontinence** involves the coexistence of urge and stress incontinence.

**Overflow incontinence** occurs when the bladder becomes overdistended as a result of outlet obstruction and may manifest as constant or postvoid dribbling. It is seen most often in men with benign prostatic hyperplasia but can be seen in women with pelvic organ prolapse.

relations, lifestyle, professional life, health perception, and sleep.<sup>9</sup> “Bathroom mapping” is a common behavioral technique of patients with OAB. Since they need to void frequently, they will consciously or unconsciously conduct a search for all the bathrooms in the vicinity in order to prevent an emergency. It is not uncommon for OAB patients to avoid prolonged social activities so as to not embarrass themselves with the frequency of toilet use.

### Financial cost of OAB: Direct, indirect, and intangible

The social implications of OAB can be explained by its direct, indirect, and intangible costs. Direct costs include those associated with treatment, diagnosis, routine care, and the consequences of the disease. Indirect costs encompass lost wages and productivity. Intangible costs are associated with suffering, embarrassment, and overall decreased quality of life.<sup>11</sup>

A study by Hu et al estimated that the direct cost of OAB in the United States was \$12.6 billion during 2000.<sup>12</sup> Although providers are familiar with the costs of treatment and routine care of OAB, they may not be as aware of the costs associated with the consequences of the disease, which make up greater than 50% of the overall costs. These consequences include skin irrita-

tion, urinary tract infections, falls, additional admissions to institutions, and prolonged hospital stays.<sup>13</sup> The odds ratio of a hip fracture is two times greater in an elderly woman with urge UI than in the general population.<sup>14</sup> One can only speculate on the reason for this increased risk; however, the authors have treated OAB patients who have tripped in a dark room as they raced to the bathroom and others who have slipped in a urine puddle on their way back.

The indirect costs and intangible costs of OAB are more difficult to quantify. It may be helpful to think of the indirect costs as the wages lost to missed work as a result of OAB or the decreased productivity from continually needing to find the bathroom. Although intangible costs defy being assigned an actual price by their very definition, they nevertheless can be devastating. In a national community survey, Coyne et al reported that both continent and incontinent OAB patients suffered in all health-related quality-of-life measures compared with controls who did not have OAB.<sup>15</sup> Additionally, the prevalence of depression is markedly higher in patients suffering OAB, with or without UI, than in the general population.<sup>8</sup>

Although the social implications of OAB clearly reflect a large societal burden, there is good news in the form of opportunities for intervention in treatment-naïve patients. A 2006 study by Balkrishnan et al shows that compliance with medications for OAB can result in a significant decrease in older adults' health care costs.<sup>16</sup>

## ■ PATHOGENESIS

OAB is a syndrome with a varied pathophysiology that may be multifactorial. The detrusor is composed of smooth muscle under voluntary neurologic control. Idiopathic OAB has been proposed to be secondary to myogenic or subclinical neurogenic abnormalities. A “neurogenic bladder” is a result of neurologic dysfunction. Although the etiology of OAB is not clear, the cause of its symptoms is better understood and will be reviewed below.

### How the bladder normally functions

To understand the abnormal function suffered by the patient with OAB, it is instructive to first review normal bladder function. Micturition involves two important and discrete processes: (1) bladder filling and storage, and (2) bladder emptying.<sup>17</sup> The filling and storage phase requires accommodation of increasing volumes of urine at low intravesical pressures with appropriate sensation, a closed bladder outlet (adequate outlet resistance), and absence of involuntary contractions (which result in urgency or leakage). The process of

bladder emptying requires a coordinated contraction of the bladder muscle, a lowering of the resistance of the outlet (sphincter), and an absence of anatomic obstruction. All types of voiding dysfunctions may be classified by an abnormality of one or more of the factors listed, alone or in combination.

Although its specific etiology is not known, OAB can be explained as the inability to accommodate increasing volumes of urine as a result of high intravesical pressures, along with increased sensation causing symptoms of urgency and frequency with or without a contraction.

### Abnormal urge sensation in OAB

In the OAB patient, signals to the bladder allow contraction and subsequent micturition before the bladder reaches full capacity. When this signal is sudden, intense, and difficult to deter, patients report the urgency associated with OAB. This is opposed to a normal urge sensation that allows the patient adequate warning to prepare for bladder emptying. Whether this abnormal signaling is an amplification (ie, increased sensitivity) of the afferent “sensory” fibers or increased output of the efferent motor fibers is not known. Antimuscarinic therapy aims to block these pathways from overresponding,<sup>18</sup> as discussed below.

### OAB, benign prostatic hyperplasia, and bladder outlet obstruction are interrelated

In discussing the pathophysiology of OAB, the connection between OAB, benign prostatic hyperplasia (BPH), and bladder outlet obstruction is important to note. The incidence of OAB increases with age, and many men develop OAB symptoms concomitantly with BPH. The most common cause of voiding symptoms in men is related to urethral obstruction from the prostate gland, secondary to BPH. Approximately 50% of men with some type of prostatic obstruction also have detrusor overactivity, but conversely, men younger than 60 years who present with LUTS tend not to have an enlarged prostate or a history of BPH.<sup>19</sup> The relationship between symptoms and OAB, bladder outlet obstruction, and BPH remains unclear.

### PRESENTING SYMPTOMS

Patients may avoid seeking medical care for OAB for several reasons, including embarrassment, a belief that the symptoms are part of normal aging, or the perception that it is not a valid medical condition.<sup>20,21</sup> Physicians tend not to raise the issue for lack of time, concern that the evaluation is difficult, or concern that the treatment options are minimal.

Several studies show that women are more likely to

use inconvenient and lifestyle-altering coping strategies than to seek treatment from a health care provider.<sup>20</sup> The most common strategies are wearing absorbent incontinence pads or feminine hygiene pads and always locating the nearest bathroom when away from home. In addition, women may wear special clothes or use deodorant powders or sprays to help conceal wetting accidents, and some may carry a change of clothes wherever they go.

Patients generally present because their symptoms have simply become intolerable. Women tend to present when urge UI develops and their quality of life is affected. Men will start to complain when nocturia becomes excessive. The likely reason for the difference is that UI tends to be more common in OAB among women than among men (approximately 50% vs 15% of OAB cases, respectively).<sup>4</sup>

### EVALUATION

The evaluation of the patient with OAB should focus on the history, the physical examination, and a limited laboratory evaluation. During the physical examination, it is useful to pay attention to items that may be transient or reversible.

#### Screen for symptoms

The history may be the most important component in the evaluation of the patient with OAB, and the symptoms of urgency, frequency, nocturia, and UI are paramount. Screening for OAB requires minimal time from a provider, as a self-administered screener or questionnaire can be used in most clinical settings.<sup>22</sup> In this context, a screening tool or questionnaire is not meant to diagnose OAB or UI, but rather to identify symptoms that may require treatment. Onset, duration, severity, and bother can be noted with a few key questions. **Table 1** lists examples of questions that may be useful.<sup>23</sup>

#### Components of the history

**A full neurologic history** should be taken to explore the possibility of dementia, Parkinson disease, spinal cord injury or stenosis, multiple sclerosis, or stroke. Functional and cognitive assessment should be performed in older patients.

**The gastrointestinal history** is important, as constipation can cause OAB and the medications used to treat OAB can cause or exacerbate constipation.<sup>24,25</sup>

**Dietary habits**, especially regarding fluid intake, have long been thought to be associated with urinary symptoms and should be addressed in the history.<sup>2</sup> A relationship between LUTS and consumption of caffeinated beverages or alcohol is often seen in clinical



**TABLE 1**  
Simple screening questions for evaluation of overactive bladder (OAB) and incontinence

- Do you get sudden urges to go to the bathroom that are so strong you can't ignore them? (suggests OAB)
- How often do you go to the bathroom? More than eight times in a 24-hour period? (suggests OAB)
- Do you have uncontrollable urges to urinate that sometimes result in wetting accidents? (suggests UUI)
- Do you leak urine on the way to the bathroom? (suggests UUI)
- Do you frequently get up two or more times during the night to go to the bathroom? (suggests OAB)
- Do you avoid places that you think won't have a nearby restroom? (suggests OAB or UUI)
- When you're in an unfamiliar place, do you make sure you know where the restroom is? (suggests OAB or UUI)
- Do you leak urine when you laugh, cough, or sneeze? (suggests SUI)
- Do you use absorbent pads to keep from wetting your clothes? (suggests SUI or UUI)

UUI = urge urinary incontinence; SUI = stress urinary incontinence  
Adapted, with permission, from Newman DK, Giovannini D. The overactive bladder: a nursing perspective. *Am J Nurs* 2002; 102:36-45.<sup>23</sup>

practice, although there is a lack of clear-cut data supporting such a relationship, except with tea consumption.<sup>26</sup>

**Prior surgeries** need to be considered, especially any genitourinary interventions (eg, hysterectomy or bladder suspensions). Orthopedic procedures can be the cause of transient OAB as a result of temporary mobility issues.

**Obstetrical history** should be addressed in women, as a history of several or difficult vaginal deliveries can predispose a woman to OAB or stress UI.

**Medications** should be reviewed to explore a potential association with symptoms. For example, the timing of when a diuretic is taken can have profound effects on urinary habits.<sup>2</sup> Medications that can affect urinary function are listed in **Table 2**.<sup>27</sup>

**Pearls for conducting the physical exam**

The physical examination should focus on detecting anatomic and neurologic abnormalities that could contribute to the patient's symptoms. The neurologic examination should start by observing the patient's gait as he or she walks into the room or down the hall. Limping, poor coordination, dysarthria, facial asymmetry, or other

**TABLE 2**  
Medications that affect bladder function

Medication	Effect
ACE inhibitors	Cough leading to stress UI
Alpha-adrenergic agonists	Increased urethral resistance, causing postvoid dribbling, straining, hesitancy in urine flow
Alpha-receptor agonists (pseudoephedrine, ephedrine)	Urethral constriction, urinary retention (males)
Alpha-receptor antagonists	Urethral relaxation and decreased urethral resistance, causing stress UI (females) and UI with cough, sneeze, or other activity
Anticholinergics (H1 antihistamines, antiparkinsonian agents)	Urinary retention with symptoms of postvoid dribbling, straining, hesitancy in urine flow, overflow incontinence, fecal impaction
Antipsychotics/sedatives	Sedative effect, causing confusion; may relax detrusor muscle, leading to urinary retention
Beta-receptor antagonists	Urinary retention
Calcium channel blockers	Urinary retention, fecal impaction
Diuretics	Increased urine production (polyuria) and volume, leading to urgency and frequency
Methylxanthines (caffeine, theophylline)	Polyuria, bladder irritation
Neuroleptics (thioridazine, chlorpromazine)	Anticholinergic effect, sedation
Other (caffeine and alcohol)	Diuretic effect, leading to urgency and frequency; possible sedation
Opioids	Urinary retention, fecal impaction, sedation, delirium
Sedatives and hypnotics	Sedative effect, which may relax detrusor muscle
Tricyclic antidepressants	Anticholinergic and alpha-receptor antagonist effects, causing postvoid dribbling, straining, hesitancy in urine flow

UI = urinary incontinence  
Adapted from Newman.<sup>27</sup>

findings may indicate neurologic conditions such as a stroke or multiple sclerosis. A brief mental status examination can be performed by observing the patient's general appearance and his or her response to questions. Alertness, orientation, memory, and thought content can be useful parameters in patient assessment.

If the patient appears overweight, consider calculating the body mass index (BMI). The relationship between increased BMI ( $> 30 \text{ kg/m}^2$ ) and the likelihood of UI in females is strong.<sup>26</sup> Identifying this correlation provides an opportunity for the PCP to discuss lifestyle changes with the patient, as research has shown that moderately obese women who lose 5% to 10% of their weight have a decrease in LUTS.<sup>28</sup>

Check the abdomen for masses, hernias, or a distended bladder. In women, the genitalia should be assessed for abnormalities such as prolapse of the bladder or uterus, atrophic vaginitis, or urogenital atrophy, and rectal sphincter tone should be checked. It may be useful to examine the female patient when her bladder is full in order to identify stress UI. In men, assess prostate size (an enlarged prostate can lead to OAB symptoms), the penis and scrotum for abnormalities (such as urethral discharge, epididymitis, or even urethral stricture), and rectal sphincter tone. A basic neurologic examination focusing on motor and sensory components (eg, anal wink and bulbocavernosus reflex) should be performed.

A voiding diary is a simple and practical method of obtaining detailed information about a patient's voiding habits,<sup>2</sup> and can be helpful in evaluating the extent of the problem and offering clues on how best to proceed with evaluation and treatment. The diary or log should be structured to keep track of voiding, urgency, and UI patterns over a 3-day period<sup>29</sup> (Figure 1).

### Judicious use of ancillary studies

The number of ancillary studies required is controversial. It may be prudent to check chemistries, especially renal function and blood glucose, in certain patients. For example, the onset of polyuria/polydipsia in the diabetic patient could certainly mimic the symptoms of OAB. Furthermore, if the clinician suspects obstruction in a man, renal function studies may identify upper urinary tract involvement. A urinalysis should be performed to rule out urinary tract infection. Many elderly women will have asymptomatic bacteriuria that does not require treatment. The role of further studies is questionable.

Checking the patient's postvoid residual urine volume using portable ultrasonographic equipment is useful for detecting retention, but it has a limited role in the neurologically normal female. In the male, it becomes more important because the symptoms of a large, obstructing prostate are similar to those of OAB. A postvoid residual volume check is necessary in any patient in whom there is concern about incomplete bladder emptying as a result of neurologic dysfunction, anatomic abnormality, or a pharmacologic cause. It is

VOIDING RECORD					
Time interval	Urinated in toilet	Amount of incontinent episode (large/small)	Reason for urine leakage	Changed wet pad (damp/wet/saturated)	Type/amount of liquid intake
6 AM					
7 AM					
8 AM					
9 AM					
10 AM					
11 AM					
NOON					
1 PM					
2 PM					
3 PM					
4 PM					
5 PM					
6 PM					
7 PM					
8 PM					
9 PM					
10 PM–MIDNIGHT					
MIDNIGHT–2 AM					
2–4 AM					
4–6 AM					
Type of pad _____		No. pads used _____			
Used with permission of Diane K. Newman.					

**FIGURE 1.** Example of a voiding diary to assess symptoms of overactive bladder.

also necessary in the postoperative patient who develops OAB. The incidence of postoperative urinary retention is recognized but poorly understood, with rates ranging from 4% to 25%.<sup>18</sup> Some patients may present in frank retention, whereas others may present with OAB symptoms from incomplete emptying.

Urodynamic studies are not necessary in most patients, especially those without neurologic compromise. If the patient's symptoms are refractory to therapy, if they worsen, or if there is significant postvoid residual volume, then urodynamic studies may be considered as one looks for other causes, such as detrusor sphincter dyssynergia. In our view, a significant postvoid residual volume is any amount greater than 75 to 100 mL in persons younger than 65 years; in the elderly, we consider a volume less than 150 mL to be acceptable. There are no studies supporting specific values for acceptable postvoid residual volume, but there are guidelines.<sup>30</sup>

Cystoscopy has a role only in the patient with hematuria or the patient who is refractory to therapy.

**TABLE 3**  
**Differential diagnosis of symptoms suggestive of overactive bladder**

In women	In men
Urinary tract infection	Benign prostatic hyperplasia
Prolapse	Bladder outlet obstruction
Urethral obstruction	Urethral stricture
Atrophic vaginitis	Bladder stones
Bladder cancer	Bladder cancer
Interstitial cystitis	Prostate cancer
Postsurgical incontinence	Diabetes
Diabetes	Congestive heart failure
Congestive heart failure	Medications/diuretics
Multiple sclerosis	Neurogenic bladder
Medications/diuretics	Postsurgical incontinence
Neurogenic bladder	
Recent pelvic surgery	
Stress urinary incontinence	

Radiologic evaluation beyond portable bladder ultrasonography is reserved for those with hematuria or a palpable mass noted on examination.

**DIFFERENTIAL DIAGNOSIS**

As mentioned, the diagnosis of OAB can be based on symptoms. As with any symptom complex, however, a differential diagnosis should be considered. A history combined with a directed physical examination, urinalysis, and chemistries will exclude most of the alternate diagnoses listed in **Table 3**. **Table 4** presents findings that should prompt further evaluation or referral to a specialist.

**TREATMENT**

The goal of treatment is to teach the patient to inhibit urgency and to improve voluntary control over bladder function.

**Behavioral treatment**

Behavioral modification involves educating patients about the normal process of micturition and how their specific symptoms define an abnormal situation. If patients are actively involved in the diagnosis and subsequent treatment, their expectations are more readily attainable.

Behavioral therapy may involve pelvic floor muscle exercises, bladder retraining and urge-suppression

techniques, changing the timing of various medications (eg, diuretics), or encouraging exercise and weight loss. Although most patients will be treated using drug therapy, the combination of behavioral and pharmacologic therapies greatly enhances the likelihood of a positive outcome compared with either intervention alone. Burgio et al conducted a crossover study among older women with UI to assess the effects of behavioral therapy, drug therapy, and their combination on patients' baseline frequency of UI episodes.<sup>31</sup> Patients receiving behavioral therapy alone in the initial study phase had a 57% reduction in the frequency of UI, which increased to an 89% reduction after the addition of drug therapy. Similarly, patients receiving drug therapy alone in the initial phase had a 73% reduction in the frequency of UI, which increased to an 84% reduction after the addition of behavioral therapy. The authors concluded that combination therapy yields better outcomes.<sup>31</sup>

**Pharmacologic management: Antimuscarinics are first-line**

The principle behind pharmacologic management of OAB is inhibition of the disturbed bladder contraction, and the antimuscarinics are the primary medications used for this effect.

Antimuscarinics exert their clinical effect through two potential pathways: one on the motor pathway via central and peripheral actions that block a facilitatory mechanism and stimulate an inhibitory mechanism; and the other on the sensory pathway via central and peripheral actions that modulate afferent innervations.<sup>19</sup>

As a class, antimuscarinics are safe and effective. Comparisons among these agents have been limited, but, as with any drug class, there are subtle differences that PCPs should be aware of. Dose adjustment, side effects, or metabolism may be important to consider on an agent-by-agent basis for the individual patient. The various antimuscarinics and their properties are detailed in **Table 5**.<sup>32</sup> All of these agents are administered orally; in addition, oxybutynin is also available for delivery by transdermal patch.

Most antimuscarinics have not been directly compared in clinical trials, and outcome measures and patient characteristics differ between trials, making comparisons difficult. Two comparative efficacy studies deserve attention, the OPERA (Overactive Bladder: Performance of Extended Release Agents) trial and the STAR (Solifenacin and Tolterodine as an Active Comparator in a Randomised) trial.<sup>33,34</sup>

The **OPERA trial** compared the long-acting oral versions of oxybutynin (10 mg) and tolterodine (4 mg). There was a reduction of UI with oxybutynin

over tolterodine, but it came at a slight and almost proportional increase in dry mouth.<sup>33</sup>

The **STAR trial** compared a single dosage strength of long-acting tolterodine (4 mg) with a flexible-dose regimen of solifenacin (5 or 10 mg). Using pooled data for the two solifenacin doses, the study found that titratable solifenacin was associated with slightly better efficacy than tolterodine with an almost proportional increase in side effects.<sup>34</sup>

Another recent head-to-head study compared the effects of darifenacin (7.5 mg) and long-acting oral oxybutynin (10 mg) on cognitive end points in subjects 60 years of age or older.<sup>35</sup> The premise of the study was that an agent with selectivity for the M3 receptor (the prominent muscarinic receptor on the bladder) would not affect the M1 receptors in the brain. The outcome studied was performance on the Name-Face Association Test, which measures delayed recall, at week 3 of treatment. Subjects randomized to oxybutynin performed statistically worse on this test than did placebo recipients, indicating significant memory impairment, whereas no reduction in performance was seen in darifenacin recipients.<sup>35</sup>

### Secondary medications

Although the antimuscarinic class is the first line of pharmacologic therapy for OAB, other medications have a role. There is some evidence that the stress component of mixed UI may respond to the tricyclic antidepressant imipramine or to an alpha-adrenergic agonist such as pseudoephedrine, which increases outlet resistance.<sup>36</sup> Furthermore, these drugs may work synergistically with antimuscarinic therapy in patients with mixed UI. However, imipramine is not indicated in the elderly and pseudoephedrine should be used with caution in the elderly. Treatment should be geared to the symptom that appears to be most bothersome.<sup>37</sup> Neither imipramine nor pseudoephedrine is approved by the US Food and Drug Administration for treating OAB or stress UI.

Transvaginal estrogen therapy also may have a role in treating the irritative symptoms of urgency and frequency associated with vaginal and urogenital atrophy; however, data are lacking to support any particular dosing regimen, route of administration, or treatment duration.<sup>38</sup> A recent analysis from the Women's Health Initiative found that oral estrogen replacement not only failed to improve UI but may actually worsen symptoms.<sup>39</sup>

### Risk of urinary retention with therapy is low

A common concern among PCPs is that antimuscarinic therapy may place a patient at risk of urinary

**TABLE 4**  
**Red flags that should prompt further studies or referral to a specialist**

Uncertain diagnosis and inability to develop a reasonable management plan
Lack of response to an adequate trial of conservative therapies (eg, bladder training, pelvic muscle exercises, and drug therapy)
Hematuria without infection
Severe (beyond the introitus) pelvic organ prolapse
Abnormal postvoid residual urine volume
Prostate nodule/enlargement
Neurologic condition (eg, multiple sclerosis, spinal cord lesions) in which a component of neurogenic bladder is suspected
History of pelvic surgery

Adapted from Fantl et al.<sup>30</sup>

retention. However, the incidence of retention in both men and women in clinical trials is low.<sup>19,40</sup> Kaplan et al evaluated the safety and efficacy of antimuscarinic therapy in men with BPH and LUTS in whom alpha-antagonist therapy failed to relieve LUTS.<sup>40</sup> In the 39 men who completed this 6-month trial, there was a significant decrease in urinary frequency, nocturia, and postvoid residual volume, as well as an improvement in symptom scores. There were no reports of urinary retention. These findings suggest that the inhibitory effect of antimuscarinic agents on detrusor muscle contraction is unlikely to aggravate voiding difficulties in men with OAB symptoms and possible obstruction.

We believe it is prudent to do a postvoid residual volume check in a man being treated for LUTS, both initially and at follow-up. However, this practice is controversial, and the most appropriate candidates for these checks remain to be better defined.

### Symptom-based treatment can be successful

This paper has addressed the empiric diagnosis and treatment of OAB. The concept of empiric diagnosis and treatment was assessed in the recently published IMPACT (Improvement in Patients: Assessing Symptomatic Control with Tolterodine) trial.<sup>41</sup> In this study, the diagnosis of OAB was made in several hundred patients in primary care and obstetric/gynecologic offices on the basis of symptoms. Patients with OAB symptoms for at least 3 months were treated with extended-release tolterodine for 12 weeks in this

**TABLE 5**  
**Properties of available antimuscarinic agents**

	<b>Darifenacin</b>	<b>Oxybutynin</b>	<b>Oxybutynin TDS</b>	<b>Solifenacin</b>	<b>Tolterodine</b>	<b>Trospium</b>
Chemical structure	Tertiary amine	Tertiary amine	Tertiary amine	Tertiary amine	Tertiary amine	Quaternary amine
Efficacy	Not all products have been directly compared in head-to-head trials; outcome measures and patient baseline characteristics differ among trials, making comparisons difficult. Efficacy similar among products: 60%–75% median reduction of urge urinary incontinence episodes.					
Side effects	Dry mouth, constipation	Dry mouth, constipation	Skin irritation	Dry mouth, constipation	Dry mouth, constipation	Dry mouth, constipation
Dose	7.5 or 15 mg	5, 10, or 15 mg	3.9 mg	5 or 10 mg	2 or 4 mg	20 mg
Regimen	Once daily	IR: twice daily to four times daily ER: once daily	Twice weekly	Once daily	Once daily	Twice daily
Half-life	12.43 hr (7.5 mg) 12.05 hr (15 mg)	13.2 hr (10 mg)	36 hr	45–68 hr	8.8 hr (active metabolite)	12.2 ± 3.2 hr
Metabolism	Extensively metabolized in liver by CYP450 isoforms	Extensively metabolized in liver by CYP450 isoforms	No first-pass clearance, but then extensively metabolized in liver by CYP450 isoforms	Extensively metabolized in liver by CYP450 isoforms	Extensively metabolized in liver by CYP450 isoforms	Active renal tubular secretion is a major route of elimination; global hepatic esterification only, not CYP450
Potential metabolic drug-drug interactions	Flecainide, thioridazine, TCAs; do not exceed 7.5 mg when given with ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, or nefazodone	Itraconazole, miconazole, macrolide antibiotics (eg, erythromycin, clarithromycin)	Itraconazole, miconazole, macrolide antibiotics (eg, erythromycin, clarithromycin)	Do not exceed 5 mg when given with ketoconazole or other potent inhibitors of CYP3A4 (eg, nefazodone, fluvoxamine, TCAs)	Ketoconazole, itraconazole, miconazole, macrolide antibiotics (eg, erythromycin, clarithromycin), cyclosporine, vinblastine	None; active renal tubular excretion; caution if giving with digoxin, metformin, or other drugs that may compete for active renal excretion
Contra-indications	Urinary retention; gastric retention and other conditions of severe decreased gastrointestinal motility; uncontrolled narrow-angle glaucoma; hypersensitivity to the drug or its ingredients					

TDS = transdermal delivery system; IR = immediate-release; ER = extended-release; CYP = cytochrome P; TCAs = tricyclic antidepressants  
 Data are based on the medications' package inserts.<sup>32</sup>

open-label, single-arm trial. At the end of the 12 weeks, there were significant reductions from baseline in urge UI, urgency episodes, nocturnal frequency, and daytime frequency. Common side effects were dry mouth and constipation.

The conclusion drawn from this paper was that patients with OAB in the general population can be readily screened and successfully treated with minimal work-up.<sup>41</sup> The applicability to the PCP is significant, but the study lasted only 12 weeks and longer follow-up would have been useful.

#### ■ APPROPRIATE FOLLOW-UP

There is no set rule as to the follow-up interval for the OAB patient. Some clinicians find that a 2-week interval is adequate, whereas others recommend 4

weeks. The interval should be determined by consensus of the provider and the patient. The patient must be educated about what to expect and to not give up hope if these expectations are not met immediately, as a simple drug change or dose titration may provide the desired effect. There are many medication choices, and no one treatment is right for every patient.

#### ■ WHEN TO REFER

As noted above, the diagnosis of OAB can be made empirically without the need for specialized evaluation, and treatment likewise can be initiated comfortably by the PCP. If initial treatment with behavioral therapy and medications fails to alleviate the symptoms, it is appropriate to refer the patient for consultation and advanced testing (Table 4), such as urody-

nameric evaluation.<sup>30</sup> The definition of “initial treatment” may vary among clinicians. Some may try only one medication, whereas others may be comfortable changing medications and titrating doses. Our view is that any medication should be given for 2 to 4 weeks before it is considered to have failed.

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# Erectile dysfunction: A sentinel marker for cardiovascular disease in primary care

## ■ ABSTRACT

Erectile dysfunction (ED) is a common, age-related disorder that diminishes quality of life for affected men and their partners. While most ED is now recognized as organic in origin, both organic and psychogenic causes often conspire to reduce sexual function in men with ED. Vasculopathy has come to be recognized as the most common cause of ED, which has elevated ED's importance in the primary care setting as a sentinel to underlying cardiovascular disease. Identification of cardiovascular risk factors should be a routine part of the evaluation for ED and is as important as taking the patient's sexual, medication, and psychosocial histories. Involving the patient's partner in evaluation and management is often valuable. Treatment with phosphodiesterase type 5 inhibitors is effective in restoring sexual function for most men with ED, but patients and their partners should be encouraged to make an informed choice from among all available treatment options.

## ■ DEFINITION OF THE CONDITION

Erectile dysfunction (ED) is "the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance," according to the First International Consultation on Erectile Dysfunction, convened by the World Health Organization in 1999.<sup>1</sup> This definition closely mirrors that of a National Institutes of Health consensus development panel, which further specified "recurrent inability" as being 3 months or greater in duration.<sup>2</sup>

\* Dr. Kuritzky reported that he has received honoraria from Pfizer, Eli Lilly, ICOS, Bayer, and GlaxoSmithKline for teaching/speaking or consulting. Dr. Miner reported that he has received a research grant from Auxilium Pharmaceuticals and consulting fees from GlaxoSmithKline/Schering-Plough and Sanofi-Aventis for consulting and serving on speakers' bureaus.

## ■ PREVALENCE AND SOCIAL IMPLICATIONS

### Reported prevalence has varied

Reviews of the epidemiologic literature on ED suggest that about 5% to 35% of men have moderate to severe ED, with differences in prevalence stemming from differences in how ED is defined, the age groups studied, concomitant medical conditions, and methodologic differences.<sup>3</sup>

One of the largest prevalence studies to date, the multinational Men's Attitudes to Life Events and Sexuality (MALES) study, involved interviews of 27,839 men aged 20 to 75 years from the general population in Europe and North and South America, and found a 16% overall prevalence of ED and a 22% prevalence in the United States.<sup>4</sup>

The Massachusetts Male Aging Study was a community-based, random-sample survey of 1,290 men aged 40 to 70 years who were asked to categorize their erectile function as either complete impotence, moderate impotence, minimal impotence, or no impotence.<sup>5</sup> A full 52% of the men reported some degree of ED, with 25% reporting moderate ED and 10% reporting complete ED.<sup>5</sup> These findings underscore how much the reported prevalence of ED depends on how the condition is defined.

### An age-dependent disorder

Both of the above studies demonstrated that ED is an age-dependent disorder. In the Massachusetts Male Aging Study, between the ages of 40 and 70 years, the probability of complete impotence tripled (from 5.1% to 15%) and the probability of moderate impotence doubled (from 17% to 34%), while the probability of minimal impotence remained constant at 17%.<sup>5</sup> Among men at the upper end of the age range (70 years), only 32% reported that they were free of ED.<sup>5</sup> In the MALES study, though the overall prevalence of ED was lower because of how ED was defined, the prevalence again increased with age, rising steadily from 8% among men in their 20s to 37% among men in their 70s.<sup>4</sup>

The prevalence of ED, or at least of diagnosed and

recognized ED, is only expected to increase as improved awareness of the condition leads to a greater likelihood that physicians will diagnose it and as the group of men at risk grows with the aging of the overall US population.

### **Despite reduced quality of life, most cases go untreated**

Sexual function is a high priority for men and their partners throughout the life span. Loss of sexual harmony reduces the quality of life of men and their partners. Early references cite the issue of performance anxiety and the shift from lovemaking as a sensual experience to one fraught with anxiety; during subsequent attempts at lovemaking, the ability to acquire or maintain an erection dominates the sexual experience.<sup>6,7</sup> Interventional trials indicate that restoration of sexual function improves quality of life both for men with ED and for their partners.<sup>8</sup>

Unfortunately, up to 70% of men with ED go untreated.<sup>3</sup> Many men fail to seek treatment because they mistakenly believe that ED is a normal part of aging. Others admit to embarrassment as the reason for not seeking treatment or discussing ED with their physicians. In the MALES study, only 58% of men with self-reported ED sought medical attention for it.<sup>4</sup>

### **A sentinel for cardiovascular disease**

A final—and perhaps most significant—social implication of ED is its increasingly recognized status as an early marker of vascular disease, as detailed in the following section. Knowledge that a man has ED should prompt thorough scrutiny for traditional cardiovascular risk factors, since early detection may allow reduction of cardiovascular disease risk or attenuation of existing disease.

## **■ PATHOGENESIS**

ED is a neurovascular phenomenon modulated by hormonal and local biochemical interactions as well as by biomechanical mechanisms that influence neurovascular control.<sup>9</sup>

In the past, ED was believed to be largely psychogenic in origin. Today we recognize that most ED is organic in origin, although it is equally acknowledged that men with organic ED often will suffer significant psychological stress as a result. Once a man fails in his sexual performance, he usually will have fear or anxiety that the failure will recur. For this reason it often is oversimplistic to categorize ED as “solely organic” or “solely psychogenic”; rather, both components can contribute to reduce sexual function in men with ED.

### **Normal erectile function**

Penile erection is a hemodynamic process that depends on the successful interaction of neurologic and

endocrine factors and on coordination of the parasympathetic and sympathetic nervous systems.<sup>10</sup> With sexual stimulation, parasympathetic activity enhances production of cyclic guanosine monophosphate (cGMP), resulting in cavernosal smooth muscle relaxation and an influx of blood into the penis. This filling of the penis produces expansion of the sinusoidal spaces, compressing venous channels and thereby preventing outflow of blood to allow maintenance of a rigid erection.

### **What goes wrong in ED**

ED results from physical (eg, hormonal, neurologic, vascular, or cavernosal) and/or psychological factors that disrupt this sequence. Physical causes of disruption include injury, surgery (eg, prostatectomy, proctocolectomy, vascular surgery), and comorbid conditions that affect the vasculature and peripheral nervous system (eg, diabetes, hypertension, dyslipidemia, peripheral arterial disease, obesity, coronary artery disease).

The role of the vascular system is noteworthy, as it is now generally accepted that most ED results from a vascular disturbance of the endothelium. This impairment in endothelial function typically results from vasculopathy, such as in dyslipidemia, hyperglycemia, smoking toxicity, or hypertension. ED arises from a combination of endothelial disturbance and abnormal smooth muscle function with blood flow abnormalities that lead to difficulties developing or maintaining an erection. The same factors that lead to oxidative stress and impair endothelial function in the cardiovascular and peripheral vascular beds play a fundamental role in the underlying pathogenesis and progression of ED<sup>11</sup> (see “ED as a marker of vascular disease” below).

Other contributors to ED include neurogenic factors (eg, diabetes, multiple sclerosis), endocrinologic factors (eg, hypogonadism, hyperprolactinemia), or psychogenic factors (eg, excessive sympathetic tone due to performance anxiety), although the etiology is less clear in these settings.

### **A key insight: The role of nitric oxide**

Prior to the past decade, ED was managed by urologists, who generally used intracavernosal injection therapy, vacuum pumps, and penile prostheses as their primary tools. Most men with ED did not seek treatment because of the relative unpalatability of these choices. It was not simply the advent of oral medications that changed the tide; after all, oral yohimbine had been available for several decades. Rather, it took the availability of highly effective oral therapy, in the form of phosphodiesterase type 5 (PDE-5) inhibitors, to spur large numbers of men with ED to seek restoration of sexual function.



Critical in the development of highly effective oral therapy was elucidation of the role of nitric oxide. Nitric oxide is fundamental to vasodilation, including dilation of the corpora cavernosa. Insight into the relationship between nitric oxide production and successful vasorelaxation, together with the serendipitous discovery that PDE-5 inhibition enhances accumulation and survival of penile cGMP, enabled recognition of the critical nature of penile endothelial function. Although cGMP may be generated via the nitricergic nervous system or as a result of endothelial metabolism, defects in either pathway may lead to functional deficits in erection. PDE-5 inhibitors, by preventing cGMP breakdown, were shown to enhance erectile function. The advent of these medications, together with their ease of use, brought ED management into the primary care arena and brought the era of urologist-centered management to an end.

### ED as a marker of vascular disease

Vasculopathy is now recognized as the most common cause of organic ED, and ED is considered one of the earliest manifestations of vascular disease. Indeed, vasculopathy should be suspected in a man presenting with ED until proven otherwise.

Men with traditional risk factors for cardiovascular disease—hypertension, smoking, dyslipidemia, diabetes, overweight, sedentary lifestyle—are now recognized to also be at risk for ED. These risk factors are more common in men with ED than in those without ED.<sup>12-17</sup> For instance, in a survey of 2,869 men aged 20 to 80 years, hypertension, hyperlipidemia, and diabetes each increased the risk of ED twofold to threefold.<sup>16</sup> The individual components of the metabolic syndrome—central obesity, high blood pressure, elevated triglyceride level, low high-density lipoprotein cholesterol level, and glucose intolerance—are also risk factors for ED.

Endothelial dysfunction is believed to be the common initiator of ED and other atherosclerotic diseases.<sup>18</sup> Men with ED but no other clinical cardiovascular disease were found to have reduced flow-mediated vasodilation in the brachial artery in response to sublingual nitroglycerin, indicating endothelial dysfunction and abnormal smooth muscle relaxation.<sup>11</sup> Evidence is accumulating that endothelial dysfunction is an early functional change thought to precede atherosclerotic changes in the cerebrovascular, coronary, and peripheral circulations.

In addition to its commonality of risk factors with cardiovascular disease, ED is a marker of potential or occult cardiovascular disease.<sup>19,20</sup> A secondary analysis

of data from the Prostate Cancer Prevention Trial demonstrated that men with ED have a significantly greater chance of experiencing a cardiovascular event (angina, myocardial infarction, cerebrovascular accident, transient ischemic attack, congestive heart failure, or cardiac arrhythmia) than men without ED.<sup>20</sup> This study, which enrolled men aged 55 years or older, also showed that incident ED (the first report of ED of any grade) may predict the risk of later cardiovascular events as effectively as does smoking, dyslipidemia, or a family history of myocardial infarction.<sup>20</sup>

Other studies have pointed to similar conclusions. A prospective angiographic study of men with ED of vascular origin showed that 19% had angiographically documented silent coronary artery disease.<sup>13</sup> Separately, Ponholzer et al found that men with moderate to severe ED had a 65% increased risk for developing coronary artery disease within 10 years, based on Framingham risk profile assessment, compared with men without ED;<sup>16</sup> analysis of the actual event data from this study is still awaited.

ED and sexual function may be a useful tool for stratifying risk in men with known or suspected coronary artery disease. A recent prospective study of men referred for nuclear stress testing found that those with ED exhibited more severe coronary artery disease and left ventricular dysfunction and had shorter exercise times and lower Duke treadmill scores compared with men without ED.<sup>21</sup>

These findings all support the results of studies linking ED with prevalent and incident cardiovascular disease.<sup>11,22-24</sup> The literature consistently demonstrates that signs of penile endothelial dysfunction (ie, ED) are often evident in patients with existing coronary artery disease, cerebrovascular disease, or peripheral arterial disease that has not yet manifested.<sup>25</sup> The presence of ED should be a wake-up call to clinicians that vasculopathy in nonpenile beds is likely. Given that more than 50% of men do not have warning signs of coronary artery disease prior to their first cardiovascular event,<sup>20</sup> ED could be a sentinel marker for the presence of occult vascular disease in asymptomatic men. Thus, ED is clearly a potential marker of a man's vascular health.

### EVALUATION

The examination and history should be directed to identify recognized contributors to ED: diabetes, hypertension, dyslipidemia, cigarette smoking, hypogonadism, cardiovascular disease, medications known to cause ED, past surgical procedures, and psychosocial contributors such as relationship problems or depression. In the primary care setting, this can often

be streamlined if the patient's history is known. If not known, a pertinent sexual, medical, and psychosocial history can be performed efficiently within the time constraints of the typical office visit.

### Sexual history

ED can develop at any age, but because its prevalence rises steeply at about age 40 years,<sup>5</sup> it is wise to particularly inquire about sexual health for men at this age and beyond. Such inquiry is appropriate at any age, however, especially as it can also address safe sexual practices.<sup>26</sup>

Because some recognized vasculopathies (diabetes, uncontrolled hypertension, marked dyslipidemia) accelerate the process of endothelial dysfunction, men who have such disorders merit inquiry about their sexual function, regardless of age. Indeed, the case has been made that inquiry into sexual health should be one of the "vital signs of lifestyle" asked of all patients.<sup>27</sup>

Disorders during the desire phase of the sexual cycle (libido) can be elicited by asking if the patient still feels desire or has sexual thoughts or fantasies.<sup>28</sup> Difficulty in the desire phase may be a sign of hypogonadism, relationship difficulties, medication-induced ED, or depression.

Difficulties with arousal or erection can be elicited by asking if the patient has trouble obtaining and maintaining an erection.<sup>28</sup> If the patient reports erectile difficulty, inquire about onset, frequency, and any relationship to medical treatments or stressful events. The line of inquiry should then include questions about specific times and circumstances in which the patient gets erections (eg, in the morning, with masturbation, during sexual activity with his partner) and how firm these erections are. For example, ED in a patient who has strong morning erections but poor erections with his partner is likely to have a psychogenic component.

Standardized questionnaires can assist in the diagnosis of ED and facilitate discussion of sexual health, especially when the patient is reluctant to initiate such discussion. The Sexual Health Inventory for Men is a five-item survey with four questions that pertain to the ability to attain and maintain an erection and the frequency of erections sufficient for intercourse.<sup>29</sup> The results of this and any other questionnaire on sexual health must be interpreted in the context of the patient's psychosocial factors, including desire and the opportunity to have sexual relations. Although this and other questionnaires can help identify the presence of ED, they do not elucidate its etiology.

### Involve the partner

Whenever possible and when the patient is in agreement, including the patient's sexual partner in the

evaluation and management process is wise.<sup>30</sup> An Italian study reported that 40% of men with ED had never discussed the problem with their partner.<sup>31</sup>

Because most men with ED are in midlife or beyond, their similarly aged partners may be suffering burdens that make the resumption of harmonious sexual intimacy more difficult (eg, menopausal lubrication deficits, changes in libido, pain syndromes, interrupted sleep). This further argues for incorporating the partner into discussion of treatment plans. Moreover, partner involvement may enhance the chance of treatment success. Women whose partners were treated for ED have been found to experience improvements in sexual arousal, orgasm, and sexual satisfaction,<sup>32</sup> and quality-of-life scores of both patients and their partners have been shown to improve following treatment of ED.<sup>33</sup>

### Medication history

Taking a medication history can uncover a drug that may be responsible for ED, such as a narcotic analgesic, a benzodiazepine, or another central nervous system depressant prescribed for chronic pain. In current practice, the medications most associated with sexual dysfunction are hydrochlorothiazide and selective serotonin reuptake inhibitors, although the latter are more commonly associated with orgasmic dysfunction than with ED.

A comparative trial assessing sexual function in hypertensive men receiving either an angiotensin receptor blocker or a beta-blocker showed a higher incidence of ED in men taking the beta-blocker.<sup>34</sup> Although this finding might seem to be an indictment of beta-blockers, it could equally well reflect a salutary effect of angiotensin receptor blockers. Substantial controversy surrounds the potential role of beta-blockers in causing sexual dysfunction.

Because sexual dysfunction has been reported in data sets for dozens of medications, it is worth reviewing the patient's medication history to identify any clear temporal relationships between a particular drug and sexual dysfunction. If such a relationship exists, it is reasonable to substitute an alternate medication or, when possible, attempt a drug holiday or medication cessation.

### Physical examination

The traditional physical examination includes blood pressure measurement and a genital examination to assess testicular size. Testicles that are small (< 2 cm) or appear atrophic to palpation should prompt confirmation of testosterone status. Other physical findings associated with ED include penile plaques (Peyronie

**TABLE 1**  
Profile of pharmacologic therapies for erectile dysfunction<sup>41,42</sup>

Therapy	Standard dose	Recommended interval between dosing and intercourse	Duration of action
Oral phosphodiesterase type 5 inhibitors			
Sildenafil	50–100 mg	1 hr	≥ 4 hr
Tadalafil	10–20 mg	0.5–12 hr	36 hr
Vardenafil	10–20 mg	0.5–1 hr	< 5 hr
Intracavernosal injection			
Alprostadil*	5–40 µg	10–30 min	1–4 hr
Intraurethral suppository			
Alprostadil pellet*	0.5–1 mg	5–10 min	1 hr

\*The only medication approved by the US Food and Drug Administration for this method of administration.

disease), which may cause painful or deviated erections and thus lead to sexual dysfunction, and an enlarged prostate, which can be identified by digital rectal examination.

A vascular examination, including palpation of the femoral vessels and listening for bruits, may be appropriate, and neurologic examination may be helpful.

### Laboratory tests

Because ED is a sentinel for vasculopathy in other compartments, laboratory testing should seek cardiovascular risk factors. Basic initial laboratory tests for suspected ED are fasting serum glucose level and a lipid panel, especially low-density and high-density lipoprotein cholesterol. Testosterone levels should be considered in those men with ED who also have metabolic syndrome, diabetes mellitus, or decreased libido, given that low testosterone may be associated with these conditions.<sup>9,35,36</sup> Morning serum total testosterone should also be considered as an additional laboratory test in patients whose ED is refractory to initial therapy, as should prolactin, luteinizing hormone (if testosterone is < 200 ng/dL or the patient is < 50 years old), and thyroid-stimulating hormone.

Some experts suggest urinalysis to detect potential renal disease or infection, although these are rarely associated with ED.<sup>37</sup> A complete blood count and metabolic panel may identify a potential hematologic disorder or renal or liver disease.

## TREATMENT

### Lifestyle changes

Given the important vascular component of ED, behavioral modifications such as weight loss, increased exercise, and smoking cessation are an appropriate

foundation for ED therapy, although data from controlled trials on the effects of individual lifestyle changes on ED are limited.

Some data are starting to emerge, however. A recent study of obese men with ED (but without diabetes, hypertension, or hyperlipidemia) found that reducing calorie intake and increasing physical activity was associated with improved sexual function in about one third of obese men.<sup>38</sup> An Iranian study of smoking cessation in men with ED found that ED status improved at 1-year follow-up in at least 25% of men who stopped smoking during the study period compared with 0% of continuing smokers.<sup>39</sup> The benefit was greatest in younger men and in those with less severe ED prior to smoking cessation.<sup>39</sup>

Data on incident ED from a cohort study led to somewhat different conclusions: among men without ED at baseline, midlife adoption of lifestyle changes to reverse the effects of smoking, obesity, and alcohol consumption may be too late to reduce the risk of ED, although increased physical activity may reduce ED risk even if adopted in midlife.<sup>40</sup>

### Oral drug therapy (PDE-5 inhibitors)

The goal of therapy for ED is restoration of sexual function. There are several types of therapy options, and the choice among them should be an informed decision by the patient and his partner based on the efficacy, risks, benefits, and costs of each option. Most patients and their partners will, given all available choices, elect an oral agent—specifically, a PDE-5 inhibitor—but this is not to say that the other options detailed below (intracavernosal injection therapy, vacuum constriction devices, intraurethral suppositories) may not have a role.

The three PDE-5 inhibitors available in the United States—sildenafil, tadalafil, and vardenafil—are similarly effective in improving and maintaining erections suitable for intercourse, though they differ somewhat in pharmacokinetics and dosing (**Table 1**).<sup>41,42</sup> Clinical trials demonstrate that PDE-5 inhibitor therapy successfully enables almost three quarters of men with ED to achieve an erection adequate to complete intercourse,<sup>37</sup> although results are highly dependent on the patient population studied—eg, diabetic men and post-prostatectomy patients are less likely to respond.<sup>33</sup>

All PDE-5 inhibitors are approximately equally efficacious, and there are no large head-to-head randomized trials to suggest that one agent has meaningfully superior efficacy over another.<sup>43</sup> In preference trials, some patients express distinct preference for one PDE-5 inhibitor over another, but this too is hard to predict. Most couples at midlife and beyond have sexual activity no more than once within 24 hours, and any of the available PDE-5 inhibitors can be effective in this setting. The only area where these agents appear to differ is in half-life, as tadalafil has a longer half-life than the other two PDE-5 inhibitors, which translates to a longer duration of action (**Table 1**).<sup>41,42</sup> Some clinicians allow patients to try all three PDE-5 inhibitors to determine their personal preference.

All PDE-5 inhibitors require sexual stimulation to achieve an erection.

The side effect profiles of the three PDE-5 inhibitors are very similar, and all three agents are contraindicated in patients taking long-acting nitrates or nitroglycerin.<sup>43</sup>

Because absorption of sildenafil may be meaningfully reduced by food, it is best not to take it in close proximity to meals, especially high-fat meals. Vardenafil shows some diminution in absorption after a high-fat meal, but not enough to impair efficacy. Absorption of tadalafil is not affected by food.<sup>41</sup>

Patients should be instructed that near-maximal concentrations are reached about 1 hour after administration of sildenafil and vardenafil and about 2 hours after administration of tadalafil.<sup>41</sup> Some patients achieve a therapeutic response within 15 minutes, but since most do not experience such rapid onset, it is wise to suggest the more conservative timing at first.<sup>44</sup> Over time, patients will become more and more familiar with the time to onset of action.

Patients should be instructed about the timing of administration, the need for sexual stimulation, the expected success rate, and the fact that the first few doses may not be successful. Based on data from sildenafil trials (similar data are not available for the

other PDE-5 inhibitors), patients should be made aware that any PDE-5 inhibitor should be tried six to eight different times at full dose before it is deemed ineffective. Because patient misadventure and misadministration may occur despite the best instructions, it is wise to ask patients to return after whatever interval is required for this six- to eight-dose trial period. For most couples, this will be 3 to 4 weeks, but the interval should be tailored to the couple's preference.

### **Intracavernosal injection therapy**

Another approach to ED involves injection of alprostadil, a prostaglandin, into the corpora cavernosa (**Table 1**). Despite the development of intracavernosal injection products that are fully appropriate to primary care settings, most primary care providers have not been trained in their use.<sup>45</sup> Additionally, most patients will prefer methods of treatment other than injection. Nonetheless, an occasional patient may prefer intracavernosal injection therapy for personal reasons, and it is an option for patients who are intolerant of or unresponsive to PDE-5 inhibitors or in whom those drugs are contraindicated.

### **Vacuum constriction devices**

Vacuum constriction devices (VCDs) consist of a cylinder that is placed over the penis and a pump that creates a vacuum within the cylinder. The negative pressure generated within the cylinder causes blood to flow into the corpora cavernosa, facilitating erection. Once an erection is achieved, a constrictor ring is placed around the base of the penis so that blood is retained within the corpora cavernosa.

Prior to the availability of PDE-5 inhibitors, VCDs were used successfully in many men with ED. The device can be viewed as cumbersome, however, and VCD-induced erections can differ from “spontaneous” erections in color and/or temperature as a result of the constriction ring. Still, VCDs have essentially no serious side effects, can work in ED of multiple etiologies,<sup>46</sup> and are economical; for these reasons a VCD may be a viable option for couples who are attracted by its simplicity, avoidance of systemic medications, or cost.<sup>45,47</sup>

Long-term continuation rates with VCDs vary widely (35% to 81%),<sup>48-50</sup> but in our experience, dropout rates are inversely related to the thoroughness of initial instruction in VCD application and use. Frequent reasons for VCD discontinuation include inadequate penile rigidity, the “unnaturalness” of the erection produced, pain from the pressure of the constriction ring, difficulty in use, and failure to ejaculate.<sup>51</sup>

### Intraurethral alprostadil suppositories

Like intracavernosal injection therapy, another treatment approach employs the prostaglandin alprostadil but applies it topically as a urethral suppository using an applicator (Table 1). The penis is then massaged to dissolve the alprostadil pellet, after which venous flow delivers alprostadil to the corpora cavernosa, where it will induce erection.<sup>52</sup> The patient generally needs to be standing when the pellet is inserted and walk around for about 10 minutes before the erection will develop. Pellet insertion should be preceded by urination to moisten the urethra and ease insertion. The patient should be instructed on the proper technique for inserting the suppository, which requires that the initial insertion be done in the primary care provider's office.<sup>41,43</sup>

Because of lower levels of efficacy (30% success rate),<sup>53</sup> local adverse effects, and relatively high cost, intraurethral suppositories do not enjoy as widespread popularity as other forms of therapy for ED.

### Treatment for psychogenic factors

Cognitive-behavioral interventions and relationship counseling are among the treatment approaches for psychogenic ED. These interventions are often combined with pharmacologic therapy. Primary care clinicians should consider referral to a sexual therapist if psychogenic factors are the cause of, or contribute to, ED.

### ■ APPROPRIATE FOLLOW-UP

After treatment is prescribed, follow-up is important to evaluate treatment success, monitor for adverse effects, and adjust the dose or type of treatment as necessary. There is no evidence-based guidance for the follow-up schedule, which should be tailored to the couple's preference and usual frequency of sexual activity. Generally, follow-up should be sufficiently soon so that obstacles to successful treatment can be promptly addressed, and should be at least periodic thereafter.

### ■ WHEN TO REFER

The role of the primary care clinician in ED management will depend on personal preference. It may vary from simple identification of ED and subsequent referral, to the use of oral medications, VCDs, intracavernosal injection, and urethral suppositories. Despite the typically supportive relationship between primary care clinicians and their patients, some patients may prefer the relative anonymity of a consultant for a condition as intimate as ED.

Referral to a urologist is appropriate for complex cases of ED, when an anatomic problem such as

Peyronie disease is present, or when there is a lack of treatment success.<sup>28</sup> As noted, referral to a sex therapist should be considered when relationship problems appear to be the cause of ED or an important contributor to it.

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# Evolving issues in male hypogonadism: Evaluation, management, and related comorbidities

## ■ ABSTRACT

Hypogonadism in men has a complex and varied pathogenesis. In addition to multiple established causes of the disease, low testosterone levels are associated with various comorbidities, including metabolic syndrome and type 2 diabetes. Symptoms associated with hypogonadism include reduced sex drive, fatigue, and mood disturbances, but accurate diagnosis requires biochemical testing. Total testosterone is considered the appropriate testosterone measurement in most situations in primary care, although free testosterone is a more accurate marker and is indicated in some situations. Testosterone replacement therapy is a valid treatment option for men with testosterone deficiency accompanied by symptoms of hypogonadism. The goals of therapy are to restore physiologic testosterone levels and alleviate symptoms. A potential association of testosterone replacement therapy with prostate cancer is the biggest safety concern, so patient monitoring should include regular digital rectal examination and prostate-specific antigen tests.

## ■ DEFINITION OF THE CONDITION

Hypogonadism in men is classified as primary (testicular failure), secondary (insufficient testicular stimulation by pituitary gonadotropins), or mixed. Regardless of age or disease etiology, men with a total testosterone level less than approximately 300 ng/dL often develop signs and symptoms associated with classic hypogonadism, which can have consequences for their long-term health.<sup>1,2</sup> Notably, there is some variation in what is considered the threshold total testosterone level for indicating hypogonadism, with the Endocrine Society and the American Association of Clinical Endo-

crinologists (AACE) recognizing 200 ng/dL as the threshold and the US Food and Drug Administration (FDA) recognizing 300 ng/dL.<sup>1,2</sup>

## ■ PREVALENCE AND SOCIAL IMPLICATIONS

Declines in total testosterone with advancing age have been documented in longitudinal studies.<sup>3-5</sup> As men age, serum testosterone declines by about 1% to 2% a year after age 30.

As noted in a 2003 report from the Institute of Medicine,<sup>6</sup> a simultaneous age-associated increase in sex hormone-binding globulin (SHBG) results in an even lower concentration of free testosterone, eventually culminating in a condition that some have called ADAM (androgen deficiency in aging males), andropause, late-onset hypogonadism, or EDAM (endocrine decline in aging males). The term “andropause” is a misnomer in that true andropause exists only in men who have lost all testicular function, which occurs only after disease, accident, or castration.

Published estimates of the frequency with which testosterone concentrations reach levels that can be interpreted as hypogonadal (ie, two standard deviations below the mean for young men) vary from 30% to 40% in men older than 65 years to as high as 70% in men 80 years of age or older.<sup>4,7,8</sup> However, not all men with a low testosterone level should be treated for the condition. As with many other medical conditions, therapy for hypogonadism is often initiated to resolve bothersome symptoms or to reduce risks posed by the condition. Notably, asymptomatic men with low testosterone levels are at increased risk for certain other conditions, as outlined below.

## Associated comorbidities

Low serum testosterone levels are associated with several comorbid conditions, including metabolic syndrome, diabetes mellitus, dyslipidemia, and erectile dysfunction.

**Metabolic syndrome.** Observational data summarized in the 2003 Institute of Medicine report support an association between hypogonadism and several

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components of metabolic syndrome.<sup>6</sup> For example, low levels of testosterone are inversely associated with concentrations of insulin, glucose, and triglycerides, and positively associated with levels of high-density lipoprotein (HDL) cholesterol.<sup>9</sup> A series of data analyses from the Kuopio Ischemic Heart Disease Risk Factor Study, conducted in Finland, shows that nondiabetic men were nearly four times more likely to develop metabolic syndrome if they were hypogonadal.<sup>9</sup>

Other recent studies have confirmed that hypogonadism predisposes men to insulin resistance, obesity, abnormal lipid profiles, and borderline or overt hypertension.<sup>10</sup> In 2005, a systematic review concluded that the evidence linking hypogonadism and metabolic syndrome is strong enough that the definition of metabolic syndrome in men may be expanded in the future to include hypogonadism as a diagnostic parameter.<sup>10</sup>

**Diabetes.** Dhindsa et al found that one third of men with type 2 diabetes referred to their diabetes center were hypogonadal, and that levels of luteinizing hormone and follicle-stimulating hormone were lower in the hypogonadal men than in those with normal levels of free testosterone.<sup>11</sup>

Hypogonadism also predicts the subsequent development of diabetes and metabolic syndrome in middle-aged men, and has been proposed to be involved in the pathogenesis of these diseases.<sup>12</sup> Stellato et al demonstrated that lower levels of free testosterone and SHBG predicted incident type 2 diabetes in middle-aged men.<sup>13</sup> A 2006 meta-analysis by Ding et al confirmed that testosterone levels were significantly lower in men with type 2 diabetes than in controls, and that higher baseline levels of testosterone and SHBG significantly reduced the risk of type 2 diabetes in men.<sup>14</sup>

**Dyslipidemia.** Although there have been no long-term studies of cardiovascular morbidity and mortality among recipients of testosterone replacement therapy, total testosterone levels are positively correlated with HDL cholesterol levels and negatively correlated with triglycerides in men with and without diabetes.<sup>15</sup> Moreover, Zmuda et al confirmed that reductions in testosterone levels were associated with unfavorable changes in triglycerides and HDL cholesterol among male participants in the Multiple Risk Factor Intervention Trial.<sup>3</sup>

**Erectile dysfunction.** Low serum testosterone can manifest as diminished sexual desire. Recent studies support the long-held belief that adequate testosterone concentrations are important for sexual function, and that reduced testosterone levels are associated with reduced sexual health, specifically in terms of libido.<sup>16,17</sup> Although the exact level of testosterone

required for adequate sexual function is unknown, treatment with testosterone replacement alone has been shown to improve sexual desire and function in hypogonadal men.<sup>18-20</sup>

In men with erectile dysfunction who are treated with testosterone replacement and the phosphodiesterase type 5 (PDE-5) inhibitor sildenafil, testosterone levels have been shown to correlate with penile arterial blood flow.<sup>21</sup> Similarly, testosterone therapy given in combination with PDE-5 inhibitors in short-term studies improved sexual function in androgen-deficient men (total testosterone < 400 ng/dL) who had suboptimal response to PDE-5 inhibitor therapy alone, yielding greater potency, erectile function, orgasmic function, and overall satisfaction.<sup>22,23</sup> There is uncertainty, however, whether the effect of this combination therapy can be sustained beyond 3 months, as well as over the exact role that testosterone replacement might have in salvaging PDE-5 inhibitor therapy failures.

In an analysis of men aged 50 years or older being treated for erectile dysfunction, nearly one fifth (18.7%) of the 2,823 subjects who had testosterone checked were found to have low testosterone levels (< 280 ng/dL).<sup>24</sup> The authors therefore concluded that routine screening for testosterone deficiency may be warranted in the work-up for erectile dysfunction.<sup>24</sup>

## ■ PATHOGENESIS

Hypogonadism has a complex and varied pathogenesis.<sup>25</sup> In addition to multiple established causes, low testosterone levels are associated with stress, aging, disease, and medications that have antiandrogen effects.<sup>5,8,26</sup> Many medical disorders are associated with low testosterone as well:

- Acute severe illness
- Chronic illnesses, including diabetes, cardiovascular disease, hypertension, hereditary hemochromatosis, and human immunodeficiency virus infection
- Lifestyle habits, including alcohol and tobacco use
- Malnutrition or obesity.

Because the underlying cause may be multifactorial and complex, a definitive etiologic diagnosis is not always attainable.<sup>27</sup> However, hypogonadism is thought to be either primary (ie, testicular) or secondary (ie, pituitary or hypothalamic) in etiology.

The most common congenital cause of hypogonadism is Klinefelter syndrome, a primary testicular disorder that results in small, undeveloped testes and elevated serum gonadotropin levels.

Most cases of hypogonadism in men aged 30 to 50 years have a combination of primary and secondary



**TABLE 1**  
**Questions used as part of the Saint Louis University ADAM questionnaire**

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A positive questionnaire result is defined as a "yes" response to questions 1 or 7 or to any three other questions.

ADAM = androgen deficiency in aging males

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causes. A gradual increase in serum concentrations of luteinizing hormone indicates a degree of primary hypogonadism.

## ■ PRESENTING SYMPTOMS

The diagnosis of hypogonadism in men is based on a combination of clinical signs and symptoms and laboratory tests.<sup>28</sup>

The most commonly noted symptoms include rather vague complaints such as lack of energy, loss of motivation, cantankerous mood, inability to concentrate, and sexual symptoms such as loss of desire, sexual dysfunction, erectile difficulties, impotence, and decreased ejaculate volume. Less commonly reported symptoms include hot flushes, slow beard growth, and muscular aches.

Symptoms may be elicited through use of a questionnaire, such as the ADAM (**Table 1**) or EDAM questionnaires.<sup>29</sup> However, the usefulness of symptom-based screening questionnaires may be limited by considerable variation in symptoms among different men. Kelleher et al noted that among a mixed population of men with primary, secondary, and mixed hypogonadism, the threshold for symptoms of androgen deficiency was highly reproducible in individual men but varied widely among different men.<sup>30</sup>

Symptoms depend on the patient's age at the time that hypogonadism develops. The symptoms men-

tioned above are manifestations of hypogonadism in postpubertal men, whereas small testes, reduced muscle mass, gynecomastia, a high-pitched voice, and scant pubic and axillary hair predominate in prepubertal boys with hypogonadism, which often goes unrecognized unless accompanied by short stature or endocrine abnormalities.

## ■ DIFFERENTIAL DIAGNOSIS

**Table 2** outlines symptoms and signs that call for the inclusion of hypogonadism in the differential diagnosis, along with other possible diagnoses.

## ■ EVALUATION

Because of the vague nature of the symptoms of hypogonadism, corroborating symptom-based impressions with actual biochemical assessment is important when making the diagnosis. Biochemical assessments for suspected hypogonadism include measures of total testosterone, free testosterone, SHBG, follicle-stimulating hormone, and luteinizing hormone.

### Start by checking testosterone

Measurement of serum total testosterone levels is the most simple means of screening for hypogonadism and monitoring therapy. Total testosterone is considered the appropriate testosterone measurement in most situations in the primary care setting by most expert groups. Because of the circadian rhythm of plasma testosterone levels, which leads to higher levels in the morning than in the evening, a total testosterone assay is preferably performed between 8:00 AM and 10:00 AM. This circadian rhythm is generally lost in elderly men, so advanced age may make the sampling time less important.

Measuring free testosterone levels may be more useful than total testosterone levels in the presence of elevated or decreased SHBG levels, which will alter the fraction of measured testosterone that is biologically available. Obesity, type 2 diabetes, and hypothyroidism are associated with low SHBG levels, whereas older age is associated with increasing SHBG levels. Measuring free testosterone levels or total bioavailable testosterone can provide more accurate measurements in these situations, although it is more labor-intensive, as it requires equilibrium dialysis or a formula-based calculation using the SHBG level. Measurement of free testosterone also is useful for confirming abnormal total testosterone levels.

A low testosterone level (< 200 ng/dL as defined by the ACE<sup>1</sup> or < 300 ng/dL as defined by the FDA) indicates hypogonadism, with lower levels obviating

the need for further testosterone analyses or quantification of SHBG.

### Confirm abnormal levels

Abnormal testosterone levels should be confirmed by a repeat test, preferably in the morning to take advantage of the diurnal secretion pattern. If testosterone is confirmed to be abnormally low, luteinizing hormone and prolactin levels should be obtained to distinguish primary forms of hypogonadism (testicular dysfunction or failure) from secondary forms (pituitary disease or hypothalamic dysfunction with resultant decreased gonadotropin-releasing hormone secretion). An elevated level of luteinizing hormone signals testicular dysfunction. An elevated prolactin level suggests the possibility of a pituitary tumor. Prolactin measurement is also useful because prolactin elevation may suppress gonadotropins, causing secondary hypogonadism.

### Indications for MRI

Magnetic resonance imaging (MRI) to detect a pituitary macroadenoma is appropriate in men with low testosterone when the luteinizing hormone level is also low or the prolactin level is elevated, especially in men younger than 50 years who have no comorbidities consistent with secondary hypogonadism. Older men with secondary hypogonadism should undergo MRI under the following circumstances:

- If the serum testosterone is very low (< 150 ng/dL) and if either (1) luteinizing hormone is normal or low or (2) prolactin is increased<sup>31</sup>
- If symptoms such as visual changes or headache are present.

### Vigilance for sleep apnea

Because obstructive sleep apnea has been associated with low levels of testosterone as well as with testosterone replacement therapy, patients should be evaluated for obstructive sleep apnea both prior to and following initiation of testosterone therapy. It is unknown whether obstructive sleep apnea precedes testosterone deficiency or is a manifestation of it.

## TREATMENT

A low testosterone level alone is not a sufficient indication for testosterone replacement therapy. However, when testosterone deficiency is accompanied by specific clinical symptoms of hypogonadism, testosterone replacement therapy is a medically valid treatment option regardless of the cause of the condition.<sup>1,2</sup> In men who are concerned about fertility, however, testosterone therapy should be used with caution, given that it impairs spermatogenesis. Gonadotropin-releasing hormone agonist therapy may be used

**TABLE 2**  
Differential diagnosis of symptoms and signs that may suggest hypogonadism

Symptoms	Other possible diagnoses
Headache, visual problems, galactorrhea, prior irradiation to sella	Pituitary tumor
Polyuria, polydypsia	Diabetes insipidus
Cold intolerance, weight change	Pituitary tumor, hypothyroidism
Memory loss	Alzheimer disease, vascular dementia
Malaise, fatigue, anorexia, weight loss	Hypopituitarism
Dramatic symptoms and hypoglycemia	Partial deficiency of adrenocorticotrophic hormone
Sudden onset of symptoms	Acute infection, inflammatory disease
<b>Signs</b>	
Papilledema, optic disc pallor	Pituitary tumor

instead of testosterone in some men if secondary hypogonadism is present, but this form of treatment is expensive and is usually reserved for hypogonadal men who also have fertility problems.

The exact levels of testosterone that require testosterone replacement at various ages and under varying circumstances are not clear and may be laboratory-dependent. However, levels that fall below the generally accepted normal levels for a practitioner's usual laboratory and that are accompanied by clear symptoms indicate a trial of testosterone replacement therapy.

### Goals of therapy

The goals of testosterone replacement therapy are to restore physiologic concentrations of testosterone and to alleviate symptoms of hypogonadism.<sup>1</sup>

The biochemical goal is to mimic normal concentrations of testosterone (350 to 1,050 ng/dL) and avoid excessively high levels. A digital rectal examination (DRE) and a prostate-specific antigen (PSA) test to rule out prostate cancer are required before initiating treatment (see below section, "Special concern: Prostate cancer").

### Contraindications

The presence of prostate cancer or male breast cancer is an absolute contraindication to testosterone replacement. Studies of PSA changes following testos-

terone replacement have yielded varying results, ranging from no increase to a rise of 0.96 ng/mL in PSA value.<sup>32</sup> The presence of voiding symptoms attributable to benign prostatic hyperplasia (BPH) has also been considered an absolute contraindication, but clinical studies have been equivocal. Some believe that close monitoring of the testosterone level can help to prevent an increase in prostate size beyond that of a similarly aged eugonadal man.

Conditions considered to be relative contraindications to testosterone replacement, which include sleep apnea and social or mood disorders, are more likely to be exacerbated by testosterone preparations that cause a supraphysiologic testosterone level.

### Three-month trial warranted

In appropriate candidates, a 3-month trial of testosterone replacement may be useful to determine the response. Such a trial does not appear to have serious adverse effects,<sup>33</sup> although more studies are needed to confirm whether a therapeutic trial of this length should be more formally recommended.

If treatment does not resolve symptoms within 3 months and if testing demonstrates a resolution of biochemical testosterone deficiency, treatment should be stopped and the patient should be evaluated for a different cause of his symptoms.

Three actions are important when considering testosterone replacement:

- Identify the key symptom or finding that is related to low testosterone and use it to monitor the efficacy of replacement therapy
- Evaluate for potential risk factors for adverse events with replacement therapy
- Ascertain that the testosterone level is low enough to allow replacement and still remain in the physiologic range.

### Testosterone formulations

The ideal form of testosterone replacement therapy should be convenient and minimize adverse effects.

**Intramuscular injections** of the testosterone esters testosterone enanthate and cypionate can be administered in the office or by the patient's family. With these formulations, the testosterone concentration peaks within a few days of administration and may be supraphysiologic, after which concentrations slowly decline over the following 2 to 3 weeks. Injections are given at 2- to 3-week intervals. The wide swings of plasma testosterone levels cause some men to develop undesirable physiologic and emotional effects (eg, breast tenderness, hyperactivity) during peak-level periods and to develop fatigue, depression, or anger

during periods of lower levels. Some patients report peaks and valleys of mood and energy. Starting with lower doses, especially in older men, and titrating upward as tolerated will lessen mood fluctuations and abrupt changes in sexual interest.

**Transdermal formulations** provide the closest approximation of normal circadian plasma concentrations of testosterone. These are applied nightly and provide peak levels that follow a physiologic decline over the day. Scrotal patches are not popular because of the need to shave the skin before application, and because adherence to the scrotal skin is poor. Transdermal patches applied in the evening can provide physiologic testosterone levels, but transient skin irritation may occur. A low-dose steroid cream applied prior to patch placement can diminish skin irritation without hindering testosterone absorption. Doses can be difficult to adjust, and patches are more expensive than injection therapy.

**Rapid-absorbing gels** can be applied directly to non-scrotal skin once daily. The gel dries quickly and produces less irritation than patches, but there is a risk that unabsorbed gel may be transferred to the patient's sexual partner. About 10% of men experience absorption problems. The dose can be easily titrated, with packets or tubes of gel designed to deliver testosterone at dosages of 5 or 10 g/day. Gels are the most expensive form of testosterone replacement. As with injections, starting with lower doses in older men may help diminish adverse effects.

**Buccal mucosal system administration** of testosterone twice daily can restore testosterone concentrations to the physiologic range within 4 hours. The small mucosal adhesive tablet is placed in a comfortable area of the gum just above one of the upper front teeth. The tablet needs to be pressed firmly for 30 seconds to promote adhesion so that it will remain in the mouth for a full 12 hours. The used tablet is discarded at the end of the 12-hour period. Steady state is achieved within 24 hours of dosing in most patients. The incidence of adverse events is low, although buccal/gingival irritation, taste perversion, and bitter taste have been reported.

**Oral preparations** for testosterone replacement that are available in the United States are alkylated to avoid first-pass liver metabolism. These preparations are rarely prescribed because they can cause serious liver toxicity.

### Other potential benefits of testosterone therapy

Studies of testosterone replacement therapy in hypogonadal men have demonstrated several potential benefits beyond improvement in the symptoms of

hypogonadism. Although these potential effects, outlined below, continue to be explored, it is unclear whether they are long-term benefits.

**Bone density, lean body mass.** Prevention of bone loss and improvement in body mass composition have been observed with testosterone replacement therapy. In men older than 65 years with low levels of bioavailable testosterone, 12 months of transdermal testosterone increased bone mineral density in the femoral neck compared with placebo ( $P = .015$ ) and increased lean body mass ( $P = .001$  vs baseline).<sup>34</sup> Additional studies have demonstrated improvements in lean body mass and percentage of body fat in hypogonadal men with 20 weeks of injectable or topical testosterone therapy compared with placebo.<sup>35–37</sup> In a meta-analysis of 29 randomized controlled trials of testosterone replacement in middle-aged and elderly men, Isidori et al found testosterone therapy to be associated with significant improvements in total body fat, fat-free body mass, and lumbar spine bone mineral density.<sup>38</sup>

**Insulin sensitivity.** Simon et al reported a significant improvement in indexes of insulin sensitivity ( $P < .01$ ) after 3 months of therapy with a dihydrotestosterone gel compared with placebo in a group of healthy men with low levels of plasma total testosterone.<sup>39</sup> Whether such therapy can affect the management of type 2 diabetes or reverse components of metabolic syndrome remains unknown at this time.

**Functional capacity.** Malkin et al conducted a randomized, double-blind, placebo-controlled trial to assess the effect of testosterone therapy (5 mg/day for 12 months) in men with chronic heart failure; therapy was given to maintain serum testosterone levels within the physiologic range.<sup>40</sup> They found testosterone replacement to be associated with an increase in walking distance that correlated with a rise in bioavailable testosterone.

**Sexual function.** Erectile function scores have improved with testosterone therapy in men treated for sexual dysfunction,<sup>18–20</sup> including when used as an adjunct to PDE-5 inhibitor therapy.<sup>22,23</sup> In a meta-analysis of 17 randomized, placebo-controlled trials in men who were mildly or moderately hypogonadal (but not eugonadal), Isidori et al found that, compared with placebo, testosterone therapy was associated with more nocturnal erections, sexual thoughts, and successful intercourse attempts and with higher scores of erectile function and overall sexual satisfaction.<sup>41</sup> The effect of therapy was progressively weaker with increasing baseline testosterone levels.<sup>41</sup> In men with erectile dysfunction who were nonresponders to sildenafil, addition of a 1% testosterone gel produced

significantly greater improvement in erectile function and a trend toward better orgasmic function and overall sexual satisfaction compared with placebo.<sup>23</sup>

### Risks and adverse events

The risk-benefit ratio of long-term testosterone replacement therapy is unclear. Despite more than 50 years of clinical use, the long-term safety of testosterone replacement has yet to be demonstrated in controlled clinical trials.<sup>1,2</sup> Potential concerns include the following:<sup>42</sup>

**BPH.** Although prostate volume increases significantly during testosterone therapy, usually to the level of men without hypogonadism, exacerbation of voiding symptoms attributable to BPH has not been demonstrated.

**Cardiovascular effects.** The overall body of evidence indicates no association between testosterone and development of cardiovascular disease.<sup>42</sup> Past concerns about adverse lipid effects of testosterone replacement no longer seem warranted; in fact, testosterone therapy may confer beneficial lipid effects, but the jury is still out.

**Erythrocytosis.** The incidence of erythrocytosis reported in clinical trials of testosterone replacement has been 3% to 18% with transdermal forms and up to 44% with injectable short-acting forms; variations in rates depend on the dose and route of administration.<sup>42</sup> Although hemoglobin and hematocrit levels rarely rise above normal with testosterone therapy, they should be monitored when therapy is initiated. No thromboembolic events have been reported in relation to testosterone therapy.

**Gynecomastia.** Breast tenderness and swelling resulting from changes in SHBG levels occurs in a small number of men who receive testosterone replacement, but is usually reversible.

**Sleep apnea.** Exacerbation or development of sleep apnea, especially in those with risk factors for it, occurs infrequently with testosterone therapy.

**Hepatotoxicity** is associated with oral forms of testosterone, although apparently not with other formulations.

### Special concern: Prostate cancer

The major safety concern with testosterone replacement therapy raised in the 2003 Institute of Medicine report was the risk of prostate cancer.<sup>6</sup> Based on the available evidence at that time, the report concluded that “the influence of testosterone on prostate carcinogenesis and other prostate outcomes remains poorly defined, but could greatly influence the risk-benefit ratio for supplementation in both young and

**TABLE 3**  
**Summary recommendations for prostate monitoring before and during testosterone replacement therapy**

**Before initiating therapy**

Normal digital rectal examination (DRE)  
 Prostate-specific antigen (PSA) level < 4.0 ng/mL  
 Evaluate individual risk of prostate cancer<sup>47</sup>

**During therapy**

Measure PSA:  
 —At 3 to 6 months  
 —Semiannually as long as treatment continues

Perform DRE:  
 —Annually or semiannually as long as treatment continues

Refer for urologic evaluation and possible prostate biopsy in any of the following cases:  
 —Prostate is abnormal on DRE  
 —PSA > 4.0 ng/mL  
 —PSA rises by more than 1 ng/mL after 3 to 4 months on testosterone therapy  
 —PSA rises at rate > 0.75 ng/mL/yr<sup>42</sup>  
 —PSA rises at rate > 0.4 ng/mL/yr over an observation period of less than 3 years (using PSA after 6 months on testosterone as reference point)<sup>47</sup>

elderly populations.” The report cited preclinical and clinical evidence that androgens may promote or inhibit prostate cancer growth.

Indeed, the fear of unmasking occult prostate cancer prevents many physicians from using testosterone replacement therapy. However, there appears to be no evidence that testosterone replacement increases the risk of prostate cancer even in those men at highest risk for it.

Three recent clinical studies suggest that higher endogenous testosterone concentrations are associated with less aggressive forms of prostate cancer:

- An examination of total testosterone levels in 82 men with localized prostate cancer demonstrated that pretreatment levels were lower among the men with non-organ-confined cancer than among those with organ-confined cancer.<sup>43</sup>

- An evaluation of total testosterone in 326 men about to undergo radical prostatectomy for clinically localized cancer found that lower preoperative testosterone levels were associated with advanced pathologic stage.<sup>44</sup>

- A retrospective study of 279 patients with clinically localized prostate cancer determined that poorly

differentiated prostate cancer was associated with significantly lower testosterone levels.<sup>45</sup>

An additional study showed that 1 year of testosterone therapy produced no greater increase in PSA values in hypogonadal men with prostatic intraepithelial neoplasia, a precancerous prostate lesion, than in those without this lesion.<sup>46</sup>

We recommend that clinicians perform a baseline DRE and obtain a baseline PSA measurement before starting testosterone replacement, regardless of patient age. The PSA level should be checked 6 months after initiation of testosterone therapy, regardless of the route of administration. The PSA level should then be monitored semiannually as long as the patient remains on testosterone replacement, and a DRE should be performed annually or semiannually. **Table 3** presents recommendations for PSA monitoring during testosterone replacement therapy.<sup>42,47</sup>

Use of PSA monitoring for prostate cancer screening remains controversial in primary care (see separate article in this supplement on screening for urologic malignancies). At minimum, the risks and benefits of such screening should be discussed with the patient, especially if he is 50 years of age or older.

■ **APPROPRIATE FOLLOW-UP AND MONITORING**

Monitoring guidelines for patients receiving testosterone replacement therapy have been published by leading professional societies, including the AACE and the American Society for Reproductive Medicine.<sup>1,2</sup> These guidelines recommend periodic follow-up of patients receiving testosterone replacement, with routine examination of the prostate and regular determinations of PSA levels, similar to those outlined above.

Before starting testosterone replacement therapy, a baseline DRE should be performed and baseline values for the following should be obtained:

- Total serum testosterone
- PSA
- Hematocrit/hemoglobin
- Liver function enzymes
- Lipid profile (total cholesterol, low-density lipoprotein cholesterol, HDL cholesterol, and triglycerides).

Once therapy is started, dose adjustment is guided by serum testosterone monitoring and clinical response. Morning serum testosterone should be tested 1 or 2 months after therapy is started by monitoring the nadir testosterone level—ie, prior to the next injection, 3 to 12 hours after application of a transdermal patch, or at any time after the patient has been receiving topical gel treatment for several days. Normal testosterone levels range from 350 to 1,050

ng/dL; to optimize treatment response, we aim for the middle to upper portion of this range. Final dose adjustment, however, may also depend on the patient's response since some men respond well to levels in the low normal range. Supraphysiologic levels should be avoided for more than transient periods.

Laboratory values should be monitored periodically to ensure patient safety. Intermittent follow-up hematocrit measurements are appropriate, as is intermittent evaluation for sleep apnea. Patients should also be monitored for acne, breast tissue increase or tenderness, and skin irritation (if receiving topical preparations).

### ■ WHEN TO REFER

Referral to a specialist is indicated for patients whose hypogonadism is refractory to testosterone replacement. In patients receiving testosterone therapy, a rate of change in PSA level greater than 0.75 ng/mL per year, regardless of the baseline PSA level, should prompt further investigation with a prostate biopsy, as should detection of a nodule on DRE (Table 3).

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# Identifying and treating premature ejaculation: Importance of the sexual history

## ■ ABSTRACT

Premature ejaculation (PE) is one of the most common sexual dysfunctions in men, with prevalence rates ranging from 21% to 31%. Because many physicians do not inquire about sexual dysfunction and patients are reluctant to offer it as a medical complaint, PE is underreported in clinical practice. A sexual history is therefore necessary to uncover the diagnosis. PE can have a significant impact on the quality of life of the patient and his sexual partner, and may lead to psychological distress and loss of self-esteem. It appears that PE has no single etiology, and treatments have been based on both its neurophysiologic and behavioral components. Although no therapies are currently approved for PE by the US Food and Drug Administration, medications that have shown some success include selective serotonin reuptake inhibitors, tricyclic antidepressants, phosphodiesterase type 5 inhibitors, and topical anesthetics. Behavioral techniques have been the mainstay of PE treatment, and include techniques to decrease sensory input.

## ■ DEFINITION OF THE CONDITION

Finding a universally accepted definition for premature ejaculation (PE) has been problematic. The three most commonly cited clinical definitions of PE (**Table 1**) all have two basic components: an inability to control or delay ejaculation, and resultant distress.<sup>1-3</sup> The Second International Consultation on Erectile and

Sexual Dysfunctions/World Health Organization<sup>1</sup> in 2004 and the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*<sup>2</sup> define PE as ejaculation before a person wishes it, leading to distress for one or both partners. The American Urological Association (AUA) 2004 guideline on PE<sup>3</sup> defines it as ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either partner.

The American Psychiatric Association's DSM-IV further categorizes PE as either lifelong (primary), in which the patient has rarely, if ever, been able to control ejaculation, or acquired (secondary), in which the patient initially had a period of good ejaculatory control but later in life develops PE with all or specific partners or in specific situations (**Table 1**).<sup>2</sup> Lifelong PE is the most common form. Acquired PE usually begins in men in their 40s to 50s.

None of the three definitions quantifies objectively a "normal" time to ejaculation. For research purposes, the quantitative assessment used to measure ejaculatory function is the intravaginal ejaculatory latency time (IELT). It refers to the time between vaginal penetration and ejaculation, usually measured with a stopwatch or simply estimated in retrospect. Men with PE will measure this time in seconds, and almost always have an IELT less than 4 minutes.<sup>4</sup> A small percentage of men will ejaculate even before penetration.

An observational study in the United States showed that men with PE had a mean IELT of 3 minutes (median of 1.8 minutes) and men without PE had a mean IELT of more than 9 minutes (median of 7.3 minutes), with considerable overlap between the two groups.<sup>4</sup> A multinational population survey of IELT showed that 90% of 110 men with self-reported lifelong PE had an IELT of less than 60 seconds.<sup>5</sup> Although decreased IELT was associated with the complaint of ejaculating too early, in the clinical setting, the subjective report of loss of control and distress appears to be more important to the patient. As a result, the diagnosis of PE encompasses four dimensions:<sup>6</sup>

\* Dr. Payne reported that he has received honoraria, consulting fees, and an educational grant from Eli Lilly/ICOS for teaching/speaking, consulting, and contracted research; honoraria and consulting fees from Sanofi-Aventis for teaching/speaking and advisory board membership; consulting fees from Boehringer Ingelheim for teaching/speaking and consulting; consulting fees from Pfizer, Johnson & Johnson, and Thomson Healthcare for consulting; and consulting fees from Reliant Pharmaceuticals for serving on an advisory committee. He also reported having an ownership interest in and receiving consulting fees from MedVantx. Dr. Sadovsky reported that he has no financial relationships that pose a potential conflict of interest with this article.



**TABLE 1**  
Definitions/diagnostic criteria for premature ejaculation

World Health Organization <sup>1</sup> (2004)	American Psychiatric Association DSM-IV <sup>2</sup> (2000)	American Urological Association <sup>3</sup> (2004)
Persistent or recurrent ejaculation, often but not always with minimal stimulation, before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has little or no voluntary control, which causes the sufferer or his partner dissatisfaction, bother, or distress.	<p>A. Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity.</p> <p>B. The disturbance causes marked distress or interpersonal difficulty.</p> <p>C. The premature ejaculation is not due exclusively to the direct effects of a substance (eg, withdrawal from opioids).</p> <p>Specify type: Lifelong vs acquired</p> <p>Specify type: Generalized vs situational</p>	Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.

- The ejaculatory latency
- The degree of voluntary control
- The presence of marked distress or interpersonal disturbance
- Symptoms not due to any other mental, behavioral, or physical disorder.

**PREVALENCE AND SOCIAL IMPLICATIONS**

PE is arguably the most common form of male sexual dysfunction.<sup>7,8</sup> The National Health and Social Life Survey was a probability-based household survey in 1992 that included 1,410 men aged 18 to 59 years.<sup>7</sup> It revealed that approximately 30% of all men reported “climaxing too soon.” Of note, the likelihood of PE was not affected by age, marital status, or race/ethnicity. Similarly, the Global Study of Sexual Attitudes and Behaviors (GSSAB) survey of 13,618 men in 29 countries showed prevalence rates of 21% to 31%.<sup>8</sup>

The prevalence of PE is similar across countries. In the Premature Ejaculation Prevalence and Attitudes study, 23.4% to 25.6% of men in Germany, Italy, and the United States had the disorder.<sup>9</sup>

**Frequent correlation with erectile dysfunction**

Epidemiologic studies have found a high rate of correlation between PE and erectile dysfunction (ED). In the GSSAB survey, 41% of men who reported ED also reported PE, and 30% of men reporting PE also had ED.<sup>8</sup> Other studies indicate that about 30% of men with PE also have ED.<sup>10,11</sup> Although ED increases in prevalence with age, PE does not.<sup>7</sup>

**Reluctance to report**

The above prevalence rates of PE may be higher than many physicians would expect, since most physicians do not inquire about the condition and men do not frequently offer it as a medical complaint. Under-reporting of PE is attributable to a number of factors, including embarrassment and loss of self-esteem on behalf of the patient, traditional low prioritization of the condition by the medical system, a lack of physician comfort with and knowledge of PE, and a lack of effective treatment options.

The interpersonal implications of PE can produce significant psychological distress. Men with PE report significantly more emotional distress, loss of self-esteem, anxiety, depression, and social isolation than men without PE.<sup>12</sup> In a study on the quality-of-life impact of PE, 50% of men with self-diagnosed PE were reluctant to start a new relationship and felt distress in not satisfying their partner, and 68% believed that their eroded sexual self-confidence and self-esteem was a primary concern.<sup>12</sup>

**Effects on the partner and the relationship**

These effects frequently take a toll on the patient’s relationship with his sexual partner, often leading couples to avoid intercourse and intimacy altogether.<sup>13,14</sup> The effects can extend beyond the purely sexual aspects of the relationship: female partners of men with PE often report that although sex may be disappointing, they are more bothered by the break in emotional intimacy after the man has his early ejaculation. Men with PE

are often anxious, hurrying the progression of intercourse and disengaging from their partners to hide their shame. The partner sees this behavior as rejection, and both partners are often angry and frustrated.<sup>6</sup>

In a preliminary report of a 2005 survey of 129 women presenting in a community practice, 23.2% of women reported that their partner had PE (defined as ejaculating before she desired at least half of the time they had sex).<sup>15</sup> Although only 40% of these women stated that their partner's PE was a problem for them, these women were significantly more likely than the rest of the surveyed women to report difficulty reaching orgasm or "feeling rushed," and 65% of them said they would be interested in counseling and/or medication to address their partner's PE.<sup>15</sup>

### Limited awareness of impact and treatments

Physicians may not routinely ask patients about PE, may feel uncomfortable about asking, and may lack knowledge of the condition.<sup>16</sup> Since PE has no significant physical comorbidities, physicians may consider it a "quality-of-life" disorder and thus relegate it to a lower priority. Our current medical system strains the patient-physician relationship, often not allowing for these discussions during brief and time-pressured appointments with patients.

The success of the phosphodiesterase type 5 (PDE-5) inhibitors for treating ED has brought the treatment of that sexual dysfunction to the forefront. As a result of direct-to-consumer marketing and education, patients more easily initiate discussions of ED with their physicians.

In contrast, with no treatment for PE approved by the US Food and Drug Administration (FDA), little patient awareness of nonapproved treatments that are available, and even less awareness that physicians may be able to help, men and their physicians adhere to a course of "don't ask, don't tell" when it comes to PE. Physicians generally prefer to treat disorders that have effective treatments backed by clear, evidence-based guidelines.

The Global Study of Sexual Attitudes and Behaviors revealed that only 9% of men reported that they had been asked about their sexual health by a physician during a routine visit in the prior 3 years.<sup>16</sup> In contrast, 48% of the men believed that a physician should routinely ask about sexual health concerns.<sup>16</sup>

### ■ PATHOGENESIS

Although the etiology of PE remains to be fully elucidated, the neurobiological phenomenon can be described in detail. The normal male sexual response

results from a complex integrated neurophysiologic pathway with four phases: excitement, plateau, ejaculation (which includes emission and ejection) and orgasm, and resolution.<sup>17</sup> With PE, there is a blunting of the normal curve of ejaculatory response, characterized by a steep excitement phase with a shortened plateau phase followed by ejaculation/orgasm and a rapid resolution phase.

### A trio of mechanisms

Ejaculation involves three basic mechanisms: emission, expulsion, and orgasm. Emission is a sympathetically mediated neural function (spinal nerves T10 through L2) that leads to contraction of the prostate gland and seminal vesicles, causing deposition of sperm/seminal fluid into the posterior urethra.<sup>18</sup> Expulsion is also a sympathetically mediated event (spinal nerves S2 through S4) that initiates with bladder neck closure and relaxation of the external striated urinary sphincter, causing rhythmic contraction of the skeletal pelvic floor muscles.

The forebrain structures involved in ejaculation include the thalamus, amygdala, stria terminalis, nucleus paragigantocellularis, and medial preoptic area. Neurotransmitters involved with ejaculation include serotonin, dopamine, norepinephrine, oxytocin, and gamma-aminobutyric acid. Serotonin (5-HT) is known to have an inhibitory role in sexual behavior in the male. Injection of a selective serotonin reuptake inhibitor (SSRI) into rat hypothalamus has been shown to delay ejaculation, whereas administration of a selective serotonin receptor agonist has been shown to cause PE in the rat.<sup>19</sup>

### Neurophysiologic and behavioral components

Theories of the etiology of PE have both neurophysiologic and behavioral components. Until recently, PE was believed to be predominantly a psychological disorder. Many researchers now believe that primary PE is caused mostly by neurophysiologic factors while secondary PE has more associated psychological contributors.

Organic theories of PE include penile hypersensitivity (reaching ejaculatory threshold more rapidly and/or having a lower ejaculatory threshold), a hyperexcitable ejaculatory reflex (faster emission/expulsion phase, faster bulbocavernosus reflex, or both), genetic predisposition (there may be a higher incidence of PE in men whose first-degree relatives have PE), and central 5-HT receptor sensitivity (possible lower 5-HT neurotransmission, 5-HT<sub>2c</sub> receptor hyposensitivity, and/or 5-HT<sub>1a</sub> receptor hypersensitivity, as suggested in animal models).

**TABLE 2**  
Symptoms and factors that may be associated with premature ejaculation

Anxiety	Relationship change
Depression	Erectile dysfunction
Substance abuse	Low libido
Relationship distress/ marital discord	

Behavioral theories of PE, from Semans and then Masters and Johnson, proposed that PE was a learned behavior conditioned from early sexual experiences.<sup>20,21</sup> In more recent years, sex therapists have focused more on the role of anxiety in the disorder. They suggest that anxiety may distract from the premonitory sensations that precede ejaculation and activate the sympathetic nervous system or lower the ejaculatory threshold. Additionally, these men may not be able to monitor and adequately manage their bodies' response to the sensations of escalating levels of sexual arousal.

Overall, it appears likely that PE does not have a single etiology but rather consists of multiple variable subtypes caused by varying contributions of biological and psychological factors.

**■ PRESENTING SYMPTOMS**

Patients often do not present with PE as their chief complaint. As such, they will not be diagnosed unless a sexual history is taken. The challenge in primary care is to make the sexual history a routine part of patient wellness evaluations and to identify those diagnoses that may predict a higher risk for sexual problems such as PE.

ED is of particular interest in this context, since an overlap of PE and ED is well established.<sup>8,10,11</sup> Patients with PE may present reporting difficulty with erections when in reality they may be experiencing PE followed by a resolution-phase loss of erection. Therefore, if a patient presents with ED or is asking for a prescription for a PDE-5 inhibitor, consider the possibility of PE.

Additionally, PE may be associated with signs and symptoms of anxiety, depression, or substance abuse, as well as with difficulties or changes in the patient's relationship (Table 2), although these factors are absent in many cases of PE. Because some cases of PE have physiologic causes, symptoms suggestive of prostatitis, urinary tract infection, or similar genitourinary complaints should be noted.<sup>22</sup>

**■ EVALUATION AND DIFFERENTIAL DIAGNOSIS**

The evaluation of any problem with sexual function should be grounded in a recognition that the patient is placing great trust in his physician to treat his problem with respect and sensitivity. Active listening and a compassionate acceptance of the patient are key components of "allowing" the patient to discuss a sensitive issue such as PE. Any discomfort physicians may feel should be assuaged by the knowledge that most patients appreciate it when their physician asks about their sexual health and function.

The sexual history can be performed in the context of the review of symptoms, often during discussion of urinary tract symptoms or with the behavioral/relationship questions that are appropriate in the social history.

An appropriate initial question is, "Are you satisfied with your current sexual functioning?" This can be followed by inquiries such as, "Are you satisfied with your erections?" and "Do you ejaculate (or climax) earlier than you wish?" To determine whether the problem is one of ED or PE, the clinician should ask if the loss of erection occurs before or after ejaculation. To assess partner reaction, the clinician can ask, "Is this concern distressing to you, your partner, or both of you?" or "How has this affected your sexual relationship?"<sup>23</sup>

Other assessments relate to the patient's perception of "loss of control" of ejaculatory function, and dissatisfaction with intercourse or the relationship. The frequency, duration, and percentage of attempts with PE can also be ascertained. The patient should be asked his subjective estimate of the time between penetration and ejaculation (the IELT), which may help clarify whether ejaculation is occurring prior to penetration.

There is no laboratory test currently available to assist clinicians with the diagnosis of PE.

Keep in mind that men may have mixed sexual dysfunction, with multiple phases of sexual activity negatively affected at the same time. A combination of libido and ejaculatory problems, or a mixture of ED and PE, is possible. Ascertaining which problem concerns the patient most, or which problem is the primary one, can lead to a therapeutic plan that is likely to meet the patient's needs.

**■ TREATMENT**

Managing PE has been a challenge for physicians, as there are currently no FDA-approved therapies for the condition and most physicians have not been trained in behavioral techniques for managing it.

### Pharmacologic interventions

**Topical anesthetics** have been used in an attempt to desensitize the penis in hopes of prolonging the time to ejaculation. Lidocaine/prilocaine cream (2 g/5 g) applied to the penis 20 to 30 minutes prior to intercourse, and then washed off (with or without a condom), may increase IELT, but few controlled studies have been performed.<sup>24,25</sup> Drawbacks of this and other topical anesthetic approaches are the possibility of loss of erection, excessive loss of pleasurable sensation, and loss of sensation for the partner, as well as the potential for allergic reactions.

**PDE-5 inhibitors** prolong erections and may increase IELT in men with ED. The combination of SSRIs with PDE-5 inhibitors seems to improve PE compared with SSRI therapy alone in some studies,<sup>26</sup> but most investigators believe that PDE-5 inhibitors have limited benefit in the management of PE except for those men with acquired PE secondary to ED.<sup>27</sup> Most of the benefit of PDE-5 inhibitors is believed to be due to reduced performance anxiety as a result of improved erections.<sup>28</sup>

**Tricyclic antidepressants (TCAs) and SSRI antidepressants** have some efficacy in the treatment of PE, but their side effects may outweigh their benefits. Adverse effects of SSRIs and TCAs may include reduced libido, ED, anorgasmia/anejaculation, drowsiness, fatigue, and gastrointestinal symptoms (Table 3).

Multiple placebo-controlled clinical trials have been conducted using the SSRIs fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine as well as TCAs such as clomipramine (the most widely studied TCA for PE).<sup>29</sup> In a comparative trial in men with PE, clomipramine was associated with a significantly higher incidence of adverse effects (23%) than were sertraline (12%) or fluoxetine (13%).<sup>30</sup> On the basis of multiple trials, paroxetine appears to exhibit the strongest effect on IELT, with fluoxetine and sertraline close behind.<sup>29</sup> More studies are needed to further define the role of citalopram and other SSRIs in PE.<sup>29</sup>

Since SSRIs and TCAs are not FDA-approved for the treatment of PE, doses and dosing regimens have not been standardized. Daily use of an SSRI may have greater ability to prolong IELT than on-demand SSRI use.<sup>31</sup> For clomipramine, on-demand use appears to be most effective in men whose PE is less severe.<sup>32,33</sup>

All medications that are effective for PE may lose their efficacy shortly after their use is discontinued.

**Dapoxetine** is an investigational short-acting SSRI developed specifically for the treatment of PE and submitted for FDA approval in 2004.<sup>34</sup> Although dapoxetine has been shown to significantly prolong

**TABLE 3**  
Available medications most widely studied for treatment of premature ejaculation\*

Drug	Dosage	Side effects
<b>Antidepressants</b>		
<u>Antidepressants</u>		
Citalopram	20–60 mg/day	Nausea, headache, diarrhea, fatigue, sweats, drowsiness, erectile dysfunction, reduced libido, anejaculation
Clomipramine	25–50 mg/day or 25 mg 2–14 hrs before intercourse	Dry mouth, drowsiness, erectile dysfunction, nausea, vomiting, fatigue
Fluoxetine	5–20 mg/day	Nausea, headache, diarrhea, fatigue, sweats, insomnia, erectile dysfunction, reduced libido, anejaculation
Paroxetine	10–40 mg/day or 20 mg 3–4 hrs before intercourse	Nausea, headache, diarrhea, fatigue, sweats, drowsiness, confusion, erectile dysfunction, reduced libido, anejaculation
Sertraline	25–200 mg/day or 50 mg 4–8 hrs before intercourse	Nausea, headache, diarrhea, fatigue, sweats, drowsiness, erectile dysfunction, reduced libido, anejaculation
<b>Phosphodiesterase-5 inhibitor</b>		
Sildenafil	25–100 mg 1–4 hrs before intercourse	Headache, dyspepsia, nasal congestion, flushing, visual color distortion, low back pain
<b>Topical anesthetic</b>		
Prilocaine-lidocaine cream	Apply to penis 20–30 mins before intercourse	Loss of sexual sensation (both partners)

\*None of these agents has been licensed to treat premature ejaculation.

IELT relative to placebo in a pair of double-blind controlled trials,<sup>35</sup> the company developing the drug received a “not approvable” letter from the FDA in October 2005.<sup>36</sup> The questions raised in the FDA letter were not disclosed, but dapoxetine’s developer stated that it plans to address the questions and continue the drug’s global development program.<sup>36</sup>

**Choosing among treatment options.** The AUA guideline on the pharmacologic management of PE<sup>3</sup> states: “The risks and benefits of all treatment options should be discussed with the patient prior to any

intervention. Patient and partner satisfaction is the primary target outcome of the treatment of PE.” One of the guideline’s recommendations is that the optimal treatment course should be based on both physician judgment and patient preference.<sup>3</sup>

### Behavioral therapy

Behavioral techniques have been the mainstay of PE management for many years, although evidence of their short-term efficacy is limited. Some men use self-help approaches gained through personal experience, bibliotherapy (books), or online research. These techniques have included masturbation just prior to intercourse, the use of multiple condoms to reduce penile sensitivity, or engaging in distraction techniques (mental exercises) during foreplay, intercourse, or both.

Semans proposed the “stop-start” technique in 1956.<sup>20</sup> The purpose was for the man to stop thrusting prior to the sensation of impending ejaculation, possibly lengthening the plateau phase, and increasing awareness of the sensory input. Once the couple feels comfortable with vaginal penetration, they may be instructed to engage in “quiet vagina,” in which the female partner temporarily stops moving during intercourse when the man indicates that he is approaching ejaculation, resuming once he says that he has regained control.

Masters and Johnson introduced the “squeeze” technique—stopping the thrusting motion during which the man (or his partner) squeezes the frenulum of the penis until the need to ejaculate abates.<sup>21</sup> “Sensate focus” was also taught to couples to learn to enjoy touching and being touched in the absence of “performance pressures.” However, subsequent trials reported high failure rates with these techniques.<sup>37</sup>

More recently, sex therapists have combined psychotherapy with behavioral exercises with more success. Therapy focuses on the emotional implications of the man’s PE, on relationship dynamics, and on performance anxiety management. Therapy is limited by cost, the local availability of trained therapists, and the willingness of patient and partner to participate. As might be expected, the best results have been seen in men who are motivated, are hopeful, and are in a stable monogamous relationship with a cooperative partner.<sup>38</sup>

### ■ APPROPRIATE FOLLOW-UP

Primary care providers manage chronic disease with specific follow-up time intervals, but no follow-up management guideline exists for PE. Time should be spent to properly educate the patient about his disorder, legitimize his concerns, and offer help. Offering

to arrange follow-up visits and encouraging the partner to attend may help the clinician gain insight into the impact of PE on the partner and the relationship.

If pharmacologic therapy is undertaken, allow sufficient time for the medication to take effect, as well as enough intercourse attempts to assess response to therapy. With this in mind, follow-up visits are best aimed at assessing the efficacy and tolerability of the medication and should be scheduled on the basis of how often the patient has sex, although follow-up is a necessity for all patients. As side effects often occur before the drugs become effective, patients should be educated about what to expect and instructed to call you if they experience side effects.

Long-term maintenance management, which consists of intermittent inquiries about sexual activity and satisfaction, and a review of treatment options when necessary, may make an initial response to treatment more durable.

### ■ WHEN TO REFER

The primary care provider may consider referral to a psychotherapist (preferably a sex therapist), a psychiatrist, or a physician with specific interest in PE if he or she is uncomfortable or insufficiently trained to care for men with PE and their partners. A team approach involving both a therapist and a physician may best help those couples who have the greatest distress or who do not respond to initial therapy. The concept of “coaching” is within the reach of primary care providers who have the sensitivity, time, interest, and knowledge to offer the patient brief and targeted psychoeducational interventions. These basic sexual counseling sessions, integrated with medication management, should include efforts to gain feedback on the efficacy of self-help and behavioral techniques in the context of the couple’s sexual relationship. Efforts should focus on reducing performance anxiety and bolstering the patient’s self-esteem and the couple’s communication.

In the broadest sense, managing PE not only has an impact on the patient’s mental well-being but fosters the health of his most important relationship. As is true with treating any sexual dysfunction, this compassionate approach reaches into the well-being of the family and beyond. If you do not think that your patient could have PE, you will not diagnose it.

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# Interstitial cystitis/painful bladder syndrome: Symptom recognition is key to early identification, treatment

## ■ ABSTRACT

Once thought to be rare, interstitial cystitis (IC) is now believed to have a markedly higher prevalence. This potentially devastating disease is also known as painful bladder syndrome (PBS) and can significantly impact quality of life. It is diagnosed by its symptoms, as there are no proven pathological findings. Unfortunately, the symptoms of IC/PBS overlap those of other common disease states such as overactive bladder, endometriosis, urinary tract infection, and prostatitis, which complicates the differential diagnosis. Understanding the presenting symptoms of urinary frequency, urinary urgency, and pelvic pain in the presence of otherwise normal findings can enhance primary care providers' ability to appropriately identify the disease. Early identification may allow initiation of therapy or referral before the disease becomes refractory to standard treatment, which typically includes behavioral therapy and possibly multimodal drug therapy.

## ■ DEFINITION OF THE CONDITION

Interstitial cystitis (IC) is a chronic condition defined by its symptoms of urinary frequency, urgency, pelvic pain relieved with voiding, nocturia, and dyspareunia.<sup>1-3</sup> The International Continence Society advocates use of the term "painful bladder syndrome" (PBS), which it defines as "the complaint of suprapubic pain related to bladder filling, accompanied by

other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology."<sup>4</sup>

## ■ PREVALENCE AND SOCIAL IMPLICATIONS

### More common than previously appreciated

In the past, the prevalence of IC/PBS was seemingly low, likely because the diagnosis was based on a very restrictive and possibly inappropriate standard.

Historically, the diagnosis of IC hinged on a classic triad of factors: (1) symptoms, (2) the absence of any identifiable causes, and (3) the presence of bladder lesions on cystoscopy.<sup>5</sup> Using this historical definition, the prevalence of IC/PBS was generally less than 0.1%. The reality is that cystoscopic findings are not always present in the patient with IC/PBS and that bladder lesions, if present at all, might be found only in advanced cases. This overly restrictive requirement may lead to misdiagnosis of patients presenting in the early stages of IC/PBS, resulting in a missed opportunity for earlier identification and treatment.

Today, most would agree that IC/PBS is a symptom-based disease and that its prevalence is markedly higher than 0.1%. Leppilähti et al surveyed 1,000 Finnish women and found a prevalence of 0.45%.<sup>6</sup> Although this study was pivotal in that the authors used a symptom score to detect prevalence, they chose the O'Leary Sant symptom and problem indices, which are intended not for screening but for monitoring response to therapy.<sup>7</sup>

A recent study by Rosenberg and Hazzard<sup>8</sup> challenged the findings from the Finnish study. They administered the pelvic pain and urgency/frequency patient symptom (PUF) scale, a validated screening tool (Table 1),<sup>9</sup> in addition to the O'Leary Sant indices (Table 2) in a comparable group of 1,218 women in a primary care practice setting. The prevalence of IC/PBS was 0.57% with the O'Leary Sant indices and 12.6% with the PUF scale. The true prevalence may fall somewhere between these extremes.<sup>8</sup>

\* **Dr. Rosenberg** reported that he has received consulting fees and honoraria from Indevus Pharmaceuticals/ESPRIT Pharma, Pfizer, and GlaxoSmithKline for consulting, teaching/speaking, and serving on advisory committees; honoraria and consulting fees from Verathon Medical for consulting and serving on advisory committees; honoraria from Eli Lilly and Auxilium Pharmaceuticals for teaching/speaking; a research grant from Sanofi-Aventis; and consulting fees and honoraria from Ortho-McNeil for consulting and teaching/speaking. **Ms. Newman** reported that she has received honoraria from Watson Pharmaceuticals, Pfizer, Astellas Pharma, GlaxoSmithKline, Novartis, and SCA Personal Care for teaching/speaking, as well as for serving on an advisory committee (for Watson) and for consulting (for SCA Personal Care). **Ms. Page** reported that she has no financial relationships that pose a potential conflict of interest with this article.

**TABLE 1**  
**Pelvic pain and urgency/frequency patient symptom (PUF) scale<sup>9</sup>**

	Points					Symptom score	Bother score
	0	1	2	3	4		
1 How many times do you go to the bathroom during the day?	3–6	7–10	11–14	15–19	20+	_____	
2 a) How many times do you go to the bathroom at night?	0	1	2	3	4+	_____	
b) If you get up at night to go to the bathroom, does it bother you?	Never	Occasionally	Usually	Always			_____
3 Are you currently sexually active? Yes _____ No _____							
4 a) If you are sexually active, do you now have or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always		_____	
b) If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always			_____
5 Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes, or scrotum)?	Never	Occasionally	Usually	Always		_____	
6 a) If you have pain, is it usually...		Mild	Moderate	Severe		_____	
b) Does your pain bother you?	Never	Occasionally	Usually	Never			_____
7 Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always		_____	
8 a) If you have urgency, is it usually...		Mild	Moderate	Severe		_____	
b) Does your urgency bother you?	Never	Occasionally	Usually	Always			_____
<b>Symptom score (1, 2a, 4a, 5, 6a, 7, 8a)—Subtotal</b>						_____	
<b>Bother score (2b, 4b, 6b, 8b)—Subtotal</b>							_____
<b>Total score* (Symptom score + Bother score)</b>						_____	

\*In the published assessment of the PUF scale by Parsons et al,<sup>9</sup> a total PUF score of 15 or greater was associated with an 84% likelihood of having a positive potassium sensitivity test, which is a strong predictor that interstitial cystitis may be present. In the authors' view, any PUF score greater than 5 warrants further investigation into a patient's symptoms.  
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As part of a separate exploratory prevalence study, Rosenberg and Hazzard screened 3,883 asymptomatic men and women using the PUF scale.<sup>10</sup> Subjects were excluded if they had prior genitourinary surgery or radiation therapy or a prior diagnosis of IC or PBS. The prevalence of IC/PBS in this population was 13.1%, and was twice as high among women as among men.<sup>10</sup>

These findings strongly suggest that physicians should more frequently consider IC/PBS in the differential diagnosis of patients who present with pelvic/bladder pain and urinary urgency and frequency.

### Urgency can progress to debilitating pain

As the disease progresses, the social implications of IC/PBS can be devastating. Initially, the patient has urinary urgency, urinary frequency, and mild pain.

These symptoms, which overlap other disease states, frequently lead to multiple physician visits and numerous misdiagnoses. Over time, IC/PBS can become debilitating as the patient is voiding with tremendous frequency (up to several times an hour) simply to relieve the pain. The result can be marked limitations on the patient's lifestyle and professional life.

With disease progression, the severity of dyspareunia may interfere significantly with intercourse and sexual intimacy. Patients with IC/PBS are five times more likely to be treated for emotional disorders than those without the disease.<sup>11</sup>

IC/PBS has the dubious distinction of possessing a disability code, which indicates how severely it can affect patients' lives

Not every patient will suffer the refractory, debilitat-



**TABLE 2****O'Leary Sant indices for symptoms and quality-of-life effects of interstitial cystitis/painful bladder syndrome****Section A: Urinary symptoms**

- A1. During the past month, how often have you:
- Had a burning feeling when you urinate?
  - Felt the strong need to urinate with little or no warning?
  - Had to urinate again within 10 minutes of urinating?
  - Had to urinate again less than 2 hours after you finished urinating?
  - Found it difficult to postpone urination?
- A2. Over the past month, in a typical day, about how many times did you urinate from the time you got up until the time you went to bed at night?
- A3. Over the past month, once you had the urge to urinate, how long could you usually wait comfortably before going to the bathroom?
- A4. Over the past month, how many times did you most typically get up at night?
- A5. Over the past month, how many times did you most typically get up at night to urinate?
- A6. Over the past month, when you did urinate at night, were you:
- Mostly awakened by the need to urinate?
  - Mostly awake already for other reasons?
- A7. Over the past month, how often did you leak or drip urine before you could reach the bathroom?
- A8. Over the past month, did you ever drip or leak urine:
- When you were running or doing vigorous exercise?
  - When you coughed, laughed, or sneezed?
  - When you were walking fast or walking up the stairs?
  - When you stood up from a chair?
  - When you were lying down or sleeping?

**Section B: Pain symptoms**

- B1. During the past month, how often have you experienced pain in your bladder? Was that pain or burning relieved by urinating?
- B2. During the past month, how often have you experienced any kind of discomfort or pressure in your bladder? Was that discomfort or pressure relieved by urinating?
- B3. During the past month, have you experienced:
- Pain or burning in your urethral area?
  - Discomfort or pressure in your urethral area?
  - Pain in your pelvis or lower abdomen?
  - A dull pain in the middle of your lower back?

**Section C: Sexual function**

- C1. Over the past month, how would you rate your level of sexual interest?
- C2. Over the past month, have you had any kind of sexual activity (ie, intercourse, masturbation)?
- C3. Over the past month, how often have you experienced pain or discomfort while having sexual intercourse?

**Section D: General health**

- D1. Thinking back, how long have you had urinary symptoms?
- D2. Over the past month, how did stress affect your urinary symptoms?
- D3. Thinking back, how long have you had any other symptoms of pain, burning, or discomfort?

**Section E: Symptom relationship with menstrual cycle**

- E1. Have you been pregnant in the past 12 months?
- E2. During the past 12 months, have you had any menstrual periods at all? How were your urinary symptoms affected when you stopped having periods?
- E3. How are the following affected during your menstrual period?
- Frequent urination
  - Pain or pressure in your bladder, lower abdomen, or urethral area
  - A dull pain in the middle of your lower back
  - Pain or discomfort while having sexual intercourse
  - Feeling tired

**Section F: Quality of life**

- F1. During the past month, how much has each of the following been a problem for you?
- A burning feeling when you urinate
  - Frequent urination during the day
  - Getting up at night to urinate
  - Need to urinate with little warning
  - Burning, pain, discomfort, or pressure in your bladder or urethral area
  - Pelvic pain or discomfort
  - Getting enough sleep
  - Concern about being too far away from the bathroom
  - Embarrassment about going to the bathroom too often
  - Concern about your sexual functioning
- F2. During the past month:
- Has your urinary condition kept you from doing the kinds of things that you would usually do?
  - Has your urinary condition limited your ability to take part in light sports, such as swimming or bowling?
  - Has your urinary condition limited the kinds of vigorous activity that you can do, such as running or participating in strenuous sports?
  - Has your urinary condition interfered with your normal social activities?
  - Has concern about your sexual functioning been a problem for you?
  - Has your urinary condition affected your mood?
  - Has your urinary condition caused you to worry about your health?
  - Has your urinary condition affected your sleep?
- F3. If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?

Reprinted from O'Leary et al,<sup>7</sup> copyright 1997, with permission from Elsevier Inc.

ing course that IC/PBS can potentially create. As primary care providers recognize the true prevalence of the disease, it is hoped that more patients will receive timely and appropriate treatment.

## ■ PATHOGENESIS

### Glycosaminoglycan disruption may be the key

The etiology of IC/PBS is not established and is controversial. Most literature supports the belief that its symptoms are associated with abnormal permeability of the epithelium in the lower urinary tract. Normally, the bladder epithelium is coated with a protective mucin layer that contains glycosaminoglycan (GAG).<sup>12</sup> Disruption of this normally impermeable structure allows penetration of the underlying urothelium by potentially caustic agents in the urine, thereby affecting nerves and muscles in the bladder wall.<sup>13,14</sup> This process of nerve and muscle irritation will lead to the IC/PBS symptoms of urgency, frequency, and pain. The cause of initial injury to the GAG layer is unknown.

Supportive evidence for the role of a dysfunctional and irritated GAG layer in the pathogenesis of IC was recently provided with the identification of antiproliferative factor (APF).<sup>15</sup> APF is a glycosylated frizzled-related peptide inhibitor of cell proliferation that is secreted by the epithelial cells in patients with IC/PBS. It is believed that APF inhibits repair of the GAG layer and normal turnover of the urothelium. APF has been heralded as a possible future marker of IC/PBS.

It has been proposed that irritation of the GAG layer initiates an inflammatory response, which in turn leads to further disruption (Figure 1).<sup>16</sup> This model is particularly helpful in identifying the various targets for multimodal treatment of IC/PBS, which includes both repair of the disrupted GAG layer and stabilization of the inflammatory response.

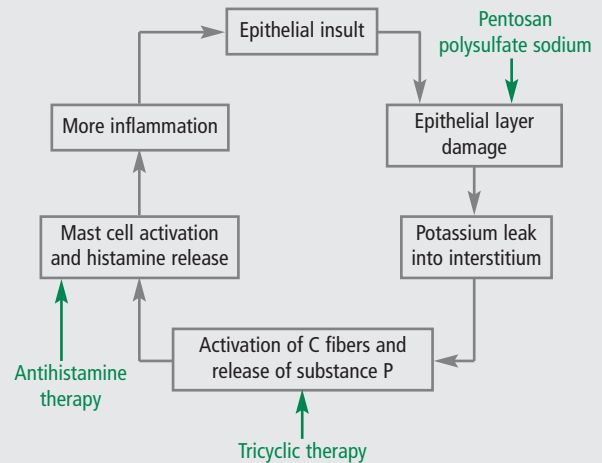
### Other theories

Other theories on the pathogenesis of IC/PBS have been proposed,<sup>17</sup> but the weight of evidence currently favors the GAG theory. Other factors—such as lymphatic, infectious, neurogenic, autoimmune, hormonal, and vasculitic components—have been investigated, but no studies have determined a role for any of these.<sup>18</sup> Many believe that there may be a genetic component to IC/PBS, and this possibility is the subject of several ongoing studies.

## ■ PRESENTING SYMPTOMS

The classic symptoms of IC/PBS are a combination of urinary frequency, urinary urgency, nocturia, and blad-

### Etiology of IC/PBS and the role of multimodal therapy



Adapted from Evans<sup>16</sup> with permission from MedReviews, LLC. Copyright 2002.

**FIGURE 1.** Proposed model for the pathogenesis of interstitial cystitis/painful bladder syndrome (IC/PBS), along with various therapies targeted at different points in the pathogenic process.

der or pelvic pain that may be temporarily relieved by voiding. These symptoms may progress from mild and intermittent to severe and constant. Voiding is usually but not always involved, so that in the occasional patient the pain may not be perceived as being generated from the bladder, which can misdirect the diagnosis away from the urinary tract. As a result, the clinician may be misled to think of processes other than IC/PBS, such as endometriosis, vulvodynia, vaginitis, or prostatitis.

### Diagnosis often lags symptom onset by years

On average, the patient with IC/PBS has had the disease for more than 7 years before actual diagnosis.<sup>2</sup> Typically patients are in their 20s to 40s at the time of diagnosis. As children, many of these patients were labeled incorrectly as having frequent urinary tract infections (UTIs) or pelvic pain of unknown etiology.

Urinary frequency is a common initial symptom. Some patients report that they void up to 15 times per day. Urgency and pain generally develop next.<sup>1</sup> As the disease progresses, it is thought that the GAG layer becomes more permeable, increasing the proportion of unprotected urothelium that is exposed to the caustic solutes in the urine. This exposure, in turn, initiates neurogenic upregulation and provokes a pain response.<sup>19</sup> A significant difference in presentation between patients with overactive bladder and

patients with IC/PBS is that the former void frequently for fear of urine leakage, whereas the latter void frequently to relieve pain.

The patient with IC/PBS generally will present with pain (pelvic or bladder) as the most bothersome symptom. A frequent component of the pelvic pain is dyspareunia, which has been reported to occur in 63% of women with IC/PBS.<sup>1</sup> Although similar incidence data are not available for men, pain with sexual activity is common in both men and women with IC/PBS (Table 3).<sup>20–22</sup>

### Note history and patterns of symptom onset

The history of symptom onset is another clue in unraveling the disease. Patients will often recall that their symptoms generally occur in patterns of flares and remissions. The flares may last for several days and can be triggered by diet, allergies, stress, and sexual activity.<sup>4</sup> Women will note this exacerbation of symptoms during the premenstrual week.

Flares are frequently misdiagnosed—and mistreated—as recurrent UTIs or prostatitis. Since the flare will generally resolve, clinicians often can be fooled that antibiotic therapy worked when in fact the resolution of symptoms was merely part of the disease's natural pattern. It is the recurrence of flares and the lack of identified microbes that should draw attention.

Interestingly, nearly 12 million primary care office visits per year result in the diagnosis of a UTI, yet urine culture results are negative in nearly half of these cases.<sup>23</sup>

Prostatitis is a common diagnosis in men who present with symptoms of urinary urgency, frequency, and pain. Rarely, however, do these patients have an identifiable bacterial cause of their symptoms, and most are not helped by a prolonged course of antibiotics.<sup>24–26</sup>

## EVALUATION

The initial evaluation of IC/PBS starts with a detailed history of symptoms. Generally, the patient will note the onset of urinary urgency and frequency years before the onset of discomfort. Pain, which is relatively minor initially, becomes more prominent as the disease progresses. In fact, pain is generally what brings patients to the physician's office, since they usually adapt to urgency and frequency.

### Surveys to assess symptoms

As mentioned earlier, two surveys are used commonly to assess the symptoms of IC/PBS—the O'Leary Sant indices and the PUF scale.<sup>7,9</sup> The O'Leary Sant indices (Table 2) were developed for monitoring progress following treatment. The PUF scale (Table 1) was designed for screening. Patients with multiple and more

pronounced symptoms will have higher PUF scores and, consequently, a greater likelihood of IC/PBS.

Clinicians should keep in mind that surveys and questionnaires can never diagnose a disease but rather should be viewed as a tool in the decision-making process. Further, a survey may not always be practical for the busy clinician, in which case a few questions regarding the symptoms of urgency, frequency, nocturia, or pain will provide a good starting point.

### No specific physical findings

No physical findings are specific to the patient with IC/PBS; however, many have noted exquisite tenderness at the bladder neck in both men and women. In men, this trigger point is at the perineum between the anus and scrotum; in women, it is at the anterior vaginal wall near the urethral orifice. Women with severe IC/PBS pain will report discomfort, pain, or both upon vaginal examination.

### Laboratory tests play an exclusionary role

There are no laboratory findings that will identify IC/PBS. It is paramount, however, to exclude diseases that have similar symptoms, such as diabetes or UTI. A blood glucose test and a urinalysis are generally sufficient to rule out these processes. The need for urine cytology is frequently mentioned in the literature as a consideration in high-risk patients (eg, smokers) in order to rule out carcinoma. Urine cytology should certainly be performed for any patient with hematuria.

### Further testing to support the diagnosis

With supportive information from the patient's symptoms, and in the absence of physical or laboratory abnormalities, treating for IC/PBS would not be unreasonable. However, there are further tests to isolate the bladder as the source of symptoms, and these may offer the patient and provider a greater degree of comfort. The typical patient with IC/PBS has gone from physician to physician for several years and has received myriad diagnoses. Educating patients by providing further evidence that IC/PBS is the problem is essential to initiating treatment and seeing it through to success.

Two tests that involve bladder catheterization can be helpful in this regard: the potassium sensitivity test and the anesthetic bladder challenge.

The potassium sensitivity test (PST) is based on the premise that potassium in the urine plays a major role in provoking symptoms in the patient with a defective GAG layer. When potassium is instilled into the bladder of a patient with suspected IC/PBS, it may induce the symptoms. Potassium will follow the osmotic gradient from the bladder, where its con-

centration is high, to the interstitium, where its concentration is low. Normally, this movement is blocked by the impermeable GAG layer. Parsons et al showed that potassium did not provoke symptoms of urgency and pain in healthy subjects unless the bladder mucosa had been injured with protamine.<sup>27</sup> The actual PST procedure assesses the symptoms induced when 40 mL of a solution of potassium chloride (0.4 mol/L) is instilled into the bladder in comparison with the symptoms induced by 40 mL of water.<sup>28</sup>

The correlation between PST results and symptom-defined IC/PBS has been documented in numerous studies.<sup>29</sup> In one primary care study, the PST was used to evaluate 188 patients who had PUF scores of 5 or greater. Of these patients, 166 had a positive result on the PST, whereas the PST results of 26 controls (with a PUF score of 0) were all negative.<sup>30</sup>

Although the utility of the PST is well documented in the literature,<sup>29</sup> it is still the subject of debate. One concern is that the PST measures the response to provoked pain. However, when properly performed, it is well tolerated.<sup>31</sup>

**The anesthetic bladder challenge (ABC)** is an alternative to the PST.<sup>32</sup> It can be useful if the patient has active discomfort and the physician is attempting to determine if the origin of the pain is the bladder. The procedure entails intravesical administration of lidocaine and bicarbonate (to promote absorption of the lidocaine). The lidocaine is absorbed as a result of the disrupted urothelium. (This procedure is also used as treatment, as explained later.) If the instillation results in dissipation of symptoms, then one can be comfortable that the bladder is involved.

It is essential to note that the PST and the ABC are tools to assist in identifying a potential bladder origin for the symptoms of IC/PBS but that they do not confirm the disease. Because these tests involve catheterization, they may not be practical for all primary care providers. For those not comfortable performing the PST, assessment for anterior vaginal wall pain on physical examination may be a reasonable alternative, as a recent study showed a positive PST to be significantly correlated with such pain.<sup>33</sup>

### No consistent pathological findings

There is no pathological finding consistent with IC/PBS. Glomerulations (pinpoint-size petechial hemorrhages in the bladder), long thought to be the hallmark of the diagnosis, have been found equally in controls and IC/PBS sufferers. As a result, there is no diagnostic role for cystoscopy or bladder hydrodistension under anesthesia (distending the bladder well

**TABLE 3**  
Symptoms that should prompt consideration of interstitial cystitis/painful bladder syndrome (IC/PBS)\*

Pelvic and/or bladder pain—most patients with IC/PBS present with pain that is relieved upon voiding
Dyspareunia/pain with or following sexual intimacy (during vaginal penetration in women and upon orgasm and ejaculation in men)
Frequent symptoms that suggest urinary tract infection without microbes being identified
Frequent symptoms that suggest vaginitis
Urinary frequency or urgency with pain relieved by voiding
Nighttime urination with or without pain (generally two or more voids per night)

\* Any of these symptoms may indicate IC/PBS; not all need be present.

above normal capacity, thereby stretching the mucosal and nerve fibers), although these procedures may have a role in treatment of the patient with refractory IC/PBS, as stretching of the bladder can offer temporary (3 to 6 months) relief from pain.

Office cystoscopy alone has a place in the evaluation only if hematuria or a positive cytology is noted during laboratory testing. Urodynamics have a role only if another process, such as detrusor overactivity, needs to be excluded. Caution is warranted, however, as the findings of urodynamic testing may not be specific to a disease process.

### DIFFERENTIAL DIAGNOSIS

Symptoms suggestive of IC/PBS are listed in **Table 3**. However, when the clinician encounters the symptoms of pelvic pain, urgency, and frequency, the differential diagnosis can be quite extensive. The hierarchy of diagnosis may well depend on the clinician's specialty. The gynecologist, for example, may focus on endometriosis, pelvic inflammatory disease, vulvovaginitis, or UTI. The urologist may think UTI, overactive bladder, or prostatitis.

The key is to focus on the history and listen to the patient, as the assessment must make logical sense. If recurrent UTI is diagnosed, then a urine culture should be positive. The same rule applies to pelvic inflammatory disease. The diagnosis of prostatitis may not require a culture, but if the disease does not respond to therapy after a reasonable time (1 to 3 months), then another diagnosis should be entertained (for more information, see the article on pros-

tatitis in this supplement). If symptoms presumed to be due to overactive bladder are not responsive to antimuscarinics, then the diagnosis must be reconsidered. Endometriosis is certainly a common diagnosis; however, it has been shown to coexist with IC/PBS, the degree of pain does not correlate with the degree of endometriosis, and surgical treatment consisting of hysterectomy and oophorectomy does not always resolve the pain.<sup>34,35</sup>

### ■ TREATMENT

#### Nonpharmacologic therapy is the cornerstone

Conservative or behavioral therapy is the cornerstone of treatment for the patient with IC/PBS. It involves educating patients about symptoms, behavior modification for urinary urgency and frequency, physical therapy for trigger point release, stress reduction, and dietary manipulation.

Certain foods, especially those rich in potassium, can cause bladder irritation. Foods commonly thought of as irritants include tomatoes, chocolate, citrus fruits and juices, coffee, alcohol, and carbonated beverages. The list can be fairly exhaustive, and each patient will respond differently. To help identify offending foods, a patient can be advised to keep a diary of foods consumed and symptoms that may result. A list of potentially aggravating foods can be found on the Web site of the Interstitial Cystitis Network ([www.painfulbladder.com/handbook/](http://www.painfulbladder.com/handbook/)).

Although it remains unclear whether stress is a precipitant or consequence of IC/PBS, alleviation of stress may help control symptoms or help patients cope with them.<sup>36</sup>

#### Multimodal pharmacologic approach

The goals of pharmacologic therapy for IC/PBS are to restore bladder surface integrity, modulate neuronal dysfunction, and reduce any coexisting inflammation. These goals can be achieved by targeting the specific points in the postulated cycle of the disease (Figure 1) with a multimodal pharmacologic approach.<sup>16</sup>

**Pentosan polysulfate sodium (PPS)**, the only oral medication currently approved by the US Food and Drug Administration (FDA) for the treatment of IC, provides the bladder with a compound structurally analogous to the GAG layer.<sup>37</sup> Although its mechanism of action is unknown, it is believed to facilitate restoration of the defective layer, thereby preventing further urothelial insult.<sup>38</sup> The approved dose of PPS is 100 mg three times per day. Unfortunately, patients may be slow to respond to PPS, as it sometimes takes several months before any relief is noted. Treatment

with PPS should continue for at least 6 months.

**Hydroxyzine.** To suppress mast cell degranulation, which is part of the inflammatory response, the addition of the oral antihistamine hydroxyzine is recommended. Hydroxyzine is unique among antihistamines in its ability to bring about this specific suppression.<sup>39</sup> Dosing starts at 25 mg, given at bedtime, and may increase to 50 to 100 mg/day during the allergy season.

**Amitriptyline**, an oral tricyclic antidepressant, is used in the IC/PBS patient to regulate pain and urgency in the bladder by modulating neuronal dysfunction. An additional benefit may be its antihistaminic properties. In an early study, amitriptyline (25 to 75 mg/day taken nightly) provided mild to moderate central pain modulation in 60% to 90% of patients with IC/PBS.<sup>40</sup> A recent placebo-controlled, double-blind study showed amitriptyline to be safe and effective in patients with IC/PBS for up to 4 months.<sup>41</sup>

The studies of oral medications for the IC/PBS sufferer have generally shown benefit, although a few have shown mixed results. This lack of uniformity may be due, in part, to the confusion surrounding the diagnosis of IC/PBS and the previously restrictive diagnostic criteria, which tended to isolate patients with very severe, possibly refractory, disease that may not respond to conservative therapy. As a recent example, the combination of PPS and hydroxyzine was not found to be helpful in a group of patients with IC/PBS,<sup>42</sup> but this small cohort had fairly refractory disease as a result of the study's inclusion criteria.

In contrast, in a study in which patients were screened for the disease based on symptoms, initiation of PPS and hydroxyzine therapy early in the disease process was associated with improved outcomes.<sup>43</sup> This study compared outcomes between patients who had symptoms for less than 1 year and patients with symptoms for more than 1 year, finding a faster response to therapy in the former group. It is not unreasonable to conclude that early identification and intervention will result in more efficacious treatment; however, whether outcomes are improved with early intervention has not yet been proven and will need to be studied further.

The practice of triple therapy (with PPS, hydroxyzine, and amitriptyline) is speculative. We know how each medication functions in the treatment of IC/PBS, so it is thought that some patients may require all modalities.

#### Other medications and pharmacologic approaches

Other medications may be appropriate, depending on a patient's symptoms and response to therapy. Anti-

muscarinics may alleviate urgency and frequency but will not relieve pain associated with these symptoms. Phenazopyridine may subdue irritation and pain in the lower urinary tract. Judicious and responsible use of analgesics, including narcotics, may be appropriate in some cases.

Instillation therapy, which targets the bladder directly, offers another level of IC/PBS treatment for the experienced clinician. Intravesical dimethyl sulfoxide (DMSO) has been approved by the FDA for the relief of IC/PBS symptoms; unlike PPS, however, it does not address the deficient GAG layer.

Fairly recent additions to the armamentarium for IC/PBS include novel instillation therapies that use a combination of sodium bicarbonate, lidocaine, and heparin. The sodium bicarbonate allows neutralization, thereby facilitating absorption of the lidocaine, which in turn provides pain relief. Intravesical heparin is thought to play a role in restoration of the dysfunctional mucin layer.<sup>44</sup>

### Surgical options for refractory patients

Investigation of the use of implanted neurostimulators to reduce IC/PBS-associated pain is ongoing.<sup>45</sup> Although the role of surgery is quite limited, cystectomy with urinary diversion may be considered in refractory patients who have no other options.

### ■ APPROPRIATE FOLLOW-UP

Follow-up for patients with IC/PBS can be challenging. These patients have frequently had symptoms for an extended time and usually have received many different diagnoses. They may have become disillusioned with the health care community and wary of new treatments. Not uncommonly, patients have been told that their symptoms were “in their head,” which further alienates them from providers.

Follow-up at 1-month intervals for the first 3 months and then every 3 months thereafter offers an opportunity to monitor patients' progress and address their concerns. Since symptoms may be slow to respond, encouraging treatment compliance is important. The O'Leary Sant indices (Table 2)<sup>7</sup> are a useful tool for following these patients.

### ■ WHEN TO REFER

When to refer the patient with IC/PBS depends on the comfort level of the provider. Some choose to refer upon identifying symptoms, whereas others may be comfortable with further evaluation, including the PST or ABC. Helping the patient is crucial, all the while understanding the limits of one's own abilities.

Specific findings during the evaluation that should trigger referral include hematuria, chronic UTI, pyuria, intractable pain, and confusing symptoms. If the primary care provider has initiated treatment and the symptoms do not respond after a reasonable amount of time (3 to 6 months), then further evaluation and consultation is appropriate. During this consultation, the patient can generally expect further tests, including cystoscopy and possibly urodynamic evaluation.

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# Prostatitis: Infection, neuromuscular disorder, or pain syndrome? Proper patient classification is key

## ■ ABSTRACT

Prostatitis is a broad term used to describe inflammation of the prostate that may be associated with a myriad of lower urinary tract symptoms and symptoms of sexual discomfort and dysfunction. The condition affects 5% to 10% of the male population and is the most common urologic diagnosis in men younger than 50 years. Prostatitis is classified into four categories, including acute and chronic bacterial forms, a chronic abacterial form, and an asymptomatic form. The bacterial forms are more readily recognized and treated, but symptoms in most affected men are not found to have an infectious cause. Indeed, chronic abacterial prostatitis (also known as chronic pelvic pain syndrome) is both the most prevalent form and also the least understood and the most challenging to evaluate and treat. This form of prostatitis may respond to non-prostate-centered treatment strategies such as physical therapy, myofascial trigger point release, and relaxation techniques. Because the various forms of prostatitis call for vastly different treatment approaches, appropriate evaluation, testing, and differential diagnosis are crucial to effective management.

## ■ DEFINITION OF THE CONDITION

Prostatitis is defined as painful inflammation of the prostate that is often associated with lower urinary tract symptoms (LUTS), such as urinary burning, hes-

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## National Institutes of Health classification system for prostatitis

**Category I:** Acute bacterial prostatitis

**Category II:** Chronic bacterial prostatitis

**Category III:** Chronic abacterial prostatitis/chronic pelvic pain syndrome, which is subdivided into IIIA (inflammatory) and IIIB (noninflammatory) disease

**Category IV:** Asymptomatic prostatitis (histologic or andrologic diagnosis)

itancy, and frequency, as well as with sexual dysfunction or discomfort, including erectile dysfunction, painful ejaculation, and postcoital pelvic discomfort; adverse sexual effects are reported in approximately half of men with prostatitis.<sup>1,2</sup>

The International Prostatitis Collaborative Network and the National Institutes of Health (NIH) have established a classification system for prostatitis.<sup>3</sup> The system's four categories, which are outlined in the sidebar above, describe acute and chronic infectious forms (NIH categories I and II) as well as the more prevalent forms that have not been correlated with infectious etiologies (NIH categories III and IV).

This article places particular emphasis on NIH category III, chronic abacterial prostatitis/chronic pelvic pain syndrome (CPPS), as it is both the most common form of prostatitis and the most challenging to evaluate and treat. Because NIH category IV prostatitis describes an asymptomatic form of this inflammatory disease, it is a diagnosis unlikely to be addressed in the primary care setting and is therefore addressed only briefly here.

## ■ PREVALENCE AND SOCIAL IMPLICATIONS

Population-based estimates of the prevalence of prostatitis in the general male population range from 5% to 10%.<sup>4,5</sup> In one study of health care professionals, the



self-reported incidence of prostatitis was approximately 16%.<sup>6</sup> Prostatitis is the most common diagnosis coded in outpatient urologic consultations in men younger than 50 years.<sup>7</sup> However, bacterial prostatitis represents merely 5% to 10% of cases.<sup>8</sup> Recent international collaborations reveal comparable estimated prevalence rates in other populations, including in Europe and Asia.<sup>9</sup>

Chronic prostatitis has substantial economic impact. Men in the United States with chronic prostatitis incur direct and indirect costs averaging more than \$4,000 annually, which is significantly greater than the annual medical costs associated with a number of other pain-related conditions frequently encountered in primary care settings.<sup>10</sup>

### ■ PATHOGENESIS

Although prostatitis is a relatively common urologic diagnosis, little is known about the pathogenesis of its most common form, chronic abacterial prostatitis/CPPS (NIH category III). Indeed, prostatitis experts have noted that NIH category III prostatitis has yet to be proven an infectious disorder or even a malady of the prostate itself.<sup>3</sup>

#### Acute bacterial prostatitis

Infection of the prostate occurs when bacteria-laden urine from the urethra refluxes into the intraprostatic ducts. Most of the infectious agents are from the Enterobacteriaceae family, specifically *Escherichia coli* and *Klebsiella* or *Proteus* species. These bacteria reflect the spectrum of organisms known to cause urethritis, urinary tract infection, or deeper genital infections. Other causative agents include *Enterococcus*, *Pseudomonas*, and *Staphylococcus* species as well as gonococcal organisms.

Recent catheterization, cystoscopy, or other instrumentation of the urinary tract may be a precipitating event. Urethral strictures caused by prior urethritis (typically as a result of gonococcal infection) can also increase the likelihood of infection. Risk of infection is increased in patients with impaired host defenses (eg, due to diabetes or human immunodeficiency virus infection). Men with spinal or neurologic disorders that impair the detrusor or pelvic floor musculature may be at higher risk. Other purported risk factors, such as trauma due to bicycle riding, sexual abstinence, and dehydration, have not been supported by well-controlled studies.

#### Chronic bacterial prostatitis

Chronic bacterial prostatitis is differentiated from acute prostatitis when bacteria continue to be isolated

in prostatic fluid, even after appropriate antimicrobial therapy. The organisms can be cultured and localized to the prostate even in the setting of normal midvoid urinalysis and negative midvoid urine cultures. Chronic bacterial prostatitis is not usually suspected until a man experiences recurrent urinary tract infections, although clinicians must also consider persistent primary infections that were inadequately treated.

In contrast, chronic *abacterial* prostatitis is diagnosed when symptoms of pelvic or genital discomfort with or without LUTS persist for greater than 3 months in the setting of negative localized urine cultures.

Chronic bacterial prostatitis is more common in men older than 50 years and should be suspected when a man has *recurrent* urinary tract infections as proven by urine cultures. Risk factors are similar to those for acute bacterial prostatitis. Instrumentation of the lower urinary tract may be considered a risk factor, as catheterization or endoscopy can be a vector for bacterial seeding or can cause urethral strictures that could lead to reflux of bacteria-laden urine from the urethra to the prostatic ducts. Repeated isolation of the same organism (with the same susceptibility profile) in urine cultures is considered the hallmark of chronic bacterial prostatitis.

#### Chronic abacterial prostatitis/CPPS

The pathophysiology of abacterial prostatitis remains an enigma. Theories abound, and include nanobacteria, elevated prostatic pressures, voiding dysfunction and bladder neck dyssynergia (nonrelaxation of the external urinary sphincter during urination), male interstitial cystitis, pelvic floor myalgia, functional somatic syndrome, and emotional disorders. It is helpful to review what has been proven or disproven thus far.

The presence or absence of inflammatory cells in the expressed prostatic secretions (EPS) differentiates chronic abacterial prostatitis into category IIIA (inflammatory) or IIIB (noninflammatory) disease. However, this distinction is merely historical, and white blood cell (WBC) counts have not been shown to correlate with symptoms or with the presence or absence of infection.<sup>11,12</sup> Moreover, the relevance of abnormal WBC counts in the EPS is questionable, given the prevalence of abnormal counts in the EPS of asymptomatic men. In one study, for instance, 122 asymptomatic men underwent prostate massage for the retrieval of EPS during urologic consultation for elevated prostate-specific antigen (PSA) levels, and 42% of these asymptomatic men had abnormally elevated WBC counts in their EPS specimens.<sup>13</sup>

It has not been possible to histologically confirm a correlation between prostatitic inflammation and

symptoms. Histologic evidence of acute and chronic inflammation is identified in prostate pathology specimens with increasing prevalence over time, and the rate of identification can be as high as 90%. In a study of asymptomatic men without a history of chronic prostatitis, transrectal prostate biopsy (performed to evaluate elevated PSA levels) revealed inflammation in 50%.<sup>13</sup> However, in a separate study evaluating symptomatic men previously diagnosed with chronic abacterial prostatitis/CPPS, only 5% of cases demonstrated significant levels of inflammation by histology.<sup>14</sup> The tremendous discord between the findings of these two studies<sup>13,14</sup> underscores the importance of extending our focus beyond the prostate when evaluating men with symptoms traditionally attributed to an infected prostate.

Likewise, microbiologic studies do not support an infectious etiology. No correlation has been seen between symptom severity and the results of cultures to localize the area of infection with the Meares–Stamey 4-glass test.<sup>15</sup> (The 4-glass test involves collection of sequential urine specimens before and after prostate massage and of prostatic fluid during prostate massage.<sup>16</sup>) One large study found that normal controls were just as likely as men with chronic prostatitis to have positive localization cultures (incidence of 8% in both groups).<sup>17</sup> A randomized, placebo-controlled trial showed that 6 weeks of levofloxacin therapy for chronic prostatitis yielded no advantage over placebo,<sup>18</sup> and a subsequent trial found that neither ciprofloxacin, the alpha-blocker tamsulosin, nor their combination reduced symptoms of chronic prostatitis compared with placebo.<sup>19</sup>

Nickel et al followed 100 patients with chronic prostatitis over 1 year, during which time they received sequential monotherapies that included antibiotics, alpha-blockers, and antiandrogen therapies.<sup>20</sup> One third of patients showed modest symptom improvement, but only 19% experienced significant improvement (patients were not characterized in terms of NIH IIIA or IIIB subcategories).<sup>20</sup> One might argue that this response rate is even less than the expected placebo response, which begs the question, What are we really treating?

### Asymptomatic prostatitis

The diagnosis of prostatitic inflammation can be made in asymptomatic patients as well. Such cases are usually identified in men who present because of infertility or are identified incidentally, through histologic findings obtained through biopsy or prostatectomy.

Initial evaluations for male infertility involve

exclusion of genitourinary tract infections; however, many patients have no evidence of infection. Still, these patients may exhibit abnormally high WBC counts in the semen (leukocytospermia) or abnormally high levels of reactive oxygen species and oxidative stress. Although leukocytospermia is a known cause of oxidative stress, oxidative stress can be detected in the absence of high WBC counts.<sup>21</sup>

In the second setting, acute or chronic inflammation is detected in pathology specimens obtained through prostate biopsy performed to detect prostate cancer, transurethral resection of the prostate to relieve obstructive uropathy, or prostatectomy for treatment of benign prostatic hyperplasia or removal of cancer. This finding of inflammation is not uncommon, as it is seen in 50% of prostate biopsy specimens and as many as 90% of prostatectomy specimens.<sup>22</sup>

Because it is usually an incidental finding and is not correlated to symptoms, this form of prostatitis may not be considered clinically relevant. However, inflammatory changes within the prostate architecture may be the cause of PSA elevation, leading to false-positive readings and potentially unnecessary biopsies.<sup>11</sup> In one study, for instance, prospective detection of inflammation via examination of EPS before prostate biopsy (> 10 WBCs per high-power field), followed by 4 weeks of antibiotic treatment, led to normalization of PSA levels in 45% of patients.<sup>13</sup> It remains unclear, however, if this response was due to treatment of an underlying infectious process or to a nonspecific anti-inflammatory property of the antimicrobial agent.

Alternatively, interest is growing in the theory that inflammation may be a precursor to cancer, including prostate cancer. Investigators have noted that at least some high-grade prostatic intraepithelial neoplasias and early adenocarcinomas appear to arise from proliferative inflammatory atrophy. It is believed that inflammation and other environmental factors may lead to destruction of prostate epithelial cells, and increased proliferation may occur as a response to this cell death. The decreased apoptosis associated with these events may also be related to increased expression of Bcl-2, which is implicated in other malignant settings.<sup>23</sup> However, no data yet indicate a higher incidence of prostate cancer in patients previously diagnosed with specific NIH categories of prostatitis.

Additionally, a review of epidemiologic data has found prostatitis and sexually transmitted infections to be correlated with increased prostate cancer risk, and has likewise found intake of anti-inflammatory drugs and antioxidants to be correlated with decreased prostate cancer risk.<sup>24</sup>

### ■ PRESENTING SYMPTOMS

#### **Acute bacterial prostatitis: Fever and severe LUTS**

Patients presenting with acute bacterial prostatitis are usually febrile and suffering severe LUTS, specifically dysuria and urinary urgency, frequency, and hesitancy. At times, inflammation of the prostate can be so severe that patients present with urinary retention. Gross hematuria is not uncommon.

#### **Chronic bacterial prostatitis: Asymptomatic spells between urinary tract infections**

Men with chronic bacterial prostatitis are usually asymptomatic in between episodes of urinary tract infections; however, the organism can still be found and localized to the prostate. Episodes of urinary tract inflammation may occur with subtle LUTS but can also manifest with severe symptoms and urosepsis. Therefore, patients with chronic bacterial prostatitis may be at risk for recurrent urinary tract infections and bouts of acute prostatitis.

#### **Chronic abacterial prostatitis/CPPS: Think beyond the prostate**

Patients suffering from chronic abacterial prostatitis often complain of associated LUTS. Kaplan et al found that urodynamically proven voiding dysfunction is often misdiagnosed as prostatitis.<sup>25</sup> Other investigators have observed urodynamic abnormalities, including detrusor-sphincter pseudodyssynergia, which is characterized by nonrelaxation of the external urinary sphincter during urination. Normally, the external sphincter should exhibit relaxation during urination when sustained detrusor contraction takes place.<sup>26,27</sup> Although urodynamic testing has revealed voiding dysfunction previously diagnosed or misdiagnosed as prostatitis, clinicians must also consider these urodynamic abnormalities as components of the more accurately redefined and expanded diagnosis of chronic abacterial prostatitis/CPPS.

### ■ EVALUATION

#### **Acute bacterial prostatitis: Exam is revealing, infection is readily identified**

The history and physical examination are very revealing in acute bacterial prostatitis. A gentle digital rectal examination may reveal a soft, enlarged, boggy, and tender prostate. An overvigorous examination may cause undue pain and possibly increase the risk of bacteremia. If the gland is enlarged and abdominal examination shows a palpable or percussible bladder, urinary retention due to benign prostatic hyperplasia should be considered.

Infection is readily identified via a remarkable urinalysis demonstrating pyuria and organisms. Infection of the upper urinary tract may be differentiated from acute bacterial prostatitis by more prominent back pain and fewer or no LUTS. Blood cultures should be obtained to rule out bacteremia.

PSA testing is not recommended unless a nodule is present on digital rectal examination. Acute prostatitis can raise the PSA level, which often does not return to normal until 1 month after therapy; the free PSA remains low even 1 month after infection.<sup>28</sup>

One of the most serious complications of acute prostatitis is the formation of prostatic abscesses. Because catheterization of the urethra increases the risk of abscess formation, suprapubic catheterization is recommended in cases of associated urinary retention. Abscesses may be palpable during digital rectal examination but are typically identified by computed tomography (CT) in patients with persistent symptoms or fever.

Transrectal ultrasonography is not a routine part of the work-up for acute bacterial prostatitis.<sup>29</sup>

#### **Chronic bacterial prostatitis: Confirm with localization cultures**

Confirmatory tests for chronic bacterial prostatitis include localization cultures that involve retrieval of EPS via prostate massage (**Figure 1**), such as the Meares-Stamey 4-glass test.<sup>16</sup> A simplified version of the 4-glass test is the "Pre and Post Massage Test" (2-glass test) popularized by Nickel.<sup>30</sup> It involves culturing a midvoid urine specimen before prostate massage along with a postmassage specimen (typically only 10 mL); the test is considered positive if there is growth of a single organism in the postmassage specimen, even if the midvoid specimen is sterile. The 2-glass test has a reported sensitivity and specificity of 91% each.<sup>30</sup> Because of the risk of possible contamination, results should be interpreted with caution and repeat cultures should be considered, if clinically feasible.

Evaluation for underlying causes is appropriate, and indications for evaluation are similar to those for acute bacterial prostatitis.

#### **Chronic abacterial prostatitis/CPPS: Keep thinking beyond the prostate**

Evaluation of the patient with suspected chronic abacterial prostatitis/CPPS should rule out risk factors for bacterial prostatitis, remote or recent trauma, exposure to a sexually transmitted disease, and instrumentation-induced inflammation.

**History.** Question patients about their occupation, with the aim of identifying any repetitive tasks that might affect the back and lower extremities, such as

long bouts of sitting at a desk or behind the wheel (eg, truck driving) or performance of physical labor. Ask about exercise regimens to reveal any improper techniques during weight training or inadequate warm-up or stretching.

Other findings from the history or physical examination can further support the multiple facets of CPPS, such as migratory abdominal or pelvic discomfort or cramping, urinary hesitancy, bowel irregularity, and nonrelaxation of the anal sphincter. Colorectal researchers have observed similar symptoms (eg, pain of the perineum, fullness, pressure, or the sensation of “sitting upon a golf ball”) among men and women diagnosed with coccygodynia or levator ani syndrome.<sup>31</sup>

A psychosocial history should include a review of systems to reveal possible functional somatic syndromes, as psychological stress is common among men with prostatitis.<sup>32</sup> In some cases, a formal psychological evaluation should be considered.

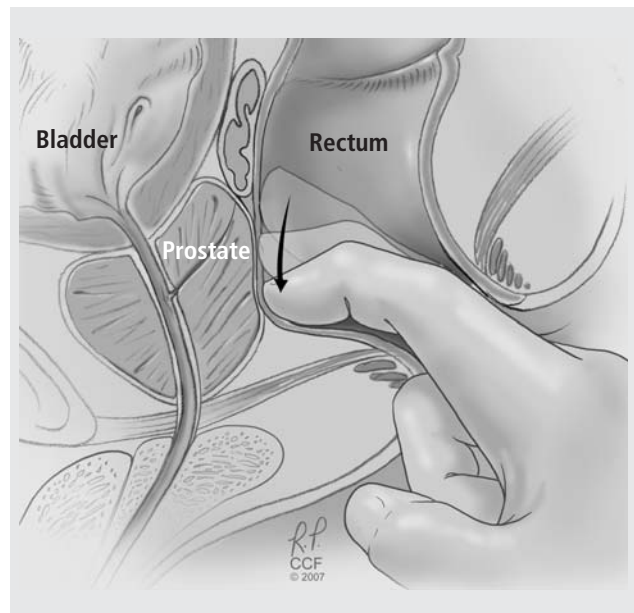
**Physical examination.** The physical examination should devote special attention to the back, abdomen, and genitalia. If pain is present in the left lower quadrant, consider diverticular disease. An external and internal pelvic floor assessment should be conducted; for the internal evaluation, place the patient in the lithotomy position to allow assessment of the striated muscles of the pelvic floor by digital rectal examination.

Urinary retention often can be ruled out by percussion or palpation of the abdomen, with confirmation by ultrasonography or in-office Doppler imaging.

The anal sphincter and anal vault should be examined to rule out fissures, stenosis, and spasticity.

**Consider myofascial pain.** Various pain syndromes, particularly those of the pelvis, have also been described as myofascial pain syndromes. Muscles with myofascial trigger points exhibit increased responsiveness, delayed relaxation, referred spasm, and inhibition. The occasional patient may have associated autonomic dysfunction (similar to the unexplained bowel spasticity or urinary urgency/frequency syndromes). Painful contractions and referred pain are also characteristic of myofascial trigger point disorders.<sup>33</sup>

Sensitive examiners are able to detect taut bands, tender nodules, and even twitch responses in the affected muscle groups. While this may seem like a daunting task, physicians can begin learning about these techniques by consulting the manual on this topic by Travell and Simons.<sup>33</sup> Physical therapy workshops also can provide invaluable hands-on training. Like anything else, however, proficiency in these



**FIGURE 1.** Technique for prostate massage to elicit expressed prostatic secretions (EPS) in the evaluation for chronic bacterial prostatitis. Gentle digital pressure is applied in movements along a lobe of the prostate for approximately 1 minute. Within 2 to 3 minutes after the massage, several drops of EPS should be secreted from the urethra. These secretions, together with the first 10 mL of urine after massage, represent the prostate’s microbiologic environment.

examination techniques requires special interest and practice. To successfully carry out this form of evaluation or therapy, clinicians must acquire a gentle confidence about these techniques.

## ■ DIFFERENTIAL DIAGNOSIS

As alluded to above, the differential diagnosis of acute bacterial prostatitis includes urinary retention due to benign prostatic hyperplasia and infection of the upper urinary tract. Urinary tract infection also figures into the differential diagnosis of chronic bacterial prostatitis, which explains the need for localization culture techniques as detailed above.

The differential diagnosis of chronic abacterial prostatitis/CPPS is more extensive, as outlined in **Table 1**, but begins with urinalysis and localization cultures to rule out infection.

## ■ TREATMENT

### **Acute bacterial prostatitis:**

#### **Start with broad-spectrum intravenous antibiotics**

Hospital admission is indicated for any patient with unstable vital signs, sepsis, or intractable pain. Other indications for admission include frailty,

**TABLE 1**  
**Differential diagnosis of chronic abacterial prostatitis/  
 chronic pelvic pain syndrome**

<b>Infection:</b> Sexually transmitted diseases, chronic bacterial prostatitis, fungal infection
<b>Gastrointestinal:</b> Appendicitis, diverticulitis, constipation, anal fissures, hemorrhoids
<b>Abdominal wall defects:</b> Inguinal or ventral wall hernias, myofascial trigger points
<b>Musculoskeletal:</b> Neoplasm (primary or metastatic), degenerative joint disease of the hips, sacroileitis
<b>Neurologic:</b> Low thoracic or lumbar herniated nucleus pulposus, lumbar stenosis, Parkinson disease, diabetic cystopathy, demyelinating disease
<b>Urologic:</b> Renal calculi, varicocele, epididymitis, testicular neoplasm, interstitial cystitis

immunosuppression, diabetes, history or evidence of renal insufficiency, and poor social support.

Treatment should be initiated using a broad-spectrum antibiotic regimen similar to protocols established for acute febrile urinary tract infection. Ampicillin (or erythromycin for patients with penicillin allergy) and gentamycin are given intravenously until cultures confirm the organism and its susceptibilities, which will enable more specific antibiotic tailoring and early conversion from intravenous to oral therapy. Usually fever abates and LUTS improve within 2 to 6 days of intravenous therapy initiation.

The hospitalized patient may be converted to oral therapy after he has been afebrile for 24 to 48 hours and his blood cultures are negative. Oral fluoroquinolones are the treatment of choice for most cases, as they effectively target the usual bacterial pathogens in this setting. In otherwise healthy men, oral quinolones can be prescribed as the initial, and usually definitive, oral therapy. Weak bases such as trimethoprim will not concentrate well in the alkaline environment of seminal fluid, especially during infection, but because quinolones are neither pure acids nor bases, their concentrations in the prostate tissue compare favorably with their plasma concentrations.<sup>34</sup>

The choice of antibiotic for treatment of enterococcal prostatitis may differ and will be directed by the results of urine culture.

Duration of therapy varies in the literature from a minimum of 2 weeks to a maximum of 6 weeks. In our practice, we consider 4 weeks an appropriate treat-

ment duration. However, when organism susceptibility profiles dictate the use of antibiotics other than quinolones or macrolides, we prefer a 6-week regimen.

We recommend avoiding any pain medications that could cause constipation or worsen urinary retention.

In cases of prostatic abscess, surgical drainage is usually required along with extended antibiotic therapy. In the case of microabscesses, there is evidence of resolution without surgical intervention, which can be observed via serial CT scans. Such close observation would be reserved for patients who exhibit consistent improvement but may require longer courses of antimicrobial therapy.

**Chronic bacterial prostatitis:  
 Base treatment on culture and sensitivity testing**

For chronic bacterial prostatitis, treatment should consist of a 2- to 4-week regimen of appropriate antibiotics as dictated by culture and sensitivity testing of urine specimens from previous bouts of acute urinary tract infection and/or localization cultures that include mid-void and post-prostate massage urine specimens.

In the only study of antibiotic therapy for chronic bacterial prostatitis with long-term follow-up, ciprofloxacin was given for 4 weeks to men with localization cultures positive for *E coli*.<sup>35</sup> Three months after therapy, 92% of the men exhibited cure as demonstrated by negative EPS cultures and absence of symptoms. At 24 months after therapy, 80% of patients remained asymptomatic and had negative EPS cultures.<sup>35</sup>

Suppressive therapy is a consideration in men who have three or more recurrences per year. Suppressive therapy may be prescribed using one fourth or one half of the treatment dose at bedtime for antibiotics such as trimethoprim-sulfamethoxazole, trimethoprim, tetracycline, amoxicillin, or nitrofurantoin.

We have initiated suppressive therapy even when recurrences are less frequent than three times per year, due to the gravity of the recurrences. This tactic merits consideration in patients who have comorbidities that might lead to delayed diagnosis and treatment or in whom rapid progression to urosepsis has occurred, such as in the setting of diabetes or other states of immunocompromise. We also have recently implemented suppressive therapy in patients who are on chronic warfarin therapy, as 2- to 4-week antibiotic regimens can potentially elevate the prothrombin time and the International Normalized Ratio beyond therapeutic levels, requiring close monitoring and frequent alteration of the warfarin dose. With suppressive therapy, long-term predictability is more feasible since treatments are daily and long-term.

### Chronic abacterial prostatitis/CPPS

**General principles.** From the outset, the management of patients with suspected chronic abacterial prostatitis should be guided by several general principles:

- Antibiotics should be avoided in patients who are afebrile and have normal urinalysis results.

- A brief course of anti-inflammatory therapy may be tried until urine localization cultures are completed. There is no clear evidence that any particular anti-inflammatory agent is superior to others in this setting.

- An empiric trial of alpha-blocker therapy can be considered, although the effectiveness of such therapy is uncertain, according to a recent systematic review of six randomized, placebo-controlled trials comprising 386 patients with chronic abacterial prostatitis.<sup>36</sup> While four of the six trials showed a statistically significant improvement in symptom scores with alpha-blocker therapy, two of these trials demonstrated no significant difference in quality-of-life scores. Of the remaining two studies, one showed no difference between alpha-blocker therapy and placebo and the other had limitations in statistical methodology. The authors noted that these trials used differing alpha-blockers (no head-to-head studies have been reported) and lacked uniformity in how they defined significant change.<sup>36</sup> Alpha-blockers may exert their effects to varying degrees at sites besides the prostate and bladder neck, which could potentially influence symptoms linked to receptor sites within the bladder or spinal cord.

- Contributing factors should be addressed, such as stress, overlapping syndromes, and neuromuscular factors.

- It is helpful to identify a team of physiotherapists who specialize in myofascial pain syndromes (discussed later in this section) and who are comfortable dealing with male genitalia and the pelvic floor.

- It is helpful to identify or establish a team of psychotherapists or social workers who address stressful life events and offer relaxation therapy. Referral to such providers must be presented as a part of the physician's comprehensive treatment approach so as not to discredit the patient's real physical suffering.

**'Beyond-the-prostate' treatment options.** In general, patients with chronic abacterial prostatitis/CPPS who are conscientiously evaluated and provided with a non-prostate-centric approach to their symptoms can sooner explore more appropriate management strategies, such as the following:

- Physical therapy

- Myofascial trigger point release therapy, which involves the methodical compression and massage of trigger points on the levator, obturator, adductor, and gluteal muscles or on the abdominal wall, and is per-

formed by specially trained physiotherapists

- Relaxation techniques, including paradoxical relaxation therapy, which instructs patients to pace their breathing rate according to their heart rate and is usually taught by a psychologist or biofeedback specialist

- Thiele massages, which involve internal digital manipulation of the pelvic floor muscles, usually in a sweeping motion, parallel to muscle orientation.<sup>31</sup>

Such alternate therapies can be considered, however, only after appropriate evaluation and consideration of disorders affecting pelvic floor muscular function.

Pelvic floor myalgia has long been suspected as the cause of symptoms attributed to prostatitis,<sup>37</sup> but only recently has this suspicion been studied in a longitudinal fashion in urology. Using both a neurobehavioral component and a myofascial trigger point perspective for the evaluation and treatment of chronic abacterial prostatitis/CPPS, investigators at Stanford University studied 138 men who were refractory to traditional therapy.<sup>38</sup> All patients received at least 1 month of pelvic floor myofascial trigger point release therapy combined with paradoxical relaxation therapy and were subsequently assessed using a pelvic pain symptom survey and the NIH Chronic Prostatitis Symptom Index. By these measures, 72% of patients exhibited improvement consistent with clinical success as defined by the investigators. This case study analysis indicates that myofascial trigger point release therapy combined with paradoxical relaxation therapy represents an effective therapeutic alternative for chronic abacterial prostatitis/CPPS.<sup>38</sup> The significant response rate also helps to dispel the belief that this disorder is caused by an infectious etiology or prostate abnormality.

Similar response rates were seen when myofascial trigger point release therapy was prescribed to patients, mostly female, diagnosed with interstitial cystitis.<sup>39</sup> Of the 42 patients treated, 83% reported moderate to marked symptom improvement. The amelioration of urinary urgency and frequency and pelvic pain were attributed to the decrease in pelvic floor hypertonus.<sup>39</sup>

Interstitial cystitis and prostatitis share many characteristics: chronic genital and/or pelvic pain, LUTS, sexual dysfunction, disability, and reduced quality of life. As with prostatitis and CPPS, the approach to the management of interstitial cystitis has broadened in recent years and the condition itself is increasingly considered a painful bladder syndrome (see the article in this supplement devoted to interstitial cystitis/painful bladder syndrome).

NIH-supported research is under way to study the use of physical therapy and myofascial trigger point

**TABLE 2**  
**Indications for referral of patients with a history of prostatitis**

Recurrent infection
History of urosepsis
Infection associated with gross hematuria
Persistence of microscopic hematuria after adequate therapy
Sterile pyuria
Abnormal testicular examination
Urinary retention
Abnormal digital rectal examination
Persistent fevers or night sweats

release therapy both in patients with chronic prostatitis/CPPS and in patients with interstitial cystitis/painful bladder syndrome.

**Should treatment address an overlapping somatic syndrome?** Patients with chronic abacterial prostatitis/CPPS incur increased medical costs that are not directly attributable to prostatitis. It may be that these patients are more susceptible to comorbidities. A retrospective chart review of men with chronic abacterial prostatitis found that 45% of them had psychological disorders and 65% met the criteria for other functional somatic syndromes, such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and multiple chemical sensitivities.<sup>40</sup> This is a dramatic observation, as the lifetime prevalence of functional somatic syndromes in the general population is estimated to be much lower (> 4%).<sup>41</sup>

Similarly, a comparative study of 127 twins with chronic fatigue syndrome and their nonfatigued co-twins found that the prevalence of disorders such as fibromyalgia, irritable bowel syndrome, chronic abacterial prostatitis, pelvic pain, and interstitial cystitis was significantly higher in the chronically fatigued twins than in their co-twins.<sup>42</sup> In another study, patients with interstitial cystitis were found to be 100 times more likely than the general population to have inflammatory bowel disease, 30 times more likely to have systemic lupus erythematosus, and also more likely to have fibromyalgia, allergies, skin sensitivity, and irritable bowel syndrome.<sup>43</sup>

Because many of these diagnoses coexist, we might consider a more global overlapping syndrome, as specific somatic syndromes may be “largely an artifact of medical specialization,” as argued by Wessely et al.<sup>44</sup> Cer-

tainly, this notion would be validating to the primary care provider, who may observe and intuit the overlapping nature of this phenomenon on a daily basis.

■ **APPROPRIATE FOLLOW-UP**

A single recurrence of a urinary tract infection in a man is suspicious for bacterial prostatitis and, as such, requires additional testing. Indications for upper urinary tract studies depend on the patient’s history of surgery or renal calculi and the persistence of microscopic hematuria after treatment.

Lower urinary tract evaluation with a cystourethroscope is strongly recommended for all patients with recurrent infection or in whom hematuria, even microscopic, persists after treatment. This brief outpatient procedure, performed with appropriate antibiotic prophylaxis and local anesthesia, can be most helpful in identifying abnormalities that may be corrected to prevent subsequent recurrence or other pathologies such as bladder tumors, urethral strictures, bladder calculi, or diverticulae.

Adequate bladder emptying should be confirmed as well, using Doppler imaging or ultrasonography to measure the volume of urine remaining immediately following normal urination.

We recommend follow-up every 3 to 6 months to assess patient progress. It is also important for the patient to have a sense of commitment from the caregiver who is orchestrating the multidisciplinary approach.

■ **WHEN TO REFER**

Indications for referral are listed in **Table 2**. In general, because chronic prostatitis is a relapsing condition that is difficult to manage, referral of chronic cases to a urologist for comanagement should be considered. It is important to seek out urologists who are interested in and specialize in this diagnosis, as well as physical therapists who are comfortable with pelvic floor rehabilitation and familiar with myofascial pain syndromes. Because of the stress associated with the symptoms of chronic prostatitis and the tendency for many of these patients to “catastrophize,” referral for psychological assessment should be considered.

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