Benign prostatic hyperplasia (BPH) is common in older men. The prostate is about the size of a walnut (20 cm³) in men younger than 30 years, but its size increases gradually, leading to BPH in most men older than 60 years.1,2 Benign prostatic hyperplasia results from the growth of epithelial and stromal cells. Hyperplasia begins in the transition zone of the prostate gland,3 causing urinary outflow resistance. Eventually, this resistance may lead to detrusor dysfunction, bladder trabeculation, and uninhibited bladder contractions.4

There is evidence that BPH progresses when untreated. Rhodes et al5 showed that prostate volumes increase steadily by 1.6% per year. For 6 years, Roberts et al6 monitored 492 men older than 40 years and showed that peak urinary flow rates declined by 2.1% per year. Jacobsen et al7 studied 2115 men older than 40 years who experienced a gradual increase in prostate symptom severity. Furthermore, the 5-year cumulative incidence of acute urinary retention ranged from 1.6% among men aged 40 to 49 years to 10% among men aged 70 to 79 years.8 Other complications of BPH include hypotonic bladder, hematuria from friable prostatic blood vessels, bladder calculi, urinary tract infections, and obstructive nephropathy.4

Diagnosing BPH and determining its clinical prevalence is challenging because diagnostic criteria are not always reliable in men presenting with lower urinary tract symptoms (LUTS). Specifically, prostate size correlates poorly with LUTS,4,11 and numerous conditions other than BPH can cause LUTS.12,13 Nevertheless, criteria such as symptom severity, prostatic enlargement on digital rectal examination (DRE), and abnormal results from uroflow studies with increased postvoid residual urine aid in diagnosis of BPH.14 On the basis of clinical criteria, the Baltimore Longitudinal Study of Aging found that the prevalence of BPH is approximately 25% in men aged 40 to 49 years, 50% in men aged 50 to 59 years, and 80% in men aged 70 to 79 years.1 Notably, the clinical prevalence of BPH generally correlates with autopsy data.1,2,15

EVALUATING MEN WITH BPH

MEDICAL HISTORY AND PHYSICAL EXAMINATION

When obtaining a medical history, consideration of a patient’s age is important. Because the prevalence of BPH increases with age, LUTS in men older than 50 years are probably due to BPH; LUTS in men younger than 40 years are usually due to other causes.2 Review of a patient’s medications is also important because many medications can cause LUTS. Examples include urinary frequency from diuretics, increased urethral sphincter contractility from sympathomimetic agents, and decreased detrusor contractility from anticholinergic medications.16,17 Although surprisingly little is known about the relationships between medications and BPH,18 Su et al19 reported that daily use of antidepressants and antihistamines is associated with increased prostate symptom scores in 40- to 79-year-old men compared with age-matched controls. Physicians also should identify use of over-the-counter medications, especially cold remedies, which can cause LUTS by various mechanisms. Indeed, men with subclinical BPH sometimes develop symptoms with initiation of a new medication. In these men, simply stopping the new medication leads to symptom resolution. Finally, a focused review of systems should be obtained to identify fever, hematuria (indicating urothelial cancer, infection, or bladder calculi), urethral instrumentation or sexually transmitted diseases (raising the

From the Division of General Internal Medicine, Men’s Health Center for Urology, and Department of Urology, Mayo Clinic College of Medicine, Rochester, Minn.

A question-and-answer section appears at the end of this article.

Individual reprints of this article are not available. Address correspondence to Thomas J. Beckman, MD, Division of General Internal Medicine, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: beckman.thomas@mayo.edu).

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TABLE 1. Differential Diagnosis of Symptomatic BPH*

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause of BPH</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>Adenocarcinoma of the prostate, transitional cell carcinoma of the bladder</td>
<td>Men should be offered PSA testing in conjunction with DRE. Microhematuria on urinalysis should raise suspicion for urothelial malignancies.</td>
</tr>
<tr>
<td>Infectious</td>
<td>Cystitis, prostatitis, sexually transmitted diseases (eg, chlamydia, gonorrhea)</td>
<td>Urinalysis and urine Gram stain are useful in evaluating for cystitis. Prostatic massage specimens (void bottle 3 [VB3] test) assist in diagnosing prostatitis. Sexually transmitted diseases may cause LUTS from urethral scarring and stricture.</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Spinal cord injury, cauda equina syndrome, stroke, parkinsonism, diabetic autonomic neuropathy, multiple sclerosis, Alzheimer disease</td>
<td>Primary mechanisms for neurologic causes of LUTS are detrusor weakness and/or uninhibited detrusor contractions. Alzheimer disease can cause functional urinary incontinence.</td>
</tr>
<tr>
<td>Medical</td>
<td>Poorly controlled diabetes mellitus, diabetes insipidus, congestive heart failure, hypercalcemia, obstructive sleep apnea</td>
<td>Medical conditions associated with urinary frequency are often overlooked causes of LUTS.</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Prostatectomy, cystectomy, traumatic urethrocystoscopic procedures, radiation cystitis</td>
<td>Surgery sometimes causes neurologic impairment. Traumatic urethrocystoscopic procedures can cause scarring and urethral strictures.</td>
</tr>
<tr>
<td>Anatomical</td>
<td>Ureteral and bladder stones</td>
<td>Hematuria may be seen on urinalysis. Consider obtaining urine cytology, cystoscopy, and renal imaging studies.</td>
</tr>
<tr>
<td>Behavioral</td>
<td>Polydipsia, excessive alcohol or caffeine consumption</td>
<td>Consider assessing serum sodium. A voiding diary may provide useful information regarding habits of fluid consumption.</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>Diuretics (eg, furosemide, hydrochlorothiazide), sympathomimetics (eg, ephedrine, dextroamphetamine), anticholinergics (eg, oxybutynin, amantadine, diphenhydramine, amitriptyline), over-the-counter decongestants</td>
<td>Diuretics cause urinary frequency, sympathomimetics increase urethral resistance, and anticholinergics decrease detrusor contractility. Over-the-counter medications may cause LUTS by various mechanisms.</td>
</tr>
<tr>
<td>Other</td>
<td>Overactive bladder</td>
<td>UDS can help differentiate BPH from isolated detrusor dysfunction.</td>
</tr>
</tbody>
</table>

* BPH = benign prostatic hyperplasia; DRE = digital rectal examination; LUTS = lower urinary tract symptoms; PSA = prostate-specific antigen; UDS = urodynamic studies.

possibility of urethral stricture), sleep disturbances, patterns of fluid consumption, and use of alcohol and caffeine.

Lower urinary tract symptoms are divided typically into the categories of obstructive, which includes straining, hesitancy, weak stream, intermittency, and sense of incomplete bladder emptying, and irritative, which includes urgency, frequency, and nocturia. Lower urinary tract symptoms are associated with numerous medical conditions other than BPH. For this reason, a broad differential diagnosis should be considered for all patients presenting with LUTS (Table 1).

The American Urological Association Symptom Score (AUA-SS), otherwise known as the International Prostate Symptom Score, is an objective measurement of symptoms associated with BPH. The AUA-SS aids in diagnosis of BPH and in monitoring of patients with BPH over time (ie, in watchful waiting or in gauging therapeutic response to medical therapy). The AUA-SS is a major criterion for clinical decision making regarding the therapeutic approach to men presenting with symptoms of BPH (Figure 1). The AUA-SS has been tested rigorously for reliability and validity and has been shown to have good internal and test-retest reliability, strong correlation with global symptom severity, and the ability to discriminate men with BPH from controls. The AUA-SS includes 7 questions representing the following symptoms: frequency, nocturia, weak stream, hesitancy, intermittency, incomplete bladder emptying, and urgency. Each of the 7 questions is rated on a 5-point Likert scale: a sum of 0 to 7 represents mild symptoms of BPH, 8 to 19 represents moderate symptoms, and 20 to 35 represents severe symptoms.

When examining patients with LUTS, evaluating for neurologic deficits is important, especially if patients have a history or presenting symptoms suggesting a neurologic disorder. In such patients, useful findings include saddle anesthesia, decreased rectal sphincter tone, absent cremasteric reflex, or lower extremity neurologic abnormalities. Examination of the abdomen may reveal masses resulting from a renal tumor or bladder distention. The penis should be examined for stricture or other pathologic findings.
FIGURE 1. Treatment algorithm for benign prostatic hyperplasia (BPH) shows treatment decisions based partly on patient symptom severity as determined by the American Urological Association Symptom Score. AUA = American Urological Association; DRE = digital rectal examination; IPSS = International Prostate Symptom Score; PE = physical examination; PSA = prostate-specific antigen; PVR = postvoid residual urine; UTI = urinary tract infection.

*In patients with clinically significant prostatic bleeding, a course of a 5α-reductase inhibitor may be used. If bleeding persists, tissue-ablative surgery is indicated.

†Patients with at least a 10-year life expectancy for whom knowledge of the presence of prostate cancer would change management or patients for whom the PSA measurement may change the management of voiding symptoms.

‡After exhausting other therapeutic options as discussed in detail in the text.

§Some diagnostic tests are used in predicting response to therapy. Pressure-flow studies are most useful in men before surgery. From J Urol,12 with permission.
When performing DRE, findings most consistent with BPH are symmetrical enlargement and firm prostate consistency, often likened to the thenar muscle or tip of the nose. In contrast, findings consistent with adenocarcinoma of the prostate are prostate asymmetry and induration or nodularity that is sometimes likened to the consistency of a knuckle or the forehead.

LABORATORY TESTING

The American Urological Association recommends routine urinalysis, which can reveal pyuria and bacteriuria suggesting infection, hematuria suggesting inflammation or urothelial malignancy, or active urinary sediment suggesting postobstructive nephropathy. Optional studies include serum creatinine and prostate-specific antigen (PSA). The PSA study is optional because it fails to discriminate adenocarcinoma of the prostate. Nonetheless, we always inform patients that LUTS may indicate prostate cancer, and on this basis, PSA testing is offered routinely. Also, we endorse annual screening for prostate cancer with DRE and PSA testing in men aged 50 to 75 years and sometimes beyond 75 years, depending on the patient’s preference and anticipated life expectancy.

Although serum PSA discriminates poorly between adenocarcinoma of the prostate and BPH, serum PSA levels correlate strongly with prostate volume in men with BPH. Other causes of serum PSA elevation are prostate carcinoma, bacterial prostatitis, acute urinary retention, and prostate incision. There is also evidence that serum PSA levels persist for 48 hours after ejaculation, which is why some physicians recommend that patients avoid ejaculation for 2 days before undergoing DRE. Conditions generally not believed to elevate serum PSA level are routine DRE, transrectal ultrasonography without biopsy, cystoscopy, and bladder catheterization.

There are several ways to interpret serum PSA test results. The traditional cutoff is 4 ng/mL. Because prostate volume (and thus serum PSA level) increases with age, age-adjusted normal limits also are commonly used. The level of free (unbound) PSA is lower in men with adenocarcinoma of the prostate, hence, a low ratio of free to total PSA is more consistent with prostate carcinoma than with BPH. Finally, the PSA trend over time can be useful because a rapidly increasing PSA level is more suggestive of carcinoma than of BPH. Specifically, a PSA velocity greater than 0.75 ng/mL per year is considered abnormal.

The uroflow study is an objective, noninvasive way to evaluate LUTS. An accurate study requires a urine volume of at least 150 mL. Peak urinary flow rates of less than 15 mL/s and increased urine residuals often are seen in men with BPH (Figure 2). Importantly, abnormal results also are seen in patients with detrusor muscle dysfunction. Consequently, as with any test, interpreting the results of uroflow studies depends on the pretest probability of disease. If the pretest probability of BPH is high, then abnormal test results are useful for confirming the diagnosis. However, if the pretest probability of BPH is intermediate, then abnormal results from the uroflow study are less useful. In such cases, patients may need to undergo complete urodynamic studies to further separate BPH from other causes of LUTS.

MEDICAL MANAGEMENT OF BPH

This article focuses on the medical management of BPH, but it is important for clinicians to recognize the indications for referral to a urologist for consideration of invasive therapy. These indications are severe symptoms, persistent gross hematuria, urinary retention, renal insufficiency due to BPH, recurrent urinary tract infections, and bladder calculi.

Watchful waiting is a reasonable approach for patients with mild to moderate symptoms. These patients may be advised to practice scheduled voiding (every 3 hours during the day) to avoid excessive evening fluid intake, and to be aware of the potential adverse effects that over-the-counter decongestants can have on voiding.

Most patients presenting initially with BPH are candidates for medical therapy. Moreover, medical therapy has replaced interventional therapy as the most common treat-
ment of BPH.13 The categories of prescription medications currently available for treating BPH are α1-adrenergic antagonists (eg, tamsulosin) and 5α-reductase inhibitors (eg, finasteride). These medications act on dynamic and static components of bladder outlet obstruction.13,29

α1-Adrenergic antagonists are the initial choice of medical therapy for most men with BPH. Medications from the α1-adrenergic antagonist category act on the dynamic component of bladder outlet obstruction by relaxing prostate smooth muscle. A meta-analysis by Djavan and Marberger30 reviewed the randomized controlled trials of the α1-adrenergic antagonists used for treatment of BPH. The authors found that, although all these medications are equally efficacious for treating BPH, terazosin and doxazosin have higher adverse effect profiles (namely, orthostatic hypotension) than do other medications from this class. Other common adverse effects of α1-adrenergic antagonists include dizziness, headache, nasal congestion, hypotension, edema, palpitations, erectile dysfunction (ED), and fatigue.

Because aging men make up a large proportion of the population, the prevalence and treatment of BPH and ED will increase (indeed, this fact has spawned recent research regarding the relationship between BPH and ED).31 Therefore, it is important to recognize that combining phosphodiesterase type 5 inhibitors (eg, sildenafil) with medications from the α1-adrenergic antagonist class can cause profound hypotension. Recommendations regarding combinations of these medications are as follows: (1) sildenafil should not be taken within 4 hours of any α1-adrenergic antagonist, (2) vardenafil should not be taken with any α1-adrenergic antagonist, and (3) tadalafil should not be taken with any α1-adrenergic antagonist except tamsulosin at a 0.4-mg dose.

The second class of medications available for treatment of BPH is the 5α-reductase inhibitors, which act on the static (anatomical) component of bladder outlet obstruction. These medications work by reducing the conversion of testosterone to dihydrotestosterone (DHT) in the prostate, thereby limiting prostate growth. The 2 currently available 5α-reductase inhibitors are finasteride and dutasteride.

Numerous studies reveal the efficacy of, and guide the appropriate prescribing of, finasteride. McConnell et al32 showed that finasteride, compared with placebo, reduces the risks of urinary retention (relative risk, 0.57; P < .001) and surgery (relative risk, 0.55; P < .001), improves urinary flow rates, and decreases prostate volume (P < .001). Results from this study also showed that 6 to 12 months of therapy may be required to see the full effect from the drug. Hence, patients are counseled that they may need to take finasteride for several months before they notice symptom improvement. Abrams et al13 reported that outcomes with finasteride are most favorable in men with large prostate glands (>40 mL). For this reason, finasteride often is used as initial therapy for men with moderate to severe BPH. A randomized placebo-controlled trial by Gormley et al34 showed that finasteride significantly decreased symptom scores and prostate volume and increased maximal urinary flow rates. Moreover, patients taking finasteride experienced significant reductions in serum PSA level. On this basis, experts advocate correction of the assessment of PSA level in patients taking finasteride by multiplying the PSA value by 2.13,35

Finasteride is well tolerated, and serious adverse effects are uncommon. The most frequent adverse effects are related to sexual dysfunction and include decreased libido, ejaculatory dysfunction, and ED. Other adverse effects include gynecomastia and orthostatic hypotension.

Dutasteride, the second medication from the 5α-reductase inhibitor class, inhibits 5α-reductase isoenzyme types 1 and 2,36 whereas finasteride inhibits only 5α-reductase isoenzyme type 2. Likewise, clinical trials in men with BPH showed that dutasteride reduced serum DHT levels by 93%,37 whereas finasteride reduced serum DHT levels by only 70%.38 The safety of dutasteride was shown by a pooled analysis of 3 randomized, blinded placebo-controlled trials. In this analysis,37 at 2-year follow-up, patients taking dutasteride experienced significant reductions in symptom scores, prostate volumes, and risk of surgical intervention. Only 1 clinical trial compared outcomes in patients taking dutasteride vs finasteride.39 The Enlarged Prostate International Comparison Study randomized 1630 patients with BPH to either dutasteride or finasteride.40 Study findings included no significant differences in prostate volume reduction or improvement in urinary flow rates.39 The most common adverse effects, which did not differ significantly between intervention groups, were related to sexual dysfunction.39

Evidence supports combining an α1-reductase inhibitor and a 5α-reductase inhibitor when treating BPH; in men with large prostate glands and elevated PSA levels, combination therapy should be considered the first-line approach. The Medical Therapy of Prostatic Symptoms (MTOPS) trial involved 3407 men with BPH who were randomized to placebo, doxazosin, finasteride, or combination therapy.41 Significant findings were a 66% reduction of clinical progression with combination therapy (P < .001), a reduced risk of acute urinary retention or need for invasive therapy with combination therapy (P < .001), and improved symptom scores with invasive therapy (P < .001). However, the most remarkable finding was the low number needed to treat (8.4) to prevent 1 instance of overall clinical progression with combination therapy.
Herbal medicines used to treat BPH include derivatives from African star grass, African plum tree bark, rye grass pollen, stinging nettle, and cactus flower.\(^4\) The most commonly used alternative treatment for BPH is saw palmetto (\textit{Serenoa repens}). Many mechanisms for saw palmetto have been entreated, yet none are proven.\(^4\) Saw palmetto is considered safe, and available evidence supports its effectiveness.\(^43\)-\(^45\) In a large European trial by Carraro et al,\(^44\) 1098 men were randomized to saw palmetto or finasteride. Both treatment arms experienced the same improvement in symptom scores. Furthermore, a meta-analysis by Boyle et al\(^49\) showed that compared with placebo, saw palmetto improves peak urinary flow rates and reduces nocturia in men with BPH.

CONCLUSIONS

Benign prostatic hyperplasia is common, with clinical evidence for BPH occurring in most men older than 60 years. Although diagnosing BPH can be challenging, obtaining a medical history including an AUA-SS, performing a careful physical examination, and using urinalysis, PSA, and uroflow studies can help exclude other causes of LUTS. Before initiation of medical therapy, indications for referral to a urologist and consideration of invasive therapy should be reviewed. \(\alpha_1\)-Adrenergic antagonists, which act on the dynamic component of bladder outlet obstruction, are the initial choice of medical treatment in most men with BPH. However, in men with large prostate glands (>40 mL), higher PSA levels, and moderate to severe symptoms, treatment with 5\(\alpha\)-reductase inhibitors or combination therapy should be considered. Finally, evidence supports the use of saw palmetto for treatment of BPH in men who prefer herbal therapies.

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REFERENCES

Questions About BPH

1. Which one of the following regarding the natural history of BPH is false?
   a. Most men older than 60 years develop BPH
   b. BPH results from growth of epithelial and stromal cells
   c. There is no evidence to indicate that BPH progresses over time
   d. Urinary flow obstruction may lead to detrusor hypertrophy and bladder contractions
   e. Worrisome complications of BPH include infection and obstructive kidney disease

2. Which one of the following is false regarding the diagnosis and prevalence of BPH?
   a. Prostate size on physical examination correlates poorly with LUTS
   b. Numerous conditions other than BPH cause LUTS
   c. Symptom severity, physical examination, and prudent use of tests usually allow accurate diagnosis of BPH
   d. The clinical prevalence of BPH correlates well with autopsy data
   e. A minority of men aged 70 years or older have some clinical evidence of BPH

3. Which one of the following regarding the AUA-SS is false?
   a. It is useful for diagnosing BPH and monitoring a patient’s response to therapy
   b. It is among the criteria for clinical decision making regarding the treatment of BPH
   c. It has been tested rigorously for reliability and validity characteristics
   d. It has been shown to discriminate between men with and without BPH
   e. It represents mild symptoms when the sum of the 7 questions, each rated on a 5-point Likert scale, equals 10

4. Which one of the following regarding the treatment of BPH is true?
   a. Patients with recurrent urinary tract infections and obstructive kidney disease can safely continue receiving medical therapy alone
   b. Watchful waiting is a reasonable approach to managing BPH in men with mild to moderate symptoms
   c. Most men presenting with BPH are best treated with interventional therapy
   d. Medications from the α1-adrenergic antagonist category act on the fixed component of bladder outlet obstruction
   e. All medications from the α1-adrenergic antagonist category have equivalent adverse effect profiles

5. Which one of the following regarding finasteride is false?
   a. Finasteride acts on the dynamic component of bladder outlet obstruction
   b. Finasteride works by reducing the conversion of testosterone to DHT in the prostate
   c. Patients may need to take finasteride for 6 to 12 months before experiencing the full effect of treatment
   d. Finasteride is most effective in men with large prostate glands (eg, >40 mL)
   e. Finasteride lowers serum PSA levels