#### ALBERT LEVY, MD\*

# GEORGE P. SAMRAJ, MD\*

Assistant Clinical Professor of Medicine, Mount Sinai School of Medicine, New York, NY Associate Professor, Family Medicine, Department of Community Health and Family Medicine, University Of Florida, Gainesville, FL

# 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 alphablocker, 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-

<sup>\*</sup> Drs. Levy and Samraj reported that they have no financial relationships that pose a potential conflict of interest with this article.

#### 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-

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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 DREbased 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>T</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.)

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# 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, hydroureter, 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-

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Common drugs used to treat benign prostatic hyperplasia

	Dosage	Side effects
Alpha-blockers		
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
5 alpha-reducta	ase inhibitors	
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

Dased on the drugs package inserts

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

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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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Address: Albert Levy, MD, Manhattan Family Practice, 911 Park Avenue, New York, NY 10021; alevymd@earthlink.net.