Preface

Benign prostatic hyperplasia (BPH) is the most common neoplastic condition afflicting men and constitutes a major health factor impacting patients in every part of the world. Bladder neck obstruction secondary to BPH can result in significant medical complications including renal failure, urinary retention, recurrent urinary tract infection, bladder stones, significant hematuria, and marked and disruptive bladder symptoms. Current studies estimate that upwards of 30% of males will require some type of surgical or other significant intervention to correct this problem sometime in their lives. Because there is a major restructuring of the treatment algorithms used to manage this important clinical problem and because of new medications and advances in technology, a great need for *Management of Benign Prostatic Hypertrophy* has arisen.

How best to approach patients is a common question posed by urologists. What is to be made of these newer therapies, and what are their roles vis-à-vis our more established treatments? *Management of Benign Prostatic Hypertrophy* is designed to address those needs for the practicing urologist who is often caught in the middle of these newer therapies and confused by the significant hype. Despite this clear need for interpretation of new data, a text that is not grounded in the principles and hallmarks of our specialty will offer little to budding urologists; rather, this text serves as a single source for quick reference on most aspects of this broad spectrum of BPH treatments.

Management of Benign Prostatic Hypertrophy is divided into three main categories: (1) pathophysiology and natural history of BPH, (2) epidemiology: definitions and prevalence of the disease, and (3) the urodynamic evaluation of lower urinary tract symptoms. The first category is also buttressed by a more current understanding and treatment of postobstructive diuresis, a significant medical complication and frequent source of urologic consultation. A second component of the text addresses medical therapies for BPH, namely α-adrenergic antagonists, 5α-reductase inhibitors, and their combination in the treatment of BPH. The most extensive portion of the text is an up-to-date, concise evaluation of each of the minimally invasive therapies as well as the time-tested surgical treatments.

I think you will find *Management of Benign Prostatic Hypertrophy* concise, readable, and up-to-date.

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Glenn S. Gerber, MD

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common neoplasm in men and is a significant cause of urinary symptoms in the aging male *(1)*. Although much is unknown about the pathophysiology of BPH, the condition results in a diminished quality of life for many patients. The symptoms of BPH can be broadly divided into obstructive and irritative components. The former symptoms include a weakened urinary stream, hesitancy, and the need to push or strain to initiate micturition. Irritative symptoms can be much more bothersome for many men and include frequency, nocturia, and urgency *(2)*. When assessing the importance and magnitude of BPH, one must consider several factors. First, the typical symptoms of BPH are nonspecific *(3)*. There are many other potential causes of urinary symptoms in aging men, including diabetes mellitus, Parkinson's disease, and stroke, which can lead to the

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same urinary problems seen in men with prostatic enlargement. Second, unlike most other common, chronic medical disorders such as diabetes, hypertension, or hypercholesterolemia, there is no standardized medical test or measurement that can be used to quantify the problem or assess the response to treatment for men with BPH. Rather than lowering blood pressure or maintaining blood glucose levels in the desired range, the primary goal in the management of BPH for most patients is a subjective improvement in urinary symptoms and quality of life. Although objective measurements such as urinary flow rate and postvoid residual urine volume can be used to evaluate BPH, the reproducibility and correlation of these measures with urinary symptoms is often limited *(4,5)*. Finally, much is unknown about the natural history of BPH, and this may dramatically impact our understanding of the magnitude and prevalence of the problem *(6)*.

BPH DEFINITIONS

One of the most basic, yet most important, difficulties in the evaluation and management of men with BPH concerns definitions. In a strict sense, BPH is a histologic diagnosis that is established by the presence of hyperplastic glands on pathologic inspection of prostatic tissue *(1)*. In common usage, however, the term BPH is used to indicate that a patient has an enlarged prostate or that the patient has urinary symptoms that are believed to be the result of bladder outlet obstruction by the prostate. Peak urinary flow rate (Qmax) has also been used by many investigators to help define the presence of BPH *(3,4)*. A decrease in Qmax is a nonspecific finding and may be attributable to detrusor dysfunction rather than bladder outlet obstruction *(4,5)*. Nevertheless, BPH has commonly been defined as Qmax less than 15 mL/s on a voided volume of at least 125–150 mL and has been diagnosed based on this finding.

Issues regarding the definition of BPH may be confusing for both patients and primary care physicians, and it is important to keep this in mind when counseling men regarding BPH. In addition, there is a poor correlation between histologic changes within the gland, the size of the prostate, and the severity of urinary symptoms *(3)*. These confounding relationships may be attributed in part to physiologic changes in the aging bladder, alterations in the volume and pattern of urine production, and/or other unspecified factors *(7)*. To help clarify the terminology associated with the diagnosis of BPH and to focus attention on the lack of specificity of urinary symptoms, the alternative definition of lower urinary tract symptoms (LUTS) has been recommended and should be used when referring to such patients *(8)*.

Although beyond the scope of this chapter, it is generally accepted that the most important cause of LUTS in aging males is bladder outlet obstruction resulting from prostatic enlargement *(3)*. However, as discussed above, urinary symptoms commonly attributed to BPH are nonspecific and may result from a variety of other causes. An important but largely unanswered issue concerns the relationship between LUTS and bladder outlet obstruction. The gold standard in defining such obstruction is urodynamic study, in which the detrusor pressure is measured during voiding *(9)*. The single most important measure of obstruction is detrusor pressure at Qmax *(10)*. Using urodynamic evaluation, it has been demonstrated that as many as one-third of men with urinary symptoms attributed to BPH do not have obstruction *(9,11)*. Further evidence supporting the disparity between LUTS and prostatic obstruction comes from studies of age-matched women, who have been shown to have urinary symptoms similar to those of men with BPH *(12)*. Overall, the nonspecific nature of LUTS and the lack of concordance between symptoms and obstruction make it very difficult to arrive at a generally accepted definition of what constitutes BPH.

One of the most important developments in defining the extent and magnitude of BPH has been the introduction of validated symptom scores *(13)*. Health measurement scales such as the American Urological Association (AUA) symptom score must have demonstrated reliability and validity to be clinically useful *(14)*. Several factors must be considered when determining the utility of such measures. First, internal-consistency reliability must be considered. This refers to the relatedness of the different items in the scale and is evaluated by administering the questionnaire to a group of subjects *(2)*. Second, the test-retest reliability of the questionnaire must be established. This can be accomplished by demonstrating that there is minimal change in the results when the test is given to the same patients after a short interval *(2)*. Third, a questionnaire such as the AUA symptom score should have the same degree of accuracy as any other diagnostic test used to assess a disease process *(2)*. To be valid, the symptom score results should accurately quantify the severity of BPH in the same manner that serum lipid levels reflect the disease status in patients with hypercholesterolemia. Finally, health measurement scales must be responsive to be useful in discriminating among patients who get better, get worse, or remain the same with or without treatment over time *(2,15)*.

Based on the criteria described above, the AUA symptom score has been shown to be reliable and valid in the assessment of patients with BPH *(7,13)*. The seven questions that comprise the symptom score address seven separate but related urinary symptoms that are typically

associated with prostatic enlargement in the aging male. The results of these questions are scored from 0 to 5 based on the frequency of occurrence of each symptom. The scores for the seven questions may then be added to give a total score of 0–35. Based on this score, patients can be categorized as having mild (0–7 points), moderate (8–19 points), or severe (20–35 points) LUTS. In addition, an impact question designed to assess the overall quality of life associated with urinary symptoms has been added to the AUA symptom score *(16)*. The initial seven questions plus the quality of life question comprise the International Prostate Symptom Score (I-PSS) *(16)*. This questionnaire has been translated into many languages and has been used worldwide to measure the incidence and prevalence of BPH in many countries *(17,18)*.

Because the I-PSS has been the benchmark evaluation used to establish the prevalence of BPH across the world, it is important to understand the extent and reliability of testing that has been used to determine its validity. Statistical measurements of internal consistency reliability and 1-wk test–retest correlation have been shown to be 0.86 and 0.92, respectively *(13)*. Both of these measures highly support the reliability of the I-PSS in these areas. Because there is no gold standard comparison for assessing the presence and severity of LUTS, it is also important that the I-PSS be tested in other ways to determine its validity *(2)*. The I-PSS has been shown to correlate well with older questionnaires used to assess voiding symptoms in men with BPH *(19)*. Higher scores in the I-PSS have also been demonstrated to correlate well with health measurement scales designed to evaluate general health and well-being *(2,20)*. Additionally, the symptom score has been shown to be a reliable predictor of whether men would choose to undergo prostatectomy for BPH and in determining the response to surgical and medical therapy *(2,13,21,22)*. Overall, the I-PSS has been shown to be reliable and valid through a variety of testing modalities. Therefore, its use in measuring the prevalence of BPH and helping to understand the quality of life changes, epidemiology, and health care costs associated with prostatic enlargement is extremely valuable.

PREVALENCE

BPH is one of the most common conditions for which patients seek medical attention. In recent years, a variety of factors have led to further increases in the number of men evaluated and/or treated for LUTS. These include increased attention to prostate diseases in the lay press, the escalating use of the Internet as a source of information for patients, advertising by pharmaceutical companies in mainstream pub-

lications, and the growing elderly population in the United States and other developed countries. In addition to those patients diagnosed with BPH, surveys of men over 40 yr of age have demonstrated a significant incidence of urinary symptoms among unevaluated groups *(17,18,23)*.

Using a histologic definition, the prevalence of BPH is greater than 50% by age 60 and almost 90% by age 85 *(1)*. It is estimated that about half of these men will have detectable prostatic enlargement and that half of those will seek medical attention because of LUTS *(1)*. The Agency for Health Care Policy and Research Diagnostic and Treatment Guidelines for BPH in 1994 estimated that approx 25% of white males in the United States in 1990 had an AUA symptom score of 8 or greater (moderate-to-severe symptoms) and Qmax less than 15 mL/s *(1)*. Additional information concerning the prevalence and demographics of BPH has come from the Rochester Epidemiology Project, which has studied the population of Olmstead County, Minnesota *(24)*. Based on symptom questionnaires administered to unselected men living in this community, it was found that moderate-to-severe urinary symptoms were present in 13% of men between 40 and 49 yr and in 28% of those older than 70 yr *(24)*. Longitudinal studies in this group have demonstrated that the 10-yr cumulative risk acute urinary retention developing in a man with moderate symptoms is almost 14% *(2,24)*. In addition, a consistent decline in Qmax was noted when this parameter was measured longitudinally in this community-based cohort *(25)*. Although most American studies of BPH prevalence have focused on white men, there does not appear to be an increased risk of BPH in African Americans *(26)*.

Investigators in other countries have studied the prevalence of BPH using symptom questionnaires and have found similar results *(17,18,23,27)*. Chicharro-Molero et al. evaluated 1106 men in a Spanish community using the I-PSS *(17)*. In addition, prostate size was measured by transrectal ultrasonography (TRUS), and Qmax was measured. Overall, the prevalence of moderate or severe symptoms was approx 25% and, as expected, tended to increase with age. Using the impact question (quality of life measure) from the I-PSS, it was concluded that 12.5% of men had a poor quality of life. Interestingly, among younger men, moderate symptoms were perceived as resulting in poor quality of life, whereas the same symptoms in older men led to a subjective sense of a good quality of life. Qmax less than 15 mL/s was noted in more than 55% of men. Using a definition of BPH that included an I-PSS more than 7, prostate size more than 30 g, and Qmax less than 15 mL/s, the authors found that the prevalence of BPH in this population was 11.8%. Among patients less than 50 yr of age, however, the prevalence

Table 1
Prevalence of LUTS in 2096 Austrian Men

Age (yr)	*Mean I-PSS*	*Moderate to severe LUTS*	*Previous TURP*
20–29	2.1	6.3%	0%
30–39	2.6	8.4%	0%
40–49	3.0	11.1%	0%
50–59	5.8	27.1%	1.3%
60–69	5.7	28.3%	4.2%
70–79	6.4	36.0%	20.9%
80 or greater	6.1	35.7%	27.5%

Adapted from ref. *18*.

using this definition was less than 1%, and in men older than 70 yr, the prevalence using this definition was 30%. In another study, the I-PSS was administered to 2096 men 20 yr or older in Austria, who also underwent a digital rectal examination (DRE) and provided a detailed urologic history *(18)*. When stratified by decade, patients with advancing age showed an increase in the I-PSS and the incidence of previous surgical treatment for BPH (Table 1).

The prevalence of BPH was also studied in a Dutch population of 502 men between the ages of 55 and 74 yr who had no history of prostate cancer or surgical treatment for BPH *(27)*. In addition to the I-PSS, prostate volume, Qmax, and postvoid residual urine volumes (PVR) were measured. Using the I-PSS, moderate or severe symptoms were noted in 24% and 6% of men, respectively. A good correlation was found between the total symptom score and the single disease-specific quality of life question included with the I-PSS. However, weak correlations were noted between the I-PSS results and prostate volume, Qmax, PVR, and age. Based on the poor correlation between the magnitude of urinary symptoms and the observed objective measures, the authors of this study concluded that symptom scores should not be independently used as a criterion for determining the prevalence of clinical BPH.

A subsequent Dutch study of nearly 4000 men between 50 and 75 yr of age further demonstrated the difficulty in defining the clinical prevalence of BPH *(28)*. In this trial, men completed the I-PSS and also underwent physical examination, measurement of prostate volume by TRUS, and determination of Qmax. To define the prevalence of BPH, a variety of definitions of BPH that had been suggested by earlier studies to be most valid were assessed *(29,30)*. Using an I-PSS of eight or greater to define the presence of clinical BPH, the overall incidence in this study among all men was 25% *(28)*. However, there were significant

differences in the prevalence of BPH when alternative definitions were used. As defined by a symptom score of eight or greater and a prostate volume of more than 30 g, the incidence of BPH in this study was 14%. When also requiring a Qmax of less than 15 mL/s, 12% of men met the criteria used to define the presence of BPH. Because no clear consensus has been reached as to how BPH should be defined, it is apparent that there will be wide differences in the reported prevalence rates depending on the choice of criteria used.

EPIDEMIOLOGY OF BPH

A number of investigators have studied the epidemiology of BPH. Clearly, the most important demographic factor in the incidence and severity of BPH is aging. Not only does prostate size correlate closely with age, but worsening LUTS is also seen commonly as men get older. Rhodes et al. studied men using serial prostatic ultrasonography performed during a follow-up period of approx 7 yr *(31)*. In general, higher prostate growth rates were seen in men with larger baseline glands, and the average annual change was 1.6% across all age groups. Although urinary symptoms may worsen because of ongoing prostatic enlargement, it is also likely that some component of symptom progression is attributable to increased bladder dysfunction associated with aging and other factors.

In addition to aging, a variety of other factors have been investigated in men with BPH. In many cases, disparate results have been noted in different trials. Platz et al. studied the role of racial or ethnic origin in the prevalence of BPH among American male health professionals *(26)*. Included in the study were 1508 men who underwent surgery for BPH between 1986 and 1994 and 1837 men who had moderate-to-severe LUTS during approximately the same time period. In addition, more than 23,000 asymptomatic men were also included. The authors of this study found that African-American men were not at increased risk for BPH compared with white men. Although Asian men were less likely to have undergone surgery for BPH than white men, the relative risk for symptoms was similar in the two groups. White men of Scandinavian heritage had a slightly decreased likelihood of BPH symptoms than white men of southern European origin. Homma et al. studied approx 7500 men in Asia and Australia using the I-PSS and compared their results to those found in studies of men in Europe and North America *(32)*. They concluded that the prevalence of symptomatic men in Asia and Australia is similar or greater than the number among the comparison group. Studies have also been conducted concerning the role of

family history in the development of BPH and urinary symptoms *(33)*. Using the Olmstead County population in Minnesota, 2119 men completed symptom scores, had their flow rates measured, and were questioned regarding their family history of BPH and prostatic enlargement *(33)*. The age-adjusted odds ratio of having moderate or severe urinary symptoms was elevated to 1.3 among those with a family history. The relative risk was also greater for men with relatives diagnosed with BPH at a younger age. Finally, men with a family history were also 1.3 times more likely to have a diminished Qmax.

The role of a variety of lifestyle factors in the development of BPH has also been investigated. Three studies have addressed the effect of cigarette smoking on prostate size and BPH *(34–36)*. Meigs et al. followed 1709 men age 40 to 70 yr for a mean of 9 yr *(34)*. Men were classified with clinical BPH if they reported frequent or difficult voiding and were told by a physician that they had an enlarged prostate, or if they had undergone surgery for BPH. Using this classification, cigarette smoking appeared to lower the risk of developing clinical BPH. Similarly, in a study of Japanese men who underwent transrectal ultrasonography with measurement of prostate size, it was found that men who smoked cigarettes had a lower risk of prostatic enlargement *(35)*. Contrasting results regarding the effects of cigarette smoking were noted, however, in a study of Greek men *(36)*. In this investigation, which included men who were surgically treated for BPH and normal controls, cigarette smoking had no major effect on the incidence of BPH.

The relationship between diet and BPH has been explored by several investigators *(34,35,37)*. Lagiou et al. studied Greek men with and without prostate disease and found that increased consumption of both butter and margarine was positively associated with the risk of BPH *(37)*. In addition, fruit intake appeared to lower the risk of BPH. In an American study, no association between total or fat calorie intake and the development of BPH was noted *(34)*. Nukui has reported that higher serum levels of β-carotene were seen in men with BPH compared to those without prostate disease *(35)*. In addition to dietary factors, it has been suggested that obesity may play a role in the development of BPH *(38)*. Possible reasons for this include the increase in estrogen-androgen ratio that occurs in obesity and greater sympathetic nervous system activity *(38)*. Giovannucci et al. studied the association between obesity and BPH in men age 40 to 75 yr who were participants in the Health Professionals Follow-Up Study *(38)*. These investigators found that abdominal obesity may increase the frequency and severity of urinary obstructive symptoms and did increase the likelihood of men undergoing surgical treatment for BPH. In contrast to these results, Meigs et al.

reported that body mass index and waist-hip ratio were not helpful in predicting the presence of clinical BPH *(34)*.

Hyperinsulinemia has been suggested to be a risk factor for the development of BPH *(39)*. Hammarsten and Hogstedt studied 307 men with LUTS to investigate the effects of metabolic disease and fasting plasma insulin levels on the annual growth rate of the prostate *(39)*. Prostate volume was determined by serial transrectal ultrasound, and insulin levels were assessed from fasting blood samples. Serum cholesterol levels, blood pressure, history of hypertension, body height and weight, and body mass index were also assessed. In the entire group of patients, the median annual prostatic growth rate was 1.03 mL/yr. This growth rate was significantly faster in men with metabolic disease, noninsulin-dependent diabetes mellitus, treated hypertension, obesity, and dyslipidemia. In addition, the prostatic growth rate correlated positively with the diastolic blood pressure and the body mass index and correlated negatively with the high-density lipoprotein cholesterol level. High fasting plasma insulin levels also correlated with the annual prostate growth rate and were an independent predictor of prostate gland volume using multivariate analysis. The authors of this study concluded that hyperinsulinemia is a causative factor in the development of BPH and felt that their findings supported the concept of increased sympathetic activity in men with BPH.

Oh et al. investigated the association of BPH and male-pattern baldness *(40)*. Both are androgen-dependent and it is logical to presume that there may be an increased incidence of prostatic enlargement and/or BPH symptoms among bald men. The study involved 225 patients with BPH and 160 controls of similar age *(40)*. Baldness was graded on a scale of 1 to 7 (Norwood classification), and BPH was evaluated using the I-PSS. The investigators found that patients with BPH had a higher grade of male-pattern baldness compared with controls. Overall, the proportion of men with baldness of grade 4 or greater in the BPH group was significantly larger than that of the control group (54 vs 37%). Finally, limited study suggests that physical exercise may have a protective effect against the development of clinical BPH, and alcohol intake was not helpful in predicting the presence of BPH *(34,35)*.

ECONOMICS OF BPH

It is likely that the cost of treatment associated with BPH will continue to rise in upcoming years for a variety of reasons. The aging population in the United States and other Western countries will result in a greater number of men with BPH who will require treatment. It has

been estimated that by the year 2020 there will be 65 million Americans 65 yr of age or older *(41)*. In addition, new pharmacologic and technologic developments are likely to improve the therapy of BPH and lower the incidence of side effects, thus leading more men to choose to be treated. Newer technology is generally more expensive, however, which will further increase costs. Finally, a greater awareness among laypersons regarding prostate disease and treatment options is likely to increase the number of men seeking medical attention for BPH.

There is a great deal of information that is unknown regarding the cost-effectiveness associated with the evaluation and management of men with BPH *(42)*. Although the details are beyond the scope of this chapter, a variety of diagnostic methods are available to the physician when assessing men with LUTS. There remains much controversy surrounding the use of these tests, and no clear consensus has been reached in many cases. Similarly, the growing treatment options available for men with BPH have only added to the confusion regarding the best and/or most cost-effective options. Although medical therapy may be less expensive in the short term, surgical or device therapy may ultimately be less expensive when long-term costs are considered *(43)*. Much work needs to be done in these areas as we strive to define the best approach to evaluate and manage men with BPH.

SUMMARY

BPH is an important cause of diminished quality of life among aging men, and the prevalence of this condition in the United States is likely to grow as the population ages. A variety of definitions of BPH is available based on the presence of urinary symptoms, prostatic enlargement, and/or the histologic finding of hyperplastic glands. In addition, urodynamic results demonstrating decreased urinary flow rates or bladder outlet obstruction may also be used to help define the presence of BPH. Although nonspecific, the presence of LUTS such as frequency, hesitancy, or nocturia are most commonly used to define the prevalence of BPH. Overall, the introduction and validation of symptom questionnaires such as the I-PSS has added greatly to our understanding of the extent and magnitude of BPH in a variety of populations.

A number of epidemiologic factors have been investigated among men with BPH. Although aging clearly has the most important effect on the development of prostatic enlargement and urinary symptoms, a variety of other factors may also play a role in the occurrence of BPH. It appears that racial or ethnic background may play a minor role in the incidence of BPH. However, African-American men do not appear to be

at increased risk compared with whites and other groups. Although a family history of BPH appears to increase the overall likelihood that urinary symptoms and prostatic enlargement will occur, the ambiguity associated with the definition of BPH among relatives is a limiting factor. Among lifestyle factors, cigarette smoking seems to lower the risk of BPH, whereas obesity and a high-fat diet may increase the incidence of prostatic enlargement. Conflicting results have been reported, however, in different studies, and the precise role of many factors in the development of BPH remains largely unknown. As the importance of BPH grows, it is likely that further information will become available regarding the role of epidemiologic factors in BPH.

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