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# Benign prostatic hyperplasia: epidemiology, economics and evaluation

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VUICHOUD C, LOUGHLIN KR. Benign prostatic hyperplasia: epidemiology, economics and evaluation. *Can J Urol* 2015;22(Suppl 1):1-6.

**Introduction:** Benign prostatic hyperplasia (BPH) is arguably the most common benign disease of mankind. As men age, the prostate inexorably grows often causing troubling symptoms causing them to seek out care. While traditionally treated by transurethral resection or open surgical removal of the hypertrophied adenoma, today the urologist has numerous medical, surgical and minimally invasive techniques available. In this supplement *The Canadian Journal of Urology* provides a review of the various techniques and medications available today.

**Materials and methods:** As an introduction to the supplement, the aim of this article is to review the epidemiology and economy of BPH as well as its natural history and diagnosis. A systematic review

of available literature was looking for articles on BPH and its epidemiology, economics, natural history and management using PubMed database.

**Results:** The prevalence of this condition is increasing with the population aging and so does the economic burden. The exact etiology of this condition is unknown, but some risk factors have been identified. The diagnostic and treatment of this very common disease should rely on a strong collaboration between primary care physician and urologist.

**Conclusion:** There are multiple options in treating BPH including medical, surgical and newer minimally invasive options. The challenge with having a variety of options is to review them with the patient and help the patient select the best treatment option for their condition.

**Key Words:** benign prostatic hypertrophy, lower urinary tract symptoms

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## Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases of mankind. The exact prevalence varies by the definition used and the population studied. However, a seminal study by Berry et al<sup>1</sup> summarizing data from five prior studies showed that no men younger than 30 had evidence of BPH and the prevalence of BPH was 8 percent in the fourth decade, while 50 percent of men had evidence of pathologic BPH when they were between 50 to 60 years old. They estimated that the doubling time of BPH growth is 4.5 years between the ages of 31-50 and 10 years between the ages of 51 to 70.

BPH growth is inexorable with aging, the rate of growth is variable from individual to individual. The Olmstead County Study reported longitudinal data that suggested an annual prostate growth rate of 1.6% as measured by transurethral ultrasonography.<sup>2</sup> Roehrborn et al<sup>3</sup> followed a cohort of 344 men between the ages of 40-60 years old without clinical evidence of BPH and measured their prostate volume by endorectal coil MRI. The mean total prostate volume increased from 31.3 to 33.7 to 36.1 to 43.1 mL in increments of 5 years.

## Risk factors

Analytical epidemiological studies have been undertaken to evaluate risk factors for the development of BPH. Studies by Lytton et al<sup>4</sup> and Glynn et al<sup>5</sup> have reported an association between the Jewish religion and a higher rate of prostate surgery. However, it is

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unclear whether these studies represent selection bias, as this patient population may seek medical care more often than others. Araki et al<sup>6</sup> and Glynn et al<sup>5</sup> found higher rates of BPH in upper income groups, but again this may be due to selection bias due to higher utilization of medical care. Jacobsen et al<sup>7</sup> utilizing data from the Olinstead County study found no relationship between the frequency of ejaculation and BPH.

Although autonomic hyperactivity has been implicated in the development of lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) in the older man, McVary et al<sup>8</sup> did not find a convincing association between hypertension and BPH. Inflammation, whether local or systemic, can be an etiologic factor in the development of BPH. Several studies have shown that BPH is an immune inflammatory disease,<sup>9</sup> and that chronic prostatic inflammation has a role in the pathogenesis of this disease.<sup>10</sup> Increased serum C reactive protein levels have been associated with LUTS in men with BPH.<sup>11</sup> The action of PDE-5 inhibitors on BPH is thought to be due, in part, to an anti-inflammatory action.<sup>12</sup>

Obesity markedly increases the risk of BPH,<sup>13,14</sup> and a link is suspected between BPH and diabetes.<sup>15</sup> In addition, the metabolic syndrome is thought to be associated with BPH and LUTS,<sup>16,17</sup> probably through chronic inflammation. Similarly, physical activity decreases the risk of BPH.<sup>18,19</sup> Several mechanisms for this relationship have been proposed, including decreased sympathetic tone and reduced oxidative damage to the prostate. Since obesity seems to attenuate the dutasteride effect,<sup>20</sup> these observations support the development of novel prevention strategies and treatment targeted toward adiposity, weight loss and lifestyle, and a personal management of BPH, based on patient comorbidities.<sup>21</sup> There also appears to be a genetic component to BPH. Studies on twins identified a hereditary component<sup>22</sup> with an autosomal dominant inheritance profile.<sup>23</sup>

## Economics of BPH treatment

The true cost of intervention and treatment of BPH is comprised of three components. First, direct costs (drugs, procedures, imaging, office visits), second, indirect costs (lost earnings) and third, intangible costs (pain and suffering). It has been estimated that BPH treatment costs approximately \$4 billion annually in the United States.<sup>24</sup> It should be acknowledged, that although BPH is commonly thought of a disease of older men, the costs of treating BPH begin to accrue with men in their 40s. By examining medical claims data, Saigal and Joyce<sup>25</sup> found a prevalence of BPH

TABLE 1. Demographics of urologic practice

Percent diagnosis seen by urologists	
Urinary tract infection	32%
Benign prostatic hyperplasia	23%
Painful bladder	12%
Prostate cancer	10%
Kidney/bladder stones	8%
Erectile dysfunction	8%
Urinary incontinence	7%

adapted from Amerson D<sup>26</sup>

treatment of 4.7% in men between 45 to 54 years old which rose to 14.3% in men between 55 to 64 years old. They calculated the incremental cost associated with a diagnosis of BPH to be \$1536 annually. They reported that the average time lost from work was 7.3 hours yearly. The diagnosis and treatment of BPH represents the largest segment of urologic practice, representing 23% of all office visits, Table 1.<sup>26</sup> An analysis of the BPH market reveals that 12.2 million BPH patients are managed each year, Table 2.<sup>26</sup> The majority, 54.8%, are treated with medication, 35.0% are observed and 1.1% are treated surgically.

It is reasonable to expect that the economic costs of BPH treatment will only increase in the future. This is due in large measure to the aging of the population. It is estimated that by 2030, 20% of the United States population will be 65 years of age or older and the fastest growing segment in that population will be those older than 85 years.<sup>27</sup>

TABLE 2. United States benign prostatic hyperplasia (BPH) market

2015 patient population breakdown	
38.1 million men with BPH pathology (age > 30)	
21.3 million men with IPSS > 7 (age 40-79)	
12.9 million men who consulted MD for BPH	
12.2 million men actively managed for BPH/LUTS	
Actively managed (12.2 million)	
54.8% drug management	
35.0% watchful waiting	
9.1% drugs discontinued – watchful waiting	
1.1% surgery / procedure	

adapted from Amerson D<sup>26</sup>

## Pathogenesis and natural history

The precise etiology of BPH is not well understood. It is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate. The increase in cell number may be due to epithelial and stromal proliferation or due to decreased programmed cell death. Either mechanism can lead to cellular accumulation. Androgens are critical to the development of BPH. However, it is not testosterone, but rather its active metabolite, dihydrotestosterone (DHT) that causes prostatic growth. Testosterone is converted to DHT by the enzyme 5-alpha reductase.<sup>28</sup> However the pathogenesis of BPH goes beyond just DHT. Androgen receptors in the prostate appear to be critical for the development of BPH. In fact, there is animal data to suggest that estrogens sensitize the prostate to the effects of androgens.<sup>29</sup> BPH appears to be primarily a stromal disease, but it is unclear where the initiating events occur. There has also been consideration that inflammation may be related to the genesis of BPH.<sup>30</sup> Cytokines (IL-2, IFN alfa, IL-6, IL-8 and IL-15) have been identified in areas of fibromuscular prostatic growth, but their exact role in BPH development remains unanswered.<sup>31,32</sup>

## Current terminology

Various terms are employed in the literature to describe BPH and its consequences. Below is a glossary of these terms following the international guidelines.<sup>33</sup>

**BPH (benign prostatic hyperplasia)** is a histological diagnosis, defined by an unregulated proliferation of connective tissue, smooth muscle and glandular epithelium within the prostate transition zone.<sup>34,35</sup> Clinically, BPH is diagnosed when a bladder outlet obstruction (BOO) (urodynamic or suspected by voiding symptoms or flow rate measurement) is attributed to a prostatic enlargement (clinical or not). However, LUTS that are suggestive of BOO may be caused by a poorly functioning detrusor muscle instead of a prostatic pathology.

**BPE (benign prostatic enlargement)** refers to the objective prostatic volume increase, linked with the cellular proliferation, without prejudging the clinical consequences of this enlargement (symptomatic or not). The term prostatic enlargement should be employed when BPH has not been histologically confirmed.

**BOO (bladder outlet obstruction)** defined by the International Continence Society as an increase in detrusor pressure and reduced urine flow rate, without presuming its cause (prostatic or not). It can be highly suspected in a modification of flow rates.<sup>36</sup>

**LUTS (lower urinary tract symptoms)** are classified in three categories related to storage, voiding, or post micturition.<sup>37</sup> Historically, terms such as "prostatism", or "clinical BPH" have been employed to describe male urinary symptoms. But as these symptoms can have different origins (prostatic, bladder, neurologic), it is now recommended to use the more inclusive term LUTS, which doesn't prejudge the etiology of the symptoms.<sup>38</sup> **Voiding symptoms** correspond to urinary hesitancy, delay in initiating micturition, intermittency, weak urinary stream and dysuria. **Storage symptoms** correspond to urinary frequency, nocturia, urgency with or without incontinence. **Post micturition symptoms** which correspond to sensation of incomplete voiding, and/or postmicturition dribbling. LUTS is an expression of bladder, bladder neck, prostate, sphincteral or urethral lesions. We will focus our discussion in this supplement on LUTS due to BPH.

**OBS (overactive bladder syndrome)** associates urgency with or without incontinence, urinary frequency and nocturia.<sup>36</sup> This syndrome occurs between 12% and 15% of men,<sup>22,39</sup> and the incidence increases with age.<sup>22</sup> OBS or OAB (overactive bladder) is due to intrinsic bladder dysfunction.<sup>23</sup>

**DO (detrusor over activity)** is defined urodynamically by involuntary detrusor contraction during the bladder filling phase. It is important to take this into account, especially in cases of OBS, as nearly 50% of men with LUTS and urodynamically confirmed BOO have DO.<sup>40</sup>

## Diagnostic approaches to BPH

The aim of the clinical exam is to evaluate symptoms, look for other potential etiologies of LUTS, and estimate the consequences. The urologic history should include the onset and the severity of LUTS with identification of medications like diuretics, as 10% of LUTS are iatrogenic.<sup>41</sup> The history will focus on excluding other etiologies of LUTS, such as neurologic causes or bladder dysfunction. The history will also inquire about associated symptoms such as gross hematuria or urinary tract infections.

Voiding symptoms are most common, with polyuria a common complaint,<sup>42</sup> but storage symptoms are the most bothersome.<sup>43</sup> To assess the severity of LUTS, two symptom score systems which are self administered and internationally validated are utilized.<sup>44,45</sup>

The AUA-SI (American Urological Association-Symptoms Index) assesses the severity of three storage symptoms and four voiding symptoms.<sup>46</sup> The IPSS (International Prostate Symptoms Score), contains the same topics with one more question about quality of life, which is useful for BPH management. The use of

one of these two scores is recommended for an objective assessment of symptoms at the time of diagnosis, and to follow therapeutic efficacy. BPH severity is quantified as mild (AUA-SI score  $\leq 7$ ), moderate (from 8 to 19) and severe ( $> 20$ ). A minimum of 3 point-changes is considered as a clinically meaningful improvement. It is important to assess the impact of symptoms on quality of life. The impact of LUTS symptoms shouldn't be underestimated, as it can be highly bothersome and lead to anxiety and depression in older men with severe LUTS.<sup>47</sup>

In evaluation of a patient for LUTS history, it is also important to inquire about sexual function.<sup>48</sup> Men with multiple LUTS are more likely to have sexual dysfunction,<sup>49,50</sup> which can play a synergic role in deteriorating quality of life. It is important to document the presence of ED as some BPH medications can impact sexual function.<sup>50</sup>

Physical examination should include digital rectal examination (DRE) to assess prostate volume, nodularity and asymmetry. However, DRE tends to underestimate the prostate volume and has a low sensitivity for detecting prostate cancer. The physician should assess for bladder distension and neurologic impairment, to rule out causes of LUTS independent from BPH.

The following are recommended tests in primary management, according to AUA guidelines:<sup>33</sup>

- 1) Serum prostate-specific antigen (PSA) in men who have more than 10 years of life expectancy, to detect any associated prostate cancer. Moreover, among patients without prostate cancer, serum PSA may be a valid marker of prostate size and also predict risk of BPH progression.<sup>51</sup>
- 2) Urine analysis to evaluate for hematuria, proteinuria or leukocyturia which would require more investigation.

The following are considered optional tests based on the clinical situation:

- Post void residual urine measurement if chronic urinary retention is suspected.
- Frequency volume chart when nocturia is predominant to detect nocturnal polyuria.
- Serum creatinine is not recommended routinely as baseline renal insufficiency appears not to be more common in men with BPH. It may be necessary if a surgery is planned.
- Prostate or upper urinary tract ultrasonography, or pressure flow studies are not recommended routinely.

Several promising biomarkers of BPH are still under study, for BPH diagnosis and progression to assist physicians in treatment decisions, but none is routinely validated currently.<sup>52</sup>

## BPH management

The management of BPH has two goals: to reduce the bother of the symptoms, and to prevent or delay the progression of BPH related symptoms. Different levels of treatments exist for BPH symptoms and its consequences, from watchful waiting, to surgery, to medication. Treatment choices should be guided by severity of BPH symptoms (IPSS or AUA-SI score) existing signs of complicated LUTS (gross hematuria, recurrent urinary tract infection), how much the symptoms are bothering the patient and patient preference. Physicians should equally consider the presence of age-related comorbidities (e.g., diabetes, metabolic syndrome or ED) and the potential for a given treatment to negatively affect these conditions.

Patients with mild symptoms, or non-bothersome moderate to severe symptoms, do not require further treatment. In these cases watchful waiting is appropriate, which is based on pure medical follow up after reassurance about the disease without any treatment. Patients are usually reexamined yearly, repeating the initial evaluation.

Patients with bothersome symptoms may be primarily treated either medically or surgically. The first step for each patient should be "self management" including patient information about his condition, lifestyle and behavioral modifications to reduce urinary symptoms and to avoid or delay the disease progression and escalation in symptoms.<sup>53</sup> These lifestyle modifications include: weight loss, decreasing evening fluid intake, avoiding excess alcohol or caffeine, altering the timing of medications such as diuretics and smoking cessation.

Medical therapy is a common primary option in patients with mild or moderate voiding symptoms. Six classes of drugs are currently available to manage symptomatic LUTS associated with BPH: alpha blockers, 5-alpha reductase inhibitors, phosphodiesterase type 5 inhibitors, antimuscarinics, beta-3 adrenoreceptor agonists and a variety of complementary and alternative medicines. Van Asseldonk and associates provide a review of currently approved agents in the management of BPH and Keehn and Lowe describe the current state of complementary and alternative medications used for this condition.<sup>59,60</sup> The AUA recommends surgery if medical therapy fails, or the patient develops BPH related complications such as hematuria, bladder calculi or recurrent urinary tract infection, renal insufficiency or chronic urinary retention. There are now a wide variety of surgical approaches to the management of BPH. These include traditional and newer transurethral approaches using electro-surgical and laser techniques, open, laparoscopic

and robotic techniques as well as newly approved and evolving minimally invasive approaches. All of these approaches are reviewed later in this supplement.

## Conclusions

As BPH is a very common disease among older men and with the aging of the population there is a greater emphasis on the role of the primary care physician (PCP) in the management of BPH patients. Despite many differences in initial management of BPH between PCPs and urologists,<sup>54,55</sup> the PCP and the urologists should work as a team. Several studies have shown that only 1/3 of patients bothered by LUTS were aware of the pharmacologic or surgical interventions available to treat BPH, and only a minority sought treatment.<sup>56,57</sup> This underscores the need for better education about BPH and its treatments. With proper education, PCPs can assume an important role in the detection of BPH and LUTS, and in the identification of those at risk of progression. It is imperative that PCPs routinely inquire about urinary function with men over the age of 50.<sup>58</sup> Primary care providers have the option of either assuming the responsibility of BPH treatment or referring the patient to a urologist.

## Disclosure

Dr. Camille Vuichoud and Dr. Kevin R. Loughlin have no disclosures. □

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