Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia (LUTS/BPH): More Than Treating Symptoms?

Mark J. Speakman*
Musgrove Park Hospital, Taunton & Somerset NHS Foundation Trust, Taunton, Somerset TA1 5DA, United Kingdom

Article info

Keywords:
Acute urinary retention
Aetiology
Benign prostatic hyperplasia
Pathogenesis
Progression
Quality of life
Treatment

Abstract

Context: During the last two decades, it has become clear that the management of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) is much more than just treating symptoms.

Objective: This review paper gives an overview of the main factors influencing individual treatment decisions for LUTS/BPH patients.

Evidence acquisition: This paper summarizes the content of an update lecture held during a symposium on the management of LUTS/BPH at the 2008 European Association of Urology meeting. During the presentation, the current decision drivers were discussed based upon recent literature and illustrated with the results of a Web-based survey evaluating urologists' opinions on LUTS/BPH management.

Evidence synthesis: The treatment of choice depends on the severity and type of LUTS, which are nowadays believed to have a multifactorial aetiology. Consequently, treatment for LUTS/BPH should not focus merely on the prostate, but also on other organs involved in disease pathogenesis. In addition, the progressive character of LUTS/BPH is an important driver when taking treatment decisions. Patients at low risk of disease progression require a fast and sustained symptom relief with minimal treatment morbidity, while patients at high risk of progression additionally require continuous treatment delaying LUTS/BPH progression and the development of complications. Therefore, clinicians should be able to determine a patient's individual risk of progression. At present, seven baseline parameters and three dynamic variables have been identified as predictors of LUTS/BPH progression. Furthermore, as the quality of life (QoL) of both patients and their partners is severely affected by LUTS/BPH, this aspect should also be considered. Finally, treatment decisions are also influenced by existing comorbidities in the patient.

Conclusions: Treatment for LUTS/BPH should aim at relieving the symptoms and especially at improving the patient's QoL with minimal treatment morbidity. Furthermore, LUTS/BPH treatment should be adapted to the patient's individual risk of disease progression.

© 2008 European Association of Urology. Published by Elsevier B.V. All rights reserved.
1. Introduction

Benign prostatic hyperplasia (BPH) is a disorder that is macroscopically characterized by an enlargement of the prostate gland and histologically caused by the progressive hyperplasia of stromal and glandular prostatic cells. This nonmalignant overgrowth of prostatic tissue might ultimately lead to constriction of the urethral opening. Consequently, clinical BPH is often associated with lower urinary tract symptoms (LUTS). In fact, BPH is the main cause of LUTS in ageing men. About half of the male population over the age of 50 can be diagnosed with histological BPH, and this prevalence increases with age to about 90% over the age of 80[1]. Clinically, about one-third of men in their sixth decade of life suffer from moderate-to-severe LUTS, and this percentage rises to about 45% in men older than 70[2].

The classical treatment for LUTS/BPH mainly focused on symptom relief by surgical removal of the enlarged prostate, thereby relieving urinary outflow obstruction[3]. However, during the last two decades, it has become clear that the management of LUTS/BPH—either by watchful waiting, by pharmacological treatment with \(\alpha_1\)-adrenoceptor (\(\alpha_1\)-AR) antagonists and/or 5a-reductase inhibitors, or by (minimally invasive) surgery—is much more than just treating symptoms. To date, four modern drivers for taking individual treatment decisions for LUTS/BPH can be discerned.

In this paper, the impact of the multifactorial aetiology and the progressive character of LUTS/BPH on the management of this condition will be discussed. In addition, the risk factors for disease progression, as well as additional factors influencing individual treatment decisions, will be reviewed.

2. Evidence acquisition

This paper summarizes the content of an update lecture held during the symposium “The future of LUTS/BPH: management beyond the prostate” at the annual meeting of the European Association of Urology in 2008. During the presentation, an overview of the current drivers for taking individual treatment decisions on LUTS/BPH was given based on recent literature. Furthermore, the results of a Web-based survey evaluating urologists’ opinions on the management of LUTS/BPH were used to illustrate the key points of the presentation.

3. Evidence synthesis

3.1. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia have a multifactorial aetiology and a progressive character

3.1.1. Multifactorial aetiology of lower urinary tract symptoms suggestive of benign prostatic hyperplasia

Lower urinary tract symptoms secondary to BPH can generally be classified as voiding symptoms (previously called obstructive), storage symptoms (previously called irritative), and post-micturition symptoms[4]. Voiding symptoms such as slow stream, splitting or spraying of the urine stream, intermittent stream, hesitancy, straining, and terminal dribble are believed to result from obstruction at the level of the prostate. This obstruction can be caused by an increase in prostate volume (mechanical or static component of obstruction) and/or by an increased smooth muscle contraction in the prostate, bladder neck, and urethra (dynamic component of obstruction).

In contrast, storage symptoms such as nocturia, urgency, increased daytime frequency, and urinary incontinence are thought to have a more complex aetiology[3,5]. For a long time, these symptoms were believed to result from obstruction- and/or age-induced detrusor instability (see 3.1.2.1.)[6,7]. However, it has now become clear that extraprostatic mechanisms such as stimulation of \(\alpha_1\)-ARs in the bladder, and especially the \(\alpha_{1D}\)-AR subtype, which predominates in the human detrusor, also play a role in the development of storage symptoms[5,8,9]. However, further studies are needed to define exactly the role of these receptors in humans.

In addition, \(\alpha_1\)-ARs located in peripheral ganglia and/or spinal cord segments are also thought to contribute to the aetiology of LUTS/BPH. They might facilitate the release of acetylcholine, resulting in the activation of muscarinic receptors in the detrusor, increased bladder contractions, and the concomitant development of storage symptoms[5]. Furthermore, bladder muscarinic receptors and purinergic receptors themselves might also play a role in the pathogenesis of LUTS, as witnessed by the effectiveness of antimuscarinic agents in the treatment of overactive bladder (OAB) and by the changes in muscarinic and purinergic receptor expression in OAB (idiopathic or induced by bladder outlet obstruction)[9–12].

Finally, several other factors have been suggested to affect bladder function and to contribute to LUTS, such as the endocrine, renal, and cardiac systems[3,9].
In conclusion, it is clear that not only obstruction at the level of the prostate, but many other, often overlapping, factors are also involved in the aetiology of LUTS/BPH. Therefore, treatment should not only focus on the prostate, but should also take the other players in the pathogenesis of the disease into account.

3.1.2. Progressive character of lower urinary tract symptoms suggestive of benign prostatic hyperplasia

3.1.2.1. Progressive cellular changes in the bladder

Although the bladder is one of the aetiopathological factors in the development of LUTS/BPH, the organ itself also suffers from outlet obstruction. Indeed, following partial outlet obstruction, the bladder undergoes progressive pathological changes in which three distinct phases can be discerned [6,13,14].

As an initial response to the progressive increase in urethral resistance, the bladder reacts with hypertrophy of smooth muscle cells, urothelial and interstitial fibroblast hyperplasia, and increased collagen synthesis and deposition. Together, these events result in a progressive increase in bladder mass during this initial stage. As soon as the bladder mass is sufficient to maintain detrusor contractility and bladder emptying, the bladder enters the compensated stage. In this phase, bladder mass remains stable, but the progressive changes in cellular structure and function still continue. Finally, these alterations interfere with the compensatory mechanisms, resulting in destabilization of bladder function and in the initiation of the decompensated phase. This final stage is characterized by a further increase in bladder mass and a progressive decrease in smooth muscle in the bladder wall, leading to a deterioration of bladder contractility. In addition, the increase of connective tissue negatively affects bladder elasticity. Therefore, end-stage decompensated bladders have a poor contractile function and/or poor compliance.

These progressive pathological processes in the bladder might not only be evoked by chronic outlet obstruction, but also by age-related changes in the lower urinary tract. Indeed, increasing age was shown to be associated with a decrease in detrusor contractility, bladder capacity, and ability to withhold voiding and an increase in postvoid residual (PVR). Moreover, the prevalence of detrusor overactivity and nocturia increases with age [7].

In animal models, these pathological events have been shown to be reversible as long as the bladder is in the compensated stage [13]. However, as soon as it enters the decompensated stage, removal of partial outlet obstruction only induces a partial recovery of bladder function proportional to the level of decomposition. Finally, when decompensation progresses beyond a critical point, bladder damage becomes irreversible, and bladder dysfunction proceeds to end-stage decompensation.

In the long term, this obstruction- and/or age-induced bladder damage can result in the development of serious complications in humans such as urinary tract infections, bladder stones, acute urinary retention (AUR), or renal failure [14].

From the aforesaid, it is clear that LUTS/BPH have a progressive character, at least in some of our patients. Therefore, it is important to initiate treatment at an early stage in those patients at risk, when pathological changes are still reversible. Only in this way can bladder function be maintained and disease progression and the development of serious complications be avoided.

3.1.2.2. Natural history of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: incidence of clinical progression events

The importance of early treatment initiation for LUTS/BPH is further underscored by the substantial incidence of disease progression events in the general population, which can be assessed either from longitudinal community-based studies or from placebo arms of controlled trials.

One of the longitudinal studies that provided the largest body of evidence was the Olmsted County study, in which a randomly selected cohort of 2115 middle-class North American Caucasian men aged 40–79 yr was followed. In this study, severity of LUTS was significantly increased at follow-up, as illustrated by the progression of 22% of men with mild symptoms at baseline to moderate-to-severe symptoms after 42 mo and by a mean annual increase in International Prostate Symptom Score (IPSS) of 0.18 points [15]. Moreover, median peak urinary flow rate (Qmax) also decreased by 2.1% per year [16], while prostate volume was significantly increased at follow-up, as illustrated by a cumulative incidence of AUR of 2.7% over 4 yr [18].

Comparable results, showing a clear deterioration of symptoms but a low incidence of serious complications such as AUR, were also obtained from several other longitudinal population-based studies [19–21].

This progressive character of LUTS/BPH and the main contribution of symptom worsening to overall clinical progression was also confirmed in the placebo arm of the Medical Therapy Of Prostatic Symptoms (MTOPS) study [22]. This double-blind controlled trial, following a total of 3047 men aged...
≥50 yr with moderate-to-severe LUTS and a Qmax of 4–15 ml/s, was designed to assess the impact of medical therapies on the risk of BPH progression. The cumulative incidence of overall clinical progression (defined as the first occurrence of a ≥4-point increase in IPSS, AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infection) appeared to be 16.6% over 4 yr. Symptom deterioration accounted for the largest proportion (79.5%) of these progression events, while AUR (14.8%, corresponding to a cumulative incidence of 2.4% over 4 yr), incontinence (4.9%), and urinary tract infection or urosepsis (0.8%) occurred less frequently.

From the studies described above, it is clear that—despite the low incidence of serious progression events such as AUR and BPH-related surgery—disease progression occurs significantly in patients with LUTS/BPH when left untreated. Since reversion of the pathological bladder changes underlying these progression events becomes impossible beyond a certain point, treatment should aim at preventing progression of LUTS/BPH at an early disease stage. Consequently, medical physicians should be able to determine a patient’s individual risk of disease progression before taking treatment decisions. The currently known risk factors for progression of LUTS/BPH, as well as other modern drivers for taking decisions in the management of the disease, will be discussed extensively in the next section.

3.2. Modern drivers for taking individual treatment decisions

3.2.1. Risk factors for the progression of lower urinary tract symptoms suggestive of benign prostatic hyperplasia

Until now, seven parameters have been described to be predictors of LUTS/BPH progression at baseline; that is, age, severity of LUTS at baseline, prostate volume, prostate-specific antigen (PSA) levels, Qmax, PVR, and prostatic inflammation. In addition, three dynamic variables have been recognized as predictors of future disease-related events [23]. Convincing evidence that the baseline parameters age, severity of symptoms, prostate volume, Qmax, and PVR have a predictive value for the risk of LUTS/BPH progression was obtained from the Olmsted County Study. The relative risk of AUR was shown to be increased about eight times in men aged 70–79 yr compared to men aged 40–49 yr. Furthermore, a more than three times increased relative risk of AUR was observed for men with moderate-to-severe symptoms compared to men with mild LUTS, while men with a prostate volume >30 ml had a threefold increased relative risk of AUR. In addition, a baseline Qmax ≤12 ml/s increased the relative risk of AUR about fourfold [18], and a PVR >50 ml augmented this risk about three times [24].

The findings of this longitudinal community-based study were subsequently confirmed in the placebo arms of several controlled studies, such as the MTOPS study [22,25] and the PROscar Long-Term Efficacy and Safety Study (PLESS), a finasteride study which enrolled 3040 men in the US with moderate-to-severe LUTS, Qmax <15 ml/s, and an enlarged prostate [26]. Moreover, two new baseline variables were identified as predictors of LUTS/BPH progression in these studies; that is, PSA levels and prostatic inflammation.

Serum PSA was demonstrated to be a powerful predictor of the risk of AUR and the need for BPH-related surgery in men with BPH in the PLESS trial, showing an increase in 4-yr cumulative incidence of AUR from approximately 6.5% in men with a serum PSA level <1 ng/ml to about 14% in men with PSA levels >7 ng/ml [26]. The predictive character of PSA levels and prostate volume was subsequently confirmed in a larger multinational patient population [27] (Fig. 1).

![Fig. 1](image_url) - Impact of baseline prostate-specific antigen (PSA) levels and prostate volume on the risk of developing acute urinary retention (AUR). Data are obtained by pooling the results of three identical 2-yr multinational non-US finasteride-controlled trials (SCAndinavian Reduction of the Prostate study [SCARP], PROscar Safety Plus Efficacy Canadian Two-year study [PROSPECT], and PROscar Worldwide Efficacy and Safety Study [PROWESS]) in men with mild-to-moderate symptomatic benign prostatic hyperplasia (BPH) [27]. The percentage of patients in the placebo group developing AUR during follow-up is depicted as a function of baseline PSA level and prostate volume. High baseline PSA levels and large prostate volumes significantly increase the incidence of spontaneous AUR.
Inflammation has been thought to be involved in the pathogenesis of LUTS/BPH for over a decade. This idea was based on the observation that prostatic inflammation and LUTS/BPH frequently occur together [28,29]. However, only recently, inflammation was also suggested to be an independent risk factor for disease progression. The most convincing evidence for this hypothesis came from the MTOPS study [30]. Examination of baseline prostate biopsies in a subgroup of 1197 patients showed the presence of an acute and/or chronic infiltrate in 45% of men. In the placebo group, these men—who also had larger prostate glands and higher PSA values—displayed a remarkably faster progression rate over time than men without inflammation, as witnessed especially by the significantly higher incidence of AUR in these patients (Fig. 2).

Further support for these data was provided by several recent studies. Analysis of the baseline data from the REDuction by DUtasteride of prostate Cancer Events (REDUCE) trial, a randomized double-blind placebo-controlled study in 8224 men evaluating the effects of 0.5 mg dutasteride once daily on reducing the risk of prostate cancer, showed a weak but statistically significant correlation between the degree of histological chronic inflammation and the degree of LUTS [31].

Furthermore, by examination of longitudinal data from the Olmsted County Study, it was demonstrated that physician-diagnosed prostatitis is associated with a more than twofold increased risk of later development of BPH-associated events (prostatitis, enlarged prostate, or BPH) and a greater risk of requiring later treatment (medication or surgery) for BPH [32].

Finally, the role of inflammation in the pathogenesis and progression of BPH was confirmed in a single-centre, retrospective study in 406 patients undergoing transurethral resection of the prostate for AUR or LUTS. Men with acute and/or chronic intraprostatic inflammation were shown to have a greater risk of AUR than men without inflammation [33].

Although all these data are in line with inflammation being a risk factor for disease progression, more studies are needed to confirm this hypothesis. In this regard, the longitudinal 4-yr follow-up in the REDUCE study might provide useful information. In addition, as daily use of nonsteroidal anti-inflammatory drugs has already been shown to be inversely related to the onset of moderate-to-severe LUTS, low \( Q_{max} \), increased prostate volume, and elevated PSA levels in the Olmsted County Study [34], the potential of anti-inflammatory agents in the prevention of LUTS/BPH progression needs to be further evaluated.

Next to these seven baseline variables, three dynamic variables have been identified as predictors of LUTS/BPH progression; that is, deterioration of LUTS over time, increase in PVR over time, and symptom deterioration and/or increasing bother while receiving treatment [23].

Progressive deterioration of symptoms was first recognized as a risk factor for LUTS/BPH progression in the Health Professionals Follow-up study, a prospective cohort study analyzing the incidence of AUR among 6100 male US health professionals aged 45–83 yr. In this study, the risk of AUR was shown to be increased two- to threefold in men who had a worsening of LUTS during the 2-yr follow-up period. Moreover, this risk seemed to be independent of baseline symptom severity [21].

Next, the role of changes in PVR over time as a predictor of future LUTS/BPH-related events became clear from the placebo arm as well as from the treatment arms of the MTOPS study. Indeed, patients who did not develop AUR during the follow-up had a stable PVR throughout the study, while those who subsequently developed AUR displayed a steady increase in PVR [35].

Finally, symptom deterioration during treatment—and increasing bother during treatment, in particular—were identified as dynamic variables predicting LUTS/BPH progression in the ALFuzosin ONCe daily (ALF-ONE) study, a large open-label
“real-life” study assessing the efficacy and safety of alfuzosin at 10 mg once daily in real-life practice. Failure to respond to alfuzosin, defined as a worsening of IPSS ≥4 or a bother score >3 at the last available assessment under treatment, was shown to be a powerful predictor of AUR and BPH-related surgery in the short term (6 mo) [36] as well as in the long term (3 yr) [37].

Based on these predictors of LUTS/BPH progression, nomograms can be developed. These models use a mathematical algorithm to help physicians predict a patient’s individual risk of disease progression [38]. Currently, the MTOPS Prostatic Sample Analysis (MPSA) Consortium is trying to identify and validate new molecular markers that may identify risk of LUTS progression. Using different approaches, a high stromal-to-epithelial ratio in the prostatic transition zone, as well as 19 unique autoantigens, were shown to be associated with BPH progression. Moreover, detailed studies of various PSA isoforms revealed that incorporation of baseline serum levels of BPH-A, a mature, enzymatically inactive, uncomplexed form of PSA, significantly enhances the accuracy of nomograms in predicting AUR and BPH-related surgery [39].

Hence, it is clear that the baseline and dynamic predictors of LUTS/BPH progression can help physicians to tailor treatment to a patient’s individual risk profile of progression. Patients who are at low risk of disease progression require only a fast and continued symptom relief with minimal morbidity associated with treatment. However, for patients at higher risk of progression, symptom relief should be combined with continuous treatment aimed at delaying the progression of the disease and the development of complications [40]. In this way, the management of LUTS/BPH can become more cost-effective.

Fig. 3 – Impact of lower urinary tract symptoms (LUTS) on the quality of life (QoL) of both patients and their partners: (a) Comparison of impact on QoL of LUTS and different stages of prostate cancer (PCa) [42]. Total International Prostate Symptom Score (IPSS) and total Functional Assessment of Cancer Therapy–General (FACT–G) score (QoL questionnaire) are compared among a control population, patients with moderate or severe LUTS (IPSS score in parentheses), and patients in different clinical stages of prostate cancer (T1–T2: organ-confined prostate cancer; T3–T4: metastatic prostate cancer). Severe LUTS cause a similar decrease in the QoL as 80% advanced prostate cancer. (b) Impact of symptomatic LUTS/BPH (benign prostatic hyperplasia) on QoL of patients’ partners. The percentage of partners affected by several QoL-related issues is depicted (n = 90). QoL is considerably affected in partners of LUTS/BPH patients [44].
3.2.2. Other modern drivers for taking individual treatment decisions

Next to a patient’s current degree of symptom severity and his risk of progression and future complications, at least two additional factors also influence a medical physician’s treatment decision; that is, the patient’s quality of life (QoL) and existing comorbidities.

Although LUTS/BPH is not associated with pain and does not involve a threat to life, the disease has a significant impact on the QoL of patients. Men with LUTS, and especially nocturia and incomplete bladder emptying, experience a higher degree of bother and interference with daily activities and a higher degree of worry and impact on psychological well-being than men without symptoms [41,42]. Severe LUTS have an even greater impact on the QoL than do chronic illnesses such as diabetes, hypertension, angina, and gout [43] and advanced prostate cancer (Fig. 3a) [42]. Moreover, the QoL of both patients and their partners decreases as the severity of LUTS increases (Fig. 3b) [41,42,44]. Therefore, it is not surprising that the fear of symptom deterioration and concomitant QoL worsening is the main reason for patients to consult a physician [45]. Hence, it is clear that a patient’s QoL is one of the most important aspects that should be taken into account by clinicians when deciding upon LUTS/BPH management, as illustrated by the outcomes of a Web survey among urologists (Fig. 4).

Another factor influencing the management of LUTS/BPH is the presence of comorbidities. Indeed, as this condition is quite common in ageing men, it often occurs concomitantly with other common age-related disorders such as cardiovascular disease, hypertension, diabetes, metabolic syndrome, and erectile dysfunction [46]. Therefore, treatment decisions should also be guided by the existence of these comorbidities, since side-effects of medications might exacerbate the comorbid conditions.

4. Conclusions

From the above, it is clear that the management of LUTS/BPH is more than just treating symptoms. Four main drivers for taking individual treatment decisions can be discerned (Fig. 5).

Firstly, the treatment of choice depends on the severity and type of LUTS, which are known to have a multifactorial etiology. Voiding symptoms are believed to be caused by obstruction at the level of
the prostate, while many different mechanisms, including detrusor overactivity and aberrant stimulation of receptors in the bladder or its innervating structures, can contribute to the development of storage symptoms. Therefore, treatment for LUTS/BPH should focus not merely on the prostate, but also on other organs that play a role in disease pathogenesis such as the bladder.

Secondly, the progressive character of LUTS/BPH is an important driver for taking treatment decisions. As progressive pathological changes in the bladder become irreversible beyond a certain stage, treatment should aim at preventing disease progression in an early disease phase. Only in this way, bladder function can be maintained and the development of serious complications such as AUR can be avoided.

Consequently, physicians should be able to determine a patient’s individual risk of disease progression before taking treatment decisions. Until now, seven parameters have been described to be predictors of LUTS/BPH progression at baseline; that is, age, baseline severity of LUTS, prostate volume, PSA levels, Qmax, PVR, and prostatic inflammation. In addition, three dynamic variables; ie deterioration of LUTS over time, increase in PVR over time, and symptom worsening and/or increasing bother during treatment, have also been recognized as predictors of future LUTS/BPH-related events. Moreover, an extensive search for new biomarkers of disease progression is still going on and should result in a more accurate prediction of a patient’s risk and, therefore, in a more cost-effective management of the disease.

Thirdly, as the QoL of both patients and their partners is severely affected by LUTS/BPH and is inversely correlated with the severity of LUTS, this parameter should be considered carefully by clinicians when deciding upon LUTS/BPH treatment.

Finally, the treatment of choice for LUTS/BPH will also depend on the existence of comorbidities in the patient, since side-effects of several medications might negatively affect these concomitant disorders.

All four factors should be taken into account in the current management of LUTS/BPH. After assessing the causes of the disease and the risk factors for progression, a differentiation should be made between patients at low or at high risk of disease progression. Treatment of patients at low risk should aim at relieving the symptoms and especially at improving the QoL, thereby causing minimal morbidity or exacerbation of comorbid conditions. On the other hand, patients at higher risk of disease progression require a combination of the previous strategy with a continuous treatment that protects the bladder and avoids the development of complications. This current approach is more cost-effective and better adapted to a patient’s individual symptoms, risks, and needs than the classical treatment approach focusing merely on symptom relief.

**Conflicts of interest**

Mark Speakman received an honorarium for presenting the lecture at the EAU symposium on which this paper was based.

**Funding support**

The publication of this review was supported by Astellas Pharma Europe.
Acknowledgements

The author is grateful to Ismar Healthcare NV for their assistance in writing the manuscript.

References


