

# Rational Treatment Strategies for Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia

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## INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histological diagnosis characterized by stromal and epithelial cell hyperplasia [1]. Lower urinary tract symptoms (LUTS) are - patients' subjective perception, which are further divided into storage (increased daytime frequency, nocturia, urgency, urinary incontinence), voiding (slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribble) and post micturition (feeling of incomplete emptying, post micturition dribble) symptoms [2]. Both BPH and LUTS are very common in aging men [3]. Approximately half of patients with BPH present with moderate to severe LUTS [3], however, not all men with an enlarged prostate will develop LUTS [3]. In contrast, LUTS are neither BPH-specific nor even male-specific [2-5]. The symptoms may originate from neurophysiologic changes that may or may not be associated with bladder outlet obstruction [6]. The 4th International Consultation on BPH recommended use of the term "LUTS suggestive of BPH" (LUTS/BPH) referring to LUTS that may be attributed to an enlarged prostate [7].

## INITIAL EVALUATION

For all patients presented with LUTS/BPH, medical history should be taken to identify other possible cause(s) of voiding dysfunction and associated co-morbidities which might influence treatment strategy. A focused physical examination especially a digital rectal examination should be performed to evaluate prostate size and screen for prostate cancer. Urinalysis or at least dipstick testing should be done to screen for hematuria and urinary infection. Measurement of serum prostate-specific antigen (PSA) should be offered to patients with a life expectancy of at least 10 years [8].

To monitor disease progression and evaluate the response to therapy, the severity of LUTS should be quantified by the International Prostate Symptom Score (I-PSS). The I-PSS is a patient self-administered questionnaire consisting of seven questions related to obstructive and irritative symptoms, and has been validated linguistically in different cultural backgrounds (including Chinese) [3,8-10]. LUTS may interfere with normal daily activities, and have a negative impact on patients' quality of life. However, the degree of bother differs greatly among individuals. The Disease Specific Quality of Life (QoL) question of the I-PSS is used to evaluate the degree of bother and level of interference in daily life.

## DIAGNOSTIC TESTS

Some diagnostic tests might be necessary before discussing treatment options with patients.

### *Uroflowmetry (UFR)*

Recording of the urinary flow rate, including the voided volume, maximal flow rate (Q<sub>max</sub>), average flow rate, time to Q<sub>max</sub>, and flow pattern should be performed in the initial examination of patients with LUTS. A voided volume exceeding 150 mL is necessary for meaningful interpretation. Because of test-retest variability, serial flows (two to three) are preferred. Men with a Q<sub>max</sub> less than 10 mL/sec are more likely to have bladder outlet obstruction (BOO) and are therefore more likely to benefit from surgical intervention [8,11]. However, older men might have functional changes of the detrusor muscle, and only a pressure flow study can confirm the diagnosis of BOO [11]. Men with LUTS but a normal Q<sub>max</sub> are more likely to have a non-BPH related condition [8,11]. UFR is an optional test in AUA (American Urological Association) guidelines [8], but is recommended for all patients with LUTS, and is considered a mandatory test prior to surgical intervention in EAU (European Association of Urology) guidelines [11].

### *Post-void residual urine (PVR)*

Measurement of the PVR by means of transabdominal ultrasonography is recommended by the EAU and is optional in AUA guidelines. A large PVR (e.g. >250 or 300 mL) may indicate bladder dysfunction, predict a less favorable response to treatment, and herald disease progression [8,11]. However, there is no established PVR "cut-off point" for treatment decisions [11].

### *Serum creatinine measurement*

In an evaluation of 246 men presenting with LUTS/BPH, Gerber et al found 11% of patients had renal insufficiency [12]. Patients with BPH and renal insufficiency tend to have a higher risk of developing post-operative complications [13], and might have additional problems when taking certain alpha-blockers [11]. The routine measurement of creatinine is highly recommended by the EAU [11], the Agency for Health Care Policy and Research [14] and the Fourth International Consultation on BPH [15], but is not recommended in AUA guidelines [8].

### *Imaging of the urinary tract*

The role of routine imaging of the urinary tract in all patients with LUTS has been increasingly questioned in recent years [11,16,17]. However, measurement of the prostate size by transrectal ultrasound might be helpful in predicting the response to therapy with 5-alpha reductase inhibitor. The size and shape of the prostate are of impor-

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tance in selecting patients for transurethral thermotherapy. Furthermore, anatomical features, such as intravesical protrusion of the prostate, may impact the choice of therapy [8,11]. Patients with significant intravesical protrusion of the prostate may benefit from early surgical intervention, especially those who experience acute urinary retention [18].

### *Urethracystoscopy*

Endoscopic examination should not be considered as routine unless patients have a history of hematuria or urethral stricture. It can be optional when considering invasive therapy [8,11].

### *Pressure-flow study*

The pressure-flow study is the only confirmative test for the diagnosis of BOO. Patients with a high voiding pressure and low Qmax have the best outcome following surgical intervention [19,20]. It is not indicated for patients who are being managed with watchful waiting or medical treatment. It can be optional when considering invasive therapy. In the report of the 5th International Consultation on BPH, pressure-flow study was highly recommended for patients with a Qmax greater than 10 mL/sec in whom surgical intervention is being considered [21].

## TREATMENT

The selection of treatment mainly depends on the patient's perception of the severity of his disease, as well as the degree of interference in his daily life [22,23]. The goals of treatment are to reduce the severity of LUTS, to improve the quality of life and to correct any BPH-related complications. The benefits and risks of any therapy should be balanced against the risks of watchful waiting. Both efficacy and adverse events of any treatment options should be discussed with patients, and patients must be invited to participate actively in the decision-making process [8,11].

### *Watchful waiting*

Watchful waiting is a management strategy consisting of education, reassurance and lifestyle modification (such as decreasing fluid intake at bedtime, reducing intake of caffeine- and alcohol-containing products, maintaining time-voiding schedules). It can be an appropriate management for men with mild LUTS (I-PSS 0-7) or men with I-PSS  $\geq 8$  but a low level of bother, since BPH is a disease with slow progression and treatment is still effective even when delayed. Watchful waiting is often a patient-driven treatment of choice, however, physicians should exclude any absolute indication for intervention (e.g BPH-related complications). Patients on watchful waiting should have I-PSS, QoL, Qmax, serum PSA and creatinine levels re-evaluated at least annually [8,11].

### *Medical treatment*

Patients with moderate (I-PSS 8-19) to severe (I-PSS 20-35) LUTS and sufficient bother are candidates for medical treatment. Medical therapies commonly used for LUTS/BPH are alpha-adrenergic blockers and 5 alpha-reductase inhibitors [24-28].

1. **Alpha-blockers** such as doxazosin, terazosin, alfuzosin, and tamsulosin can cause a 4 to 6 point decrease in the I-PSS and improvement in the Qmax of 20%-30% within 2-4 weeks [25,26]. The efficacy of alpha-blockers is dose-dependent and hence they need

to be titrated to the optimal dose [24]. Approximately one-third of patients do not experience significant symptom reduction. For these patients, there is no justification in prolonging alpha-blocker therapy after an 8-week trial [11]. The most commonly reported adverse events are postural hypotension, headache, dizziness, drowsiness, asthenia, nasal congestion and ejaculatory problems. Meta-analyzed data suggest that all alpha-blockers are similarly effective but vary slightly in adverse events [8].

2. **The 5 alpha-reductase inhibitors (5ARI)** finasteride and dutasteride can cause regression of the epithelial element, shrink prostate size, decrease the static component of BOO and hence improve the I-PSS and Qmax [27-29]. Maximal benefits are seen at a mean 6 months after starting treatment. The 5ARI are less effective in relieving LUTS than alpha-blockers, especially for patients with smaller prostates (e.g. <40 mL) [8,30,31]. The 5ARI may alter the natural history of BPH by reducing the incidence of BPH-related surgery and acute urinary retention [32]. The side effects are mainly related to sexual function, such as decreased libido, erectile dysfunction and decreased ejaculate. Some patients may also experience breast enlargement or tenderness [28,33]. The 5ARI significantly lower the serum PSA level, however, detection of prostate cancer would not be masked if only the detected PSA level was doubled for interpretation, so the PSA level is doubled when interpreting levels indicative of prostate cancer [34].
3. **Combination therapy** Recent study has shown that a combination of alpha-blockers and 5ARI is more effective in relieving LUTS and reducing the risk of acute urinary retention or BPH-related surgery than the use of one agent alone [35]. Patients with larger prostates and higher PSA values (i.e. higher baseline risk of progression) are more likely to benefit from combination therapy. In practice, patients may be started on a 4-to-8 week trial with an alpha-blocker. Adding a 5ARI can be considered for patients with large prostates who do not have significant reduction in LUTS after alpha-blocker monotherapy. To reduce the cost and possible adverse events, the alpha-blocker may be discontinued after 9 to 12 months of combination therapy, since recent studies have shown that this will not result in symptom deterioration [36,37].
4. **Anticholinergics** Both AUA and EAU guidelines do not recommend anticholinergics in patients with LUTS/BPH for fear of increases in the PVR or even acute urinary retention. However, some recent placebo controlled studies have suggested that the use of antimuscarinic drugs may not result in acute urinary retention [38]. However, anticholinergics had better - be used in association with an alpha-blocker and are not recommended for patients with a PVR >50 mL.
5. **Phytotherapy** There are no data supporting the use of phytotherapy in LUTS/BPH. Plant extracts are currently not recommended by the American and European Association benign prostatic hyperplasia guidelines.

### *Surgical intervention*

Patients who experience repeated urinary retention, recurrent urinary tract infection, refractory gross hematuria, renal insufficiency secondary to BOO, and bladder calculi are strongly indicated for surgical treatment [8,11]. Patients unwilling to make a lifelong commitment to medication, who fail to respond to medical treatment, or who cannot tolerate medication -associated adverse events are also candidates

for surgical intervention [8,11].

1. **Transurethral resection of prostate (TURP)** Despite the development of new technologies, TURP is still considered as the gold standard for surgical intervention because of the published evidence of efficacy from randomized clinical trials with long-term follow-up [8]. Possible complications include retrograde ejaculation, erectile dysfunction, incontinence, bladder neck contracture, urethral stricture, hematuria, and TURP syndrome (dilutional hyponatremia) [39,40].
2. **Transurethral incision of prostate (TUIP)** TUIP is limited to patients with a prostate smaller than 30 gm without significant middle lobe enlargement.
3. **Open prostatectomy** is rarely indicated nowadays except for extremely large prostates.
4. **Laser therapy** Transurethral coagulation, vaporization and resection/enucleation of the prostate using different types of laser energy have been developed recently. Intermediate-term results of laser prostatectomy are comparable to TURP with less intraoperative bleeding and no TURP syndrome [41,42]. Laser therapy may be considered an alternative for TURP in patients with high operative risks or those who are taking anticoagulants.

#### *Minimally invasive therapies*

Such as transurethral needle ablation of the prostate (TUNA®) [43] and transurethral microwave therapy (TUMT) [44,45] may be considered acceptable alternatives for patients who prefer to avoid surgery or those in whom surgery is considered too risky.

#### CONCLUSIONS

The goals of treatment are to improve the quality of life and to correct BPH-related complications. Watchful waiting can be an appropriate management for the majority of patients with mild LUTS. Alpha-blockers with/without 5ARI are recommended for patients with bothersome LUTS. For patients who do not respond to medical treatment, adjustment of medication (including dose) or a comprehensive urodynamic study is advised. Patients with BPH-related complications, and those with proven bladder outlet obstruction urodynamically and clinically are candidates for surgical intervention. Newly developed minimally invasive therapies may be considered acceptable alternatives to TURP. Both efficacy and adverse events of any treatment options should be discussed with patients before making any decision.

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