

# AN OVERVIEW OF THE MANAGEMENT OF MALE LOWER URINARY TRACT SYMPTOMS AND BENIGN PROSTATIC OBSTRUCTION

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## ABSTRACT

Lower urinary tract symptoms (LUTS) in older men are common and often bothersome, resulting in a significant use of healthcare resources. Symptoms were thought to be secondary to benign prostatic obstruction (BPO) or benign prostatic enlargement (BPE). However, it should be noted that such storage symptoms are also seen in men without enlarged prostates and in women. These symptoms may be caused by detrusor overactivity, non-urological conditions, medications, or lifestyle factors. Management of BPO constitutes to a significant proportion of a urologist's workload, and will continue to do so with an increasingly ageing population. This review aims to provide an overview of the current understanding of BPE and male LUTS as well as investigations and treatment options. The primary source of data was PubMed, this was searched using Boolean strategies and by scanning a list of related articles. We also examined secondary sources from reference lists of retrieved articles.

**Keywords:** Alpha-blockers, benign prostatic obstruction, combination therapy, lower urinary tract symptoms, 5-alpha reductase inhibitors, phosphodiesterase-5-inhibitors, transurethral resection of the prostate, laser vapourisation.

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## INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histological diagnosis, the prevalence increases from 25% in men aged 40-49 years to >80% aged 70-79 years.<sup>1</sup> Many men with histological findings of BPH and clinical findings of benign prostatic enlargement (BPE) have no symptoms, but >50% of men in their 60's, and as many as 90% of those in their 80's, present with lower urinary tract symptoms (LUTS).<sup>2</sup>

### Definitions

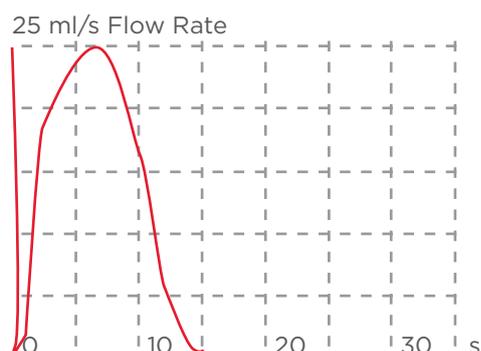
The now redundant term 'prostatism' was used to cover the clinical, pathological, and pathophysiological elements of BPH and LUTS; this wrongly suggested organ and gender specificity. In response, Abrams<sup>3</sup> and Chapple et al.<sup>4</sup> proposed a series of definitions thought to more accurately reflect the clinical, pathological, and pathophysiological components (Table 1).

### Evaluation

LUTS are broadly divided into storage, voiding, and post-micturition symptoms. Although the predominant types of symptoms may aid diagnosis, one should remember that the bladder has been described as an unreliable witness and thus further investigations are required to establish a diagnosis.<sup>5</sup> A thorough history must determine the presence of haematuria, urinary tract infection (UTI), erectile dysfunction, diabetes, and hypertension, as well as any previous urological conditions including acute urinary retention (AUR) and any subsequent interventions.<sup>6</sup> Current medical therapy should be reviewed to determine current treatment and the use of anticholinergics and alpha-sympathomimetics. Clinical examination should include the abdomen, external genitalia, and a digital rectal examination to estimate prostate size.

**Table 1: Definitions of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms.**

Term	Definition
Benign prostatic enlargement	Clinical finding of an enlarged prostate due to BPH.
Bladder outlet obstruction	Urodynamic diagnosis characterised by increased voiding detrusor pressure and reduced urine flow rate.
Benign prostatic obstruction	Obstruction of the bladder outlet secondary to benign prostatic enlargement in the absence of prostate cancer.
Benign prostatic hyperplasia	Histological diagnosis of hyperplasia i.e. a proliferation of cells within the prostate.
Storage symptoms	Symptoms experienced during the filling/storage phase i.e. daytime frequency, nocturia, urgency, incontinence.
Voiding symptoms	Symptoms experienced during the voiding/emptying phase i.e. hesitancy, poor stream, straining, a feeling of incomplete emptying, intermittency, and terminal dribbling.
Post-micturition symptoms	Symptoms experienced immediately after micturition i.e. incomplete bladder emptying, post-micturition dribble.



Results of Uroflowmetry

Voiding Time	T100	14	s
Flow Time	TQ	14	s
Time to max Flow	TQmax	6	s
Max Flow Rate	Qmax	24.8	ml/s
Average Flow Rate	Qave	15.5	ml/s
Voided Volume	Vcomp	221	ml

**Figure 1: A normal flow rate.**

### Urinalysis, bladder diary, and uroflowmetry

Urinalysis should be performed to exclude haematuria or UTI, which necessitate further investigation. A bladder diary is an accurately completed chart over at least 3 days that can provide a useful assessment of storage symptoms such as nocturia, give information on bladder capacity, and indicate other causes of LUTS such as nocturnal polyuria or excessive fluid intake. Uroflowmetry measures the volume voided per second but is non-specific, i.e. it cannot determine if a poor flow is due to bladder outlet obstruction (BOO) or detrusor failure. Furthermore, maximum flow rate (Qmax) values on their own do not correlate well with either LUTS or bladder outlet resistance.<sup>7</sup> Ideally more than one flow rate should be performed and can only be considered

representative if >150 ml is voided.<sup>8</sup> See [Figure 1](#) for a normal flow rate.

### Residual volume and prostate-specific antigen (PSA)

Residual volume can either be estimated by ultrasound scan or by catheterising after voiding. Measurements should be assessed as a series rather than as a single reading as there may be considerable variation between repeated measurements.<sup>9</sup> Persistently high residual volumes may be due to detrusor dysfunction or BOO. PSA may be used in the detection of prostate cancer (PrC); the potential benefits and disadvantages of using serum PSA to detect PrC should be discussed with the patient. However, PSA seems to correlate directly with prostate volume, as well as

the risk of symptom progression. Patients with a PSA of >1.6 at baseline were at an increased risk of progression.<sup>10</sup>

### Scoring systems

Symptom score questionnaires have become a standard part of the assessment of male LUTS, the most widely used being the International Prostate Symptom Score (IPSS) also known as the American Urological Association Symptom Index. It consists of seven questions (three based on storage and four based on voiding symptoms). Each question is scored from 0-5 (0 being never affected and 5 being constantly affected). The sum of all 7 questions gives an overall score out of 35. Patients are classified as suffering from mild (0-7), moderate (8-19), and severe (20-35) LUTS. IPSS also includes a quality of life score (QoL) which has been shown to be consistent, and has been validated in a wide range of languages. The main problem with IPSS is that it does not assess for urinary incontinence. International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms has been derived from the International Continence Society (ICS) male questionnaire, which resulted from an outcome of the ICS 'Benign Prostatic

Hyperplasia' Study.<sup>11</sup> It is a widely used and validated patient-completed questionnaire for evaluating MLUTS.<sup>11</sup> Scoring systems are a useful tool in follow-up to see if medical or surgical therapies have effected symptoms.

### Urodynamics

The information obtained from invasive urodynamics can be extremely useful. Storage LUTS may be caused by detrusor overactivity and voiding LUTS by detrusor underactivity or by outflow obstruction. Various nomograms are available, such as the ICS nomogram (also called the Abrams-Griffiths nomogram) to determine whether a patient is obstructed based on the information obtained from the pressure flow studies. This is calculated during the voiding phase of urodynamics by using the formula  $P_{det}Q_{max} - 2Q_{max}$ , a value of >40 suggests obstruction, 20-40 equivocal, and <20 unobstructed.<sup>12</sup> The bladder contractility index can be calculated by  $P_{det}Q_{max} + 5Q_{max}$ . If <100, it suggests that the bladder is underactive.<sup>13</sup> Due to the invasive nature of urodynamics, they are usually reserved for patients in whom conservative and medical therapies have failed and intervention is planned.

**Table 2: European Association of Urology (EAU) guidelines for specialist assessment in BPE.**

Investigation	EAU recommendations	Level of evidence	Grade of recommendation
Medical history and examination	Recommended	4	A
Symptom score	Recommended	3	B
Urinalysis	Recommended	3	A
Uroflowmetry and post void residual	Recommended	3	B
Pressure flow studies	Optional	3	B/C
Cystoscopy	Optional	3	B
Upper tract imaging	Optional	3	B
Voiding chart	Optional	3	B
PSA and creatinine	Recommended	1b	A
Excretory urography	Not routinely recommended	-	-
Filling cystometry	Not routinely recommended	-	-
Retrograde urethrography	Not routinely recommended	-	-
CT/MRI	Not routinely recommended	-	-

BPE: benign prostatic enlargement; PSA: prostate-specific antigen; CT: computed tomography; MRI: magnetic resonance imaging.

The indications for urodynamics in BPE can be seen in the European Association of Urology (EAU) guidelines.<sup>14</sup> The EAU has produced guidelines<sup>14</sup> that suggest relevant investigations for LUTS/BPO (Table 2).

## Natural History

The progression of BPH in untreated patients can only be inferred because of the nature of the disease and the infeasibility of a longitudinal study. Therefore, conclusions are derived from placebo arms of long-term interventional studies. A sub-analysis of the Olmstead County Data demonstrated a mean increase in prostatic volume of 1.6% per year and a mean increase in IPSS score of 0.18 symptom units per year.<sup>15,16</sup> Jacobsen et al.,<sup>17</sup> using the Olmstead County data, identified the following risk factors for AUR: age (men in their 70's are 8 times more likely to have AUR than men in their 40's), prostate volume >30 ml, IPSS >7, Qmax <12 ml/s, and post-void residual >50 ml. The annual incidence was 0.7% over the 4 year study interval.

## MANAGEMENT

### Lifestyle Advice

There are a number of conservative strategies for patients with mild-to-moderate LUTS. These involve patient education, reassurance, and periodic monitoring. Specific lifestyle advice includes: reduction of fluid intake at specific times, avoidance of bladder stimulants such as coffee, use of double voiding techniques, urethral milking, and bladder retraining along with a review of current medications. When lifestyle measures are adhered to they may have a significant improvement on IPSS as an alpha blockade.

### Alpha-Adrenergic-Receptor Blockers (ARBs)

Alfuzosin, doxazosin, tamsulosin, terazosin, and the most recently developed ARB, silodosin have all been approved by the FDA for the treatment of male LUTS. A meta-analysis, published in 2004, suggests that there is no significant difference in the efficacy between different ARBs (not including silodosin) in terms of IPSS reduction 35-40% and increased Qmax 15-30%, although tolerability was variable.<sup>18</sup> Improvements in LUTS are usually seen within 2 weeks and evidence exists to show that effects can be seen within hours to days, and last up to 4 years.<sup>19</sup> The side-effects of ARBs include asthenia, postural hypotension, and an ejaculation. It is recommended that men with LUTS secondary

to BPE should be asked about any planned cataract surgery to avoid the risk of intraoperative floppy iris syndrome. Those with planned cataract surgery should not start ARBs until their surgery has been completed.

### 5-Alpha Reductase Inhibitors (5ARIs)

The effect of testosterone and dihydrotestosterone (DHT) in the development of BPH are well described. The 5-alpha reductase enzyme converts testosterone to the more potent DHT, this is competitively inhibited by the 5ARIs. This effectively shrinks the prostate by 25-30% and reduces further prostatic growth. There are two approved 5ARIs: finasteride, which blocks the Type 2 5 $\alpha$ -reductase isoenzyme, leading to a fall in serum DHT levels by 70-90%, and dutasteride blocks, both Type 1 and Type 2 5 $\alpha$ -reductase isoenzymes, reducing DHT to levels that approach zero.<sup>20</sup> Both have demonstrated an improvement in LUTS over a period of 2-6 months with a corresponding improvement in IPSS by four to five points.<sup>21</sup> In a direct comparison between the two agents the effects of finasteride and dutasteride were similar.<sup>22</sup> The PLESS study<sup>23</sup> demonstrated a 55% and 57% relative risk reduction in those requiring surgery and those having an episode of AUR respectively in the finasteride arm. However, this translates to a 4% relative risk reduction over 4 years, so although finasteride does reduce the risk of retention, it is reducing the risk of something which is already quite rare. Side-effects of 5ARIs included decreased libido, erectile dysfunction (ED), and ejaculatory dysfunction and gynaecomastia. Trials have also been conducted to try to ascertain if finasteride or dutasteride could prevent PrC. Treatment with finasteride resulted in an absolute risk reduction of 6% when compared to placebo, but was also associated with an increased risk of moderate-to-high grade PrC (Gleason >7).<sup>24</sup> The REDUCE study,<sup>25</sup> which looked at dutasteride, showed similar results. In a more recent study men treated with a 5ARI for LUTS had a decreased risk of low-grade PrC (Gleason 2-7) and showed no evidence of increased risk of high-grade cancer (8-10) after up to 4 years treatment.<sup>26</sup> It should also be noted that patients on 5ARIs should be aware that their PSA will fall by 50%, this needs to be considered in any eventual PSA directed cancer strategy.

### Combination Therapy

A number of studies have looked at the potential benefit of combination therapies in the

management of BPO. Short-term studies, such as the Veterans Affairs Co-operative and the PREDICT trial, demonstrated that patients on both ARB monotherapy and ARB + 5ARI combination therapy show a significant improvement in outcomes (Qmax and IPSS). However, there is no significant difference between monotherapy or combination therapy in the short term.<sup>27,28</sup> Long-term data from the MTOPS trial<sup>19</sup> demonstrated that combination therapy significantly reduced the risk of clinical progression when compared with placebo and monotherapy over a mean 4.5 year follow-up. The COMBAT trial<sup>29</sup> (dutasteride and tamsulosin) looked at the management of LUTS in men with larger prostates. It suggested that combination therapy had a significantly greater improvement in symptom score as well as Qmax from baseline than either tamsulosin or dutasteride alone. Combination therapy also reduced the relative risk of AUR or BPO surgery over 4 years by 66% compared with tamsulosin monotherapy. However, those on combination therapy suffered from a higher frequency of adverse effects.<sup>29</sup>

### Antimuscarinics

In some cases a degree of bladder overactivity may co-exist or be the results of BOO. In this case standard treatment for BOO may fail and may not be sufficient to control the storage symptoms. Kaplan et al.<sup>30</sup> compared the combination of ARB and antimuscarinics to individual therapy. It demonstrated that as monotherapy, the therapies performed less well compared with placebo, but in combination showed good efficacy in improving QoL scores. The risk of AUR in the antimuscarinic group was not significant.

### Phosphodiesterase-5 Inhibitors (PDE5-I)

PDE5-I were initially approved for use in the management of ED but they also seem to improve LUTS. PDE5 is present in prostatic tissue, particularly the transition zone as well as the detrusor and the smooth-muscle cells relating to the urinary tract. Inhibition of PDE5 leads to smooth muscle relaxation. This may also have anti-proliferative effects in prostatic and bladder smooth-muscle cells. Thus far only tadalafil has received FDA approval for the treatment of LUTS. In a randomised, placebo-controlled trial involving men with LUTS for at least 6 months, a 5 mg dose of tadalafil resulted in an average decrease in the IPSS by 2.8 points at 6 weeks and 3.8 points at 12 weeks.<sup>31</sup> Efficacy was shown as

early as 4 weeks.<sup>32</sup> Interestingly, none of the studies looking at PDE5I use for LUTS have shown a significant effect on urinary flow rate (Qmax). This may be explained by PDE5-Is primarily affecting detrusor activity rather than BOO itself.

### Phytotherapy

Saw palmetto is thought to be the active agent derived from *serenoa repens*. Apart from a single systematic review and meta-analysis in 1990, the general opinion from more recent randomised controlled trials (RCTs) do not support the efficacy of saw palmetto over placebo and hence it is excluded from many guidelines.<sup>33</sup>

## SURGERY

### Transurethral Resection of Prostate (TURP)

TURP continues to be the gold standard in the treatment of BPO. The basic principles are of removal of prostatic tissue from the transition zone to improve voiding symptoms. The indications for TURP can be found in the EAU guidelines.<sup>14</sup> The number of TURPs being performed has declined over the last two decades, primarily due to the significant benefits of medical therapy and to a lesser extent the advent and proliferation of alternative surgical techniques. In a systematic review, TURP has been shown, on average, to improve the mean IPSS score from 18.8 to 7.2 (-62%) after 12 months post-op, as well as improve Qmax by 9.7 ml/s, a mean increase of 120%.<sup>34</sup> Bipolar TURP is a valid alternative to monopolar TURP with equivalent outcomes and a similar side-effect profile. Transurethral resection syndrome has not been reported with bipolar TURP due to the use of physiological saline irrigation fluid and reduced fluid absorption during the procedure. While transurethral incision of prostate reduces LUTS secondary to BPO by incising the bladder outlet without tissue removal. This technique is used in men with LUTS with prostate size <30 ml and without a middle lobe.

### Open Prostatectomy

Open prostatectomy is the oldest surgical treatment for moderate to severe LUTS secondary to BPO. It is usually reserved for those with large prostates (>80-100 ml) the obstructive prostatic adenoma is enucleated either via the bladder (Freyer's transvesical prostatectomy) or through the anterior prostatic capsule (Millin's retropubic prostatectomy). Open prostatectomy results in

a reduction of LUTS by 63-86% (12.5-23.3 IPSS points). It has been described using both laparoscopic and robotic-assisted approaches.<sup>35</sup>

### Transurethral Laser Surgery

Lasers have been used in the surgical management of BPE either by coagulating, vapourising, or enucleating the prostate. Potassium-titanyl-phosphate (KTP) lasers (Greenlight laser-KTP) has been used for photoselective vapourisation of the prostate (PVP); over time the power of these lasers has increased from 60 W to 180 W. Two RCTs comparing TURP with 80 W PVP have shown similar<sup>36</sup> or improved flow rates<sup>37</sup> at up to 1 year follow-up. KTP laser has been shown to reduce intraoperative blood loss and blood transfusion rates when compared to TURP. Urethral stricture, retrograde ejaculation, and retreatment rates are comparable with TURP.

Initially holmium lasers were used to vaporise the prostate, then to resect the prostate, and now to enucleate the prostate (HoLEP). The lobes are resected and then pushed back into the bladder and then morcellated. There have been six RCTs comparing TURP to HoLEP. Essentially there is no statistically significant difference between HoLEP and TURP in improving symptom and QoL scores at up to 7 years.<sup>38,39</sup> Less blood loss and transfusion rates have been observed with HoLEP but there is a significant learning curve. HoLEP has been described as an endoscopic Millin's prostatectomy - at 5 years follow-up HoLEP is comparable with open prostatectomy.<sup>40</sup> Transfusion rates for HoLEP are significantly lower than for open prostatectomy. NICE suggests that HoLEP be offered as an alternative to TURP or open prostatectomy. It should be performed in a centre specialising in the technique, or with mentorship arrangements in place.<sup>41</sup>

Thulium laser allows better tissue vaporisation than holmium - at 1 year follow-up there does not appear to be any difference between Thulium techniques and HoLEP.<sup>42,43</sup> A multicentre trial is being conducted in the UK funded by the National Institute for Health Research to compare Thulium vapourectomy of the prostate to TURP. Laser techniques in the management of BPO appear to have equivalent results to TURP but there is limited long-term data available. They may be superior to TURP in anti-coagulated patients where risks of bleeding and the requirements for post-op blood transfusion remain low. Another advantage of

laser procedures is that saline can be used as an irrigant solution avoiding the risks of development of TURP syndrome. The advantages of shorter catheterisation period and reduced length of stay need to be balanced against the increased operating costs (in terms of equipment and increased operating time) and the procedural learning curve for the holmium laser.

### Injection Therapy

Injection therapy of the prostate involves administration of dehydrated ethanol at four to eight sites in the prostate. It can be administered transurethrally, transrectally, or transperineally. It results in coagulative necrosis reducing prostate volume. IPSS and Qmax do improve, but significant adverse events have been recorded including bladder neck necrosis and ureteric injury requiring reimplantation.<sup>44,45</sup> These techniques are rarely utilised. There have also been small studies examining the use of intraprostatic botulinum toxin use as well as NX-1207; these have shown a decrease in prostatic volume and symptom scores.<sup>46</sup>

## MECHANICAL DEVICES

Intraprostatic stents have been used for patients who were not fit for surgery and who did not want to be managed with a long-term catheter. A variety of stents are available, however, they are rarely used due to complications such as migration and encrustation. Urethral lift is a technique that works by pulling the lateral lobes of the prostate laterally to increase the calibre of the urethral lumen. It can be performed under local anaesthesia or sedation. A non-absorbable monofilament suture with a nitinol capsular tab is inserted in an anterolateral fashion to compress the lateral prostatic lobes additional sutures are placed as required to achieve a cystoscopically open urethral channel. NICE issued procedure guidance approving the prostatic lift in 2014. Late complications are uncommon but may include UTI prostatitis and transient ED. Short-term results show a 40% reduction in IPSS scores, 40-50% improvement in QoL scores, and 30% improvement in Qmax. This improvement is seen within 2 weeks and appears to be sustained up to 2 years later.<sup>47-49</sup>

## CONCLUSION

BPO is a complex condition which remains incompletely understood. Treatment options for BPO have become more widespread ranging

from lifestyle advice, medical therapy, minimally invasive surgery, and conventional TURP and open prostatectomy. As urologists, we now have many treatment modalities, however, only time will tell which will become the 'gold standard'.

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