The medical management of LUTS/BPH – an update

By Matthew Megson and Sid Singh

For many years it has been recognised by both medical professionals and the general public that the development of lower urinary tract symptoms (LUTS) is highly prevalent and is predominantly age-dependent. Medical professionals understand that in men this is often, but by no means exclusively, associated with benign prostatic enlargement (BPE) [1]. The most common cause of prostatic enlargement is benign prostatic hyperplasia (BPH), which involves hyperplasia of both the stromal and epithelial aspects of the prostate [2]. However, the etiology of male LUTS is multifactorial and may be a consequence of various prostatic, bladder and other urological disorders, as well as conditions external to the urinary tract.

As medical management has become more predominant, the number of surgeries being done has decreased despite an increase in the number of patients with BPH. Ingimarsson studied this in Iceland where in 2008, 81 and 3.4 of 1000 men over the age of 50 used BPH medications or underwent transurethral prostatic resection (TURP), respectively [3]. This change is driven by patient expectations and wishes. Percy showed that the majority of patients (60-67%) would prefer medical management for their BPH over surgery [4].

Conservative measures: no medication

For those patients with mild to moderate LUTS associated with their BPH, a trial of conservative treatment and watchful waiting is recommended. Conservative treatment should include the institution of a self-management programme for men which comprises education and reassurance, fluid management, avoidance of caffeine and alcohol, adjustment of concurrent medication which may be contributing to LUTS (e.g. diuretics) and various types of toileting advice and bladder re-training [4]. In patients with mild LUTS, even with concomitant bladder outflow obstruction, Netto found that 81.2% of patients were clinically stable after a mean follow-up of 17 months of watchful waiting [5]. For men with moderate symptoms of BPH, Flannigan found that at five years’ follow-up, there was no difference in bother from genitourinary symptoms for watchful waiting as compared to TURP [6]. However, 36% crossed over to a TURP and patients who had been randomised to TURP had better improvement of lower urinary tract function than those who subsequently crossed over.

We developed a suggested stepwise algorithm (Figure 1 - overleaf) which we use in our own clinical practice.

Stratification

The patients in whom bothersome symptoms persist despite conservative measures need to be stratified into treatment orientated subgroups. These include those at risk of progression, nocturnal polyuria, predominantly storage symptoms, predominantly voiding symptoms, and associated erectile dysfunction (ED). We will discuss these subgroups below in the discussions on monotherapy, dual therapy or triple therapy.

Monotherapy

Every patient with a risk factor for progression of LUTS/BPE should be offered a 5-alpha reductase inhibitor (5ARI) [7]. Clinical progression of BPH events is defined as increasing peak urinary flow rates in both storage and voiding symptoms, predominantly voiding symptoms, and associated erectile dysfunction (ED). We will discuss these subgroups below in the discussions on monotherapy, dual therapy or triple therapy.

“The patients in whom bothersome symptoms persist despite conservative measures need to be stratified into treatment orientated subgroups.”
Figure 1. Medical management of BPH.

**Step 1: Clinical assessment**

**Step 2: Self-management programme**
- Patient education
- Provide advice on fluid intake / bladder stimulants
- Consider bladder training
- Consider urethral milking

**Step 3: Any risk factors for progression?**
- Prostate more than 30mls / PSA >1.4 AND
- Flow rate <10 OR
- IPSS>12

**Step 4**

**Predominantly voiding symptoms**
- Alpha-1 antagonist
- Add PDE5i

**Mixed or predominant storage symptoms**
- Alpha-1 antagonist
- Add anticholinergic
- Add Mirabegron

**Symptoms of ED**
- Alpha-1 antagonist
- Add PDE5i + daily PDE5 inhibitor

If storage symptoms persist
PDE5Is have been shown to have therapeutic actions on all these pathways, with effects on bladder, prostate, pelvic vasculature as well as spinal cord. To date, only Tadalafil 5mg once daily has been officially licensed for the treatment of male LUTS with or without ED. The evidence suggests that younger men with lower body mass index (BMI) and more severe LUTS are likely to benefit the most from treatment with PDE5Is [23]. Long-term experience with tadalafil in men with LUTS is limited, therefore conclusions about its efficacy or tolerability greater than one year are not possible at the moment.

**Dual therapy**

In a population-based study of medical management of BPH, Bishr showed that 53.7% of 1120 participants with a history suggestive of BPH were on medical treatment, and only 12.4% of these were on combination therapy; a combination of alpha-blocker and 5ARI therapy was the commonest combination in 97.3% of men on combination therapy [10]. Long-term efficacy of combination therapy was demonstrated in 2003, when McConnell showed that this combination significantly reduced the risk of clinical progression in symptoms, AUR and BPH surgery at a follow-up of six years [24]. This group showed that reduction in risk associated with combination therapy (66% for the comparison with placebo, P<0.001) was significantly greater than that associated with doxazosin (P<0.001) or finasteride (P<0.001) alone. Most recently, Roehrborn in 2010 also confirmed these results [25]. He also showed that the risk of acute urinary retention and the need for invasive therapy were significantly reduced by combination therapy (P<0.001) and finasteride (P<0.001) but not by doxazosin alone. However, doxazosin (P<0.001), finasteride (P=0.001), and combination therapy (P<0.001) each resulted in significant improvement in symptom scores, with combination therapy being superior to both doxazosin (P=0.006) or finasteride (P<0.001) alone.

Men with significant storage or post-micturition symptoms form the largest subgroup within the male LUTS population. Those who continue to have storage symptoms despite monotherapy may be considered for an anti-cholinergic combined with an alpha-blocker. Van Kerrebroeck showed tamsulosin and solifenacin significantly improved storage and voiding symptoms as well as QoL parameters compared with placebo [26].

In most instances, patients do not progress to triple drug therapy as they end up having bladder outlet surgery when they experience either lack of efficacy of medication or experience clinical progression. Consequently, only a minority of patients ever become eligible for triple therapy and for this reason it would be difficult to conduct large scale studies that would provide high quality evidence on this treatment strategy.

**Future**

Over the next few years there may be many advancements in the treatment of male LUTS. For example at the EAU 2018 Annual Meeting, Tamalunas presented a study on how thalidomide can be used to inhibit prostate stromal cell growth in vitro [32].
Although in vivo studies still need to be conducted, this has been previously noted to be a tolerable medication in adult men. Another recent study by Galmes showed there is a new target of PDE4b which is unregulated in canine BPH models [33]. If this expression is proven in human BPH patients then a new drug targeting this newly found overexpression may lead to new treatments for BPH.

There are several phase III randomised controlled trials for the treatment of OAB (antiepileptics, PDEIs, and other β3-agonists) or BPH (intraprostatic injections of PRX-302, botulinum toxin, NX-1207, and combination therapies of PDEI + α1-blockers or finasteride) are ongoing or have recently been completed. Being recent lines of investigation, none of these have long-term data.

Conclusion
The medical management of male LUTS is a constantly evolving field as new pathogenetic pathways and consequent treatment targets are discovered. The old paradigm that male LUTS are caused by an enlarged prostate is no longer considered accurate. The lower urinary tract is considered as a functional unit, and symptoms as ever remain ‘an unreliable witness’ in terms of their pathogenesis. Combination treatment is already routine medical practice; however, the use of newer classes of drugs and triple therapy requires more long-term, real-life evidence to support widespread clinical use.

References

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