

# Differential Diagnosis of Male Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia and Non-Benign Prostatic Hyperplasia

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## INTRODUCTION

Lower urinary tract symptoms (LUTS) include storage symptoms (increased bladder sensation, frequency, urgency, urge incontinence and nocturia), emptying symptoms (hesitancy, dysuria, intermittency, slow stream, terminal dribble and residual urine sensation) and pain symptoms (pelvic pain, perineal pain and urethral pain). LUTS are highly prevalent in men and women, and increase with age [1]. LUTS are common among elderly men and are therefore usually considered synonymous with benign prostatic hyperplasia (BPH). However, it has been estimated that only 25% to 50% of men with BPH have LUTS and only 50% of men with LUTS have urodynamically proven bladder outlet obstruction (BOO) due to BPH or other urethral conditions [2].

## PREVALENCE OF MALE LUTS

The prevalence and severity of LUTS increases with age, and the progressive increase in the ageing population has increased the social economic burden and severity of LUTS [3]. Among LUTS, prevalence that increases with age is found only for urgency, weak stream and nocturia; the other symptoms are equally distributed among age groups [4]. Although the prevalence rates of nocturia, frequency, urge incontinence and nocturnal incontinence are relatively low, the bothersomeness of these symptoms is very high [5]. In an epidemiological study in eastern Taiwan, nocturia (>2 voids per night) was the most bothersome LUTS in aborigines and non-aborigines, with a prevalence rate of 31.1% and 19.8%, respectively. About 15% of men reported their LUTS have a great impact on their quality of life [6].

## PATHOPHYSIOLOGY OF MALE LUTS

The pathophysiology of LUTS could be bladder dysfunction (bladder hypersensitivity, detrusor overactivity (DO)), BOO (bladder neck dysfunction, prostatic obstruction, urethral stricture, poorly relaxed urethral sphincter, urethral sphincter dyssynergia) or a combination of these etiologies [7]. Many men have both storage and emptying symptoms. In men, emptying symptoms are more common but storage symptoms are also encountered frequently [8]. Frequent comorbidity with prostatic diseases adds to the complexity of diagno-

sis and management of male LUTS.

## ASSESSMENT OF MALE LUTS

Assessment of male LUTS includes a self-assessed symptom score questionnaire such as the American Urological Association (AUA) symptom score and International Prostate Symptom Score (IPSS) [9]. A voiding diary recording the frequency of urgency episodes and the voided volume provides great help in the initial diagnosis of overactive bladder (OAB) or polyuria conditions. Uroflowmetry and postvoid residual urine (PVR), prostatic measurement using digital rectal examination (DRE), transrectal or transabdominal sonography are available clinical investigations for assessment of uroflow and bladder outlet condition. In order to assess the lower urinary tract neurophysiology, a neurological examination is necessary, such as bulbocavernosus reflex, perineal sensation and spontaneous anal sphincter contraction. Cystometry, urethral sphincter electromyography (EMG) and pressure flow study with or without cinefluoroscopy can provide further information of detrusor function and sphincter activity. Cystoscopy can also help us in the diagnosis of urethral stricture or severe prostatic obstruction. After the initial diagnosis, male patients with LUTS can be classified into LUTS suggestive of BPH, LUTS suggestive of DO, detrusor underactivity or of neurological origin. Patients might have a combination of detrusor dysfunction and BOO or urethral conditions.

## LUTS IN BOO

BOO is a urodynamic condition implying voiding with a high pressure and/or low flow rate. Patients will develop LUTS (storage and/or emptying LUTS) when BOO has developed to a considerable degree. BOO can occur in men and women, in adults and children, and in anatomical and neurogenic conditions. In a study investigating men without BOO and LUTS, the maximum flow rate (Q<sub>max</sub>) reached up to 20 mL/s with a mean voided volume of 290 mL (Table 1). One third of men with LUTS do not have BOO. Many clinical studies have demonstrated that LUTS have a poor diagnostic specificity for BOO and 5%-35% of patients with BPH and LUTS do not have improved symptoms after transurethral resection of the prostate (TURP) [10]. The prostate size and uroflowmetry have better correlation with a urodynamic study than symptoms alone.

Clinical BPH is defined as having at least two of the following: (1) moderate to severe LUTS (IPSS ≥ 8), (2) an enlarged prostate (total prostatic volume (TPV) ≥ 30 mL) and (3) decreased Q<sub>max</sub> (<15 mL/s)

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**Table 1.** Normal Uroflow rate in Taiwanese Men by Age

Age years	Qmax (mL/S)	Voided volume (mL)	CQmax
≤ 45	23.9±8.73 (127)	339.8±191.1	1.41±0.51
46-55	19.7±6.81 ( 68)	305.4±159.2	1.21±0.42
56-65	20.2±6.20 (134)	286.8±138.8	1.27±0.42
66-75	19.2±6.10 (143)	262.8±109.3	1.23±0.39
76-85	18.7±7.50 ( 42)	225.3±101.5	1.31±0.47
All ages	20.7±7.30 (514)	290.7±123.2 (514)	1.29±0.45 (514)

**Table 2.** Differential Diagnosis of Male LUTS/BOO & Non-BOO

<ul style="list-style-type: none"> <li>• Badder neck dysfunction</li> <li>• Bladder hypersensitivity</li> <li>• Overactive bladder</li> <li>• Spastic urethral sphincter</li> <li>• Poor relaxation of urethral sphincter</li> <li>• Urethral stricture</li> <li>• Low detrusor contractility</li> <li>• Pseudodyssynergia due to neuropathy</li> </ul>
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[11]. Although an enlarged prostate might not indicate the presence of BOO, the mean TPV of patients with BOO is significantly higher than that of patients without BOO [12]. In addition, patients with LUTS suggestive of BPH and with a Qmax of <10 mL/s have a greater improvement in Qmax after TURP compared with those with a Qmax of >10 mL/s. Patients without evidence of BOO preoperatively also have a poor prognosis after TURP [13]. Patients with postoperative LUTS are found to have a small TPV at the time of surgery, suggesting that a non-BPH etiology might account for their LUTS [14]. Therefore, diagnosis of clinical BPH should be carefully undertaken, especially when an invasive procedure such as TURP is going to be performed. The differential diagnosis for non-BPH LUTS is listed in Table 2.

## LUTS IN NON-BPH CONDITIONS

### Bladder hypersensitivity

Among the various etiologies of LUTS due to non-BPH conditions, bladder hypersensitivity and DO are commonly found, especially in elderly men. Sensory urgency may be the presenting symptom of patients with DO, poor relaxation of urethral sphincter, interstitial cystitis, BOO or neurogenic voiding dysfunction. Recent investigation has shown that the urothelial release of neurotransmitters, such as acetylcholine (Ach), adenosine triphosphate (ATP) and the neuropeptide substance P, and the expression of TRPV1 and P2X<sub>3</sub> receptors strongly imply a role for the urothelium in human bladder mechanosensation [15,16]. The release of urothelial Ach decreases but ATP production increases with ageing. These physiological changes indicate the high prevalence rate of bladder hypersensitivity and OAB, and are possibly responsible for the occurrence of detrusor hyperactivity and impaired contractility (DHIC) in elderly men [17].

### Polyuria

A number of patients may have large daily urine output of over 2800 mL/day. Patients may have polydipsia and high water intake,

and therefore may have frequency with voided volume >350 mL yet are likely to be physiologically normal [18]. However, for these patients, we should check their metabolic status, including diabetes, azotemia, hyperlipidemia, diuretic medications and sleep apnea syndrome.

### Psychological factors

Another condition is psychological, social or psychiatric factors that might cause frequency in male patients. These patients may have a high level of distress and a high level of anxiety. The symptoms may worsen in relation to work or stress. They may also believe there is a relationship between their symptoms and diseases such as uremia, infection or cancer.

### Urothelial dysfunction

Sensory urgency might be micro-motor urgency due to micro-movement of the detrusor during rapid bladder filling, such as in diuresis. Patients may have severe urgency when their bladder volume is small and this condition might be the cause of urothelial dysfunction, such as in trigonal mucosa dysfunction. The trigone is abundant in sensory nerves and subtrigone denervation has been used to treat OAB in women [19]. Increased TRPV1 receptor expression has been found in sensory urgency but not in idiopathic detrusor overactivity (IDO), and trigonal and bladder base injection of botulinum toxin A (BTX-A) is effective in patients with severe urgency frequency syndrome refractory to conservative medical treatment and electrical stimulation [20]. Patients with pseudomembranous trigonitis usually suffer from severe urgency that is refractory to antimuscarinics. Under this condition, intravesical resiniferatoxin instillation or subtrigonal BTX-A injection might reduce sensory urgency in patients with OAB dry. Increased nerve growth factor (NGF) levels have been found in bladder biopsies with sensory urgency, chronic cystitis and interstitial cystitis compared to levels in controls [21]. Immunostaining has shown increased NGF expression in the urothelium, most marked in idiopathic sensory urgency, therefore anti-NGF treatment may be appropriate in patients with sensory urgency. Intravesical BTX-A has been found to decrease symptoms of DO and clean intermittent catheterization (CIC), and the production of NGF has been found to reduce after BTX-A treatment in patients with neurogenic detrusor overactivity (NDO), IDO or CIC (unpublished data).

### Overactive bladder

Recent investigations of male LUTS noted that bladder dysfunction plays an important role in addition to BOO. LUTS suggestive of OAB have been estimated to be present in 16% of people in Europe and the United States [1]. A multinational large scale study revealed

that 90% of men aged 50 to 80 years suffer from potentially troublesome LUTS, and many men have both storage and voiding symptoms [22]. OAB symptoms comprise the same symptoms as storage LUTS in BPH and their prevalence increases with age. Since most men with OAB do not experience incontinence, men with storage LUTS are often misdiagnosed with clinical BPH [23]. However, storage LUTS correlate poorly with BOO as male OAB symptoms may be caused by bladder dysfunction such as DO or DHIC, or occur in combination with BOO [7]. However, many studies have reported only 45%-50% of men with LUTS have urodynamically confirmed DO and BOO [2,24].

DO can be due to idiopathic myogenic overactivity, poor cortical perfusion, post-obstructive DO, the ageing process or DHIC. In men with LUTS, we should exclude BOO first. In a recent study of the pathophysiology of male LUTS, only 29.4% of men had benign prostatic obstruction (BPO) and 51.1% of male LUTS was due to DO (unpublished data). Among the patients with BPO, 80.9% of men had DO. However, among the patients with urodynamic DO, only 48% of men had urodynamic BPO. Patients with BPO but without OAB symptoms might develop de novo OAB after TURP, suggesting that destruction of the trigone mucosa might lead to OAB [25]. Treatment of patients with BPO and OAB should include agents that relieve urethral resistance as well as antimuscarinics when the OAB symptoms cannot be resolved by treating with an alpha-blocker or combined 5 alpha-reductase inhibitor.

#### *Nocturia and nocturnal polyuria*

LUTS are common in the elderly and nocturia is the third most bothersome LUTS. The prevalence of nocturia increases to 80% in patients aged over 80 years. Nocturia is one of the most common causes of disturbed sleep patterns in the elderly. The causes of nocturia include DO, hypersensitive bladder, BOO, nocturnal polyuria or small bladder capacity. When the nocturnal urine volume >900 mL or more than 35% of the daily voided volume, nocturnal polyuria is likely. Lack of diurnal desmopressin rhythm can cause nocturnal polyuria and can be treated with exogenous desmopressin such as DDAVP [26]. In addition, for patients with combined nocturnal polyuria and BOO or OAB, combined multiple medication is necessary to relieve the complex male LUTS.

#### *Poor relaxation of the urethral sphincter*

Among the various causes of non-BOO male LUTS, poor relaxation of the urethral sphincter is the most frequently encountered condition [27]. Patients might have symptoms of hesitancy, intermittency, slow stream or postvoid dribble. Some patients might also have storage symptoms such as urgency or frequency. The causes of poor relaxation of the urethral sphincter might be learned habit, chronic prostatitis, pelvic floor hypertonicity, occult neuropathy or increased bladder sensitivity. Although this condition does not affect urinary tract function, the symptoms might have a great impact on the quality of life, especially in a young population. Diagnosis can be made by uroflowmetry, combined EMG study or videourodynamic pressure flow study.

#### *Pain symptoms*

Several conditions can cause pain symptoms in men. Interstitial cystitis, BOO, poor compliant bladder and transitional cell carcinoma can cause a painful bladder. Urinary tract infection, urethral stricture,

BPO and chronic prostatitis can cause a painful urethra. A painful pelvis or painful perineum can be due to pelvic floor hypertonicity, chronic prostatitis, spastic urethral sphincter or perianal inflammation. Treatment of pain symptoms in men is not easy and should be based on the exact diagnosis of the pain symptoms. Digital rectal examination (DRE) and prostatic massage for examination of prostatic fluid, urethrocystoscopy to exclude urethral stricture, or performing random bladder biopsies to investigate the possibility of carcinoma in situ are diagnostic procedures necessary for pain symptoms in men.

Transitional cell carcinoma of the bladder usually mimics interstitial cystitis in men with LUTS and painful bladder syndrome. Characteristic glomerulation may appear after cystoscopic hydrodistention and bladder biopsy reveals nonspecific chronic cystitis. However, when long-term medications such as pentosan polysulphate or COX-2 inhibitor fail to relieve the symptoms, repeat cystoscopy, urine cytology and repeat random bladder biopsy are necessary in order to detect early bladder carcinoma.

#### *Post-prostatectomy male LUTS*

Over half of the patients with post-prostatectomy LUTS have a small total prostate volume and resected adenoma weight, indicating their LUTS were non-BPH or non-BOO conditions before TURP. Among patients with post-prostatectomy LUTS, normal urethra and bladder are noted in 9.1%, DO in 9.6%, detrusor underactivity in 18.7%, poor relaxed external sphincter in 19.3%, DHIC in 14.4% and residual BOO in 27.8% [14]. Detailed cystoscopy and videourodynamic study are necessary for these patients, especially when they are diagnosed to have residual BPH or BOO and are to undergo repeat transurethral surgery. A narrow urethral segment might not necessarily be responsible for the post-prostatectomy LUTS. DHIC, bladder hypersensitivity or OAB can also be causes of male LUTS in the presence of a small BPH.

#### *Other conditions*

Urethral sphincter pseudodysynergia in patients with chronic stroke, intracranial lesions, Parkinson's disease or spondylolisthesis can cause severe emptying or storage symptoms in elderly men [28]. These patients might have BPH but the LUTS are caused by conditions other than BPH. Searching for evidence of BOO is mandatory before proceeding with invasive procedures to treat male LUTS because LUTS usually cannot be resolved with such procedures. Urethral stricture or urethral meatal stenosis can cause BOO and LUTS, especially in patients who have had a previous transurethral procedure. A detailed physical examination and urethral dilatation can relieve the LUTS without necessitating an invasive diagnostic procedure.

## CONCLUSIONS

LUTS in men can be caused by both bladder dysfunctions and bladder outlet dysfunctions, occurring alone or in combination. The presenting symptoms of male LUTS are similar in patients with or without BPO. Many patients without BOO also complain of dysuria. By comparison, urgency was highly prevalent in patients with DO and DHIC, as well as in patients with bladder outlet dysfunctions such as bladder neck dysfunction and BPO. Bladder symptoms are not reliable indicators of the presence of DO. LUTS is not useful for the differential diagnosis of BPO or non-BPO in men. The key symptom of OAB,

i.e. urgency, cannot be used to make a definite diagnosis of DO. The etiologies of LUTS may involve both bladder dysfunctions and bladder outlet dysfunctions. Accurate diagnosis of lower urinary tract dysfunction should be based on a comprehensive urodynamic study, which will enable correct selection of a therapy that is aimed at the underlying pathophysiology.

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