

# Differential Diagnosis of Benign Prostate Hyperplasia with Lower Urinary Tract Symptoms

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## ABSTRACT

The differential diagnosis of LUTS/BPH is an important issue need to be addressed since the accurate diagnosis and appropriate prescription is only around 10% for both BPH and OAB diseases. The more different specialists involved in this field, the more inadequate treatment will be. This is because that we usually treat LUTS as a very simple situation suggestive of BPH. This is not true. The same clinical presentations may have totally different anatomic or functional problems. A large proportion of overlap in the diagnosis of BPH and OAB is almost over than 60%. In addition, the bladder outlet obstruction such as BPH may induce secondary bladder detrusor muscle changes. This will cause a more complicate clinical presentation. As a result, a special training including how to make a differential diagnosis and sometimes the urodynamic based diagnosis is beneficial and unavoidable. By introducing a 2 × 2 diagnostic grid, we can therefore familiar with more than one single diagnosis. In actuality, combined diagnosis is not uncommon in our daily practice. To approach a patient with BPH is just like to peeling off an onion; finally, we will find something new and something different which is out of our expectation. Based on a 2 × 2 diagnostic grid, one can be easier to analyze the voiding problem. This is not a simple problem of  $\alpha$ -blocker or 5- $\alpha$  reductatase inhibitor.

**Key words:** LUTS, BPH, diagnosis

## INTRODUCTION

Benign prostate hyperplasia (BPH) is a common disorder of aging men, occurring in 19%-30% of men aged over 59 years, and is therefore a significant contributor to the daily practice of urologists and general practitioners [1,2]. Lower urinary tract symptoms suggestive of BPH (LUTS/BPH) must be understood by all physicians who intend to take care of aging men. Basically, a bladder disorder is now a public health problem that can be associated with three major contributing factors: the nervous system, the bladder and general health. Unfortunately, increasing numbers of different specialists deal with bladder disorders based solely on a very simple diagnosis of BPH in aging men. Is LUTS/BPH an easy topic and does it need a specialist to take care of it? In actuality, a bladder dysfunction may be caused by a neurogenic bladder such as impaired detrusor contractility or upper motor neuron disease; pathology of the bladder mucosa or detrusor

muscles, such as interstitial cystitis, carcinoma in situ and overactive bladder (OAB); and bladder outlet obstruction (BOO), either from anatomic or functional entities, in addition to the male with BPH. All of these may present with a group of symptoms, LUTS. How to make a differential diagnosis or how to approach such a patient is a challenge for all physicians.

Sixty-seven men experience symptoms of both OAB and BPH [3]. The large proportional of overlap may be a key problem in making a diagnosis of LUTS/BPH or OAB/BPH. As a result, the accuracy of treatment is not what we would have expected. From a presentation at the International Continence Society (ICS) in 2005, of 4,806 patients with OAB and BPH, only 8% of patients received treatment for both diseases. Further, of 12,192 patients who had OAB alone only 11% of patients received accurate treatment [4]. The rest received inadequate or no treatment at all. What causes this large discrepancy in diagnosis and treatment? Knowledge, adequate available investigating tools and experience are very important. In fact, the storage symptoms of LUTS, such as frequency, urgency, nocturia and urge incontinence are those that can be used to make a diagnosis of OAB [5]. Therefore, the most common missed diagnosis for BPH is undoubtedly OAB. Since the differentiation of LUTS/BPH is very important and may change treatment strategy, we propose some principles and strategies to help us feel comfortable in approaching such patients.

## WHAT QUESTIONS SHOULD BE RAISED REGARDING AN AGING MAN WHO PRESENTS WITH LUTS?

A 76 year-old patient suffered from urgency, frequency, nocturia (7 times/night) and voiding difficulty, with small stream and abdominal straining. The international prostate symptom score (I-PSS) was 13 for storage and 17 for empty symptoms. Prostate specific antigen was 4.5 ng/mL. The transrectal ultrasound revealed a 53 gram homogenous prostate. The maximal flow rate was 7 mL/sec. Although the voiding volume was 55 mL, this was his usual voiding amount. The post void residual (PVR) urine was 112 mL. What is your diagnosis? Undoubtedly, BPH would be the most common diagnosis.

What else could the diagnosis be? If we take the voiding diary into the diagnostic consideration, his nocturnal voiding volume was 500 mL and the 24 hours total urine was 1250 mL. We can calculate the nocturnal polyuria index as (500/1250) 40%. However, the maximal voiding volume was 135 mL for this patient. The nocturia index (500/135) was 3.7 and this may explain the unavoidable nocturnal frequency for him. The predicted nocturnal voiding (PNV) is the nocturia index minus 1 (3.7-1=2.7). However, the actual nocturnal voiding (ANV) was 7. Therefore, the nocturnal bladder capacity index is ANV-PNV (7-2.7

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= 4.3) which means decreased nocturnal functional bladder capacity [6-9]. From the calculation, we can make a combined diagnosis for this patient: BPH with nocturnal polyuria and decreased nocturnal functional bladder capacity. This patient suffered from a significantly complicated voiding problem apart from the presumed BPH. So, what are the possible treatment options for this patient other than treatment for BPH? Can we prescribe the antimuscarinics at this moment or should we defer the treatment owing to the significant PVR urine?

There are so many questions that may be raised for this patient other than the above possible diagnosis. Is the bladder outlet obstructed other than by BPH? Is the bladder irritated? Is the LUTS caused by an enlarged prostate or by something else (increased urethral resistance)? Is the LUTS caused by a detrusor problem? How can we make a diagnosis of obstructed BPH? Can it occur with mixed problems? Are we treating LUTS or BPH? Can the treatment for BPH reduce the storage symptoms due to LUTS? Can we treat a patient with LUTS before the diagnosis of BOO is made? All these questions should be considered before you write a prescription or make a decision about the next step. We can conclude that a simple symptomatic presentation can be so complicated in its causes. We can not over emphasize special training in making an accurate diagnosis and giving appropriate treatment. LUTS/BPH is never a simple issue for any physician who wants to get involved in this field.

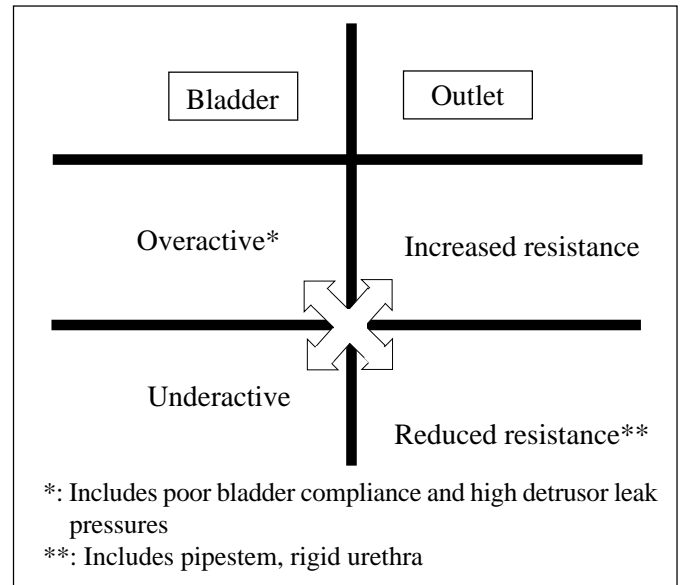
**THE DIFFERENTIAL DIAGNOSIS OF LUTS/BPH**

From the EPIC study, we can see that the overall prevalence of male LUTS for men over 18 years of age is about 61.3% [3]. The most bothersome problems are storage symptoms just like OAB affects about 49.7% of the population. BPH may cause BOO and therefore cause the secondary response of detrusor muscles such as smooth muscle cell proliferation and changes of their contractility. Then, LUTS develop due to the detrusor response. In addition, the detrusor may develop from compensated to decompensate detrusor [10]. The changes may cause the presentation of storage symptoms of LUTS, which are similar to the presentations of OAB. Of course, factors other than BPH such as polyuria, aging effect, primary bladder disease, neurogenic disease and non-BPH BOO may be causes too. The differentiation of OAB is clearly considered in the 5th International Consultation on Urologic Disease (ICUD) consensus in the treatment algorithm of BPH [11]. From this report, OAB is only a part of the LUTS/BPH differential

diagnosis, which is not the whole picture in this issue. In fact, many differential diagnoses may be raised for LUTS (Table 1).

Here, we focus on the functional issue arising from bladder and urethral abnormalities. The anatomic or pathological issues should be already familiar to the members. An etiological approach to this problem may be somewhat confused or not straight forward enough for us. A more detailed and comprehensive diagnostic thinking process must be introduced. In actuality, a bladder dysfunction may be classified into four quadrants [12]. The bladder may be overactive or underactive; and the bladder outlet may have an increased or decreased urethral resistance (Fig. 1). However, the symptoms may be the same whether a patient suffers from an overactive bladder or reduced bladder outlet resistance. Conversely, an underactive bladder may present with the same symptoms as increased bladder outlet resistance. From this 2 x 2 diagnostic grid, we can very easily make a single diagnosis of overactive or underactive bladder due to a myogenic problem or an afferent/efferent neurogenic problem.

A thorough history taking, examination and urodynamic study may be necessary for diagnosis and differentiation. On the other hand, we



**Fig. 1.** A 2 x 2 diagnostic grid offers an easy structural framework to help us when considering voiding problems.

**Table 1.** Categories of Causing Underlined Disease in LUTS

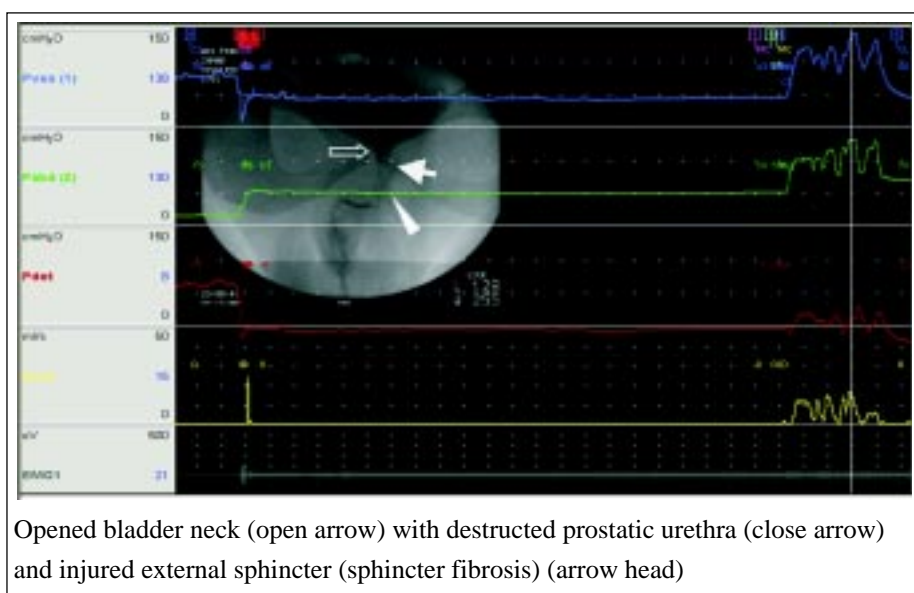
Category	Cause of LUTS	Comments
Malignant	Prostate/bladder cancer	PSA, DRE and ultrasound should be offered
Infectious	Cystitis, prostatitis, STD	Urinalysis, culture and prostatic massage specimens
Neurological	Spinal cord injury, cauda equine syndrome, stroke, peripheral neuropathy	Primary mechanism for neurological cause of LUTS is detrusor weakness and/or uninhibited detrusor contraction
Pharmacological	Diuretics, sympathomimetics, anticholinergics	Diuretic cause frequency, sympathomimetics increase urethral resistance, anticholinergics decrease detrusor contractility
Medical	Diabetes, congestive heart failure, obstructive sleep apnea	An overlooked cause of LUTS
Iatrogenic	Prostatectomy, cystectomy, trauma, radiation cystitis	Surgery may cause scarring and urethral stricture
Anatomical	Ureteral and bladder stone	Hematuria may be seen. Cystoscopy, urine cytology and renal imaging studies may be offered
Behavioral	Polydipsia, alcohol or caffeine	Voiding diary may provide useful information
Other	Overactive bladder	UDS can help differentiate BPH from isolated detrusor dysfunction

can easily make a differentiation between anatomic or functional increased urethral resistance through cystoscopy and imaging studies. Through the Q-tip test, video-urodynamic study (VCUD) or magnetic resonance imaging, we can also differentiate urethral hypermobility and intrinsic sphincter deficiency. However, the differentiation diagnosis may be more complicated. A patient may have overactive and underactive detrusor such as in the clinical diagnosis of detrusor hyperactivity with insufficient detrusor contractility based on detrusor overactivity and poor contracting strength and elevated urinary

residual volumes in the urodynamic study. This kind of diagnostic combination has not been part of our previous thinking process. If we can think about the problems based on the four major abnormal quadrants, we can easily picture a more clear analysis in our mind.

For example, the most severe cases would be the ones comprising four quadrant abnormalities with a typical clinical presentations of urgency, frequency, with or without urge incontinence, stress incontinence, poor force of urinary stream, intermittency, hesitancy, feeling of incomplete bladder empty

and terminal dribble. The urodynamic study will revealed detrusor overactivity, urine loss with increased abdominal pressure, and low amplitude detrusor contraction with increased urethral resistance. The typical case will be the one with mixed urine incontinence after retropubic sling with chronic obstruction and hypo-contractile bladder. If we consider the problems from the 2 x 2 grid perspective, we will not be confused if the patient has these complicated combinations. In fact, fifteen combinations of diagnosis may be included in this 2 x 2 diagnostic grid (Table 2). From this 2 x 2 diagnostic table, we can more easily see an unusual diagnostic classification. In actuality, the ability of the nervous system to change transmitters, reflexes or synaptic transmission with disease or injury may involve neural plasticity. This plasticity may shift the balance between detrusor hyperactivity and impaired contractility [13]. Fig. 2 shows the VUDS of a 32-year-old man suffering from voiding difficulty, abdominal straining, urinary incontinence, frequency and urgency, and who received an inadequate transurethral operation. The VUDS revealed a very complicated prostatic urethra and external sphincter injury, which caused secondary bladder dysfunctions including bladder overactivity and decompensated detrusor contractility. If we can take this 2x2 grid table as our diagnostic reference, we will not feel any difficulty in dealing with this patient. This patient finally received an implantation of an AMS 800CXM artificial sphincter.



Opened bladder neck (open arrow) with destructed prostatic urethra (close arrow) and injured external sphincter (sphincter fibrosis) (arrow head)

Fig. 2. A complicated voiding dysfunction diagnosed with a video-urodynamic study VUDS.

Table 2. Diagnostic Combinations in 2 x 2 Diagnostic Grid

Diseased entity	Associated entities	Diagnosis
Overactive		Detrusor overactivity
Underactive		Acontractile detrusor, Atony of bladder
Increased resistance		Bladder neck dyssynergia or contracture, Prostate enlargement, Detrusor sphincter dyssynergia
Reduced resistance		Stress urine incontinence, Urethral hypermobility, Intrinsic sphincter deficiency
Overactive	Increased resistance	BPH with overactive bladder
Overactive	Reduced resistance	Mixed urinary incontinence
Overactive	Underactive	Detrusor overactivity with insufficient contraction
Increased resistance	Reduced resistance	s/p TUR-P with bladder neck contracture
Increased resistance	Underactive	BPH with de-compensated detrusor
Reduced resistance	Underactive	Sacral agenesis with residual urine and stress incontinence
Overactive	Increased resistance + Reduced resistance	Post-prostatectomy stricture and stress incontinence
Overactive	Underactive + Reduced resistance	BPH with overactive and de-compensated detrusor s/p TUR-P
Overactive	Underactive + Increased resistance	BPH with overactive and de-compensated detrusor
Underactive	Increased resistance + Reduced resistance	Bladder neck contracture after prostatectomy with stress incontinence and residual urine
Underactive	Overactive + underactive + Increased resistance + Reduced resistance	Mixed incontinence after retro-pubic sling with chronic obstruction and hypo-contractile bladder

## CONSIDERING INVESTIGATING TOOLS

Basically, when a patient presents with LUTS with BPH who has significant quality of life impairment, we should consider an urodynamic study [14]. In fact, VUDS is not designed to be a substitute for a thorough history taking, physical examination, voiding diary, pad test, and other noninvasive testing. On the contrary, based on the results of initial evaluation, the correct diagnosis may be established obviating the need for a VUDS. Most urologists would agree that a VUDS is indicated when a diagnosis cannot be made with a less invasive means and potential harm could result from a missed or mistaken diagnosis. The major and minor complication rate associated specifically, with urethral catheterization in men may be as high as 19% [15]. In addition, recent studies have suggested that certain office-based criteria can be highly sensitive and specific for the diagnosis of uncomplicated female stress urinary incontinence without the need for invasive urodynamic testing [16-18]. Therefore, even in male patients with complex voiding dysfunction, the benefit versus cost, inconvenience, and morbidity of VUDS testing should be balanced at all times.

Indication for a VUDS may include neurogenic voiding dysfunction. This is because urinary symptoms are often unreliable in neurological illness and the severity of neurological deficits does not correlate well with the type of urologic pathology. Therefore, neurogenic voiding dysfunction therapy should be based on urodynamic findings. In addition, a suspected urethral pathology in the setting of urinary incontinence, re-evaluation of failed anti-incontinence surgery, unexplained or persistent voiding dysfunction, re-evaluation of medical or surgical treatment failures and voiding dysfunction in young men are indications for VUDS [19]. However, some noninvasive methods have been used to diagnose BOO. In particular a combination of noninvasive urodynamic measures and ultrasound-derived measures appear promising for diagnosis of BOO. Currently, pressure flow studies remain the gold standard and are the objective assessment used for of BOO in men [20].

Some noninvasive diagnostic methods for BOO and LUTS include single ultrasound measurements (PVR; bladder weight, BW; bladder wall thickness, BWT). The interactions between BOO and detrusor contractility is complex. It is known that increased PVR occurs in patients with BOO. However, a large PVR may reflect detrusor underactivity rather than BOO [21,22]. Manieri et al reported that BWT is significantly influenced by bladder volume. A total of 174 male patients with LUTS underwent 3 measurements of BWT at 3 sites (anterior and lateral walls). Average BWT correlated with urodynamic parameters of obstruction. Of 58 patients with a BWT of greater than 5 mm, 88% had obstruction on pressure flow studies. The specificity of a BWT of more than 5 mm for diagnosing BOO was 92% [23]. A pilot study of the change in ultrasound estimated bladder weight (UEBW) parameters after tamsulosin treatment in 32 patients demonstrated a decrease in UEBW at 30 days that was maintained at 6 months [24]. Using an UEBW cutoff of greater than 35 gm, the test sensitivity was 85% with 87% specificity.

## CONCLUSION

In spite of the use of several diagnostic investigations or tools in the differentiation of LUTS/BPH, bladder ultrasound and urodynamics, such as pressure flow study and VCUD offer valuable information. Voiding dysfunction presenting with LUTS may be a complicated com-

bination of abnormal function or anatomy of the bladder and urethra. Accurate diagnosis is not an easy matter. A 2 x 2 diagnostic grid can help us use a straight forward approach to having a clear understanding of the real voiding dysfunction. As a result, we will not be confused or puzzled when facing combined clinical or urodynamic presentations.

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