

Lower Urinary Tract Symptoms, Benign Prostatic Hyperplasia, and Urinary Retention



Omar Al Hussein Alawamlh, MD¹, Ramy Goueli, MD²,
Richard K. Lee, MD, MBA^{*,1}

KEYWORDS

- Voiding dysfunction • Lower urinary tract symptoms • Benign prostatic hyperplasia
- Acute urinary retention • Chronic urinary retention

KEY POINTS

- Lower urinary tract symptoms (LUTS) is a common set of urologic symptoms that can affect men of all ages, with a predilection for the elderly.
- Benign prostatic hyperplasia is the most common cause of voiding dysfunction, leading to higher prevalence of LUTS in the elderly.
- Managing a patient with LUTS starts with obtaining a thorough medical history and establishing symptom severity, followed by the appropriate utilization of diagnostic modalities.
- A variety of medical treatments exist for LUTS, which can be used either as monotherapy or in combination.

INTRODUCTION

Advancements in health care over the past several decades have significantly contributed to the increase in quality of life and life expectancy. It is projected that the elderly population in the United States will be 83.7 million in the year 2050, comprising about 21% of the entire population.¹ This change in demographics does not come without challenges, most notably an increase in the incidence and prevalence of chronic illnesses along with the associated economic burden.²

Conflicts of Interest: None.

Department of Urology, Weill Medical College of Cornell University, James Buchanan Brady Foundation, New York, NY, USA

¹ Present address: 425 East 61st Street, New York, NY 10065.

² Present address: 525 East 68th Street, STAR 9, New York, NY 10065.

* Corresponding author.

E-mail address: ril9010@med.cornell.edu

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It is well known that advanced age is associated with a higher likelihood of morbidity, including urologic conditions such as lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH).^{3,4} One may assume that the prevalence of LUTS and BPH will significantly rise with increasing age. This increase warrants a more active role by primary care physicians (PCPs) in both the diagnosis and management of patients presenting with those conditions because PCPs typically are the first point of medical contact.⁵

VOIDING DYSFUNCTION

Voiding dysfunction is abnormal, slow, and/or incomplete micturition as defined by the International Continence Society (ICS) and the International Urogynecological Association.⁶ The different types of voiding dysfunction, however, are described by the term LUTS.⁷ LUTS are divided into 3 groups of symptoms (storage, voiding, and postmicturition) according to the ICS (**Box 1**).⁸ It is estimated that by the year 2018, 2.3 billion people will be affected by at least 1 of the LUTS.⁹

VOIDING DYSFUNCTION AND BENIGN PROSTATIC HYPERPLASIA

Prostatic hyperplasia is a phenomenon that affects more than 70% of men aged 60 to 69 years in the United States.¹⁰ Several mechanisms have been proposed to explain the causes behind the development of this nonmalignant growth. Some investigators looked at modifiable factors, such as obesity, as a cause of metabolic derangements, whereas others considered the role of inflammation. Perhaps the most popular proposed mechanism is the effect of androgens on the prostate gland.^{11–13}

Box 1

The 3 groups of lower urinary tract symptoms

Storage symptoms

- Daytime frequency
- Nocturia
- Urgency
- Different types of incontinence
- Enuresis
- Abnormal bladder sensation

Voiding symptoms

- Slow or intermittent stream
- Splitting or spraying
- Hesitancy
- Straining
- Terminal dribble

Postmicturition symptoms

- Feeling of incomplete emptying
- Postmicturition dribble

Data from Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21(2):167–78.

BPH is considered the most common cause that leads to LUTS in men.¹⁴ BPH promotes bladder outlet obstruction (BOO), which then gives rise to LUTS via 2 components:

1. A dynamic obstruction component characterized by smooth muscle hyperplasia
2. A static component consisting of the enlargement of the prostate gland driven by the excessive growth of stromal and epithelial elements.

LUTS that results from BOO is also complicated by the detrusor's response to obstruction, which can manifest as impaired contractility or overactivity.^{15,16}

BENIGN PROSTATIC HYPERPLASIA AND URINARY RETENTION

Urinary retention is a fairly common complication of BPH. Estimates show that 10% of men in their seventies and one-third of men in their eighties will experience acute urinary retention (AUR) within the next 5 years.¹⁷

Acute Urinary Retention

AUR is a sudden unexpected inability to pass urine that is usually associated with pain.¹⁸ Acute retention is regarded as an emergency requiring urgent medical attention. Patients usually present with lower abdominal pain and swelling (palpable pelvic mass that is dull to percussion), and either the frank inability to pass urine or the ability to pass only a small amount.¹⁹

AUR can either occur spontaneously or secondary to a precipitating event. Spontaneous AUR represents almost all cases and is most commonly associated with BPH, in which it serves as a sign of progression. Precipitated AUR, however, follows a triggering factor, such as a surgical procedure (pain, anesthesia, or immobility), excessive fluid intake (eg, alcohol), a urinary tract infection (UTI), medications with sympathomimetic or anticholinergic effects, or neuropathic causes (diabetic cystopathy). Distinguishing between the 2 types of AUR is relevant because BPH surgery is required more often in cases of spontaneous AUR.^{17,19}

CHRONIC URINARY RETENTION

The ICS defines chronic urinary retention (CUR) as a "non-painful bladder, which remains palpable or percussable after the patient has passed urine. Such patients may be incontinent."⁸ Patients with CUR may complain of increased urinary frequency, hesitancy, poor urinary flow, nocturnal incontinence, or may even be asymptomatic.²⁰ The literature varies in its criteria for diagnosis of CUR, with multiple sources using postvoid volumes ranging between 300 to 500 mL as their cutoff.^{19,21} CUR may occur in young or elderly patients, and can be independent of prostatic volume.²²

This condition can be divided into high-pressure and low-pressure CUR, referring to the detrusor pressures generated either during filling or micturition. High-pressure CUR accounts for most cases of CUR and is associated with BOO; it often leads to the development of hydronephrosis and resultant renal failure from the backward pressure generated. In contrast, patients with low-pressure CUR have a very compliant bladder and retain a large volume without the development of hydronephrosis or renal failure.^{19,22}

DIAGNOSIS OF VOIDING DYSFUNCTION

For basic management of BPH-related LUTS, the American Urological Association (AUA) classifies diagnostic tests into recommended or optional, in which a

recommended test should be had by every patient, whereas an optional test is performed for select patients and is generally carried out by a urologist. A review of the recommended tests follows.

History and Patient-Specific Questionnaires

Obtaining a thorough patient history is a key element with any patient presenting with LUTS. In the initial work-up of LUTS, the symptoms must be identified and the degree of severity established. BPH-associated symptoms are best quantified using the AUA Symptom Index and the International Prostate Symptom Score. The AUA describes the 2 indices as self-administered questionnaires that assess the severity of both storage and voiding symptoms. Another survey instrument is the Overactive Bladder Questionnaire. Additionally, AUA guidelines recommend the use of frequency volume charts in patients with nocturia as the dominant symptom.

Physical Examination

A physical examination includes assessing the abdominal and genital regions for abnormalities. Particular attention should be given to suprapubic distension and tenderness or neurologic (sensory and motor) dysfunction. A critical component of the examination is the digital rectal examination (DRE) that evaluates prostate size, consistency, tenderness, and surface, in addition to sphincter tone.

Laboratory Testing

Despite its importance, DRE must be concomitantly used with other diagnostic tools. One such tool, which provides more accuracy in assessing prostate volume and can correlate with symptom progression, is the prostate-specific antigen (PSA) test.²³ Specifically, serum PSA has been shown to be a strong predictor of prostatic growth. However, testing serum PSA to diagnose prostate cancer (PCa) in men with LUTS should be discussed with the patient, including false-positive or false-negative results, as well as potential overdiagnosis and treatment of PCa.^{24,25} Additional laboratory tests should be performed at the discretion of the provider, although the AUA recommends against checking creatinine in the initial diagnosis of LUTS secondary to BPH.

Urinalysis

Urinalysis (UA) is another recommended test used to assess LUTS. Dipstick tests are able to detect hematuria, proteinuria, pyuria, ketonuria, and glucosuria. Abnormalities in dipstick tests indicate the need to examine the urinary sediment and perform a culture.²⁶ UA can provide guidance in both determining the cause of LUTS and directing further testing.

DIFFERENTIAL DIAGNOSIS

The differential for LUTS in men is incredibly broad and relies on the diligence of the clinician to obtain a good history, and physical and symptom-directed diagnostic evaluations ([Table 1](#)).

Infectious Cause

In patients who have a sudden onset of dysuria, increased frequency, urgency, and foul smelling or discolored urine, an infectious cause should be considered. On UA, the presence of either positive leukocyte esterase or nitrates, yields a sensitivity of 81% and a specificity of 77% for diagnosing a UTI with greater than 100,000 colony-forming units.²⁷ If the urine culture is negative with ongoing LUTS, despite a

Table 1	
Differential diagnosis for lower urinary tract symptoms	
Differential Diagnosis	
Infectious	UTI <ul style="list-style-type: none"> • Bacterial • Parasitic • Viral • Fungal
Obstruction	BPH Bladder neck contracture Urethral stricture
Inflammation	Interstitial cystitis or bladder pain syndrome Foreign body (bladder calculus, ureteral stent, urethral catheter) Vesicoenteric fistulas
Neoplastic	Urothelial carcinoma Locally invasive PCa Metastatic disease Extrinsic pelvic mass
Metabolic	Diabetes mellitus
Medication Induced	Diuretics Chemo-immunotherapy (ie, cyclophosphamide and intravesical therapeutics)
Neurologic	Multiple sclerosis Normal pressure hydrocephalus Stroke or cerebrovascular accident Parkinson disease Cauda equina syndrome Tethered cord syndrome Spinal shock or spinal cord injuries Pelvic surgery

positive UA, then one should consider atypical infectious causes, including mycoplasma or ureaplasma infections that are difficult to culture. Additionally, consider urinary tuberculosis or schistosomiasis in patients who have a history of travel to an endemic area or have known risk factors or contact exposures.^{28,29} Finally, for patients who are sexually active, gonococcal and nongonococcal urethritis should be on the differential diagnosis.³⁰

Obstruction

Patients who present with a history of LUTS, including nocturia, increased frequency, postvoid dribbling, and a sensation of incomplete emptying with no known infectious cause, should be considered for an obstructive cause.³¹ A bladder neck contracture should be considered in any patient who has undergone a transurethral procedure, most commonly including transurethral resection of the prostate. Although advanced BPH can present with obstructive symptoms, it can be distinguished from PCa by the presence of an abnormal PSA and/or DRE.³² A stricture of the urethra should be considered in patients with history of trauma, gonococcal urethritis, urethral instrumentation or surgery, and penile or pelvic radiation.^{33,34}

Inflammation

Inflammation in the absence of infection that can lead to LUTS may arise from a foreign body (bladder stone, Foley catheter, or ureteral stent), vesicoenteric fistulae, prior

pelvic radiation, interstitial cystitis or bladder pain syndrome. A vesicoenteric fistula should be considered in select patients with risk factors and recurrent multiple organism UTIs, and/or pneumaturia or fecaluria.²⁶

Neoplasm

Locally advanced PCa was previously discussed as a potential obstructive cause of LUTS. Additional possible neoplastic causes for LUTS in men are urothelial carcinoma, extrinsic pelvic mass, or metastatic disease. Urothelial carcinoma is more common in men and should be highly considered in patients with known risk factors (smoking, chronic cystitis, or chemical or radiation exposure) and either microscopic or gross hematuria on evaluation. These patients should warrant a prompt referral to a urologist.^{35,36}

Metabolic

Patients who complain of LUTS related to polyuria and urinary frequency should undergo evaluation for diabetes mellitus because this can present with polyuria and polydipsia. Patients with diabetes mellitus should work to achieve tight glycemic control to minimize urinary symptoms and limit microvascular insults to the kidneys.³⁷

Medication-Induced

There are 2 major classes of medications that can precipitate LUTS, specifically diuretics and chemoimmunotherapy (ie, cyclophosphamide). Diuretics will cause increased urination, which is particularly bothersome when taken before bed, thus affecting the patient's quality of life. Cyclophosphamide increases the risk for both hemorrhagic cystitis and associated bladder cancer, therefore warranting further workup from a urologist.

Neurologic

Neurologic conditions that can cause LUTS include multiple sclerosis, normal pressure hydrocephalus, stroke, Parkinson disease, cauda equina syndrome, tethered cord, and spinal shock, as well as prior pelvic surgery with manipulation of the sacral plexus.^{38,39} The presentation of LUTS with associated neurologic dysfunction requires further investigation by a specialist. The use of pressure-flow studies may be helpful in this population.

TREATMENT

The treatment of LUTS largely depends on the likely causes of the patient's symptoms and level of bother. Treatment options should include lifestyle modifications; behavioral modifications; and, when necessary, pharmacotherapy. The AUA recommends addressing all 3 aspects in creating a treatment plan.

Watchful Waiting

Men whose urinary symptoms are not bothersome to their lives may be candidates for watchful waiting or active surveillance. In these patients, the AUA recommends annual reassessment of symptoms, including a medical history and physical examination; an evaluation of symptom severity; and, in appropriate men, PSA measurement.^{26,40} Watchful waiting should also include lifestyle and behavioral modifications, such as avoiding caffeine, alcohol, and spicy and acidic food.³⁷ Clinicians can specifically address bothersome nocturia by recommending decreased evening fluid intake and

avoidance of diuretics before sleep.⁴¹ Additionally, treatment of a patient's underlying disease (diabetes, obstructive sleep apnea, or edema) can also improve symptoms.

Medical Therapy

For men who are significantly bothered by their LUTS, the AUA recommends that risk and benefits of treatment of LUTS secondary to BPH should be discussed with patients before starting any and all treatments, with the following available options.

Phytotherapy

Phytotherapeutic agents include saw palmetto, African plum tree, stinging nettle, pumpkin seed, African star grass, and rye grass pollen. Those agents are claimed to benefit patients with LUTS related to BPH; however, due to the paucity of available data, the AUA currently does not recommend their use.⁴²

Alpha-Blockers

Alpha-blockers work through the antagonism of alpha-1 adrenergic receptors, which causes a relaxation of the smooth muscle in the prostate and bladder neck. Alpha-blockers differ in their selectivity and, thus, differ in their dosing and side effect profile.⁴³ Terazosin, doxazosin, and alfuzosin are nonselective alpha-blockers, whereas tamsulosin and silodosin are alpha-1A selective blockers. Terazosin; immediate release doxazosin; and, occasionally, tamsulosin will require dose titration based on symptoms, whereas the others will not require titration. These medications have all been shown to have equal clinical significance and can be tailored to a patient's individual needs.⁴⁴ The AUA recognizes that older, generic alpha-blockers remain a reasonable choice but require dose titration and blood pressure monitoring. The long-term use and safety of alpha-blockers was partly demonstrated in the Medical Therapy of Prostatic Symptoms (MTOPS) study.⁴⁵ Use of alpha-blockers was shown to have long-term symptom improvement but had no effect on progression to AUR or the need for surgery. Improvement in urinary symptoms can happen within a couple of days of starting the medication but may take 1 to 3 months for maximal improvement.⁴⁶

All alpha-blockers can cause variable levels of fatigue, nasal congestion, orthostatic hypotension, and retrograde ejaculation. Silodosin and tamsulosin have the highest rate of retrograde ejaculation with 28% and 18% of patients experiencing this adverse effect, respectively. Tamsulosin, silodosin, extended release doxazosin, and alfuzosin have been shown to cause less dizziness and orthostatic hypotension than their counterparts.⁴³ Floppy iris syndrome can occur with the continued use of any alpha-blocker during cataract surgery, in which the AUA recommends against the initiation of alpha-blockers in men planning to undergo cataract surgery.

5-Alpha Reductase Inhibitors

The inhibition of 5-alpha reductase blocks the conversion of testosterone to dihydrotestosterone, the reduction of which has been shown to reduce prostate volume by 25%, decrease total PSA by 50%, and reduce the risk of AUR and the need for surgical BPH management.⁴⁷ There are 2 medications available, finasteride, a type 2 5-alpha reductase inhibitor (ARI), and dutasteride, a type 1 and 2 5-ARI.

The benefit and efficacy of 5-ARIs was demonstrated in the Proscar (Finasteride) Long-term Efficacy and Safety Study (PLESS), which showed an improvement in urinary symptoms and flow rates in select patients taking this medication.⁴⁸ The 5-ARI arm of the MTOPS and Combination Avodart and Tamsulosin (CombAT) trial both confirmed improvement in voiding symptoms, as well as a decrease BPH progression

and a lower need for surgical BPH treatment.⁴⁵ Because these studies focused on patients with larger prostates (>30 g), the AUA recommends against the use of 5-ARIs in men with LUTS without demonstrable prostatic enlargement. The adverse effects of 5-ARIs include decreased volume of ejaculate; impotence; decreased libido; and, rarely, breast and nipple tenderness. After starting 5-ARIs, patients will need to wait 6 to 9 months before noticing a full effect of the medication.

Phosphodiesterase 5 Inhibitors

Tadalafil (Cialis) is the only phosphodiesterase 5 (PDE5) inhibitor approved by the US Food and Drug Administration for treatment of BPH-related LUTS. Although its exact mechanism of action in BPH-related disease is unknown, its use has been shown to improve erectile dysfunction, voiding symptoms, and quality of life in men with LUTS related to BPH, although no change was seen in objective voiding parameters.⁴⁹

After starting tadalafil, the effect may be noted within a week but may take up to 2 months for a full effect. Like other PDE5 inhibitors, patients are at risk for headaches and flushing; and, less commonly, nasal congestion, back pain, diplopia, impaired color vision, and priapism. PDE5 inhibitors should be used with caution in patients taking alpha-blockers and are contraindicated in patients taking nitrates.⁵⁰

Antimuscarinics

Anticholinergic medications can be useful in treating the associated overactive bladder related to BOO from BPH.⁵¹ These medications have been shown to be an effective adjunctive treatment of management of storage symptoms. The AUA recommends that, before starting these medications, obtain a postvoid residual assessment because caution is advised when it is greater than 250 mL.^{52,53} The adverse effects of these medications include dry mouth; constipation; blurry vision; headache; dizziness; and, rarely, cognitive impairment and AUR.

Combination Therapy

Several studies have shown the improved efficacy of combining alpha-blockers and 5-ARIs in select patients. According to the AUA, this combination is a viable option for patients with LUTS associated with BPH diagnosed via PSA, DRE, or volume measurement. Two paramount studies were the MTOPS trial and the CombAT trial, which focused mainly on men with larger glands (>30 g) and higher serum PSA levels (PSA >1.5 ng/mL). Both studies showed combination therapy, compared with either agent alone, prevented BPH progression, and improved individual voiding symptoms and voiding parameters.^{45,54}

In select patients, the combination of alpha-blockers and anticholinergics has also been studied. In men with predominant storage or irritative voiding symptoms related to BPH, this combination has been shown to lead to greater improvement in symptoms and quality of life than either agent alone.^{55,56}

MANAGEMENT

Patient follow-up depends on the therapies initiated. Patients started on alpha-blockers or PDE5 inhibitors should be reevaluated in 2 to 4 weeks, whereas patients started on 5-ARIs can be seen in 3 months to ensure enough time is given for treatment effect. Following reevaluation, if the patient is satisfied, they can transition to yearly follow-up. As mentioned, follow-up should consist of history and physical, a validated voiding symptom questionnaire, and a PSA.³¹

Patients who have undergone basic therapies with no benefit warrant a referral to a urologist. Additionally, patients who present with complicated LUTS, defined as voiding symptoms combined with an abnormal PSA, abnormal DRE, hematuria, a palpable bladder, upper tract dysfunction, or neurologic disease, also warrant referral to a urologist for further management.

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