Lower urinary tract symptoms in men

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INTRODUCTION

The term "lower urinary tract symptoms" (LUTS) is nonspecific. It has been used as a general term to refer to any combination of urinary symptoms or as a more specific term to refer to those symptoms primarily associated with overactive bladder (frequency, urgency, and nocturia). An international consensus conference defined LUTS to include symptoms relating to storage and/or voiding disturbances common among aging men [1]. This topic will review the symptoms, etiology, evaluation, diagnosis, and treatment of lower urinary tract dysfunction in men.

Discussions of incontinence, benign prostatic hyperplasia (BPH), and nocturia are presented separately.

- (See "Urinary incontinence in men".)
- (See "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia".)
- (See "Medical treatment of benign prostatic hyperplasia".)
- (See "Nocturia: Clinical presentation, evaluation, and management in adults".)

PREVALENCE AND RISK FACTORS

The prevalence of lower urinary tract symptoms (LUTS) in men increases with age. LUTS often has a significant negative impact on a patient's quality of life. A survey of over 5000 community-dwelling men age ≥65 in the United States without history of prostate cancer found that 46 percent reported moderate to severe LUTS [2]. Another community-based study found that the

prevalence of LUTS increases steadily with age into the 10th decade, affecting 70 percent of men older than 80 years [3].

Diabetes mellitus (DM) appears to be a risk factor for LUTS, but the presence of urinary symptoms is not explained by the degree of glycemic control [4]. This relationship was strongest in younger men (<70 years old) and in those with longstanding (>5 years) disease. Other conditions associated with LUTS include cardiovascular disease [5], obesity, sedentary lifestyle, and erectile dysfunction. Although the pathophysiologic connection of LUTS to erectile dysfunction is not clearly defined, this observation has resulted in new approaches to the evaluation and management of both disorders.

Increased fluid intake and caffeine use have been associated with urinary frequency and urgency, and modest alcohol use (one to three drinks per day) has been associated with decreased LUTS in men [6].

SYMPTOMS

Lower urinary tract symptoms (LUTS) can be categorized as symptoms related to storage, voiding, or post micturition [7-9]. Men with LUTS may report one or any combination of symptoms. LUTS typically fluctuate over time and may remit spontaneously [10]. LUTS are associated with severe sleep disturbance [11], increased depressive symptoms [12], and decreased ability to perform activities of daily living [2].

Storage — Storage symptoms, experienced during the bladder filling and storage phase of micturition, include:

- Urgency – A sudden compelling desire to pass urine that is difficult to defer
- Daytime frequency – A patient's perception that he voids too often by day
- Nocturia – The need to wake at night one or more times to void
- Incontinence – Involuntary leakage
- Abnormal bladder sensation

Voiding — Voiding symptoms are those experienced at the time of urine flow and include:

- Slow stream – The individual's perception of reduced urine flow, usually compared with previous performance and sometimes compared with observations of other men. Splitting or spraying of the urine stream may be reported.

- Intermittent stream or intermittency – Urine flow that stops and starts, on one or more occasions, during micturition.

- Hesitancy – Difficulty in initiating micturition, resulting in a delay in the onset of voiding after the individual is ready to pass urine.
- Straining to void – An abdominal muscular effort used to initiate, maintain, or improve the urinary stream.
- Terminal dribble – Prolongation of the final part of micturition, when the flow has slowed to a trickle/dribble [8].
- Dysuria – Pain, burning sensation, or general discomfort at the time of passing urine.

Post-micturition — Post-micturition symptoms include:

- A sensation of incomplete emptying after passing urine
- Post-micturition dribble – The involuntary loss of urine shortly following urination, usually after leaving the toilet [8]

ETIOLOGIES OF LUTS

Traditionally, lower urinary tract symptoms (LUTS) in men have been primarily attributed to benign prostatic hyperplasia (BPH) and consequent bladder outlet obstruction (BOO). However, the significance of other etiologies for voiding dysfunction is increasingly recognized. Overactive bladder (OAB), characterized by involuntary contraction of the detrusor muscle, may be the principal cause or a contributory cause of LUTS in some men. Careful evaluation is indicated to identify the primary factors responsible for LUTS in an individual patient in order to target appropriate treatment.

Bladder outlet obstruction from BPH — LUTS with symptoms of BOO in men traditionally have been attributed to an enlarged prostate or benign prostatic enlargement (BPE). BPH refers to a specific histologic diagnosis, although the term is commonly used interchangeably with benign prostatic enlargement despite the absence of tissue confirmation. We will use BPH here as synonymous with BPE.

Clinically significant BPH presents as LUTS with a predominance of voiding symptoms. Patients experience progressive symptoms that can range from nocturia to acute urinary retention and may include incomplete emptying, urinary hesitancy, weak stream, frequency, and urgency. Long-term or chronic BOO may eventually lead to bladder/detrusor decompensation. (See "Acute urinary retention" and 'Detrusor overactivity following BOO' below.)

Clinical manifestations and diagnostic evaluation for BPH are discussed in detail elsewhere. (See "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia".)

Other causes of bladder outlet obstruction — Other conditions that may cause BOO in men include urethral stricture, primary bladder neck obstruction, bladder neck contracture, detrusor-sphincter dyssynergia, prostate cancer, and, less likely, meatal stenosis.

Overactive bladder and detrusor overactivity — OAB is defined by the International Continence Society as a syndrome of urinary urgency, with or without urgency incontinence, usually accompanied by increased frequency during both daytime and nighttime nocturia. Although overactive bladder is typically associated with storage symptoms rather than voiding symptoms, OAB often accounts for symptoms in men who are thought to have BOO but who fail to respond to therapy.

The incidence of OAB and LUTS symptoms is the same for older adult men and women [13]. Urgency, urgency incontinence, and frequency have been reported in 10 to 13 percent of European men 50 to 59 years old and in 18 percent of American men 45 to 54 years old [14,15]. The prevalence of OAB rises with increasing age.

Typically, the storage symptoms of OAB are more bothersome than the voiding symptoms of BPH. Men with OAB and urgency incontinence in particular have higher rates of depression and are more likely to alter activities (eg, decrease work hours, change employment, or take early voluntary retirement) compared with men with OAB who do not have incontinence [16].

OAB symptoms are often attributed to detrusor overactivity, characterized by involuntary detrusor contractions during bladder filling [17]. Uninhibited detrusor contractions can be detected on the cystometrogram portion of urodynamic testing.

OAB may be classified as either neurogenic or non-neurogenic. Although the specific mechanism triggering overactivity is essentially unknown, neurogenic OAB symptoms are thought to be related to decreased suprapontine inhibition of the micturition reflex, leading to enhanced excitatory neurotransmission in the micturition reflex pathway [18]. Neurogenic causes include cerebrovascular accident, Parkinson disease, multiple sclerosis, and spinal cord injury. Non-neurogenic, or idiopathic, causes of OAB include BOO (usually secondary to BPH), postoperative pelvic surgery, and bladder stones or other foreign bodies.

Treatment modalities for OAB are directed principally at blocking the muscarinic receptor, the presumed site of neurogenically mediated detrusor overactivity [19]. (See 'Treatment options' below.)

Detrusor overactivity following BOO — Symptoms of OAB overlap with those attributed to BOO secondary to BPH. The incidence of detrusor overactivity with BOO has been reported to range from 30 to 60 percent [20]. Because of the similarities and the overlap in symptoms of clinical BPH and OAB, it can be difficult to separate the two conditions [20]. The presence of both BOO and detrusor overactivity in an individual does not confirm causality. Nonetheless, animal models do suggest that BOO can lead to the development of detrusor dysfunction.

Tissue ischemia appears to play a central role in BOO-induced detrusor overactivity. Mild bladder distension can cause relative hypoxia in bladder muscle in a canine model, with documentation of reduced detrusor blood flow during filling of hypertrophic bladders [21,22]. Tissue hypoxemia results from increased oxygen demand by hypertrophic tissue and diminished oxygen supply in the presence of elevated intravesical pressures. Vasodilatory substances, such as nitric oxide synthase, are found in bladder tissue shortly after obstruction and suggest induction of mechanisms to restore blood flow to underperfused areas [23]. It is hypothesized that smooth muscle injury results from a cycle of relative tissue hypoxia during bladder distension, followed by reperfusion injury after micturition [19,24].

BOO may also cause detrusor overactivity via cholinergic denervation of the detrusor muscle and consequent supersensitivity of muscarinic receptors to acetylcholine [25,26]. Animal models suggest that increased bladder outlet resistance may also result in increased detrusor collagen content, changes in electrical properties of detrusor smooth muscle cells [19], and/or reorganization of the spinal micturition reflex [27].

INITIAL PATIENT EVALUATION

Patients who present with symptoms of lower urinary tract symptoms (LUTS), whether to their primary care clinician or to a specialist, should undergo an initial evaluation including history and physical examination. It is important to determine the degree to which symptoms impact the quality of life [1,28]. This assessment can be semiquantitative but may be facilitated by use of a structured questionnaire. (See 'International Prostate Symptom Score' below.)

An algorithm for the initial management of LUTS in men has been developed by an international consortium representing multiple urological societies from Europe, the United States, Latin America, and Asia (algorithm 1) [1].

History, physical, and testing — History should include the onset, duration, and severity of symptoms. Medications should be reviewed, as antidepressants, diuretics, bronchodilators, and antihistamines are associated with LUTS [29]. Factors associated with urinary incontinence

should be clearly ascertained, and patients should be questioned regarding any previous neurologic symptoms, injury, or disease. (See "Urinary incontinence in men", section on 'History and examination'.)

Physical examination should include evaluation of the abdomen, pelvis, perineum, and a focused neurological exam. A more extensive neurologic examination is indicated for patients with possible neurogenic lower urinary tract dysfunction. An attempt should be made to recreate activities that typically cause incontinence in the patient. Digital rectal exam should be performed to estimate prostate size and detect any abnormalities suggestive of prostate cancer.

Urinalysis is performed to evaluate for hematuria, pyuria, and bacteriuria [9]. Urine cultures are not recommended routinely but should be included if bacteriuria or pyuria are present or if there is otherwise suspicion for a urinary tract infection.

Initial laboratory studies may also include blood tests for renal function and glucose. The American Urological Association (AUA) recommends against routinely checking creatinine during the initial evaluation of LUTS. However, reasons to consider measuring creatinine include evaluation of possible upper urinary tract deterioration (eg, hydronephrosis) or high postvoid residual (PVR) volumes due to bladder outlet obstruction.

The benefits and risks of prostate-specific antigen (PSA) testing should be discussed with the patient. PSA testing as a screen for prostate cancer should be considered only in patients with life expectancy greater than 10 years. Another indication for measuring PSA in men with LUTS without cancer is as a proxy for prostate volume. PSA is also needed before treatment with a 5-alpha reductase inhibitor, and monitoring for prostate cancer should be done during treatment, with the understanding that these medications effect the PSA levels. (See '5-alpha reductase inhibitors' below.)

International Prostate Symptom Score — The International Prostate Symptom Score (IPSS) is a reproducible, validated index designed to determine disease severity and response to therapy. By itself, it is not a reliable diagnostic tool for LUTS suggestive of benign prostatic hyperplasia (BPH) but serves as a quantitative measure of LUTS after the diagnosis is established [30].

The IPSS, similar to the AUA's Symptom Score (AUASS), consists of seven questions related to voiding symptoms (table 1). Scores of 0 to 7, 8 to 19, and 20 to 35 signify mild, moderate, and severe symptoms, respectively.

In addition, the IPSS includes a quality of life score as a single 7-point scale question asking the patient how he would feel if he were to spend the rest of his life with his current urinary condition. Similarly, the International Consultation on Incontinence Modular Questionnaire - Male LUTS (ICIQ-MLUTS) asks patients to rate, on a scale of 0 to 10, how much leaking urine interferes with everyday life [31].

Indications for specialist referral — It is reasonable to initiate a trial of therapy for BPH when the primary care clinician is comfortable that presenting signs and symptoms are consistent with bladder outlet obstruction (BOO) due to BPH as the probable source of LUTS.

Men who predominantly have storage symptoms, suggesting overactive bladder (OAB), should be evaluated for PVR before anticholinergic or beta-3 agonist (ie, mirabegron) medications are initiated. A referral to urology should be considered if the PVR cannot be determined in the primary care setting or if the patient has not responded to a trial of medication for BPH.

Referral to a urological specialist may also be appropriate for patients with LUTS and any of the following:

- Men <45 years old
- Abnormality on prostate examination
- Presence of hematuria in the absence of infection
- Failure to respond to initial treatment for LUTS
- Men who desire surgical treatment
- Men with incontinence
- Men with severe symptoms
- PVRs >300 to 400 mL that are increasing

DIAGNOSTIC TESTING

There is some controversy regarding the role of diagnostic studies in the evaluation of men with lower urinary tract symptoms (LUTS) who are referred to a urologist. Guidelines from the American Urological Association (AUA) advise that all testing (including uroflowmetry, postvoid residual [PVR], pressure-flow urodynamics, and cystoscopy) be considered optional [32]. The 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases recommends urine flow rate measurement (Qmax) and PVR, measured by ultrasonography, prior to initiating active treatment and for subsequent monitoring [1]. Pressure-flow studies are recommended for the evaluation of patients before invasive therapies (when Qmax is greater than 10 mL per second) or when a precise diagnosis of bladder outlet obstruction (BOO) is

important. Both panels suggest cystoscopy and imaging of the prostate and upper tracts when indicated for evaluation of possible renal or malignant disease (eg, recurrent urinary infection, hematuria, renal insufficiency).

Noninvasive studies — Noninvasive studies for LUTS include uroflowmetry to measure Qmax, bladder scan or ultrasound to determine PVR, or transabdominal ultrasound to assess bladder anatomy for evidence of outlet obstruction.

Uroflowmetry — Uroflowmetry is a simple non-invasive urodynamic measurement in which a patient urinates into a device that measures the volume/time of urine accumulation. Combined with a measurement of PVR (see 'Postvoid residual' below), it is an excellent screening tool for BOO in men with LUTS but does not provide information regarding the presence of overactive bladder (OAB). Additionally, a diagnosis of BOO cannot be made or excluded based on uroflowmetry alone [33].

Uroflowmetry measures voided volume, voiding time, average flow rate, and Qmax. It also provides a linear analysis of the flow rate/voiding time so that the voiding pattern can be evaluated (figure 1).

Qmax is the single best measurement obtained by this study to assess voiding dysfunction. However, a low Qmax does not distinguish between BOO and decreased detrusor contractility, and a normal Qmax does not exclude BOO. Qmax may be normal in the early stages of obstruction due to compensatory increase in detrusor contractility resulting in high voiding pressures.

Approximately 85 to 90 percent of men with a Qmax less than 10 mL/s are found to be obstructed on pressure-flow studies. BOO can be accurately diagnosed in men with a Qmax of less than 10 mL/s and an International Prostate Symptom Score (IPSS) greater than 16 [34].

In addition to Qmax, the flow pattern should be noted; characteristic patterns may have diagnostic relevance. Obstruction generally demonstrates a flattened flow pattern with a low Qmax, a prolonged flow time, and a slow time to maximum flow (figure 2).

Postvoid residual — Although most urologists perform a PVR as part of their assessment, PVR does not correlate with the severity of LUTS, the presence of BOO, or treatment outcomes [35]. An elevated PVR is found with obstruction but may also indicate detrusor decompensation due to various causes, including chronic BOO. PVR does not provide diagnostic information for OAB.

Measurements from uroflowmetry, and sometimes pressure-flow urodynamics, are necessary to determine the etiology of an elevated PVR [33]. As an example, a man with a low Qmax and a high PVR may have either BOO or detrusor decompensation. Urodynamic studies could determine if the etiology of the elevated PVR were due to BOO, requiring treatment with alpha-blockers or surgery, or to detrusor decompensation which might require catheter drainage or close surveillance.

For men with an elevated PVR without obstruction, we typically check the PVR once per year. If the initial PVR is >500 mL, then patients should be checked two to three times per year.

An elevated PVR in some patients may have a secondary effect on the upper tracts. The presence of hydronephrosis and/or renal insufficiency could be evaluated with a renal ultrasound and serum creatinine. Although evidence-based cutoffs and formal consensus guidelines do not exist, we believe that upper tract imaging should be considered in men with postvoid residuals that are increasing and greater than 300 to 400 mL [33].

Transabdominal ultrasound — Transabdominal ultrasound can be used to assess bladder wall thickness, detrusor wall thickness, and bladder weight. Although there is no established cutoff value, increased detrusor wall thickness is associated with urodynamically confirmed BOO [36].

Invasive diagnostic studies — More invasive studies include pressure-flow urodynamic studies, cystoscopy, and measurement of prostate volume by transrectal ultrasound.

Pressure-flow studies and urodynamics — Urodynamic studies are the gold standard for diagnosis of uninhibited detrusor contractions that occur during the filling phase of voiding in OAB [37]. Urodynamics are important in the evaluation of male patients with neurologic disease and in patients who fail treatment for BOO. Urodynamics are often performed before empiric treatment, when a non-BOO etiology is suspected, or when invasive treatment is contemplated. Additionally, men under age 50 should be evaluated with urodynamic studies prior to treatment due to the high incidence of non-obstructive etiology for LUTS in this population [38].

The urodynamic evaluation involves the concurrent multichannel measurement of bladder and abdominal pressures during the filling/storage and voiding phase of micturition. Detrusor pressure is calculated as the difference between the bladder and abdominal pressures. Urodynamics are the best method to diagnose high-pressure, low-flow voiding that is typical of BOO and differentiate it from low or normal pressure low-flow voiding due to detrusor decompensation.

Several parameters are measured to assess the relationship between flow and pressure during micturition. These include the Abrams-Griffiths nomogram and the more commonly used BOO index (BOOI) [39,40]. The BOOI relates the detrusor pressure at maximum flow (Pdet) to Qmax; an elevated BOOI indicates obstruction.

The cystometrogram provides information regarding bladder storage capacity, bladder sensation, the presence or absence of detrusor overactivity, and bladder compliance (the ability of the bladder to expand and accommodate increasing volumes of urine). The role of the cystometrogram to evaluate the bladder as a source of male LUTS is often overlooked because of a focus on the prostate as the sole cause of symptoms.

Storage LUTS symptoms in men may result from detrusor overactivity, obstruction, or other bladder abnormalities. The cystometrogram may demonstrate a normal pattern or some combination of the following abnormalities during filling: reduced maximum cystometric capacity (<150 mL), involuntary detrusor contractions (>10 cm H_20), or loss of bladder compliance. A man with urgency incontinence may demonstrate high-pressure involuntary detrusor contractions, low bladder capacity, and poor reflex contraction of the urethral sphincter mechanism [33,41].

TREATMENT OPTIONS

For a man with symptoms that are bothersome enough that he wants treatment, several factors must be taken into account in developing an appropriate treatment regimen [1,9]. Based on the initial evaluation, patients may be found to have bladder outlet obstruction (BOO), overactive bladder (OAB), or both. Algorithms for initial treatment of lower urinary tract symptoms (LUTS) and for treatment of persistent bothersome LUTS have been developed by an international consortium representing multiple urological societies from Europe, the United States, Latin America, and Asia (algorithm 1 and algorithm 2) [1].

Initial treatment for BOO secondary to benign prostatic hyperplasia (BPH) is generally pharmacologic, especially in patients with mild to moderate symptoms and no clear indication for surgical intervention. Medical therapy consists of alpha-blockers, 5-alpha reductase inhibitors, or a combination of these agents. (See "Medical treatment of benign prostatic hyperplasia".)

Behavioral therapy — Behavioral modifications and therapies may be helpful [42], particularly as an adjunct to medication.

Lifestyle changes include avoiding fluids prior to bedtime or before going out, and reducing consumption of mild diuretics such as caffeine and alcohol. Pelvic floor muscle training, including the use of biofeedback, may be particularly helpful for patients with urgency symptoms.

> A randomized trial found that men with LUTS who were given an intervention that included education, lifestyle advice, and problem-solving skills were significantly less likely to experience treatment failure (increase in International Prostate Symptom Score (IPSS) or requirement for medication) compared with the control group (watchful waiting) [43].
>
> In a trial among 204 men with overactive bladder symptoms, the combination of behavioral (pelvic floor muscle training and bladder diary) and drug therapy (antimuscarinic and an alpha blocker) resulted in greater symptom improvement than drug therapy alone at 12 weeks [44].

Alpha adrenergic-receptor antagonists — Alpha-blockers are first-line agents used for the treatment of symptomatic BPH. They function to relax the smooth muscle tone at the bladder neck and prostate. (See "Medical treatment of benign prostatic hyperplasia", section on 'Alpha-adrenergic receptor blockers'.)

In the United States, five agents are approved: terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin. Terazosin and doxazosin require dose titration and are associated with dizziness and hypotension, a particular problem in an older adult population. Tamsulosin, alfuzosin, and silodosin more specifically target the bladder neck and prostate and have fewer adverse cardiovascular side effects.

5-alpha reductase inhibitors — 5-alpha reductase inhibitors (eg, finasteride and dutasteride) are useful for LUTS secondary to BPH only in the presence of prostate enlargement (documented by digital rectal examination, prostate-specific antigen [PSA] for volume proxy, or transrectal ultrasound) [45,46]. Issues regarding pretreatment evaluation, mechanism of action, efficacy, administration, side effects, and monitoring of 5-alpha reductase inhibitors are reviewed in detail separately. (See "Medical treatment of benign prostatic hyperplasia", section on '5-alpha reductase inhibitors to prevent progression'.)

Combination drug therapy — Combination therapy with both alpha blocker and alpha reductase inhibitor drugs has been evaluated in multiple studies [47-50]. A randomized trial sponsored by the National Institutes of Health found that combination therapy (doxazosin plus finasteride), compared with placebo or monotherapy with either drug, showed greater improvement in IPSS score and Qmax after four years of therapy [51]. The greatest reduction in rates of acute urinary retention and the need for BPH-related surgery were in the finasteride-

only and combination groups. The multicenter randomized CombAT study also found that combination therapy with dutasteride and tamsulosin was more effective than monotherapy with either drug alone for long-term symptom improvement (IPSS score) in men with moderate to severe LUTS related to BPH [52]. (See "Medical treatment of benign prostatic hyperplasia", section on 'Combination of alpha-adrenergic blockers and steroid 5-alpha reductase inhibitors'.)

Anticholinergics — For patients with LUTS related to OAB, the primary goal is to decrease involuntary detrusor contractions. Normal bladder contractions are primarily triggered by the neurotransmitter acetylcholine [53].

Initial studies of anticholinergic agents evaluated atropine, an acetylcholine muscarinic receptor antagonist. Atropine increases the bladder volume before the first involuntary contraction, increases maximum bladder capacity, and decreases the amplitude of the contraction. Clinically, atropine decreases episodes of urgency incontinence and the frequency of urgency episodes but is most effective when combined with behavioral modification [54].

The human bladder has five cholinergic muscarinic receptor subtypes [55,56]. The M2 and M3 types are found on detrusor muscle [57]. Most smooth muscle contractions are mediated via the M3 type. The M2 type contributes to bladder contraction in certain disease states (eg, outflow obstruction and denervation) [55].

Tolterodine, oxybutynin, darifenacin, solifenacin, fesoterodine, and trospium are approved in the United States for OAB and, in placebo-controlled trials, have been shown to reduce the sensation of urgency, decrease episodes of frequency and urgency incontinence, and increase voided volume [58-63]. A 2006 systematic review found that, compared with placebo, anticholinergic drugs for OAB were more likely to cure or improve symptoms (relative risk [RR] 1.4, 95% CI 1.3-1.5), decrease urinary leakage (weighted mean difference [WMD] -0.54, -0.67 to -0.41), and decrease the number of voids in 24 hours (WMD 0.69, -0.84 to -0.54) [64].

Significant peripheral side effects, attributed to M2 blockade, limit drug tolerability and dose escalation. Side effects include inhibition of salivary secretion (dry mouth), blockade of the ciliary muscle of the lens to cholinergic stimulation (blurred vision for near objects), tachycardia, drowsiness, decreased cognitive function, and inhibition of gut motility and constipation. Antimuscarinic agents are contraindicated in patients with gastric retention and angle closure glaucoma. A discussion of the association between anticholinergics and dementia is presented elsewhere. (See "Epidemiology, pathology, and pathogenesis of Alzheimer disease", section on 'Medications'.)

The anticholinergic tertiary amines, including darifenacin and solifenacin, are selective M3 receptor antagonist. Selective M3 blockade theoretically may decrease peripheral side effects

[60-62]. Trospium is a quaternary amine and is classified as a smooth muscle relaxant with some anticholinergic effects. It has limited ability to cross the blood-brain barrier and may have less impact on cognitive dysfunction [65,66].

A systematic review of 86 randomized trials and meta-analysis of 70 trials in patients with OAB symptoms compared differing doses and formulations of four anticholinergic drugs [67]. Findings were that tolterodine was better tolerated than oxybutynin and that extended-release formulations of these agents were better tolerated than immediate release. Fesoterodine had better efficacy than extended-release tolterodine but caused more dry mouth leading to drug withdrawal. Solifenacin was more effective and better tolerated than immediate-release tolterodine. Data were not available for other comparisons. There were incomplete data to make conclusions about comparative costs, long-term outcomes, or the impact on quality of life.

The use of anticholinergics in men with OAB has traditionally been considered contraindicated due to concerns about precipitating urinary retention. However, most placebo-controlled studies have demonstrated safety and efficacy of anticholinergic medications in patients with OAB, with or without BOO.

In the 2011 AUA BPH clinical guidelines, anticholinergic agents were considered effective treatment alternatives for the management of LUTS secondary to BPH in men without an elevated post void residual (PVR) urine and when LUTS are predominantly irritative [32]. The panel recommended that, prior to initiation of anticholinergic therapy, baseline PVR urine should be assessed. Anticholinergics should be used with caution in patients with a PVR greater than 250 to 300 mL. Randomized trials evaluating the use of tolterodine as monotherapy or in combination with an alpha blocker in men with OAB/LUTS/BPH were identified [17,68,69]. Although these trials did not consistently demonstrate efficacy of tolterodine, the AUA panel concluded that the use of anticholinergics could be beneficial. A subsequent meta-analysis of randomized trials found that some endpoints, but not all, did improve with combination therapy [70].

Beta3-adrenoceptor agonists — Mirabegron is a first-in-class beta3-adrenoceptor agonist that is available and effective for treatment of LUTS related to OAB. Mirabegron is available in 25 or 50 mg doses in the United States; a 100 mg dose is available in some countries. We start at 25 mg per day and follow up with the patient in six weeks to evaluate effectiveness. Patients with little or no response on 25 mg can increase to 50 mg if they are tolerating the drug.

Vibegron 75 mg daily is also approved in the United States to treat patients with OAB symptoms [71].

A 2016 systematic review of eight studies involving over 10,000 patients found that mirabegron 50 mg reduced incontinence episodes and urgency episodes per 24 hours compared with placebo (WMD -0.38 and -.053, respectively) [72]. Furthermore, a 2014 systematic review of 44 randomized trials including over 27,000 patients found that mirabegron 50 mg was as efficacious as the other anticholinergics in reducing frequency and urinary incontinence episodes with less dry mouth [73]. An exception was that solifenacin 10 mg appeared somewhat more effective than mirabegron. A higher dose of mirabegron (100 mg) does not appear more effective than mirabegron 50 mg [72]. Most data were from industry-led trials.

These agents do not raise the same concern for urinary retention as do the anticholinergic medications. Vibegron, a newer agent, appears to be well tolerated [74]. Mirabegron may increase blood pressure, although in a systematic review mirabegron 50 mg was not associated with a greater risk of hypertension or arrhythmia compared with placebo; however, mirabegron 100 mg did show a slight trend towards these side effects [72].

Phosphodiesterase 5 inhibitors — The observation that men with erectile dysfunction treated with phosphodiesterase-5 (PDE5) inhibitors reported a decrease in LUTS led to several clinical trials. These trials have demonstrated marked improvement in LUTS among men with BPH taking PDE5 inhibitors compared with placebo, regardless of the presence of erectile dysfunction [75]. (See "Medical treatment of benign prostatic hyperplasia", section on 'Phosphodiesterase type 5 inhibitors'.)

Combination therapy with PDE5 inhibitors and alpha 1-adrenergic blockers seemed to have an additive beneficial effect on BPH/LUTS compared with monotherapy [76].

Surgical treatment — Surgical treatment is usually reserved for medication failure, progressive symptoms, or patient preference. Surgical options include minimally invasive surgical therapies (microwave therapy, transurethral radiofrequency ablation), laser vaporization of prostate, transurethral resection of prostate, and open prostatectomy. An extensive discussion of surgical treatment options for BOO related to BPH is discussed separately. (See "Surgical treatment of benign prostatic hyperplasia (BPH)".)

TREATMENT FOR URODYNAMICALLY PROVEN OAB

No obstruction and low PVR — Anticholinergics can be used safely and effectively in patients with urodynamically proven, non-neurogenic overactive bladder (OAB) without bladder outlet obstruction (BOO) and low postvoid residual (PVR). Mirabegron is an option for patients who do not tolerate anticholinergic medications, for patients who have contraindications to

anticholinergic medications (eg, narrow-angle glaucoma), or as second-line therapy for patients who fail to respond to anticholinergic medications.

No obstruction and high PVR — For patients with urodynamically proven OAB without BOO but with high PVR, there is a limited role for outlet reduction surgery in the absence of clear evidence for BOO. Patients with elevated PVR and no obstruction are described to have detrusor hyperactivity with impaired contractility [77].

A cautious trial of anticholinergic therapy may be initiated, with close attention to the PVR. If the PVR remains high, patients may need additional measures to empty their bladder, including intermittent catheterization. Mirabegron is an option for patients who do not tolerate anticholinergic medications, for patients who have contraindications to anticholinergic medications (eg, narrow-angle glaucoma), or as second-line therapy for patients who fail to respond to anticholinergic medications.

A large PVR may be well tolerated as long as bladder compliance is normal and the patient does not become prone to urinary tract infections. Some patients may be treated with a combination of outlet reduction surgery, biofeedback (to teach pelvic floor relaxation techniques), and Valsalva or Crede voiding to empty the bladder. In this subset of patients (equivocal BOO), removing even a minor obstruction may aid in emptying the bladder when combined with other interventions [78]. Valsalva voiding involves tightening the lower abdominal muscles so that pressure is transmitted to the bladder to help in emptying; Crede voiding is the application of direct pressure (fist or hand) over the lower abdomen or suprapubic area to transmit pressure to the bladder. For men with an elevated PVR without obstruction, we typically check the PVR once per year. If the initial PVR is >500 mL, then patients should be checked two to three times per year.

BOO with low PVR — Symptoms of OAB with BOO and low PVR are the most common combination of findings in clinical practice. These men are often started on alpha-blockers, which, in addition to relieving obstruction by relaxing prostatic smooth muscle, may also improve symptoms of OAB. On urodynamic testing, patients receiving tamsulosin monotherapy showed an increase in the volume at first involuntary contraction [69]. Anticholinergics can be added if OAB symptoms persist.

Surgical reduction of BOO is an acceptable treatment alternative. Up to 60 percent of men with BOO have evidence of detrusor overactivity. BOO reduction surgery results in resolution of detrusor overactivity in one-half of men with detrusor overactivity preoperatively [79]. Importantly, relieving the obstruction may prevent worsening of OAB [80].

Men with detrusor overactivity and BOO may have postoperative urinary urgency and urgency incontinence. Unlike postoperative stress urinary incontinence (resulting from injury to the continence mechanism during resection), this urgency may be due to longstanding benign prostatic hyperplasia (BPH), urinary tract infection, and/or postoperative irritability of the prostatic fossa. Symptoms may continue until the urinary tract infection is treated or the prostatic fossa heals. In most cases, conservative treatment is recommended. Urodynamics can be helpful for persistent urge symptoms to distinguish detrusor overactivity from other causes of irritative symptoms. Anticholinergic medication, combined with antiinflammatory therapy, usually provide effective treatment.

BOO with high PVR — Patients with OAB who have evidence of BOO and elevated PVR should initially be treated for relief of their obstruction by either medical or surgical therapy. This group is at high risk of urinary retention with anticholinergic therapy, and therapy for OAB symptoms should be delayed until obstruction is relieved.

If symptoms persist after medical treatment or surgery, patients should be reevaluated with urodynamic studies, including the determination of PVR [78]. A subset of these patients will have OAB with detrusor decompensation. It is important to closely monitor those patients as they are at the highest risk of developing urinary retention with anticholinergic treatment. Less than 5 percent of men will have worsening BOO without being symptomatic [1]. Therefore, the PVR should be checked at periodic assessment (generally, every 6 to 12 months) for lower urinary tract symptoms (LUTS).

Refractory OAB

Sacral neuromodulation — Men with OAB symptoms refractory to medical therapy may be candidates for sacral neuromodulation (SNM). The exact mechanism of action is uncertain. Most clinical studies of these devices have focused on women with urgency urinary incontinence; the common innervation of the bladder makes it likely that clinical outcomes would be similar for men. SNM and its risks and benefits are described separately. (See "Treatment of urgency incontinence/overactive bladder in females", section on 'Third tier: Procedures and other therapies'.)

Botulinum toxin — Botulinum toxin causes muscle relaxation through inhibition of acetylcholine release. Cystoscopic injection of botulinum toxin directly into the detrusor muscle results in chemical denervation that is reversible after six to nine months. Type A serotype is used in the United States [81,82]. Botulinum toxin A can be used for neurogenic causes of detrusor overactivity (eg, spinal cord injury and multiple sclerosis). It has also been used in

patients with non-neurogenic OAB but is typically reserved for patients with symptoms refractory to anticholinergic agents.

Limited data on intravesical botulinum suggest benefit but are somewhat mixed, and there are no robust data regarding safety or optimal dose. A 2007 systematic review of randomized trials of botulinum, compared with no treatment, nonpharmacologic treatment, and pharmacologic treatment for OAB, found few well-controlled trials [83]. Eight small trials, including patients of mixed gender with predominantly neurogenic OAB, demonstrated superiority of botulinum to placebo in episodes of incontinence, bladder capacity, and quality of life. However, in a retrospective study of 88 men who initiated botulinum toxin A for OAB and were followed for almost six years, nearly 75 percent discontinued treatment, mostly due to lack of sufficient effect or to side effects including urinary retention, need to self-catheterize, or voiding LUTS [84].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Benign prostatic hyperplasia".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Benign prostatic hyperplasia (enlarged prostate) (The Basics)" and "Patient education: Neurogenic bladder in adults (The Basics)")

- Beyond the Basics topics (see "Patient education: Benign prostatic hyperplasia (BPH) (Beyond the Basics)" and "Patient education: Urinary incontinence in women (Beyond the Basics)" and "Patient education: Urinary incontinence treatments for women (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Lower urinary tract symptoms (LUTS) can be classified as storage symptoms (urgency, frequency, nocturia, urgency incontinence), voiding symptoms (hesitancy, weak stream, dysuria), or post-micturition symptoms (incomplete bladder emptying, post-micturition dribbling). (See 'Symptoms' above.)

- LUTS in men have most often been attributed to bladder outlet obstruction (BOO) resulting from benign prostatic enlargement (BPE) or benign prostatic hyperplasia (BPH). Voiding symptoms are suggestive of BOO but are not diagnostic. (See 'Bladder outlet obstruction from BPH' above.)

- Overactive bladder (OAB) is related to detrusor overactivity and is most commonly associated with storage symptoms that are frequently more bothersome than voiding symptoms. The cause of OAB is often unknown. OAB may be neurogenic (eg, secondary to stroke or other neurologic condition) or may be caused by chronic obstruction. (See 'Overactive bladder and detrusor overactivity' above.)

- Male patients with LUTS should be evaluated initially with history, physical examination, and laboratory studies, which may include creatinine, glucose, prostate-specific antigen (PSA), urinalysis, and urine culture. Determining the International Prostate Symptom Score (IPSS) can be helpful in monitoring treatment response. (See 'Initial patient evaluation' above.)

- Patients with significant symptoms and findings consistent with BPH and BOO as cause for LUTS may be treated empirically. We suggest urological referral for men who are less than 45 years old or who do not respond to empiric therapy. (See "Medical treatment of benign prostatic hyperplasia" and 'Indications for specialist referral' above.)

- The role for urological studies in evaluating LUTS is controversial. Postvoid residual does not correlate with LUTS severity or provide diagnostic information regarding BOO or OAB. However, awareness of an elevated postvoid residual (PVR) may guide treatment with anticholinergic medication as well as the need for closer follow-up. (See 'Diagnostic testing' above.)

- Medical treatment for BPH and BOO includes alpha blockers, phosphodiesterase-5 (PDE5) inhibitors, 5-alpha reductase inhibitors, or a combination. Surgical treatment is usually reserved for medication failure, progressive symptoms, or patient preference. Relief of obstruction may not relieve symptoms related to OAB, and urodynamic studies may be helpful. (See "Medical treatment of benign prostatic hyperplasia" and "Surgical treatment of benign prostatic hyperplasia (BPH)".)

- Surgical options for BPH include minimally invasive surgical therapies (microwave therapy, transurethral radiofrequency ablation), laser vaporization of prostate, transurethral resection of prostate, and open prostatectomy. (See "Surgical treatment of benign prostatic hyperplasia (BPH)".)

- We suggest that men with urgency symptoms and no evidence of a significantly elevated PVR be treated with an anticholinergic medication (**Grade 2B**). Anticholinergic medications are used for OAB treatment but can cause orthostasis, dry mouth, blurred vision, and urinary retention. Side effects may be minimized by using a low dose of medication, long-acting preparations, or tolterodine. (See 'No obstruction and low PVR' above and 'Anticholinergics' above.)

- We suggest that men with symptoms of OAB and BOO be treated with a combination therapy of an anticholinergic plus an alpha blocker (**Grade 2B**). Caution should be taken to observe for symptoms suggesting urinary retention. (See 'BOO with low PVR' above.)

- We recommend that men who have a significantly elevated PVR not be treated with an anticholinergic medication until obstruction is relieved, either medically or surgically (**Grade 1C**). (See 'BOO with high PVR' above.)

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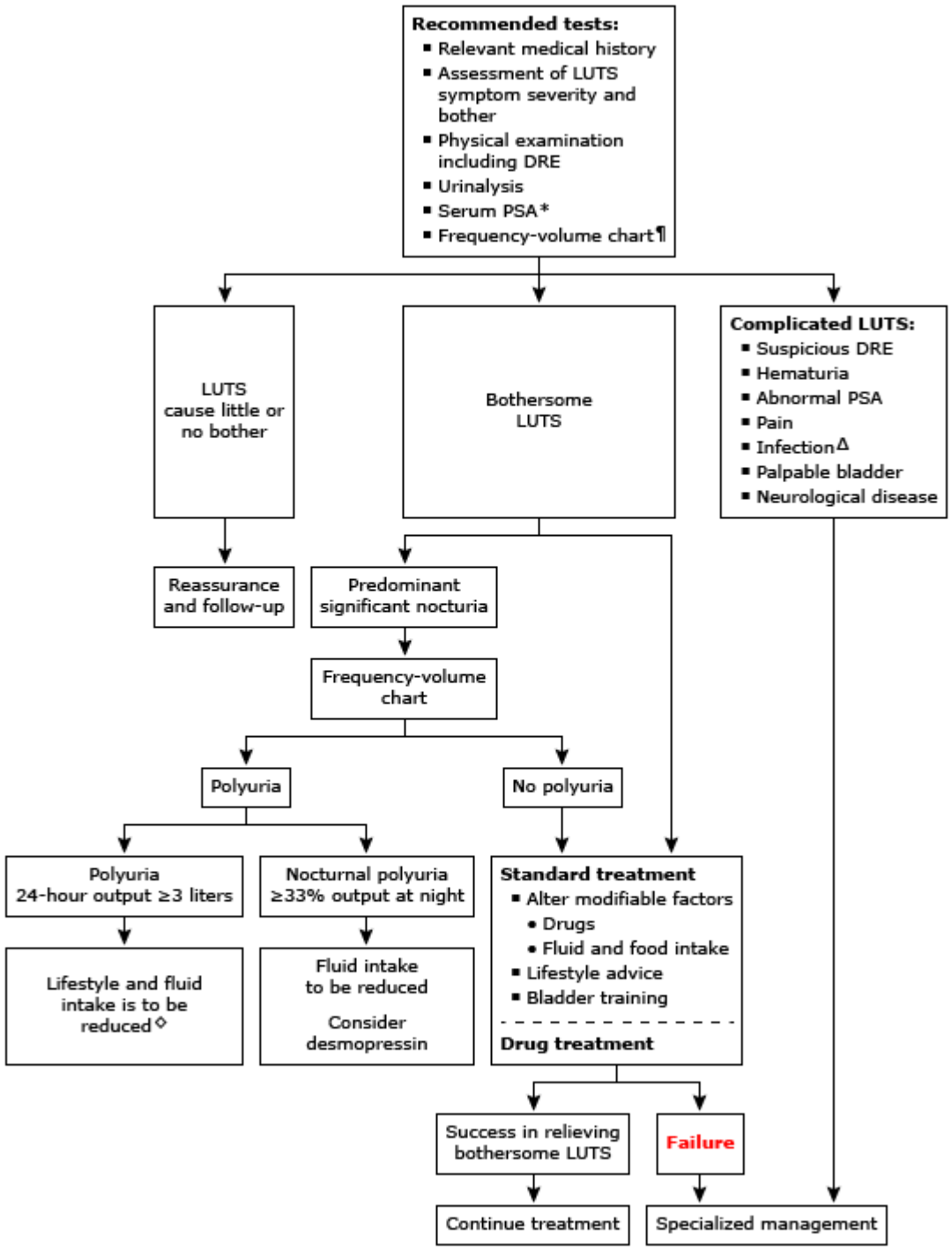
Topic 6879 Version 56.0

GRAPHICS

Basic management of LUTS in men



LUTS: lower urinary tract symptoms; DRE: digital rectal examination; PSA: prostate-specific antigen.
* When life expectancy is >10 years and if the diagnosis of prostate cancer can modify the management.
¶ When significant nocturia is a predominant symptom.
Δ Assess and start treatment before referral.
◊ In practice, advise patients with symptoms to aim for a urine output of about 1 liter/24 hours.

Graphic 57955 Version 2.0

American Urological Association (AUA) urinary symptom score/International Prostate Symptom Score (IPSS)

Questions to be answered	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5	
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 (none)	1 (1 time)	2 (2 times)	3 (3 times)	4 (4 times)	5 (5 or more times)	
						Sum of numbers (AUA symptom score):	

Total score:

0 to 7: Mild symptoms

8 to 19: Moderate symptoms

20 to 35: Severe symptoms

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed - about equally satisfied and unsatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

The AUA symptom score and the IPSS use the same questions and scale. The IPSS additionally includes the last disease-specific quality of life question.

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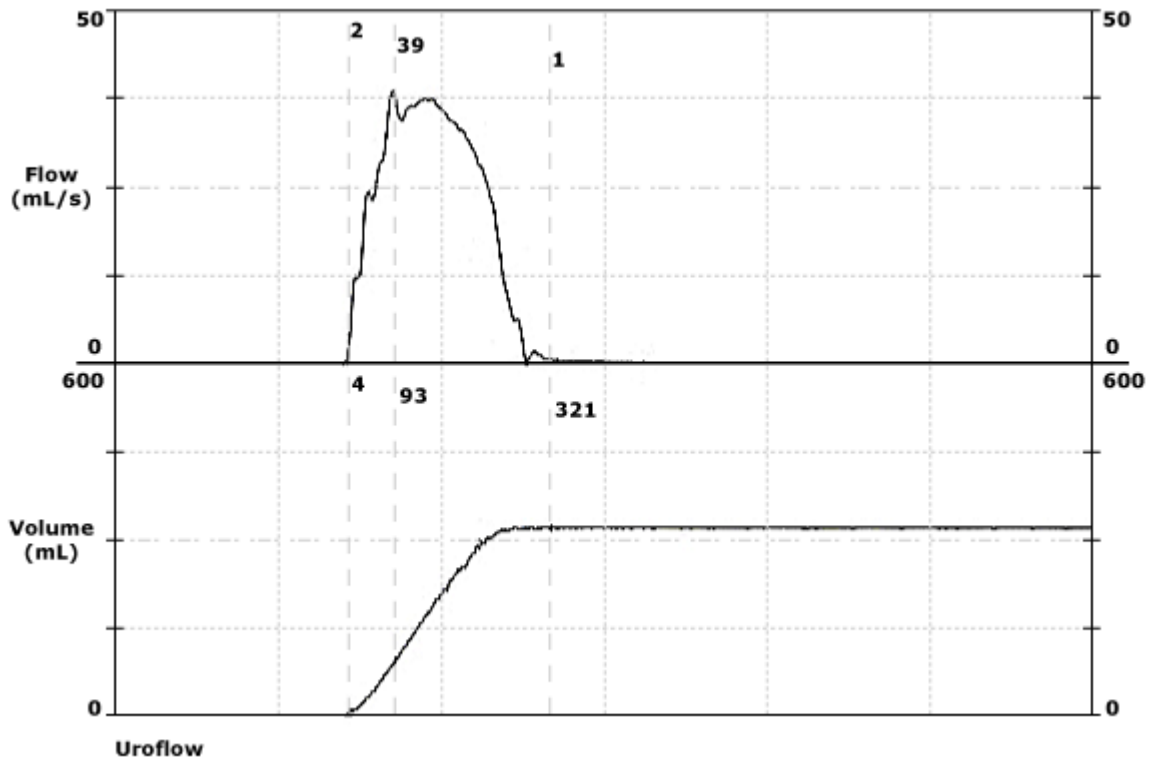
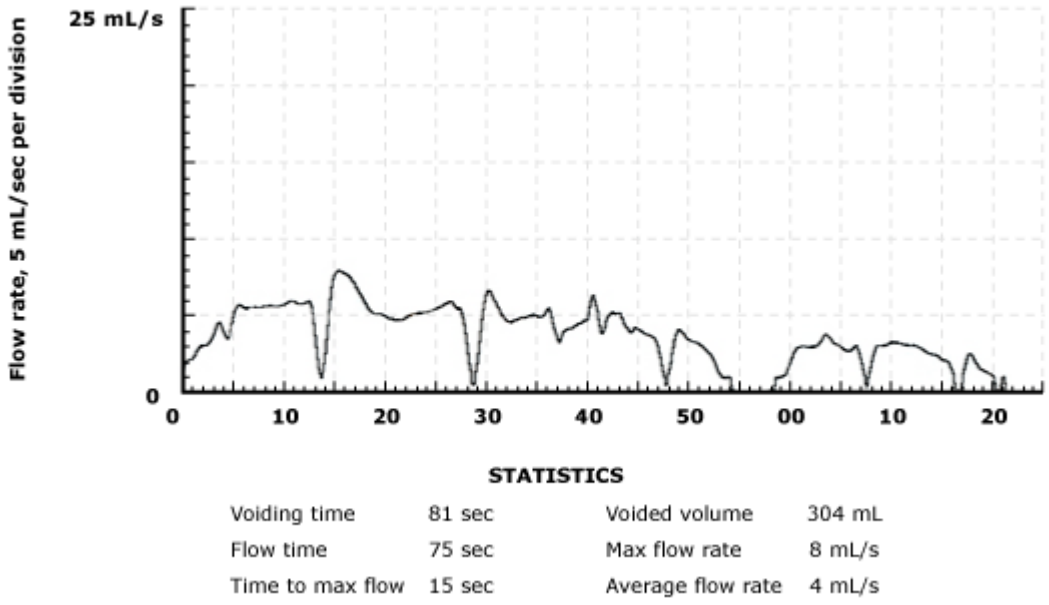
Graphic 57680 Version 11.0

Uroflometric tracing: normal uroflow



Graphic 79658 Version 1.0

Uroflowmetry obstruction



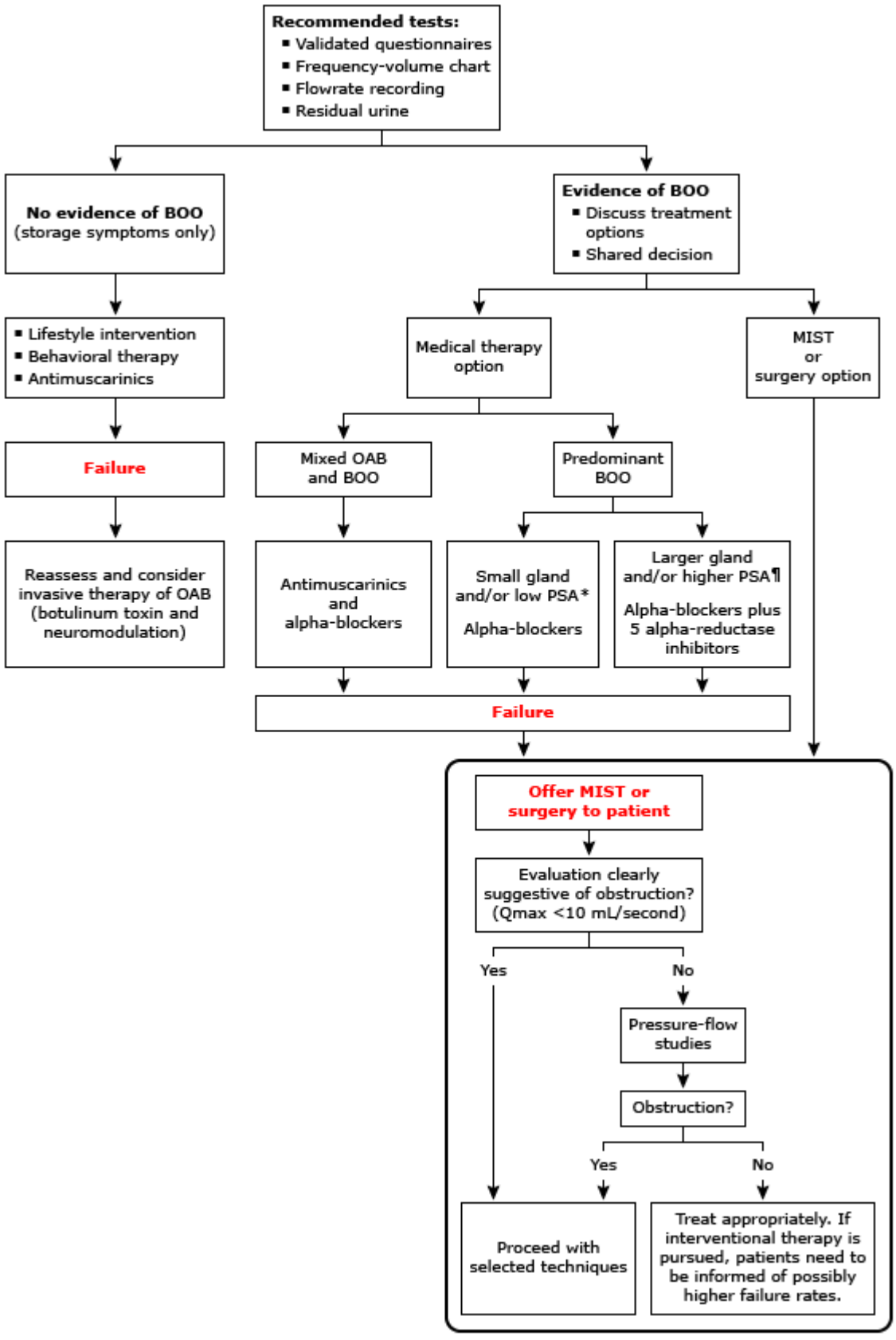
STATISTICS

Voiding time	81 sec	Voided volume	304 mL
Flow time	75 sec	Max flow rate	8 mL/s
Time to max flow	15 sec	Average flow rate	4 mL/s

This uroflow study demonstrates male obstruction, with an intermittency plateau pattern. The Qmax is 8 mL/s.

Graphic 58694 Version 2.0

Specialized management of persistent, bothersome LUTS after basic management



LUTS: lower urinary tract symptoms; OAB: overactive bladder; BOO: bladder outlet obstruction; MIST: minimally invasive surgical treatment.

* PSA <1.5 ng.

¶ PSA >1.5 ng.

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Graphic 60795 Version 2.0

Contributor Disclosures

Kevin T McVary, MD, FACS Patent Holder: Thermal-Activated Penile Prosthesis [Erectile dysfunction]. Grant/Research/Clinical Trial Support: Olympus [Benign prostatic hyperplasia]; Boston Scientific [Benign prostatic hyperplasia]; Astellas [Overactive bladder]. Consultant/Advisory Boards: Boston Scientific [Benign prostatic hyperplasia]; Astellas [Overactive bladder]. **Rajiv Saini, MD** Nothing to disclose **Michael P O'Leary, MD, MPH** Nothing to disclose **Jane Givens, MD** Consultant/Advisory Boards (Partner): CVS Health/CVS Omnicare [Pharmaceutical management of formulary decision-making].

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