Initial management of lower urinary tract symptoms and bladder outlet obstruction

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Abstract

Lower urinary tract symptoms (LUTS) affect >60% of men and women aged >40 years. Symptoms may be classified as storage, voiding or post-micturition and have a variety of systemic, neurological, drug-related or urological causes. There is growing evidence that obesity and metabolic syndrome are linked to LUTS. Initial evaluation of LUTS should follow a structured system, with symptom scores and frequency–volume charts. Several features have been identified as risk factors for progression of LUTS, and stratification using these factors can aid in planning management. For example, older age and a high-normal prostate-specific antigen can suggest a higher risk of progression to acute urinary retention. Many patients with LUTS require no treatment. If indicated, first-line treatment for LUTS should be conservative with lifestyle changes, and then medical therapy, involving selective α-adrenoceptor blockers, 5α-reductase inhibitors, antimuscarinics, mirabegron or a combination of these. Phosphodiesterase-5 inhibitors may also improve symptom scores and quality of life, and may become more routine in use for LUTS in the future.

Keywords Benign prostatic hyperplasia; combination therapy; investigation; lower urinary tract symptoms; metabolic syndrome; MRCP; phosphodiesterase-5 inhibitors; treatment

Key points

- Lower urinary tract symptoms (LUTS) are common and impact upon quality of life
- The storage symptoms are generally more bothersome than the voiding LUTS
- In the UK most of the first-line assessment and management is carried out in primary care
- Identification of patients at higher risk of disease progression is important
- Drug therapies help the majority of patients and can be utilised in a number of combinations

Introduction and terminology

A significant number of men and women over the age of 40 – around 62.5% of men and 66.6% women – suffer from bothersome lower urinary tract symptoms (LUTS). The causes of these symptoms are multifactorial and include systemic, neurological, drug-related and urological (Table 1). The term 'lower urinary tract symptoms' (LUTS) is therefore preferred over terms used in the past, such as 'prostatism', or 'clinical benign prostatic hyperplasia' (BPH) as it does not presume a diagnosis.

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LUTS can be subdivided into *storage*, *voiding* and *post-micturition* symptoms (Table 2). Voiding symptoms, although more common, are less frequently complained about. Storage symptoms, particularly those of urgency and nocturia, are more bothersome. However, it is rare for patients to present with one group of symptoms in isolation; most have mixed symptoms. Although LUTS do not usually cause illness, they can considerably reduce men's quality of life and can point to serious pathology of the urinary tract.

The Epidemiology of LUTS (EpiLUTS) study was an investigation of >14,000 men, 71% of whom complained of LUTS (Figure 1);[1] this showed that most men have mixed LUTS.

Evaluating LUTS

According to the latest National Institute for Health and Care Excellence (NICE) guidelines (2015, updated 2019), general practitioners can perform the initial assessment, with referral to urologists for specific tests, in complicated cases or after failed medical treatment.

Initial assessment of LUTS

The following should be carried out for men presenting with bothersome LUTS:

- a comprehensive medical history and physical examination, including digital rectal examination and assessment of the urethral meatus
- urine dipstick to check for blood, glucose, protein, leucocytes and nitrites
- a validated symptom score (e.g. International Prostate Symptom Score (IPSS))
- a urinary frequency–volume chart (FVC).

The 2015 NICE pathway suggests that prostate-specific antigen (PSA) testing should be offered to men who have LUTS suggestive of prostatic enlargement, have an abnormal prostate on digital rectal examination, or are particularly concerned about prostate cancer. However, there is evidence that PSA can also be a good indicator of risk of progression. Marberger et al. demonstrated that, in men with LUTS, a PSA measurement of >1.4 ng/

Causes of urinary symptoms in men

Neurological diseases
Parkinson's disease
Dementia
Diabetic neuropathy
Multiple sclerosis
Other systemic diseases
Diabetes mellitus
Diabetes insipidus
Cardiac failure
Metabolic syndrome
Drugs
Opioids
Antimuscarinics (including tricyclic antidepressants and ipratropium bromide)
Diuretics
Alcohol
Caffeine
Benzodiazepines
Lithium
Antipsychotics
Other causes
Prolapse
Pelvic mass
Urological causes
Benign prostatic enlargement
Urethral strictures
Calculi
Bladder and prostate cancer
Urinary tract infections
Phimosis
Meatal stenosis
Interstitial cystitis

Table 1

Types of urinary symptoms

Storage symptoms
Frequency
Nocturia
Urgency
Incontinence
Altered bladder sensation
Voiding symptoms
Slow stream
Intermittent stream
Hesitancy
Straining
Splitting or spraying of stream
Terminal dribbling
Post-micturition symptoms
Incomplete emptying
Post-micturition dribble

Table 2

ml was associated with a 9-fold increase in risk of acute urinary retention.[2] Patients should be fully informed and counselled before carrying out PSA testing.

Renal function tests (serum creatinine, estimated glomerular filtration rate): these are indicated (according to the latest NICE guideline) only where there is a clinical suspicion of renal impairment based on the history, for example patients with nocturnal enuresis, palpable bladder, recurrent urinary tract infections (UTIs) or renal tract calculi. Renal function should also be tested in the presence of hydronephrosis or when surgical treatment is being considered; this is in line with the European Association of Urology (EAU) guidelines 2018 (see Further reading).

Frequency–volume charts and bladder diaries: these are useful in formulating a diagnosis and for monitoring response to treatment. They are helpful in identifying urinary frequency, nocturnal polyuria and polyuria caused by excess fluid intake. FVCs record the time and volume of each void, while bladder diaries also include measurement of fluid intake. However, FVCs and bladder diaries are not standardized, and some capture additional information such as use of pads or bladder sensation. The consensus is to record them for at least 3 *complete* days, so they are sufficiently accurate for diagnosis or monitoring.

The International Prostate Symptom Score: this is an eight-item questionnaire for the assessment of LUTS. It allows stratification of symptom severity into mild (1–7), moderate (8–19) or severe (20+). It is particularly valuable if used again after treatment to measure its effectiveness. Quality of life (QoL) is assessed in an eighth question; this is the most valuable question in practice and is also sensitive to change with treatment.

Flow-rate testing, post-void residual (PVR) volume and urodynamic testing: flow-rate testing and post-void residual measurement are not indicated in the first-line management of LUTS (according to the latest NICE guideline). Flow rates can give a probability of obstruction but cannot discriminate between poor detrusor function and bladder outlet obstruction. Flow-rate testing is recommended in specialist assessment of LUTS together with PVR measurement, which also has a poor correlation with obstruction.

More accurate assessment of obstruction is carried out using urodynamics (pressure–flow testing). This is the only accurate way to discriminate between bladder outlet obstruction, detrusor overactivity and reduced detrusor contractility but is an invasive investigation. Urodynamics should be considered in significantly older (and younger) patients, in those with coexisting neurological disease or unusual symptom combinations, or when previous surgical treatment has failed.

Upper tract imaging and cystoscopy

Upper tract imaging or cystoscopy is not recommended in the initial evaluation of uncomplicated LUTS but can have a place in specialized management.

Treatment

Several factors drive the decision to treat. These include the severity of the symptoms and their impact on a patient's QoL, the risk of disease progression, the patient's co-morbidities and other

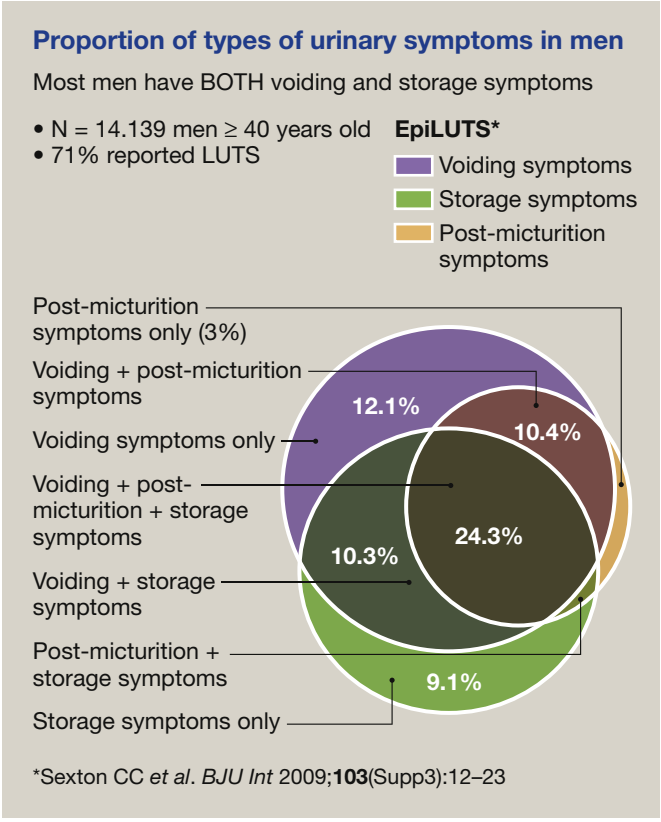

Figure 1

complications of the disease.[3] LUTS in association with any of the following 'red flags' should trigger referral to a urologist:

- digital rectal examination suggestive of prostate cancer
- elevated age-related PSA
- renal dysfunction
- haematuria
- bladder pain
- recurrent infection
- palpable or percussible bladder
- very severe symptoms.

Conversely, many patients can be reassured and/or treated conservatively with lifestyle modifications, such as avoidance of caffeinated drinks and excessive alcohol, or limitation of fluid intake. Patients with non-bothersome LUTS can be reassured after baseline investigations, and relatively few progress or develop complications.

Identification of high-risk patients

Data from the Medical Therapy of Prostatic Symptoms (MTOPS) trial identified the following baseline features as risk factors for progression to acute urinary retention, a need for surgery or an increase of at least 4 points in IPSS:[3]

- age (an eight times increased risk in those aged 70–79 years, compared with ages 40–49)
- severity of LUTS at baseline (three times the risk if symptoms are moderate/severe rather than mild)
- prostate volume (three times the risk if prostate volume is >30 cm^3)
- PSA concentration (nine times increased risk if PSA is >1.4 ng/ml)[2]
- Maximum flow (Qmax) (four times the risk if <12 ml/second)
- PVR (three times the risk if >50 ml)
- prostatic inflammation.

Three dynamic variables have also been shown to predict progression of LUTS:

- recurrent episodes of retention
- an increase in PVR over time
- increasing inconvenience or deterioration of symptoms while undergoing treatment.

Risk stratification in patients with LUTS can aid in planning management.

Urinary retention

Acute urinary retention is a fairly straightforward clinical diagnosis and usually triggers urgent intervention with catheterization and specialist referral. A more insidious and difficult diagnosis is that of chronic retention, when a patient persistently retains substantial amounts of urine after voiding. Patients with chronic retention may be asymptomatic or present with nocturnal enuresis. Some of these patients have highly compliant bladders with low detrusor pressures, a state known as low-pressure chronic retention. Others have high-pressure chronic retention, with high end-void pressures. This results in hydronephrosis and renal failure, and requires urgent urological referral.

Metabolic syndrome and LUTS

Metabolic syndrome is defined by the presence of central obesity and two of the following: raised triglycerides (triacylglycerols), reduced high-density lipoprotein-cholesterol, hypertension and raised fasting plasma glucose. It is accepted as a strong predictor of cardiovascular disease and overall mortality, and also appears to be associated with the development and progression of LUTS. The latest histopathological evidence suggests that men with metabolic syndrome experience chronic inflammation of the prostate, a key factor in the pathogenesis of BPH in this group.[4]

Two other possible mechanisms are: a direct action of insulin on induction of prostate growth because of its structural similarity to insulin-like growth factor (IGF), and the increased bioavailability of IGF through reduction of IGF-binding protein 1; and insulin resistance linked to sympathetic activation, which can increase both bladder and prostate smooth muscle tone. The strong evidence that metabolic syndrome is associated with larger prostate size supports a role for metabolic derangements in the development and progression of BPH.

There is also emerging evidence that dyslipidaemia represents an independent risk factor associated with LUTS. Raised levels of low-density lipoproteins have recently been found to increase the secretion of growth factors (e.g. β-basic fibroblast growth factor) and proinflammatory factors (interleukin-6 (IL-6), IL-8, IL-7) by isolated stromal BPH cells. Hence, it can be speculated that dyslipidaemia could induce the development of an inflammatory response within the prostate, leading to BPH progression and LUTS.[4]

Medical treatment of LUTS

Several classes of drug are used, and the particular choice of drugs or their combination depends largely on the type of symptoms experienced by the patient and their risk of progression.

Selective α-adrenoceptor blockers, such as tamsulosin, doxazosin and alfuzosin, act on α_1 receptors in the bladder neck and prostatic urethra, causing smooth muscle relaxation and improved urinary flow. They are relatively quick to act (within days) and are particularly effective in treating voiding symptoms but can cause postural hypotension and abnormal ejaculation in some patients. They are recommended for first-line treatment of moderate to severe LUTS.

5α-Reductase inhibitors, such as finasteride and dutasteride, block the conversion of testosterone into the more potent androgen dihydrotestosterone, thereby reducing prostate size and improving voiding symptoms. They take 6 months to be fully effective, and can cause decreased libido, erectile dysfunction and gynaecomastia.

5α-Reductase inhibitors reduce the risk of progression of LUTS, acute urinary retention and need for surgery. They are therefore recommended for use in men at higher risk of progression and in men with an enlarged prostate (>40 cm^3). Patients with bothersome symptoms and an enhanced risk of progression merit combination therapy with an α-adrenoceptor blocker and a 5α-reductase inhibitor. This combination provides significantly better improvement in symptoms and QoL than monotherapy, as well as reducing the risk of acute urinary retention and need for surgery.

Antimuscarinics, such as oxybutynin, tolterodine, solifenacin festoteridine and trospium, are useful in the treatment of storage symptoms. They act on muscarinic receptors in the detrusor muscle and inhibit involuntary contraction, and also increase bladder storage capacity. Adverse effects include dry eyes, dry mouth and gastrointestinal disturbances. They can be used effectively in patients with mixed storage and voiding symptoms, in combination with α-adrenoceptor blockers, but should not be used in patients with high PVRs.

The selective β_3-adrenoceptor agonist mirabegron can be used when antimuscarinics are ineffective, contraindicated or not tolerated for the treatment of storage symptoms. Mirabegron activates β_3-adrenoceptors in the bladder, enhancing bladder relaxation and increasing bladder storage capacity. UTIs and tachycardia are the most commonly reported adverse effects.

Phosphodiesterase-5 inhibitors (PDE5-Is), such as sildenafil, tadalafil and vardenafil, are widely used to treat erectile dysfunction but may also have a role in the treatment of LUTS. Current evidence suggests that PDE5-Is significantly improve LUTS in men with or without erectile dysfunction, while having less effect on flow rates. Several mechanisms of action have been proposed, including changes in prostate and bladder neck tone mediated by nitric oxide, and a concomitant relaxation of detrusor muscle perhaps offsetting any change in urinary flow rate. PDE5-Is can be an option for men with LUTS particularly if they have concomitant erectile dysfunction. As LUTS and erectile dysfunction often coexist and are probably related, significant improvements in overall QoL can be achieved.[5] The latest NICE guidelines do not advocate commencing PDE5-Is in patients without erectile dysfunction.

Some patients benefit from combinations of the above-mentioned drugs. Patients initiated on treatment should be reviewed for symptoms, effects on QoL and adverse effects after 4–6 weeks and then every 6–12 months. Patients who do not respond to conservative management or drug treatment can be referred to urologists for specialist assessment and consideration of surgery. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 62-year-old man presented with poor flow, hesitancy, urinary frequency and nocturia three times per night.

Which of the following would not be required in the initial assessment of lower urinary tract symptoms (LUTS)?

A. A comprehensive medical history
B. Digital rectal examination (DRE)
C. Urine dipstick
D. An International Prostate Symptom Score (IPSS)
E. Urea and electrolytes

Question 2

A 72-year-old man presented with severe lower urinary tract symptoms (International Prostate Symptom Score 22 (maximum 35)).
On clinical examination, the prostate was enlarged to >40 cm^3.

Investigations

- Serum prostate-specific antigen 2.5 micrograms/litre (<4)
- Ultrasonography showed a residual volume of 200 ml after voiding

He wishes to try medical treatment first. Which is the best treatment for him?

A. α-Adrenoceptor blocker monotherapy (e.g. tamsulosin)
B. 5α-Reductase inhibitor (5ARI) (e.g. finasteride)
C. Combination treatment with an α-adrenoceptor blocker and 5ARI
D. An antimuscarinic drug treatment such as oxybutynin or solifenacin
E. A combination of β_3-adrenoceptor agonists and phosphodiesterase-5 inhibitors (PDE5-Is)

Question 3

A 66-year-old man presented in primary care with general malaise and voiding difficulties associated with nocturnal bedwetting.
On clinical examination, the bladder was dull to percussion up to the umbilicus. The man was, however, still able to void.

Investigations

- Urea 32 mmol/litre (2.5–7.0)
- Creatinine 346 micromol/litre (60–110)

What is the most appropriate next step?

A. Catheterization and management at home
B. Conservative management without catheterization
C. Medical treatment
D. Urgent referral to secondary care for catheterization
E. Routine referral to secondary care for consideration of surgery