

Guidelines

Clinical guideline for male lower urinary tract symptoms

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Abstract: This article is a shortened version of the clinical guideline for lower urinary tract symptoms (LUTS), which has been developed in Japan for symptomatic men aged 50 years and over irrespective of presumed diagnoses. The guideline was formed on the PubMed database between 1995 and 2007 and other relevant sources. The causes of male LUTS are diverse and attributable to diseases/dysfunctions of the lower urinary tract, prostate, nervous system, and other organ systems, with benign prostatic hyperplasia, bladder dysfunction, polyuria, and their combination being most common. The mandatory assessment should comprise medical history, physical examination, urinalysis, and measurement of serum prostate-specific antigen. Symptom and quality of life questionnaires, bladder diary, residual urine measurement, urine cytology, urine culture, measurement of serum creatinine, and urinary tract ultrasonography would be optional tests. The Core Lower Urinary Tract Symptom Score Questionnaire may be useful in quickly capturing important symptoms. Severe symptoms, pain symptoms, and other clinical problems would indicate urological referral. One should be careful not to overlook underlying diseases such as infection or malignancy. The treatment should be initiated with conservative therapy and/or medicine such as α_1 -blockers. Treatment with anticholinergic agents should be reserved only for urologists, considering the risk of urinary retention. The present guideline should help urologists and especially non-urologists treat men with LUTS.

Key words: α_1 -blockers, benign prostatic hyperplasia, guideline, lower urinary tract symptoms, men.

Introduction

A number of clinical guidelines are now available for lower urinary tract disorders; however, these are designed for a specific disorder/disease thus not applicable to patients with no definite diagnosis, multiple diseases, or diseases for which no guidelines are available. Considering that most patients visit physicians with complaints of lower urinary tract symptoms (LUTS) and the etiology of LUTS would be more complicated in aged men due to the prostate pathology, a guideline for male LUTS has been developed in Japan to help urologists and especially non-urologists. This article is the English translation of a shortened version of the guideline for convenience of readers worldwide.

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Targeted patients and anticipated users

The guideline is targeted to men aged 50 years and over complaining of any LUTS. The anticipated users include urologists, non-urological physicians, nurses, and other health providers who may be involved in the care of such men. The clinical algorithm and treatment options are prepared primarily for non-urologists.

Methodology

The guideline was developed by the committee members recommended by the Japanese Society of Neurogenic Bladder and endorsed by the Japanese Urological Association. To prepare the guideline, the members meticulously reviewed relevant references that were retrieved via the PubMed database between 1995 and 2007. Other sources included the Japanese Guideline for Benign Prostatic Hyperplasia,¹ the Japanese Clinical Guideline for Overactive Bladder,² the guidelines on benign prostatic hyperplasia published by the American Urological Association and the

European Association of Urology (<http://www.auanet.org/guidelines/bph.cfm>; http://www.uroweb.org/fileadmin/user_upload/Guidelines/11%20BPH.pdf), and the meeting report of the International Consultation on Urological Diseases (ICUD) on male lower urinary tract disorder.³

Definition of LUTS

Male LUTS are diverse in nature and may reflect underlying disorders of the prostate and lower urinary tract organs. LUTS comprise important elements in the diagnosis and assessment of severity and therapeutic outcomes. Precise use of terminology should facilitate clinical and scientific communications on LUTS.

The 2002 standardization committee report on terminology from the International Continence Society (ICS)⁴ defined three important LUTS categories: storage symptoms, voiding symptoms, and post-micturition symptoms. Storage symptoms include increased daytime frequency, nocturia, urgency, urinary incontinence (stress urinary incontinence, urge urinary incontinence, mixed urinary incontinence, enuresis, nocturnal enuresis, continuous urinary incontinence, other type of urinary incontinence), and bladder sensation (normal, increased, reduced, absent, non-specific). Voiding symptoms cover slow stream, splitting or spraying, intermittent stream, hesitancy, straining, and terminal dribble. Post-micturition symptoms indicate feeling of incomplete emptying and post-micturition dribble. Other related symptoms are pain symptoms of the genitourinary tract (bladder pain, urethral pain, vulval pain, scrotal pain, perineal pain, and pelvic pain). Symptom syndromes serve to group some of these symptoms exemplified by overactive bladder syndrome (OAB) and lower urinary tract symptoms suggestive of bladder outlet obstruction.

Male LUTS and female LUTS are essentially the same; however, men are more likely to complain of voiding symptoms than women, and are less likely to experience urinary incontinence. LUTS comprise the important elements for diagnosis, treatment selection, and assessment of clinical severity or therapeutic efficacy, since they are closely related with the degree of bothersomeness or quality of life (QOL) impairment.⁵⁻⁷ Research on relative importance of symptoms indicated that storage symptoms exert greater bother on patients' QOL than voiding symptoms.⁸⁻¹⁰ Contrarily, LUTS have low specificity to underlying disorders and are unreliable for the correct diagnosis, and storage and voiding symptoms do not necessarily reflect disorders of storage and voiding function, respectively.¹¹ There is weak or almost no correlation between LUTS and other clinical indicators such as prostate volume, urinary flow rate, residual urine volume, or the degree of infravesical (outflow) obstruction.^{12,13} Within the individuals of the particular disorder, however, LUTS and urodynamic findings are modestly correlated.¹⁴

Related terminology

Prostatism

The term 'prostatism' has been used widely on the assumption that LUTS in middle-aged and older men are related to the prostate, although this is not necessarily the case.¹⁵ It is recommended that this term not be used to avoid misunderstanding.

Infravesical (outflow) obstruction

This implies increased resistance of urinary flow downstream of the bladder as a result of benign prostatic hyperplasia, urethral stricture or other conditions. Bladder outlet obstruction (BOO) is an almost identical term.

Urinary retention and overflow incontinence

Urinary retention signifies a condition in which the patient is unable to pass urine despite a large amount of urine having accumulated in the bladder (300 mL or more, for example). Such patients may be incontinent, since intravesical pressure exceeds the urethral closure pressure, leading to urinary leakage (overflow incontinence). These terms are not recommended by the ICS report,^{4,16} however, urinary incontinence associated with chronic urinary retention must not be overlooked.

Epidemiology and QOL

In Japan, 78% of males aged 60 years and older complain of some kind of LUTS. The most common symptom in men is nocturia followed by daytime frequency. The presence of LUTS shares risk factors with chronic lifestyle diseases and erectile dysfunction. LUTS, storage symptoms in particular, can impair QOL.

The representative epidemiological survey on LUTS in Western individuals is the EPIC Study.¹⁷ The study, which recruited 19 165 subjects aged 18 to 80 years, found that 62.5% of men and 66.6% of women were symptomatic, respectively. The most common symptom was nocturia in both men and women, and almost all symptoms were more prevalent with advanced age. In Japan, a survey involving 4480 men and women aged 40 years and older was reported in 2003.¹⁸ The frequencies of all LUTS increased with age, and approximately 78% of individuals aged over 60 years experienced some kind of LUTS. Weak stream and feeling of incomplete emptying were more common in men, while stress urinary incontinence was more common in women. The most prevalent symptom was nocturia followed by daytime frequency. Health seeking behavior was low (18.0%), with men (27.4%) visiting physicians more often than women (9.0%).

The risk factors for LUTS include heart disease, diabetes, hypertension, hyperlipidemia, obesity, alcohol consumption, smoking, and lack of exercise. These lifestyle factors are also related to the so-called lifestyle diseases.^{19–22} Recent epidemiological researches indicate a robust linkage between LUTS and erectile dysfunction.²³

Investigations on QOL in men with LUTS have been almost limited to benign prostatic hyperplasia. Analyses using the Short Form-36 and other generic QOL questionnaires²⁴ or disease-specific instruments have uniformly shown that LUTS, storage symptoms in particular, have negative effects on QOL,²⁵ and that medical therapy²⁶ and surgical interventions²⁷ improve the lowered QOL. Few investigations have looked into the relationship between LUTS and QOL. A Japanese epidemiological study¹⁸ indicates that 14.7% of people have their daily life affected by some kind of LUTS in various domains including mental health, vitality, physical activity, and social activities. Assessment of QOL impairment would be crucial in determining the severity of therapeutic outcomes for male LUTS.

Etiology and pathogenesis

The causes of LUTS in middle-aged and older men are diverse, including lower urinary tract, prostate, nervous system, systemic diseases, and other pathological conditions (Table 1). The most common causes would be benign prostatic hyperplasia, overactive bladder, underactive bladder, cerebrovascular disorder, polyuria, and their combination.

Table 1 Possible diseases/disorders for male lower urinary tract symptoms (LUTS)

- | |
|---|
| 1. Prostate and lower urinary tract |
| Prostate: benign prostatic hyperplasia, prostatitis, prostate cancer |
| Bladder: bacterial cystitis, interstitial cystitis, bladder cancer, bladder stones, bladder diverticulum, overactive bladder, other (aging) |
| Urethra: urethritis, urethral stricture |
| 2. Nervous system |
| Cerebral: cerebral infarction, dementia, Parkinson's disease, multiple system atrophy, brain tumor |
| Spinal cord: spinal cord injury, multiple sclerosis, spinal cord tumor, spinal infarction, spinal degenerative disease, spina bifida |
| Peripheral nerves: diabetic neuropathy, post-pelvic surgery |
| Other: aging, autonomic hyperactivity |
| 3. Miscellaneous |
| Drug-related, Polyuria, Sleep disorder, Psychogenic |

In many instances, multiple causes are involved or no specific causes can be definitely identified.

Prostate and lower urinary tract

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is highly prevalent in aged men and associated with various combinations of voiding and storage symptoms.²⁸ Presumably, BOO by the enlarged prostate accounts for LUTS in BPH; however, the severity of LUTS are not necessarily correlated with the degree of BOO or the prostate volume.¹² Bladder overactivity in BPH would be explained by denervation hypersensitivity,²⁹ modulated detrusor properties,³⁰ increased release of urothelial neurotransmitters (e.g. ATP, NO, prostaglandin, acetylcholine),³¹ or increased afferent stimulation from the urethra.³²

Other prostate diseases

Prostatitis: Prostatitis, acute or chronic, may occur in men of any age.³³ Pain and/or discomfort, in addition to storage and voiding symptoms, are perceived in the lower abdomen, perineum, and other areas of the pelvis. Chronic prostatitis and interstitial cystitis are symptomatically alike and postulated for common etiologies.³⁴

Prostate cancer: No specific LUTS is known to prostate cancer, especially in its early stage. LUTS can be a clue to prostate cancer detection; prostate cancer was reportedly detected in 7.2% of men complaining of LUTS.³⁵

Diseases and pathological conditions of the bladder

Bacterial cystitis: Bacterial cystitis is commonly associated with frequency, urgency and pain. It is rarely identified in isolated forms in men and may coexist with bladder stones or BPH.

Interstitial cystitis: Interstitial cystitis is predominant in women yet not uncommon in men. Typical clinical features include normal urinalysis and severe LUTS including frequency, urgency, bladder hypersensitivity, and bladder pain. It is sometimes misdiagnosed as chronic prostatitis.³⁶

Bladder cancer: Bladder cancer, carcinoma *in situ* in particular, produces storage symptoms.

Bladder stones: Storage symptoms are common in men with bladder stones. Abrupt interruption of urinary stream may occur when the stones block the bladder outlet. Associated infection may cause painful micturition.

Bladder diverticulum: A large bladder diverticulum is associated with a substantial amount of residual urine, which may result in slow urinary stream or urinary tract infection.

Overactive bladder: OAB syndrome is a constellation of symptoms constituting urgency, usually associated with daytime frequency and nocturia, with or without urgency incontinence. Obvious local pathologies (bladder cancer, bladder stones, infection, etc.) should be excluded.⁴ OAB is caused by diverse conditions including BPH, neurological disorders, and unknown etiologies (idiopathic).

Other (aging): Underactive bladder is often found in the elderly.³⁷ Recurrent or persistent voiding symptoms after surgical resection of the prostate are commonly explained by detrusor acontractility.³⁸ Decreased smooth muscle, increased fibrotic changes, and detrusor overactivity are associated with advancing age.^{39,40}

Urethral diseases

Urethritis: Urethral pain and discharge are common complaints in urethritis.

Urethral stricture: Urethral stricture can occur as a sequela of urethritis or urethral injury. Voiding symptoms such as weak urinary stream or straining are often described.

Nervous system

Cerebral

Cerebrovascular disorder: Forebrain lesions tend to cause storage symptoms, while brainstem lesions cause voiding symptoms.⁴¹ Lowered mobility by paralyzed extremities may cause functional urinary incontinence.

Dementia: Impaired function of the forebrain may deregulate inhibition of micturition and produce OAB symptoms. Cognitive deficits sometimes result in functional urinary incontinence.

Parkinson's disease: Parkinson's disease is often associated with various LUTS, with storage symptoms predominant rather than voiding symptoms.

Multiple systemic atrophy: LUTS are often complained of at an early stage, which mostly comprise OAB symptoms.

Brain tumor: The type and sequence of LUTS are variable, depending on the tumor location.

Spinal cord

Spinal cord lesions should be classified into supra-nuclear, nuclear, and infra-nuclear lesions. Supra-nuclear lesions are often associated with detrusor overactivity and detrusor sphincter dyssynergia (DSD), which may cause high infravesical pressure, leading to deterioration of the upper urinary tract. The other lesions usually accompany detrusor underactivity with varying degrees of urethral closing function.

Spinal cord injury: Total or partial abolishment of voiding function and urinary sensation develop in the acute phase, which restore in due time to varying degrees of dysfunctions.

Multiple sclerosis: This demyelinating disease, more common in women, brings a variety of symptoms due to variable etiologies including detrusor overactivity, detrusor sphincter dyssynergia and underactive bladder. In Japan, voiding symptoms are reportedly more common than storage symptoms.

Spinal cord tumor, spinal vascular disorder: LUTS and functional impairment vary depending on the affected site.

Spinal degenerative disease: Spinal canal stenosis and disc herniation compress nerves, producing various LUTS. Urinary retention may result from an acute phase of herniation.

Spina bifida: Spina bifida is a congenital anomaly in unifying the vertebral arch, and when occurring at the lumbosacral level, results in vesico-rectal dysfunction. The dysfunction and associated LUTS are diverse in combination and severity.

Peripheral nerves

Neuropathy peripheral to the sacral micturition center impairs contractility of the detrusor and causes voiding symptoms.

Diabetes mellitus: Degenerated autonomic nerves in the bladder wall as a consequence of diabetic neuropathy cause detrusor underactivity and voiding symptoms. Patients may be unaware of dysfunction or symptoms because of the weakening urinary sensation.⁴²

Pelvic surgery: Pelvic surgery may injure the nerves and blood vessels supplying the lower urinary tract. Detrusor underactivity, low-compliance of the bladder and incompetent urethra are common urodynamic abnormalities, resulting in various LUTS including urinary incontinence.

Others

Aging of the central nervous system: With advancing age, the number of dopamine D1 and D2 receptors decreases in the corpus striatum. The production and release of acetylcholine in the brain and the number of correspondent receptors diminishes with age.^{43,44} These changes are likely to cause overactive bladder symptoms and may explain age-related increases in those symptoms.

Autonomic hyperactivity: The activity of the sympathetic nervous system is upregulated with aging, and this may contribute to the prevalence of LUTS in aged populations. Spontaneously hypertensive rats are found to have elevated noradrenaline levels in the bladder, urethra and prostate, marked proliferation of the glandular component

of the prostate, a threefold increase in the urinary frequency, and increased nerve growth factor in the bladder.^{45–47}

Other conditions

Drug-associated

A variety of medicines including anticholinergics, antispasmodics, antiparkinsonian drugs, antihistamines, and psychotic drugs influence lower urinary tract function and may cause LUTS.

Polyuria

Increased urinary frequency is often caused by polyuria due to diabetes mellitus, diabetes insipidus, or over-drinking. Nocturnal polyuria is an important etiology for nocturia and potentially results from congestive heart failure, renal failure, overactivity of the autonomic nervous system, obstructive sleep apnea, lost diurnal variation of antidiuretic hormone secretion, or excessive consumption of water, caffeine, or alcohol.⁴⁸

Sleep disorder

Sleep disorder results in frequent arousal and consequent frequent voiding during the night. It is also a cause of nocturnal polyuria.⁴⁹

Psychogenic

Lower urinary tract symptoms can be caused by psychogenic reasons. The worsening and improvement of symptoms should be closely correlated with psychogenic episodes with no detectable organic disorders.

Diagnosis

Diagnosis of male LUTS requires evaluation for subjective aspects (symptoms and quality of life issue) and objective aspects (physiological function of lower urinary tract). One should be careful not to overlook underlying diseases such as infection or malignancy.

Clinical history

Focused questions on LUTS should be made for the present symptoms, the time-course of the symptoms including factors that may influence the symptoms, and the effect of the symptoms on the patient's QOL. The Core Lower Urinary Tract symptoms Score (CLSS)⁵⁰ would be a simple and valuable instrument for capturing the whole profile of LUTS without significant omission. Non-urological medical

histories to be asked include neurological disease, diabetes mellitus, lower abdominal surgeries, and medications used.

Symptom and QOL questionnaires

Men are more likely to complain of voiding symptoms, although it is storage symptoms that are more bothersome.^{8,18} It is difficult to diagnose the underlying condition of the lower urinary tract from the symptoms alone.⁵¹ Symptoms are usually assessed by questionnaires. Valid symptom questionnaires for BPH include the American Urological Association (AUA) Symptom Score,⁵² the International Prostate Symptom Score (IPSS),⁵³ and the Benign Prostatic Hyperplasia Impact Index (BII).⁵⁴ Incontinence Impact Questionnaire (IIQ),⁵⁵ Incontinence Quality of Life Instrument (I-QOL),⁵⁶ King's Health Questionnaire (KHQ),⁵⁷ International Consultation on Incontinence Questionnaire (ICIQ),⁵⁸ ICIQ Short Form (ICIQ-SF),⁵⁹ Overactive Bladder Questionnaire (OAB-q),⁶⁰ and the Overactive Bladder Symptom Score (OABSS),⁶¹ are used to evaluate urinary incontinence or OAB symptoms. Symptoms associated with interstitial cystitis are evaluated by the Interstitial Cystitis Symptom Index (ICSI), the Interstitial Cystitis Problem Index (ICPI),⁶² and the Pain Urgency Frequency Score (PUF).⁶³ The National Institute of Health–Chronic Prostatitis Symptom Index (NIH–CPSI) is used for chronic prostatitis.⁶⁴ Questionnaires that are not disease-specific, and thus are usable for patients with no definite diagnosis or multiple conditions include the International Consultation on Incontinence Modular Lower Urinary Tract Symptoms Questionnaire (ICIQ-MLUTS)⁶⁵ and the Core Lower Urinary Tract Symptoms Score (CLSS).⁵⁰ In particular, the CLSS is a simple questionnaire with questions addressing 10 important symptoms, and should be useful for the basic assessments.

Physical findings

The lower abdomen, pelvis, and external genitalia should be inspected for any abnormalities including neurological ones. Lower abdominal distension suggests urinary retention. Enlarged, indurated and painful prostate may imply BPH, prostate cancer and prostatitis, respectively.

Bladder diary

Bladder diary is the recording of micturition time and voided volume throughout the day and night. This is particularly useful for measuring the precise voiding frequency, functional bladder capacity and urine production. The recording period is preferably 3 to 7 days.⁶⁶ Nocturnal polyuria is defined as nocturnal urine volume $\geq 20\%$ (<65 years old) or $\geq 33\%$ (≥ 65 years) of the 24 h urine volume, or

≥ 10 mL/kg bodyweight.⁶⁷ A maximum voided volume ≤ 4 mL/kg bodyweight is regarded as a small functional bladder capacity.⁶⁷

Urine tests

Urinalysis should be examined for all patients.⁶⁸ Hematuria needs urological consultation. Pyuria should be treated with antimicrobial agents as presumptive urinary tract infection. Treatment-resistant pyuria should be referred to a urologist. Urine cytology is indicated when bladder cancer is suspected.

Blood tests

Serum creatinine measurement is recommended as a screening test for renal dysfunction. Prostate-specific antigen (PSA) is highly sensitive to prostate cancer,⁶⁹ and recommended for all men complaining of LUTS.

Residual urine test and ultrasonography

Residual urine is urine remaining in the bladder immediately after voiding. Trans-abdominal ultrasonography rather than catheter insertion is less invasive, and thus recommended as the measurement method. A clinically significant amount of urine (>100 mL, for example) necessitates further urological evaluation. Abdominal ultrasonography may reveal tumors, stones, and other abnormalities in the kidneys, prostate and bladder.

Urinary flow measurement

Uroflowmetry measures the volume of urine voided per unit of time. It is a simple and non-invasive test for voiding function.

Other tests

Other tests include endoscopy, imaging tests such as computed tomography scanning and excretory urography, and urodynamic investigations. These should be considered at urological referral.

Testing and diagnostic procedures

The basic assessment 1 (present illness, past history, physical examination, urinalysis, and serum PSA measurement) is mandatory in all cases. The basic assessment 2 (symptom and QOL questionnaires, bladder diary, residual urine measurement, urine cytology, urine culture, serum creatinine, and urinary tract ultrasonography) is selected on an individual basis. Men with severe symptoms or bladder pain should be referred to a urologist. Nocturia, if present as the

predominant symptom, should be managed according to the Clinical Guidelines for Nocturia. Before starting treatment, some of the basic assessment 2 should be conducted; measurement of residual urine is most recommended. Patients who failed to respond to the initial treatment should be referred to a urologist.

Treatment

The causes of male LUTS in middle-aged and elderly men can be classified into diseases or dysfunction of the prostate, bladder, urethra, or other organs. Treatment should be optimized to the condition being treated.

Grades of recommendation for treatments

The guidelines deal primarily with treatments that are used by general physicians rather than urological specialists. The grade of recommendation (Table 2) was determined for each treatment by examining not only the level of evidence (Table 3) but the variability of efficacy, magnitude of efficacy, clinical applicability, morbidity and cost. The levels of evidence and grades of recommendation for individual treatments are shown in Table 4.

Table 2 Grade of recommendation

Grade	Nature of recommendation
A	Highly recommended
B	Recommended
C	No clear recommendation possible
C1	Can be considered
C2	Not recommended
D	Recommend not to do
Reserved	

Table 3 Levels of evidence

Level of evidence	Type of evidence
1	Evidence obtained from multiple randomized controlled trials (RCTs)
2	Evidence obtained from a single RCT or low quality RCTs
3	Evidence obtained from non-randomized controlled studies
4	Evidence obtained from observational studies or case series
5	Evidence obtained from case studies or expert opinions

Table 4 Treatments for male lower urinary tract symptoms (LUTS)

Treatment method	Level of evidence	Grade of recommendation†
α₁-adrenoceptor antagonists (α₁-blockers)		
Prazosin	1	C1
Terazosin, Urapidil, Tamsulosin, Naftopidil	1	A
Silodosin	2	B
Alfuzosin	1	Not approved‡
Anti-androgens		
Chlormadinone, allylestrenol	3	C1
Finasteride, Dutasteride	1	Not approved
Other oral medications		
Paraprost, Eiprostat, Cernilton, Chinese herbal medicines, flavoxate	3–5	C1
Tricyclic antidepressants	5	C2
Anticholinergics	1	Reserved§
Cholinergics	1	Reserved
Sildenafil, Tadalafil	2	Not approved
Combination therapy with α₁-blockers		
Chlormadinone	3	C1
Finasteride	1	Not approved
Anticholinergics	1	Reserved
Electrical or magnetic stimulation		
Interferential low-frequency therapy	3	C1
Others	3	Not approved
Conservative therapy		
Lifestyle modification	2	A
Saw palmetto	1	Not definable¶
Supplements other than saw palmetto	5	C2
Conservative therapy for prostatitis	5	C1

†Assumed that treatment is provided by general physicians rather than urological specialists. Indwelling catheter and clean intermittent catheterization are not included in this table because they should be undertaken under the guidance of urologists.

‡Not approved for clinical use in Japan. §Reserved for urologists only. ¶The same level of evidence for efficacy and lack of efficacy.

Pharmacotherapy

α₁-adrenoceptor antagonists (α₁-blockers)

There is ample evidence to support the efficacy and safety of α₁-blockers for BPH, indicating that α₁-blockers would be the first choice medicine for male LUTS.

α₁-Blockers relieve outlet obstruction by inhibiting contraction mediated by prostatic α₁ adrenaline receptors (α₁-AR), thereby ameliorating symptoms of BPH. The magnitude of efficacy of various α₁-blockers would be 16–25% (2.0–2.5 mL/s) increase in the maximum flow rate and 30–40% (4–6 points) reduction of average IPSS. The well-known adverse reactions such as postural hypotension and asthenia are as uncommon as placebo (4–10%) for alfuzosin and tamsulosin.^{70–72} Other adverse events include ejaculatory dysfunction and intraoperative floppy iris syndrome (IFIS).⁷³

Prazosin: Grade of recommendation: C1

Clinical studies have been conducted on prazosin since before 1995, providing adequate evidence to support

efficacy for BPH (1). Compared with newer α₁-blockers, however, adverse events such as postural hypotension are more frequent with prazosin (1).

The efficacy of prazosin has been confirmed in a Western large-scale, placebo-controlled, randomized controlled trial (RCT), and in a Japanese RCT.^{74,75} However, hypotension and other adverse reactions are more common than newer agents.

Terazosin: Grade of recommendation: A

There is adequate evidence to support the efficacy of terazosin for BPH (1). The incidence of orthostatic hypotension and other adverse reactions may be relatively high (1).

Improvement in IPSS and urinary flow rate was significantly better for terazosin than a placebo or finasteride, and similar to tamsulosin. However, vascular adverse reactions may be more common than with tamsulosin and other α₁-blockers.⁷⁶ A Japanese study found no significant difference between terazosin and tamsulosin in improvement of symptoms or urinary flow rate or in the incidence of adverse

events.⁷⁷ Significant symptomatic improvement has been demonstrated for chronic prostatitis in a placebo-controlled RCT.⁷⁸

Urapidil: Grade of recommendation: A

There is adequate evidence to support the efficacy of urapidil for BPH and neurogenic bladder (1).

Urapidil significantly improved residual urine and maximum flow rates than placebo in an RCT on BPH.⁷⁹ The efficacy of urapidil for neurogenic bladder has also been confirmed in a placebo-controlled RCT.⁸⁰

Tamsulosin: Grade of recommendation: A

There is adequate evidence to support efficacy for BPH, including long-term efficacy (1). Adverse reactions, including postural hypotension, were uncommon (1).

A Japanese RCT of tamsulosin on BPH demonstrated its superiority to a placebo, and found the optimal dosage to be 0.2 mg/day.⁸¹ Western studies have yielded an optimal dosage of 0.4 mg/day.^{82,83} Long-term studies showed that efficacy and safety were unchanged over treatment durations exceeding 3 years (at longest 9 years).⁸⁴

Naftopidil: Grade of recommendation: A

There is adequate evidence to support the efficacy of naftopidil for BPH (1).

The efficacy of naftopidil for BPH has been demonstrated in RCTs in comparison with placebo and other agents.^{85,86} Comparisons between naftopidil and tamsulosin have found no discernible differences between the two agents.^{87,88}

Silodosin: Grade of recommendation: B

There is evidence to support the efficacy of silodosin for BPH, albeit limited to a single Japanese study (2).

Silodosin is a selective α_{1A} -subtype blocker developed in Japan. An RCT indicated significantly larger decreases in IPSS and QOL score for silodosin compared with placebo.⁸⁹ Of adverse events, ejaculatory dysfunction was reported by 25% of subjects, although this was the cause of discontinuation in only 2.9%.⁸⁹

Alfuzosin: Grade of recommendation: Not approved

There is adequate evidence to support the efficacy of alfuzosin for BPH and chronic prostatitis (1). Alfuzosin is widely used in Western countries, but is at the clinical trial stage in Japan.

In placebo-controlled RCTs alfuzosin produced significant improvements in symptoms and urinary flow rate.^{90,91} The efficacy is roughly comparable with tamsulosin.⁹² The reported incidences of adverse events are similar to those seen with other α_1 -blockers.⁹² Significant symptomatic improvements were reported for chronic prostatitis.⁹³

Anti-androgens

Antiandrogens inhibit the action of androgens on the prostate, thereby shrinking the prostate and lessening the symptoms associated with BPH. One should be careful for

to overlook prostate cancer, since PSA is decreased by approximately 50%.

Chlormadinone, allylestrenol: Grade of recommendation: C1

Evidence to support the efficacy of chlormadinone and allylestrenol for BPH is less than adequate (3). Reported adverse events included hepatic dysfunction, erectile dysfunction, loss of libido, and gynecomastia (3).

In an RCT comparing chlormadinone and Eviprostat (Mn-ethamsylate and plant extracts) for BPH, symptomatic improvement was reported by 90% and 70% of subjects, and prostate volumes decreased in 50% and 0%, respectively.⁹⁴ There was no significant difference for efficacy between chlormadinone and allylestrenol.⁹⁵ Reported adverse events included hepatic dysfunction, erectile dysfunction, loss of libido, and gynecomastia.

Finasteride, dutasteride: Grade of recommendation: Not approved

There is adequate evidence to support the efficacy of finasteride and dutasteride for BPH (1). Adverse reactions affecting sexual function are relatively rare (1). However, neither agent has been approved in Japan.

Finasteride and dutasteride are 5 α -reductase inhibitors that prevent the activation of testosterone. Finasteride significantly reduced prostate volumes and improved symptoms in subjects with prostate volumes exceeding 40 mL.⁹⁶ It also reduced the relative risk of acute urinary retention and surgery by 57–59% and 36–55%, respectively.⁹⁷ Dutasteride, a more potent inhibitor of testosterone activation, proved to be similarly efficacious for symptomatic and uroflowmetric improvement.⁹⁸

Combination therapy involving α_1 -blockers plus anti-androgens: Grade of recommendation: C1 (chlormadinone), Not approved (finasteride)

Evidence to support efficacy in BPH is adequate for finasteride (1), but not for chlormadinone (3).

In a 16-week RCT in which BPH men were randomized to tamsulosin, chlormadinone, or combination, significantly better symptomatic improvement was seen in the tamsulosin group and combination group than in the chlormadinone group, and the uroflowmetric improvement was greatest in the combination group.⁹⁹ However, a 52-week RCT with these three arms failed to show significant inter-group differences in symptomatic improvement.¹⁰⁰ The addition of finasteride to doxazosin could not confirm benefits of the combination therapy in 1-year RCTs.¹⁰¹ When the study period was extended to 4.5 years, the combination therapy significantly decreased the risk of acute urinary retention and surgical intervention.¹⁰²

Anticholinergics: monotherapy and combination with α_1 -blockers

Grade of recommendation: Reserved

There is adequate evidence to support the efficacy and safety of anticholinergics for male OAB symptoms (1). The efficacy and safety of anticholinergic agents have not been confirmed in Japanese men, however, the risk of urinary retention remains to be a concern (5). Treatment with anticholinergic agents should be reserved only for urologists.

For OAB symptoms α_1 -blockers are effective as monotherapy,¹⁰³ although their efficacy is limited for patients with detrusor overactivity.¹⁰⁴ Anticholinergics are most commonly used for OAB symptoms, and the reported incidence of acute urinary retention is <1%, which is comparable to placebo.¹⁰⁵ The efficacy and safety of anticholinergic monotherapy have also been confirmed in the treatment of BPH associated with OAB.¹⁰⁶ Combined therapy of anticholinergics and α_1 -blockers improved storage symptoms, with urinary retention being extremely rare over the 12-week observation period.^{107–109} A Japanese study also found that combination therapy improved storage symptoms, especially urgency, in BPH.¹¹⁰ In a 12-week trial of combination therapy in men with LUTS, the benefits were significantly greater in the combination therapy group, with only a mild increase in residual urine volumes, and a 1% incidence of urinary retention, with no difference between groups.¹¹¹

It should be noted, however, that most of these studies were conducted with Caucasian men with strict exclusion criteria, specialists' supervision, and relatively short-term observational period. There remains a concern about exacerbation of voiding difficulty and possible urinary retention by a wider and longer use of anticholinergics with or without α_1 -blocker in the practical clinical setting.

Other oral medications

Paraprost, Eviprostat, Cernilton (cernitine pollen extract), Chinese herbal medicines (Hachimi-jio-gan, Gosha-jinki-gan), Flavoxate: Grade of recommendation: C1

Efficacy of these agents is suggested for symptoms of BPH and chronic prostatitis, although evidence is scant (3–5). Adverse events are rare and mild.

Several studies have suggested efficacy for these agents, but they had small sample sizes, limited efficacy, and lack of reproducibility of results in multiple studies.^{86,112,113–115}

Tricyclic antidepressants: Grade of recommendation: C2

Evidence to support efficacy is scant (5). Adverse events include arrhythmia and drowsiness.

Theoretically, imipramine is potentially effective for various forms of urinary incontinence, but no studies have convincingly demonstrated its efficacy.

Cholinergics: monotherapy or combination with α_1 -blockers: Grade of recommendation: Reserved

Evidence to support the efficacy of cholinergic agents in underactive bladder is lacking (1). Japanese and overseas studies have demonstrated the usefulness in certain patient groups only (3). Serious adverse reactions may occur, especially in elderly individuals. Treatment with cholinergic agents should be reserved for a urologist.

A recent review article found no evidence of a therapeutic effect on voiding difficulty.¹¹⁶ Combination therapy with α_1 -blockers significantly improved symptoms and urinary flow in underactive bladder.¹¹⁷ Adverse reactions include abdominal pain and diarrhea, as well as the risk of a cholinergic crisis.

Phosphodiesterase-type 5 inhibitors: Grade of recommendation: Not approved

These drugs are intended for treatment of erectile dysfunction, but adequate evidence exists to support their efficacy in male LUTS (2). They are not approved in Japan.

In a placebo-controlled RCT in middle-aged and elderly men with erectile dysfunction and LUTS, sildenafil and tadalafil significantly improved symptoms.^{118,119}

Electrical and magnetic stimulation therapy

Grade of recommendation: C1 (electrical stimulation), Not approved (magnetic stimulation)

There is evidence of efficacy but it is far from adequate (3). Adverse events are almost completely absent.

In comparison with placebo, electrical and magnetic stimulations showed significantly higher efficacy for OAB symptoms and urgency incontinence.^{120–122} Other studies have shown equivalent efficacy to oxybutynin.^{123,124} The efficacy of interferential low-frequency therapy has also been demonstrated in an RCT.¹²⁵ However, there are no investigations in male patients only, and its long-term effects remain uncertain.

Conservative therapies

Lifestyle modification

Grade of recommendation: A

There is evidence supporting the efficacy of lifestyle modification (2). Adverse events are almost completely absent, and the financial burden is low.

In a study where men with BPH were allocated to either transurethral resection of the prostate (TURP) or to lifestyle modifications only (restrictions on fluid intake and information on provision), voiding symptoms improved in over one-quarter of subjects in the latter group.¹²⁶ The benefits of behavioral therapy for elderly subjects with LUTS, including female subjects, have been demonstrated in an RCT.¹²⁷ The therapy included moderate physical activity, ameliora-

Table 5 Core Lower Urinary Tract Symptom Score (CLSS) Questionnaire

Please circle the number that applies best to your urinary condition during the last week.

	0	1	2	3						
Q1: How many times do you typically urinate from waking in the morning until going to sleep at night?	0–7	8–9	10–14	15+						
Q2: How many times do you typically urinate from going to sleep at night until waking in the morning?	0	1	2–3	4+						
How often do you have the following symptoms?	Never	Rarely	Sometimes	Often						
Q3: A sudden strong desire to urinate, which is difficult to postpone	0	1	2	3						
Q4: Leaking of urine because you cannot hold it in	0	1	2	3						
Q5: Leaking of urine when you cough, sneeze, or strain	0	1	2	3						
Q6: Slow urinary stream	0	1	2	3						
Q7: Need to strain when urinating	0	1	2	3						
Q8: Feeling of incomplete emptying of the bladder after passing urine	0	1	2	3						
Q9: Pain in the bladder	0	1	2	3						
Q10: Pain in the urethra	0	1	2	3						
CLSS (Sum of Q1–10) _____										
From symptoms 1–10, please circle the numbers corresponding to <i>no more than three</i> symptoms you find bothersome.										
Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Not applicable
Of the symptoms you chose above, please circle the number of the symptoms that you find most bothersome (1 only).										
Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Not applicable
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?										
Delighted	Pleased	Mostly satisfied	About equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible				
0	1	2	3	4	5	6				

tion of constipation, and avoidance of sitting for extended periods or exposing the lower body to cold temperature.¹²⁸

Supplements and alternative remedies

Saw palmetto (*Serenoa repens*): Grade of recommendation: Reserved

There is adequate evidence to support efficacy for BPH, but there is also adequate evidence for its lack of efficacy (1). No serious adverse events are known.

A meta-analysis found saw palmetto to be effective in the treatment of BPH.¹²⁹ A placebo-controlled RCT found absolutely no difference in efficacy between saw palmetto and a placebo, however.¹³⁰ A separate review article also raised doubts about its efficacy.¹³¹

Supplements other than saw palmetto: Grade of recommendation: C2

There is no evidence to support efficacy (5).

Treatments requiring urological expertise

Grade of recommendation: Reserved

These therapies should either be performed under supervision by urologists or by urologists in person.

Indwelling catheter and clean intermittent catheterization (CIC): An indwelling catheter is frequently used as a treatment for urinary retention where other therapies cannot be carried out or are unsuccessful. However, long-term use of an indwelling catheter impairs QOL, and increases the risk of urethral injury, urinary tract infection, and bladder stones. An RCT comparing clean intermittent catheterization (CIC) with an indwelling catheter demonstrated a significantly lower incidence of symptomatic urinary tract infection in the CIC group.¹³²

Surgical treatment for BPH: Transurethral resection of the prostate (TURP) is the surgical gold standard for BPH.¹³³ Possible complications include bleeding, TUR syndrome (hyponatremia and water intoxication), and postsurgical urethral stricture. Less invasive surgical methods are under development, with laser resection and ablation appearing particularly promising.

Algorithm

Figure 1 shows an algorithm for management of lower urinary tract symptoms in males.

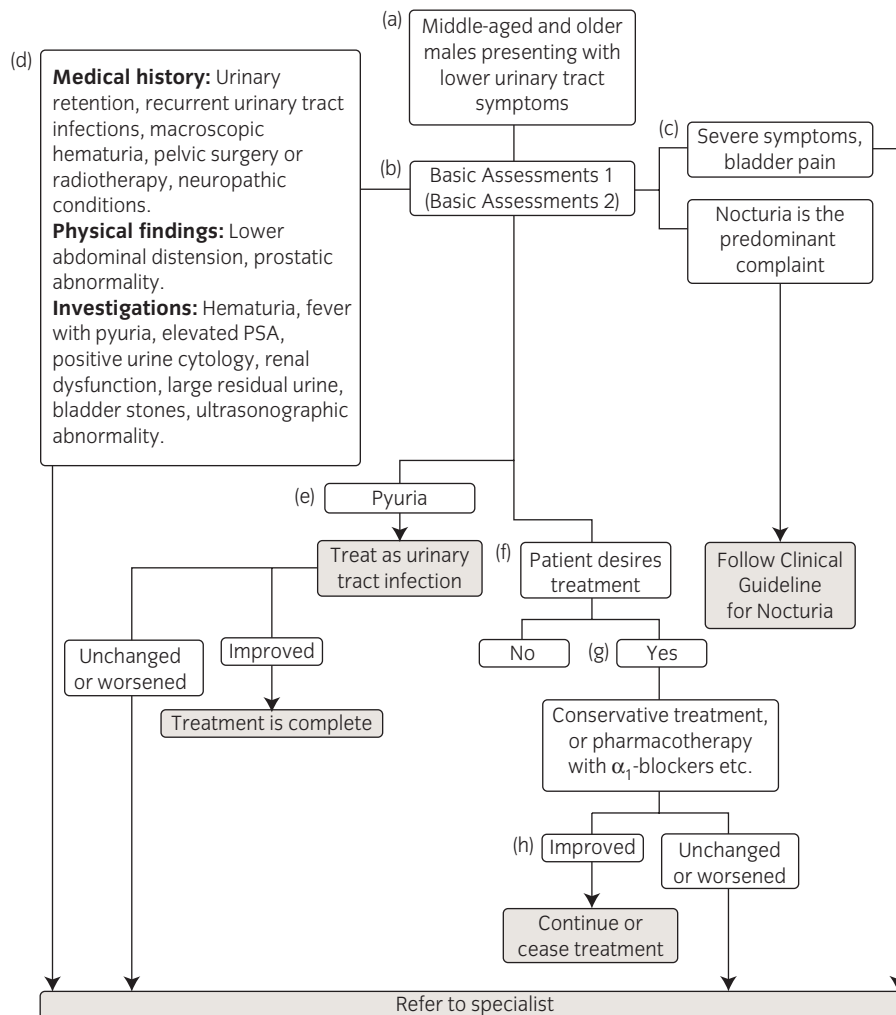


Fig. 1 Algorithm for management of lower urinary tract symptoms in males: (a) This algorithm is applicable to middle-aged or older men who present with some kind of LUTS. (b) The basic assessment 1, mandatory in all cases, comprises present illness, past history, physical examination, urinalysis, and measurement of serum PSA. The basic assessment 2 is selected on an individual basis. It includes symptom and QOL questionnaires, bladder diary, and residual urine measurement, as well as urine cytology, urine culture, measurement of serum creatinine, and urinary tract ultrasonography. (c) If the symptoms are severe or include bladder pain, the patient should be referred to a urologist. If the predominant symptom is nocturia, the Clinical Guidelines for Nocturia should be consulted. The CLSS questionnaire (Table 5) may be useful in capturing important symptoms and their effects on QOL. (d) If any of these problems are revealed, the patient should be referred to a urologist. (e) Pyuria without fever is likely indicative of urinary tract infection and should be treated with appropriate antimicrobials. Note that urinary tract infection in men is sometimes associated with underlying diseases. (f) When the assessments reveal no problems, the patient should be asked for his desire for therapy. (g) At this stage the LUTS would be most probably attributable to BPH, bladder dysfunction, or both. Before initiating treatment, it is preferable that some of the tests of the basic assessment 2 be conducted, such as symptom and QOL questionnaires, bladder diary, and residual urine measurement. Of these, residual urine measurement is highly recommended. Patients who do not respond to the initial treatment should be referred to a urologist. (h) Re-assessment should be conducted on a regular basis, where changing, discontinuing or reducing the medications should be considered.

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