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Review

Assessment and management of male lower urinary tract symptoms (LUTS)

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HIGHLIGHTS

- Male lower urinary tract symptoms are common causes of impairment of quality of life.
- Detailed assessment is needed to confirm the underlying mechanism(s).
- Different treatment modalities are available according to individual patient preference.

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ABSTRACT

Male lower urinary tract symptoms (LUTS) are common, causing significant bother and impair quality of life. LUTS are a spectrum of symptoms that may or may not be due to benign prostatic obstruction (BPO). LUTS are divided into storage, voiding or post micturition symptoms, which each need to be considered in terms of impact, mechanism and treatment options. In most patients, a mixture of symptoms is present. In order to have a better insight about which symptoms are affecting quality of life, a thorough evaluation should include medical history, examination, validated symptom questionnaires, bladder diary, and flow rate (with post void residual measurement). Other tests, particularly urodynamic tests may be needed to guide treatment selection, particularly for surgery. Management of male LUTS is tailored according to the underlying mechanisms. Different treatment modalities are available according to individual patient preference. These range from watchful waiting, behavioral and dietary modifications, and/or medications – either as monotherapy or in combination. Surgery to relieve BPO may be needed where patients have significant bothersome voiding LUTS, and are willing to accept risks associated with irreversible treatment. Interventions for storage LUTS are available, but must be selected judiciously, using particular caution if nocturia is prominent. In order to achieve better outcomes, a rational stepwise approach to decision making is needed.

1. Introduction

Lower urinary tract symptoms (LUTS) in men are common with up to 41% of men reporting bothersome symptoms over the age of 40 years [1]. LUTS can be caused by multiple conditions. Benign prostatic obstruction (BPO) and/or overactive bladder (OAB) are two important and prevalent causes of LUTS in male patients [2], but the range of conditions that can present primarily with LUTS is substantial (see Fig. 1). Accordingly, detailed assessment is needed to confirm the underlying mechanism(s) and ensure a suitable treatment pathway is followed. In this review, we focus on the assessment of LUTS and the treatment recommendations where BPO and/or OAB are the causative problem.

During the past decade, the pathophysiology of LUTS/BPO has been completely revisited, such that the diagnosis and medical and surgical management of LUTS has evolved considerably [3]. Likewise, OAB has seen substantial progress in understanding and therapy [4]. Crucially, the healthcare profession has switched focus from *presumed mechanism* when selecting treatment, to *symptom bother and quality of life*. However this implementation of a rational approach to decision making is based on picking up the necessary information required from the clinical assessment, and tailoring therapeutic options to individual patients, with the expectation that this should lead to better patient outcomes.

In the past, LUTS in adult men have often been simplistically

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Causes of male lower urinary tract symptoms (LUTS)

Obstruction:
- Benign Prostatic Obstruction
- Foreign Body
- Urethral stricture

Infectious:
- Urinary Tract Infection
- Prostatitis

Neurogenic bladder dysfunction

Primary Bladder Pathology:
- **Overactive Bladder**
- **Detrusor Underactivity**

Malignant:
- Bladder Tumor
- Prostate Cancer

Diuretic causes:
- Diabetes
- Nocturnal Polyuria

Extra- vesical cause:
- Distal Ureteric Stone

Fig. 1. Conditions that may give rise to a presentation as male LUTS [8].

attributed to the enlargement of the prostate gland, even if the type of symptoms were storage LUTS [5]. This causal link between the prostate and the pathogenesis of LUTS has come into question in recent years [6]. Although benign prostatic enlargement (BPE) can significantly contribute to the onset of LUTS in a proportion of men over 40 years of age, other metabolic, neurological, inflammatory, and anatomical factors should be considered [7].

2. Terminology of LUTS

LUTS is a general term that entails several pathological entities (Fig. 2).

2.1. Voiding and post micturition LUTS

The International Continence Society (ICS) has developed standardized terminology in the area of LUTS [9]. Voiding and post micturition LUTS are symptoms encountered during or immediately following the voiding phase. Voiding LUTS comprise slow stream, intermittency, hesitancy, splitting of stream, straining to void and terminal dribble [9]. The extreme form of voiding LUTS is acute retention of urine, which is complete inability to void requiring emergency catheterization.

Post micturition symptoms include a sensation of incomplete bladder emptying and/or a post micturition dribble. Voiding and post micturition LUTS might be due to either BPO or detrusor underactivity (DUA) [10].

Bladder outlet obstruction (BOO) is the generic term for obstruction during voiding and is characterised by increased detrusor pressure and reduced urine flow rate [9]. It is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure, and so it requires urodynamic studies to formalise the diagnosis of BOO. Benign prostatic obstruction (BPO) is a form of bladder outlet obstruction and may be diagnosed when

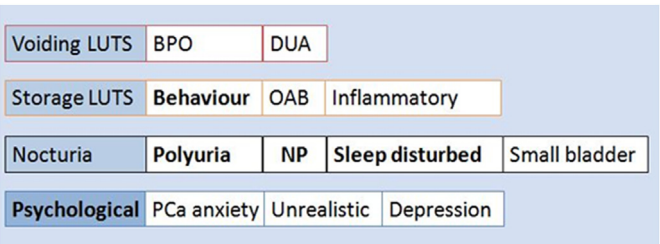

Fig. 2. Mechanisms underlying individual male LUTS. (BPO: Benign Prostatic Obstruction, DUA: Detrusor Underactivity, OAB: Overactive Bladder, NP: Nocturnal Polyuria, PCa: Prostate Cancer).

the cause of outlet obstruction is known to be benign prostatic enlargement, due to histologic benign prostatic hyperplasia [9]. Benign prostatic hyperplasia (BPH) is a term used (and reserved for) the typical histological pattern which defines the disease [9]. Accordingly, BPH is a term that should be avoided unless histological confirmation has been obtained. In the absence of histology information, BPE is more appropriate terminology.

In men referred with LUTS only around half have BPO/BOO (48% [11] and 53% [12]). The remainder typically have detrusor underactivity (DUA), which is defined as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span [9]. Like BOO, this is a urodynamic diagnosis and can only be assessed by studying the synchronous values of detrusor pressure and flow during the voiding phase [13]. Regarding DUA, there remains a lack of accepted terminology, definition, diagnostic methods and criteria [14].

2.2. Storage LUTS

The lower urinary tract spends substantially more time in storage mode than voiding [15]. Symptoms affecting the storage phase include increased daytime frequency, urgency, nocturia and incontinence. According to one study [16], urinary urgency is the most bothersome LUTS in men, alongside post micturition dribble. Storage LUTS can result from inflammation affecting the lower urinary tract. The overactive bladder syndrome (OAB) is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [17].

Nocturia is defined by the ICS as the complaint that the individual has to wake at night one or more times to void, each void being preceded and followed by sleep [9]. According to the underlying pathophysiology, nocturia can be divided into four distinct categories; an overall increase of urine production (24-h polyuria), an increase in urine production only at night (nocturnal polyuria [NP]), a primary or secondary sleep disorder, or a reduced bladder capacity (which may at all times, or predominantly nocturnal) [18]. Due to the range of contributory factors, nocturia may be regarded as a systemic symptom, even more than a LUTS [19].

3. Assessment

Life-related stress factors, concern about personal health, anxiety about having prostate cancer, depression and unrealistic expectation about the management path all affect the quality of life of a men suffering from LUTS [20]. These concerns must be identified and addressed early on in the assessment.

3.1. Medical history

A medical and surgical history must be taken from men with LUTS [21]. This helps in identifying the probable causes, impact and associated co-morbidities. In addition, current medications, lifestyle habits, emotional and psychological factors should be reviewed. Sexual function should be evaluated (since erectile dysfunction often co-exists with LUTS [22]). Similarly, bowel symptoms may be relevant-inflammatory bowel syndrome (IBS) may occur in OAB in one third of patients [8]. If present, full investigation of haematuria is essential to exclude urinary tract malignancy. Any underlying neurological condition should be excluded before initiating management of LUTS.

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3.2. Symptom score questionnaires

European Association of Urology (EAU) guidelines recommend the use of validated symptom score questionnaire to qualify the patient's LUTS and to identify which type of symptoms is predominant [23]. The most widely used symptom questionnaires are the International Prostate Symptom Score (IPSS), and the International Consultation on Incontinence Questionnaire for Male LUTS (ICIQ-MLUTS). The IPSS evaluates specific LUTS and has one global quality of life (QoL) question; physicians are more familiar with it and it is useful in assessing treatment outcome [24]. On the other hand, the ICIQ-MLUTS has a more comprehensive approach in assessing all LUTS, each LUTS is weighted against degree of bother to the patient, it is more detailed and helps in decision making-largely because as it shows *which* LUTS is most bothersome to the patient [25].

3.3. Bladder diaries

Bladder diaries are usually a true reflection of the urinary behavior. They are used to confirm the findings of assessment. They are used to categorize the mechanism of LUTS into either; low functional bladder capacity, polyuria, nocturnal polyuria and sleep disorders or behavioral factors [18]. The validated ICIQ 3 day bladder diary has recently been published for this purpose [26]. On interpreting the bladder diary, it gives an overview of the patients' symptoms as regards to total fluid intake, daytime frequency episodes, nocturia episodes, incontinence episodes, average voided volume, 24 h voided volume. From it, the nocturnal polyuria index [27] can be calculated, which is crucial for understanding mechanisms underlying nocturia.

3.4. Physical examination

Physical examination is routine part of the assessment of LUTS and entails examination of the suprapubic area, the external genitalia, the perineum and lower limbs. Urethral discharge, meatal stenosis, phimosis and penile cancer must be identified if present [23]. Digital rectal examination (DRE) is essential to exclude an overtly malignant prostate, loss of anal tone or saddle paraesthesia, and it is the simplest way to assess the prostate volume. However DRE isn't very accurate in estimating the exact size of the prostate but can give a broad view whether the prostate is more or less than 50 ml in size [28]. A lower limb neurological assessment is needed to exclude any potential neurological findings.

3.5. Investigations

Special tests are encountered to give a broader view of the cause of the patient's LUTS. Not all of these tests are mandatory in the assessment of each individual patient, but they are tailored according to each situation.

Urinalysis is recommended in most Guidelines in the primary evaluation of patients with LUTS [3,21,29]. This is done to determine conditions, such as UTI, microscopic haematuria and diabetes mellitus, which may need further evaluation according to the specific guidelines [30,31]. Prostate-specific antigen (PSA) should be carried out if diagnosing prostate cancer (PCa) will change the management plan, or if PSA can assist in decision-making in patients at risk of progression of BPE [23]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient. However, it should be remembered that many men harbor significant worry that LUTS are down to the potential presence of cancer, even though the link is tenuous.

Uroflowmetry together with post-void residual (PVR) urine measurement should be part of the routine assessment of LUTS. They give an idea as to whether the bladder is functioning normally. However, low maximum flow rate (Q_{max}) and/or a high PVR can arise as a consequence of BOO, detrusor underactivity or an underfilled bladder [32,33]. Thus, it is limited as a diagnostic test because it is unable to discriminate between the underlying mechanisms [34] and it has been removed from some initial assessment algorithms [35]. Specificity can however be improved by repeated flow rate testing.

Kidney function tests and ultrasound of the kidneys are not part of the routine investigations for LUTS. However, they are indicated in patients with high PVR, if renal impairment is suspected based on history and clinical examination [36,37].

Urethrocystoscopy should only be performed in men with LUTS and haematuria, to exclude suspected bladder or urethral pathology, and/or prior to minimally invasive/surgical therapies if the findings may change treatment [38].

Based on the history, symptom questionnaire, bladder diary and above diagnostic tests, initial treatment can be initiated. If patients are still symptomatically bothered and initial treatment has been a failure, more specialized tests should be undertaken to diagnose any coinciding condition as explained below.

Pressure flow studies (PFS), also known as urodynamics, are the basis for the definition of BOO, which is characterized by an increased detrusor pressure and decreased urinary flow rate during voiding. BOO/BPO has to be differentiated from detrusor underactivity (DUA), which signifies decreased detrusor pressure during voiding in combination with decreased urinary flow rate [39]. There are no published RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS. The EAU guidelines indications for performing PFS are: in individual patients for specific indications prior to surgery based on age, findings from other diagnostic tests and previous treatment or when evaluation of the underlying pathophysiology of LUTS is warranted, failure of previous invasive therapy, men who can't void >150 ml, men with a PVR >300 ml, men with predominantly voiding LUTS who are <50 years or >80 years of age [23].

4. Treatment

The ideal therapy for LUTS aims to improve the current situation through; identifying the direct causative mechanisms, applying treatment options logically, and carrying out informed decision-making. Therapy should avoid making the symptoms worse by: avoiding treating LUTS that cause a low baseline “bother” to the patient; using irreversible therapy that won't worsen LUTS when possible; maintaining sexual function if possible; and minimising complications. It is also an important to inform patients about realistic outcomes and potential adverse effects of the treatment options. An overview on treatment is given in Fig. 3.

4.1. Predominant storage LUTS

In men complaining of non bothersome storage LUTS, watchful waiting (WW) could be offered as an option as most men will remain stable for years [40]. Behavioral and dietary modifications as part of self management are proven to reduce both symptoms and their progression [41,42]. If conservative measures fail, a trial of muscarinic receptor antagonists may be beneficial. Several randomized controlled studies were carried out to assess the efficacy of muscarinic antagonists in the treatment of men with OAB without presumed BOO [43–47]. Those have shown that muscarinic antagonists have a significant beneficial effect in reducing

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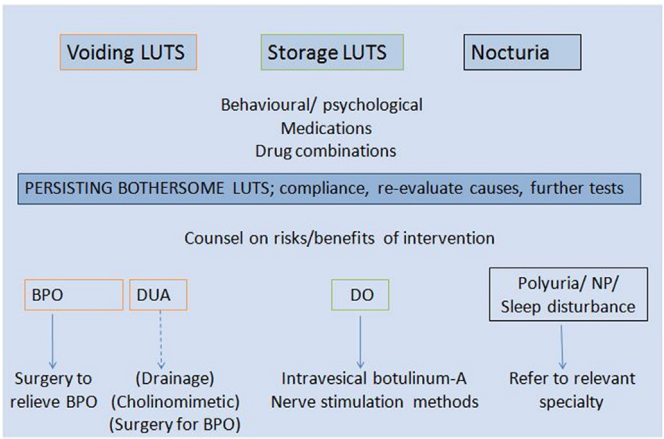

Fig. 3. Summary diagram for treatment of LUTS according to the underlying mechanism.

urgency incontinence, daytime frequency and urgency related symptoms. They are generally well-tolerated, but adverse events (such as dry mouth and constipation) can be an issue. Mirabegron is a new agent working through its novel beta-3 adrenergic agonist action for the treatment of symptoms of OAB. It is currently used if muscarinic antagonists are ineffective or poorly tolerated. The most common treatment related adverse events of mirabegron are hypertension, urinary tract infection and headache [48,49]. Combination therapy using Mirabegron and muscarinic antagonist is under investigation [50].

If symptoms are still persistent after the above treatment, it is appropriate to check for compliance with treatment, and potentially to re-evaluate the cause by performing PFS. If DO (without BOO) is present, invasive intervention could be initiated after careful patient counseling about risks and benefits. Intravesical botolinum-A or nerve stimulation methods may be undertaken by specialist urologists.

4.2. Predominant voiding LUTS

α_1-adrenergic receptor antagonists (α_1-blockers) are indicated after failure of conservative measures [51]. Typically, α_1-blockers reduce IPSS by approximately 30–40% and increase Q_{max} by approximately 20–25% [52]. Effects usually take a few weeks to develop. However, α_1-blockers don't seem to be efficacious in patients with larger prostates (>40 ml), nor do they reduce the prostate size [53,54]. The most frequent adverse events of α_1-blockers are asthenia, dizziness and (orthostatic) hypotension [55]. An alternative is to use the phosphodiesterase type 5 inhibitor tadalafil [56].

In men with moderate-to-severe LUTS and an enlarged prostate (>40 ml) and/or elevated PSA (>1.4–1.6 ng/ml), treatment with 5α-Reductase inhibitors (5-ARIs) can be offered [23]. Two types of 5-ARIs are available; dutasteride and finasteride. 5-ARIs reduce the prostate size by about 18–28% and PSA by about 50% [57]. Clinical effects are generally seen several months after initiation of treatment [58]. The adverse effects of 5-ARIs are reduced libido, erectile dysfunction and, less frequently, ejaculation disorders (retrograde ejaculation, ejaculation failure, or decreased semen volume) [57].

An α_1-blocker/5-ARI combination is beneficial in men with moderate to severe LUTS, where prostate volume is >30 ml, who are at risk of disease progression and when medical treatment is intended for more than a year [59]. The combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α_1-blocker in reducing the risk of acute urinary retention or need for surgery [60,61]. However, combination therapy is also associated with more adverse events [62].

Transurethral resection of the prostate (TURP) should be reserved for men with moderate to severe LUTS secondary to BPO where medical therapy is unsuccessful/intolerable. Surgical intervention is also warranted in situations such as chronic urine retention, renal impairment due to BPO, recurrent acute urine retention (AUR) and/or recurrent UTI [63]. No other treatment modality provides similar durability to that of TURP [64]. Failure of improvement of symptoms after TURP were mainly associated with DUA rather than re-development of BPO [65].

4.3. Nocturia

Nocturia is potentially challenging in its treatment due to its multifactorial etiology. If nocturia is proven to be due to lower urinary tract dysfunction (LUTD), a combination of behavioral modifications, bladder re-training and muscarinic antagonists can sometimes reduce nocturia episodes [66]. Also, a combination of muscarinic antagonists and α_1-blockers are superior to placebo in reducing nocturia episodes [67]. If the cause of nocturia is a disturbance in the salt/water balance, referral to a specialist for further assessment of the cause is needed. However, the use of antidiuretics such as desmopressin has proven to decrease the frequency of nocturnal voids and decrease nocturnal diuresis, but the sodium level needs to be monitored in individuals commencing this therapy [68]. In addition, men with nocturnal polyuria may benefit from diuretics such as furosemide 6 h before sleep [69]. The International Consultation on Urological Disease (ICUD) committee recommends the referral of male patients suffering from nocturia with sleep disturbances to be considered for specialist advice [70].

4.4. Mixed LUTS

In the real world, most patient present with mixed LUTS. Multiple aspects need to be addressed to solve this issue. Mixed LUTS are addressed with a combination of α_1-blocker and muscarinic antagonists. This combination therapy is more effective in improving storage LUTS and quality of life than α_1-blocker monotherapy [71].

Men complaining of mixed storage and voiding LUTS could benefit from a combination of α_1-blockers and muscarinic antagonists [72]. The combination treatment is efficacious in reducing urgency, urgency incontinence, voiding frequency and/or nocturia episodes. Persistent LUTS during α1-blocker monotherapy can be reduced by the additional use of a muscarinic antagonist, especially when detrusor overactivity is demonstrated [73].

In men with mixed LUTS (storage & voiding) and erectile dysfunction, a combination of phosphodiesterase 5 inhibitors (PDE5Is) and α_1-blockers have been found to significantly improve IPSS, International Index of Erectile Function (IIEF) score and Q_{max} as compared to α_1-blocker monotherapy [56]. A schematic diagram of combination therapy according to patient phenotype is shown in Fig. 4.

4.5. Technological advances in surgical treatment of BPO

TURP has been the gold standard surgical management of BPO. Its aim is to remove the bulky obstructing prostatic tissue and allow improved urinary flow. A modification of the monopolar (glycine) TURP is the bi-polar TURP which has a major advantage in allowing resection to be performed using normal saline, thus avoiding the development of the devastating TUR syndrome (cardiac and cerebral dysfunction from fluid shifts due to glycine irrigant absorption)

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Behavioral and dietary modifications	
LUTS addressed	**Action**
Frequency & Nocturia	Reduction of fluid intake at specific times of bothersome
Urgency	Bladder re-training i.e. holding on when sensory urgency arises
Frequency, Urgency & Nocturia	Reviewing medications and optimizing administration times e.g. diuretics
Frequency, Urgency & Nocturia	Avoid intake of bladder irritants e.g. caffeine & alcohol
Poor flow	Implication of relaxed voiding techniques
Sensation of incomplete bladder emptying	Double voiding technique
Post void dribble	Urethral milking

Fig. 4. Behavioral and dietary modifications.

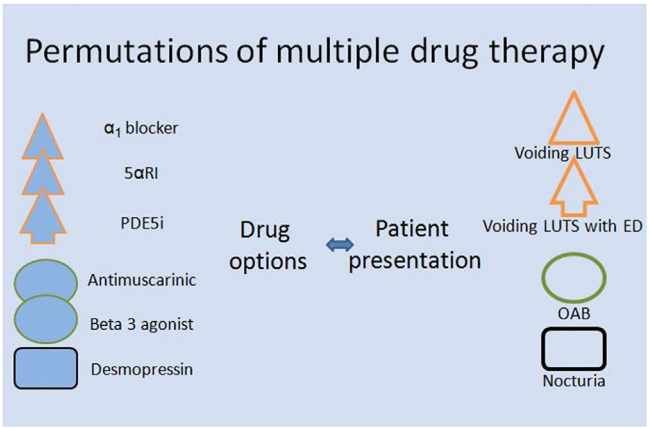

Fig. 5. Choice of combination drug therapy according to patient phenotype.

[74]. As regards to complications following TURP, these can be divided into short and long term complications. Short term complications include; bleeding, clot retention, acute urine retention, TUR syndrome and UTIs. Long term complications could entail; urine incontinence, UTIs, retrograde ejaculation, erectile dysfunction, urethral stricture and bladder neck stricture [75]. TURP has been the reference standard in treatment of BPO owing to the durable long term results in the form of an improvement in the mean Qmax (−162%), a significant decline in IPSS (−70%), QoL score (−69%) and PVR (−77%). The overall incidence of a secondary TURP was 2.9%, 5.8%, 7.4% at 1, 5 and 8 years of follow up [76].

Alternatives to TURP are transurethral incision of the prostate (TUIP), transurethral microwave therapy (TUMT), transurethral needle ablation of the prostate (TUNA) and open prostatectomy.

TUIP involves incision of the bladder neck without tissue removal. This is reserved for use in young, sexually active men with prostate volumes <30 ml without a median lobe. Data from RCTs comparing TURP and TUIP found similar improvements in LUTS in the short and long term but significantly lower improvements in Qmax in the TUIP group. However, TUIP had superior results in the need for blood transfusion and retrograde ejaculation outcome [77]. TUMT works by destroying tissue using microwave radiation. Data showed that TUMT was less effective than TURP in reducing LUTS. Symptom score after TUMT decreased by 65% in 12 months, compared to 77% after TURP. TURP achieved a greater Qmax improvement (119% vs. 70%). As regards to TUMT morbidities, catheterisation time, dysuria/urgency and urinary retention rates were significantly less with TURP. Hospitalization time, haematuria, clot retention, transfusion, TUR syndrome, and urethral stricture rates were significantly less for TUMT [78]. TUNA induces coagulative necrosis in the transition zone of the prostate using needles inserted transurethrally. TUNA significantly improved IPSS and Qmax, but compared to TURP these improvements were significantly lower at 12 months. TUNA has a significantly higher re-treatment rate compared with TURP. TUNA is associated with fewer adverse events compared to TURP, including mild haematuria, urinary infections, strictures, incontinence, ED, and ejaculation disorders [79]. Open prostatectomy is the oldest surgical technique for treatment of BPO. Nowadays, it is reserved for large prostates (>80–100 ml) (Fig. 5).

Over the years, novel therapies have developed. The use of laser has been widely utilized in the surgery of BPO. Several types of laser has been used for cystoscopic prostate surgery, including; holmium laser (HOLEP), diode laser and the thulium laser. Generally speaking, the available laser treatments have comparable results to TURP as regards to functional outcome and improvement in patient based questionnaires [80–82]. Treatment requires a shorter hospital stay, shorter catheterization time and a decreased incidence of blood transfusion and clot retention [83]. Laser-based options may allow operations to take place in anesthetically high risk, patients even when on anticoagulants [84]. However, laser treatment of prostatic obstruction is currently more expensive, has a significantly longer operative time and a higher learning curve. Laser-based approaches are still being evolved, as surgical methods and technical advances continue to evolve.

The most recent surgical treatment is the prostatic urethral lift (PUL). The concept of the PUL relies on compression of the obstructing lateral lobes of the prostate by using permanent suture based implants that are deployed cystoscopically under local or general anesthesia. This results in opening of the prostatic urethra, leaving a channel for voiding without disrupting the bladder neck [85]. Results of an RCT is available comparing the results of PUL to TURP, with a relatively short follow up of 12 months. The results of this study showed superior outcome in favor of TURP as regards to improvement in IPSS, quality of life, Q_{max} and PVR [86]. This is a technique that still needs more RCTs, but preliminary results indicate faster post-operative recovery [87].

5. Conclusion

In order to achieve a better patient outcome, identification and recognition of the broad basis of symptoms (voiding LUTS, storage LUTS, nocturia and psychological) is essential. Real-life patients typical manifest a mixture of LUTS - thus a rational, stepwise approach to decision-making and treatment is required, based on selection of therapy aimed at the bothersome symptoms present. Combination therapies are appropriate. Surgical interventions continue to evolve, and options are now available that can be offered to patients with significant co-morbidity.

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Author contribution

Haitham Abdelmoteleb: manuscript writing, collecting of research material.

Edward R. Jefferies: editing.

Marcus J. Drake: final editing and originally invited to write the review article.

Conflicts of interest

None.

Guarantor

Haitham Abdelmoteleb.
Edward R. Jefferies.
Marcus J. Drake.

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