



Review Article

Precision medicine in the diagnosis and treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia

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Submission : 11-May-2019
Revision : 11-Jun-2019
Acceptance : 26-Jun-2019
Web Publication : 21-Aug-2019

ABSTRACT

Male lower urinary tract symptoms (LUTSs) are highly prevalent in men and the incidence increases with aging. The pathophysiology of male LUTSs might be bladder outlet dysfunctions such as bladder neck (BN) dysfunction, benign prostatic obstruction, and poor relaxation of external sphincter and bladder dysfunctions such as detrusor overactivity (DO), detrusor underactivity, DO, and inadequate contractility. Male LUTSs include voiding and storage symptoms, and precision diagnosis should not be done based on the symptoms alone. Videourodynamic study provides a thorough look at the bladder and bladder outlet and can clearly demonstrate the underlying pathophysiology when the initial medication fails to relieve LUTS. Medical treatment should be given based on the underlying pathophysiology of LUTS, and surgical intervention to remove prostate should only be performed when a definite bladder outlet obstruction due to prostatic obstruction has been confirmed by invasive urodynamic study.

KEYWORDS: *Benign prostatic hyperplasia, Bladder outlet obstruction, Lower urinary tract symptoms, Overactive bladder, Voiding dysfunction*

MALE LOWER URINARY TRACT SYMPTOMS

Male lower urinary tract symptoms (LUTSs) include storage, voiding, and postvoid symptoms. Previously, male LUTS had been considered as a synonym of benign prostatic hyperplasia (BPH). However, nowadays, the scope of male LUTS has involved both bladder and bladder outlet dysfunctions. The storage symptoms include frequent urination, urgency, urgency incontinence, nocturia, and bladder pain at a full bladder. The voiding symptoms include hesitancy, slow stream, intermittency, dysuria, residual urine sensation, and urinary retention. The postvoid symptoms include terminal dribble and terminal dysuria. Patients might complain of several kinds of LUTSs in these three categories. The International Prostate Symptom Score (IPSS) has been widely applied to assess the severity of male LUTS, with the score of ≤ 7 , 8–20, and ≥ 21 , indicating mild, moderate, and severe LUTS, respectively [1].

Although LUTS is highly prevalent in men and the incidence increases with aging [2], it has been estimated that only 25%–50% of men with BPH have clinically significant LUTS, while bladder outlet obstruction (BOO) proven by urodynamics is noted only in 50% of men with LUTS [3]. Since 30 years ago, LUTS has been demonstrated to have a poor diagnostic specificity for male BOO [4]. Part of the patients with LUTS suggestive of BPH does not actually

improve their symptoms after transurethral resection of the prostate (TURP) [5].

In a recent study investigating the bladder and bladder outlet dysfunctions, which contributes to the pathophysiology of male LUTS, bladder outlet dysfunction was noted in 64.9% whereas bladder dysfunction was noted in 30.7% [6] [Table 1]. The bladder outlet dysfunctions included BOO with detrusor overactivity (DO) (33.8%), BOO without DO (14.8%), and poor relaxation of the urethral sphincter (PRES, 16.3%). The incidence of these bladder and bladder outlet dysfunctions varied with ages. In an earlier study, among 1407 male patients with LUTS, BOO due to BPH (BPO) comprised 29.4% and DO was noted in 51.5% of men. The incidence of BPO and DO increases with age, whereas PRES contributed to LUTS in 45.3% of patients younger than 55 years [7]. Detrusor underactivity (DU) and DO with detrusor hyperactivity and inadequate contractility (DHIC) also increased in patients with older age.

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How to cite this article: Chen JL, Jiang YH, Lee CL, Kuo HC. Precision medicine in the diagnosis and treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Tzu Chi Med 2020;32(1):5-13.

Access this article online

Quick Response Code:



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DOI: 10.4103/tcmj.tcmj_107_19

Table 1: The distribution of bladder and bladder outlet dysfunction in the pathophysiology of male lower urinary tract symptoms [6]

Pathophysiology	Percentage
Normal bladder and outlet function	131 (4.4)
Bladder dysfunction	919 (30.7)
DU	153 (5.1)
DO and inadequate contractility	159 (5.3)
DO (DO, without BOO)	508 (17.0)
HSB	99 (3.3)
Bladder outlet dysfunction	1941 (64.9)
Bladder outlet obstruction with DO	1011 (33.8)
Bladder outlet obstruction without DO	443 (14.8)
Poor relaxation of urethral sphincter	487 (16.3)
Total	2991 (100)

DO: Detrusor overactivity, DU: Detrusor underactivity, BOO: Bladder outlet obstruction, HSB: Hypersensitive bladder

ALGORITHM FOR DIAGNOSIS OF LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA BASED ON VOIDING AND STORAGE SUBSCORE RATIO

Because male LUTS is composed by the storage and voiding symptoms, patients with LUTS might have storage or voiding-predominant symptoms. The total LUTS assessed by the IPSS might not reflect the true underlying pathophysiology of male LUTS. If we can use the ratio of voiding to storage symptom score (V/S ratio) to evaluate the bladder outlet dysfunction or bladder dysfunction, we might be able to prescribe the initial medication for patients according to the predominant LUTS. In a retrospective analysis of the video urodynamic findings in a cohort of male LUTS, we found that IPSS-V/S ratio ≥ 1 was a good indicator to separate the male LUTS into voiding lower urinary tract dysfunction (LUTD) or not [8].

Both EAU and AUA guidelines recommend that evaluating the symptom severity with a symptom score is an important part of the assessment of male LUTS [9,10]. Measuring IPSS-S and IPSS-V subscore separately and using IPSS-V/S ratio can help differentiate bladder and bladder outlet dysfunction [8]. An IPSS-V/S < 1.0 was noted in 80% of patients with bladder-related LUTD and IPSS-V/S ≥ 1.0 in 76% of patients with bladder outlet-related LUTD, including BPO, BND, and non-BPH voiding dysfunction [8]. The area under the receiver operating characteristic curve was 0.81 (confidence interval [CI]: 0.75–0.87) for IPSS-V/S ≥ 1 , with a sensitivity of 8.2% and specificity of 69.3% to predict voiding LUTD [8]. Initial medication using doxazosin to treat male patients with IPSS-V/S ≥ 1 and tolterodine to treat IPSS-V/S < 1 yielded a satisfactory rate of 80% [11]. The treatment outcome based on this V/S ratio was effective and safe, except that elderly people (≥ 70 years) and patients with a maximum flow rate (Q_{max}) of < 10 mL/s were more likely to have increased postvoid residual (PVR) [11].

In analysis of IPSS-V/S, we also found that the higher total IPSS, the higher incidence of IPSS-V/S ≥ 1 was. IPSS-V/S ≥ 1

was noted in 18.6%, 54.9%, and 71.1% of patients with a total IPSS score of ≤ 7 , between 8 and 19, and ≥ 20 , respectively, suggesting that the higher total IPSS score is, the more incidence of voiding LUTD may exist [12]. Based on this concept, treating male LUTS with severe LUTS (IPSS total score ≥ 20) with antimuscarinics can only be successful in 33.3% of patients with V/S < 1 , while treating patients with V/S ≥ 1 can be successful in 50% of patients, suggesting patients with severe LUTS might not be adequately treated by monotherapy [13]. Because male LUTS involves both voiding and storage components, tailoring medication for voiding or storage LUTS according to the changes of IPSS-V/S ratio might be necessary and could improve patients' satisfaction. In patients who were not satisfied with the initial medication for 1 month based on the IPSS-V/S ratio (alpha-blocker for V/S > 1 or OAB medication for V/S < 1), we may add or switch to another class medication to improve their LUTS. This customized medication program based on the subjective IPSS-V/S ratio presentation can provide satisfactory outcomes for men with mild-to-moderate LUTS [14].

DIAGNOSIS OF BLADDER OUTLET OBSTRUCTION IN MALE LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

In general, BOO contributes to two-thirds of male LUTS. The other part of the patients with LUTS might have DO alone (16.7%), hypersensitive bladder (3.3%) DU (5.2%), DHIC (5.3%), or even normal lower urinary tract function (4.6%). Diagnosis of BOO due to anatomical or functional LUTD is important because the treatment targeting at the BPH is only effective when patients' LUTS is resulting from BPH.

LUTS alone is difficult to differentiate male LUTS due to BPH obstruction or non-BPH [15]. In the old days, cystoscopy and intravenous pyelography to directly observe the prostatic hypertrophy obstructing the urethra or an elevated bladder base by the intravesical prostatic protrusion (IPP) can provide evidence for the LUTS suggestive of BPH. Later on, direct measurement of the total prostatic volume (TPV), transition zone index (TZI), and presence of IPP also provide strong evidence that an enlarged prostate might contribute to LUTS. The mean TPV and TZI of patients with BOO are significantly greater than that in patients with non-BPH [15]. Further studies revealed that patients with LUTS/BPH and a Q_{max} of < 10 mL/s have a greater improvement in Q_{max} after TURP compared with those with a $Q_{max} > 10$ mL/s [16]. Patients without urodynamic evidence of BOO might have a poor surgical outcome after TURP [16]. Patients with persistent LUTS after TURP were found to have a small TPV at the time of surgery, suggesting that a non-BPH etiology might account for their LUTS [17].

In order to precisely differentiate LUTS due to BPH or non-BPH, Kuo proposed a clinical prostate score in patients with LUTS/BPH [18]. The parameters that have a positive prediction of LUTS due to BPH were scored +1 ($Q_{max} \leq 10$ mL/s, compressive flow pattern, TPV > 20 and < 40 mL, voided volume < 250 mL, and TZI > 0.3 but 0.5) or +2 (constrictive flow pattern, intermittent flow pattern, TPV ≥ 40 mL,

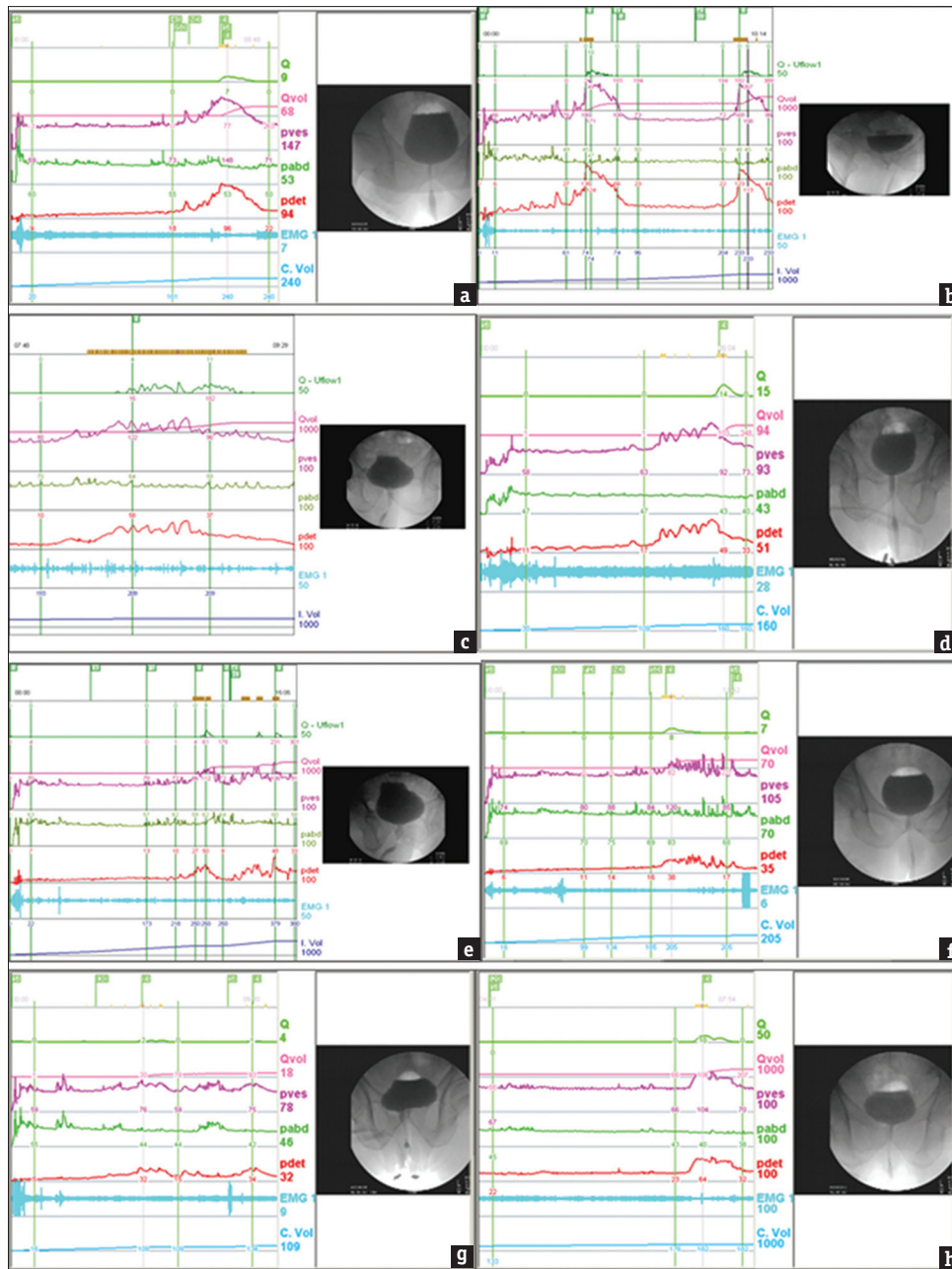


Figure 1: The videourodynamic differentiation of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia. (a) Bladder neck dysfunction, (b) benign prostatic obstruction, (c) poor relaxation of external sphincter, (d) dysfunctional voiding in patients with neurogenic lower urinary tract dysfunction, (e) detrusor overactivity without bladder outlet obstruction, (f) detrusor underactivity, (g) detrusor overactivity and impaired detrusor contractility, (h) hypersensitive bladder without bladder outlet obstruction

PVR ≥ 100 mL, TZI ≥ 0.5 , and presence of IPP), whereas those have a negative prediction have a-1 ($Q_{max} \geq 15$ mL/s, normal flow pattern, and TZI ≤ 0.3) or 0 point. The sensitivity and specificity of BPO diagnosis in patients with at least one favorable predictive factor by total score ≥ 3 were 91.6% and 87.3%, respectively. Although a larger TPV indicates higher incidence of BPO in male LUTS, patients with LUTS and BOO might also result from BN dysfunction (BND), especially in the patients with a TPV < 40 mL. According to an analysis of videourodynamic study of male LUTS, BND and PRES are the other causes for male LUTS in patients with small TPV [19] [Table 2].

DIFFERENTIAL DIAGNOSIS OF BPO, BND, AND PRES IN MALE LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA BY PRESSURE FLOW STUDY AND VIDEOURODYNAMICS

For precise diagnosis of voiding-predominant male LUTS, a pressure flow study to demonstrate the presence of BOO is important. Pressure flow study provides valuable information on detrusor function and impaired contractility in patients with or without BOO [20]. Griffiths developed a pressure flow plot that demonstrates the relationship between voiding Pdet

Table 2: The distribution of lower urinary tract dysfunction in men with lower urinary tract symptoms by total prostate volume [19]

TPV (mL)	Bladder outlet dysfunction				Bladder dysfunction					Total
	BND (243)	BPO (317)	PRES (116)	Total (676)	DO (177)	HSB (25)	DU (38)	DHIC (55)	Total (295)	
≤30	114 (42.5)	75 (28.0)	79 (29.5)	268	98 (61.3)	17 (10.6)	17 (10.6)	28 (17.5)	160	428
31-40	59 (51.8)	36 (31.6)	19 (16.7)	114	41 (66.1)	5 (8.1)	8 (12.9)	8 (12.9)	62	176
41-60	50 (32.5)	94 (61.0)	10 (6.5)	154	32 (65.3)	2 (4.1)	5 (10.2)	10 (20.4)	49	203
≥61	20 (14.3)	112 (80.0)	8 (5.7)	140	6 (25.0)	1 (4.2)	8 (33.3)	9 (37.5)	24	164

BND: Bladder neck dysfunction, BPO: Benign prostatic obstruction, DHIC: Detrusor overactivity and inadequate contractility, DO: Detrusor overactivity, DU: Detrusor underactivity, HSB: Hypersensitive bladder, PRES: Poor relaxation of external sphincter, TPV: Total prostate volume

and Q_{max} , and hence the Abrams–Griffiths (AG) number was widely adapted for demonstration of BOO (AG number >40) or non-BOO (AG number <20) [21]. The pressure flow relationship can also be plotted to demonstrate the continuous change throughout the voiding phase, and we can get a linear curve for the urethral resistance relation [22]. Schafer also proposed the prostatic obstruction nomogram that further inserts the factor of detrusor contractility into the pressure flow plot [23]. Based on these nomograms, we can roughly differentiate male LUTS into BOO and non-BOO by the urodynamic pressure flow study using the parameters of Q_{max} and Pdet at Q_{max} . However, the pressure flow study still cannot differentiate BPH, BND, PRES, or urethral stricture in male LUTS suggestive of BOO. Under this consideration, video urodynamic study plays an important role of precision diagnosis of male LUTS/BPH [24].

A recent study investigating the underlying LUTD in male LUTS with storage symptoms after medical treatment revealed that BND and BPO comprised 62.4% of men with persistent storage LUTS after initial medical treatment for LUTS/BPH [24]. The VUDS study can clearly differentiate the LUTD of male LUTS by the Pdet, Q_{max} , and the narrow part of the BN, prostate urethra, and external sphincter in the voiding cystourethrography. In male patients with LUTS/BPH which does not satisfactorily respond to medical treatment based on the initial diagnosis, videourodynamic study can be used to identify the underlying vesicourethral dysfunctions, such as BND, BPO, PRES, dysfunctional voiding, DO without BOO, DU, DHIC, and hypersensitive bladder [Figure 1a-h]. With clear demonstration of the obstructive site of the bladder outlet, surgical intervention should be performed at the precise obstructive site, but not targeting solely at the prostate. In the International Consultation of Incontinence report in 2016, the committee recommended that pressure flow study or videourodynamic study should be performed before invasive procedure is planning to treat male LUTS/BPH [25].

ROLE OF BLADDER NECK DYSFUNCTION AND POOR RELAXATION OF EXTERNAL SPHINCTER IN MALE LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

In men younger than 50 years old with voiding LUTS, BND had been reported in 54%, PRES in 24%, and a low detrusor contractility in the remaining patients [26]. Our previous study also showed that BND and PRES are more common in patients younger than 70 years and having a TPV <40 mL [27]. Among various causes of male LUTS due

to non-BPH, PRES is the most frequently encountered LUTD in young men [7].

During normal voiding, detrusor contraction starts following the urethral sphincter relaxation and BN funneling, which are innervated by the sympathetic nervous system [28]. Alpha-adrenergic nerves are postulated to keep the bladder outlet (BN and urethra) closed and inhibit the parasympathetic activation of the detrusor muscle during bladder filling phase, whereas beta-adrenergic nerves relax the detrusor muscle and make the bladder in stable condition [29]. The adrenergic nerves release norepinephrine which exerts an inhibitory effect on detrusor function [30]. Sympathetic activity can be affected by the environment or body conditions which not only increase bladder outlet resistance but also inhibit the detrusor contractility [29]. Increased sympathetic tone has been speculated as a possible cause to inhibit the detrusor contractility in the neuropathic patients with low detrusor contractility or chronic urinary retention. Increased detrusor pressure after transurethral incision of the BN (TUI-BN) was noted in some high-level spinal cord injury patients with low voiding pressure at baseline [31].

LUTS in nonobstructive men can result from an underactive detrusor, DO, PRES, or a combination of these conditions [26,27]. The causes for PRES might be learned habit, chronic prostatitis, pelvic floor hypertonicity, occult neuropathy, or increased bladder sensitivity. The PRES symptoms in men have great impact on the quality of life, especially in the young aged population [32]. Patients with PRES tend to be younger and had a small TPV, low voiding pressure, and less incidence of urodynamic DO [26]. Because patients with PRES might not satisfactorily respond to alpha-1 blocker therapy, they could be mistakenly diagnosed as clinical BPO and undergo TURP, resulting in unpredictable complication or even exacerbated LUTS.

DETRUSOR UNDERACTIVITY AND TREATMENT STRATEGY IN MALE LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

In elderly patients with chronic medical diseases such as diabetes mellitus and congestive heart failure or neurological diseases such as cerebrovascular accident, Parkinson's disease, or dementia, chronic urinary retention due to underactive bladder (UAB) is frequently encountered and difficult to manage [33]. Patients with UAB usually have a diminished bladder fullness or urgency sensation and cannot have sustained detrusor contraction, resulting in complete bladder emptying. Therefore, patients with UAB usually void with

abdominal straining and an intermittent flow pattern with large PVR is noted. The bladder sensation in patients with UAB may be normal or reduced in sensing the first bladder sensation; therefore, UAB patients usually void insufficiently because they cannot perceive the bladder fullness [34].

The etiology of UAB could be due to true DU, central or peripheral neuropathy, or prolonged BOO. According to a recent study, two-thirds of the patients with DHIC have a small TPV (<40 mL) and low Q_{max} (<12 mL/s), while 1/3 of patients have a larger TPV and low Q_{max} [19]. Identification of BOO in patients with DU should be cautious because the prostatic urethra usually will not open when the detrusor contractility is not adequate and sustained. In patients who cannot be actually proven to have BOO, medical treatment or clean intermittent catheterization should be the first management priority to facilitate efficient voiding rather than surgical intervention, especially when patients have overt neurological lesion.

INITIAL TREATMENT FOR MALE LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

In patients with LUTS/BPH, the alpha-blocker and 5-alpha-reductase inhibitors (5ARIs) are effective treatment for men with BOO due to BPH. Patients with non-BPH voiding dysfunctions such as BND or PRES can also benefit from alpha-blocker with or without skeletal muscle relaxant. However, these agents might not be effective treatment for the storage symptoms [35]. Treatment of LUTS/BPH can start from low-dose alpha-blocker. After 8 weeks treatment with 0.2 mg tamsulosin, 63.4% of patients were satisfied with the treatment results. The treatment satisfaction was affected by the symptom duration, baseline IPSS severity, and prostate volume [36]. When the LUTS improved after 24 weeks of treatment with alpha-blocker (alfuzosin), the medication could be discontinued in 40.85% of patients. Among them, 57.1% did not need to resume medication. The discontinuation group showed a smaller TPV (mean, 28.7 mL) than readministration group (mean, 32.2 mL) [37].

Combined alpha-blocker and 5ARIs to treat patients with LUTS/BPH and an enlarged BPH has been well documented [38]. The rates of BPH progression and the need for surgical intervention are significantly reduced after 4-year combination treatment. After combination treatment, only patients with a TPV >40 mL can benefit from reduction of TPV and prostatic-specific antigen (PSA) level, whereas patients with TPV <40 mL can only slightly decrease the TPV [39]. In patients with a small BPH and bothersome LUTS, alpha-blocker monotherapy is adequate. The AUA guidelines on the management of BPH also recommended that 5ARIs are not appropriate treatment for men with LUTS who do not have evidence of prostatic enlargement. The combination of an alpha-adrenergic receptor blocker and a 5ARI is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement [10]. 5ARI had also been recommended to treat patients without bothersome LUTS but having an enlarged prostate and high PSA

level [40]. The SMART study also revealed that patients with severe LUTS/BPH (baseline IPSS total score >20), discontinuing alpha-blocker from combination medication resulted in symptom exacerbation and need to return to combined 5ARI and alpha-blocker therapy [41]. The progression of LUTS/BPH after discontinuing 5ARI resulted in increase of TPV and occurrence of acute urinary retention leading to TURP. Patients with a larger TPV (mean 45.9 mL) and larger TZI (mean 0.43) tended to have LUTS/BPH progression and resume combination medication [42].

OAB TREATMENT IN MALE LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

LUTSs in men >50 years of age are highly prevalent and that storage LUTSs are frequently reported. Patients with mild and moderate LUTS of 81.4% and 45.1% have storage-predominant LUTS (IPSS-V/S ≤ 1), respectively [12]. In male patients with BPO, that OAB wet symptoms are associated with urodynamic DO [7]. Urinary incontinence may be due to detrusor dysfunction without or with BOO. The guidelines suggest that the initial treatment for male LUTS can be based on the predominant symptoms, without urodynamic testing [25]. When the initial management fails to resolve the LUTS, UDS is highly recommended, especially in the elderly patients with urinary incontinence. DO and urethral sphincter dysfunctions such as BND or PRES should also be considered in young men with LUTS or men with a small prostate [26]. In men with LUTS/BPH, UDS or videourodynamic study can differentiate different bladder dysfunctions (DO, DU, and DHIC) and bladder outlet dysfunction (BND, dysfunctional voiding, and BPO) [24].

Antimuscarinic or anticholinergic agents are the first-line treatment for patients with OAB [43]. When the storage symptoms persist after medical treatment for LUTS/BPH, adding antimuscarinics can effectively improve the LUTS in 75% of patients [35]. If patients with LUTS are treated based on the IPSS-V/S ratio, 75% of bladder-related condition (IPSS-V/S ≤ 1) and 80% of urethral-related condition (IPSS-V/S >1) reported an improved outcome after medical treatment with antimuscarinic agent and alpha-blocker, respectively [11]. Clinical studies have shown that antimuscarinic therapy alone or in combination with alpha1-receptor antagonists improve OAB symptoms in men with and without BOO [44]. The current guidelines also suggest that antimuscarinic monotherapy can be used for men without BOO while combination therapy is usually suggested for men with concomitant BOO and OAB [45,46]. However, in clinical practice, antimuscarinics is usually reserved as the second-line medication in men with OAB because of fearing of the risk of precipitating urinary retention.

In fact, first-line antimuscarinic monotherapy is safe and effective for men with enlarged prostate and predominant storage symptoms. Smaller TPV, higher Q_{max} , and greater IPSS-S subscore are predictors of successful first-line antimuscarinic monotherapy [47]. Because the persistent storage symptoms in men with LUTS/BPH usually result from

undertreated BOO, patients with BOO have less improvement of IPSS storage subscore, overactive bladder symptom score (OABSS), and patient's perception of Inedvus urgency score (PPIUS) than those without BOO [48]. In patients with BOO and OAB and after alpha-blocker therapy, combined antimuscarinic and alpha-blocker treatment is generally more effective than monotherapy or placebo in unimproved male LUTS [35,49].

In elderly men with BPH and OAB, combined alpha-blocker and antimuscarinics has also been proved safe and effective to improve LUTS in short term without increasing the risks of increased PVR and urinary retention [50,51]. Recently, beta-3 adrenoceptor agonist, mirabegron, has been widely used to treat male LUTS and OAB. Because mirabegron does not reduce detrusor contractility during voiding, mirabegron has been recommended as the first-line therapy for patients with OAB due to BOO, considering the safety of mirabegron treatment on male BOO [52]. Phase IV randomized, placebo controlled, multicentric clinical trial further confirmed that daily 50 mg dose of mirabegron for 12 weeks reduced OAB symptoms in men, and there was no significant adverse events compared to the placebo group [53]. In older patients with OAB and multiple comorbidities, mirabegron 25 mg once daily has also been reported safe and effective treatment [54]. However, the improvement of storage LUTS was less in patients with BOO and the rates of adverse events were higher [48].

CONCERNS IN DIAGNOSIS AND TREATMENT OF LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

In making decision of the diagnosis and treatment for male LUTS/BPH, the following questions should be considered: (1) Is the patient with LUTS obstructed? (2) Are the LUTS caused by an enlarged prostate? (3) Are we treating BPH or LUTS? (4) Can the managements targeting BPH reduce LUTS? (5) What are the appropriate tools to diagnose an obstructed BPH? and (6) Should patients with LUTS be adequately treated before diagnosis as BOO? The ICI recommendations of male LUTS/BPH reported in 2016 suggested that UDS is a valuable investigation tool in differential diagnosis of male LUTS/BPH, especially in elderly men with urinary incontinence or young men with LUTS not responding to treatment based on clinical examination [25]. Because invasive UDS test is the only test to distinguish between BOO and bladder dysfunctions such as DO or DU and can change decision-making in the management of male LUTS, invasive UDS should be considered when invasive surgery is planned to performed for men with complex LUTS.

Although TURP to relieve prostatic obstruction is the gold standard surgery for male LUTS due to enlarged BPH, TUI of the prostate might be sufficient to restore voiding function and preserve ejaculatory function in young patients with small BPH. Regardless of the surgical procedure for male LUTS/BPH, improvement of uroflow and LUTS after TURP was

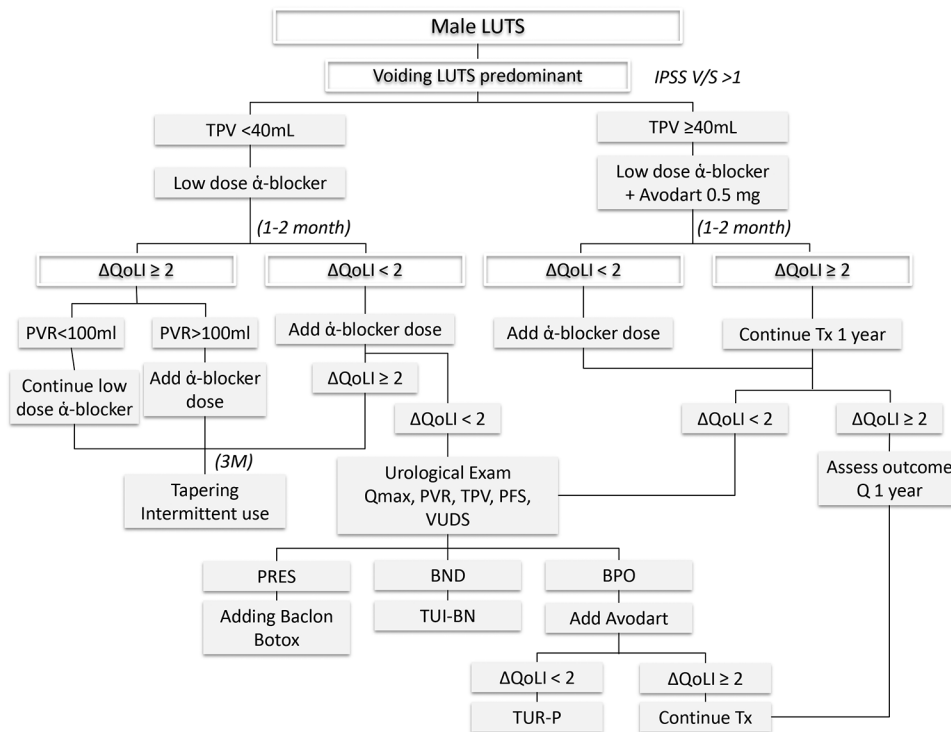


Figure 2: The algorithm for the treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia with voiding symptoms predominant. α-blocker: Alpha-blocker, BND: Bladder neck dysfunction, BPO: Benign prostatic obstruction, IPSS-V/S: International prostate symptom score voiding-to-storage ratio, LUTSs: Lower urinary tract symptoms, PFS: Pressure flow rate study, PVR: Postvoid residual urine, Q_{max}: Maximum flow rate, QoLI: Quality of life index, TPV: Total prostate volume, TUI-BN: Transurethral incision of the bladder neck, TURP: Transurethral resection of the prostate, Tx: Treatment

only noted in male LUTS proven to have low Q_{max} and high pressure obstruction [16].

There has been no consensus regarding the most optimal timing for surgical intervention for LUTS/BPH. Progression of voiding or storage symptom after long-term medical treatment, occurrence of complications, and patients' will are all indications for surgical intervention for LUTS/BPH [55]. Nevertheless, accurate diagnosis and identifying the cause of male LUTS is paramount importance and can help improve quality of treatment. Therefore, urodynamic pressure flow study or videourodynamic study is considered mandatory in the male patients with mild or moderate severity of LUTS who desire to surgery [56].

Whether patients with UAB and LUTS/BPH can benefit from TURP remains undetermined. Because the pathophysiology of UAB and chronic urinary retention might involve neurogenic, myogenic, or bladder outlet etiologies, the presence of an enlarged BPH might not be the main cause of LUTS [33]. Patients with chronic urinary retention might not regain voiding efficiency after TURP. Interestingly, TUI-BN or TURP to ablate urethral smooth muscle not only disrupts the continuity of the tight BN but also might abolish the inhibitory effect on the detrusor contractility [31]. In patients with an acontractile bladder, 78.9% of them had significant return of detrusor contractility after laser enucleation of the prostate [57]. After TUI-BN, part of the patients had been observed to have recovery of detrusor contractility after the surgical procedure [58]. Recent urodynamic study also revealed that Pdet and bladder contractility index improved after TURP or TUIP in men with DU and chronic retention, suggesting that relief of BOO can restore detrusor contractility possibly through the ablation of sympathetic inhibition on the detrusor contractility [59].

PRECISION MEDICINE IN DIAGNOSIS AND MANAGEMENT OF MALE LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

Based on the above paragraphs, the rational algorithm of the diagnosis and treatment of male LUTS/BPH can be postulate. A diagnostic algorithm for LUTS/BPH based on evidence-based medicine may aid in determining the therapeutic strategy [40]. In the initial assessment, the history, questionnaire such as IPSS, OABSS or PPIUS, digital rectal examination, uroflowmetry and PVR provide information for the diagnosis of BPO and non-BPO. Based on the IPSS-V/S ratio, OAB medication can be prescribed for IPSS-V/S ≤ 1 , whereas short-term and low-dose alpha-blockers can be used for patients with LUTS/BPH and IPSS-VS > 1 for 2–4 weeks [36,60]. Recent studies also confirmed that a fixed dose of alpha-blocker is also safe and effective in improving male LUTS, with acceptable adverse events [10,11,35,45,46]. If patients do not respond to initial treatment, measurement of the TPV and PSA should be done and 5ARIs such as dutasteride or finasteride can be added in the presence of an enlarged prostate (TPV > 40 mL) [61,62]. If patients do not respond to the combination therapy for 6 months, a voiding diary (for nocturnal polyuria), pressure flow study (for DO or

DU), or videourodynamic study (to confirm the presence of BPO and BND or PRES) should be carried out to investigate the possible diagnosis other than BPO. Cystoscopy may be an additional procedure to diagnose urethral stricture, bladder stones, or other urethral lesions. Surgical intervention for BPH should be considered only when a diagnosis of BPO has been clearly established and the medical treatment cannot relieve the bothersome LUTS [Figure 2].

CONCLUSION

BPH and BOO is the cause in only 30% of male patients with LUTS. Men with older age and larger TPV are usually associated with higher rate of BOO based on videourodynamic analysis. Long-term medical treatment with 5ARI and alpha-blocker is effective in reducing TPV and LUTS in men with LUTS/BPH. Baseline large BPH (TPV > 40 mL) usually indicates a higher success rate in improvement of LUTS/BPH by 5ARI. Discontinuing 5ARI in patients with larger TPV (> 45 mL) might fail and resuming 5ARI is necessary. For patients with persistent OAB after medical treatment for LUTS/BPH, BOO should be considered and adding OAB medication may improve LUTS, although the presence of BOO might have less therapeutic effect. After medical treatment for LUTS/BPH, UDS or videourodynamic study is mandatory to find out underlying bladder or bladder outlet dysfunction for patients who do not have a satisfactory treatment outcome. If medical treatment fails, TURP is always the best treatment of choice for male LUTS/BPH proven to have BOO.

Financial support and sponsorship

Nil.

Conflicts of interest

There is no conflict of interest.

REFERENCES

1. Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The measurement committee of the American Urological Association. *J Urol* 1992;148:1549-57.
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87:760-6.
3. Eckhardt MD, van Venrooij GE, Boon TA. Symptoms, prostate volume, and urodynamic findings in elderly male volunteers without and with LUTS and in patients with LUTS suggestive of benign prostatic hyperplasia. *Urology* 2001;58:966-71.
4. Neal DE, Ramsden PD, Sharples L, Smith A, Powell PH, Styles RA. Outcome of elective prostatectomy. *BMJ* 1989;299:762-7.
5. Liu Z, Li YW, Wu WR, Lu Q. Long-term clinical efficacy and safety profile of transurethral resection of prostate versus plasmakinetic resection of the prostate for benign prostatic hyperplasia. *Urology* 2017;103:198-203.
6. Jiang YH, Liao CH, Kuo HC. Role of bladder dysfunction in men with lower urinary tract symptoms refractory to alpha-blocker therapy: A video-urodynamic analysis. *Low Urin Tract Symptoms* 2018;10:32-7.
7. Kuo HC. Videourodynamic analysis of pathophysiology of men with both storage and voiding lower urinary tract symptoms. *Urology* 2007;70:272-6.
8. Liao CH, Chung SD, Kuo HC. Diagnostic value of international prostate symptom score voiding-to-storage subscore ratio in male lower urinary

- tract symptoms. *Int J Clin Pract* 2011;65:552-8.
9. de la Rosette JJ, Alivizatos G, Madersbacher S, Perachino M, Thomas D, Desgrandchamps F, et al. EAU guidelines on benign prostatic hyperplasia (BPH). *Eur Urol* 2001;40:256-63.
 10. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J Urol* 2003;170:530-47.
 11. Liao CH, Lin VC, Chung SD, Kuo HC. Therapeutic effect of α -blockers and antimuscarinics in male lower urinary tract symptoms based on the international prostate symptom score subscore ratio. *Int J Clin Pract* 2012;66:139-45.
 12. Jiang YH, Lin VC, Liao CH, Kuo HC. International prostatic symptom score-voiding/storage subscore ratio in association with total prostatic volume and maximum flow rate is diagnostic of bladder outlet-related lower urinary tract dysfunction in men with lower urinary tract symptoms. *PLoS One* 2013;8:e59176.
 13. Jhang JF, Liao CH, Kuo HC. Severity of lower urinary tract symptoms reflects different composition of bladder storage dysfunction and bladder outlet obstruction in men with symptomatic benign prostatic hyperplasia. *Int J Clin Pract* 2014;68:743-8.
 14. Lee CL, Kuo HC. Tailoring medication for lower urinary tract symptoms in men based on international prostate symptom score voiding to storage ratio. *Urology* 2018;120:30-5.
 15. Chen JL, Kuo HC. Implications of prostatic volume measurements on the degree of bladder outlet obstruction in men with benign prostatic hyperplasia and lower urinary tract symptoms. *JUTA* 2006;17:41-7.
 16. Kuo HC, Tsai TC. Assessment of prostatic obstruction and bladder function by urodynamic pressure flow study. *Taiwan Yi Xue Hui Za Zhi* 1987;86:1084-92.
 17. Kuo HC. Analysis of the pathophysiology of lower urinary tract symptoms in patients after prostatectomy. *Urol Int* 2002;68:99-104.
 18. Kuo HC. Clinical prostate score for diagnosis of bladder outlet obstruction by prostate measurements and uroflowmetry. *Urology* 1999;54:90-6.
 19. Lee CL, Kuo HC. Videourodynamic analysis in men with lower urinary tract symptoms: Correlation between age and prostate size with lower urinary tract dysfunction. *Urol Sci* 2016;27:21-5.
 20. Jiang YH, Kuo HC. Recent research on the role of urodynamic study in the diagnosis and treatment of male lower urinary tract symptoms and urinary incontinence. *Ci Ji Yi Xue Za Zhi* 2017;29:72-8.
 21. Griffiths D, Höfner K, van Mastrigt R, Rollema HJ, Spångberg A, Gleason D. Standardization of terminology of lower urinary tract function: Pressure-flow studies of voiding, urethral resistance, and urethral obstruction. International continence society subcommittee on standardization of terminology of pressure-flow studies. *Neurourol Urodyn* 1997;16:1-8.
 22. Lim CS, Abrams P. The Abrams-Griffiths nomogram. *World J Urol* 1995;13:34-9.
 23. Schäfer W. Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: From complex to simple. *World J Urol* 1995;13:47-58.
 24. Jiang YH, Wang CC, Kuo HC. Videourodynamic findings of lower urinary tract dysfunctions in men with persistent storage lower urinary tract symptoms after medical treatment. *PLoS One* 2018;13:e0190704.
 25. Kaplan SA, Ikeguchi EF, Santarosa RP, D'Alisera PM, Hendricks J, Te AE, et al. Etiology of voiding dysfunction in men less than 50 years of age. *Urology* 1996;47:836-9.
 26. Ke QS, Jiang YH, Kuo HC. Role of bladder neck and urethral sphincter dysfunction in men with persistent bothersome lower urinary tract symptoms after α -1 blocker treatment. *Low Urin Tract Symptoms* 2015;7:143-8.
 27. Rosier PF, Kuo HC, De Gennaro M, Gammie A, Finazzi Agro E, Kakizaki H, et al. International consultation on incontinence 2016; executive summary: Urodynamic testing. *Neurourol Urodyn* 2019;38:545-52.
 28. Tanagho EA, Miller ER. Initiation of voiding. *Br J Urol* 1970;42:175-83.
 29. Andersson KE, Arner A. Urinary bladder contraction and relaxation: Physiology and pathophysiology. *Physiol Rev* 2004;84:935-86.
 30. Mattiasson A, Andersson KE, Elbadawi A, Morgan E, Sjögren C. Interaction between adrenergic and cholinergic nerve terminals in the urinary bladder of rabbit, cat and man. *J Urol* 1987;137:1017-9.
 31. Ke QS, Kuo HC. Transurethral incision of the bladder neck to treat bladder neck dysfunction and voiding dysfunction in patients with high-level spinal cord injuries. *Neurourol Urodyn* 2010;29:748-52.
 32. Wang CC, Yang SS, Chen YT, Hsieh JH. Videourodynamic identifies the causes of young men with lower urinary tract symptoms and low uroflow. *Eur Urol* 2003;43:386-90.
 33. Andersson KE. The many faces of impaired bladder emptying. *Curr Opin Urol* 2014;24:363-9.
 34. Smith PP. Aging and the underactive detrusor: A failure of activity or activation? *Neurourol Urodyn* 2010;29:408-12.
 35. Lee JY, Kim HW, Lee SJ, Koh JS, Suh HJ, Chancellor MB. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int* 2004;94:817-20.
 36. Kim JH, Park JY, Oh MM, Lee JG, Kwon SS, Bae JH. Treatment satisfaction with low-dose tamsulosin for symptomatic benign prostatic hyperplasia: Results from a multicentre cross-sectional survey. *Int J Clin Pract* 2012;66:1209-15.
 37. Chung JH, Lee JY, Kang DH, Jo JK, Lee JW, Lee SH, et al. Evaluation of patient outcome after discontinuation of alfuzosin treatment for benign prostatic hyperplasia: A multicentre, prospective study. *Int J Clin Pract* 2013;67:870-5.
 38. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr., Dixon CM, Kusek JW, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2387-98.
 39. Lin VC, Liao CH, Wang CC, Kuo HC. 5α -Reductase inhibitor is less effective in men with small prostate volume and low serum prostatic specific antigen level. *J Formos Med Assoc* 2015;114:865-71.
 40. Artibani W. Integrating the patient risk profile in the management of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). *Eur Urol Suppl* 2004;3:1-6.
 41. Barkin J, Guimarães M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5α -reductase inhibitor dutasteride. *Eur Urol* 2003;44:461-6.
 42. Lin VC, Liao CH, Kuo HC. Progression of lower urinary tract symptoms after discontinuation of 1 medication from 2-year combined alpha-blocker and 5-alpha-reductase inhibitor therapy for benign prostatic hyperplasia in men – A randomized multicenter study. *Urology* 2014;83:416-21.
 43. Andersson KE. Antimuscarinics for treatment of overactive bladder. *Lancet Neurol* 2004;3:46-53.
 44. Lee SH, Chung BH, Kim SJ, Kim JH, Kim JC, Lee JY. Initial combined treatment with anticholinergics and α -blockers for men with lower urinary tract symptoms related to BPH and overactive bladder: A prospective, randomized, multi-center, double-blind, placebo-controlled study. *Prostate Cancer Prostatic Dis* 2011;14:320-5.
 45. Kaplan SA, Roehrborn CG, Gong J, Sun F, Guan Z. Add-on fesoterodine for residual storage symptoms suggestive of overactive bladder in men receiving α -blocker treatment for lower urinary tract symptoms. *BJU Int* 2012;109:1831-40.
 46. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011;185:1793-803.
 47. Liao CH, Kuo YC, Kuo HC. Predictors of successful first-line

- antimuscarinic monotherapy in men with enlarged prostate and predominant storage symptoms. *Urology* 2013;81:1030-3.
48. Liao CH, Kuo HC. Mirabegron 25mg monotherapy is safe but less effective in male patients with overactive bladder and bladder outlet obstruction. *Urology* 2018;117:115-9.
 49. Kaplan SA, Roehrborn CG, Chancellor M, Carlsson M, Bavendam T, Guan Z. Extended-release tolterodine with or without tamsulosin in men with lower urinary tract symptoms and overactive bladder: Effects on urinary symptoms assessed by the international prostate symptom score. *BJU Int* 2008;102:1133-9.
 50. Kaplan SA, Roehrborn CG, Abrams P, Chapple CR, Bavendam T, Guan Z. Antimuscarinics for treatment of storage lower urinary tract symptoms in men: A systematic review. *Int J Clin Pract* 2011;65:487-507.
 51. Chung SD, Chang HC, Chiu B, Liao CH, Kuo HC. The efficacy of additive tolterodine extended release for 1-year in older men with storage symptoms and clinical benign prostatic hyperplasia. *Neurourol Urodyn* 2011;30:568-71.
 52. Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE. Urodynamics and safety of the β_3 -adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. *J Urol* 2013;190:1320-7.
 53. Shin DG, Kim HW, Yoon SJ, Song SH, Kim YH, Lee YG, et al. Mirabegron as a treatment for overactive bladder symptoms in men (MIRACLE study): Efficacy and safety results from a multicenter, randomized, double-blind, placebo-controlled, parallel comparison phase IV study. *Neurourol Urodyn* 2019;38:295-304.
 54. Lee YK, Kuo HC. Safety and therapeutic efficacy of mirabegron 25 mg in older patients with overactive bladder and multiple comorbidities. *Geriatr Gerontol Int* 2018;18:1330-3.
 55. Ferretti M, Phillips J. Prostatectomy for benign prostate disease: Open, laparoscopic and robotic techniques. *Can J Urol* 2015;22 (Suppl 1):60-6.
 56. El-Zawahry A, Alanee S, Malan-Elzawahry A. The use of urodynamics assessment before the surgical treatment of BPH. *Curr Urol Rep* 2016;17:73.
 57. Mitchell CR, Mynderse LA, Lightner DJ, Husmann DA, Krambeck AE. Efficacy of holmium laser enucleation of the prostate in patients with non-neurogenic impaired bladder contractility: Results of a prospective trial. *Urology* 2014;83:428-32.
 58. Jhang JF, Jiang YH, Kuo HC. Transurethral incision of the bladder neck improves voiding efficiency in female patients with detrusor underactivity. *Int Urogynecol J* 2014;25:671-6.
 59. Lee KH, Kuo HC. Recovery of voiding efficiency and bladder function in male patients with non-neurogenic detrusor underactivity after transurethral bladder outlet surgery. *Urology* 2019;123:235-41.
 60. Lepor H, Nieder A, Feser J, O'Connell C, Dixon C. Effect of terazosin on prostatism in men with normal and abnormal peak urinary flow rates. *Urology* 1997;49:476-80.
 61. Kaplan SA, Roehrborn CG, McConnell JD, Meehan AG, Surynawanshi S, Lee JY. Long-term treatment with finasteride results in a clinically significant reduction in total prostate volume compared to placebo over the full range of baseline prostate sizes in men enrolled in the MTOPS trial. *J Urol* 2008;180:1030-2.
 62. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, Nandy I, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the combAT study. *Eur Urol* 2010;57:123-31.