

Comparison of ICUD, AUA and EAU Treatment Guidelines for Male LUTS/BPH

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ABSTRACT

Benign prostate hyperplasia (BPH) or obstruction (BPO) is a common disorder among aging males. However, there are also 67% men experiencing symptoms of both overactive bladder and BPH together. This overlap causes major diagnostic difficulties in daily practice. In fact, different cultures may have an impact on how one approaches and conceptualizes diagnostic strategy. For example, the PSA policy in the AUA guidelines may be not the same as that of the EAU, ICUD or even the consensus from the TUA treatment guideline committee. Moreover, some basic examinations are regarded as optional by some and as recommended tests by others. There is no conclusive answer to that issue so far, but we are offering here a prototype diagnosis and treatment approaching algorithm as a reference for all, which we hope will contribute to discussions that might lead to greater consensus. *Key words:* Guideline, LUTS, BPH, OAB

INTRODUCTION

Benign prostate hyperplasia (BPH) or obstruction (BPO) is a common disorder among aging males, occurring in 19%-30% of men over age 59, and is therefore a significant contributor to the daily practice of urologists and primary-care physicians [1,2]. Lower urinary tract symptoms suggestive of benign prostate hyperplasia (LUTS/BPH) must be understood by urologists, general practitioners and some associated internal physicians. A voiding dysfunction may be caused by neurogenic bladder, pathology of the bladder detrusor muscles and the bladder outlet, either anatomical or functional entities, overactive bladder (OAB), and by BPH. All of them may present their symptoms as a LUTS. How to approach such a patient to make a differential diagnosis is a challenge for all physicians. 67% of men experience symptoms of both OAB and BPH [3,4]. This large proportion of overlap is the key issue for making a differential diagnosis of LUTS/BPH. In fact, the accuracy of treatment is out of our expectations. From a presentation at ICS in 2005 regarding a total of 4,806 patients with OAB and BPH, only 8% of patients received both treatments. Conversely, 11% of 12,192 patients who had OAB alone received the accurate treatment [5]. The rest received inadequate treatment or no at all. What causes this discrepancy in diagnosis and treatment? Since storage symptoms of LUTS, such as frequency, urgency, nocturia and urge incontinence, are the same as the definition of OAB, we cannot omit the issues relating to

OAB when considering the guidelines for male LUTS/BPH [6]. Accurate differentiation of OAB and LUTS/BPH is very important for deciding treatment strategy. We have to pay more attention to current available diagnostic and treatment guidelines. We reviewed and compared the guidelines for male lower urinary tract symptoms (LUTS) in the European Association of Urology (EAU), the American Urological Association (AUA) and International Consultation of Urologic Disease (ICUD) [7-11]. Diagnosis and treatment algorithms were proposed in the AUA and ICUD guidelines. However, the EAU did not propose a similar algorithm in its guideline. The purpose of this mini report is to raise concerns relating to these differences and to help us understand these guidelines, which may prove useful for creating a consensus on the issue of male LUTS/BPH.

THE CROSS RELATIONSHIPS BETWEEN LUTS, BPH AND OAB

The EPIC study observed a 61.3% prevalence of LUTS in men over 18 years old [3]. The most bothersome problems are storage symptoms, like OAB, which affect about 49.7% of the population [3]. Prostatic hyperplasia may cause bladder outlet obstruction as well as secondary responses in the detrusor muscle, such as smooth muscle cell proliferation and contractility [12]. Eventually, LUTS may develop. Other factors such as polyuria, the effects of aging, primary bladder disease, neurogenic disease and non-BPH bladder outlet obstruction may cause LUTS as well. Bladder outlet obstruction can induce ischemic changes in detrusor muscle and expression of nerve growth factor, which causes a series of changes, including super-sensitivity to acetylcholine, instability of membrane action potential, altered intracellular Ca^{2+} regulation and hypertrophy of afferent and efferent neurons. Finally, the spinal micturition reflex is re-organized and the Na^+ channel altered to induce the detrusor overactivity presenting in urodynamics. The clinical presentation is therefore similar to the overactive bladder. This may be associated with nerve growth factor triggering bladder overactivity [13]. In other words, LUTS may involve problems of bladder outlet obstruction and detrusor overactivity or OAB simultaneously. These facts tell us that although LUTS/BPH is different from OAB, the latter is an important issue to differentiate and has its significance in the diagnosis and treatment algorithm for LUTS/BPH.

DIFFERING APPROACHES TO DIAGNOSIS: EAU, AUA AND ICUD GUIDELINES

Diagnostic tests are classified as recommended, optional or not recommended in all guidelines discussed here. Recommended tests/techniques include histories, quantification of symptoms, physical examination including a digital rectal exam, urinalysis, the PSA test and

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frequency-volume charts for patients with nocturia. Maximal flow rate recordings (Qmax) and post void residual (PVR) urine measurements are listed as optional tests in the AUA guidelines, but are recommended in the EAU guidelines [7-10]. It is clear, however, that not every physician and health care provider engaged in the evaluation and treatment of LUTS/BPH can have uroflowmetry and ultrasound at hand to record Qmax and PVR. Furthermore, the measurement of PVR through insertion of a catheter is considered too invasive in exchange for the diagnostic information gained. However, the Committees of the EAU and the ICUD recommended a urinary flow rate measurement during the initial diagnostic assessment, as well as during or after treatment, to determine the response to treatment [7-9,11]. A low maximum urinary flow rate does not allow one to distinguish between obstruction and decreased bladder contractility. PVR can really help physicians avoid pharmacotherapy-induced urine retention. To assure validity, patients should have voiding volume of more than 150 mL for a physician to make an interpretation of the uroflow rate. Our previously unpublished data reveal that 45.3% (29/64) of patients' medications needed to be changed after measurement of Qmax and PVR. The changes are significant if the PVR is more than 80 mL ($p < 0.0001$) and the empty score of I-PSS (International Prostate Symptom Score) > 15 ($p = 0.0512$). In other words, Qmax and PVR may be very important for physicians when writing prescriptions. Using both measurements, we can treat patients suspected of having simultaneous BPH and OAB earlier and can avoid urine retention due to antimuscarinics. In a study of 796 French urologists, 59.6% of urologists prescribed medication on the first visit [14]. That means if they do not understand voiding efficiency and PVR, they may jeopardize the patient, putting him at higher risk of urine retention, especially if the OAB is combined with BPH.

Frequency volume charts are another test recommended in the EAU and ICUD guidelines, but are not discussed as well in the AUA guidelines. In addition to the EAU and ICUD guidelines, nocturia and assessment of risk factor are also important items in the BAUS diagnostic algorithm [15]. I would like to recommend this test during the initial investigation. This is because patients complaining about nocturia may have nocturnal polyuria, global polyuria or decreased nocturnal functional bladder capacity. A physician can make a differential diagnosis based on a mathematical analysis of the 24-hour voiding diary [16].

The prostate specific antigen (PSA) is an issue that needs to be discussed. In the AUA guidelines, measurement of PSA should be offered to the following patients: (1) those with at least a 10-year life expectancy and for whom knowledge of the presence of prostate cancer would change clinical management, or (2) those PSA measurement might change the management of their voiding symptoms [10]. In actuality, various factors (cancer, BPH, infection, trauma and age) may influence serum PSA levels, in addition to prostate volume. The higher the PSA level, the greater is the probability of having prostate cancer. PSA levels may predict the natural history of BPH [7]. In past years, a routine PSA test was recommended as a first-line test for men with LUTS and BPH. However, the Consensus Committee of the AUA proposed that serum PSA measurement should be recommended only if the patient has an anticipated life expectancy over 10 years and, specifically, when establishing a diagnosis of prostate cancer would change current treatment [11]. The benefits and risks of PSA testing include the possibility of all positive and negative test results and possible complications subsequent to trans-rectal prostate biopsy. In

actuality, the policy may make little difference for many countries and peoples. For example, a routine PSA check is now included in the treatment guidelines identified by the consensus committee for the TUA. Members of the board regard routine PSA testing as a preferred approach for two reasons. First, PSA testing is not expensive as in Western countries; second, members worry about future unforeseen legal problems if they do not check PSA levels, which could raise physicians' suspicions of prostate cancer. This is not a matter of a 10-year life expectancy. This is an issue for physicians who might fail to notice an existing problem. For this reason, the 10-year life expectancy criterion will not be an indication for a PSA test in the future BPH treatment guidelines of the TUA. Another minor revision is the serum creatinine measurement, which is likewise no longer recommended for the initial evaluation in the AUA guidelines.

The ideal guidelines should be based on strategic approaches when confronting a patient with LUTS/BPH. The AUA guidelines provide an excellent step-by-step approach to diagnosis and treatment of patients with LUTS/BPH (Fig. 1) [10]. However, the guidelines do not consider the common issue of overactive bladder combined with BPH. On the contrary, this issue is addressed well in the ICUD treatment guidelines' algorithm (Fig. 2) [11]. Excellent guidelines for diagnosis and treatment should be very clear and capable of addressing such important issues relating to laboratory tests, differential diagnosis, and final treatment options (Fig. 3). In actuality, there are more than six commonly used sets of guidelines for diagnosis and treatment of LUTS/BPH. The question of comparing these guidelines was raised by Dr. Novara G, et al [17]. In addition to the history, all these guidelines also recommend physical examination, digital rectal exam and urinalysis, and the symptom score. Apart from the controversial issues above, investigations listed by the guidelines as optional include pressure flow studies, cysto-urethrosopy, prostate ultrasound and upper urinary tract imaging.

DIFFERENCES BETWEEN EAU, AUA AND ICUD GUIDELINES REGARDING TREATMENT OPTIONS

The medical treatment of LUTS/BPH may be handled differently according to whether it is a dynamic or static problem. Four alpha 1-adrenoceptor antagonists including Alfuzosin, Doxazosin, Tamsulosin and Terazosin are recommended for dynamic problems. They can relax the smooth muscle tone of the bladder neck and prostate. They have almost equal clinical benefits, although trivial differences, especially among adverse, effects can be found among them. The α -blockers may have a 30%-40% effect on improvement of symptom scores, and may increase maximal flow rate by 16%-25% [18]. However, there is insufficient evidence to recommend Prazosin and nonselective α -blockers such as Phenoxybenzamine for patients. The 5- α reductase inhibitors (5-ARIs) including Finasteride (type-2) and Dutasteride (type 1 and 2 subtypes) reveal basically the same effectiveness for static prostate problems. They can effectively reduce symptom scores up to 3.7 to 4.5 points, increase Qmax by 1.3 to 2.2 mL/sec and significantly shrink the prostate volume by up to 25%-26% [18]. It is clear that combination therapy with 5-ARIs and α -blockers may obtain a better response in IPSS, uroflow rate, less acute urine retention and the necessity of surgery than any single treatment [19,20]. Another important benefit of 5-ARIs is that they can be used to treat hematuria associated with BPH, which is clearly mentioned in these three

guidelines [7,10,11].

In addition to treatment with 5-ARIs and/or α -blockers, simultaneous therapy with anti-muscarinics is not discussed in either the EAU or AUA guidelines. In contrast, OAB receives clear consideration in the 5th ICUD consensus in the treatment algorithm for BPH [11]. At present, the use of anti-cholinergics as primary therapy for LUTS/BPH or in combination with α -blockers, cannot be recommended for routine use in the absence of an adequate base of published evidence according to one 2004 review [18]. However, a study from Korea showed that an additional three months of combination therapies using Doxazosin (4 mg Qd) and Detrusitol (2 mg Bid) may confer additional effectiveness up to 37.5% vs. 73.5% for patients with BPH only,

in contrast to patients with BPH combined with detrusor overactivity (clinical OAB) who failed to respond to three-month mono-therapy with Doxazosin (4 mg Qd) [21]. Combination therapies with α -blockers and anti-muscarinics for selected patients with OAB and BPH may be safe and produce a very low incidence (<1%) of urine retention [22]. The treatment of OAB in patients with LUTS/BPH should not be treated separately since the problems may be mixed together with considerable overlap in clinical presentation. Therefore, all guidelines for LUTS/BPH should cover issues relating to OAB, as the ICUD guidelines do.

A selected therapy should be adopted through a shared decision-making process involving providers and patients, especially when surgery is not clearly imperative. Antibiotics are recommended for

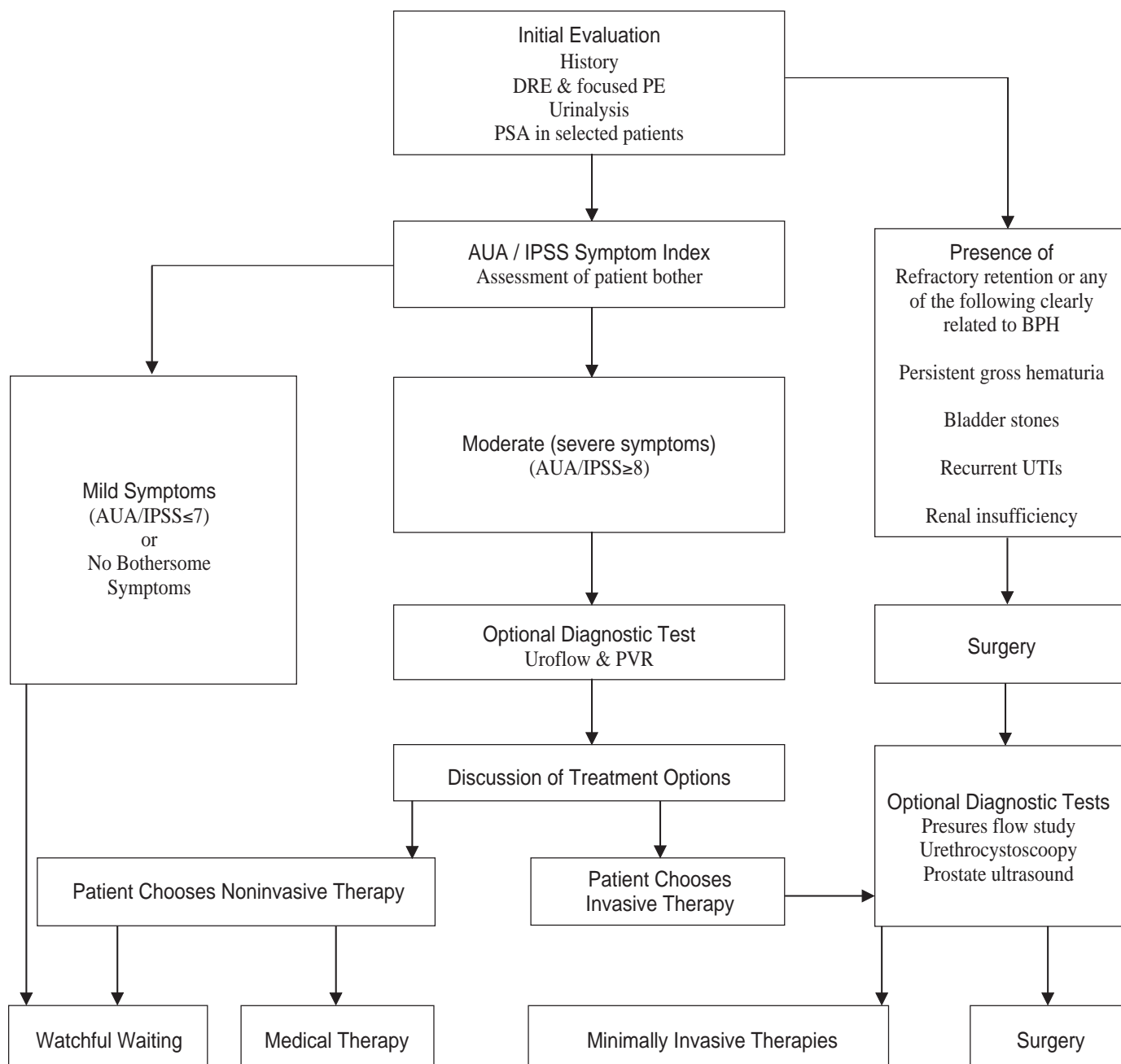


Fig. 1. AUA guidelines for LUTS/BPH.

patients who are catheterized prior to surgery, in addition to those known to have a urinary tract infection before the operation. Minimally invasive treatments show little difference when compared to each other. The choices include Prostatron®, transurethral needle ablation (TUNA), UroLume endo-prosthetic stent, and water-induced thermotherapy including transurethral microwave therapy (TUMT). However, the use of prostate ethanol or Botulinum toxin injections and high-intensity focused ultrasound (HIFU) are not recommended any longer by these treatment guidelines.

The transurethral resection/incision of prostate (TUR-P/TUIP) is still the operation of choice for BPH. Surgical prostatectomy (open, TURP, TUIP, TUVP) results in significant subjective and objective improvement superior to medical or minimally invasive treatments. All four surgical procedures have been evaluated in randomized controlled trials. For a man with a prostate less than 30 mL in size with absence of a middle lobe, TUIP is the therapy of choice [23]. Four kinds of laser are mentioned in the EAU guidelines including Nd:YAG, Hol:YAG, KTP:YAG and diode lasers. Visual laser ablation of the prostate (VLAP) and interstitial laser coagulation (ILC) uses the Nd:YAG laser. Laser prostatectomy is indicated for those receiving anticoagulant medication or unfit for TURP and who want to maintain ejaculatory ability (side-fire or ILC). The green light KTP and an emerging Thulium Continuous Wave vapor resection (RevoLix®) are now available. The latter possesses soft

tissue cutting characteristics like a CO₂ laser and produces coagulation as efficiently as the Nd:YAG laser. These are minimally invasive surgeries which are gradually increasing in popularity. However, it is too early to draw conclusions.

Phytotherapy is an emerging therapy mentioned in the AUA treatment guidelines. The mode of action of phytotherapeutic agents is unknown. The biological effects are unclear, although a few randomized clinical trials show encouraging results. Phytotherapeutic agents and other dietary supplements cannot be recommended for treatment of BPH at this time by the AUA guidelines however, they have been popular in Europe for many years. These agents are composed of various plant extracts and it is always difficult to identify their major biological activity. Some randomized trials and meta-analyses show clinical efficacy without major side effects for compounds such as Pygeum africanum and Serenoa repens, which seem to be equivalent to Finasteride and α -blockers [7]. However, there are several problems with these preparations. First, production is generally not controlled by health authorities in various countries, but rather, they are sold as food supplements. Second, issues of purity, content declaration, and batch-to-batch and lot-to-lot variability are addressed poorly if at all. Before composition, extraction methods and the mechanism of action of these phytotherapeutic agents are identified or a clear pathophysiological rationale and mechanism of action for them understood, phytotherapy

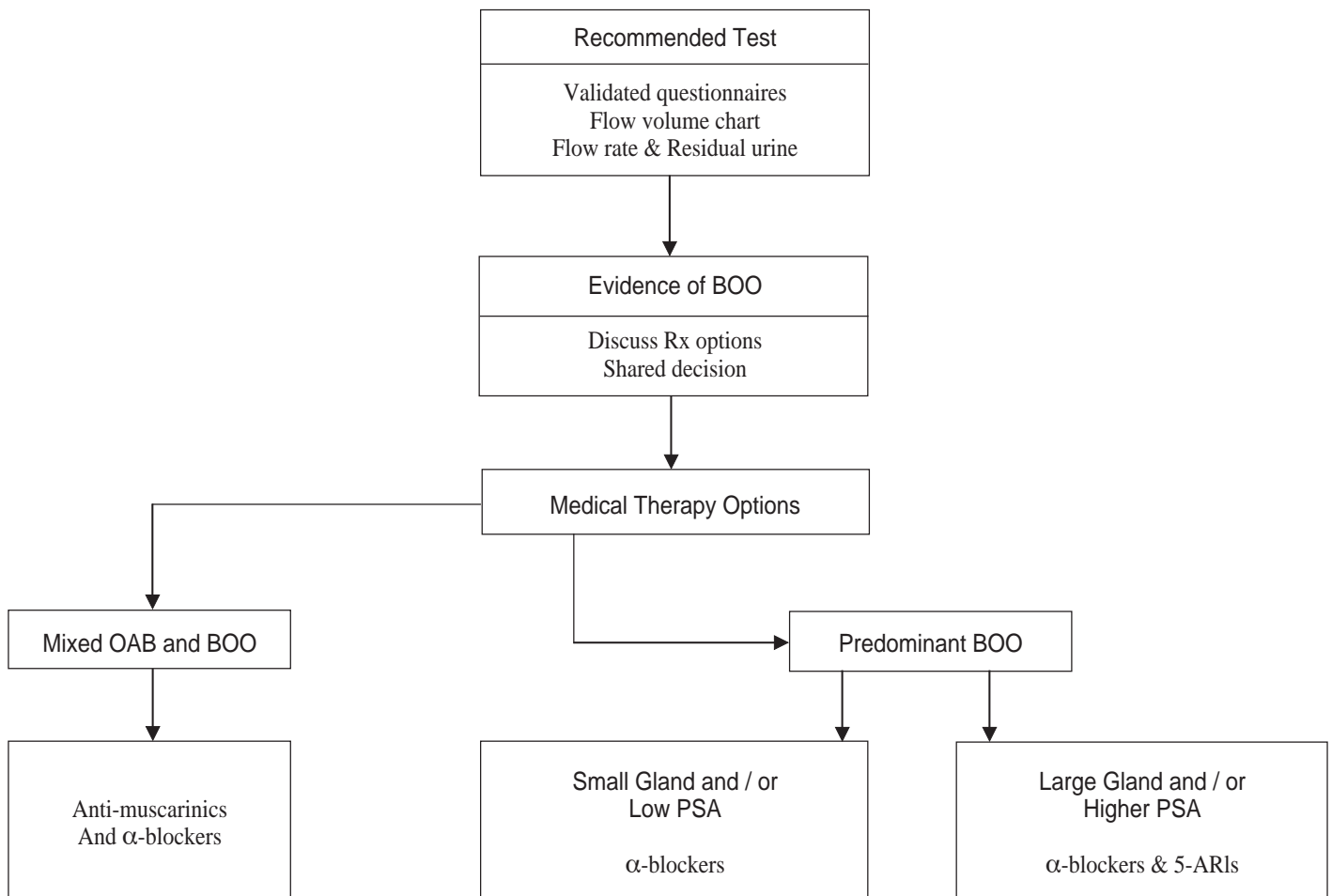


Fig. 2. ICUD recommended LUTS/BPH approaching algorithm.

can not be included in the treatment guidelines.

CONCLUSION

Though there are several diagnosis and treatment guidelines identified in the literature, not one is perfect. Basically, guidelines offer a comparison for medical quality, standard requirements for clinical practice and a reference for decision-making as to what to do or what not to

do. In the past, we focused on LUTS/BPH and did not take OAB into consideration for diagnosis and treatment. It is time for us to think about how to set up guidelines on the topic of LUTS inclusive of OAB and/or BPH, since diagnosis and treatment of these conditions involve a very high proportion of symptomatic overlapping. Our proto-type diagnosis and treatment algorithm is proposed in Fig. 3. This algorithm can be reviewed and revised in the future as a consensus emerges. The consensus may consist of an opinion from the TCS, since BPH treatment

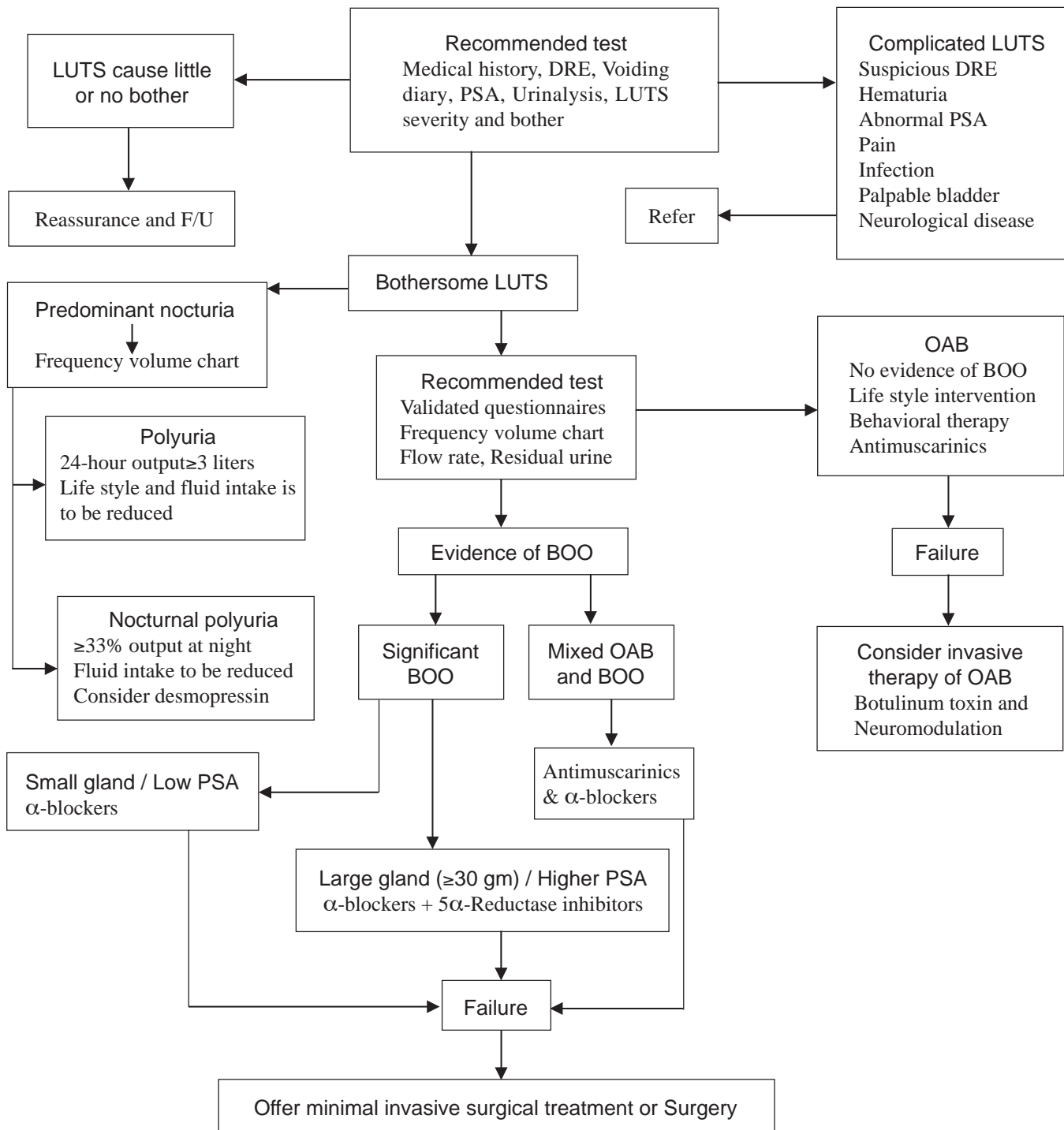


Fig. 3. TCS Proto-type basic approaching algorithm for LUTS/BPH.

guidelines of the Taiwanese Urological Association have been constructed based solely on the AUA treatment guidelines. We expect some stimulating interaction from both sides, the TCS and TUA.

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