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REVIEW

A practical algorithm management of patients with benign prostatic hyperplasia

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Abstract: Benign prostatic hyperplasia (BPH) is a progressive disorder and a common occurrence in aging men, characterized by increased risk of acute urinary retention (AUR) and which may eventually require surgery due to enlargement of the prostate. The treatment of BPH is a choice between no treatment (watch-and-wait scenario), various surgical procedures, and pharmacotherapy in the majority of cases (>80%). Pharmacotherapy of BPH is based on two concepts, i.e. firstly, that alpha–adrenergic blockade reduces smooth muscle tone in the prostate and bladder neck, and secondly that 5 alpha–reductase inhibition causes atrophy of prostate epithelium. Studies have shown that both classes of drugs used as monotherapy produced improvements in patients symptoms. Combination therapy of those drugs is most appropriate in men who are symptomatic, are at high risk of progression of enlarged of prostate (EP), and produced improvements in patients with BPH (relief of voiding symptoms, improvement in urinary flow and quality of life). Surgical treatment should be considered for patients with progressive disease and complications of BPH, and who present worsening of symptoms not adequately controlled by medical therapy. This article discusses diagnosis and treatment strategies for BPH and proposes a practical algorithm for treatment based on available literature data and the author's clinical experience.

Key words: benign prostatic hyperplasia, urinary outflow obstruction, enlargement of the prostate, alpha1-adrenoreceptor blocker, 5 alpha-reductase inhibitor, combination therapy, surgical treatment

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common disorder in the aging male. It has been well established that age and hormones are important factors in the development of BPH. It is a progressive condition, characterized by on increased risk of acute urinary retention (AUR) and BPH related surgery [1]. BPH is associated with benign prostatic enlargement (BPE), benign prostatic obstruction (BPO), bladder dysfunction (BD), and lower urinary tract symptoms (LUTS). This disease is of heterogeneous etiology affecting patients suffering from a combination of BPE, BPO, BD and LUTS [2, 3]. LUTS caused by BPH can be extremely bothersome to patients and the relevant treatment is aimed at its reduction and improvement of the quality of life (QoL) [3, 4, 5]. The clinical or/and urodynamic manifestations of the disease are often attributed to sub-bladder obstruction. The bladder outlet obstruction secondary to BPH has a static (mechanical) component, related to the anatomical obstruction caused by the enlarged prostate, and a dynamic component related to the neutrally-controlled tone of prostatic smooth muscle. The diagnosis of BPH is based on microscopic, clinical or urodynamic criteria that implicate further treatment. The incidence of BPH increases with older age. Clinical manifestations of prostate enlargement range from various degrees of LUTS to AUR and renal failure. Clinically, BPH patients are usually identified by the LUTS (symptom assessment using score system like IPSS – International Prostate Symptom Score, or AUA-SI American Urological Association Symptom Index) and digital rectal examination (DRE), or by elevated prostate specific antigen (PSA) [3].

LUTS are not specific for BPH, and differential diagnoses are important, which may indicate other urologic and non-urologic conditions [6]. Physical examinations, urine analysis and subsequent serum PSA test are an important part of diagnostic procedure. Other important symptoms, such as refractory retention, persistent gross hematuria, bladder stones, abnormally high PSA levels, recurrent urinary tract infections (UTI) and renal insufficiency, may require more immediate management [3, 7, 8].

BPH is a progressive disorder. Progression indicators include increased LUTS and prostate size, AUR risk, bladder complications, hematuria and reduced rate of urinary flow. Prevention of AUR is needed for men with BPH with risk factors such as moderate to severe LUTS and poor urinary flow rates [1, 8, 9, 10]. There is a wide spectrum of treatment which may include the watch-and-wait strategy, and treatment focused primarily on symptom management with anticholinergics agents and alpha 1-adrenolitic, or plant extracts. As the next step, a pharmacological treatment could be considered that is based on alpha 1-adrenolitic and 5 alpha-reductase inhibition drugs, administered as monotherapy, and subsequently, in the case of disease progression, as a combined therapy. Worsening of symptoms, AUR and other complications should be considered for surgery [11]. This article discusses diagnosis and treatment strategies for BPH and proposes a practical algorithm of treatment based on available literature data and the author's clinical experience.

Analysis was based on data of BPH patients treated by the author in several centers. Various methods, either watch-and-wait, pharmacotherapy or surgical management were applied. The results of own clinical experience are dealt with, compared with literature data, and conclusions drawn.

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Table 1 provides a proposal of practical algorithm for treatment of BPH.

DISCUSSION

BPH is the most common disease in men ,and the age-dependent prevalence is remarkably similar in populations throughout the world. Aging and the function of the testes are the two prerequisites for the development of this disease. The molecular basis of BPH development is still poorly understood. BPH, at the histological level, refers to prostatic cellular proliferation which may be detected at the clinical level as prostatic enlargement on DRE or imaging studies. Prostatic enlargement may produce LUTS or evidence of physiological obstruction on urodynamic measurement. Although diagnostic and treatment recommendations are available for urologist, no guidelines have been specifically designed to guide primary care physicians. Clinically, patients are usually identified by the presence of LUTS, by prostate enlargement found on DRE, or by elevated PSA measurement during a routine examination. Because LUTS are not specific to BPH it is necessary to conduct differential diagnosis. LUTS may include other urologic and non-urologic conditions (obesity, medications that increase obstructive urinary symptoms, cigarette smoking, regular alcohol consumption, and elevated blood pressure) [3, 6]. Taking a careful medical history, symptom assessment with the help of IPSS or AUA-SI, physical examination, urinalysis and serum PSA are recommended diagnostic activities. About 10-20% (approx.) of patients with BPH suffer from hypertension and diabetes, and should be treated by a internal medicine specialist [3, 5, 11].

Depending on LUTS severity and size of prostate the treatment of BPH may include the watch-and-wait scenario, i.e. no treatment, but patient monitoring by a doctor, symptom management and lifestyle modifications [12]. Phytotherapeutic agents have shown that there is a place for their use, and in the opinion of the author they should be recommended because many plants are rich in phytosterols and their pharmacological activity is attributed to their flavonoid component [5]. Treatment is primarily focused on LUTS with anticholinergic (ANTCH) drugs or/and alpha 1-adrenergic (A-1-ADRN) blockers. Patients with urge incontinence resulting from an overactive bladder (OAB) must be treated with ANTCH (oxybutynin, solifenacin, tolterodine), and with obstructive symptoms – A-1-ADRN (especially patients with hypertension.: terazosin, doxazosin, alfuzosin or with hypotension: tamsulosin) that improve the rate of urinary flow. The A-1-ADRN drugs target smooth muscle receptors in the bladder neck and prostate by relaxing the muscle fibres (dynamic component), thereby making urination easier. These group of drugs are similarly efficacious (improving urinary flow rates up to 30%) but tolerability profiles may differ among agents (due to e.g. pharmacokinetics properties) [5, 13]. The majority of side effects are classified as minor or mild, and may include dizziness, fatigue, headache (which

Table 1 Practical management algorithm of patients with BPH associated with bothersome LUTS, age, volume of prostate (VP), progressive disease and co-existed illness.

Patient	Volume of Prostate (VP)	Management
LUTS slight (IPSS <7), good urination and without or scanty urostasis	VP < 30 ml	Wa-Wa; plants extracts and herbs (monitoring tests periodically)
LUTS mild (IPSS > ; slightly BOO; PSA <1,3 mg/ml)	VP < 31 ml	A-1-ADRN, (ex. doxazosin particularly doxazosin XL; alfuzosin, terazosin)
a) Normotension patient.		A-1-ADRN
b) Hypotension patient.		A-1-ADRN – (ex. tamsulosin, alfuzosin SR or UNO)
c) Hypertension patient.		A-1-ADRN (ex. doxazosin, alfuzosin, terazosin)
When domination vesical tenesmus (urgent) because OAB		ANTCH – (oksybutonin, tolterodine, solifenazyna)
When necessary, fast regression middle LUTS pt's with soft or medium hypertension and with other illness, e.g. hipercholesterolemia and/or insulin independent diabetes, and pt's without success therapy diuretic drugs or inhibitor ACE, beta-blockers and calcium canals antagonists	VP < 31 ml	A-1-ADRN – (ex. doxazosin, doxazosin XL, alfuzosin SR or UNO, terazosin)
When necessary, fast regression bothersome LUTS pt's with hypertension and normotension or effectively treated by cardiology drugs	VP < 31 ml	A-1-ADRN – (tamsulosin OCAS, or MR)
Slight LUTS, PSA<1,3 ng/ml, without other illness	VP > 31 ml	5-ARI –(ex. finasteride, dutasteride)
Burdensome and/or vesical tenesmus causing OAB	VP > 40 ml	5-ARI and A-1-ADRN as well as ANTCH
a) after recovery from severe LUTS, particularly when there is a relative risk of progression; notable EP; age > 70 years; IPSS > 14; PSA>2 ng /ml		5-ARI or continuation a combination therapy with A-1-ADRN
b) when considerably bothersome LUTS		Combination therapy 5-ARI with A-1-ADRN and ANTCH
When considerably bothersome LUTS, especially when vesical tenesmus a cause OAB	VP > 40 ml	Combination therapy A-1-ADRN with 5-ARI and ANTCH, possibly next step of A-1-ADRN and/or ANTCH
Pt's with bothersome LUTS, and age >70 years and relative risk progression	VP > 40 ml	Long term combination therapy A-1-ADRN and 5-ARI and ANTCH
When disease progression appears besides pharmacotherapy, and if PSA elevated, LUTS are severe step AUR, gross hematuria recurrence, UTI, urosepis	VP > 40 ml	For invasive therapy surgery (ablation; vaporization)

A-1-ADRN – alpha-1-adrenolitic**; ANTCH** – anticholinergic agents; **5-ARI** – 5-alpha-reductase inhibitors; **BPH** – benign prostatic hyperplasia; **BPO** – benign prostatic obstruction; **BOO** – bladder outflow obstruction; **EP** – enlarged prostate; **IPSS** – International Prostate Score System; **LUTS** – lower urinary tract symptom; **OAB** – overactive bladder; **VP** – volume of prostate; **Wa-Wa** – wait-and-watch; **UTI** – urinary tract infection; **ACE** – angiotensin convertase inhibitors; **MR** – Modified Release; **OCAS** – Oral Controlled Absorption System.

are often treated), orthostatic hypertension, and ejaculatory problems (tamsulosin). The A-1-ADRN show a rapid action and are likely to produce therapeutic results in many patients within weeks [5, 14, 15, 16]. The ANCTH and A-1-ADRN are considered for symptom management because they do not affect the natural course of the disease [17].

The 5-A-RIs decrease DHT-dihydrotestosterone levels, slowing BPH process and causing shrinkage of prostate epithelial cells. Finasteride and dutasteride are the 5-A-RIs and effectively relieve LUTS and prevent disease progression in men with BPH. Both drugs inhibits 5-alpha-reductase enzyme, but the first drug targets type 2 only while the second influences both type 1 and 2 isoforms of the isoenzyme, reducing DHT levels by 85% and 90%, respectively [18]. Treatment with finasteride alone produced a 50% reduction in the relative risk of patients with BPH developing these processes [20]. Side effects can lead to impotence, decreased libido or ejaculatory disorders. Men with a small prostate may not to be suitable candidates for 5-ARI [5, 19].

Combination therapy with A-1-ADRN and 5-ARI for early symptom reduction and long-term disease management is appropriate in men who are at risk of progression (enlarged prostate, PSA>1,3 ng/ml, age>70 years, high LUTS level). During the combination therapy, A-1-ADRN may be discontinued in the majority of men once the therapeutic efficacy of the 5-ARI has been confirmed, i.e. within 6-9 months [21, 22]. Some patients, however, may benefit from continuation of the combination therapy. Patients undergoing treatment for BPH should be periodically assessed for disease progression [23]. Although in the case of A-1-ADRN and 5-ARI there are data to support delays in AUR and the need for surgery, only the 5-ARIs reduce the long-term risks of both events. Current evidence suggests that combination therapy should be considered in men with VP>40ml, elevated PSA level and LUTS, and moderate or severe bother. The Medical Therapy of Prostate Symptoms (MTOPS) study provided evidence that VP threshold for the benefit of a 5-ARI, and therefore of combination therapy, is lower than previously thought. The rate of AUR was significantly lower in both the finasteride (68% risk reduction, p=0.009) and the combination groups (81% risk reduction, p=0,001), compared with placebo. Finasteride (64%) and combination therapy (67%) significantly reduced risk of invasive therapy, p<0,001 [24]. One other trial, SMART (Symptom Management After Reducing Therapy) was examined - the combination of dutasteride and tamsulosin, followed by withdrawal of tamsulosin in symptomatic men. Patients were randomized to dutasteride and tamsulosin. The combination therapy produced a rapid improvement [20, 22]. All trials had similar results of combination therapy A-1-ADRNs and 5-ARIs [21, 22, 24-29]. In the subsequent combination therapy, the number patients was significantly better than any other therapy at preventing progression, and reduced the risk AUR by up to 80%. The risk of invasive therapy was reduced by up to 67%. Serum PSA was an accurate marker for prostate size. For the many men who wish to avoid surgery, combination therapy offers significant benefits over monotherapy. For men with a prostate < 30 ml and slight symptoms, treatment with A-1-ADRNs and/or ANTCH may be beneficial. For men with VP > 30 ml and moderate symptoms a 5-ARI should be used. Combination therapy with A-1-ADRNs and 5-ARI is recommended for men who are symptomatic and have a high risk of progression. To recapitulate: A-1-ADRN and 5-ARI combination therapy should be recommended as standard therapy for BPH, but in the author's opinion it should not be considered for every case. Patients with coexisting hypertension and/or diabetes with progression and severe obstructive symptoms should be treated surgically [11].

Surgical treatment is indicated for patients who have complications of BPH, such AUR, chronic retention due to prostatic obstruction, recurrent urinary tract infections (UTIs), haematuria, bladder stones, renal insufficiency due to BPH, large bladder diverticulum [3, 9, 11, 12]. The most common surgical procedure for BPH is transurethral resection of the prostate (TURP), but this procedure has complications (bleeding, erectile dysfunction and retrograde ejaculation) [30]. As yet, open surgery enucleation of prostate adenoma exists and remains the definitive treatment especially for patients with markedly enlarged prostate, AUR, bladder calculi, UTIs, renal insufficiency secondary to BOO or severe LUTS refractory to medical management [11, 31, 32].

Alternative surgical therapies are aimed at reducing the level of complications while maintaining efficacy. Laser prostatectomy (LP) has been developed to reduce complications and TURP – associated costs. The three principle types of LP are: coagulative, cutting (enucleative) with the holmium (Ho), YAG of the thulium; YAG lasers and vaporization with the Ho: YAG, diode and Green light potassium-titanyl phosphate (KTP), the utilizing of which has paved the way for considerably more success in the photoselective vaporization of the prostate (PVP) (technical simplicity, excellent clinical outcomes, low morbidity) [30, 33, 34].

CONCLUSION

Management of BPH combines the watch-and-wait scenario, phytotherapy, the use of A-1-ADRN, either alone or in combination with ANCTH, and monotherapy by 5-ARIs. The 5-ARIs provide symptomatic relief, reduce prostate volume and delay the disease process. The initiation of combination therapy with A-1-ADRN and 5-ARI should be considered in men with prostate enlargement, elevated PSA level and LUTS. Candidates for combination treatment are patients with severe LUTS and larger prostate volume, for whom withdrawal of the A-1-ADRN is not an option. Combination therapy with A-1-ADRN and 5-ARI seems to be significantly more effective than either agent alone and reduces disease progression, AUR, or the requirement for invasive therapy. In the case of progression, complications, severe LUTS, and other indications for surgical treatment, the following invasive methods should be considered: TURP, laser prostate tissue coagulation or vaporization, or laser enucleation of the prostate. The most recent laser therapy for BPH is based on photoselective vaporization. There is a growing body of clinical evidence for effectiveness of both the holmium and KTP lasers, and these therapies currently represent a valid clinical alternative to TURP.

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