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Referral criteria for benign prostatic hyperplasia for primary care. Consensus document☆

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A B S T R A C T

Benign prostatic hyperplasia (BPH) is a high prevalence condition in men over 50 years that requires continued assistance between primary care and urology. Therefore, consensus around common referral criteria was needed to guide and support both levels. Medical history, symptom assessment with International Prostate Symptom Score (IPSS) questionnaire, digital rectal examination and prostate-specific antigen (PSA) measurement are diagnostic tests available for general practitioners that allow setting a correct BPH diagnose. Patients with an IPSS<8 should be monitored by evaluating them annually. Treatment with α-blockers and an evaluation at the first and third month is recommended in patients with an IPSS 8-20 and if the prostate is small, if the prostate size is large treatment with α-blockers or 5α-reductase inhibitors and evaluation at the third and six month is recommended, and in patients with a large prostate and a PSA >1.5 ng/ml combined treatment and evaluation at the first and sixth month is recommended. Some clear criteria for referral to urology are established in this document, which help in the management of these patients. Those patients with BPH who do not show any improvement at the third month of treatment with α-blockers, or the sixth month with 5α-reductase inhibitors, will be referred to urology. Patients will also be referred to

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urology if they have lower urinary tract symptoms, a pathological finding during rectal examination, IPSS>20, PSA>10 ng/ml or PSA>4 ng/ml and free PSA<20% or if they are <50 years with suspected BHP, or if they have any urological complication.

Criterios de derivación en hiperplasia benigna de próstata para atención primaria

RESUMEN

La hiperplasia benigna de próstata (HPB) es una enfermedad con alta prevalencia entre los varones de más de 50 años que requiere una continuidad asistencial entre los 2 niveles existentes en nuestro país, el de atención primaria (AP) y el de atención especializada; motivo por el que era necesario consensuar unos criterios de derivación o de continuidad que sirvan de orientación a ambos colectivos. La historia clínica del paciente, el Índice Internacional de Síntomas Prostáticos (IPSS, *International Prostate Symptom Score*), el tacto rectal y el antígeno prostático específico (PSA, prostate-specific antigen) son herramientas accesibles en el ámbito de la AP que permiten un diagnóstico adecuado de la HBP. Conscientes de tal necesidad, las sociedades científicas de atención primaria (Sociedad Española de Médicos de Atención Primaria [SEMERGEN], Sociedad Española de Medicina General [SEMG], Sociedad Española de Medicina de Familia y Comunitaria [semFYC]) y la Asociación Española de Urología (AEU) elaboraron este documento de consenso. A los pacientes con IPSS<8 se los deberá mantener en vigilancia y evaluar anualmente; en los pacientes con IPSS 8-20, si el tamaño de la próstata es pequeño, se recomienda el tratamiento con bloqueadores alfa y evaluación al primer y tercer mes, si el tamaño de la próstata es grande se recomienda el tratamiento con bloqueadores alfa o inhibidores 5-alfa-reductasa y evaluación al tercer y sexto mes, y en el caso de pacientes con próstata grande y PSA 41,5 ng/ml se recomienda el tratamiento combinado y la evaluación al primer y sexto mes. En este documento se establecen unos criterios de derivación al urólogo claros, que facilitan el tratamiento de este tipo de pacientes. Se derivarán al urólogo aquellos pacientes con HBP que no presenten mejoría al tercer mes de tratamiento con bloqueadores alfa, o al sexto mes de tratamiento con inhibidores 5-alfa-reductasa. Se derivarán también los pacientes con síntomas del tracto urinario inferior en los que se observe algún hallazgo patológico durante el tacto rectal, IPSS >20, PSA >10 ng/ml o PSA >4 ng/ml y PSA libre <20% o pacientes con edades <50 años y sospecha de HBP, así como aquellos pacientes con alguna complicación urológica.

Palabras clave:
Hiperplasia benigna de próstata
Consenso
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Background

Benign prostatic hyperplasia (BHP) is a condition characterized by growth of prostate gland tissue causing urinary outflow obstruction and clinically by the so-called lower urinary tract symptoms (LUTS)[1]. LUTS may be very marked and significantly limit patient's quality of life[1]. Increased symptoms with age are not always associated to an impaired quality of life, which suggests some capacity to adapt with age[2,3]. Nicturia and a weak urine stream are the symptoms causing a greatest impairment in quality of life. A palpable prostate enlargement does not always induce clinical symptoms[4]. Only 50% of patients with histological changes will have clinical prostatic signs and will seek the help of a primary care (PC) physician or urologist.

The course of disease is related to age[5]. An adult prostate weighs approximately 20 g. Prostate sizes greater than 20-30 g are considered indicative of prostate enlargement[1]. Prostate growth starts at puberty and is usually complete at approximately 30 years of age. Hyperplastic foci start to appear in glandular and fibromuscular tissue from 30-40 years of age. A second growth phase may start after the fifth or sixth decades of life.

BPH is the most common urological condition in males, and the first reason for outpatient consultation to a specialist[2]. It is the most common benign tumor in men over 50 years of age and the second leading cause for surgery[6]. BPH prevalence starts in middle age and gradually increases with aging. The lack of a standardized clinical definition of BPH makes it difficult to conduct epidemiological studies

to adequately assess its prevalence[7]. In Spain, the results of a study conducted by Chicharro et al[2] in accordance to the World Health Organization criteria suggested that the mean prevalence of BPH in the whole male population analyzed was 11.8%, ranging from 0.75% in males aged 40-49 years and 30% in males over 70 years of age. In a review[8] analyzing the age-related histological prevalence of BPH based on data from 10 studies including more than 1,000 prostates, BPH prevalence was 8% in men in their forties, 50% in the fifties, and up to 88% in the ninties[7,8].

BPH has a multifactorial etiology. There is currently no scientific evidence that allows for accepting smoking, vasectomy, obesity, or a high alcohol intake as risk factors[7]. The only risk factors related to BPH development include age and patient hormone status[7,9]. The prostate gland is an androgen-dependent structure that requires testosterone stimulation for development and function. The enzyme 5-alpha-reductase converts testosterone within the prostatic cell into dihydrotestosterone (DHT), the active metabolite that mediates prostate growth. Treatment with 5-alpha-reductase inhibitors decreases prostatic DHT levels and volume.

Rationale and objectives

Prostatic diseases may initially be diagnosed in PC, where the material means required for such diagnosis are available[10]. More than half the patients with BPH may be controlled in PC[2,11]. The high prevalence of BPH and the importance of a good coordination between PC and specialized care warrant the need for having standardized criteria as to when a patient with BPH may be treated and monitored in PC and when he should be referred to an urologist.

No national guidelines are available for BPH management in PC.

The Guidelines of the European Association of Urology (EAU)[7] are currently the reference, but they do not define what should be done in one or the other care level. This is the reason why the Spanish Association of Urology (AEU) has prepared, together with the Spanish Society of Primary Care Physicians (SEMERGEN), the Spanish Society of General and Family Physicians (SEMG), and the Spanish Society of Family and Community Medicine (semFYC), this consensus document.

The objectives intended are to promote optimal treatment of patients with BPH in PC and urology, and to provide unified and concise criteria, easy to apply by all care levels, for referral of patients with BPH to urologists.

The consensus document consists of two parts: an algorithm (fig. 1) outlining the management of patients attending the clinic with LUTS suggesting BPH, and a detailed account of all steps included in the algorithm, such as diagnostic tests, available treatments, patient monitoring, and criteria for referral to a urologist.

This consensus document is therefore intended to be a helpful tool to facilitate management of patients with prostate symptoms, as well as coordination between the PC and specialized care levels.

Methodology

The recommendations given in this consensus are the result of the search for, critical evaluation, and synthesis of the available scientific evidence on BPH.

Whenever possible, the level of evidence and grade of recommendation supporting each of the recommendations given in this document have been included following the classification of the Agency of Healthcare Research and Quality (Table 1) used by the EAU[2].

Differential diagnosis

Patients with suspected prostatic disease usually consult PC physicians due to the presence of LUTS and acute urinary retention, although asymptomatic patients worried about a potential prostatic disease also seek care (fig. 1).

BPH is clinically manifested by LUTS. However, not all lower urinary tract symptoms are caused by BPH. It should therefore be reminded that LUTS may also be due to the presence of other conditions[1]. A detailed history and an adequate physical examination will allow in most cases for accurate diagnosis, subsequently confirmed by any supplemental tests as may be required.

The initial diagnostic assessment of patients with LUTS must be based on the results of the following diagnostic procedures (fig. 1):

- History, including the International Prostate Symptom Score (IPSS)[12].
- Physical examination, including digital rectal examination.
- Urine and blood chemistry laboratory tests.

History

History is the first step in diagnosis and an essential procedure in the PC physician office. A detailed history should be taken that allows for ruling out diseases other than BPH which cause LUTS.

The presence or absence of potentially serious changes such as hematuria (gross and microscopic), pain, fever, urinary retention, anuria, or renal function impairment should be assessed.

The following clinical data should be recorded:

Family history of prostate disease

Presence of diseases that may cause LUTS: diabetes, heart failure, neurological disease (Parkinson, multiple sclerosis), history of sexually transmitted diseases, bladder disease, orchitis, rectal disease.

Current treatment with diuretics (increase voiding frequency), calcium channel blockers (decrease bladder contractility), tricyclic antidepressants (increase prostatic tone), or first-generation antihistamines (decrease bladder contractility).

Clinical picture of LUTS: time since onset, symptoms, and severity should be assessed. LUTS may significantly impair the quality of life of patients. Their adequate identification

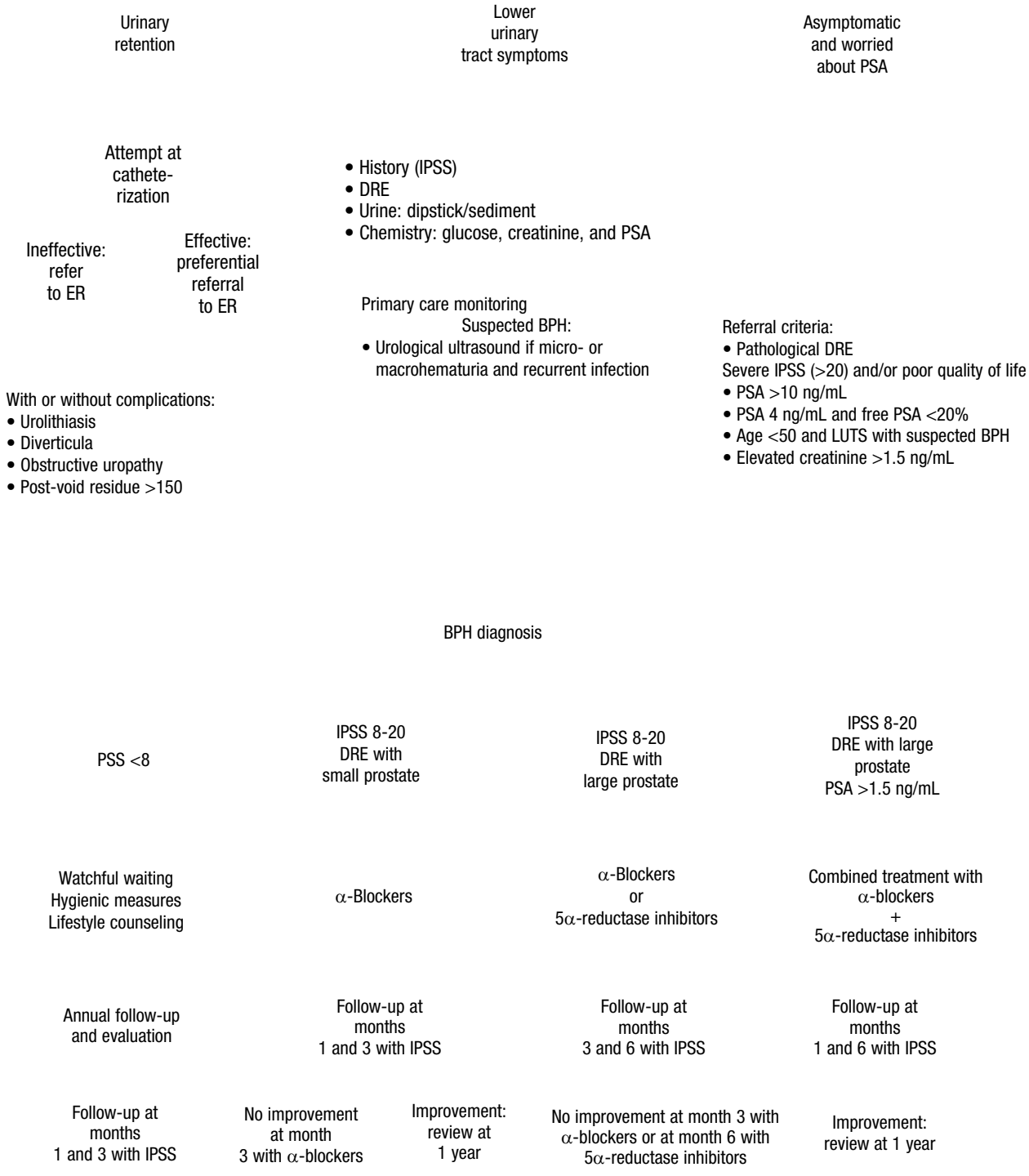

Figure 1 – Decision algorithm based on the results of history, physical examination and laboratory tests. BPH: benign prostatic hyperplasia; IPSS International Prostate Symptom Score; PSA: prostate-specific antigen; DRE: digital rectal examination.

Table 1 – Levels of scientific evidence and grades of recommendation

Classification of recommendations based on the available level of evidence
Ia. Scientific evidence comes from meta-analyses of randomized, controlled clinical trials
Ib. Scientific evidence comes from at least one randomized, controlled clinical trial
IIa. Scientific evidence comes from at least one prospective, non-randomized, controlled, well-designed study
IIb. Scientific evidence comes from at least one quasi-experimental, well-designed study
III. Scientific evidence comes from descriptive, non-experimental, well-designed studies such as comparative or case-control studies
IV. Scientific evidence comes from expert documents or opinions or clinical experiences of authorities of repute

Grades of recommendation
A. There is good research-based evidence to support the recommendation
B. There is fair research-based evidence to support the recommendation
C. The recommendation is based on expert opinion and panel consensus
X. There is evidence of harm from this intervention

Table 2 – Classification of lower urinary tract symptoms

Irritative symptoms	Obstructive symptoms
Urinary frequency	Hesitancy
Nicturia	Weak/slow urine stream
Urinary urgency	Post-void dribbling
Urge incontinence	Intermittent urination
Suprapubic pain	Incomplete emptying

is therefore essential for selecting the most adequate therapeutic measures in each individual patient. LUTS are classified as obstructive and irritative symptoms (Table 2). Irritative symptoms cause the greatest interference with activities of daily living and quality of life[13].

Most scientific societies recommend that the IPSS is used to assess LUTS severity[14] (Fig. 2) ***(level of evidence III, grade of recommendation B). The IPSS is a self-administered tool which has been translated into Spanish and validated[15]. It consists of seven questions related to different LUTS scored 0 to 5. The sum of the scores given to each question determines the severity of the condition: mild (< 8), moderate (8-19), or severe (> 20). Question 8 score indicates the impairment in patient's quality of life caused by LUTS (> 4 significant impairment). Improvement in symptom score by at least 3 units as compared to baseline score is considered as perceptible by patients, and is therefore accepted as the minimal clinical improvement threshold[16]. The IPSS should not replace clinical history, but is helpful for assessing the need for treatment and for monitoring the changes in symptom severity during follow-up.

Physical examination

Physical examination of patients with LUTS should be as complete as possible and should focus on identification of signs of nephrourological disease[7] (level of evidence III, grade of recommendation C). An adequate physical examination must always include the following:

General examination: to assess the presence/absence of edema, fever, urinary tract infection (UTI), or other signs of renal involvement (costovertebral angle tenderness on both sides).

Abdominal examination: to rule out masses and bladder distension.

Scrotal examination: testicular size, consistency, and sensitivity should be assessed, as well as the presence of hydrocele, varicocele, and indurate masses.

Digital rectal examination (level of evidence III, grade of recommendation C): this is an essential urological examination in men with LUTS[17]. The examination should be performed on an empty bladder and in the most comfortable and feasible position in the physician's experience (supine, standing, lateral decubitus, or knee-elbow positions). Under normal conditions, a symmetrical gland with a middle groove and two lateral lobes will be palpated. The following should be assessed:

- Condition of rectal mucosa: allows for ruling out fissures or assessing the presence of hemorroids.
- Anal sphincter tone.
- Sensitivity: very painful in acute prostatitis.
- Gland size: the prostate middle groove disappears due to progressive growth.
- Consistency: the normal prostate has a fibroelastic consistency, homogeneous throughout its surface; if any point with a stony hard consistency is found, tumor disease should be suspected.
- Boundaries: the limits of the gland may be sharply outlined; otherwise, tumor disease should be suspected.
- Mobility: the normal prostate is slightly mobile; if a fixed prostate is found, a neoplastic condition should be suspected.

Although digital rectal examination is highly useful for differential diagnosis of prostatic and anorectal diseases, a normal digital rectal examination does not rule out prostate carcinoma (PCa) because this procedure only diagnoses 10% of early PCas. When PCa is palpated in a digital rectal examination, it is at least in the T2 stage[18].

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. During the last month or so, how often have you had a sensation of not emptying your bladder completely after urinating?	0	1	2	3	4	5
2. During the last month or so, how often have you had to urinate again less than two hours after you have urinated?	0	1	2	3	4	5
3. During the last month or so, how often have you stopped and started several times when you urinated?	0	1	2	3	4	5
4. During the last month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. During the last month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. During the last month or so, how often have you had to push or strain to urinate?	0	1	2	3	4	5
7. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

<8 points = mild 8 to 19 points = moderate >20 points = severe

	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Fatal
8. If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Score ≥4 = significant involvement of patient's quality of life

Figure 2 – International Prostate Symptom Score (IPSS). Assessment of severity of lower urinary tract symptoms (LUTS) and quality of life related to LUTS.

Combined use of digital rectal examination and prostate-specific antigen (PSA) levels allows for ruling out the presence of PCa, prostatitis, and other pelvic diseases[7,19] (level of evidence IB, grade of recommendation B).

Urine and blood tests

The following laboratory tests should be done in PC to patients with LUTS:

Urine dipstick: to rule out the presence of nitrites, white blood cells, protein, and microhematuria. This is a simple, highly sensitive test, but poorly specific (frequent false positive results). The presence of blood should subsequently be confirmed at all times using a complete urine analysis including sediment.

Complete urine analysis including sediment and abnormal substances (level of evidence IV, grade of recommendation C): to rule out urinary tract infection and hematuria.

Blood glucose: to rule out diabetes.

Plasma creatinine (level of evidence IV, grade of recommendation C): BPH may cause upper urinary tract dilatation and renal failure[7]. Although the results of the study Medical Therapy of Prostatic Symptoms (MTOPS)[20] suggested that the risk of renal failure development in men with LUTS is less than 1%, EAU7 advises measurement of creatinine in the initial evaluation of patients with BPH. If renal function impairment is suspected (creatinine > 1.5), an ultrasound should be requested to rule out obstructive allopathy.

Prostate-specific antigen (level of evidence III, grade of recommendation B)[7]: this marker is not specific for carcinoma, but for prostate tissue. While it is true that high PSA levels have been related to an increased chance of developing PCa, other clinical conditions such as UTI, BPH, or prostatitis[21,22] may also increase PSA levels. Use of PSA without digital rectal examination is not recommended. The combination of both is the most effective method for early detection of PCa[7,19]. Normal values vary with age. Elderly men have slightly higher PSA levels than younger men[23] (Table 3). If abnormal values are seen, the following procedures should be considered:

- If PSA levels are > 10 ng/mL, an ultrasound-guided biopsy should be performed.
- If PSA levels range from 4 and 10 ng/mL, free/total PSA ratio and PSA velocity should be assessed:
  - A free/total PSA ratio > 0.2 (> 20%) suggests BPH
  - A free/total PSA ratio < 0.2 (< 20%) suggests PCa and should lead to perform a biopsy
- A PSA increase by > 0.75 ng/mL/year suggests PCa. Patients diagnosed with PCa having a PSA velocity > 2.0 ng/mL/year have a 9.8-fold greater chance of dying from PCa than those with a PSA velocity < 2 ng/mL/year.
- In patients treated with 5-alpha-reductase inhibitors, PSA levels are halved from six months of treatment[24]. Thus, in order to know the actual PSA value, PSA levels should be multiplied by two. The resultant value retains the sensitivity and specificity of the PSA obtained[25].

Table 3 – Normal ranges of prostate-specific antigen (PSA) levels by age

Age	PSA (ng/mL)
40-49	0-2.5
50-59	0-3.5
60-69	0-4.5
70-79	0-6.5

Oesterling et al[23].

Assessment of PSA levels is recommended[20,26-30] in all men over 50 years of age consulting for LUTS, in patients older than 45 years with a history of PCa in a first-degree relative, in those older than 40 years with a history of PCa in two or more first-degree relatives, and in black men over 45 years of age. An early diagnostic approach is not recommended in men over 70 years of age o with a life expectation shorter than 10 years.

Controversy exists as to whether PSA should be requested or not in asymptomatic patients older than 50 years[31]. Various scientific institutions propose that decisions on early diagnosis of PCa are shared with the patients[26] and recommend use of an informed consent[31,32] to explain to them the benefits and risks of the test[33,34] so that they may freely decide by themselves. Potential benefits include early diagnosis of cancer with a better chance of cure. Risks include increased costs of medical care, performance of unnecessary prostate biopsies, and the probability of false negative results leading to a delay in cancer diagnosis, or false positive results causing an unnecessary increased anxiety. Each patient must weigh these factors to decide whether or not routine examination is warranted in his case[1,35,36].

Other supplemental tests

Abdominal ultrasound (level of evidence III, grade of recommendation B)

Abdominal ultrasound is a safe examination that is helpful to assess the following[2,37]:

- Prostate size: prostate weight (grams) = A × B × C × 1/2, where A, B, and C are the width, height, and depth of the prostate respectively.
- Post-void residue: volume (milliliters) = A + B + C × 3/4, where A, B, and C are the width, height, and depth of the bladder respectively. A post-void volume > 100-200 mL suggests bladder dysfunction and a high probability of acute urinary retention (AUR), predicting for a poorer response to treatment. Surgery should therefore be considered as potential treatment[1]. Because of the variability of this diagnostic test, at least two ultrasound examinations are advised[37]. For patients with consistently elevated post-void residue levels, investigations and imaging tests of the upper urinary tract should be requested to rule out renal failure[38]. A permanent post-void residue may also suggest a decreased detrusor activity. If this is suspected, urodynamic studies to assess bladder function and rule out conditions other than BPH should be considered[39].
- Urinary tract in the event of hematuria, urinary infection, renal failure, or stones.

An abdominal ultrasound must be requested for patients with:

- History of renal stones.
- Gross or microhematuria.
- Bladder distension.
- Suspected obstruction.
- Severe symptoms.
- History of spinal trauma, neuropathy, and other associated neurological changes.
- Increased creatinine levels.

Transrectal ultrasound (level of evidence III, grade of recommendation B)

Transrectal ultrasound is helpful to assess prostate volume and morphology when digital rectal examination has provided evidence of neoplastic disease. However, it does not allow for assessing urinary tract or quantifying residue[2]. Although this test is not recommended in the initial evaluation, if severe prostatic disease is suspected it is fully indicated for diagnostic purposes in an outpatient setting. In patients in whom malignancy is suspected (altered PSA levels or positive digital rectal examination), a transrectal ultrasound must be requested to perform ultrasound-guided biopsies[2].

Management of benign prostatic hyperplasia

Management of BPH is aimed at decreasing symptoms, improving quality of life, and preventing complications such as urinary retention[7]. The therapeutic approach will depend on patient age, symptoms, quality of life, complications, and associated conditions.

There are three options for BPH management[7]: watchful waiting combined with hygienic and dietary measures, drug treatment, or surgery (fig. 1).

Watchful waiting plus hygienic and dietary measures

Patients on watchful waiting must understand that this is an active program that requires them to undergo regular monitoring and to make lifestyle changes such as avoidance of a sedentary life, fluid restriction at night, and a restricted intake of coffee, alcohol, and some drugs acting on smooth muscle fiber (neuroleptics, anticholinergics), as well as a change in voiding habits.

Drug treatment

Phytotherapeutic agents (plant extracts)

Most evidence on the efficacy of phytotherapeutic agents comes from clinical studies with design problems (low number of patients, follow-up shorter than 6 months, etc.). Their exact action mechanisms are therefore unknown, and a great controversy exists about their clinical efficacy. The 2004 EAU guidelines[7] do not recommend them as first choice treatments for BPH. They are usually attributed an efficacy similar to placebo. The only substance in this group for which more reliable scientific data are available (level of evidence IIa, grade of recommendation B) is *Serenoa repens* at a dose of 160 mg/12 h. A systematic review[40] reported *S. repens* to be more effective than placebo and to provide a mild to moderate improvement in urinary symptoms and flow measurements, similar to that seen with finasteride but with a lower incidence of adverse effects.

Alpha-adrenergic blockers (level of evidence Ia, grade of recommendation A)

Alpha blockers mainly act upon BPH symptoms. They have no effect on prostate volume and do not prevent prostate growth[11,12]. BPH treatment with alpha-1 blockers may achieve a 4 to 6-point symptomatic improvement in IPSS[7]. Alpha-1 adrenergic receptors are located in the bladder neck, trigone, prostatic urethra, and prostate gland. Different subtypes of alpha-1 receptors are known (A, B, D, and L). Of these, the alpha-1A subtype predominates in the prostate (98%). Sympathetic stimulation of these receptors causes an increased urethral resistance. By contrast, receptor blockade results in relaxation of smooth muscle fiber, which decreases urethral resistance to urine outflow[41].

Non-selective alpha-blocking drugs acting upon both alpha-1 and alpha-2 receptors (phentolamine, phenoxybenzamine) and having significant adverse effects were initially used. Alpha-blocking agents selective for alpha-1 receptors (doxazosin, prazosin, terazosin) having less side effects subsequently appeared. An additional therapeutic option currently available are alpha-1A blockers (alfuzosin and tamsulosin), which are uroselective and therefore have a significantly improved tolerability[42] with no significant differences in side effects as compared to placebo[1]. Side effects are minimized when these agents are administered in the evening starting at low doses, and resolve upon drug discontinuation. While non-selective alpha blockers, because of their pressure-lowering effect, have been used as a single medication to treat patients with BPH and high blood pressure (HBP)[43], alpha blockers should currently not be recommended as a single treatment for HBP, and both conditions should be considered separately when treatment is decided[44].

5-alpha-reductase inhibitors (level of evidence Ia, grade of recommendation A)

The enzyme 5-alpha-reductase converts testosterone within the prostatic cell into an active metabolite, DHT. Two isoenzymes of 5-alpha-reductase (type 1 and type 2) occur in the prostate gland. In patients with BPH, DHT contents in the prostate are three to four times higher as compared to the normal prostate[1]. 5-alpha-reductase inhibitors decrease prostate size by 20%-30% and reduce PSA levels by a half, so that for early assessment of prostate cancer it is advised to multiply by two the PSA value found. Free PSA levels are not altered[2]. Treatment benefits start to be seen after 3-6 months.

5-alpha-reductase inhibitors available in the market include finasteride and dutasteride. Finasteride inhibits the type 2 isoenzyme.

Results of studies conducted in patients with a prostate volume greater than 40 cm^3 suggest that finasteride decreases DHT levels by 70%, improves symptoms, and reduces the risk of AUR[45] and surgery. Dutasteride inhibits both type 1 and type 2 isoenzymes of 5-alpha-reductase. Studies conducted in patients with prostate volumes greater than 30 cm^3 show that dutasteride may decrease DHT by > 90%[46], continuously improve symptoms over time, and decrease the risks of AUR and surgery by 57% and 48% respectively[2,47].

The most common side effects that may occur with 5-alpha-reductase inhibitors are mainly sexual in character and due to the hormonal blockade they induce: erectile dysfunction (5%-7%), decreased libido (3%), decreased ejaculate volume or ejaculation disorders (1.5%-2%), and gynecomastia (1.3%-3%).

Combined treatment (level of evidence Ia, grade of recommendation A)

Combined treatment consists of the association of an alpha-blocker and a 5-alpha-reductase inhibitor. Results of recent prospective, randomized clinical studies[20,48] suggested that combined treatment with an alpha-blocker and a 5-alpha-reductase inhibitor was more effective than monotherapy with each of these drugs. According to the MTOPS20 and CombAT[48] (combination of Avodart^R [dutasteride] and tamsulosin) studies, combined treatment would be particularly indicated for patients presenting with moderate to severe lower urinary tract (LUT) symptoms, demonstrable prostatic growth, and PSA levels > 1.5 ng/mL, all of them prognostic factors of progressive disease.

In the CombAT study[48], combined treatment with dutasteride and tamsulosin achieved a significant symptom improvement as compared to monotherapy with dutasteride (from the third month) or tamsulosin (from the ninth month). Similar improvements were seen in patient quality of life and peak urinary flow. This evidence led us to propose in the algorithm for medical treatment of BPH the choice of combined treatment with dutasteride and tamsulosin in patients with moderate IPSS (8-20), large prostate volume on digital rectal examination, and PSA levels > 1.5 ng/mL.

Surgery

Prostate size is determinant for selecting the surgical approach[1]. The main conventional surgical procedures include[7]:

Transurethral incision of the prostate (TUIP): this is the surgical procedure of choice in patients with prostates less than 30 cm^3 in volume and with no middle lobe.

Transurethral resection of the prostate (TURP): this is indicated for patients with prostates of an intermediate volume ranging from 30 and 80 cm^3. It is the most commonly used procedure, because 90% of patients are within this range of prostate volume.

Open prostatectomy or adenomectomy: this is the surgical procedure of choice in men with prostate volumes larger than 60-80 cm^3.

After surgery, peak flow improvements greater than 10 mL/s and symptom improvements by 15-20 points in the IPSS are achieved. The most common long-term risks include retrograde ejaculation (80% after adenomectomy, 65%-70% after TURP, 40% after TUIP), bladder neck contracture or urethral stenosis (5%), and urinary incontinence (1%-2%).

Other alternative, poorly invasive surgical procedures with a clinical efficacy similar to conventional procedures and a decreased risk of bleeding, catheterization time, and hospital stay are currently available. The main alternative surgical procedures include:

Transurethral electrovaporization: This procedure is adequate for high-risk patients with small prostates.

Prostatic resection with laser energy (holmium and KTP [potassium-titanium-phosphate]): this procedure is indicated in high-risk patients requiring a poorly invasive treatment for prostates with a small or moderate volume.

Holmium laser enucleation: this is indicated for prostates of a moderate or large size.

Therapeutic recommendation

Watchful waiting

Indicated for patients with IPSS scores = 7 and no clinical complications (hematuria, infections, or AUR).

Drug treatment

Drug treatment is indicated for patients with moderate to severe symptoms (IPSS 8-20) who have no absolute indication for surgery and who do not meet the criteria for referral to the urologist (Fig. 1).

Three clinical situations may be distinguished based on symptom severity, prostate size as assessed by digital rectal examination, and PSA levels:

Patients with IPSS scores ranging from 8 and 20 and small prostates on digital rectal examination: treatment with alpha-blockers is recommended.

Patients with IPSS scores ranging from 8 and 20 and large prostates on digital rectal examination: treatment with alpha-blockers or 5-alpha-reductase inhibitors (dutasteride or finasteride) is recommended.

Patients with IPSS scores ranging from 8 and 20, large prostates on digital rectal examination, and PSA > 1.5 ng/mL:: Combined treatment with alpha-blockers and 5-alpha-reductase inhibitors (dutasteride or finasteride) is recommended.

Treatment with *S. repens* is not recommended by the 2004 EAU guidelines[7].

Surgery

According to the EAU guidelines for BPH[7], surgery would be indicated for patients with moderate to severe LUTS who do not improve after drug treatment (or who request active intervention instead of drug treatment) and who have any of the following clear indications for surgery: renal failure, bladder stone, refractory urinary retention, recurrent urinary infection, or recurrent hematuria refractory to medical treatment with 5-alpha-reductase inhibitors.

Follow-up

Patients on treatment with no surgical criteria may be followed up in PC[49].

Patients on watchful waiting: patients should be reassessed at least every year for changes in symptoms or complications.

Patients treated with an alpha-blocker: treatment efficacy and tolerability should be assessed using the IPSS one and three months after treatment start.

Patients treated with a 5-alpha-reductase inhibitor: treatment efficacy and tolerability should be assessed using the IPSS six months after treatment start.

Patients on combined treatment (alpha-blocker plus 5-alpha-reductase inhibitor): treatment efficacy and tolerability should be assessed using the IPSS one and six months after treatment start.

If improvement is seen, annual follow-up should subsequently be performed, including IPSS assessment, physical examination with digital rectal examination, urine dipstick, and measurement of creatinine and PSA levels[50,51].

In individual patients with obstruction risk, flowmetry should preferentially be performed or, failing this, an ultrasound examination of the kidney, bladder, and prostate with post-void residue measurement should be done every year.

Referral criteria

Referral to a specialist is indicated in the following conditions:

- Patients with LUTS who have any of the following after differential diagnosis:
  - Pathological digital rectal examination: irregular surface, increased consistency, nodules, or ill-defined boundaries.
  - Severe IPSS (> 20) or poor quality of life.
  - PSA > 10 ng/mL.
  - PSA > 4 ng/mL and free PSA < 20%.
  - Age < 50 and LUTS with suspected BPH.
  - Creatinine elevation > 1.5 ng/mL: if ultrasound suggests obstructive allopathy, patient must be referred to the hospital or urology department. If renal function

impairment is found and obstructive allopathy is ruled out, patient must be referred to the nephrology department.
- Patients with no BPH.
- Patients who show any of the following instruments:
  – Urolithiasis.
  – Diverticula.
  – Obstructive uropathy.
  – Post-void residue > 150.
- In patients attending the clinic for AUR, an attempt should be made at catheterization, if not contraindicated. If this is not effective they must be referred to the emergency room; otherwise, they will be referred to an urologist.
- Patients with signs of chronic urinary retention, as assessed by the post-void residue, because they usually require surgery.
- Patients on drug treatment for BPH who experience no improvement:
  – After three months of continuous treatment with alpha-blockers.
  – After six months of continuous treatment with 5-alpha-reductase inhibitors.

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