

## BENIGN PROSTATIC HYPERPLASIA

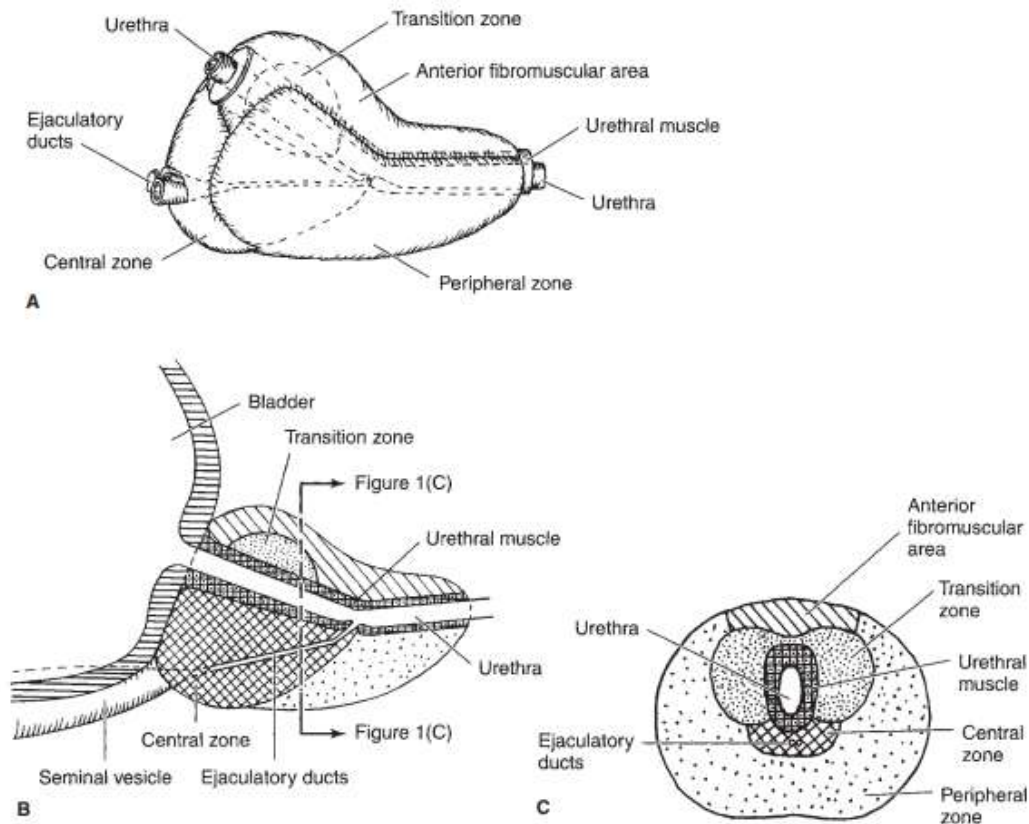
### Incidence and Epidemiology

BPH is the most common benign tumor in men, and its incidence is age related. The prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41–50, to 50% in men aged 51–60, and to >90% in men older than 80 years. Although clinical evidence of disease occurs less commonly, symptoms of prostatic obstruction are also age related. At age 55, approximately 25% of men report obstructive voiding symptoms. At age 75, 50% of men complain of a decrease in the force and caliber of their urinary stream. Risk factors for the development of BPH are poorly understood. Some studies have suggested a genetic predisposition, and some have noted racial differences. Approximately 50% of men younger than 60 years who undergo surgery for BPH may have a heritable form of the disease. This form is most likely an autosomal dominant trait, and first-degree male relatives of such patients carry an increased relative risk of approximately fourfold.

### Etiology

The etiology of BPH is not completely understood, but it seems to be multifactorial and endocrine controlled. The prostate is composed of both stromal and epithelial elements, and each, either alone or in combination, can give rise to hyperplastic nodules and the symptoms associated with BPH. Each element may be targeted in medical management schemes. Observations and clinical studies in men have clearly demonstrated that BPH is under endocrine control. Castration results in the regression of established BPH and improvement in urinary symptoms. Additional investigations have demonstrated a positive correlation between levels of free testosterone and estrogen and the volume of BPH. The latter may suggest that the association between aging and BPH might result from the increased estrogen levels of aging causing induction of the androgen receptor, which thereby sensitizes the prostate to free testosterone. There is evidence that estrogens acting through stromal and epithelial estrogen receptors may contribute, in part, to diseases of the prostate. Genetic or environmental factors that influence 5 $\alpha$ -reductase appear to be important in the development of BPH as well (Alan et al, 2008; Gail et al, 2008). Pathology As discussed earlier, BPH develops in the transition zone. It is truly a hyperplastic process resulting from an increase in cell number. Microscopic evaluation reveals a nodular growth pattern that is composed of varying amounts of stroma and epithelium. Stroma is composed of varying amounts of collagen and smooth muscle. The differential representation of the histologic components of BPH explains, in part, the potential responsiveness to medical therapy. Thus,  $\alpha$ -blocker therapy may result in excellent responses in patients with BPH that has a significant component of smooth muscle, while those with BPH predominantly composed of epithelium might respond better to 5 $\alpha$ -reductase inhibitors. Patients with significant components of collagen in the stroma may not respond to either form of medical therapy. Unfortunately, one cannot reliably predict responsiveness to a specific therapy (see later). As BPH nodules in the transition zone enlarge, they compress the outer zones of the prostate, resulting in the

formation of a so-called surgical capsule. This boundary separates the transition zone from the peripheral zone and serves as a cleavage plane for open enucleation of the prostate during open simple prostatectomies performed for BPH.



**Pathophysiology** One can relate the symptoms of BPH to either the obstructive component of the prostate or the secondary response of the bladder to the outlet resistance. The obstructive component can be subdivided into the mechanical and the dynamic obstruction. As prostatic enlargement occurs, mechanical obstruction may result from intrusion into the urethral lumen or bladder neck, leading to a higher bladder outlet resistance. Prior to the zonal classification of the prostate, urologists often referred to the “three lobes” of the prostate, namely, the median and the two lateral lobes. Prostatic size on digital rectal examination (DRE) correlates poorly with symptoms, in part, because the median lobe is not readily palpable. The dynamic component of prostatic obstruction explains the variable nature of the symptoms experienced by patients. The prostatic stroma, composed of smooth muscle and collagen, is rich in adrenergic nerve supply. The level of autonomic stimulation thus sets a tone to the prostatic urethra. Use of  $\alpha$ -blocker therapy decreases this tone, resulting in a decrease in outlet resistance.

The irritative voiding complaints (see later) of BPH result from the secondary response of the bladder to the increased outlet resistance. Bladder outlet obstruction leads to detrusor muscle hypertrophy and hyperplasia as well as collagen deposition. Although the latter is most likely responsible for a decrease in bladder compliance, detrusor instability is also a factor. On gross inspection, thickened detrusor muscle bundles are seen as trabeculation on cystoscopic examination. If left unchecked, mucosal herniation between detrusor muscle bundles ensues, causing diverticula formation (so-called false diverticula composed of only mucosa and serosa).

#### Clinical Findings

**A. Symptoms** The symptoms of BPH can be divided into obstructive and irritative complaints. Obstructive symptoms include hesitancy, decreased force and caliber of stream, sensation of incomplete bladder emptying, double voiding (urinating a second time within 2 hours of the previous void), straining to urinate, and postvoid dribbling. Irritative symptoms include urgency, frequency, and nocturia. The self-administered questionnaire originally developed by the American Urological Association (AUA) is both valid and reliable in identifying the need to treat patients and in monitoring their response to therapy. The AUA Symptom Score Questionnaire has been extensively validated and translated, and it is now more commonly called the International Prostate Symptom Score (IPSS) (see table below). The IPSS is perhaps the single most important tool used in the evaluation of patients with BPH and is recommended for all patients before the initiation of therapy. This assessment focuses on seven items that ask patients to quantify the severity of their obstructive or irritative complaints on a scale of 0–5. Thus, the score can range from 0 to 35. An IPSS of 0–7 is considered mild, 8–19 is considered moderate, and 20–35 is considered severe. The relative distribution of scores for BPH patients and control subjects is, respectively, 20% and 83% in those with mild scores, 57% and 15% in those with moderate scores, and 23% and 2% in those with severe scores (McConnell et al, 1994). As with other quality-of-life surveys, a reasonable degree of both literacy and numeracy is necessary for valid results. A multimedia version of the IPSS has been proposed which is more reliable among low-education populations (Bryant et al, 2009). A detailed history focusing on the urinary tract excludes other possible causes of symptoms that may not result from the prostate, such as urinary tract infection, neurogenic bladder, urethral stricture, or prostate cancer.

**B. Signs** A physical examination, DRE, and focused neurologic examination are performed on all patients. The size and consistency of the prostate is noted, even though prostate size, as determined by DRE, does not correlate with severity of symptoms or degree of obstruction. BPH usually results in a smooth, firm, elastic enlargement of the prostate. Induration, if detected, must alert the physician to the possibility of cancer and the need for further evaluation (ie, prostate-specific antigen [PSA], transrectal ultrasound [TRUS], and biopsy).

**C. Laboratory Findings** A urinalysis to exclude infection or hematuria and serum creatinine measurement to assess renal function are required. Renal insufficiency may be observed in 10% of patients with prostatism and warrants upper-tract imaging. Patients

with renal insufficiency are at an increased risk of developing postoperative complications following surgical intervention for BPH. Serum PSA is considered optional, but most physicians will include it in the initial evaluation. PSA, compared with DRE alone, certainly increases the ability to detect CaP, but because there is much overlap between levels seen in BPH and CaP, its use remains controversial (see Section “Prostate Cancer Screening and Chemoprevention”).

D. Imaging Upper-tract imaging (renal ultrasound or computed tomography [CT] urogram) is recommended only in the presence of concomitant urinary tract disease or complications from BPH (eg, hematuria, urinary tract infection, renal insufficiency, history of stone disease). TRUS is useful to determine prostate size for men planning to undergo prostate surgery who are suspected to have severe prostate enlargement based on DRE.

AUA Score							
Urinary symptoms (symptom score criteria)	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	
<b>1. Incomplete emptying</b> Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
<b>2. Frequency</b> Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5	
<b>3. Intermittency</b> Over the past month, how often have you found you stopped and started again several times when you urinate?	0	1	2	3	4	5	
<b>4. Urgency</b> Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
<b>5. Weak stream</b> Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
<b>6. Straining</b> Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 or more times	
<b>7. Nocturia</b> Over the past 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	
International Prostate Symptom Score (IPSS) = sum of questions A1 to A7							
Quality of life due to urinary problems							
	Delighted	Pleased	Mostly satisfied	Mixed—about equally satisfied and unsatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Source: McConnell JD: *Benign Prostatic Hyperplasia, Diagnosis and Treatment*. Clinical Practice Guideline No. 8. AHCPR Publication No. 94-0582. Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, Rockville, MD, 1994.

E.

Cystoscopy  
Cystoscopy is

not routinely recommended to determine the need for treatment but may assist in choosing the surgical approach in patients opting for invasive therapy. When marked obstructive symptoms exist in the setting of relative minimal prostate enlargement, cystoscopy may be useful to identify a high bladder neck, urethral stricture, or other

pathology. If BPH is associated with hematuria, then cystoscopy is mandatory to rule out other bladder pathology.

F. Additional Tests Measurement of flow rate, determination of postvoid residual urine, and pressure-flow studies are considered optional. Cystometrograms and urodynamic profiles are reserved for patients with suspected neurologic disease or those who have failed prostate surgery.

#### Differential Diagnosis

Other obstructive conditions of the lower urinary tract, such as urethral stricture, bladder neck contracture, bladder stone, or CaP, must be entertained when evaluating men with presumptive BPH. A history of previous urethral instrumentation, urethritis, or trauma should be elucidated to exclude urethral stricture or bladder neck contracture. Hematuria and pain are commonly associated with bladder stones. CaP may be detected by abnormalities on the DRE or an elevated PSA (see later). A urinary tract infection, which can mimic the irritative symptoms of BPH, can be readily identified by urinalysis and culture; however, a urinary tract infection can also be a complication of BPH. Although irritative voiding complaints are also associated with carcinoma of the bladder, especially carcinoma in situ, the urinalysis usually shows evidence of hematuria. Likewise, patients with neurogenic bladder disorders may have many of the signs and symptoms of BPH, but a history of neurologic disease, stroke, diabetes mellitus, or back injury may be present as well. In addition, examination may show diminished perineal or lower extremity sensation or alterations in rectal sphincter tone or the bulbocavernosus reflex. Simultaneous alterations in bowel function (constipation) might also alert one to the possibility of a neurologic origin.

#### Treatment

After patients have been evaluated, they should be informed of the various therapeutic options for BPH. It is advisable for patients to consult with their physicians to make an educated decision on the basis of the relative efficacy and side effects of the treatment options. Specific treatment recommendations can be offered for certain groups of patients. For those with mild symptoms (IPSS score, 0–7), watchful waiting is generally advised. On the other end of the therapeutic spectrum, absolute surgical indications include urinary retention refractory to medical management and attempts at catheter removal, recurrent urinary tract infection, recurrent gross hematuria, bladder stones, renal insufficiency, or large bladder diverticula.

A. Watchful Waiting Very few studies on the natural history of BPH have been reported. The risk of progression or complications is uncertain. However, in men with symptomatic BPH, it is clear that progression is not inevitable and that some men undergo spontaneous improvement or resolution of their symptoms. Retrospective studies on the natural history of BPH are inherently subject to bias, related to patient selection and the type and extent of follow-up. Very few prospective studies addressing the natural history of BPH have been reported. A large randomized study compared finasteride with placebo in men with moderately to severely symptomatic BPH and enlarged prostates on DRE (McConnell et al, 1998). Patients in the placebo arm of the

study had a 7% risk of developing urinary retention over 4 years. As mentioned earlier, watchful waiting is the appropriate management of men with mild symptom scores (0–7). Men with moderate or severe symptoms can also be managed in this fashion if they so choose. Neither the optimal interval for follow-up nor specific end points for intervention have been defined.

## B. Medical Therapy

1.  $\alpha$ -blockers—The human prostate and bladder base contains  $\alpha 1$ -adrenoreceptors, and the prostate shows a contractile response to corresponding agonists. The contractile properties of the prostate and bladder neck seem to be mediated primarily by the subtype  $\alpha 1a$ -receptors.  $\alpha$ -Blockade has been shown to result in both objective and subjective degrees of improvement in the symptoms and signs of BPH in some patients.  $\alpha$ -Blockers can be classified according to their receptor selectivity as well as their half-life (Table 23–2). Phenoxybenzamine and prazosin are the prototypical nonselective and selective  $\alpha$ -blockers, but today, they are primarily of historical interest. Long-acting  $\alpha 1$ -blockers make once-a-day dosing possible, but dose titration is still necessary. Terazosin is initiated at 1 mg daily for 3 days and increased to 2 mg daily for 11 days and then to 5 mg/d. Dosage can be escalated to 10 mg daily if necessary. Therapy with doxazosin is started at 1 mg daily for 7 days and increased to 2 mg daily for 7 days, and then to 4 mg daily. Dosage can be escalated to 8 mg daily if necessary. Possible side effects include orthostatic hypotension, dizziness, tiredness, retrograde ejaculation, rhinitis, and headache. Selective blockade of the  $\alpha 1a$ -receptors, which are localized in the prostate and bladder neck, results in fewer systemic (particularly cardiovascular) side effects, thus obviating the need for dose titration with these agents (tamsulosin, alfuzosin, and silodosin). Other side effects such as retrograde ejaculation still can occur. Several randomized, double-blind, placebo-controlled trials, individually comparing  $\alpha$ -blockers with placebo, have demonstrated the safety and efficacy of all of these agents.

2. 5-Reductase inhibitors—Finasteride is a  $5\alpha$ -reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone (DHT). This drug affects the epithelial component of the prostate, resulting in a reduction in the size of the gland and improvement in symptoms. Six-month therapy is required to see the maximum effects on prostate size (20% reduction) and symptomatic improvement. Several randomized, double-blind, placebo-controlled trials have compared finasteride with placebo. Efficacy, safety, and durability are well established. However, symptomatic improvement is seen only in men with enlarged prostates ( $>40\text{ cm}^3$ ). Side effects are uncommon and include decreased libido, decreased ejaculate volume, and impotence. Serum PSA is reduced by approximately 50% in patients being treated with finasteride, but individual values may vary. Dutasteride differs from finasteride as it inhibits both isoenzymes of  $5\alpha$ -reductase. Similar to finasteride, it reduces serum PSA and total prostate volume. Randomized, placebocontrolled trials have shown the efficacy of dutasteride in symptomatic relief, symptoms scores, peak urinary flow rate, and reduced risk of acute urinary retention and the need for surgery. Side effects are relatively uncommon and include erectile dysfunction, decreased libido, gynecomastia, and ejaculation disorders. Few studies

comparing finasteride and dutasteride head-to-head. One retrospective analysis of >5000 men older than 65 years treated with 5 $\alpha$ -reductase inhibitors in the mid-2000s found small but statistically significant differences, with rates of urinary retention of 12% and 14.7% for dutasteride and finasteride, respectively ( $p = 0.0042$ ), and rates of prostate surgery of 3.9% and 5.1%, respectively ( $p = 0.03$ ) (Fenter et al, 2008).

3. Combination therapy—The first randomized, double-blind, placebo-controlled study investigating combination  $\alpha$ -blocker and 5 $\alpha$ -reductase inhibitor therapy was a four-arm Veterans Administration Cooperative Trial comparing placebo, finasteride alone, terazosin alone, and combination finasteride and terazosin (Lepor et al, 1996). More than 1200 patients participated, and significant decreases in IPSS and increases in urinary flow rates were seen only in the arms containing terazosin. However, one must note that enlarged prostates were not an entry criterion; in fact, prostate size in this study was much smaller than that in previous controlled trials using finasteride (32 vs 52 cm<sup>3</sup>). McConnell and colleagues conducted a long-term, double-blind trial involving 3047 men to compare the effects of placebo, doxazosin, finasteride, and combination therapy on measures of the clinical progression of BPH (McConnell et al, 2003). The risk of overall clinical progression—defined as an increase above baseline of at least four points in the IPSS, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection—was significantly reduced by doxazosin (39% risk reduction) and finasteride (34% risk reduction), as compared with placebo. The reduction in risk associated with combination therapy (66% risk reduction) was significantly greater than that associated with doxazosin or finasteride alone. Patients most likely to benefit from combination therapy are those in whom baseline risk of progression is very high, generally patients with larger glands and higher PSA values.

4. Phytotherapy—Phytotherapy refers to the use of plants or plant extracts for medicinal purposes. The use of phytotherapy in BPH has been popular in Europe for years, and its use in the United States is growing as a result of patient-driven enthusiasm. Several plant extracts have been popularized, including the saw palmetto berry (*Serenoa repens*), the bark of *Pygeum africanum*, the roots of *Echinacea purpurea* and *Hypoxis rooperi*, pollen extract, and the leaves of the trembling poplar. *S. repens* has been the most well-studied agent, usually at 320 mg/day. Given the poor regulation of the nutritional supplement industry, actual tablet content may vary extremely from the dose noted on the product label (Feifer et al, 2002). A prospective, randomized clinical trial of saw palmetto showed no benefit beyond placebo for either IPSS improvement or urinary flow rate (Bent et al, 2006). An updated systematic review including this and other trials confirmed no improvement over placebo for this approach (Wilt et al, 2009).

### C. Surgical Therapy

1. Transurethral resection of the prostate—The vast majority of subtotal prostatectomies undertaken for BPH can be completed endoscopically. Most of these procedures involve the use of a spinal or general anesthetic and usually require an overnight hospital stay. Magnitude and durability of IPSS and flow rate improvement with transurethral resection of the prostate (TURP) is superior to that of any minimally invasive therapy.

However, the length of hospital stay of patients undergoing TURP is greater. Risks of TURP include retrograde ejaculation (75%), impotence (5–10%), and incontinence (<1%). Complications include bleeding; urethral stricture or bladder neck contracture; perforation of the prostate capsule with extravasation; and, if severe, transurethral resection (TUR) syndrome resulting from a hypervolemic, hyponatremic state due to absorption of the hypotonic irrigating solution. Clinical manifestations of the TUR syndrome include nausea, vomiting, confusion, hypertension, bradycardia, and visual disturbances. The risk of the TUR syndrome increases with resection times >90 minutes and is usually seen in older men. Treatment includes diuresis and, in severe cases, hypertonic saline administration. TURP can now be performed with a bipolar electrode, allowing resection to be performed under saline irrigation. This approach eliminates the hyponatremia responsible for TUR syndrome, though significant fluid volume absorption can still occur with prolonged resection.

2. Transurethral incision of the prostate—Men with moderate to severe symptoms and a small prostate often have posterior commissure hyperplasia (elevated bladder neck). These patients will often benefit from an incision of the prostate. This procedure is more rapid and less morbid than TURP. Outcomes in well-selected patients are comparable, although a lower rate of retrograde ejaculation with transurethral incision has been reported (25%). The technique involves two incisions using the Collins knife at the 5- and 7-o'clock positions. The incisions are started just distal to the ureteral orifices and are extended outward to the verumontanum.

3. Transurethral vaporization of the prostate (TUVP)—Increasingly popular in recent years, ablative techniques use photo- or electroevaporation to ablate obstructing prostate tissue. The two most commonly used devices for these procedures are the neodymium-doped yttrium-aluminum-garnet (Nd:YAG) KTP “GreenLight” laser, which is preferentially absorbed by hemoglobin, and the plasma vaporization “Button” electrode. The latter works with a standard contemporary bipolar generator used for bipolar TURP. As with modern TURP, these procedures are performed under saline irrigation. The goal of the procedure in either case is to produce a central prostate defect comparable with what would be expected after a traditional TURP, but with less bleeding and lower risk of perforation. The potential downsides are greater irritative voiding symptoms in the short term after the procedure and less durability of the result than a standard TURP. Also, as tissue is destroyed rather than resected, no specimen is sent to pathology for review.

4. Holmium laser enucleation of the prostate (HoLEP)—Rather than progressive resection or ablation of tissue from the urethra outward as with TURP and its derivatives, HoLEP denotes an anatomic dissection in the plane between the central and peripheral zones of the prostate. This approach is felt to provide the largest defect and perhaps the longest durability, but entails a longer learning curve than TURP or TUVP.

5. Simple (subtotal) prostatectomy—When the prostate is too large to be removed endoscopically, an open enucleation is necessary. What constitutes “too large” is subjective and will vary depending upon the surgeon’s experience with TURP. Glands >100 g are usually



considered for open enucleation. Open prostatectomy may also be initiated when concomitant bladder diverticulum or a large bladder stone is present or if dorsal lithotomy positioning is not possible. Open prostatectomies can be done with either a suprapubic or retropubic approach. A simple suprapubic prostatectomy is performed transvesically and is the operation of choice in dealing with concomitant bladder pathology. After the bladder is opened, a semicircular incision is made in the bladder mucosa, distal to the trigone. The dissection plane is initiated sharply, and then blunt dissection with the finger is performed to remove the adenoma. The apical dissection should be done sharply to avoid injury to the distal sphincteric mechanism. After the adenoma is removed, hemostasis is attained with suture ligatures, and both a urethral and a suprapubic catheter are inserted before closure. In a simple retropubic prostatectomy, the bladder is not entered. Rather, a transverse incision is made in the surgical capsule of the prostate, and the adenoma is enucleated as described earlier. Only a urethral catheter is needed at the end of the procedure. Robot-assisted simple prostatectomy has been reported in recent small series (Sutherland et al, 2011).

6. Transurethral microwave thermotherapy—Microwave hyperthermia is most commonly delivered with a transurethral catheter. Some devices cool the urethral mucosa to decrease the risk of injury. However, if temperatures are not  $>45^{\circ}\text{C}$ , cooling is unnecessary. Improvement in IPSS and flow rate has been documented, but as these procedures are done in the office with no visual verification of tissue ablation, results have been mixed. Strong financial incentives, however, have driven frequent utilization in certain clinical contexts. Very sparse prospective data are available to fairly compare any of the above procedures with TURP or with each other. A recent meta-analysis found few differences, but the component studies tended to be small and with limited follow-up (Ahyai et al, 2010). All of the newer procedures are more expensive than TURP, and comparative cost-effectiveness studies are sorely needed.

### QUESTIONS FOR CHECK-UP

1. Etiology of BPH.
2. Pathogenesis of BPH.
3. Differential diagnosis of BPH.
4. Clinical presentations upon BPH.
5. BPH, laboratory diagnostics.
6. BPH, instrumental diagnostics.
7. BPH, conservative treatment.

8. BPH, surgical treatment.

Recommended education resources:

1. uroweb.ru
2. uroweb.org
3. “SMITH & TANAGHO’S GENERAL UROLOGY”, 2017