The Prostate

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Anatomy and Cell Biology of the Prostate Gland

DEVELOPMENT	
Seminal vesicles	From wolffian ducts through testosterone stimulation
Prostate	From urogenital sinus through dihydrotestosterone stimulation

PROSTATE ZONES	
Anterior fibromuscular	30% of prostate mass, no glandular elements, smooth muscle
Peripheral	Largest zone, 75% of prostate glandular elements, site of carcinomas
Central	25% of prostate glandular elements; surrounds ejaculatory ducts
Transitional	Smallest zone, surrounds upper urethra complex, sphincter
	5% of prostate glandular elements, site of benign prostatic hyperplasia
	15%–30% of prostate volume

EPITHELIAL CELLS	
Basal	Small and flattened undifferentiated, nonsecretory cells with a low proliferative index (<1%) that express keratins 5, 14, and 18
Intermediate	Proliferating cell type that has characteristics intermediate between basal and secretory cells, including production of basal and secretory cell keratins
Columnar secretory	Terminally differentiated, nondividing, rich in acid phosphatase and prostate-specific antigen; 20 µm tall, most abundant cell, keratins 5 and 18
Neuroendocrine	Terminally differentiated, nonproliferating cells that express serotonin, chromogranin-A, neuron-specific enolase, and synaptophysin proteins

STROMAL CELLS	
Smooth muscle	Rich in α-actin, myosin, and desmin
Fibroblast	Vimentin rich and associated with fibronectin
Endothelial	Associated with fibronectin; alkaline phosphatase positive

TISSUE MATRIX	
Extracellular matrix	
Basement membrane	Type IV and V collagen meshwork that is laminin rich and supports basal cells, stem cells, transit-amplifying cells, and secretory epithelium
Connective tissue	Type I and type III fibrillar collagen; elastin
Glycosaminoglycans	Sulfates of dermatan, chondroitin, and heparin; hyaluronic acid
Cytomatrix	Tubulin, α-actin, and intermediate filaments of keratin
Nuclear matrix	Dynamic structure of the nucleus that directs the functional organization of DNA into loop domains; contains ribonuclear proteins

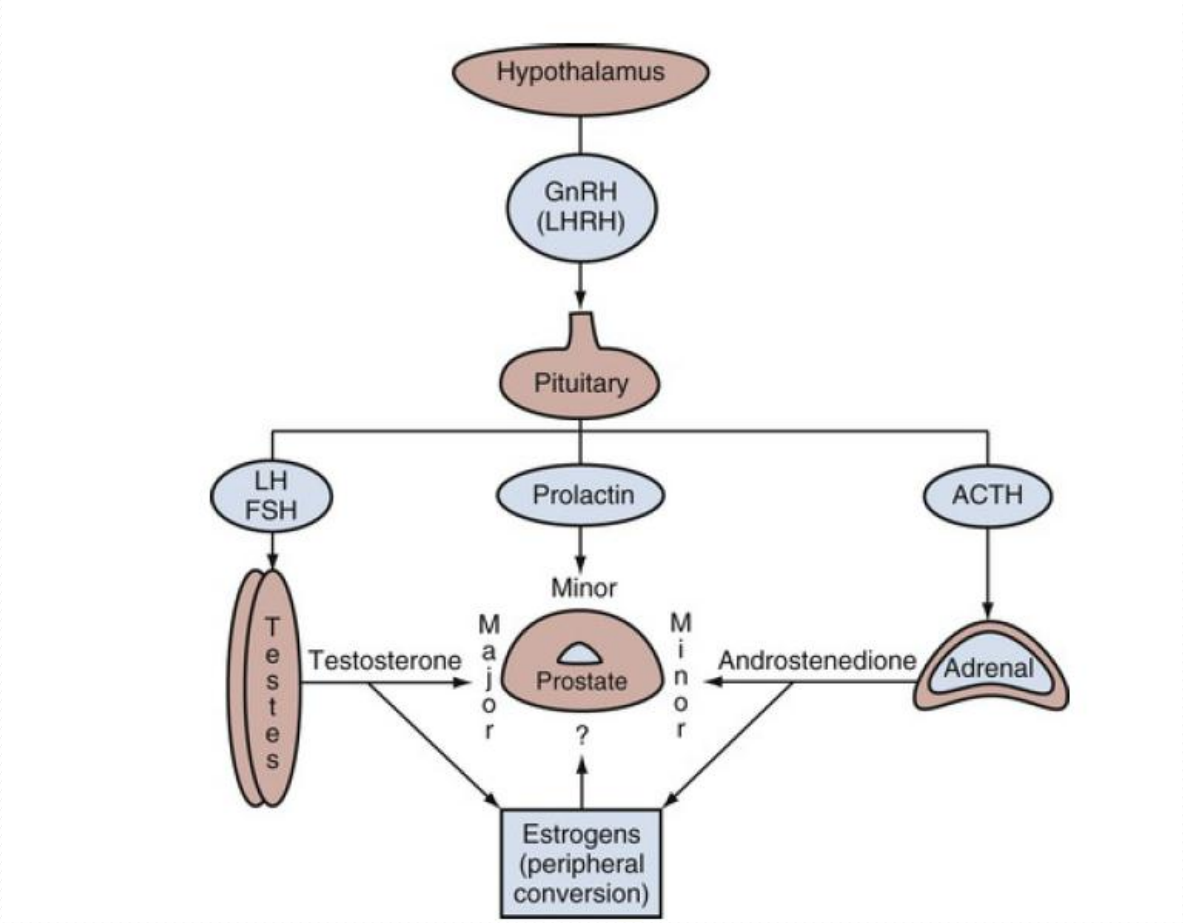
Prostate Cell Types

- The prostatic epithelium in the human is composed of two major cell compartments: epithelial cells and stromal cells.

- **In summary, the development and maintenance of the prostate occur through androgen-dependent and highly regulated tissue morphogenesis in processes involving epithelial cell differentiation, proliferation, and apoptosis**

- **Communication through numerous extracellular interactions is directed to the intracellular cytoskeleton and then to the nuclear matrix, which ultimately regulates a variety of transcriptional cell functions that control such critical phenotypic qualities as cell size and shape, cell motility, epithelial cell turnover, proliferation,and differentiation**

Endocrine Control of Prostate Growth



- Free testosterone in the plasma is converted in the prostate by ٥α-reductase type ٢ into DHT, which is ٢ to ١٠ times more active than testosterone.

- DHT, testosterone, and estrogens are responsible for multiple metabolic actions in the prostate (growth, differentiation, and biologic functions).Free testosterone can be converted to estrogens, but estrogens cannot be converted to testosterone.

- **In summary, ⁵α-reductase is of great importance because the product DHT is important in the differentiation of the prostate during fetal development and because mutations in ⁵α-reductase give rise to a rare form of pseudohermaphroditism. In prostate physiology, expression of the ⁵α-reductase gene is regulated by androgens in the prostate and liver.**

- **The ٥α-reductase inhibitors finasteride (type ٢ inhibitor) and dutasteride (type ١ and ٢ inhibitor) are clinically useful drugs in the treatment of BPH and male pattern baldness when they are given to appropriate patients.**

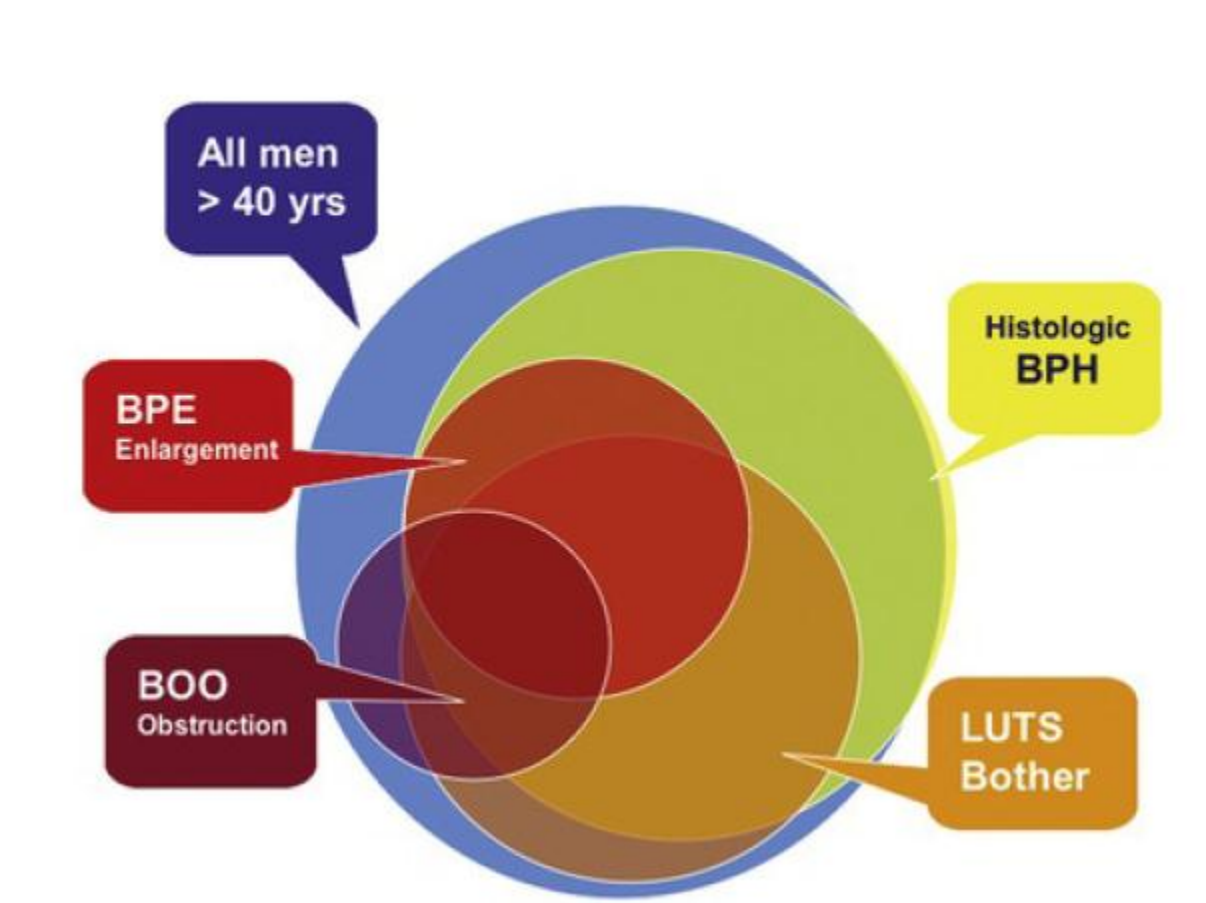
Secretory Proteins—Kallikreins

- Secreted prostate proteases exert a significant and dose-dependent effect on semen liquefaction.

- Among the most well-studied secreted prostate proteins are hKLK٣ (PSA) and a homologous protease, hK٢, which functions to cleave PSA.

- PSA and its processed derivative (i.e., BPSA, fPSA, [–٢]pro-PSA), as well as hK٢, have various associations with benign prostatic tissue and prostate cancer and are currently being used to aid in prostate cancer screening.

Benign Prostatic Hyperplasia



- **Histopathologically, BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate and thus is correctly referred to as *hyperplasia and not hypertrophy, as is often found* in the older literature.**

- **Although androgens and growth factors stimulate cell proliferation in experimental models, the relative role of cell proliferation in human BPH is questioned because there is no clear evidence of an active proliferative process.**

Histologic or Autopsy Prevalence

- summarized the data from five studies demonstrating that no men younger than ٣٠ years of age had evidence of BPH and that the prevalence rose with each age group, peaking at ٨٨% in men in their ٨٠s

Complications of Benign Prostatic Hyperplasia

Bladder Stones

- **In clinical practice, the risk for bladder stone development is small, and screening is only indicated if clinical circumstances warrant it (e.g.,hematuria, stuttering of urination).**

Bladder Decompensation

- **When endoscopically evaluating the bladder in men with BPH, urologists search for a progression from normal mucosa to advancing trabeculation, development of cellules, and diverticula, with ultimate detrusor muscle failure in mind.**

- **The critical question is whether or not delayed intervention might lead to progressive irreversible loss of bladder function and misses a window for cure. There is no direct evidence for this from longitudinal population or clinic patient studies.**

Urinary Incontinence

Urinary Tract Infections

- **Although one might intuitively assume that increased amounts of residual urine would predispose to the development of UTI, clear evidence is lacking.**

Upper Urinary Tract Deterioration and Azotemia

Hematuria

- **It has always been recognized that patients with BPH might develop gross hematuria and form clots with no other cause being identifiable. Recent evidence suggests that in patients predisposed to hematuria, microvessel density is higher compared with controls.**

Acute Urinary Retention

- **AUR is for several reasons one of the most significant complications or longterm outcomes resulting from BPH. It has in the past represented an immediate indication for surgery.**

- **The etiology of AUR is poorly understood, and obstructive, myogenic,and neurogenic causes all may play a role**

- **Prostate infection, bladder overdistension , excessive fluid intake,alcohol consumption, sexual activity, debility, and bed rest have all been mentioned . Prostatic infarction has been suggested as being an underlying event causing AUR**

- **From a clinical and prognostic point of view, spontaneous AUR should be separated from precipitated AUR, although this is by no means consistently done in the literature.**

- **Precipitated AUR refers to the inability to urinate after a triggering event such as non–prostate-related surgery; catheterization; anesthesia; ingestion of medications with α-sympathomimetic or anticholinergic effects or antihistamines; or others. All other AUR episodes are classified as spontaneous**

Evaluation and Nonsurgical Management of Benign Prostatic Hyperplasia

- **LUTS are considered as a clinical manifestation with a multifactorial pathophysiology arising from different conditions, including bladder outlet** obstruction (BOO) possibly caused by benign prostatic obstruction (BPO),associated with benign prostatic enlargement (BPE)

Diagnostic Evaluation

- **The quantification of symptom severity and the assessment of how a given level of symptoms may affect each man's QoL (degree of associated bothersome) provides valuable information in terms of the severity of disease, response to therapy, and risk for disease progression.**

- **The IPSS is currently considered the international standard tool to investigate LUTS severity.**

International Prostate Symptom Score

SYMPTOM	NOT AT ALL	<1 TIME IN 5	LESS THAN HALF THE TIME	ABOUT HALF THE TIME	MORE THAN HALF THE TIME
1. INCOMPLETE EMPTYING					
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

2. FREQUENCY					
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
3. INTERMITTENCY					
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4

4. URGENCY					
Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4
5. WEAK STREAM					
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4

6. STRAINING					
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4
	NONE	1 TIME	2 TIMES	3 TIMES	4 TIMES
7. NOCTURIA					
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

TOTAL INTERNATIONAL PROSTATE SYMPTOM SCORE					
QUALITY OF LIFE DUE TO URINARY SYMPTOMS	DELIGHTED	PLEASED	MOSTLY SATISFIED	MIXED—ABOUT EQUALLY SATISFIED AND DISSATISFIED	MOSTLY DISSATISFIEI
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you	0	1	2	3	4
feel about that?					

- The sum of the values indicates the severity of symptoms (٠ to ٧ is mild, ٨ to ١٩ is moderate, ٢٠ to ٣٥ is severe)

Physical Examination

- **DRE has a double aim: (١) to obtain a baseline estimation of prostate volume (PV), which is a useful parameter throughout the clinical decision-making process; and (٢) to exclude the presence of palpable nodules or any increased consistency that may signal the presence of PCa.**

Frequency-Volume Charts and Bladder Diaries

Laboratory Tests

Urinalysis

- **The use of a dipstick test and/or the microscopic evaluation of urine samples is suggested in all patients complaining of LUTS as a part of the baseline evaluation**

- **Urine cytology should always be requested in men with severe storage symptoms and dysuria, especially if they have a smoking history.**

Prostate-Specific Antigen

- **The value of PSA testing among patients presenting for LUTS is multiple: assess the risk and eventually rule out the presence of PCa; estimate PV;and predict BPH-related outcomes.**

- **Current international clinical guidelines suggest measurement of PSA if a diagnosis of PCa willchange LUTS management, excluding, for instance, those men with a life** expectancy of less than ١٠ years

Renal Function Assessment

- **The assessment of renal function based on serum creatinine level or estimated glomerular filtration rate is not routinely suggested in patients with LUTS**

- **As a whole, AUA guidelines no longer recommend a routine renal function assessment, but EAU guidelines suggest assessment of serum creatinine level if renal impairment is suspected on the basis of medical history or when surgical treatment is considered.**

Postvoid Residual Volume

- **In clinical practice, a PVR volume of less than ۳۰ mL is usually considered nonsignificant, whereas PVR volume persistently greater than ۵۰ mL could be regarded as important**

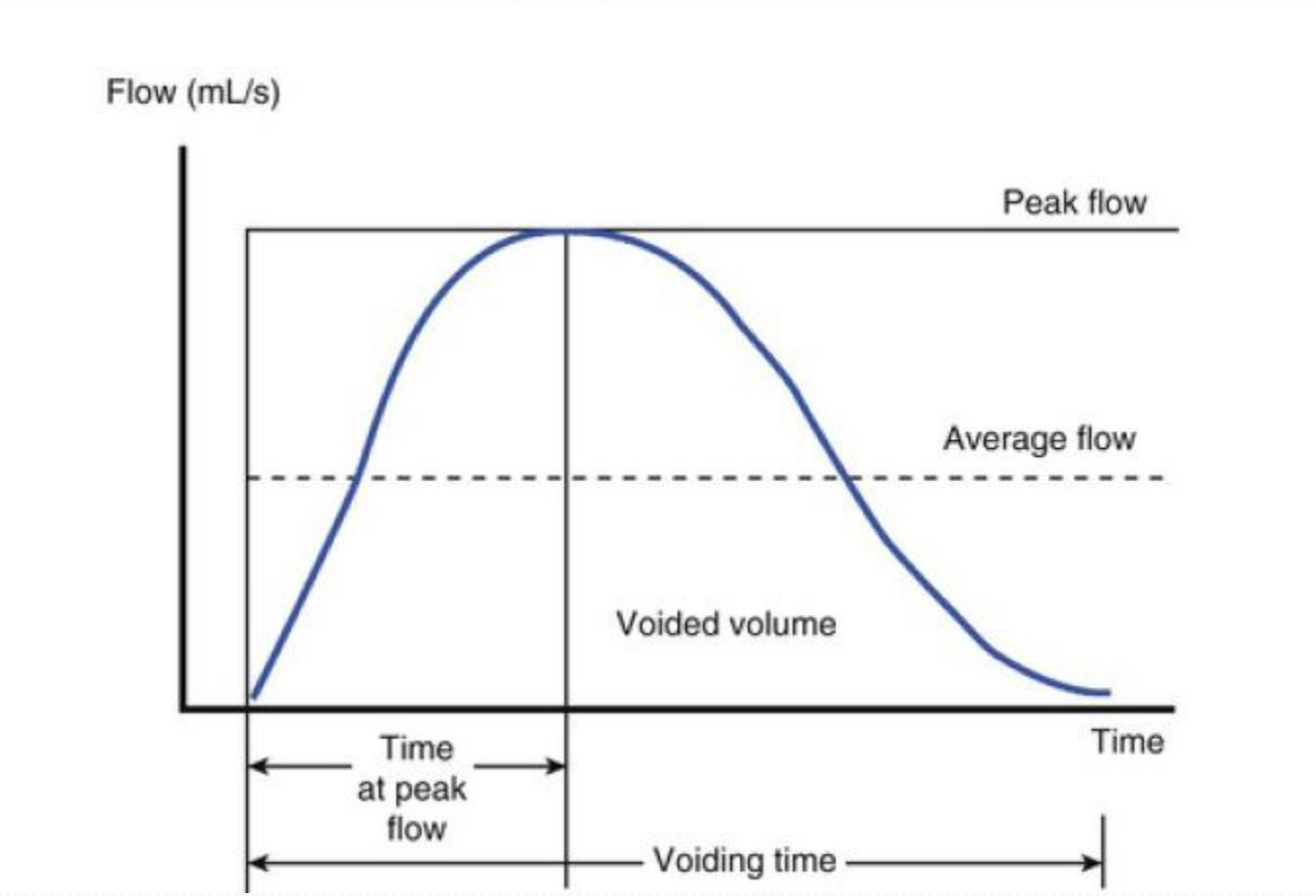
- • The interval between voiding and PVR volume measurement should be of short duration.

- Although transurethral catheterization is considered the gold standard to assess PVR volume, it could be associated with patient discomfort and the risk for UTIs and urinary tract trauma.

- **The ultrasound bladder volume measurement should be used to assess PVR volume and can be performed with either a real-time transabdominal ultrasound scanner or a portable bladder scanner.**

- **PVR volume assessment is suggested both during basic workup and during the follow-up of patients with LUTS. Men with significant PVR volume should be monitored closely if they elect to have nonsurgical therapy**

Uroflowmetry



- **According to expert opinion, a PFR cutoff of ١٥ mL/s could be used to define outlet obstruction in clinical practice However, a PFR of less than ١٥ mL/s does not differentiate between obstruction and bladder decompensation.**

- **International clinical guidelines consider uroflowmetry as on optional test in the assessment of patients with LUTS, although its use is recommended before any active treatment**

Urodynamics

- **The invasive urodynamic test is the gold standard for the assessment of LUTS pathophysiology and it is used to identify DO, DUA, low bladder compliance, and BOO.**

Pressure-Flow Study

- • Patients with previously unsuccessful invasive treatments for LUTS
- • Patients who cannot void more than ١٥٠ mL
- • Patients with PVR volume greater than ٣٠٠ mL
- • Patients older than ٨٠ years of age with predominantly voiding LUTS
- • Patients younger than ٥٠ years of age with predominantly voiding LUTS

Upper-Tract Imaging

- **The routine assessment of the upper tract with ultrasonography is not recommended in patients with LUTS**

- **imaging assessment of the upper tract is currently suggested for patients with LUTS combined with an elevated serum creatinine level or large PVR volumes. Likewise, patients with a history of hematuria, UTI, urolithiasis, or prior urinary tract surgery should also be assessed with abdominal ultrasonography**

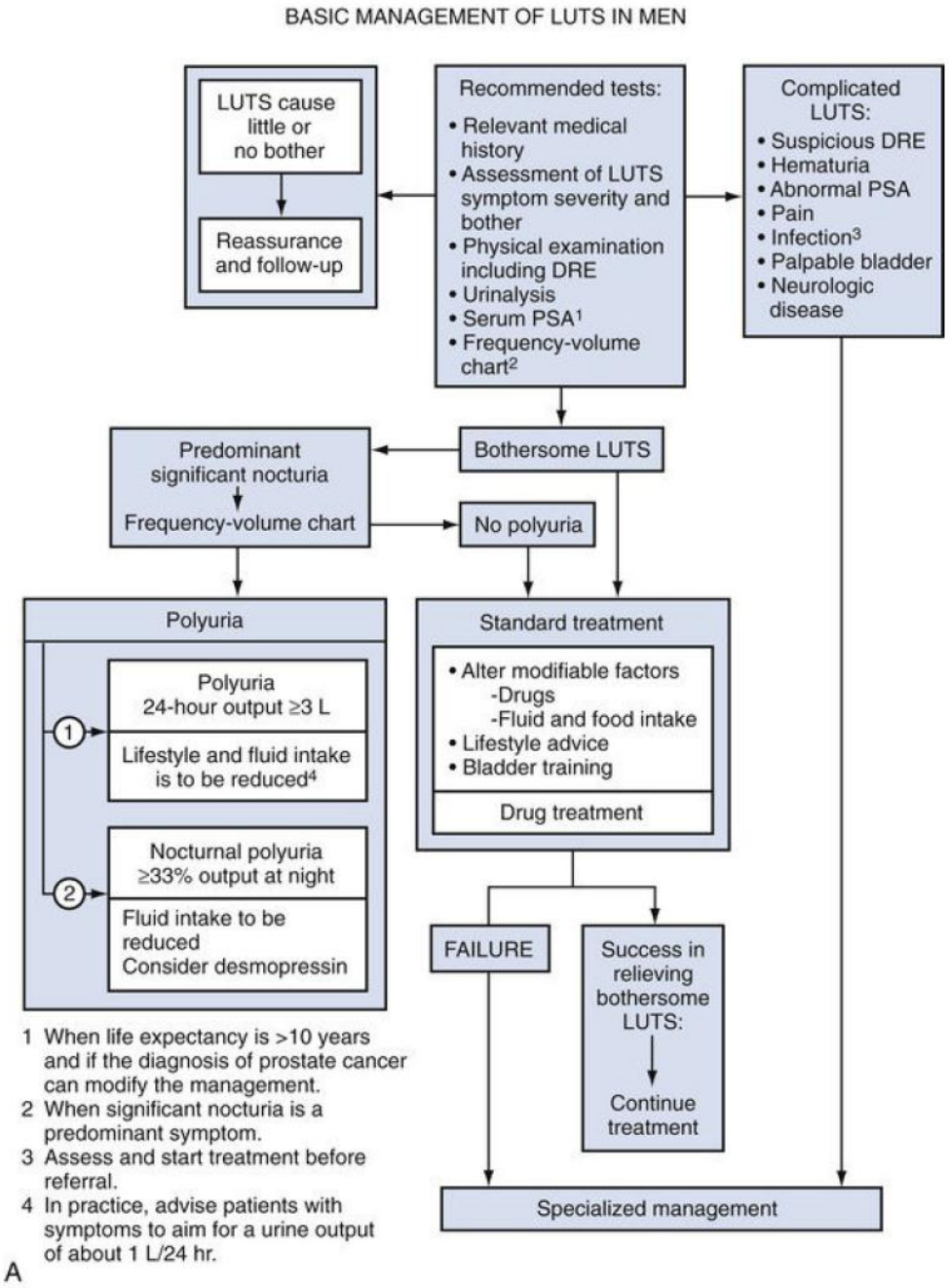
- **Ultrasound-based estimation of PV (either suprapubic or TR) should be routinely performed before any BPH surgery so as to help the physician in choosing the most appropriate technique**

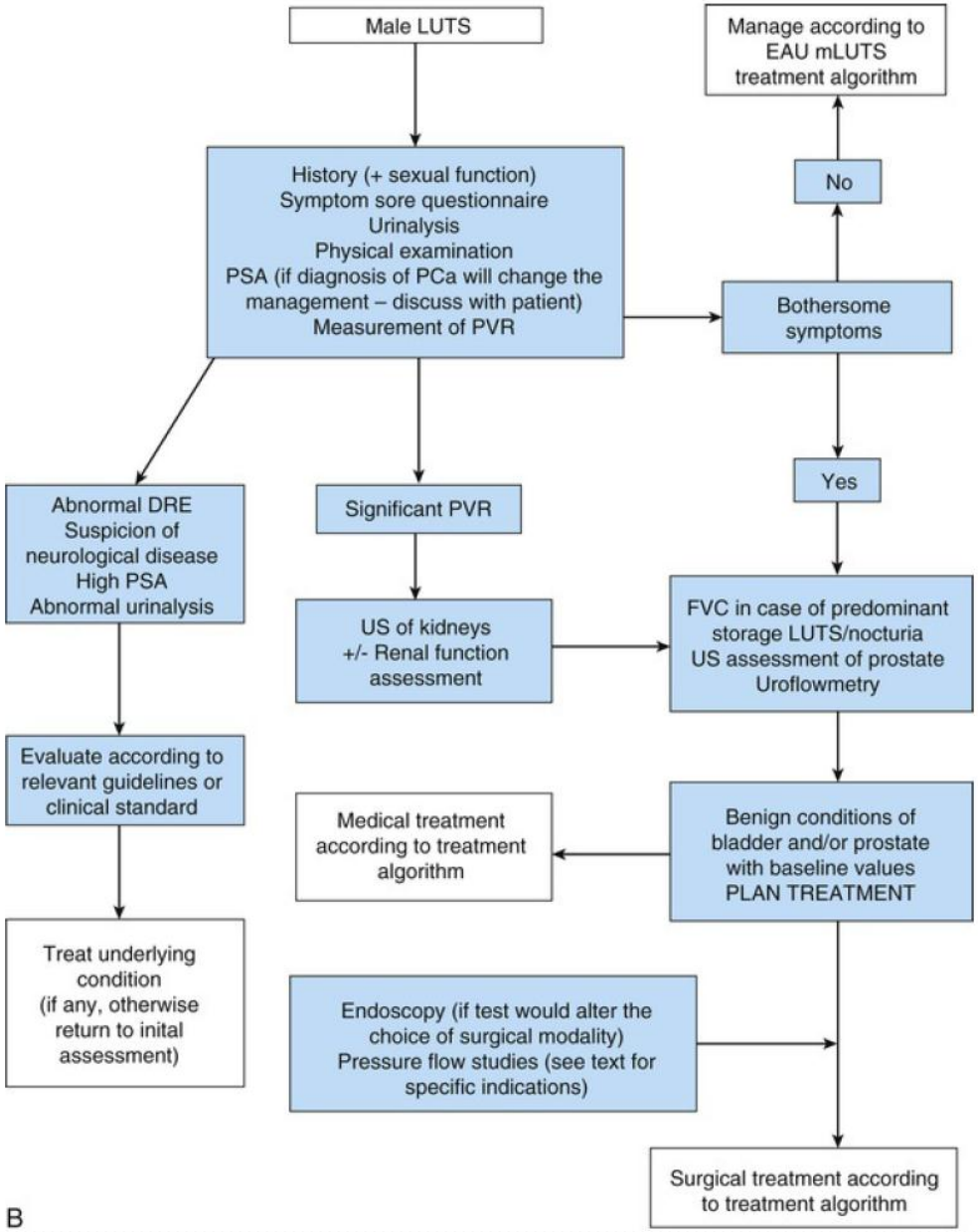
- **given the wide variability in the threshold values used and in terms of the method of assessment, there is currently no clear recommendation for using IPP as a noninvasive alternative to PFS to diagnose BOO.**

Cystourethroscopy

- **cystourethroscopy is neither useful for the diagnosis of BOO nor to determine the need for treatment.**

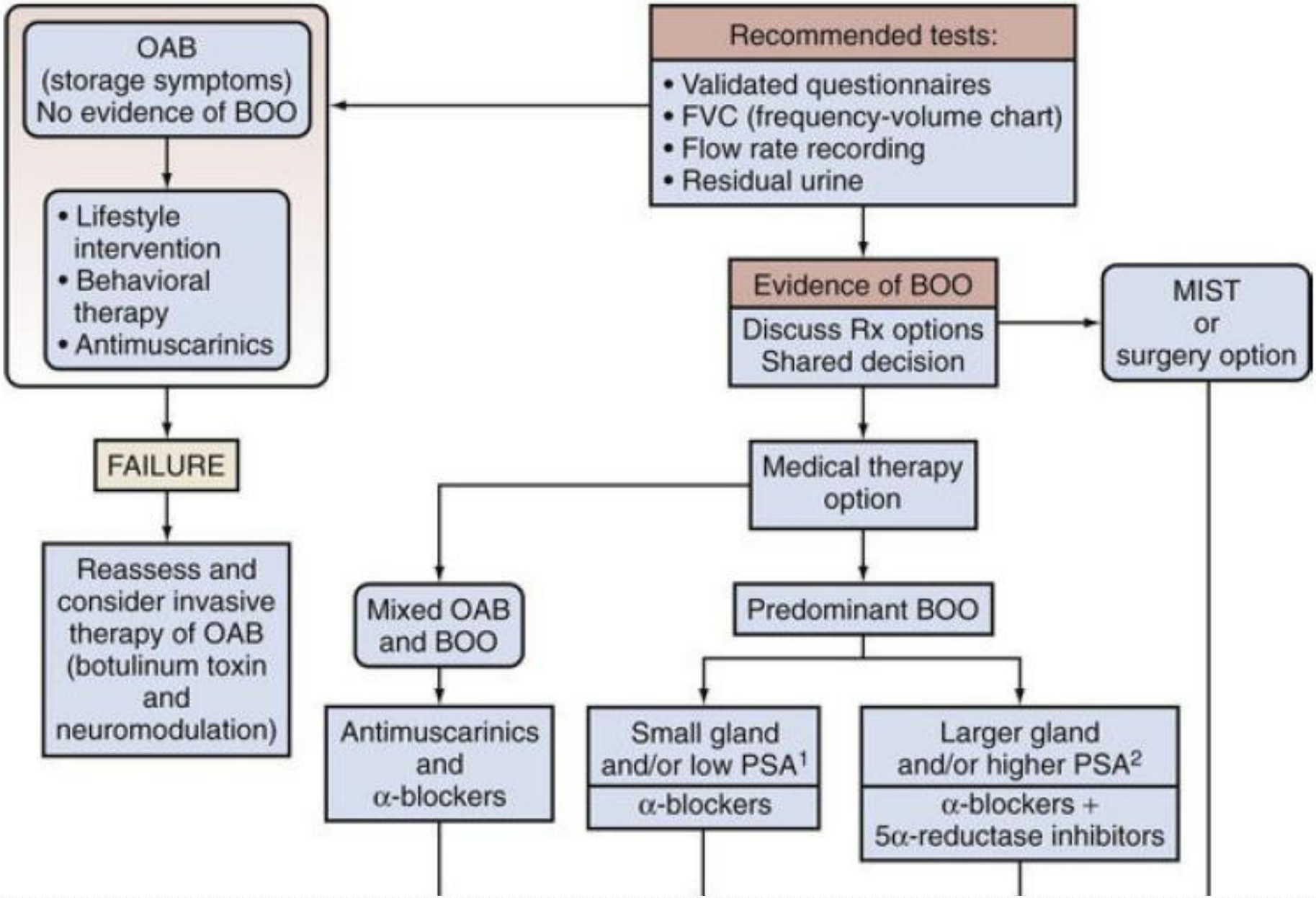
- **Clinical guidelines suggest the use of cystourethroscopy in the case ofreported gross hematuria, history of bladder cancer, history of recurrent UTIs or urethral injury (to rule out urethral stenosis), or in the case of previous surgery of the prostate or urethra.**

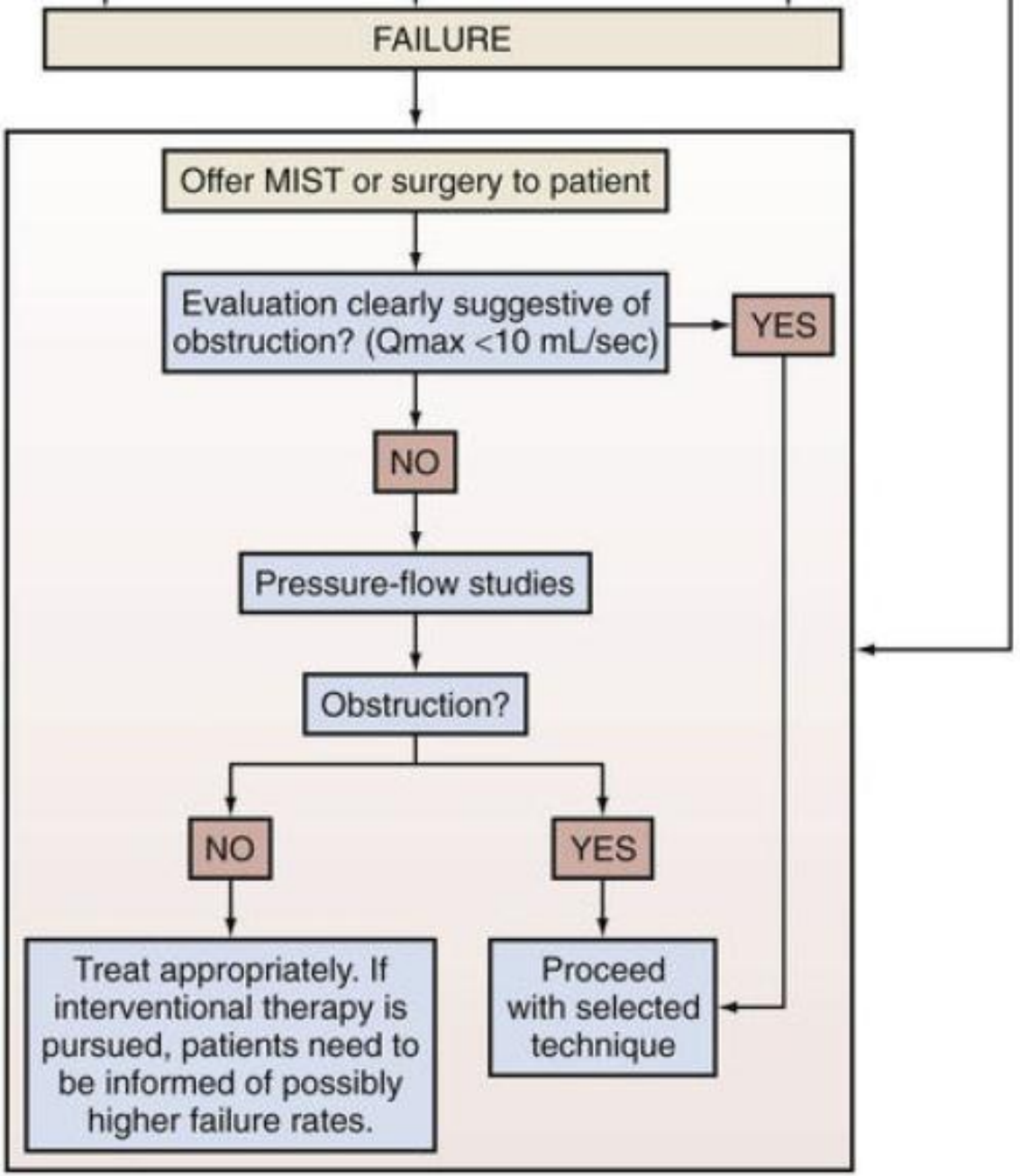

BASIC MANAGEMENT OF LUTS IN MEN
LUTS cause little or no bother
Reassurance and follow-up
Recommended tests:
• Relevant medical history
• Assessment of LUTS symptom severity and bother
• Physical examination including DRE
• Urinalysis
• Serum PSA1
• Frequency-volume chart2
Complicated LUTS:
• Suspicious DRE
• Hematuria
• Abnormal PSA
• Pain
• Infection3
• Palpable bladder
• Neurologic disease
Bothersome LUTS
Predominant significant nocturia
Frequency-volume chart
No polyuria
Polyuria
Polyuria 24-hour output ≥3 L
Lifestyle and fluid intake is to be reduced4
Nocturnal polyuria ≥33% output at night
Fluid intake to be reduced
Consider desmopressin
Standard treatment
• Alter modifiable factors
-Drugs
-Fluid and food intake
• Lifestyle advice
• Bladder training
Drug treatment
FAILURE
Success in relieving bothersome LUTS:
Continue treatment
Specialized management
1 When life expectancy is >10 years and if the diagnosis of prostate cancer can modify the management.
2 When significant nocturia is a predominant symptom.
3 Assess and start treatment before referral.
4 In practice, advise patients with symptoms to aim for a urine output of about 1 L/24 hr.
A

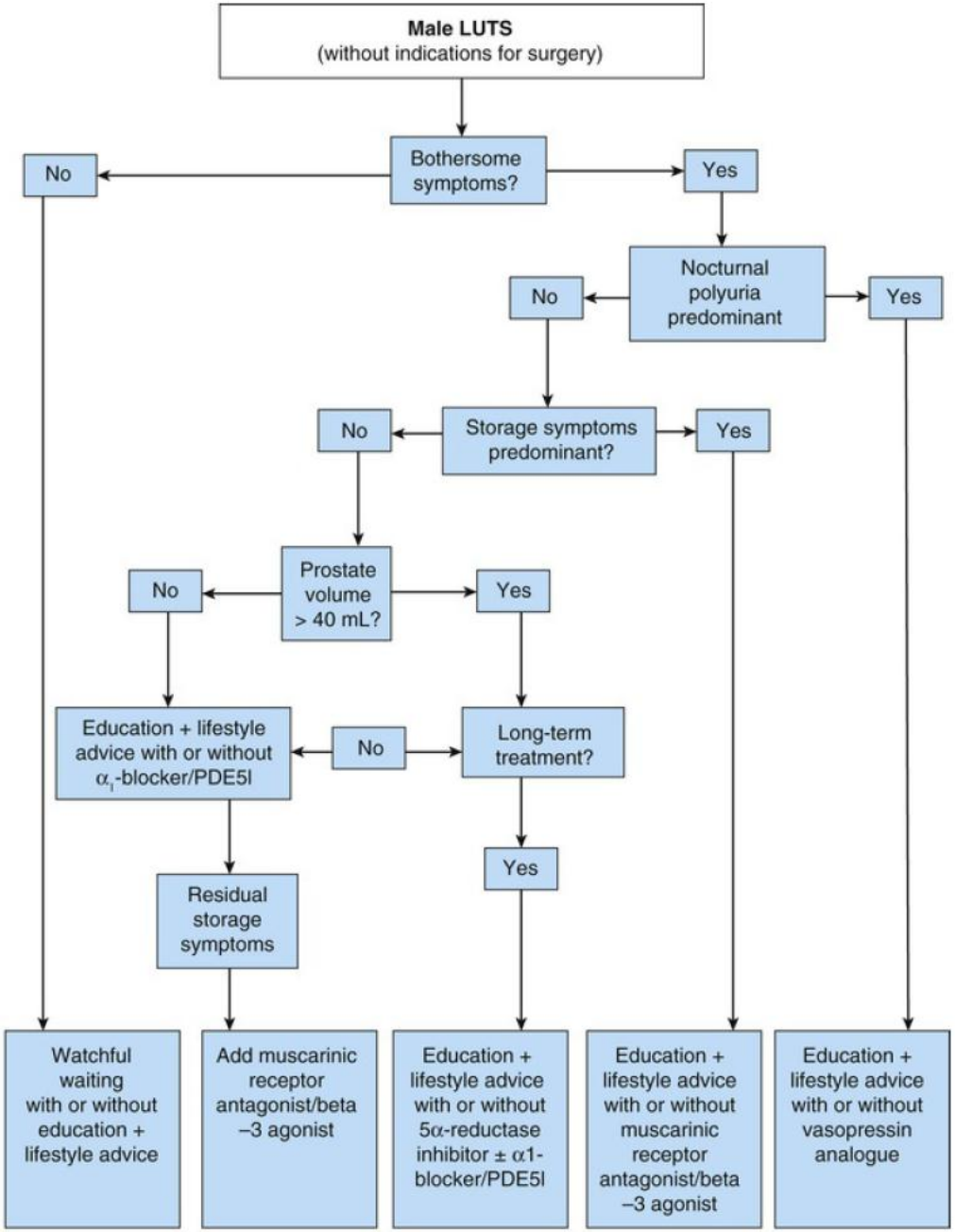

Male LUTS
History (+ sexual function)
Symptom sore questionnaire
Urinalysis
Physical examination
PSA (if diagnosis of PCa will change the management – discuss with patient)
Measurement of PVR
Manage according to EAU mLUTS treatment algorithm
No
Bothersome symptoms
Yes
Abnormal DRE
Suspicion of neurological disease
High PSA
Abnormal urinalysis
Significant PVR
US of kidneys
+/- Renal function assessment
FVC in case of predominant storage LUTS/nocturia
US assessment of prostate
Uroflowmetry
Evaluate according to relevant guidelines or clinical standard
Medical treatment according to treatment algorithm
Benign conditions of bladder and/or prostate with baseline values
PLAN TREATMENT
Treat underlying condition
(if any, otherwise return to inital assessment)
Endoscopy (if test would alter the choice of surgical modality)
Pressure flow studies (see text for specific indications)
Surgical treatment according to treatment algorithm
B

Conservative Management

- **Both the AUA and EAU expert consensus panels suggest that patients with mild-to-moderate noncomplicated LUTS who are minimally bothered by their symptoms should be offered conservative management**


OAB
(storage symptoms)
No evidence of BOO
• Lifestyle intervention
• Behavioral therapy
• Antimuscarinics
FAILURE
Reassess and consider invasive therapy of OAB (botulinum toxin and neuromodulation)
Recommended tests:
• Validated questionnaires
• FVC (frequency-volume chart)
• Flow rate recording
• Residual urine
Evidence of BOO
Discuss Rx options
Shared decision
MIST
or
surgery option
Medical therapy option
Mixed OAB and BOO
Antimuscarinics and α-blockers
Predominant BOO
Small gland and/or low PSA1
α-blockers
Larger gland and/or higher PSA2
α-blockers + 5α-reductase inhibitors


FAILURE
Offer MIST or surgery to patient
Evaluation clearly suggestive of obstruction? (Qmax <10 mL/sec)
YES
NO
Pressure-flow studies
Obstruction?
NO
YES
Treat appropriately. If interventional therapy is pursued, patients need to be informed of possibly higher failure rates.
Proceed with selected technique


Male LUTS
(without indications for surgery)
Bothersome symptoms?
No
Yes
Nocturnal polyuria predominant
No
Yes
Storage symptoms predominant?
No
Yes
Prostate volume > 40 mL?
No
Yes
Education + lifestyle advice with or without α1-blocker/PDE5I
No
Long-term treatment?
Yes
Residual storage symptoms
Watchful waiting with or without education + lifestyle advice
Add muscarinic receptor antagonist/beta –3 agonist
Education + lifestyle advice with or without 5α-reductase inhibitor ± α1-blocker/PDE5I
Education + lifestyle advice with or without muscarinic receptor antagonist/beta –3 agonist
Education + lifestyle advice with or without vasopressin analogue

Watchful Waiting

- **If patients choose WW as the preferred management, they should be followed up yearly to detect any progression in terms of symptoms or the occurrence of complications, which should prompt a more aggressive treatment approach**

Lifestyle and Dietary Modifications

Education and Reassurance

- • Discuss the causes of LUTS, including normal prostate and bladder function.
- • Discuss the natural history of BPH and LUTS, including the expected future symptoms.
- • Reassure the patient that no evidence of detectable PCa has been found.

Fluid Management

- • Advise a daily fluid intake of ١٥٠٠ to ٢٠٠٠ mL (minor adjustments may be made for climate and activity).
- • Avoid inadequate or excessive fluid intake on the basis of an FVC.
- • Advise fluid restriction when symptoms are most inconvenient (e.g., during long journeys or when out in public).
- • Advise evening fluid restriction for nocturia (no fluid for ٢ hours before retiring).

Caffeine and Alcohol

- • Avoid caffeine by replacing caffeine with alternatives (e.g., decaffeinated or caffeine-free drinks).
- • Avoid alcohol in the evening if nocturia is bothersome.
- • Replace large-volume alcoholic drinks (e.g., pint of beer) with smallvolume Malcoholic drinks (e.g., wine or spirits).

Concurrent Medication

- • Adjust the time when medication with an effect on the urinary system is taken to reduce LUTS at times of greatest inconvenience (e.g., during long journeys and when out in public).
- • Replace antihypertensive diuretics with suitable alternatives with fewer urinary effects (via the patient's general practitioner).

Types of Toileting and Bladder Retraining

- • Advise men to double-void (spending extra time on the toilet to try to empty the bladder completely).
- • Advise urethral milking for men with postmicturition dribbling.
- • Advise bladder retraining. With use of distraction techniques (predetermined mind exercise, perineal pressure, or pelvic floor exercises), aim to increase the minimum time between voids to ٣ hours (daytime) and/or the minimum voided volume to between ٢٠٠ and ٤٠٠ mL (daytime). The urge to void should be suppressed for ١ minute, then ٥ minutes, then ١٠ minutes, andso on, increasing on a weekly basis. Use FVCs to monitor progress.

Miscellaneous

- Avoid constipation in men with LUTS

Medical Therapy

- **The current drug armamentarium includes α-adrenergic blockers (α١-blockers), ٥ARIs, antimuscarinic drugs, phosphodiesterase type ٥ inhibitors (PDE٥Is), β٣-agonists, and numerous plant extracts.**

Clinical Indications

- **Medical therapy is the first-line treatment for patients bothered by LUTS without imperative indications for surgery, such as the occurrence of AUR,recurrent UTIs, renal insufficiency, bladder stones, and recurrent gross hematuria**

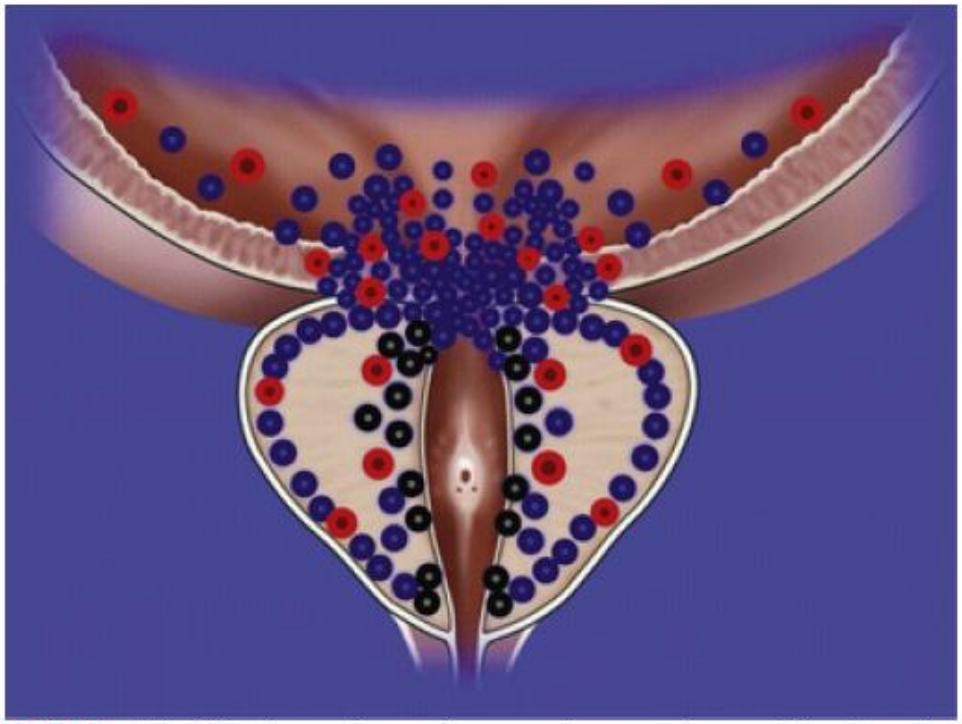


FIG. 145.5 Distribution of α_1-adrenergic receptors at the level of the prostate and bladder neck. The red dots represent α1d receptors, the blue dots represent α1a receptors, and the black dots represent α1b receptors.

Classification of α-Adrenergic Blockers and Recommended Doses

CLASS OF α-BLOCKERS	AVAILABLE FORMULATION	RECOMMENDED DAILY DOSE	RECOMMENDED ADMINISTRATION[a]
NONSELECTIVE			
Phenoxybenzamine	10-mg capsule	10 mg bid	No longer indicated for LUTS treatment

SELECTIVE			
Prazosin	0.5[c]-, 1-, 2[d]-, 5[d]-mg capsule	2 mg bid	No longer indicated for LUTS treatment
Indoramin	20-mg capsule	20 mg bid	No longer indicated for LUTS treatment
Terazosin	1[d]-, 2-, 5-, 10[d]-mg capsule	5 or 10 mg qd	Initial dose is 1 mg at bedtime. The dose should be titrated up to 5 or 10 mg.
Doxazosin IR	1-, 2-, 4-mg capsule	2–8 mg qd	Initial dose is 2 mg at bedtime. The dose should be titrated up to 4 or 8 mg.
Doxazosin SR	4-, 8-mg capsule	4 or 8 mg qd	Initial dose is 4 mg after breakfast, eventually increased to 8 mg.

UROSELECTIVE			
Alfuzosin ER[b]	10-mg capsule	10 mg qd	Initial dose is 10 mg with the same meal each day.
Tamsulosin	0.4-, 0.8[d]-mg capsule	0.4–0.8 mg qd	Initial dose is 0.4 mg with the same meal each day.
Silodosin	4-, 8-mg capsule	8 mg qd	Initial dose is 8 mg with the same meal each day.
Naftopidil	25-, 50-mg capsule	25–75 mg/day	Marketed only in Asian countries

5α-REDUCTASE INHIBITORS		
Finasteride	5 mg qd. Treatment is recommended for at least 6 months	• PSA levels decrease by approximately 50% • Finasteride is not indicated for PCa prevention because of an observed increased risk for high-risk disease • Patients should be warned regarding risk for sexual dysfunction and depression
Dutasteride	0.5 mg qd. Treatment is recommended for at least 6 months	• PSA levels decrease by approximately 50% • Dutasteride is not indicated for PCa prevention because of an observed increased risk for high-risk disease • Patients should be warned regarding risk for sexual dysfunction and depression

Antimuscarinic Drugs for the Treatment of Lower Urinary Tract Symptoms

DRUG	AVAILABLE FORMULATION	RECOMMENDED DAILY DOSE
Darifenacin ER	7.5-, 15-mg capsule	1 × day
Fesoterodine ER	4-, 8-mg capsule	1 × day
Oxybutynin ER	5-, 10-, 15-mg[b] capsule	1 × day (up to 20 mg/day)
Oxybutynin IR	2.5-, 5-mg[a] capsule	3-4 × day (max 20 mg/day)
Propiverine ER (no US)	30-mg capsule	1 × day
Propiverine (no US)	15-mg capsule	2–3 × day
Solifenacin	5-, 10-mg capsule	1 × day
Tolterodine IR	1-, 2-mg capsule	2 × day
Tolterodine ER	2-mg[b], 4-mg capsule	1 × day 1 × day
Trospium IR	20-mg capsule	2 × day
Trospium ER	60-mg capsule	1 × day

Phytotherapy

SPECIES	COMMON NAME
Serenoa repens, Sabal serrulata	Saw palmetto berry, American dwarf palm
Hypoxis rooperi	South African star grass
Pygeum africanum	African plum tree
Urtica dioica	Stinging nettle
Secale cereale	Rye pollen
Cucurbita pepo	Pumpkin seed
Opuntia	Cactus flower
Pinus	Pine flower
Picea	Spruce

Suggested Mechanisms of Actions of Plant Extracts[a]

Inhibition of 5α-reductase
Anti-inflammatory action
Interference with growth factors
Antiandrogenic effects
Estrogenic effects
Inhibition of aromatase
Decrease of sex hormone–binding globulin
Alteration of cholesterol metabolism
Action on α-adrenergic receptors
Free-radical scavenging
Alteration of lipid peroxidation
Modulation of prolactin-induced prostatic growth
Protection of bladder and detrusor function
Placebo effect