A practical primary care approach to lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH-LUTS)

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In the primary care office the evaluation of prostate related lower urinary tract symptoms (BPH-LUTS) in the male can be confusing. Are the symptoms, in fact, from the prostate or is there another etiology such as the bladder or medical conditions causing or contributing to the problems? If the cause is the prostate, how does the physician choose from the multitude of available treatment options and when is referral appropriate? The prevalence of BPH-LUTS is high and commonly encountered by the primary care physician (PCP). An understanding of the normal prostate is essential to identifying the patient when symptoms do occur. Then the evaluation and treatment of the affected patient can occur effectively and efficiently in the PCP setting.

In this article we present the background information needed for the PCP to provide this evaluation of the patient with BPH-LUTS. We explain the various treatment options that are best suited for the individual which are based on symptom severity, sexual dysfunction and risk of progression. We also identify follow up parameters and reasons for referral.

Key Words: lower urinary tract symptoms, benign prostatic hyperplasia, primary care approach

Introduction

The treatment of the symptomatic prostate has undergone a major transformation in the last few decades. Years ago, the only way to help the patient with symptomatic enlargement was to offer surgical reduction, thereby putting treatment into the hands of the urologic surgeon. However, now we have medications to treat the symptoms of obstruction (alpha blockers and phosphodiesterase inhibitors) as well as agents to shrink the gland itself (5 alpha reductase inhibitors) thereby reserving surgical intervention for the refractory patients or those with disease progression. This now places the treatment of the symptomatic patient into the domain of the primary care physician (PCP). Unfortunately, the education for the PCP in this disease state has not entirely caught up with the advances that have been made, which presents a definite opportunity where the patient is the beneficiary. Understanding that the average day of the PCP is intensely complex a simplified approach to the prostate is essential. This approach would help identify the patient with symptom distress or who is asymptomatic but at risk for progression. It would stratify treatment based on severity of symptoms, bother, age and size of the prostate, which are risk factors for disease progression. Also, this approach would include how to recognize the appropriate indications and timing for referral. In this article we present our view on a practical approach to the treatment of prostate related lower urinary tract symptoms (BPH-LUTS).

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Definition of disease

The term BPH-LUTS inherently refers to symptoms caused by obstruction which can include various degrees of poor flow, hesitancy and intermittency. There are many terms used in the literature to describe prostate related LUTS such as benign prostatic hypertrophy (BPH), benign prostatic enlargement (BPE), bladder outlet obstruction (BOO), benign prostatic obstruction (BPO) and enlarged prostate (EP) to name a few.[1] The terminology can occasionally be confusing as enlargement of the prostate does not always mean the patient has symptoms, nor does the presence of symptoms mean enlargement. However, in order to keep this practical for the PCP we will use the term BPH to define the patient having obstructive symptoms secondary to either increased smooth muscle tone within the prostate or the bulky enlargement of the prostate.

There are also many terms used to define LUTS when the bladder is involved. Overactive bladder (OAB) is a syndrome or symptom complex defined as: Urgency, with or without urgency incontinence, usually with frequency and nocturia.[2] Urgency is defined as a sudden, compelling need to void which is difficult to defer. Frequency is defined as voiding more than 8 times per day. Nocturia is defined as voiding more than once per night. Incontinence is defined as the involuntary loss of urine. It is referred to as urge incontinence when preceded by urgency and stress incontinence when this loss occurs while coughing, sneezing, laughing, or other physical activities.

Understanding symptoms

The initial challenge for the physician is to identify the existence of LUTS and then to establish the cause. In order to recognize the symptoms of lower urinary tract abnormalities it is imperative to understand the normal function of both the prostate and the bladder. In fact, both may be functioning normally and the cause could be from another medical issue.

The prostate is a gland that encircles the urethra and produces and directs the fluid for seminal emission, in concert with the bladder neck. In the unaffected male, the urinary stream is functionally unobstructed during voiding through the prostate. Experts have clinically described this good flow as a smooth arc-shaped curve with high amplitude and without interruption.[3] As the male ages, there is proliferation and expansion of cells within the gland. This normal occurrence makes BPH the most common benign neoplasm amongst men.[4] The problems associated with prostatic growth occur via two possible mechanisms. The first is direct physical bladder outlet obstruction (BOO), which is defined as the "static" component. The second mechanism is related to an increase in smooth muscle tone creating a resistance to dilation within the prostatic urethra, which is called the "dynamic" component. Either of these possible mechanisms, alone or in combination, would cause an increased resistance to flow of urine and, subsequently, a clinical finding of hesitancy, poor flow, and/or incomplete emptying.[1]

The bladder's function is to store urine and, subsequently, empty the same volume. The bladder normally holds 300 mL-500 mL of fluid. It should be able to store this amount at a comfortable and low pressure. When 300 mL-500 mL are reached, emptying should occur with an adequate bladder contraction leaving a minimal residual. Abnormal function of the bladder is seen as voiding frequently of small amounts, having an uncontrollable urge or incomplete emptying. Therefore, knowing the voided volume associated with the symptoms offers key insights into the bladder function and assists in identifying its role in the patient's symptoms. The bladder should also provide adequate outlet resistance. Abnormal resistance would be seen as leakage or incontinence.

Prevalence

There is no denying the high prevalence of prostatic hyperplasia in men. In the United States, there is a prevalence of 40% among men at or above the age of 60 and 90% for men at or above the age of 80.[5] Due to the aging population, these numbers will only increase. Not all patients will be symptomatic however, left untreated; men with these symptoms may progress. The untreated symptomatic male has a 23% lifetime risk of developing acute urinary retention.[6] If a man has obstructive symptoms, and is over the age of 60, he has a 39% probability of undergoing surgery related to the prostate within 20 years.[7]

Treatment gaps

Despite the large number of men affected by LUTS, the number of those who seek medical attention is extremely low. While 90% of men reported LUTS in the Multinational Survey of the Aging Male (MSAM-7), only 19% sought medical care and only 11% actually received treatment.[8]

Primary care approach

There are many ways for the PCP to approach the

patient with BPH-LUTS. The following algorithm describes one possibility, Figure 1. Accompanying the algorithm are the key concepts for each portion and the proceeding text explains in greater detail.

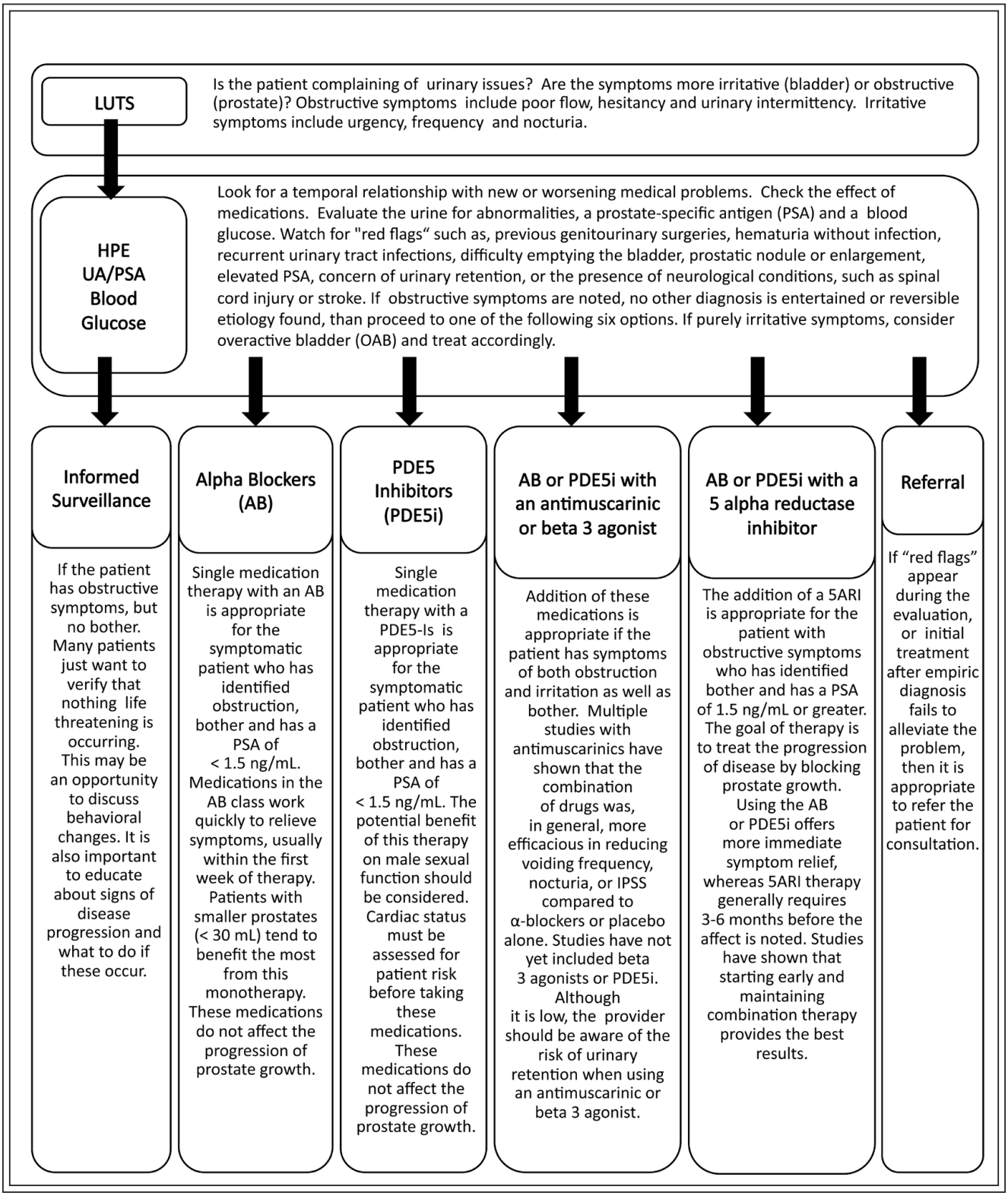

Figure 1. Algorithm describing a primary care approach to a patient with BPH-LUTS.

TABLE 1. **International Prostate Symptom Score (IPSS) questionnaire**

	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**	**Your score**
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	5	
2. Frequency Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	3	4	4	5	
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	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining 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 times or more**	
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	5	

Total IPSS score _____

mild BPH (1 to 7), moderate BPH (8 to 19), or severe BPH (20 to 35)

	Delighted	**Pleased**	**Mostly satisfied**	**Mixed**	**Mostly dissatisfied**	**Unhappy**	**Terrible**
1. Quality-of-life due to urinary symptoms 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

Basic work up: evaluating LUTS

The evaluation starts with the identification of symptoms. Although screening tools exist, they may not always be practical in the office of the busy PCP. Regardless of whether one is used by the physician, being familiar with the questions is helpful. The International Prostate Symptom Score (IPSS) is the most universal option. It has been validated, and includes an additional impact question concerning 'quality-of-life',[9] Table 1. Although helpful in obtaining a thorough history, it is not specific to BPH, as other conditions can produce similar symptoms.[10] By whatever means the PCP queries about the symptoms it is essential to differentiate between obstructive (prostate) and irritative (bladder), as well as to assess bother,[11] Table 2. Given that patients may suffer both obstructive and irritative symptoms, the provider should evaluate which, if either, cause the predominant issue.

Basic work up: history, physical, labs and role of other tests

Once BPH-LUTS is identified, whatever the cause, the next step is to proceed with a focused history and physical, as well as a few laboratory tests. The process is to screen for other factors that may cause or contribute to BPH-LUTS symptoms, including reversible issues or comorbidities that may complicate treatment or represent significant underlying disease. Table 3 lists the possible causes of LUTS.[11] The PCP should also be mindful of the "red flags" or reasons for referral.[12-14] Table 4 lists common reasons for referral.[11]

A distinct advantage for the PCP is having a prior medical knowledge of the patient, thereby making some of the needed information more readily available. The PCP should be mindful of the temporal relationship of the symptoms that the patient is describing to any change in their life or daily habits. Certain behaviors can be a major cause of the bothersome symptoms of BPH. "Urinary hygiene" is a term that has been used to describe voiding habits.[15] Good habits include relaxing the pelvic musculature and taking the time to void to

TABLE 2. **Male lower urinary tract symptoms**

BPH (obstructive)	**OAB (irritative)**
Hesitancy	Urgency
Poor flow/weak stream	Frequency
Intermittency	Nocturia
Straining to void	Urge incontinence
Terminal dribble	Stress incontinence
Prolonged urination	Mixed incontinence
Urinary retention	Overflow incontinence

BPH = benign prostatic hyperplasia; OAB = overactive bladder

TABLE 3. **Lower urinary tract symptoms: differential diagnosis and other causes**

Differential diagnosis	**Medications**	**Other risk factors**
Consider:	**May cause or exacerbate LUTS:**	**Consider:**
Prostate cancer	Trycyclic antidepressants	Obesity
Prostatitis	Anticholinergic agents	Cigarette smoking
Bladder stones	Diuretics	Regular alcohol consumption
Interstitial cystitis	Narcotics	Elevated blood pressure
Radiation cystitis	1st generation antihistamines	
Urinary tract infection	Decongestants	
Diabetes mellitus		
Parkinson's disease		
Primary bladder neck hypertrophy		
Congestive heart failure		
Lumbosacral disc disease		
Multiple sclerosis		

LUTS = lower urinary tract symptoms

TABLE 4. **Indications for referral**

History of recurrent UTIs or other infection
Microscopic or gross hematuria
Prior genitourinary surgery
Elevated PSA
Abnormal prostate exam (nodules)
Suspicion of neurologic cause of symptoms
Findings or suspicion of urinary retention
Meatal stenosis
History of genitourinary trauma
Uncertain diagnosis
Desire to see a specialist

UTIs = urinary tract infections
PSA = prostate-specific antigen

completion. For some males this may involve taking a little extra time to void or sitting on the toilet as opposed to standing. An example of poor urinary hygiene may be found in the work place when a patient is given limited time at the toilet and is not able to void to completion.[15]

A review of the patient's medical and surgical history may offer a clue as to the cause of the LUTS or an associated relationship. For example, the polyuria of the poorly controlled diabetic may increase the voiding frequency enough that the symptoms become markedly more bothersome. Similarly, the patient with congestive heart failure may find that nighttime output and urinary frequency is increased as a result of having elevated their legs in bed, allowing more fluid to reabsorption in the periphery. Sleep apnea has been associated with nocturnal diuresis as well as antidiuretic hormone deficiency. These symptoms may worsen as the condition progresses. The effects of decreased cognition or mobility may limit the patient's access to the bathroom, thereby making the symptoms more noticeable. The provider may also want to take note of comorbid conditions such as erectile dysfunction (ED) and vascular disease, as those are risk factors for BPH.

There are several medications that can affect urinary production and elimination. Polyuria associated with a diuretic could increase output. The alpha agonist effect of a cold medication may tighten the prostatic urethra enough to obstruct flow, and the antimuscarinic effect of multiple medications may contribute to impairment of bladder contractility. Medication induced constipation may exacerbate LUTS. It is important to examine the temporal relationship between when the medication regimen was started and when the symptoms began or became worse.

The physical examination should be focused. It is necessary to check the abdomen for masses or a distended bladder. A brief neurological examination is needed to evaluate a patient's mental and ambulatory status as well as neuromuscular function as these can affect toileting. The PCP should conduct a thorough examination of the genitalia. Meatal stenosis or a phimotic foreskin can mimic the enlarged prostate by impeding flow. A digital rectal examination (DRE) can provide information about the anal sphincter tone as well as prostate size, shape and consistency.[10] BPH usually results in a smooth, enlarged prostate which is not tender to palpation.[16] The gland may have a rubbery consistency, similar to the thenar eminence of the hand, and has often lost the median furrow.[17] In contrast, a nodular firm prostate raises the suspicion of carcinoma and a tender, possibly indurated, gland may indicate infection (prostatitis).[17,18] The PCP should keep in mind that the DRE does offer a basic idea about the size, shape and consistency of the gland, but it is only an estimate. This can often lead the physician to underestimate prostate size as the digital exam cannot assess the full length or anterior portion of the gland.[19] In addition, size alone does not correlate with symptom severity because obstruction is dependent on growth and dynamic changes within the prostatic urethra.[20]

The physical examination, as just reviewed, describes what should be included in the basic evaluation of LUTS in the male. However, much of this may have been done at prior visits with the PCP, so that re-examination (i.e. prostate exam) may not be necessary if it is up to date.

The required laboratory tests are minimal. A urinalysis performed by dipstick or microscopic examination is strongly recommended to check for blood, protein, glucose or any signs of infection. This may prompt treatment or referral. Although hematuria or pyuria are not always found in conditions such as bladder cancer, stones or infection, a normal urinalysis makes these diagnoses less likely.[21] It is not adequate to use the urinalysis to rule out the possibility of diabetes as the serum blood sugar must be over 180 mg/dL before glucose is spilled into the urine.[12] Consequently, a dipstick urinalysis may fail to pick up on intermittently high sugars or patients with mild diabetes. Therefore, although this is not part of the American Urological Association (AUA) guidelines, there is a good argument for testing blood sugar, either random or fasting.[12,21]

Assessment of renal function by measurement of electrolytes, blood urea nitrogen (BUN) and creatinine are useful in screening for chronic renal insufficiency in patients with a high post void residual (PVR) bladder volume.[22] However, they are not universally recommended in the initial evaluation of LUTS.[21,23-25]

There is significant controversy surrounding the benefits of checking the prostate-specific antigen (PSA).[26] Regardless of the PCP's view on use of this lab value, it must be remembered that the PSA is prostate specific and not cancer specific. It was shown by Roehrborn that a PSA value of 1.5 ng/mL, in any age male, correlates to a minimal volume of 30 cc.[27] A review of the placebo arm of Medical Therapy of Prostatic Symptoms (MTOPS) revealed that an increase in size of the prostate is directly related to increased risk of progression or worsening of LUTS caused by the prostate.[28] The prostate volume assigned to this risk was 31 cc. When used appropriately, the PSA can assist the PCP and the patient in making an educated decision about care as will be discussed in the treatment section.

A bladder or voiding diary is a useful tool in the evaluation of LUTS and should be considered especially if there is concern of low urinary volumes. It may also reveal the voiding habits that the patient has developed and where there may be opportunity to change behavior. For example, some patients may have symptoms that only occur during a certain time of the day or night. Urinary production greater than 30% in the nighttime is indicative of nocturnal polyuria. Urinary frequency may be related to a time that the patient drinks copious amounts of fluid or are unable to readily access a toilet. Thus, the diary may offer a clue to simple behaviors that can be altered to minimize symptoms.

The post void residual, or PVR, is not necessary in the initial evaluation of the uncomplicated patient. If this value is needed, it can be measured by direct catheterization or ultrasound scanning. An increased PVR may be a problem if it causes a significant decrease in functional bladder capacity which can lead to symptoms of urgency, frequency or nocturia.[29] While there is no across-the-board consensus on a safe PVR, for the PCP it is generally considered that a value of less than 50 mL represents reasonably efficient voiding and over 200 mL is consistent with clinically significant inadequate emptying.[12] In regards to the patient with BPH, a large residual urine volume is consistent with a significant risk of disease progression. One reason to check the PVR is when the patient's symptoms are refractory to initial therapy. In this case the PCP may consider checking for retention as a result of the obstruction as the source for the poor response. Ultrasonography (abdominal, renal, transrectal) and intravenous urography are also not indicated in the initial evaluation of the prostate related symptoms. If needed, these can be useful in helping determine the size of the prostate and the degree of bladder emptying, and, in the case of urinary retention, the presence of hydronephrosis (if suspected) and renal impairment.

During the evaluation of BPH the PCP should be aware of the risk factors for progression of the disease. Crawford identified five factors that put the patient at risk of progression. These include total prostate volume ≥ 31 mL, PSA ≥ 1.6 ng/mL, Qmax (flow rate) < 10.6 mL, PVR ≥ 39 mL or age ≥ 62.[28] It is understood that not all of these values may be attained in the office of the PCP; however, identification of risk may assist in eventual choice of therapy. Critical evaluation of these factors allows a few practical and logical conclusions for the PCP. As mentioned earlier, Roehrborn pointed out that the PSA is a surrogate marker for prostate size therefore the evaluation by a prostate ultrasound is not necessary.[27] Flow and PVR, however, present a problem in the PCP setting as these are not easily acquired without appropriate equipment. Having said that, it can be assumed that there is a weakened flow as the patient is presenting with symptoms of obstruction. Therefore, it is not likely that treatment choices would be altered regardless of the flow rate. Likewise, one would wonder if knowledge of the PVR would alter initial therapy. Short of flagrant retention, the answer is likely no. In the event that the patient with severe retention filters through, what are the consequences? If he responds to treatment, the PCP has helped him. If he does not respond to therapy he would be referred to a urologist for evaluation. Therefore, given no other signs of an obstructive uropathy, the choice of treatment does not hinge on the information of flow rate or PVR.[29] Through this critical thinking we propose that the clinician can assess risk by knowing the PSA and its correlation to prostate size.

Red flags

The role of the PCP in the evaluation is not only to treat the prostate, if appropriate, but also to identify other possible causes of the LUTS. Those diagnoses that cannot be addressed by the treating clinician should be referred. Table 4 lists reasons for referral.[1]

Treatment choices

Once BPH is determined to be the cause of the obstructive symptoms there are many options available for the patient. The various choices depend on the degree of bother, comorbid conditions, such as ED and irritative symptoms, and risk of progression, as well as success of prior treatment attempts. The PCP should review these options with the patient in order to choose whichever best fits their needs and expectations.

Treatment: informed surveillance

This is a good choice for the patient with obstructive symptoms, but not enough bother to choose or accept any sort of therapeutic intervention.

In reality, patients often feel that taking medications or the risks of surgery are of greater concern than symptoms or even some of the associated quality-of-life issues.[30] One simple question at this point may be enough: "Are your symptoms bad enough that it would justify taking a medication each day or having a surgical procedure?" This should be asked in such a way that the patient is aware that they can come back at any time if, and when, they are ready for intervention.

Informed surveillance refers to the idea that the patient is knowledgeable about the symptoms or the complications that may occur. This is reasonable if patient has not developed complications of BPH, such as BOO, hydroureter, hematuria, hydronephrosis, acute urinary retention (AUR), urinary tract infections (UTIs), bladder hypertrophy, or others.[31] It is critical for the PCP to explain that BPH is a progressive disease, point out the risk factors that have been identified in the evaluation and that he should speak to the physician if the symptoms worsen. In a longitudinal study, Djavan found that over a 4 year time span 87% of men with mild symptoms went on to experience worsening symptoms while 13% of men with mild symptoms experienced stability or improvement of their symptoms.[32] Understanding the risk factors puts the patient and the PCP in a good position to anticipate future issues.

The reasons why some patients choose treatment while others do not is certainly an interesting issue for speculation. Patients will often acknowledge their symptoms and seek to verify that a serious disease is not the cause (for example, prostate cancer). Many men are reluctant to reveal LUTS due to fear that these symptoms represent a serious or life-threatening problem. An education from his PCP regarding the cause of his symptoms will both enlighten and relieve the patient.

Those patients who opt for informed surveillance may benefit from lifestyle changes. Limitations of fluids, bladder training focused on timed and complete voiding, and treatment of constipation may help the patient regulate urinary symptoms. Similarly, a review of the patient's medication list will help identify opportunities to modify (i.e., change the timing of diuretics) or avoid (i.e., decongestants) medications that may impact symptoms of BPH.[15]

Treatment: alpha-blockers

Single medication therapy with an alpha-blocker is appropriate for the symptomatic patient who has identified bother and has a PSA of < 1.5 ng/mL.

Initiating treatment with an alpha-blocker, or alpha antagonist, has been an option for many years. The currently recommended medications include the non-selective second generation alpha-blockers (doxazosin and terazosin) and more uroselective third generation alpha-blockers (alfuzosin, tamsulosin, silodosin), Table 5.[33] By inhibiting alpha1-adrenergic-mediated contraction of prostatic smooth muscle, alpha-blocker therapy relieves the bladder outlet obstruction.[21] This is termed the "dynamic" component of obstruction and these medications are the "openers". For many men, this is sufficient for satisfactory relief of symptoms. Patients with smaller prostates (< 30 mL) tend to benefit the most from this monotherapy. Treatment failure with alpha-blockers is higher in men with larger prostate volumes.[34]

Medications in the alpha-blocker class work quickly to relieve symptoms, usually within the first week of therapy. Similar efficacy is seen with the alpha-blocker class of medication as evidenced by indirect comparisons as well as the limited direct comparisons. However, while alpha-blockers improve symptoms, they do not affect the progression of prostate growth. These medications do not result in long term reduction in the risk of AUR or BPH-related surgery.[34]

Common side effects reported with alpha-blocker therapy include orthostatic hypotension, dizziness, tiredness, ejaculatory problems and nasal congestion.[21] The uroselective alpha-blockers seem to have fewer side effects than the non-selective ones; however, they can be associated with light-headedness and a higher incidence of ejaculatory dysfunction. An additional risk, identified in 2005, is floppy iris syndrome noted during cataract surgery.[35] As a result of this risk, ophthalmologists preparing the patient for cataract surgery should be aware of current alpha-blocker use.

Treatment: phosphodiesterase type 5 inhibitors (PDE5i)

Single medication therapy with a PDE5i is appropriate for the symptomatic patient who has identified obstruction, bother and has a PSA of < 1.5 ng/mL. The potential benefit of this therapy on male sexual function should be considered.

The PDE5i class is relatively new as a treatment for BPH-LUTS. Vardenafil, sildenafil and tadalafil have all been studied on their effects in reducing LUTS, however, in

TABLE 5. **Medications for benign prostatic hyperplasia/lower urinary tract symptoms (BPH-LUTS)**

Drug	Brand name	Dose	Dosing	Indications
Alpha-blockers - non uroselective				
Terazosin	Hytrin	1 mg-10 mg	Daily	BPH
Doxazosin	Cardura	1 mg-8 mg	Daily	BPH
Alpha-blockers - uroselective				
Alfuzosin	Uroxatral (US) Xatral (Canada)	10 mg	Daily	BPH
Silodosin	Rapaflo	8 mg	Daily	BPH
Tamsulosin	Flomax (US) Flomax CR (Canada)	0.4 mg	Daily	BPH
Phosphodiesterase 5 inhibitors				
Tadalafil	Cialis	2.5 mg (US)	Daily	BPH
Tadalafil	Cialis	5 mg	Daily	BPH and ED
Antimuscarinics - immediate release (IR)				
Oxybutynin IR	Ditropan	5 mg	2-4 x/day	OAB
Tolterodine IR	Detrol	1 mg-2 mg	Twice daily	OAB
Trospium chloride	Sanctura (US) Trosec (Canada)	20 mg	Twice daily	OAB
Antimuscarinics - extended release (ER)				
Darifenacin ER	Enablex	7.5 mg, 15 mg	Daily	OAB
Fesoterodine ER	Toviaz	4 mg, 8 mg	Daily	OAB
Oxybutynin ER	Ditropan XL	5 mg-30 mg	Daily	OAB
Oxybutynin TDS	Oxytrol	3.9 mg = 1 patch	Twice weekly	OAB
Oxybutynin 10% gel	Gelnique	100 mg = 1 g of gel	Daily	OAB
Solifenacin	Vesicare	5 mg, 10 mg	Daily	OAB
Tolterodine ER	Detrol LA	2 mg-4 mg	Daily	OAB
Trospium chloride	Sanctura XR (US)	60 mg	Daily	OAB
Beta 3 agonists				
Mirabegron	Myrbetriq	25 mg, 50 mg	Daily	OAB
5 alpha reductase inhibitors				
Dutasteride	Avodart	0.5 mg	Daily	BPH
Finasteride	Proscar	5 mg	Daily	BPH

the United States, Canada and Europe, only tadalafil is approved for this,[36-40] Table 5. Although the exact mechanism of action is unknown, it is believed that the PDE5i increase the signaling of the NO/cGMP pathway, which, in turn, reduces smooth muscle tone in the lower urinary tract.[41] It is reasonable to believe that the PDE5i may also increase blood flow and oxidation to the prostate and pelvic organs.

The male with BPH and no erectile function concerns is fine to be treated with either and therefore availability and cost are the differentiating factors. However, the male with BPH and any degree of ED could benefit from a medication that could treat both situations. In a study published in 2012, Oekle et al compared tadalafil and tamsulosin in a placebo controlled study. They noted statistically significant, yet similar, improvements versus placebo in BPH-LUTS as early as 1 week which was sustained for the 12 week study period. They also noted similar improvement in urinary flow with both medications through 12 weeks, although it should be noted that this was the first study to demonstrate an improvement of flow with the PDE5 drug class. The most significant, yet expected, difference was that tadalafil improved ED.[42] Common side effects of the PDE5i include headache, back pain, dizziness and dyspepsia. They are contraindicated in patients who use nitrates, and should be used with caution in patients treated with alpha-blockers, since the combination may lead to hypotension. Tadalafil should not be used

in patients with a history of non-arteritic anterior ischemic optic neuropathy (NAION).[33] Cardiac status must be assessed for patient risk before taking these medications.[43] Similar to the alpha-blockers, the PDE5i have no impact on prostate growth.

Treatment: alpha-blocker or PDE5i with an antimuscarinic or beta 3 agonist

Addition of an antimuscarinics or beta 3 agonist with an alpha-blocker or PDE5i is appropriate if the patient has symptoms of both irritation and obstruction as well as bother.

LUTS can be a mixture of obstructive (outlet) and irritative (bladder) symptoms. Treatment of the bladder outlet with an alpha-blocker or PDE5i may resolve symptomology enough so that the patient is satisfied. However, in a subset of patients who have an improvement in urinary hesitancy, flow and emptying – the symptoms of urgency, daytime and nighttime urinary frequency, with or without urgency incontinence may persist and be bothersome enough for further therapy. In this case the option of using a medication for these overactive bladder symptoms has been shown to provide significant symptomatic relief. Currently there are two classes of medications available for overactive bladder: antimuscarinics and beta 3 agonists, Table 5.

The European Association of Urology (EAU) guidelines state that muscarinic receptor antagonists might be considered in men with moderate to severe LUTS who have been adequately treated for their obstruction and whose residual complaints are predominantly bladder storage symptoms.[44] The combination therapy of an alpha-blocker together with a muscarinic receptor antagonist aims to antagonize both alpha1-adrenoceptors and muscarinic cholinoreceptors in the lower urinary tract, thereby using the efficacy of both drug classes to achieve synergistic effects.[45,46] The available medications include darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium chloride. The most common side effects include dry mouth, constipation, micturition difficulty, nasopharyngitis and dizziness.[33] No differences in terms of pharmacokinetic or pharmacodynamic properties of the combined use of both drugs have been described compared to the use of the single drugs.[44]

In multiple studies, when alpha-blockers were used with antimuscarinics the combination of drugs was, in general, more efficacious in reducing voiding frequency, nocturia, or IPSS compared to alpha-blockers or placebo alone. Furthermore, the combination treatment significantly reduced urgency urinary incontinence episodes as well as urgency and significantly increased quality-of-life.[45-47] Adverse events of both drug classes appear during combination treatment of alpha-blockers and muscarinic receptor antagonists. Measuring of PVR urine is recommended during combination treatment to assess increase or urinary retention although the incidence of increased PVR and retention was rare.[44]

There is currently only one beta 3 agonist available (mirabegron). This medication is newly available and, of present, has not been studied in combination with an alpha-blocker. The indications for use include urge urinary incontinence, urgency and urinary frequency. The main adverse reactions include hypertension, nasopharyngitis, urinary tract infections and headache. Caution should be used in patients with clinically significant bladder outlet obstruction.[33]

PDE5i are also newly indicated and, currently, there are no published studies for use with antimuscarinics or beta 3 agonists.

Treatment: alpha-blocker or PDE5i with a 5-alpha reductase inhibitor (5-ARI)

The addition of a 5-ARI with either an alpha-blocker or a PDE5i is appropriate for the symptomatic patient with BPH-LUTS who has identified bother and has a PSA of 1.5 ng/mL or greater. As mentioned before, identification of sexual dysfunction may assist in the choice of the alpha-blocker or PDE5i.

Patients with a large prostate may find that treating the dynamic component of BPH-LUTS with only an alpha-blocker or PDE5i is not sufficient. Neither of those medications will halt the growth of the prostate and this enlargement may result in worsening symptoms as well as the risk of acute urinary retention and possibly the need for surgical intervention. The goal of therapy then becomes treating the progression by reducing the static component of this enlarged gland. As mentioned earlier, Crawford identified five risk factors for disease progression which include PSA, prostate size, age, urinary flow and PVR.[28] In the office of the PCP, PSA is one of practical importance as was explained earlier.

Understanding how the prostate grows is essential in understanding the role of the 5-ARI. Prostate growth is stimulated by dihydrotestosterone (DHT) with is converted from testosterone by the 5-alpha reductase enzyme. Decreases in DHT have been shown to induce prostatic epithelial apoptosis and atrophy which in turn leads to approximately 18%-28% reduction in prostate size and approximately a 50% reduction in PSA levels after 6-12 months.[48-50]

There are two 5-ARIs available, finasteride and dutasteride, Table 5. Both medications showed significant improvement over placebo in reducing prostate size and reducing the risks of symptom progression, acute urinary tract retention and surgical intervention.[50] Comparison between the medications, indirect and one direct, indicate similar efficacy.[50,51] The PCP must be cognizant that quick relief will not occur with the 5-ARI alone as both medications generally require 3-6 months before the affect is noted.

Advocacy of the combination of a 5-ARI with an alpha-blocker has been studied over a duration of many years and has shown a significant improvement in symptom and bother scores as compared to monotherapy with either medication.[52,53] There were similar results in a study showing the combination of a PDE5i and a 5-ARI significantly outperformed monotherapy with a 5-ARI in reduction of the IPSS at 26 weeks.[54] Questions have been raised regarding early adoption versus late adoption of combination therapy and whether the medication treating the dynamic component should eventually be stopped. Morlock et al have shown that early combination results in better outcomes in preventing clinical progression, acute urinary retention or the need for surgery.[55] In regards to stopping combination therapy in favor of monotherapy, expert opinion favors continuing combination therapy in the at-risk patient.[11,24]

The most commonly reported adverse reactions of the 5-ARIs include decreased libido, ejaculatory disorders, ED and gynecomastia.[33] The PCP should be aware that the PSA level will reduce approximately 50% within the first year and should never increase as long as the 5-ARI is still used. Any elevation should therefore be investigated.[1] Two crucial trials on prostate cancer chemoprevention found a slightly higher incidence of high grade cancers in the 5-ARI patients as compared to those taking placebo.[56,57] Although experts have debated the relationship the patient should be made aware of the risk and monitored appropriately.

Follow up on chosen treatment

Alpha-blockers and PDE5is work reasonably quickly so symptom resolution should be expected in the short time frame. This is also the same for the antimuscarinics and beta 3 agonists. No response to these therapies in 2-4 weeks requires consideration of medication titration switching medications or consideration of a referral to the specialist. The 5-ARIs take longer given the overall burden of the prostate size, so no improvement in 3 months or so may warrant a re-evaluation and possible referral.

When to call in the specialist

The treating PCP should consider referral for the patient with symptoms, bother and who is refractory to therapy. When to designate a patient's symptoms as refractory to therapy is going to be physician specific. However, in an effort to keep the patient informed and involved, these parameters should be communicated to them. Referral should also be considered if any of the key indicators listed in Table 4 are noted during the evaluation or treatment.

Summary

The prevalence of BPH is high and the treatment is low which results in many patients suffering needlessly. They may in fact not know therapy is available, their healthcare provider may not be aware of their symptoms or the treatment they were given did not adequately address the symptoms and risk that they had. Regardless of the cause, education of the gatekeepers probably is the key. Awareness of the symptoms, understanding the disease and the associated risk factors as well as realizing that there are many different treatment options may open the door for more patients to benefit. As shown in this paper, this can all be performed safely in the office of the PCP. It starts with education and ends in better patient care and quality-of-life.

Disclosure

Dr Matt T. Rosenberg has been a speaker and consultant for Astellas, Easai, Ferring, Forest, Horizon, Ortho-McNeil, Lilly, Pfizer and Bayer. Erik S. Witt has no potential conflict of interest. Dr. Martin Miner has been a consultant for Abbvie and Endo. He has also done research for Forest. Dr. Jack Barkin has been a clinical investigator, speaker and medical advisory board member and consultant for Abbott, Lilly, Bayer, Paladin, Actavis, AstraZeneca, Astellas, Pfizer and Triton. □

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