Clinical features and management of benign prostatic hyperplasia

Tim Lane, Julian Shah

Benign prostatic hyperplasia represents the most common benign neoplastic condition afflicting men and has a major impact on the health of the population. It refers to a regional and nodular growth of stromal proliferation which, because of its proximity to the urethra, causes varying degrees of bladder outflow obstruction.

The initial changes of benign prostatic hyperplasia (BPH) begin as early as 35 years of age and are reflected by microscopic stromal nodules which develop around periurethral glands. In turn glandular (acinar) hyperplasia develops around these and in time mature hyperplastic glands develop which may grow as large as several centimetres.

Approximately half of all men over the age of 65 years have symptoms and signs consistent with the diagnosis of prostatic outflow obstruction (Berry et al, 1984). It represents a centuries old cause of urinary dysfunction and has found mention in Egyptian papyri dating back to 1500BC as well as in writings by Hippocrates. There is much to suggest that the incidence of microscopic changes increases with age and that ultimately all men living long enough will develop BPH.

CLINICAL FEATURES OF BPH

Urinary tract symptoms in the elderly male were once referred to as 'prostatism'. However, the term fell out of favour because its complex array of voiding symptoms were neither specific for or pathognomonic of diseases of the prostate. The term lower urinary tract symptoms (LUTS) is preferred as it makes no presumption as to the aetiology of symptoms (Abrams, 1994). There is also increased awareness that there is a variable (and often weak) overlap between benign prostatic enlargement, bladder outlet obstruction and LUTS. The interaction of each of these has been elegantly represented in a series of Venn diagrams generally referred to as 'Hald' rings (Hald, 1991).

LUTS are traditionally divided into obstructive and irritative symptoms, and are caused by at least three different pathophysiological components which can be classified as static, dynamic and detrusor-related. More recently the terms voiding and storage symptoms have been introduced as alternatives for defining symptoms (*Table 1*). Benign prostatic nodular enlargement accounts for much of the static obstructive element and in the elderly male is mainly confined to the transition zone and periurethral glandular tissue. By contrast the dynamic component is a reflection of smooth muscle tone in the prostate and at the bladder neck. Variations in muscle tone cause corresponding changes in the degree of outlet obstruction.

Detrusor-related components are believed to predominate in those with principally irritative symptoms. They reflect an increase in the incidence of uninhibited detrusor contractions and loss of contractile ability of the bladder, both of which are a response to existing obstruction. In addition to a number of LUTS, patients may present with a variety of secondary sequelae of BPH such as urinary retention, haematuria or overflow incontinence (*Table 2*). Some of these represent absolute indications for intervention.

Mr Tim Lane is Specialist Registrar in Urology and **Mr Julian Shah** is Consultant Urologist and Senior Lecturer, Institute of Urology and Nephrology, The Middlesex Hospital, London W1N 8AA

Correspondence to: Mr T Lane

TABLE 1.
Lower urinary tract symptoms associated with benign prostatic enlargement

Obstructive symptoms	Weak stream*
	Intermittency*
	Straining*
	Incomplete emptying
	Hesitancy
	Terminal dribbling
Irritative symptoms	Frequency*
	Nocturia*
	Urgency*
	Urge incontinence

*Symptoms indicated in the American Urological Association (Barry et al, 1992) and International prostate symptom score (Cockett et al, 1994) indices

It is important to understand that the various symptoms cannot necessarily be attributed to any single cause. While voiding symptoms are usually related to outflow obstruction or detrusor dysfunction, it is interesting that bladder capacity and detrusor contractility decrease with age and that the incidence of detrusor instability increases. It may be that many of the symptoms associated with BPH might in fact be symptoms of an ageing bladder rather than outflow obstruction. This view has found some support in work by Van Mastrigt and Rollema (1992) who showed a significant association of symptoms with increasing age.

A number of symptom scoring indices have been developed to quantify LUTS. Boyarsky et al (1977) initially outlined a number of important symptoms which were recommended for inclusion in study protocols and these are the 'conceptual parent' of subsequent questionnaires. The International Prostate Symptom Score (IPSS) predominates today (Cockett et al, 1994). Its principal role is to distinguish men who are bothered to a greater or lesser degree by their symptoms and it does not seek to differentiate between underlying pathophysiological mechanisms. More recently the symptom problem index (SPI) and BPH impact index (BII) have been introduced and these help in deciding upon the degree to which specific interventions are indicated.

TABLE 2.
Complications secondary to benign prostatic enlargement

Haematuria
Urinary tract infection
Urinary retention
Bladder stones
Overflow incontinence
Renal impairment

TABLE 3.
Investigations for symptoms of benign prostatic hyperplasia

Recommended investigations	Urine analysis
	Assessment of renal function
	Prostate-specific antigen
	Symptom assessment
	Uroflowmetry*
	Post-void residual*
Optional diagnostic tests	Urodynamics†
	Cystourethroscopy
	Urinary tract imaging

* Recommended in international guidelines (Cockett et al, 1994). †Recommended in international guidelines (Cockett et al, 1994) if the uroflowmetry and post-void residual are not suggestive of outflow obstruction

INVESTIGATION OF SYMPTOMS

Guidelines for the investigation and treatment of BPH have been outlined recently by two groups: the American Urological Association (AUA; on behalf of the American government) and the Third International Consultation on BPH, patronized by the World Health Organization (WHO). While differing approaches were taken to the same problem they came to very similar conclusions and have been extensively reviewed (Cockett et al, 1996).

A detailed medical history and physical examination is mandatory. History should focus on the urinary tract, previous surgery and general health issues with specific reference to haematuria, urinary tract infection (UTI), diabetes, urethral stricture, urinary retention and neurological disease. A knowledge of concurrent medications which may impair bladder contractility (anticholinergics) or increase outflow resistance (sympathomimetics) is similarly recommended. As part of the physical examination a digital rectal examination (DRE) and focused neurological examination are advised. DRE will detect prostatic malignancies and evaluate anal sphincter tone. While an estimate of prostatic size does not correlate with the degree of urodynamic obstruction or with the severity of symptoms, it does allow for the selection of the most appropriate technical approach for invasive therapies should they prove necessary.

A number of investigations are considered highly recommended or mandatory (*Table 3*).

Urine analysis by dipstick (or examination of spun sediment) is necessary to rule out UTI and haematuria. Dipstick methods should include leucocyte esterase and nitrite tests for the detection of pyuria and bacteruria. Dipstick methods allow for the selective use of imaging and endoscopy in the differentiation of UTIs and bladder cancer from BPH. Renal function assessment by creatinine estimation will exclude renal insufficiency caused by the presence of an obstructive uropathy. Some 13% of patients will have renal impairment. Prostate-specific antigen (PSA) estimation is recommended where management would be altered should the diagnosis of prostate cancer be established. For men in whom the diagnosis of non-palpable prostate cancer would change the recommended BPH treatment, it is of most value. Transrectal ultrasound and biopsy is the gold standard in establishing the diagnosis of cancer. International guidelines regard the use of symptom assessment (IPSS) as mandatory in the initial evaluation and it should be regarded as the primary determinant of treatment response or disease progression in subsequent follow-up.

A large number of further investigations are often used in LUTS assessment but are not neces-

sarily mandatory in the initial assessment. In the AUA guidelines, for example, an individual with a normal initial assessment and mild symptoms (symptom score less than 7) need not undergo additional diagnostic testing and may reasonably enter a 'watchful waiting' programme. Further optional tests, e.g. uroflowmetry, pressure–flow evaluation and post-void residual (PVR) estimation, may be considered for those with moderate–severe symptom scores. We believe that flowmetry and PVR volume measurement are essential and must precede any surgical intervention.

Uroflowmetry
This is an electronic recording of urine flow rate throughout micturition. Results are non-specific for the causes of symptoms and a recorded low flow may equally be the result of detrusor hypocontractility as of obstruction. There is no threshold value for an 'abnormal' finding but those with a Q_{max} of >15 ml/s appear to have an increased risk of treatment failure. Some authors suggest that these patients would benefit from pressure–flow urodynamics in an attempt to reduce the number of failed surgical procedures.

Post-void residual estimation
This is the volume of fluid remaining in the bladder immediately following micturition. The volume should be zero, but a value of less than 12 ml is generally regarded as normal. Traditionally it had been assumed that an increase in PVR denoted disease progression but supporting evidence for this is lacking. It nevertheless remains an important safety parameter and an indication for closer monitoring of non-surgical therapy.

Pressure–flow studies
These may enable the differentiation of patients with a low Q_{max} secondary to obstruction from those with a decompensated or neurogenic bladder. Obtained values can be compared to a number of nomograms of which the Abrams–Griffith is the most widely used. Some clinicians recommend urodynamic testing and inclusion of pressure–flow data in the preoperative evaluation to reduce the subjective failure rate. However, others have found little advantage in its diagnostic specificity (positive predictive value) over uroflowmetry.

Filling cystometry provides details about bladder capacity, compliance and uninhibited detrusor contractions. In those with suspected primary bladder or neurological lesions and who are in retention (and unable to perform a pressure–flow study) it may prove useful.

Videourodynamics is undeniably the most precise method of investigating LUTS. However, it requires multichannel urodynamics and simultaneous fluoroscopic examination of the lower urinary tract, which are not always easily available.

Urinary tract imaging
These are optional and generally performed when an indication such as renal insufficiency, urolithiasis, previous surgery or haematuria exists. Ultrasonograpy and a plain X-ray of the kidneys, ureter and bladder are generally preferred.

Cystourethroscopy
This should not be used to determine the need for treatment. It is recommended in those with haematuria or risk factors for urethral stricture. It does, however, have the potential to determine technical aspects of specific invasive therapies. The decision to perform a retropubic prostatectomy, for example, may be influenced by the shape as well as the size of the gland.

MEDICAL MANAGEMENT OF BPH

The medical therapies currently available to treat BPH and its attendant LUTS include α-blocking agents, 5α reductase inhibitors and to a lesser extent phytotherapeutic agents.

Alpha-blocking agents
The rationale for using α-blockers is based on observations that smooth muscle in the prostate capsule, adenoma and bladder neck contributes a dynamic element to bladder outflow obstruction and may account for up to 40% of the outflow impedance. Pioneering work by Caine (1977), using a non-selective α-blocking agent phenoxybenzamine, showed that relaxation of this smooth muscle tone had a beneficial effect on LUTS.

More recently it has become apparent that α_1 receptors (a subtype) predominate in prostatic tissue and as a result the use of long-acting uroselective α_1-antagonists, e.g. alfuzosin, has flourished. There is ample evidence to suggest that there is a decrease in obstructive and irritative symptoms, an increase in flow rates and decreased PVRs with treatment. There is, however, a great need for long-term data to confirm the durability of results. The Medical Therapy of Prostatic symptoms Study (MTOPS) and the multicentred National Institutes of Health BPH study may ultimately provide these (Lepor et al, 1997).

Alpha receptors are not confined to the prostate, so medications may alter smooth muscle tone in the vasculature. Side-effects related to this are often mild and principally include dizziness, headache and fatigue. Not all side-effects need necessarily be regarded as deleterious. Kirby (1995) found that doxazosin significantly reduced

blood pressure in hypertensive individuals but showed little or no change in normal individuals. A further advance are α_{1A}-adrenoceptor antagonists, e.g. tamsulosin, which have 10–12 times the affinity for prostatic receptors than for those in vascular and other extraprostatic sites. These may become the α-blocker of choice for normotensive patients with LUTS while those with hypertension will be managed with less selective α-blockers, using their cardiovascular side-effects as an additional benefit (Chapple, 1998).

5α-reductase inhibitors

The role of 5α-reductase inhibitors stemmed from investigation into a congenital deficiency of 5α-reductase associated with pseudohermaphroditism, where adult males had impalpable prostates. It followed that inhibition of this enzyme might induce one of the phenotypic features of the diseased state in normal individuals: impaired prostate growth. Finasteride is one such potent inhibitor. It effectively suppresses dihydrotestosterone levels without affecting testosterone levels. It appears to cause prostatic involution through epithelial cell atrophy and cell death, achieving its therapeutic effect by effecting these changes in the transition zone. Treatment achieves sustained reduction in symptoms and improved flow rates. Anderson et al (1997) found that it can reduce the incidence of acute urinary retention and control gross haematuria, further widening its potential uses.

An important meta-analysis by Boyle et al (1996) concluded that if prostatic volumes were below 40 ml then finasteride was no more effective than placebo. Significant improvements were demonstrated in those with larger glands in whom treatment is now generally focused.

Phytotherapeutic agents

Much remains unclear about these agents, despite their popularity in mainland Europe. They are the main compounds from a variety of plant extracts which include the roots of *Hypoxis roeperi* and *Echinacea purpurea*. They are a mix of fatty acids, fatty alcohols and triterpenes (most commonly tocopherol and lipoxin). While there have been randomized controlled trials purporting to show benefit from use of these agents, they suffer from methodological weaknesses and it appears that more rigorous testing is likely before their role can be fully established (Klippel et al, 1997).

TABLE 4.
Absolute indications for intervention

Urinary retention
Recurrent urinary tract infection
Impaired renal function
Bladder stones
Gross prostatic haematuria
Dilated upper tracts
Large bladder diverticulae*

* Recommended by the international committee (Cockett et al, 1994)

SURGICAL INTERVENTIONS

There are a number of relative and absolute indications for treatment of BPH associated with LUTS. Absolute indications include complications such as acute urinary retention and recurrent UTIs (*Table 4*). For these patients, surgical intervention offers a quick and effective amelioration of symptoms and is recommended. However, those with mandatory criteria for intervention constitute only a minority of patients with BPH. Transurethral resection of the prostate (TURP) remains the gold standard. In recent years a variety of new (and some) less invasive treatment modalities have been established, which has inevitably led to the re-assessment of hitherto conventional treatments.

Open prostatectomy

This remains an efficient form of relieving LUTS in those with BPH. It is the oldest and most invasive form of treatment but has been largely superseded by endoscopic procedures. It involves manual enucleation of the adenomatous tissue by blunt dissection, having accessed the prostate by a retropubic approach. Despite its long-term results and low perioperative mortality it is generally reserved for those with very large prostates where TURP may be considered less suitable.

Transurethral resection of prostate

TURP is almost as efficient as open prostatectomy but is less invasive. Its objective is the same as that for the open procedure: removal of periurethral adenoma. Wasson et al (1995) found that TURP was associated with low morbidity and significant improvements in symptom scores and other more objective criteria such as Q_{max}. However, there are limits to the amount of tissue that can be safely resected in any period of time. The extent to which an enlarged prostate is amenable to endoscopic resection will depend heavily on the experience and judgment of the individual urologist.

Transurethral incision of prostate

Transurethral incision of the prostate (TUIP) involves one or more incisions from the bladder neck to the verumontanum and is only indicated in those with prostates of less than 50 g in weight (and generally much less). Incisions are extended to the capsule and some would advocate extension

through to the periprostatic tissue. It is a quick, safe and effective procedure which is associated with less morbidity than TURP (McConnell et al, 1994). Its role is much under-utilized.

INVESTIGATIONAL TREATMENTS

Many new techniques have emerged for the treatment of BPH, including radiofrequency transurethral needle ablation (Zlotta et al, 1997), microwave therapies (de la Rosette et al, 1997), laser treatments (Fay et al, 1997) and high-intensity focused ultrasound (Mulligan et al, 1997). While those such as transurethral electrovaporization are gaining in popularity (Thomas et al, 1997), most should be regarded as investigational until long-term results have been assessed.

TREATMENT GUIDELINES

The clinician managing a patient with LUTS has a number of options. Recommendations are based heavily on the severity of symptoms. Those with symptom scores of <7 (mild symptoms) should enter a watchful waiting programme where patients are monitored, but where no active treatment takes place. Behavioural techniques such as limiting fluid intake after the evening meal and avoiding decongestants should simultaneously be stressed. Periodic reassessment of symptoms, clinical findings and mandatory or highly recommended investigations should take place.

Patients with moderate or more severe symptoms should be informed of the cost-benefit of α-blocker therapy, finasteride and a variety of surgical interventions. No specific IPSS scores should be quoted in the decision making progress as to the level of intervention (*Table 5*). HM

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TABLE 5.
Treatment guidelines

Watchful waiting	
Alpha-blocker therapy	
Finasteride	
Transurethral incision of prostate (TUIP)	
Transurethral resection of prostate (TURP)	
Open prostatectomy	
Investigational treatments	Laser prostatectomy
	Electrovaporization
	Prostatic stents
	Thermal therapy

KEY POINTS

- Benign prostatic hyperplasia exacts a major impact on the health of the nation.
- Selective use of investigations according to internationally approved guidelines is advised.
- Alpha-blockers are effective treatment for those with mild lower urinary tract symptoms associated with bladder outflow obstruction, and finasteride is effective medical management in those with prostates of 40 g or more in size.
- Transurethral resection of the prostate remains the 'gold standard' in the management of benign prostatic hyperplasia.
- Newer treatments should be regarded as investigational for the present.
- Symptom scores should be the chief determinant of treatment failure or success.