

BENIGN PROSTATE DISORDERS

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ABSTRACT

Benign prostatic hyperplasia (BPH) is among the commonest urological abnormalities affecting the aging male. The cause of the increase in prostatic volume is multifactorial, but current research has implicated hormonal aberrations. Clinical assessment of the patient is integral to determining the optimal treatment strategy. Exclusion of prostatic cancer and complications of BPH are critical prior to the commencement of conservative and non-invasive strategies. Recently, the introduction of pharmaceutical agents has changed the landscape of management of BPH. Alpha-blockers, 5-alpha reductase inhibitors, and phosphodiesterase-5 inhibitors provide significant symptomatic improvement for BPH, particularly when used in combination. Invasive surgical therapies remain the gold standard for refractory and complicated BPH disease. Advances in technology have provided new methods to perform prostatectomy including: bipolar resection, laser resection, ablation, enucleation or vaporization. Newer, minimally invasive measures have been introduced in an attempt to limit patient morbidity, specifically operative complications, sexual and urinary function. While results are promising,

these emerging therapies have limited long-term data. The purpose of the current chapter is to provide an overview of the current knowledge of benign prostatic hyperplasia.

INTRODUCTION

The prostate is an organ linked inextricably to the endocrine system. During the development of the prostate, the epithelium and mesenchyme are under the control of testicular androgens, and interact to form an organized secretory organ. Furthermore, the endocrine system plays a key mechanistic role in many prostate diseases, and many therapies for prostatic diseases are aimed at the manipulation of the endocrine system. The gland resides in the true anatomical pelvis and forms the most proximal aspect of the urethra. It has been stated that the prostate gland is the male organ most commonly afflicted with either benign or malignant neoplasms (1). Therefore, it is an organ with which every physician and surgeon needs to be familiar. We will focus on BPH, the most prevalent of benign disorders affecting the prostate.

EMBRYOLOGY

The development, growth and cytodifferentiation of the prostate are androgen-dependent and occur via embryonic cell-to-cell interactions between the mesenchyme (undifferentiated connective tissue) that induce epithelial development while the epithelium induces mesenchymal differentiation (2).

In the developing prostate, urogenital sinus mesenchyme acting under the influence of testicular androgens induces ductal morphogenesis, the expression of epithelial androgen receptors, regulates epithelial proliferation and specifies the expression of prostatic-lobe specific secretory proteins. The developing prostatic epithelium reciprocally induces the differentiation and morphological patterning of smooth muscle in the urogenital sinus mesenchyme (2). In the prostate, it is traditional to consider androgens as promoters of growth, while activin and tumor growth factor-beta1 (TGF- β 1) are regarded as potent growth inhibitors. These factors do not act independently, however, and cross-talk occurs between the signaling pathways at a sub-cellular level (3).

The first step in development of the prostate begins with the urogenital sinus mesenchyme signaling to the epithelium, causing it to form epithelial buds. Androgens then induce bud elongation, branching and epithelial differentiation (3). Prenatally, the androgen receptor (AR) is expressed only in the mesenchyme, not in the epithelium. Initial epithelial development is thus controlled via paracrine interactions where activation of stromal androgen receptors stimulates growth factors and induces growth in adjacent prostatic epithelial cells (4).

At the 5th week, the mesonephric (Wolffian) duct opens onto the lateral surface of the urogenital sinus and gives rise to the ureteric bud (Figure 1). By the 7th week, the growth of the urogenital sinus involves the progressive incorporation of the terminal part of the mesonephric duct into the wall of the urogenital sinus. They eventually open into the Mullerian tubercle that is the future verumontanum of the prostate. At their termination the paramesonephric (Mullerian) ducts fuse and are surrounded by the mesonephric ducts. At 10 weeks, prostatic epithelial buds begin to arise from the circumference of the urethra, around the orifice of the paramesonephric ducts. They develop predominantly on the posterior surface of the junction of the mesonephric ducts, forming two concentrations, above and below them (5).

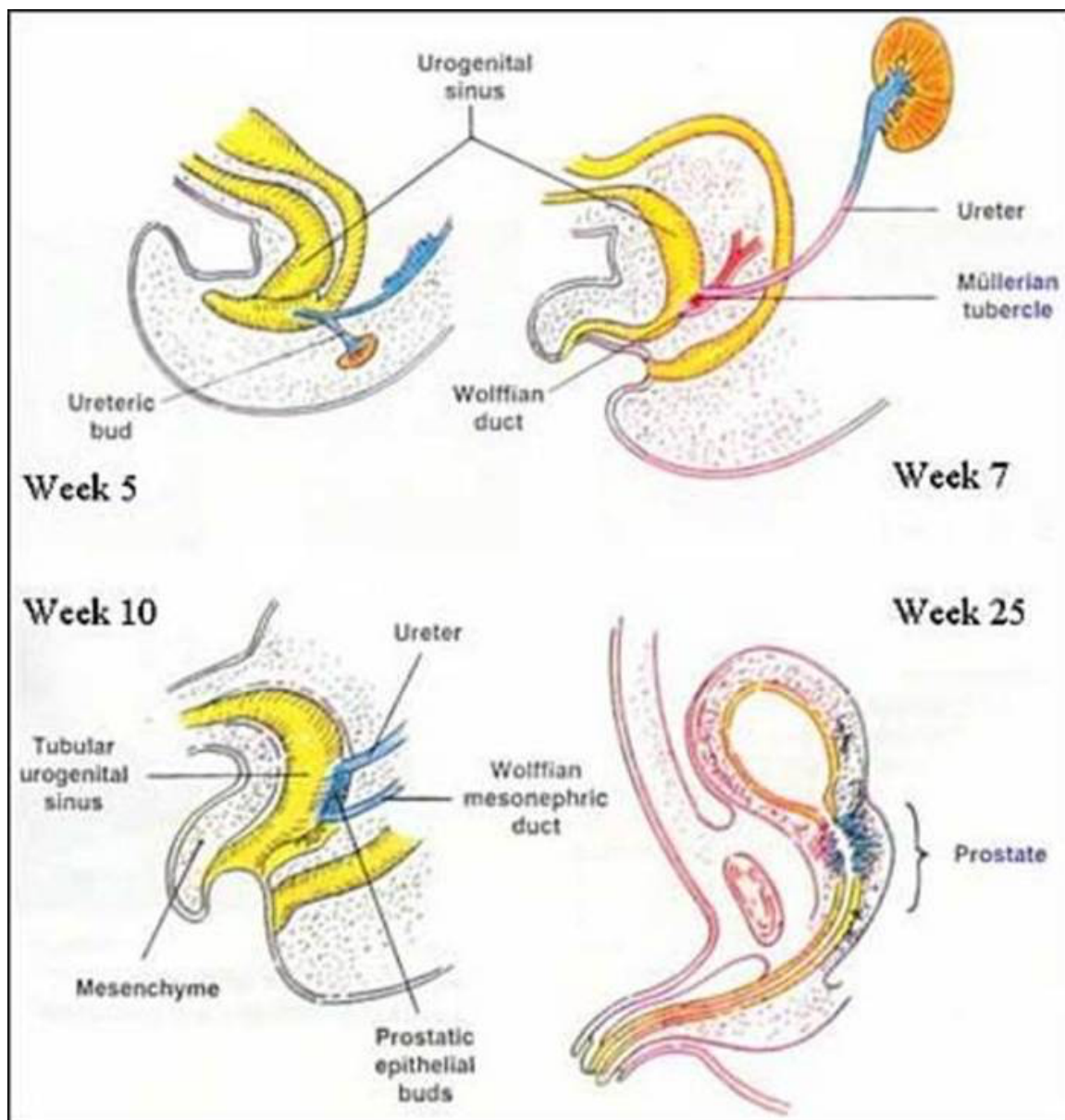


Figure 1. The embryological origin and development of the prostatic urethra and the prostate, adapted from Delmas (5).

During the fetal period at about 6 months, multiple outgrowths arise from the prostatic portion of the urethra, particularly the posterior surface of the urethra, and grow into the surrounding mesenchyme. Glandular epithelium of the prostate differentiates from the endodermal cells of the urethra, and outgrowths of

glandular epithelium protrude into the associated mesenchyme differentiate into the dense stroma and smooth muscle fibers of the prostate. In contrast, the prostatic glandular epithelium outgrowths situated on the anterior surface regress and are replaced by fibromuscular tissue. This region becomes the future anterior commissure of the prostate (5,6).

ANATOMY

According McNeal's model of the prostate (7), four different anatomical zones may be distinguished that have anatomo-clinical correlation (Figure 2):

- 1) The **peripheral zone**: is the area forming the postero-inferior aspect of the gland and represents 70% of the prostatic volume. It is the zone where the majority (60-70%) of prostate cancers form.
- 2) The **central zone**: represents 25% of the prostate volume and contains the ejaculatory ducts. It is the zone which usually gives rise to inflammatory processes (e.g., prostatitis).
- 3) The **transitional zone**: this represents only 5% of the total prostatic volume. This is the zone where

benign prostatic hypertrophy occurs and consists of two lateral lobes together with periurethral glands. Approximately 25% of prostatic adenocarcinomas also occur in this zone.

- 4) The **anterior zone**: predominantly fibromuscular with no glandular structures.

The prostate weighs approximately 20g by the age of 20 and has the shape of an inverted cone, with the base at the bladder neck and the apex at the urogenital diaphragm (8). The prostatic urethra does not follow a straight line as it runs through the center of the prostate gland but it is actually bent anteriorly approximately 35 degrees at the verumontanum (where the ejaculatory ducts join the prostate) (9).

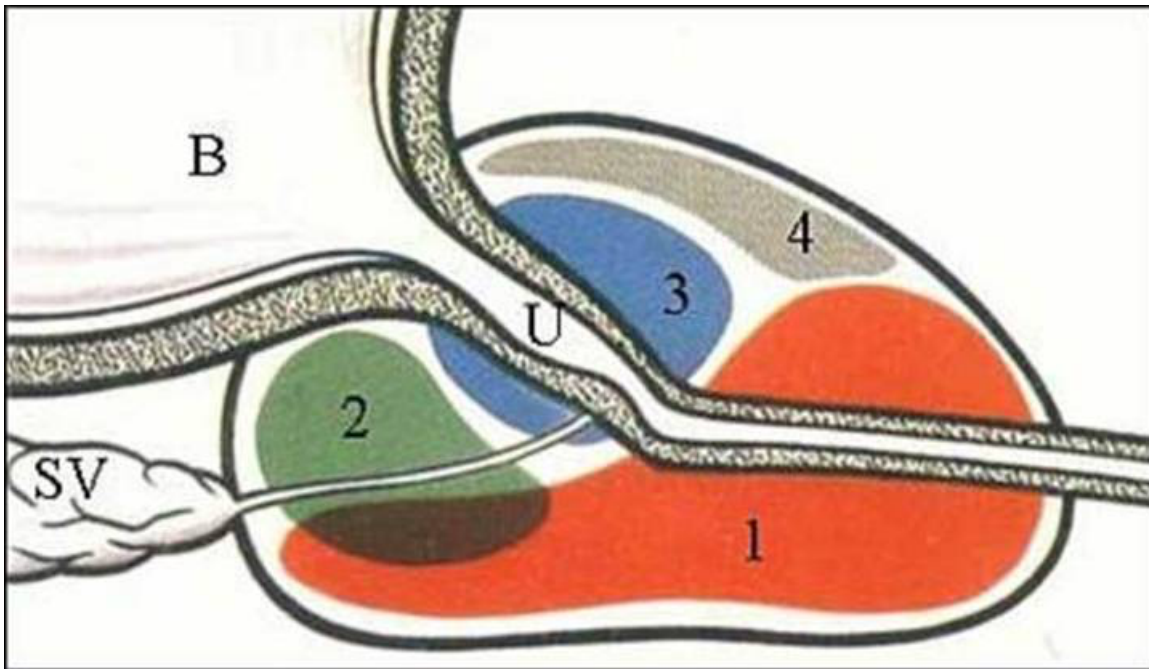


Figure 2. 1= Peripheral Zone, 2= Central Zone, 3= Transitional Zone, 4= Anterior Fibromuscular Zone. B= Bladder, U= Urethra, SV= Seminal Vesicle (adapted from Algaba (10)).

HISTOLOGY

The prostate consists of stromal and epithelial elements. Smooth muscle cells, fibroblasts and

endothelial cells are in the stroma and the epithelial cells are secretory cells, basal cells and neuroendocrine cells (Figure 3).

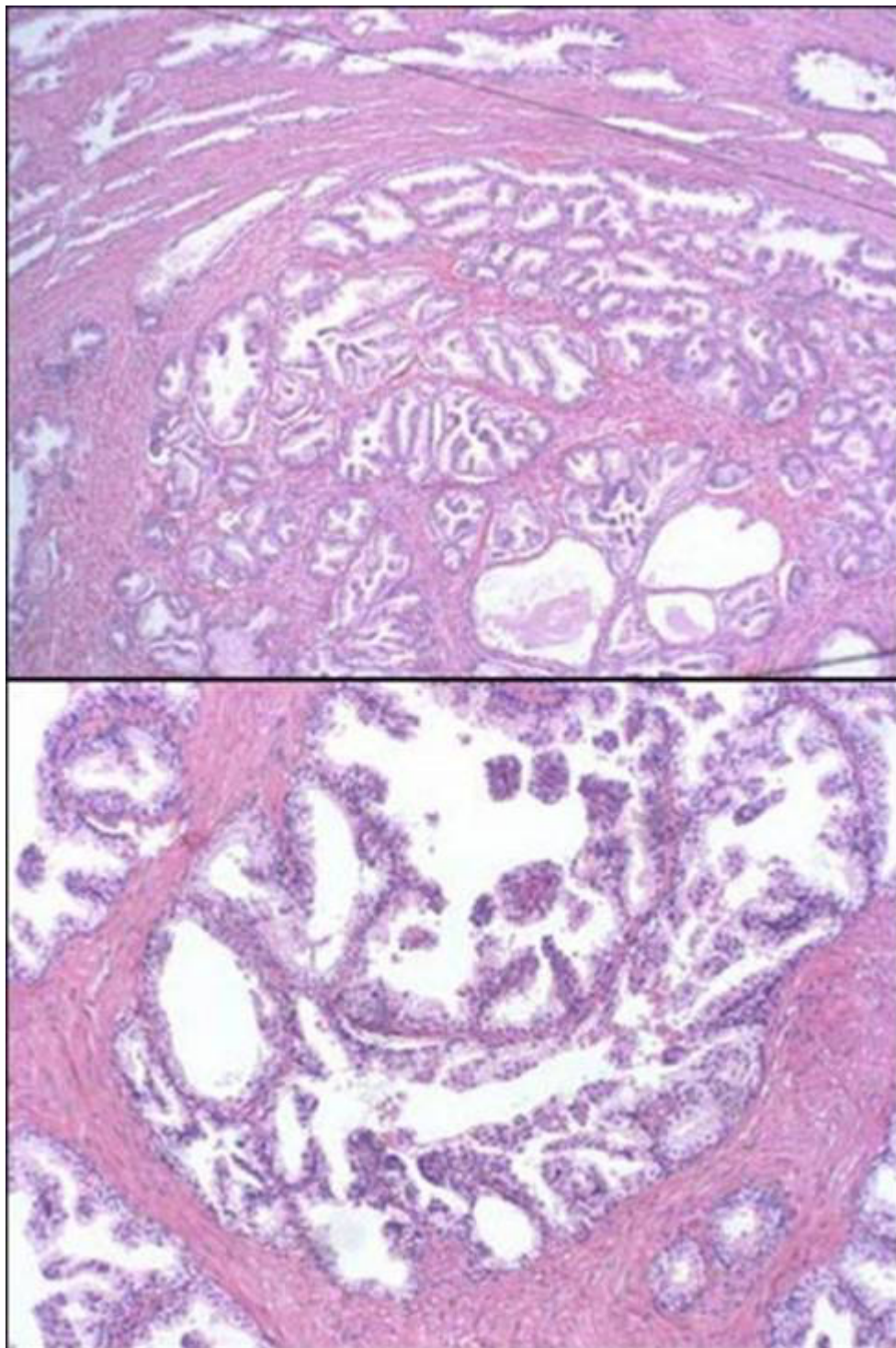


Figure 3. Histology of a prostate gland affected by benign prostatic hyperplasia.

The columnar secretory cells are tall with pale to clear cytoplasm. These cells stain positively with prostate-specific antigen (PSA) (11). Basal cells are less differentiated than secretory cells and are devoid of secretory products such as PSA (12). Finally, neuroendocrine cells are irregularly distributed throughout ducts and acini, with a greater proportion in the ducts. The prostate has the greatest number of neuroendocrine cells of any of the genitourinary organs (13). Glands are structured with open and closed cell types with the open type facing the inside of the duct having a monitoring role over its contents.

Most cells contain serotonin, but other peptides that are present include somatostatin, calcitonin, gene-related peptides and katacalcin (11). The cells co-express PSA and prostatic acid phosphatase. Their function is unclear, but it is speculated that these cells are involved with local regulation by paracrine release of peptides (11). Prostatic ducts and acini are distinguished by architectural pattern at low power magnification. The prostate becomes more complex with ducts and branching glands arranged in lobules and surrounded by stroma with advancing age.

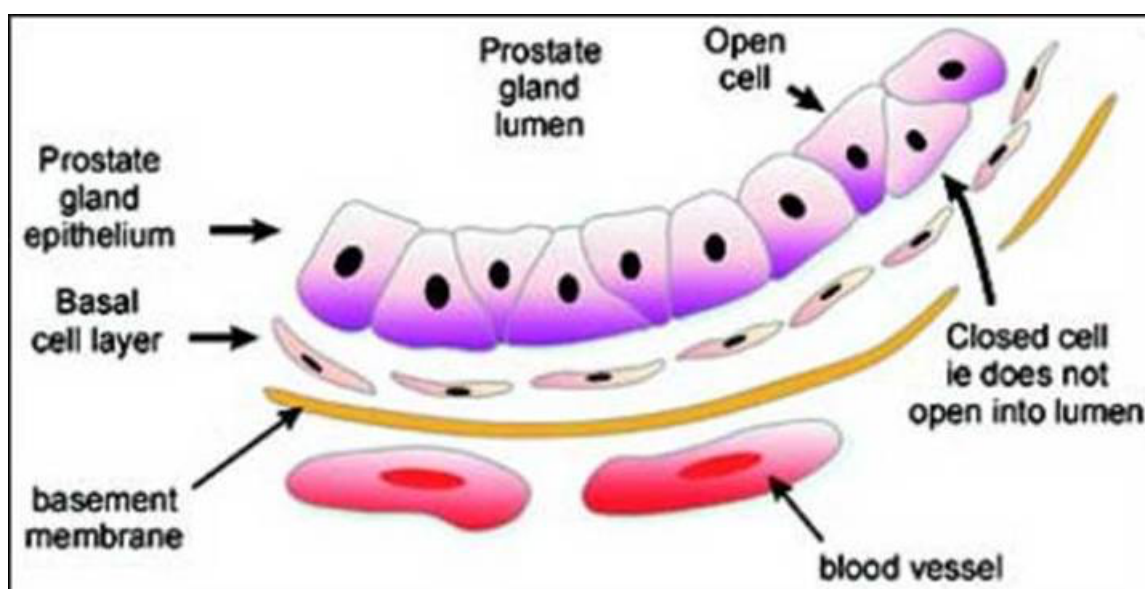


Figure 4. Diagram outlining the structure of the prostate gland with regard to ducts, glandular cells and their relationship to blood vessels.

PHYSIOLOGY

At present, there is only limited knowledge of all of the secretory products of the prostate and how these relate to reproduction and infertility. However, the main role of the prostate as a male reproductive organ is to produce prostatic fluid that accounts for up to 30 per cent of the semen volume. Prostatic fluid promotes

sperm motility, and it is a milky, alkaline fluid containing PSA, citric acid, calcium, zinc, acid phosphatase and fibrinolysin among its many constituents (Table 1) (14). During ejaculation, alpha-adrenergic stimulation of prostatic smooth muscle expresses seminal fluid containing sperm from the ampulla of the vas deferens into the posterior urethra (15). Interestingly, abnormal growth of the prostate is

only experienced by humans and dogs, and why other mammals are spared is a mystery (16).

Table 1. The Composition of Human Semen (adapted from Ganong (17))

Color	White, opalescent	
Specific Gravity	1.028	
pH	7.35-7.50	
Volume	3ml	
SPECIFIC COMPONENTS OF SEMEN		
Gland/Site	Volume in ejaculate	Features
Testis/Epididymis	0.15ml (5%)	Average approximately spermatozoa 80 million/ml
Seminal Vesicle	1.5-2ml (50-65%)	Fructose (1.5-6.5 mg/ml) phosphorylcholine ergothioneine, ascorbic acid, flavins prostaglandins, bicarbonate
Prostate	0.6-0.9ml (20-30%)	Spermine, citric acid, cholesterol, phospholipids, fibrinolysin, fibrinogenase, zinc, acid phosphatase, prostate-specific antigen
Bulbourethral Glands	< 0.15ml (<5%)	Clear mucus

ENDOCRINE CONTROL OF PROSTATIC GROWTH

Intraprostatic signaling systems are important for the regulation of cell proliferation and extracellular matrix production in the prostatic stroma. Central to this premise is the balance between factors such as TGF- β 1, that induces extracellular matrix production, suppresses collagen breakdown and cell proliferation and factors such as fibroblast growth factor 2 and insulin-like growth factors that are mitogenic in the stromal compartment (18). Other endocrine pathways are being investigated, and there is a growing body of evidence suggesting an abnormality in the insulin-like growth factor axis is playing a role in the pathogenesis of BPH (19).

TESTOSTERONE

Prostatic epithelial cells express the androgen receptor (20). From the beginning of embryonic

differentiation to pubertal maturation and beyond, androgens are a prerequisite for the normal development and physiological control of the prostate (21). Androgens help maintain the normal metabolic and secretory functions of the prostate, and they are also implicated in the development of BPH and prostate cancer. Androgens do not act in isolation, and other hormones and growth factors are being investigated (22).

Androgens also interact with prostate stromal cells which release soluble paracrine factors that induce growth and development of the prostatic epithelium (4). These paracrine pathways might be critical in regulating the balance between proliferation and apoptosis of prostate epithelial cells in the adult (22).

The appropriate balance between testosterone and its 5- α reduced metabolites is key to normal prostate physiology (note the metabolic pathways for androgen metabolism are described in Endotext, Endocrinology of Male Reproduction, Androgen Physiology, Pharmacology and Abuse, D Handelsman). The

metabolism of testosterone to dihydrotestosterone (DHT) and its aromatization to estradiol are

recognized as the key events in prostatic steroid response.

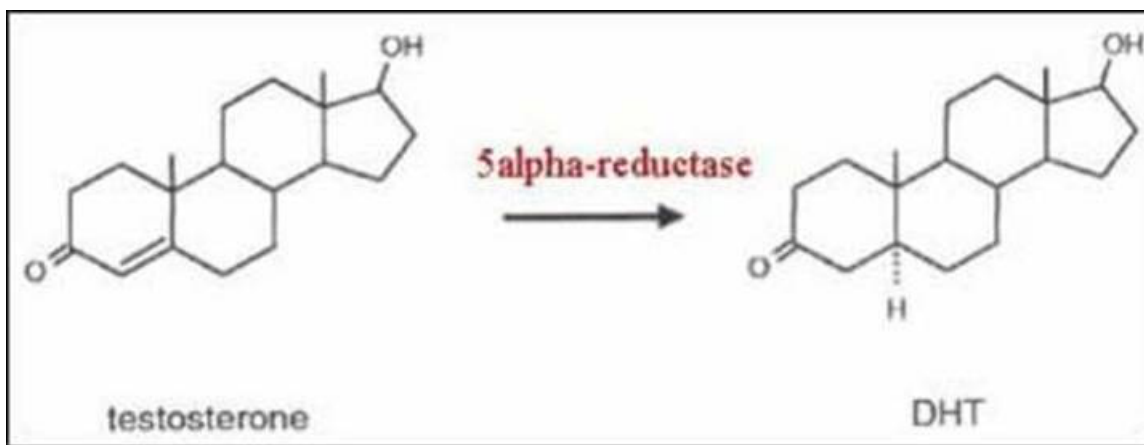


Figure 5. Conversion of testosterone to dihydrotestosterone (DHT) by 5alpha reductase

Testosterone, to be maximally active in the prostate, must be converted to DHT by the enzyme 5-alpha reductase (Figure 5) (23). DHT has a much greater affinity for the androgen receptor than does testosterone, and DHT accumulates in the prostate even when circulating concentrations of testosterone are low (24,25). Based on rat studies, DHT is about twice as potent as testosterone at equivalent androgen concentrations (26). Therefore, prostatic DHT concentrations may remain similar to those in young and elderly men, despite the fact that serum testosterone concentrations generally decline with age (23). In the prostate, the total level of testosterone is 0.4 ng/g and the total of DHT is 4.5 ng/g (27). The total serum concentration of testosterone in the blood is approximately 10 times higher than DHT (17). Circulating DHT, by virtue of its low serum plasma concentration and tight binding to plasma proteins, is of diminished importance as a circulating androgen affecting prostate growth (16). Intra-prostatic androgens are remarkably independent of serum concentrations (28), and circulating androgen concentrations often do not correlate with intraprostatic concentrations (29).

ESTROGEN

A role for estrogens in the prostate pathology of the ageing male appears likely with accumulating evidence that estrogens, alone or in combination with androgens, are involved in inducing aberrant growth and/or malignant change. Animal models have supported this hypothesis in the canine model, where estrogens “sensitize” the ageing dog prostate to the effects of androgen (30). The evidence is less clear in humans. Estrogens in the male are predominantly the products of peripheral aromatization of testicular and adrenal androgens (31). While the testicular and adrenal production of androgens declines with ageing, concentrations of total plasma estradiol do not decline. This has been ascribed to the increase in fat mass with ageing (the primary site of peripheral aromatization) and to an increased aromatase activity with ageing. However, free or bioavailable estrogens may decline due to an increase in sex hormone binding globulin, which could translate to lower intraprostatic concentrations of the hormone. The potentially adverse effects of estrogens on the prostate might be due to a shift in the intra-prostatic estrogen: androgen ratio with ageing.

Estrogen, which acts through estrogen receptors (ER) alpha and beta, has been implicated in the pathogenesis of benign and malignant human prostatic tumors (32-34). As stated above, BPH is thought to originate in the transitional zone (TZ) and prostate cancer the peripheral zone (PZ) of the prostate. Receptor studies have found ER-alpha and ER-beta types distributed in human normal and hyperplastic prostate tissues, using in situ hybridization and immunohistochemistry. ER-alpha expression was restricted to stromal cells of the PZ. In contrast, ER-beta was expressed in the stromal and epithelial cells of PZ as well as TZ. These findings suggest that estrogen might play a crucial role in the pathogenesis of BPH through ER-beta (33). Investigations are ongoing and could result in a new range of therapies directed against BPH and prostate cancer. Dietary phytoestrogens (in soy and other vegetables) or selective estrogen receptor modulators are currently being investigated with regard to their role in the development of BPH and prostate cancer (31). Such ER modifiers might oppose some of the effects of natural estrogen by modulating ER receptors, thus reducing the local impact of androgens that need active ER receptors, effectively making them anti-androgenic compounds, but this hypothesis requires more investigation (35).

BENIGN PROSTATIC HYPERPLASIA (BPH)

BPH is an age-related and progressive neoplastic condition of the prostate gland (36). BPH can only be diagnosed definitively by histology. BPH in the clinical setting is characterized by lower urinary tract symptoms (LUTS, see below and Table 2). There is no causal relationship between BPH and prostate cancer (37). Clinically apparent BPH has a significant effect on quality of life, particularly its effects on nocturia and bladder dysfunction. The overall prevalence of BPH is 10.3%, with an overall annual incidence rate of 15 per 1000 man-years, increasing with age (3 per 1000 at age 45-49 years, to 38 per

1000 at 75-79 years). For a symptom-free man at age 46, the 30-year risk of clinical BPH is 45% (38). The true prevalence and incidence of clinical BPH will vary according to the criteria used to describe the condition; however, it has been estimated that the prevalence of BPH is rising due to increases in modifiable risk factors such as obesity (39). It is crucial to acknowledge that LUTS can exist without signs of BPH – as the symptoms can be caused by variations in the sympathetic nervous stimulation of prostatic smooth muscle, variability of prostatic anatomy (viz., enlarged median lobe of the prostate), and the variable effects of bladder physiology from the obstruction and aging.

There have been several studies demonstrating the fact that clinical BPH is a progressive disease. The Olmsted county study (40) showed that with each year there were deteriorations in symptom scores, peak flow rates, and increases in prostate volumes based on transrectal ultrasound scanning (TRUS). The risk of acute urinary retention (AUR) increased with flow rates below 12 ml/sec and with glands greater than 30ml. Studies have also demonstrated that those with larger prostates (>40 ml) and with serum PSA greater than 1.4 ng/ml were more likely to develop acute urinary retention (41). Treatment, however, has changed with the advent of effective non-surgical therapies. Between 1992-1998 there has been a significant lengthening of the period between first diagnosis of LUTS secondary to clinical BPH and surgery, associated with the earlier and increased use of specific medical treatments (42). From the patients perspective, the goals of therapy are to improve quality of life, reduce symptoms, and avoid surgery while ensuring safety from the complications of BPH (43).

RISK FACTORS FOR BPH

The only clearly defined risk factors for BPH are age and the presence of circulating androgens. BPH does not develop in men castrated before the age of forty

(44), but other factors may influence the prevalence of clinical disease. These include the following:

GENETICS

Clinical BPH appears to run in families. If one or more first degree relatives are affected, an individual is at greater risk of being afflicted by the disorder (45). In a study by Sanda et al (46), the hazard-function ratio for surgically treated BPH amongst first degree relatives of the BPH patients as compared to controls was 4.2 (95% CI, 1.7 to 10.2). The incidence of BPH is highest and starts earliest in blacks than Caucasians and is lowest in Asians (37). Interestingly, despite having larger prostate glands, the age-adjusted risk of BPH was the same for blacks as for whites (RR = 1.0, 95% CI 0.8-1.2) (47). Furthermore, in an Asian population, men presenting with BPH are likely to have higher symptom scores than blacks or Caucasians (48).

DIET

Diet has been reported as a risk factor for the development of BPH. Large amounts of vegetables and soy products in the diet may explain the lower rate of BPH in Asia when compared to countries with Western, non-Asian diets. In particular, certain vegetables and soy are said to be high in phytoestrogens, such as genestin, that have anti-androgenic effects by an undetermined mechanism on the prostate in vitro (49).

Studying migrant populations with their heterogeneous environmental exposures increases the probabilities of identifying potential risk factors for BPH. Therefore, the association of alcohol, diet, and other lifestyle factors with obstructive uropathy was investigated in a cohort of 6581 Japanese-American men, examined and interviewed from 1971 to 1975 in Hawaii. After 17 years of follow-up, 846 incident cases of surgically treated obstructive uropathy were diagnosed with BPH. Total alcohol intake was inversely associated with obstructive uropathy ($p <$

0.0001). The relative risk was 0.64 (95% confidence interval: 0.52-0.78) for men drinking at least 25 grams of alcohol per month compared with nondrinkers. Among the 4 sources of alcohol, a significant inverse association was present for beer, wine, and sake, but not for spirits. No association was found with education, number of marriages, or cigarette smoking. Increased beef intake was weakly related to an increased risk ($p = 0.047$), while no association was found with the consumption of 32 other food items in the study (50).

METABOLIC SYNDROME

There is a growing body of evidence supporting the association between obesity or metabolic syndrome and the development of BPH. The risk of BPH appears to be independently associated with the individual components of BPH including central obesity, hyperinsulinemia, insulin resistance and dyslipidemia. Despite this, the precise causation of this association has not been clearly identified. Recent studies have suggested that in this setting, BPH is a consequence of the metabolic syndrome-associated metabolic derangements, altered sex hormone concentrations and lowered sex-hormone binding globulin concentrations (51). One study found in a cohort of 415 men, that indicators of metabolic syndrome (abnormal concentrations of insulin resistance, subclinical inflammatory state, and sex hormone globulin changes) were significantly associated with increased risk of BPH (52). Mechanisms associated with metabolic syndrome have been discussed as possible targets for future therapies for BPH (53).

CHRONIC INFLAMMATION

There is strong evidence to suggest that inflammation and inflammatory markers are involved in the pathogenesis of BPH. Inflammation within the prostate can be caused by several factors including bacteria, virus, autoimmune disease, diet, metabolic syndrome, and hormone imbalances (53). This leads to the activation of inflammatory cells, release of cytokines,

expression of growth factors, and ultimately abnormal proliferation of epithelial and stromal cells of the prostate. Proliferation induces a cycle of hypoxia and recruitment of more growth factors resulting in increased prostate volume and BPH (54). The REDUCE study of 8224 prostate biopsy samples of men with BPH found that 77.6% had cells of chronic inflammation on histology (55).

Anti-inflammatory medications have been studied in combination with BPH medications. A meta-analysis of three randomized controlled trials (n=183) in this area found that non-steroidal anti-inflammatory drugs improved IPSS scores by a mean of 2.89 points and increase peak urine flow by a mean of 0.89m/s (56).

OTHER RISK FACTORS

It has not been possible to delineate any other risk factors for BPH such as coronary artery disease, liver cirrhosis, or diabetes mellitus. Traditionally it has been believed that there is no causal relationship between malignant and benign prostatic hypertrophy (37) and recent data from large trials continue to support this premise (57). Alternative theories have emerged but more data directly linking association with causality are required (58).

PATHOPHYSIOLOGY OF BPH

NATURAL HISTORY

BPH is a histological diagnosis, but its clinical manifestations occur after growth has occurred to such a degree and in such a strategic location within the gland, namely the transitional zone, that it impairs bladder emptying and results in LUTS. One can consider the natural history of BPH as involving two phases:

(i) The pathological or first phase of BPH is asymptomatic and involves a progression from microscopic to macroscopic BPH. Microscopic BPH will develop in almost all men if they live long enough but in only about half will progress to macroscopic BPH. This would suggest that additional factors are necessary to cause microscopic to progress to macroscopic BPH (59). The pathological phase involves development of hyperplastic changes in the transitional zone of the prostate (60). While there is wide variability in prostate growth rates at an individual level, prostate volume appears to increase steadily at about 1.6% per year in randomly selected community men (61).

(ii) The clinical or second phase of BPH involves the progression from pathological to 'clinical BPH' that is synonymous with the development of LUTS. Only about one half of patients with macroscopic BPH progress to develop clinical BPH (59). BPH consists of mechanical and dynamic components and it is these components that are responsible for the progression from pathological to clinical BPH (62). In clinical BPH, the ratio of stroma to epithelium is 5:1 whereas in the case of asymptomatic hyperplasia the ratio is 2.7:1. A significant contribution is therefore made by stroma to the infravesical obstruction of BPH (63).

DISEASE MANIFESTATIONS OF BPH

Lower Urinary Tract Symptoms (LUTS)

Lower urinary tract symptoms (LUTS) are highly prevalent and the majority of LUTS in men is produced by BPH, but may be contributed to by a variety of conditions (Figure 6). LUTS are traditionally divided into voiding or obstructive and storage or irritative symptoms (Table 2). Voiding symptoms are more common, however it is storage symptoms that are most bothersome and have a greater impact on a patient's life (64,65). The prevalence of clinical BPH

risks with age and approximately 25% of men age 40 or over will suffer from LUTS (66).

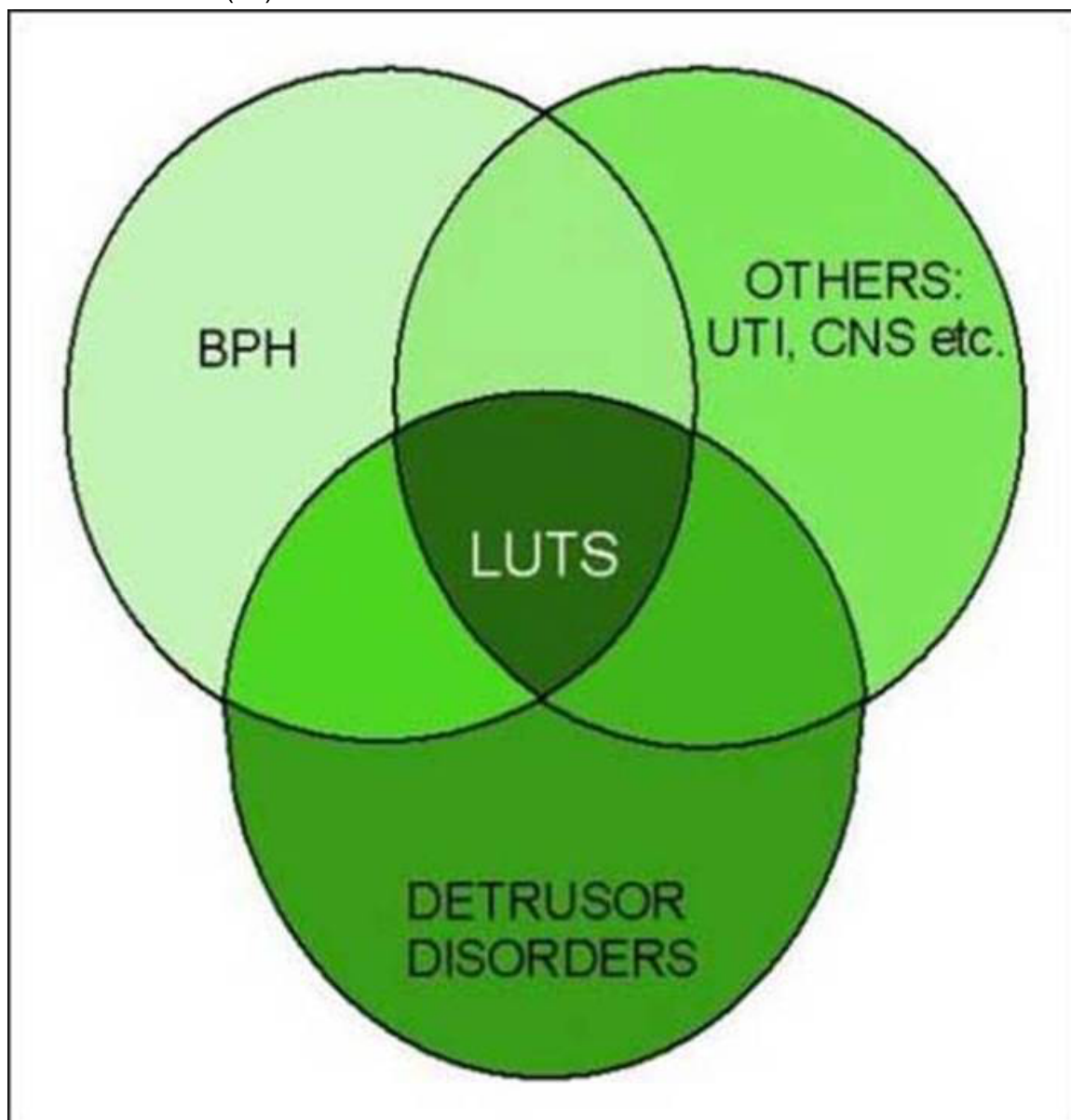


Figure 6. Interaction of the many factors involved in the pathogenesis of LUTS. Other causes of LUTS (top right) include all of the differential diagnoses included in Table 5 (see below).

Table 2. Lower Urinary Tract Symptoms

Voiding or Obstructive Symptoms	Storage or Irritative Symptoms
Hesitancy Poor stream Intermittent stream Straining to pass urine Prolonged micturition Sense of incomplete bladder emptying Terminal dribbling	Urinary frequency Urgency Urge incontinence Nocturia

In the past, LUTS suggestive of bladder outflow obstruction (BOO) secondary to BPH were referred to as 'prostatism', once other causes such as a urinary tract infection or prostate cancer were excluded. The pathology behind the symptoms was thought to be obstruction due to prostatic gland enlargement alone. However, it is now recognized that voiding/obstructive

symptoms result from direct urinary flow obstruction whilst storage/irritative symptoms appear to be due to secondary bladder dysfunction (67). Thus, LUTs occurs after the prostate enlargement causes obstruction, and the bladder voiding is secondarily affected leading irritable symptoms (Figure 7).

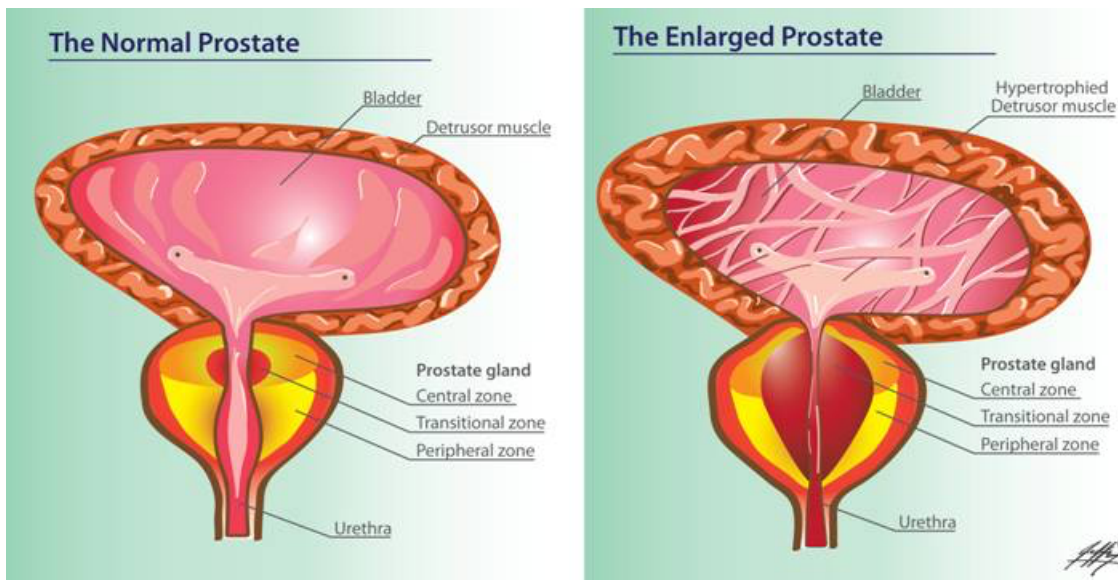


Figure 7. Diagrammatic representation of BPH with the enlarged prostate transition zone causing obstruction of the prostatic urethra and the secondary changes in the bladder leading to hypertrophy of the detrusor muscle (copyright Nathan Lawrentschuk 2012).

This concept has been further refined in that obstructive symptoms are thought to result not only from mechanical obstruction due to glandular enlargement, but also dynamic obstruction secondary to contraction of the smooth muscle of the prostate, urethra and bladder neck. This dynamic obstruction is a result of sympathetic nervous system mediated

stimulation of alpha-1 adrenoceptors. Storage symptoms appear to be caused by detrusor instability related to detrusor muscle changes in response to obstruction, such as bladder wall hypertrophy and collagen deposition in the bladder (68,69). Adrenoceptors may be further sub-divided into alpha1A and alpha1D subtypes, with alpha1A

predominant in the prostate and alpha 1D in the bladder. Thus, blockade of alpha1A may be necessary for reduction of obstruction whereas the blockade of alpha1D may be required to relieve storage symptoms (70) (see below).

It has been suggested that the etiology of LUTS related to BPH is even more complex than outlined above, with extra-prostatic mechanisms such as bladder wall ischemia and changes in the central nervous system being implicated (71). Normal lower urinary tract function is complex, and theoretically any

disruption of the pathway for micturition (Figure 8 below) may lead to LUTS (72).

It is worth noting the relationship between LUTS and sexual dysfunction, with sexual dysfunction being highly prevalent in men with LUTS (73). By sexual dysfunction, we refer to decreased libido, erectile dysfunction, decreased ejaculation and other ejaculation disorders. Kassabian (74) expands on the relationship and agrees with Leilefeld et al (75) in suggesting that the relationship is coincidental and both are common in the ageing male.

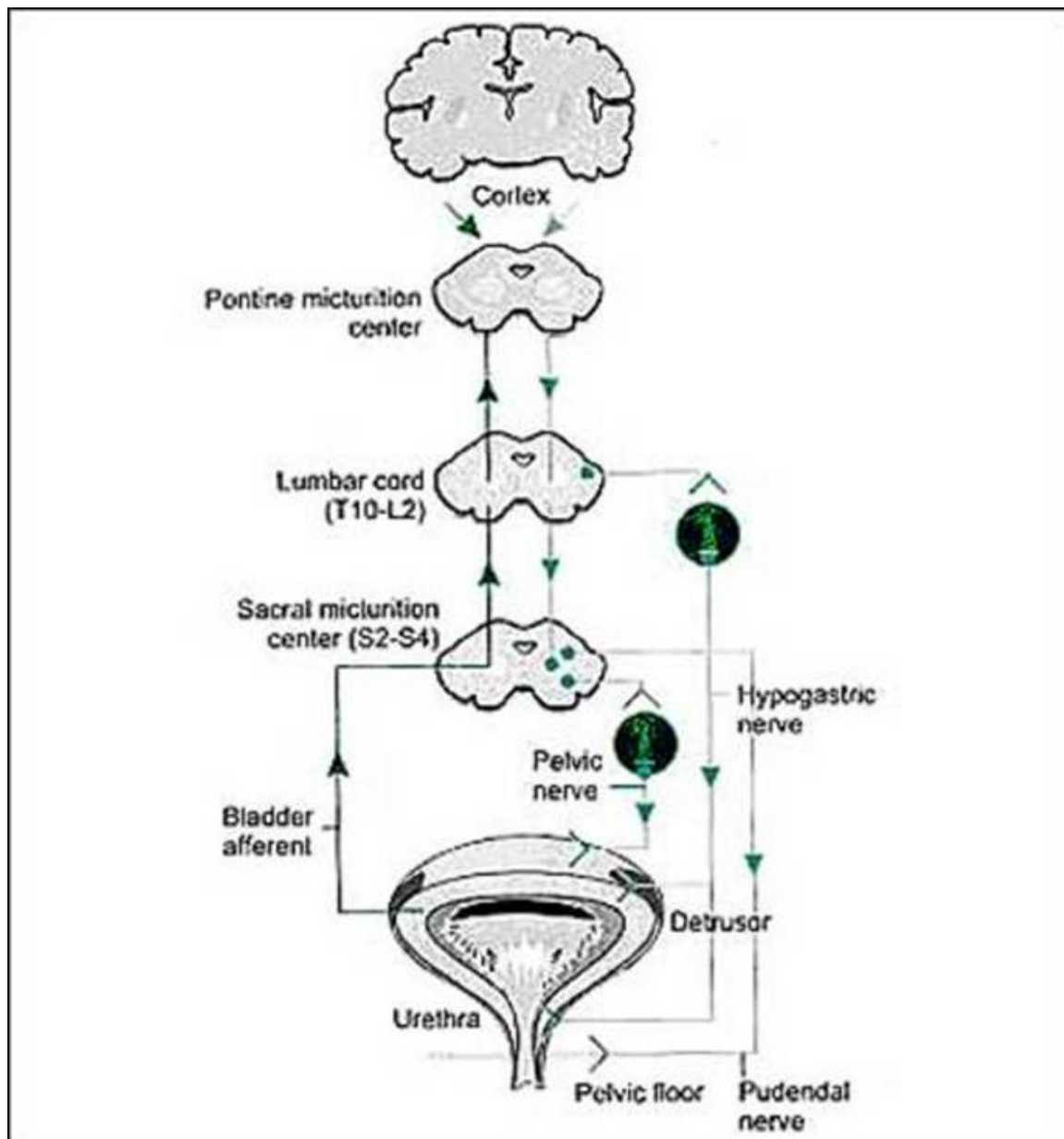


Figure 8- Normal micturition pathways (reproduced with permission from Physiology and pathophysiology of lower urinary tract symptoms, Drugs of Today, Vol 37, p. 7, Michel MC(72)).

COMPLICATIONS OF BPH

The complications of BPH are summarized in Table 3.

Table 3. Common Complications of BPH

Urinary retention
Recurrent Urinary Tract Infections
Bladder Calculi
Hematuria
Secondary bladder instability
Renal Impairment

Urinary Retention (Acute and Chronic)

As the prostate volume increases with age, the likelihood of acute urinary retention (AUR) and symptom severity both increase while urinary flow rates fall. In one study of more than 2000 men, those with a maximum urinary flow rate (Q_{max}) <12 ml/s had a 4 times greater risk for AUR than did men with a $Q_{max} >12$ ml/s (76). AUR is usually painful and necessitates the insertion of a per urethral indwelling or suprapubic urinary catheter.

If the urinary retention is not dealt with in a timely fashion, the detrusor muscle becomes distended and damaged, contributing to poor detrusor function and an inability to adequately empty the bladder. The retention of urine becomes painless over time, and the sequelae of retained urine such as recurrent UTI, calculi, and renal impairment may develop.

Furthermore, a situation of overflow incontinence may develop whereby the bladder automatically empties once the volume reached exceeds its new, larger capacity. The passage of urine is typically uncontrolled, and this may often be the first presentation for someone with advanced BPH. The bladder remains full despite the emptying, which is only partial.

In situations of chronic urinary retention, relieving the bladder outflow obstruction might not restore normal detrusor function. These patients often need to use intermittent self-catheterization or have permanent

drainage to keep their bladder empty and to reduce damage to the upper urinary tract.

Recurrent Lower Urinary Tract Infection (UTI)

The best host defense against infection in the lower urinary tract might be normal flow of urine and bladder emptying. In BPH, bladder outflow obstruction results in disruption of this mechanism with retention and pooling of urine in the bladder, giving organisms the opportunity to multiply rather than be flushed out. Despite this logical assumption, there is little evidence in the literature to support this theory. Nevertheless, men with significant clinical BPH are probably at risk of UTI, and men with UTI should be assessed for signs of BPH.

Bladder Calculi

In developed countries, the most prevalent cause of bladder calculi is bladder outlet obstruction owing to BPH (77). Of those who undergo prostate surgery for BPH, approximately 2% of all patients are found to have bladder stones (78). Stones occur in this situation due to urinary stasis combined with high urinary solute concentrations, which leads to crystal precipitation (79). Chronic infection with urease-producing organisms may predispose to the development of stones and rarely stones pass from the upper tract to act as a nidus in the bladder (79). Bladder calculi associated with BPH remains an

absolute indication for transurethral resection of the prostate (TURP) (80,81) because of the risk or recurrence of stone formation. However, the necessity of surgery is being challenged by the expanding use of medical management in treating BPH (81).

Hematuria

The incidence of hematuria with BPH is uncertain, however; in a retrospective review of almost 4000 patients undergoing TURP, Mebust et al (80) noted that hematuria was an indication for surgery in 12% of patients. It is hypothesized that BPH, with its increased acinar and stromal cell proliferation, stimulates increased vascularity via angiogenesis. These new and prolific vessels may be easily disrupted leading to recurrent bleeding (82). This is supported by Foley et al (83) who found the microvessel density to be higher in those patients with BPH having hematuria after histological studies. It is also hypothesized that 5-alpha reductase inhibitors might reduce angiogenesis and theoretically reduce the risk prostate bleeding. Finasteride has been suggested as an option in treating the problem of hematuria (84-86).

Detrusor (Bladder) Instability

The definition of detrusor instability is the development of a detrusor contraction which exceeds 15cm H₂O at a bladder volume of less than 300ml (87). Detrusor instability is not a specific term related to BPH, but implies LUTS secondary to detrusor pathology. These symptoms are normally storage related and consist of urgency, frequency, urge incontinence, and nocturia. In BPH, the normal dynamics of the bladder are altered due to detrusor muscle stretching due in turn to retention of urine and contraction against an obstructed outlet. Although not completely understood, some of the detrusor instability may be related to changes at the adrenoceptors level, rather than just from obstruction and its consequences alone. In normal bladder physiology, beta-adrenoceptors are believed to be involved in the relaxation of the bladder

during storage of urine (71). In some patients, however, the administration of noradrenaline leads to contraction of the detrusor muscle which may be blocked by an alpha-1 adrenoceptor antagonist (88). This implies the presence of alpha-adrenoceptors in the detrusor muscle in at least some patients. Furthermore, alpha-adrenoceptor antagonists have been shown to relieve storage and voiding symptoms in men without obstruction and storage symptoms in women (71,89-92). Alpha adrenoceptor subtypes in the human bladder are predominantly of the alpha1D and alpha1A type. In animal models, the alpha1D receptors become more abundant with bladder obstruction (93), and it may be speculated that this is the case in humans and that these receptors, once up-regulated, play a role in storage symptoms (71).

Renal Insufficiency

Renal insufficiency results from obstructive uropathy secondary to the bladder outlet obstruction of BPH. In an analysis of patients receiving treatment for BPH, 13.6% (range 0.3-30%) had renal insufficiency (78). Certainly, an abnormal creatinine is an indication to further investigate the upper urinary tract with imaging. Obviously, other concurrent causes of renal insufficiency need to be excluded. Those patients with renal insufficiency undergoing surgery are at increased risk (25%) of postoperative complications such as acute renal failure and urosepsis compared to patients without (17%) insufficiency (80).

HISTORY

A comprehensive medical history must be evaluated and should include the use of a voiding diary, the International Prostate Symptom Score (IPSS) and a discussion of the role of PSA testing (94). An outline of the evaluation and treatment options for LUTS is shown in Table 4 and is discussed in greater depth below (95,96). Previous urological disease should be documented including previous urological surgery, UTI, bladder or renal calculi, renal disease and penoscrotal pathology. Any risk factors for surgery

such as diabetes mellitus, immunosuppression, ischemic heart disease, respiratory problems, smoking as well as a comprehensive list of medications should be noted. Medications with anticholinergic properties should be noted, as these may contribute to the patient's symptoms. The use of antihypertensives must be noted as any alpha-blocker

treatment initiated could potentially cause severe hypotension.

As discussed in the section on differential diagnosis, consideration needs to be given to neurologic causes of voiding dysfunction such as stroke or Parkinson's disease.

TABLE 4. A SUMMARY OF DIAGNOSIS AND TREATMENT OPTIONS IN BPH

EVALUATION of LUTS
ESSENTIAL <ol style="list-style-type: none"> 1. History 2. Digital Rectal Exam (DRE) 3. Urinalysis 4. Serum creatinine 5. PSA, if > 10-year life expectancy 6. International Prostate Symptom Score (IPSS) or AUA symptom index SELECTED <ol style="list-style-type: none"> 1. Uroflowmetry 2. Imaging - especially if hematuria, UTI, urolithiasis 3. Post Void Residual (PVR) estimation 4. +/-Pressure flow studies 5. +/-Cystoscopy
TREATMENT OPTIONS
MEDICAL THERAPY <ol style="list-style-type: none"> 1. Phytotherapy 2. Monotherapy: <ol style="list-style-type: none"> a. Alpha blockers b. 5-alpha reductase inhibitors c. PDE5 Inhibitors 3. Combination therapy: <ol style="list-style-type: none"> a. Alpha blocker + 5-alpha reductase inhibitor b. PDE5 inhibitor + alpha blocker (experimental) SURGERY <ol style="list-style-type: none"> 1. Invasive surgery <ol style="list-style-type: none"> a. Transurethral resection of the prostate (TURP) b. Laser prostatectomy/treatment c. Open prostatectomy 2. Minimally invasive measures <ol style="list-style-type: none"> a. Transurethral Incision of the prostate (TUIP) b. Thermo ablative strategies (TUMT, TUNA)

-
- c. Chemical ablative (PRX-302, NX-1207, TEAP)
 - d. Mechanical (Urolift, prostatic stent)
 - e. Others (prostatic artery embolization, histotripsy, Rezum, aquablation)

INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

The American Urologic Association (AUA) Symptom Index was developed as a standardized instrument to assess the degree of bladder outlet obstruction in men (89). It is widely used and consists of seven questions that assess emptying, frequency, intermittency, urgency, weak stream and straining with each graded with a score of 0-5. Total score ranges 0-35. The index categorizes patients as:

1. Mild (score ≤ 7)
2. Moderate (score 8-19)
3. Severe (score 20-35).

The International Prostate Symptom Score (IPSS) is a modification of the AUA Symptom Index adding a single question assessing the quality of life or bother score based on the patient's perception of the problem (Figure 9) (97). Both the AUA and IPSS questionnaires, although not specific for BPH, prostate volume, urinary flow rate, post-void residual volume, or bladder outlet obstruction, have been validated and are sensitive enough to be used in the evaluation of symptoms and selection of treatment (98-100). Many would argue that the score is the primary determinant of whether or not a patient proceeds to further treatment. Further, these questionnaires are a valuable objective measure when determining the response to treatments for BPH.

INTERNATIONAL PROSTATE SYMPTOM SCORE SHEET

Dr Name: Address:

Patient Name: Address:

Date:

Age Group: 40-49 ☐ 50-59 ☐
 60-69 ☐ 70+ ☐

	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 two hours after you finished urinating?	0	1	2	3	4	5	
3. INTERMITTENCY Over the past month, how often have you found you stopped and started 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	
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?	None 0	1 time 1	2 times 2	3 times 3	4 times 4	5 or more times 5	

Which of the above do you regard as most troublesome (1-7)

TOTAL PROSTATE SYMPTOM SCORE:

	Delighted	Pleased	Mostly satisfied	Mixed - satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
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? (tick one)	0	1	2	3	4	5	6

FIGURE 9. INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS) SHEET (101,102)

EXAMINATION

General appearance is of importance, especially in identifying those with neurological disease (e.g., past stroke, Parkinson's disease) or other major co-morbidities (obesity, severe osteoarthritis, diabetes) that may impact on treatment or further investigation. An abdominal examination should identify those in marked urinary retention, any abnormal masses, and previous surgical scars. A careful assessment of the scrotum and its contents as well as the penis is also warranted to exclude any other pathology. The digital rectal examination (DRE) is important in identifying prostatic abnormalities, including clinically apparent prostate carcinoma (103). Prostate size, texture, and tenderness should all be assessed, as should anal tone. Any nodules should be carefully noted. Constipation may also be a contributing factor to urinary retention and anal tone should also be recorded.

DIFFERENTIAL DIAGNOSIS OF BPH

It is important to acknowledge that the diagnosis of BPH often relies on surrogate measures until a histological diagnosis is confirmed. These range from clinical (symptom scores), physiological (uroflowmetry), anatomical (prostatic volume on DRE or TRUS) and biochemical (PSA values) measurement. Although all of these measurements capture some component of BPH, none of them is specific for BPH (104). Surrogate measures are likely to represent a continuum of disease severity without the existence of a threshold. Thus, differential diagnoses need to always be considered and where appropriate, excluded. In table 5 below, some of the more obvious differential diagnoses are listed, but will not be examined in detail.

Table 5. Differential Diagnoses for LUTS

Inflammatory Conditions	<ol style="list-style-type: none"> 1. Urinary Tract Infection 2. Prostatitis 3. Bladder Calculi 4. Interstitial Cystitis 5. Tuberculous Cystitis
Neoplastic Conditions	<ol style="list-style-type: none"> 1. Prostate cancer 2. Bladder transitional cell carcinoma (usually CIS) 3. Urethral cancer
Neurological Conditions	<ol style="list-style-type: none"> 1. Parkinson's disease 2. Stroke 3. Multiple Sclerosis 4. Cerebral Atrophy 5. Shy-Drager Syndrome
Other Causes of Urinary Obstruction	<ol style="list-style-type: none"> 1. Urethral stricture 2. Severe phimosis 3. Bladder neck dyssynergia 4. External sphincter dyssynergia

PROSTATITIS

Prostatitis is a common condition that must be excluded from other causes of LUTS and is a common cause of visits to primary care physicians and urologists. It may present as an acute bacterial infection or may be chronic, occasionally progressing to a debilitating illness. In practice, the clinical

diagnosis of prostatitis depends on the history and physical examination, but there is no characteristic physical finding or diagnostic laboratory test. Patients with prostatitis experience considerable morbidity and may remain symptomatic for many years. Unfortunately, there is limited understanding of the pathophysiology and optimal treatment for most patients. Prostatitis has been sub-classified and an abbreviated version is shown in Table 6.

Table 6. The National Institute of Health (USA) Consensus Classification of Prostatitis Syndromes

Acute bacterial prostatitis
Chronic bacterial prostatitis
Chronic prostatitis/chronic pelvic pain syndrome
Inflammatory
Non-inflammatory
Asymptomatic inflammatory prostatitis

Acute Prostatitis

Clinical features suggestive of acute prostatitis (Type 1, in Table 6 above) include dysuria and urinary frequency as well as perineal pain (Table 7). Systemic

symptoms such as fever, rigors, myalgia and sweats are often a feature. On examination, the patient is normally febrile, and may be overtly septic depending on the infection severity. A digital rectal exam finds an extremely tender prostate, which is often intolerable to the patient. An abscess is occasionally palpated.

Table 7. Clinical Symptoms in Prostatitis (adapted from Lobel (105))

Genital symptoms	<ol style="list-style-type: none"> 1. Dribbling 2. Inguinal pain 3. Testicular pain 4. Retropubic pain 5. Perineal pain 6. Urethral Burning
General Symptoms	<ol style="list-style-type: none"> 1. Backache 2. Sweating 3. Tiredness 4. Cold feet

Investigations should include a mid-stream urine sample for microscopy, culture for bacteria, and

antibiotic sensitivity. The most common organisms are typical uropathogenic bacteria such as *Escherichia*

coli (*E. coli*). Blood cultures for bacteria and antibiotic sensitivity should also be considered. Prostatic massage is usually contraindicated in patients with acute prostatitis due to pain and the risk of precipitating sepsis. A treatment regime is highlighted in Table 8. If there is failure to respond to therapy, evaluation for a prostatic abscess using a transrectal ultrasound scan or computed tomography scan may

be required. If necessary, perineal or transurethral drainage of an abscess may be undertaken. At least 4 weeks of antibiotic therapy is recommended in all patients to try to prevent chronic bacterial prostatitis. Following resolution of acute prostatitis, the urinary tract should be investigated for any structural problems (106,107).

Table 8. Treatment of Acute Prostatitis
1. Hydration
2. Rest and hospitalization if severe
3. Empirical therapy with antibiotic until urine culture and sensitivities available
4. For patients requiring parenteral therapy antibiotics covering the likely organisms: broad spectrum cephalosporins, for example, cefuroxime, cefotaxime, or ceftriaxone plus gentamicin
5 Oral treatment according to sensitivities.: quinolones, such as ciprofloxacin or norfloxacin. For patients intolerant of, or allergic to, quinolones: trimethoprim or co-trimoxazole;
6. Analgesics, such as non-steroidal anti-inflammatory drugs Suprapubic catheterization if catheterization needed - per urethral catheters may precipitate abscess formation

CHRONIC PROSTATITIS

As the presentation may be localized to the genital region or non-specific (see Table 7) a careful history and examination along with specialized diagnostic tests are needed to identify this condition. Investigations may involve prostatic massage to express organisms and/or white blood cells for analysis. Urine sample collection is often done in phases to aid in the localization process: first void urethral urine; mid-stream bladder urine; post-prostatic massage sample. Urine microscopy and quantitative culture is then undertaken. Semen analysis for excessive white blood cell numbers may also be indicative of chronic prostatitis. Serum PSA concentrations are often elevated in acute prostatitis or in an active phase of chronic prostatitis. Trans-rectal ultrasound might be considered but not recommended to differentiate the different forms of chronic prostatitis. Urinary tract localization procedures (culture of first void urethral urine; mid-stream bladder urine; post-prostatic massage samples

of urine correlating to urethra, bladder and prostate) although theoretically correct, are often not used in clinical practice (106,107).

The various classifications of chronic prostatitis are listed in Table 6. Patients with chronic bacterial prostatitis (type II prostatitis) experience recurrent episodes of bacterial urinary tract infection caused by the same organism, usually *E. coli*, another Gram-negative organism, or enterococcus. Between symptomatic episodes of bacteriuria, lower urinary tract cultures can be used to document an infected prostate gland as the focus of these recurrent infections. Acute and chronic bacterial prostatitis represent the best understood, but least common, prostatitis syndromes (106,107).

Unfortunately, more than 90% of symptomatic patients have chronic prostatitis/chronic pelvic pain syndrome (type III). This term recognizes the limited understanding of the causes of this syndrome for most patients and the possibility that organs other than the

prostate gland may contribute to this syndrome. Urological pain (normally in the perineum or associated with voiding or intercourse) is now recognized as a primary component of this syndrome. Active urethritis, urogenital cancer, urinary tract disease, functionally significant urethral stricture, or neurological disease affecting the bladder must be excluded. Patients with the inflammatory subtype (type IIIA) of chronic prostatitis/chronic pelvic pain syndrome have leukocytes in their expressed prostatic secretions post prostate massage urine or in semen.

In contrast, patients with the non-inflammatory subtype of chronic prostatitis (type III B) have no evidence of inflammation. In essence, they have no evidence of active infection nor of inflammation on available investigative techniques taken at a particular point in time. Repeat investigations are therefore done to be sure adequate sampling has been undertaken. This condition may be difficult to treat and requires intensive counselling, information and reassurance to the patient to be successfully managed (107).

Finally, asymptomatic inflammatory prostatitis (type IV) is diagnosed in patients who have no history of genitourinary tract pain complaints. It is often an incidental finding on prostatic biopsy done for other reasons (e.g., a raised PSA). Treatment is usually not required.

TREATMENT OF CHRONIC PROSTATITIS

All patients should have investigations as outlined above. A summary of treatment options is shown in Table 9. Those patients with chronic prostatitis secondary to bacterial infection (type II) require a

prolonged course of antibiotics (often up to three months) and should then be re-cultured to ensure eradication of the organism. Some urologists argue that these patients should also have investigation of their urinary tract by way of cystoscopy and at minimum, an ultrasound to ensure no anatomical abnormality that may be responsible.

Patients with asymptomatic prostatitis (IV) require no treatment but those with the inflammatory (IIIA) and non-inflammatory (IIIB) are more difficult. Patients with type IIIA disease have excessive leukocytosis in their specimens but no bacteria. However, because their symptoms may be due to a pathogen that is difficult to isolate, a further course of antibiotics (6-12 weeks) with coverage of chlamydia and ureaplasma should be given (105). If this antibiotic course is not therapeutic, then a focus should be on anti-inflammatory medications (which may be used in conjunction with the course of antibiotics). If anti-inflammatory treatment fails, then patients should be treated as below, for type IIIB.

Current treatment for Type IIIB patients requires multiple therapies. Triple-therapy involves high dose alpha-blocker (3 month minimum), analgesia, and muscle relaxant (benzodiazepines). Initially, a narcotic analgesic should be changed to a non-steroidal anti-inflammatory (NSAID) if a response occurs after 2 weeks. The NSAID should be continued for at least 6 weeks, but stopped if there is no response at 2 weeks. If the triple treatment fails, other avenues must be explored, including biofeedback, relaxation exercises, psychotherapy, and lifestyle changes (soft cushions, cease bike-riding). The focus is on improving quality of life and minimizing symptoms, not curing the disease (105).

Table 9. Management and Treatment of Chronic Prostatitis

Oral and written patient education
Pharmacological treatment for chronic bacterial prostatitis chosen according to antimicrobial sensitivities include quinolones such as ciprofloxacin; ofloxacin; norfloxacin. For those allergic to quinolones: minocycline; doxycycline; trimethoprim-sulfamethoxazole; co-trimoxazole; in many regions, trimethoprim sulfamethoxazole is first line therapy because of better safety profile than quinolones.
Other treatments for chronic bacterial prostatitis: radical transurethral prostatectomy or total prostatectomy in carefully selected patients.
Empirical treatments for chronic abacterial prostatitis
Treat as for chronic bacterial prostatitis with a quinolone or tetracycline
Alpha blockers: terazosin, doxazosin, alfuzosin, tamsulosin, silodosin
Non-steroidal anti-inflammatory drugs
Stress management. Referral for psychological assessment as appropriate; diazepam. Note: benzodiazepines are considered but not recommended in clinical practice because of dependency
Adequate follow-up and counselling, often with professional support
Cernilton (pollen extract)
Bioflavonoid quercetin
Transurethral microwave thermotherapy

INVESTIGATIONS OF LUTS

As outlined by Tubarro et al (94), the aim of investigations for LUTS should be threefold: (1) to evaluate the possible relationship between prostatic enlargement, lower urinary tract symptoms and signs of bladder outlet obstruction; (2) to quantify the severity of benign prostatic enlargement-related symptoms and signs and (3) to rule out the presence of a prostate cancer.

URINALYSIS

Urinalysis is used to screen for urinary tract infection as a cause of LUTS in order to identify those with microscopic or macroscopic hematuria. A formal urine culture may be undertaken if the analysis was suspicious for infection.

Post-Void Residual Urine Volume (PVRU)

Although there is a high degree of intra-individual variation in the PVRU, it may still provide valuable information with regard to bladder emptying. Although it does not distinguish adequately between bladder outlet obstruction or poor detrusor function, it can identify a bladder emptying problem and be used as a marker for improvement. Due to its inability to differentiate between causes, the United States guidelines on BPH suggest it is an optional investigation (78). Greater than 300ml is considered a potential risk factor for upper urinary tract dilatation and renal impairment (108). The PVRU does have the advantage of being used as a monitoring investigation in those opting for non-surgical therapy for BPH. It is readily and quickly performed in the office or hospital setting using portable ultrasound equipment.

Laboratory Investigations

SERUM CREATININE IS RECOMMENDED BY MOST GUIDELINES FOR THE INVESTIGATION OF BPH AND AN ELEVATED SERUM CREATININE WOULD BE AN INDICATION TO EVALUATE THE UPPER URINARY TRACT (96).

Serum PSA has several implications in the diagnosis and management of BPH, including (1) providing a prediction of the prostate volume (2) providing the prediction of disease course, and (3) providing a risk assessment for prostate cancer. Indeed, in multiple placebo arms of large double-blind clinical trials, the serum PSA is an independent predictor of the risk of acute urinary retention and progression to BPH-related surgery (109). While the PSA provides useful information in the aforementioned domains, in clinical practice the main utility of PSA testing in the setting of LUTS is to exclude prostate malignancy. In patients presenting with isolated LUTS, current guidelines suggest its use only if a diagnosis of prostate cancer will change management or if the PSA can assist in decision-making in patients at high risk of BPH progression.

UPPER URINARY TRACT IMAGING

Urinary tract ultrasound or computerized tomography are appropriate modalities. Most would consider upper tract imaging as mandatory if hematuria is present and recommend it if there was a history of urolithiasis, urinary tract infection, or renal insufficiency. Intravenous pyelography still has a role in certain cases, as other modalities do not outline the anatomy of the collecting system with such definition (94).

Urodynamics

Urodynamics is a general term for a collection of investigations useful in quantifying the activity of the

lower urinary tract during micturition (110). Complete pressure-flow urodynamics are complex and usually involve fluoroscopy, video recording, bladder and rectal pressure measurement, as well as an assessment of urine flow. The simplest urodynamics are pressure-flow studies, requiring only voiding into a measuring device to obtain flow rates, and may easily be done in the office setting.

With regard to the investigation and diagnosis of conditions underlying LUTS, when considering inexpensive, safe, and completely reversible treatments, one may opt to avoid urodynamics studies initially. However, when considering irreversible, expensive, or potentially morbid therapy, such studies are considered mandatory. Many patients will not have urodynamics studies based on the first premise above (110). However, in reality, many surgeons and physicians will have simple pressure-flow studies readily available and will perform these as part of an initial consultation. More complex studies require time and are costly, and so should be reserved for particular situations as discussed below.

Urinary Flow Rate (Uroflowmetry)

Uroflowmetry is considered by some as the single most useful urodynamic technique for the assessment of obstructive uropathy. The purpose of the uroflow examination is to record one or more micturitions that are representative of the patient's usual voiding pattern. Therefore, more than one micturition is often required and it is necessary to confirm with the patient if the flow was better, worse or about the same as their normal pattern, otherwise intra-individual variability may lead to false assumptions (111). The study may be performed in the office or as part of other urodynamic studies in the laboratory or operating suite.

Figure 10 indicates the most common urinary flow parameters measured. Of these, the peak flow rate is

the most closely correlated with the extent of outflow obstruction (Table 10). Total voiding time is prolonged in obstruction and has a reduced Qmax. Poor detrusor contractility is impossible to distinguish from bladder

outflow obstruction on uroflowmetry so other urodynamics investigations such as a cytometry are indicated.

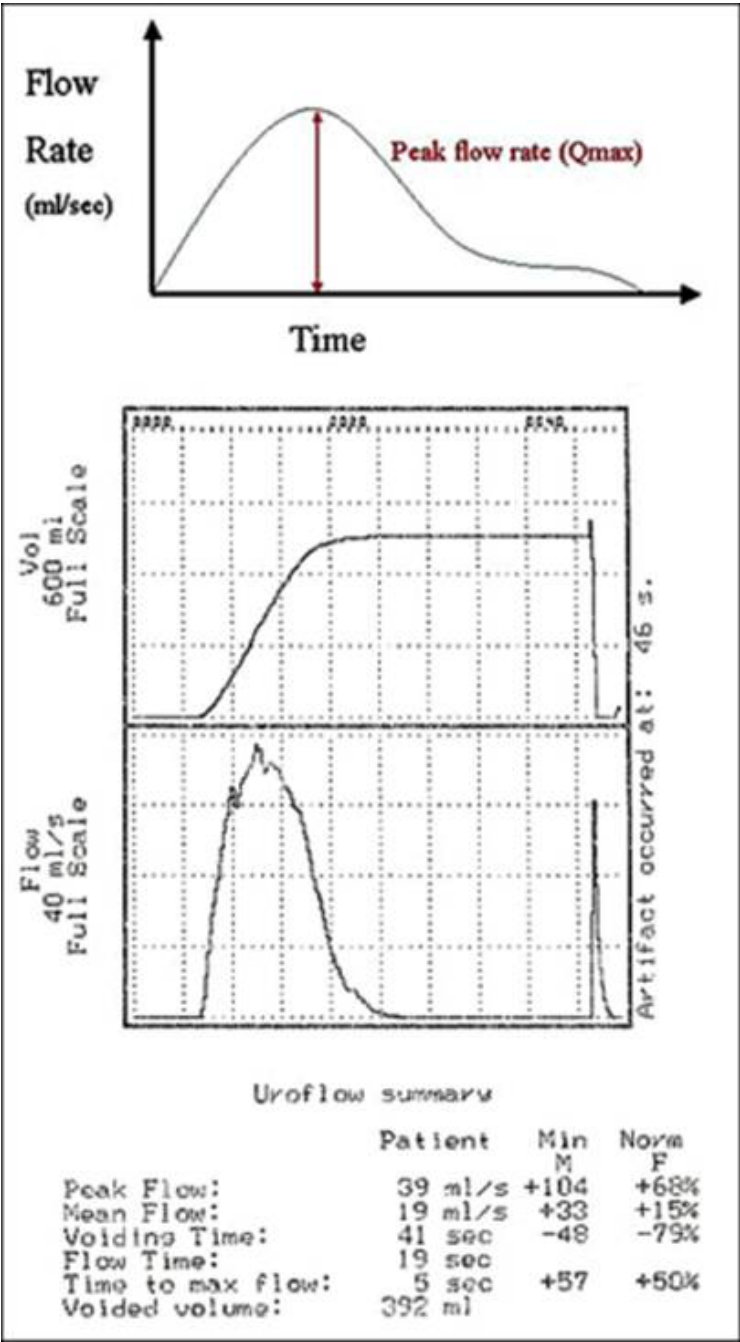


FIGURE 10. UROFLOWMETRY IN A NORMAL INDIVIDUAL- DIAGRAM ABOVE AND ACTUAL READING BELOW (TABLE 10).

Table 10. Interpretation of Uroflowmetry Results.

Flow rate- Qmax	Interpretation
>15ml/sec	Unlikely to be significant obstruction
<10ml/sec	Likely to be significant obstruction or weak detrusor activity
10-15ml/sec	Equivocal

URODYNAMICS- PRESSURE-FLOW STUDIES

Various measurements may be used to define detrusor pressures and urethral sphincter pressures as an aid to diagnosis in specific circumstances. This is relevant in patients with LUTS who have had a stroke (or other neurologic disease) where bladder function may have sensory deficits or unstable detrusor contractions that may need alternate management. Nevertheless, detrusor instability is not considered a negative factor with respect to the outcome of BPH surgery (94), provided it is adequately managed. Some have even suggested that the detection of detrusor instability in patients with LUTS is only of minor diagnostic importance (112).

URETHROCYSTOSCOPY

The performance of this investigation depends on patient history and proposed surgical intervention. It is necessary where there is a history of microscopic or macroscopic hematuria to exclude bladder tumors or stones. A history or suspicion of urethral strictures, bladder tumors, or prior lower urinary tract surgery should also prompt this investigation. Surgeons may also use urethroscopy when planning different surgical treatments or invasive therapies.

Transrectal Ultrasound Scanning (TRUS)

Compared to TRUS, methods of determining prostate size such as DRE, urethroscopy, and retrograde urethrography are poor (113). It is often conducted in unison with biopsies of the prostate for suspected carcinoma, but is also a useful tool for assessing the

size of an enlarged prostate so that the best mode of management may be undertaken, such as open versus endoscopic surgery.

OVERVIEW OF TREATMENT OF BPH

The primary aim of any treatment for BPH in the vast majority of men is to relieve bothersome obstructive and irritative symptoms (114) (Table 2). Treatment is often undertaken on an elective basis for such patients. Those in whom complications of BPH occur have treatment done urgently as a matter of course. A range of treatment options are available and may be tailored to the needs of every individual, taking into account their disease manifestations, success rates of treatment, possible complications, and patient preference.

WATCH AND WAIT/LIFESTYLE CHANGE

Many men who present with LUTS are often seeking a full assessment of their prostatic health rather than immediate treatment of symptoms that may not be exceptionally bothersome. People with mild symptoms may wish to pursue lifestyle changes as a way of improving their quality of life but with the option of review if such measures fail or symptoms worsen. Furthermore, when an adequate history is taken, hidden agendas such as fear of prostate cancer may even be revealed and fears allayed.

Often drinking habits may be responsible for symptoms such as nocturia, where considerable fluid volumes are consumed in the evening. Reducing fluid

intake may diminish nocturia and evening urgency. Furthermore, caffeine and alcohol acting as diuretics can further exacerbate LUTS. Simple shifts in daily fluid intake may fulfil patient expectations and result in satisfactory outcomes. Voiding diaries are useful for making patients aware of drinking habits and may be the catalyst for initiating and monitoring changes. Bladder retraining (by using timed voiding, strengthening pelvic floor exercises, and monitoring oral intake) is also an option in some individuals, once a voiding diary has been examined.

Medications may also play a role with LUTS. Measures such as diuretic restriction in evenings often prevents nocturia and frequency, provided the diuretic can be taken earlier in the afternoon.

It is important to discuss options with the patient and that they be made aware that the possibility of damage to their upper urinary tract or to the detrusor muscle may result if their symptoms deteriorate and they do not seek medical attention.

PHYTOTHERAPY FOR BPH

Phytotherapy, or the use of plant extracts, is becoming widely used in the management of many medical conditions including BPH (Table 11) (115). Often these agents are promoted to aid “prostatic health” and a significant proportion of men try them. Factors also contributing to their widespread use include the perception that they are supposedly “natural”

products; the presumption of their safety (although this is not adequately proven); their alleged potential to assist in avoiding surgery, and even the unproven claim that they may prevent prostate cancer. The widespread availability of these products (without prescription) in vitamin shops, supermarkets, pharmacies, and over the internet has contributed to their usage and reflects the demand for these phytotherapeutic agents. The mechanisms of action are poorly understood but have been proposed to be (1) anti-inflammatory, (2) inhibitors of 5-alpha reductase, and more recently (3) through alteration in growth factors (116).

Phytotherapy, although promising, lacks long-term, good quality clinical data (117). Nevertheless, because there is a large placebo effect associated with treatment of voiding symptoms, the use of herbal products that have few or no side effects may be a reasonable first-line approach for many patients (118). However, patients should be counselled that the efficacy, mechanisms of action and long-term effects of these agents are not known and they must be aware of the limitations before proceeding (119).

The most popular phytotherapeutic agents are extracted from the seeds, barks and fruits of plants. Products may contain extracts from one or more plants and different extraction procedures are often used by manufacturers. Thus, the composition and purity of products may differ even if they originated from the same plant. Basic research on one product may not be easily transferred to another making the gathering of data and giving of advice difficult (120).

Table 11. Phytotherapy Used in the Treatment of Benign Prostatic Hyperplasia	
Phytotherapeutic plant extract	Proposed Mechanism of action
Saw palmetto- fruit (<i>Serenoa repens</i>)	Antiandrogenic, Anti-inflammatory
African plum- bark (<i>Pygeum africanum</i>)	Antiandrogenic, potential growth factor manipulation, anti-inflammation actions
Pumpkin- seed (<i>Cucurbita pepo</i>)	Phytosterols are thought to be amongst the active compounds
Cernilton- pollen (<i>Secale cereal</i> , Rye)	Inhibition of alpha-adrenergic receptors
South African star grass- root (<i>Hypoxis rooperi</i>)	Antiandrogenic, alteration in detrusor function
Stinging nettle- root	Steroid hormone manipulation reducing prostate growth
Opuntia- flower (Cactus)	Unknown
Pinus- flower (Pine)	Unknown

SAW PALMETTO BERRY (SERENOA REPENS)

Extracts from the berries of the American dwarf palm (saw palmetto) are the most popular and widely available plant extracts used to treat symptomatic BPH today (121,122). At least eight possible mechanisms of action for saw palmetto have been advocated including anti-androgenic properties, anti-inflammatory properties, induction of apoptosis to name a few (120). Several studies have found that saw palmetto suppresses growth and induces apoptosis of prostate epithelial cells by inhibition of various signal transduction pathways (123). However, it is most commonly believed that saw palmetto works as a naturally occurring weak 5-alpha reductase inhibitor, blocking the conversion of testosterone to DHT, as demonstrated in several *in vitro* studies (118, 124-127). Thus, saw palmetto may be expected to reduce prostate size. While demonstrated in animal models (128), this is not the case in several trials using saw palmetto in men with BPH (129,130). The only trial to show *in vivo* effects of saw palmetto involved needle biopsies of the prostate gland, before and after

treatment with saw palmetto or placebo. Although the mechanism is unclear, there was a significant increase in prostatic epithelial contraction in the saw palmetto group (131).

Clinical evidence reporting the use of saw palmetto is conflicting. In a meta-analysis of 18 randomized studies relating to saw palmetto extracts, almost 3000 men with BPH were studied and the authors concluded that “the evidence suggests that saw palmetto improves urologic symptoms and flow rates but that further research is needed using standardized preparations to determine long term effectiveness” (115). When analyzing flow rate and symptom score alone from this meta-analysis, the effect of *Serenoa repens* (the scientific name of saw palmetto was to increase the flow rate by a further 2.28 ml/sec (standard error, SE, 0.29) over placebo which gave an increase of 1.09 ml/sec (SE 0.45). *Serenoa repens* also reduced the IPSS by 4.7 (SE 0.41), which is comparable to that found with finasteride and tamsulosin monotherapy (132).

Conversely, a recently published Cochrane review concluded *Serenoa repens* was no more effective than placebo for treatment of urinary symptoms consistent with BPH (133). This update of a prior review, nine new trials involving 2053 additional men (a 65% increase) were included. The main comparison was again *Serenoa repens* versus placebo where three trials were added with 419 subjects and three endpoints (IPSS, peak urine flow, prostate size). Overall, 5222 subjects from 30 randomized trials ranging from four to 60 weeks were assessed. The vast majority were double blinded and treatment allocation concealment was adequate in just over half the studies.

In summary, some saw palmetto studies have shown improved symptom scores compared to placebo but generally no change in flow rates (134). However, large reviews cast doubt on its efficacy. In general, there is a real paucity of well performed, adequately powered, and placebo-controlled trials in the use of phytotherapy in clinical BPH. It is generally well tolerated at a dose of 320mg/day, but its efficacy has not been compared with alpha-blockers regarding efficacy, and has not been shown to reduce complications of BPH with long term use. Finally, the product quality and purity cannot always be assured.

African Plum Tree (*Pygeum africanum*)

Extracts come from the bark of the African plum tree. It is hypothesized, based on *in vitro* observation, that it acts on the prostate through inhibition of fibroblast growth factors, has anti-estrogenic effects, and inhibits chemotactic leukotrienes. No strong clinical data exists of its efficacy although trials are in progress (116,119).

PUMPKIN SEED (*CUCURBITA PEPO*)

Dried or fresh seeds have been taken to relieve symptoms. Phytosterols are thought to be amongst the active compounds. Side effects have not been reported but evidence is lacking with no current clinical trials (135).

RYE POLLEN (*SECALE CEREALE*)

This is prepared from rye grass pollen extract. In a systematic review summarizing evidence from randomized and clinically controlled trials (114), rye pollen was found to be well tolerated but only achieved modest improvement in symptom outcomes and did not significantly improve objective measures such as peak and mean urinary flow rates. Again, several mechanisms of action have been proposed including an improvement in detrusor activity, a reduction in prostatic urethral resistance, inhibition of 5-alpha reductase activity, and an influence on androgen metabolism in the prostate (119).

OTHER EXTRACTS

South African Star Grass (*Hypoxis rooperi*), Opuntia (Cactus flower), stinging nettle, and Pinus (Pine flower) have also been studied and used, however the data numbers are small and the types of trials do not allow conclusions to be drawn at this stage (116).

MEDICAL THERAPY FOR BPH – MONOTHERAPY AGENTS

In 1986, Caine (62) proposed that infravesical obstruction in men with symptomatic BPH comprised both static and dynamic components. The static component of obstruction is related primarily to the mechanical obstruction caused by the enlarging prostatic adenoma whereas the dynamic component is principally determined by the tone of the prostatic smooth muscle. Two avenues for pharmacotherapy

have therefore evolved, namely shrinking the prostate tissue or relaxing the smooth muscle of the prostate. Prostatic smooth muscle tone is under the influence of the autonomic nervous system. Thus, any pharmacologic agent that may interfere with the functioning of this system could alter resistance in smooth muscle tone and resulting symptoms.

Medical therapy is now first-line treatment for most men with symptomatic BPH. They are non-invasive, reversible, cause minimal side effects, and significantly improve symptoms (81,136). With these recommendations, the rates of prescriptions for the medical management for BPH have increased drastically over the past decade (137,138). This increased interest has further led to the development of safer, more efficacious agents.

Alpha-Blockers

There are 3 main components to clinically significant BPH: static, dynamic and detrusor muscle components as outlined above. The dynamic component is associated with an increase in smooth muscle tone of the prostate. These smooth muscle cells contract under the influence of noradrenergic sympathetic nerves, thereby constricting the urethra (139). Prostatic tissue contains high concentrations of both α_1 and α_2 adrenoceptors – 98% of the α_1 adrenoceptors are associated with stromal elements of the prostate (140). Thus α_1 -receptor blockers relax smooth muscle, resulting in relief of bladder outlet obstruction that enhances urine flow (87). Different subtypes of α_1 receptors have been identified, with α_{1A} predominating. Two α_{1A} -adrenoceptors generated by genetic polymorphism have been identified with different ethnic distributions but similar pharmacologic properties (36).

It was demonstrated in 1978 that phenoxybenzamine, a non-selective α_1/α_2 blocker, was effective in relieving the symptoms of BPH (141). Side effects

were significant and included dizziness and palpitations. Many of the side effects of the α -blockers were mediated by α_2 -receptors (142). Thus, α_1 selective antagonists such as terazosin, doxazosin, and prazosin and were developed that had fewer side effects than phenoxybenzamine (67). Doxazosin, alfuzosin, and terazosin have gained favor in clinical practice because they are longer acting than prazosin. Due to side effects, many α_1 selective antagonists need to be titrated and are often started at the lowest dose and built up over time to the maximal dose or a dose where clinical effects are satisfactory.

More recently, highly uro-selective α_{1A} selective agents have been introduced including tamsulosin and silodosin. Due to the uro-selective nature, there is significant reduction in risk of systemic side-effects when compared to the less selective agents. However, the increased potency of these agents results in an increased compromise to bladder neck function and as a result, increases the risk of ejaculatory dysfunction.

PRAZOSIN

Prazosin (titrated up to 5mg day) has been shown to significantly increase flow rates by 36-59% compared to placebo 6-28% but 17% of men discontinued the drug due to side effects such as dizziness (21%), headache (14%), syncope (3.4%) and retrograde ejaculation (13%).

ALFUZOSIN

Alfuzosin (5 mg bid or 10 mg daily) has shown symptom score reduction of 31-65% (compared to placebo 18-39%) and flow rate increases of 22-54% (compared to placebo 10-30%). Hence the results were similar to those of prazosin but with only 3-7% discontinuations due to dizziness (3-7%), headache (1-6%) and syncope (<1 %) (143,144).

TERAZOSIN

Terazosin (2-10mg) had a symptom score reduction of 40-70% (compared to placebo 16-58%) and improved flow rates 19-40% (placebo 5-46%). Between 9-15 % of men discontinued the drug, related to dizziness (10-20%), headache (1-7%), asthenia (7-10%), syncope (0.5-1.0%), and postural hypotension (3-9%). Thus, terazosin was effective and superior to placebo in reducing symptoms and increasing the peak urinary flow rate. The effect of terazosin on the peak urinary flow rate was apparent in studies as soon as 8 weeks of therapy. Most importantly, the effect of terazosin on symptoms and peak urinary flow rate was independent of the baseline prostate size for the range of prostate volumes reported (145).

DOXAZOSIN

Doxazosin (4-12mg/day) is a selective α_1 -adrenoceptor antagonist, and produced a significant increase in maximum urinary flow rate (2.3 to 3.6 ml. per sec) at doses of 4 mg, 8 mg and 12 mg, and in average flow rate compared with placebo. The increase in maximum flow rate was significantly greater than placebo within 1 week of initiating therapy and the drug significantly decreased patient-assessed total, obstructive, and irritative BPH symptoms. Blood pressure was significantly lower with all doxazosin doses compared with placebo. Adverse events, primarily mild to moderate in severity, were reported in 48% of patients on doxazosin compared to 35% on placebo, with only 11% discontinuing treatment (a similar number to placebo). The main side effects were dizziness (15-24%), headache (12%) and hypotension (5-8%), and abnormal ejaculation (0.4%) (146,147).

TAMSULOSIN

Tamsulosin (0.4 mg once or twice daily dose) is a selective α_1 blocker for the α_{1A} subtype which predominates in the human prostate, having 12 times more affinity for the receptors in the prostate than in the aorta thereby reducing side effects mediated through blood vessels receptors. Symptom scores were reduced by 20-50% (placebo 18-30%), flow rates improved 20-45% (placebo 5-15%) but only 3-7% of men discontinued drug because of dizziness (3-20%), headache (3-20%), syncope (0.3%), and retrograde ejaculation (5-10%). The rate of retrograde ejaculation was much higher than alfuzosin but the blood pressure lowering side effects are less with tamsulosin(148). There are different formulations including extended release with lower pharmacological peaks and troughs which may offer fewer side effects.

SILODOSIN

Silodosin (8mg daily) is a highly selective blocker for the α_{1A} receptor subtype. It has the highest affinity for α_{1A} receptors of the medications discussed here. Symptoms scores were reduced by 40-50% (placebo 20-30%), flow rates improved by 17-30% (placebo 5-14%). Despite these favorable urinary outcomes, a significant proportion of patients experienced ejaculatory dysfunction (13-23%). These rates are higher compared to tamsulosin, however discontinuation rates secondary to ejaculatory dysfunction remains at 1-2%. Typical side effects include thirst (10%), loose stools (9%) and dizziness (5%) (149,150). Similar results were found in a recent meta-analysis of silodosin. Compared to tamsulosin, the combination of 13 studies found silodosin showed little to no difference in urological symptom scores and quality of life whilst increasing sexual adverse events. The same results were reported when silodosin was compared to naftopidil and alfuzosin (151).

Several meta-analyses have demonstrated that all non-selective alpha1-adrenoceptor antagonists seem to have similar efficacy in improving symptoms and flow rates (152). The difference between non-selective alpha 1-adrenoceptor antagonists is related to their side effect profile. Overall, alfuzosin appear to be better tolerated than doxazosin, terazosin and prazosin(153). More recent analyses suggest that the

highly uro-selective alpha_{1A} blockers are more efficacious compared to non-selective alpha blockers with regards to urinary symptoms and urine flow improvement (154-156). Further, these highly selective agents appear to have a favorable systemic side-effect profile at a cost of ejaculatory function when compared to non-selective alpha blockers.

TABLE 12. COMMONLY USED ALPHA-BLOCKERS

Group	Drug
Nonselective alpha blockers	Phenoxybenzamine Nicergoline Thymoxamine
Selective alpha1 blockers	Prazosin Alfuzosin
Super-selective alpha _{1A} blockers	Tamsulosin Silodosin
Long-acting alpha1 blockers	Terazosin Doxazosin

5-Alpha Reductase Inhibitors

The enzyme 5-alpha reductase is crucial in the amplification of androgen action in the prostate by modulating the conversion of testosterone to DHT (Figure 5). Within the prostate, 90% of testosterone is converted to DHT (78,157). There are 2 isoforms of the enzyme 5-alpha reductase which are encoded by separate genes (158). Type 1 isoenzyme is expressed highly in the skin, liver, hair follicles, sebaceous glands, and prostate whereas type 2 is responsible for male virilization of the male fetus, and in adulthood resides in prostate, genital skin, facial and scalp follicles (159,160). Inhibitors of these enzymes potentially decrease serum and intra-prostatic DHT concentrations, thus reducing prostatic tissue growth.

FINASTERIDE

Finasteride was the first of these to be studied in humans and shown to decrease DHT concentrations (161). It acts predominantly on the type 2 isoenzyme of 5-alpha reductase. There is some evidence that patients on finasteride experience fewer serious complications associated with the progression of BPH compared with those prescribed an alpha blocker, such as acute urinary retention or undergoing BPH-related surgery, but more prospective data is needed (162). Finasteride reduces serum DHT concentrations by 65-70% and prostatic concentrations by 85-90%, although the intraprostatic concentrations of testosterone are reciprocally elevated as the testosterone is not being converted to DHT.

Because 5-alpha reductase inhibitors work by reducing prostatic tissue volume, baseline prostate size has a significant impact on its efficacy with larger glands (>50ml) being likely to respond (163,164). After treatment for one year with finasteride, there was a significant decrease (17-30%) in total gland size with

the greatest size reduction in the periurethral component of the prostate, which has the greatest impact on obstructive symptoms (78,165,166). There was a 60-70% decrease in serum DHT concentration, a 25% decrease in prostate volume, and a symptom score reduction of 13-30% (vs placebo 4-20%). Urinary flow rate improved 7-20% (vs placebo 3-15%) and was more pronounced with prostates > 40ml. The side effect profile included a decreased libido in 10%, ejaculatory dysfunction in 7.7%, and impotence in 15.8%. But adverse events resulted in only 4% of patients discontinuing treatment (117,167). There was a 50% reduction in the risk of AUR and in the need for surgery (30%). Finasteride has also found a role in the treatment of BPH-related hematuria although its role in reduction of perioperative bleeding is not well defined (84,117).

More recently, as part of the Prostate Cancer Prevention Trial involving over 18,000 men, it was concluded that finasteride delays the appearance of prostate cancer whilst reducing the risk of urinary problems. However, there was a reported increased risk of high-grade prostate cancer leading to the discontinuation of this study. This point remains controversial as some believe due to the gland shrinking that sampling was altered and by virtue of a smaller area the likelihood of finding an aggressive tumor was increased (168). In any case, the benefits in terms of improved LUTS needs to be weighed against the potential sexual side effects and potential small but significant increased risk of high-grade prostate carcinoma (169,170) and compared to the option of using adrenoreceptor blockers. Despite the findings, more evidence is needed before advising patients to cease finasteride. However, they do need to be counselled on the small, but significant risks of developing aggressive prostate cancer (171).

DUTASTERIDE

Dutasteride unlike finasteride blocks both the type I and Type II 5-alpha reductase isomers showing a 60-

fold greater inhibition of the type 1 isoenzyme than finasteride plus activity against the type 2 isoform (23,117). In terms of monotherapy, a one year randomized, double-blinded comparison of finasteride and dutasteride in men with BPH (EPICS: Enlarged Prostate International Comparator Study) found a trend for dutasteride improvement over finasteride in IPSS (International Prostate Symptom Score) that did not reach statistical significance (abstract) (172). Another non-randomized comparative trial with 240 patients, published only in abstract form, showed a small improvement in AUASI and Q_{max} for dutasteride (173). However, dutasteride and finasteride have never been compared in long-term therapy, either as monotherapy or in combination with an alpha-blocker. These medications appear to exert continued effects beyond 1 year so comparison after only 1 year is likely to be premature.

The tolerability of 5-alpha reductase inhibitors in most studies has been excellent with the most relevant adverse effects being related to sexual function. They include reduced libido, erectile dysfunction, and, less frequently, abnormal ejaculation (74,174). Specifically for dutasteride in the Combat study (175), in the monotherapy arm of 1623 patients the side effect were: erectile dysfunction (6.0%) ; retrograde ejaculation (0.6%); altered (decreased) libido (2.8%); ejaculation failure (0.5%); semen volume decreased (0.3%); loss of libido (1.3%); breast enlargement (1.8%); nipple pain (0.6%); breast tenderness (1.0%), and dizziness (0.7%).

As with finasteride, the **RE**duction by **DU**tasteride of prostate cancer **E**vents (**REDUCE**) trial now fully reported has demonstrated similar results to the PCPT trial in reducing prostate cancer (176). Again, a higher risk of developing more aggressive cancer was demonstrated- but in this study it was not statistically significant. Indeed, some organizations such as the Canadian Urological Association have been dismissive of this point in recent guidelines (171). Needless to say, careful counselling of men regarding

this issue is again required, particularly for younger men who will be on dutasteride for many years.

5-Alpha Reductase Inhibitors to Reduce Hematuria and Intraoperative Hemorrhage for Prostate Surgery

While considered an off-label use, there is some evidence that suggests that 5-alpha reductase inhibitors may be useful in the setting of (177):

- 1) Recurrent hematuria secondary to BPH
- 2) To reduce gland size and/or impact on angiogenesis to reduce intraoperative bleeding for prostate surgery.

No large randomized trials exist but an extensive summary of the literature is available (177).

Phosphodiesterase 5 Inhibitors

Phosphodiesterase 5 (PDE5) inhibitors (e.g., sildenafil, tadalafil and vardenafil) have been used predominantly to treat erectile dysfunction in men. However, recent data suggest they are effective for the treatment of LUTS secondary to BPH. Specifically, the cyclic nucleotide monophosphate cyclic GMP represents an important mediator in the control of the lower urinary tract outflow region (bladder, urethra). PDE5 inhibitors exert effects by several mechanisms including: calcium-dependent relaxation of endothelial smooth muscle, alteration of the spinal micturition reflex pathways, and increased blood flow to the lower urinary tract. PDE inhibitors are regarded as efficacious, have a rapid onset of action, and favorable effect-to-side-effect ratio (178).

The rationale for using tadalafil for BPH stems from the following three observations: first, the prevalence of LUTS, BPH, and erectile dysfunction (ED) increases with age; second, phosphodiesterase-5 inhibition mediates smooth muscle relaxation in the

lower urinary tract; and third, early evidence demonstrates that PDE5 inhibitors such as tadalafil are successful in treating LUTS and ED (179). Results of several randomized controlled trials have demonstrated reproducible reductions in IPSS, symptoms, and improved quality of life compared to placebo. Data suggests tadalafil 5mg improves IPSS by 22-37% and the improvement occurs within one week of commencement, with a duration of 52 weeks (180). The adverse event profile was acceptable and consistent with that previously reported in men with ED (blurred vision, headache, back ache, nausea, etc.), with discontinuation rates of 2%. Not unexpectedly, in the same study tadalafil significantly improved the International Index of Erectile Function-Erectile Function score in sexually active men with erectile dysfunction at twelve weeks. Meta-analytical data confirms these findings suggesting that PDE5 inhibitors improve IPPS and erectile function, with no significant effect on maximal urinary flow rate (181). Other PDE5 inhibitors are being studied including sildenafil and vardenafil (178). The theoretical advantage is treating BPH and erectile dysfunction with one agent (182). To date, tadalafil is the only PDE5 inhibitor that is FDA approved for use for the treatment of BPH. Data on the long-term effects on symptoms and disease progression is not available at present.

Anticholinergic Medications

High-level evidence suggests that for selected patients with bladder outlet obstruction due to BPH and concomitant detrusor overactivity, combination therapy with an alpha-receptor antagonist and anticholinergic can be helpful (183). Such agents help particularly with the irritative urinary symptoms of frequency and urgency. Caution is recommended, however, when considering these agents in men with an elevated residual urine volume or a history of spontaneous urinary retention (171).

Botulinum Toxin A Injection

Injection of botulinum toxin A into the prostate is a novel treatment for LUTS secondary to BPH. First reported in 2003 (184), trans-perineal injection of 100 units of botulinum toxin into each lobe of the prostate under trans-rectal guidance is required. In this randomized controlled trial, thirty patients demonstrated significant improvement in IPSS (65% decrease) and serum PSA (51% decrease) compared to controls, who had injections of saline without botulinum toxin A, at a median follow-up of 20 months. Subsequent long-term follow-up of 77 patients up to 30 months has shown similar results – significant reduction in IPSS (approximately 50% lower), significant improvement in maximum flow rate (approximately 70% higher), and significant reduction in serum PSA values (approximately 50% lower). Importantly, no adverse events were noted (185).

Summary of Monotherapy Medical Treatment

The first line of medical treatment is an alpha-blocker, as the majority of patients treated have a prostate volume of less than 40ml. In men with larger prostates (greater than 40cc), a 5-alpha reductase inhibitor (e.g., finasteride or dutasteride) alone or in combination with an alpha-blocker would be appropriate. Patients who are likely to respond to 5-alpha reductase inhibition will do so at the same relative magnitude as an alpha-blocker, but it will take a longer period of time (months as opposed to weeks). There is likely to be a 20-30 reduction in symptoms and a 1-2ml per second increase in urinary flow (167). Side-effect profiles of medical treatments are also important, as discussed above. For example, with regard to sexual function, tamsulosin and silodosin have an increased risk of retrograde ejaculation and finasteride increases sexual dysfunction (74). These may be important factors in choosing therapies. Finally, the emergence of PDE5 inhibitors for the treatment of men with LUTS secondary to BPH alters the landscape with an ability

to treat men with BPH and ED with one agent. Multiple randomized trials and associated meta-analyses demonstrate the reproducible benefits of PDE5 inhibitors on urinary and erectile function.

MAJOR STUDIES OF MEDICAL TREATMENT OF BPH

The medical treatment of clinical BPH has come under increasing scrutiny through larger trials that have become imperative for their introduction into clinical practice. Some of these larger trials have been selected and are discussed below.

Veterans Affairs Study

In the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group (186), a total of 1,229 subjects with clinical BPH were randomized to 1 year of placebo, finasteride, terazosin or drug combination. The primary outcome measures were the AUA symptom score and the peak urinary flow rate. The percentage of subjects who rated improvement as marked or moderate with placebo, finasteride, terazosin and combination was 39, 44, 61 and 65%, respectively, only the latter two were superior to placebo. There was no significant relationship between baseline prostate volume and treatment response to finasteride or with the other treatments (terazosin or combination). There was a significant but weak relationship between change in AUA symptom score and peak flow rate in the finasteride and combination groups. The symptom responses with terazosin were not related to peak flow rate or baseline prostate volume. In men with clinical BPH, finasteride and placebo are equally effective, while terazosin and combination are significantly more effective. In men with clinical BPH and large prostates, the advantage of finasteride over placebo in terms of symptom reduction, impact on bother due to symptoms and quality of life was small at best, while

the advantage of terazosin (alone or in combination with finasteride) over finasteride alone and placebo was highly significant. The authors concluded that α_1 blockers, such as terazosin, should be first line medical treatment for BPH(186). Another arm of this study observing surgical treatment versus watchful waiting is discussed below.

PLESS Study

The Proscar Long-term Efficacy and Safety Study (PLESS) was a 4-year, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of finasteride 5mg (Proscar™) in 3040 men, aged 45 to 78 years, with symptomatic BPH, enlarged prostates on TRUS volume criteria, and no evidence of prostate cancer (187,188). Finasteride use reduced the risk of developing acute urinary retention by 57% and the need for BPH-related surgery by 55% (189) in comparison to placebo. A modified AUA symptom score was used (because trial was undertaken prior to formal AUA being developed) and showed a statistically significant reduction in mean score of 3 for finasteride and 1.2 for placebo, starting at a level of 15 for both groups (188). Compared with placebo, men treated with finasteride experienced an increased incidence of new drug-related sexual adverse events (erectile dysfunction, decreased libido, ejaculation disorder) only during the first year of therapy with 4% of men discontinuing because of such events (187).

PREDICT Trial

The Prospective European Doxazosin and Combination Therapy (PREDICT) Trial was constructed to evaluate the efficacy and tolerability of the selective α_1 -adrenergic antagonist doxazosin and the 5- α reductase inhibitor finasteride, alone and in combination, for the symptomatic treatment of benign prostatic hyperplasia. It was a prospective, double-blind, placebo-controlled trial involving 1,095

men aged 50 to 80 years. The dose of finasteride was 5 mg/day. Doxazosin was initiated at 1 mg/day, and titrated up to a maximum of 8 mg/day over approximately 10 weeks according to the response of the maximal urinary flow rate (Qmax) and IPSS. An intent-to-treat analysis of 1,007 men showed doxazosin and doxazosin plus finasteride combination therapy produced statistically significant improvements in total IPSS and Qmax compared with placebo and finasteride alone. Finasteride alone was not significantly different statistically from placebo with respect to Qmax or total IPSS. The treatments were generally well tolerated. They concluded that doxazosin was effective in improving urinary symptoms and urinary flow rate in men with benign prostatic hyperplasia, and was more effective than finasteride alone or placebo. The addition of finasteride did not provide further benefit to that achieved with doxazosin alone (146).

MTOPS Study and Predictors of Clinical Progression

The Medical Therapy of Prostatic Symptoms (MTOPS) study is a double-masked, placebo-controlled, multi-center, randomized clinical trial with 4 study arms 1) placebo; 2) doxazosin (4 to 8 mg); 3) finasteride (5 mg) and 4) combination of both doxazosin and finasteride. 3,047 men were randomized equally to the 4 groups (190). Baseline parameters analyzed included age at randomization, transrectal ultrasound (TRUS) volume, AUA symptom score, Qmax, PVRU, and PSA. Reduction in the risk of BPH progression was analyzed by one covariate at a time regression models of absolute risk of BPH progression versus baseline covariates. Groups compared were combination versus doxazosin, combination versus finasteride and finasteride versus doxazosin (190).

In the main finding, disease progression, defined as an increase in AUASS (American Urology Association

Symptom Score- similar to IPSS to score LUTS) of 4, AUR, renal insufficiency, recurrent UTIs and urinary incontinence, was prevented equally by doxazosin and finasteride with an even greater effect when both medications were combined. In conflict with the Veterans Affairs and PREDICT studies, finasteride alone did improve overall symptoms and peak urine flow compared to placebo at 4 years and with even more so when combined with doxazosin (190). This finding coincides with the long-term open label ARIA dutasteride study described above showing a cumulative symptom benefit of treatment up to 4 years (191).

A small part of the MTOPS study focused on the routinely available measure of serum PSA, in an attempt to predict a patient’s future risk of BPH clinical progression, acute urinary retention and BPH-related

invasive therapy, permitting an informed decision concerning the value of medical therapy over watchful waiting (192). In MTOPS, 737 patients were assigned to placebo and followed for an average of 4.5 years. Clinical progression of BPH was pre-defined as either a 4-point increase in AUA symptom score, acute urinary retention, incontinence, renal insufficiency, or recurrent UTI. The need for BPH-related invasive therapy was a secondary outcome. These data are summarized in Table 13, where those having a lower PSA, had a lower rise in symptom score, and a reduced risk of acute urinary retention or invasive treatment compared to those with a higher PSA. The sub-group with the highest baseline PSA was also likely to have larger prostate glands, making the findings intuitive. However, as with many such findings, translating an individual PSA to a population study is difficult, as other factors will determine progression or regression of symptoms, not just PSA.

Table 13. Progression of BPH Symptomatically of Placebo Group only, to AUR or Further Intervention Based on Baseline PSA (adapted from Kaplan et al).			
Baseline PSA tertiles (ng/ml)	Progression of symptom score (points)	Acute urinary retention Risk over study period	Invasive Treatment Risk
<1.2	3.10	0.18	0.6
1.2-2.5	3.47	0.35	1.33
>2.5	7.21	1.46	2.13

CombAT Trial

Combination therapy with a 5-alpha reductase (dutasteride) and the alpha blocker, tamsulosin, in men with moderate-to-severe benign prostatic hyperplasia and prostate enlargement was also further studied in the Combination of Avodart™ and Tamsulosin™ (CombAT) trial. The rationale was the same as those outlined for the MTOPS trial. In summary, it is a 4-year, global, multicenter, randomized, double-blind, parallel-group study designed to investigate the benefits of combination therapy with the dual 5-ARI dutasteride and the alpha-blocker tamsulosin compared with each monotherapy in improving symptoms and long-term outcomes in

men with moderate-to-severe symptoms of BPH and prostate enlargement. Symptoms and long-term outcomes (AUR and surgery) were assessed as separate primary endpoints at two and four years, respectively. Eligible patients were at least 50 years old with prostate volume ≥30 cm³ and PSA level ≥1.5 ng/mL. Almost 5,000 men were enrolled (193). Perhaps the only criticism is the lack of placebo control arm in the study.

The results at four years (194) demonstrated that combination therapy was superior to tamsulosin monotherapy but not dutasteride monotherapy at reducing the relative risk of AUR or BPH-related surgery. Combination therapy was also significantly

superior to both monotherapies at reducing the relative risk of BPH clinical progression. Combination therapy provided significantly greater symptom benefit than either monotherapy. Safety and tolerability were reasonable and in line with expectations for both medications. Certainly, at four years the CombAT data supports the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement.

EMERGING COMBINATION THERAPY REGIMES

With the increasing body of evidence supporting the use of PDE5 inhibitors in the setting of BPH, a number of trials support its use in combination therapy. To date, there are small studies of alfuzosin and tadalafil, tamsulosin and sildenafil, and tamsulosin and vardenafil. These early studies suggest that combination therapy is more effective than monotherapy for urinary and erectile function with a good safety profile (195,196). A meta-analysis of 11 randomized controlled trials (n=855) looked at alpha blockers with or without PDE5 inhibitors. This analysis found men receiving PDE5 inhibitors had a mean improvement of 1.66 points on IPSS, mean increase of 0.94 ml/s maximum urinary flow rate, and improved erectile function (197). Larger series with longer-term follow up is required to definitively define the role of these combination therapies in current practice.

Summary of Combination Therapy for Men with BPH

In the larger studies where the standard endpoint of prostate symptom score was measured, a greater impact of dutasteride over tamsulosin was observed. Considering urinary flow rate (Q_{max}), combination therapy outperformed dutasteride in those with PSA and prostate volumes above the 75 percentile. Clearly, those with larger prostates and higher PSAs derive a

greater benefit with dutasteride coinciding with the size reduction impact of this drug.

In summary, the results of the MTOPS and CombAT trials both suggest combination therapy is better than 5-alpha reductase monotherapy at the 4-year mark. The higher incidence of adverse effects, the increased cost of combination therapy, and the need for prolonged therapy argue for a reductionist medical approach to this condition. One recent small study investigated the discontinuation of 5-alpha reductase inhibitors in patients on combination therapy and found prostate regrowth and worsening of symptoms after 1 year of cessation, emphasizing the importance of 5-alpha reductase inhibitors in prolonged therapy (198). In an opposing design, the SMART trial (Symptom Management After Reducing Therapy) observed the effect of removing the alpha blocker (tamsulosin) after 6 months of combined therapy with dutasteride (199). With I-PSS as the primary outcome, the investigators found that 77% of patients had symptoms that were the same or better after only 3 months of alpha blocker removal. In reference to the CombAT study, the effects of dutasteride continue past two years suggesting that removal of the alpha blocker at later time points may be even less noticeable. However, the CombAT study is quite powerful as it does demonstrate that the natural history of BPH is not altered by taking alpha blocker alone. The rate of AUR and need for surgery was unaltered at about 18%, and thus while tamsulosin helps LUTS, it does not alter disease progression. Combination therapy did lead to reductions in prostate volume, and changed natural history to reduce rates of AUR and surgery. The largest benefit was in the men with the largest glands.

The emergence of newer agents including PDE5 inhibitors gives rise to an increasing number of combination-therapies under investigation. Long-term follow-up is required on these newer combinations. As such, combination treatment will continue to shape the management of BPH for years to come.

SURGICAL TREATMENT OF BPH

INVASIVE SURGICAL THERAPIES

Traditionally prostatectomy by an open approach or TURP has been considered the gold-standard for refractory or complicated BPH (indications listed in Table 14). At present approximately 90% of

prostatectomies are done by TURP. Open prostatectomy should be considered when a gland is estimated to weigh more than 75g, where large bladder calculi exist that may not be dealt with endoscopically, where large bladder diverticula requiring repair exist, if complex urethral conditions or when orthopedic abnormalities prevent positioning in lithotomy for TURP. Contraindications to open prostatectomy include a small fibrous gland, prostate adenocarcinoma, previous prostatectomy or other surgery of the pelvis preventing access (200).

Table 14. Indications for Prostatectomy

Acute Urinary Retention
Recurrent or persistent urinary tract infections
Significant bother from LUTS secondary to bladder outflow obstruction not responding to medical therapy
Recurrent hematuria known to be of prostatic origin
Bladder Calculi

TRANSURETHRAL RESECTION OF THE PROSTATE (TURP)

TURP remains the most common surgical treatment for BPH (201) and remains the ‘gold standard’ by which other surgical (and even medical) treatments are measured (74). TURP involves either regional or general anesthesia, with most patients spending a minimum of one night in the hospital. TURP involves surgically debulking the periurethral and transitional zones of the prostate to relieve obstruction. Debulking is done by electrocautery in the standard TURP through endoscopic instruments introduced into the urethra and bladder. Tissue is resected in small pieces until the hyperplastic tissue is removed and a new channel for passage in the prostatic urethra created in the capsule left behind, much like fashioning a pumpkin for a Halloween jack o’lantern. Despite using electrocautery, there are mild to severe degrees of hemorrhage, depending on the gland size. However, transfusions are rarely needed and the procedure is relatively free of life-threatening complications and most patients experience satisfactory resolution of

their micturition symptoms. Studies on urinary peak flow rates and invasive pressure flow have demonstrated the superiority of TURP over minimally invasive therapies (202). Complications of TURP include failure to void (6%), hemorrhage requiring transfusion (1-4%), clot retention (3%), infection (2%), bladder neck contracture or urethral stricture (6%), transurethral resection syndrome (2%), and rarely incontinence (80,203,204).

TURP is plagued by the potential for morbidity, specifically: retrograde ejaculation, erectile dysfunction, and urinary incontinence. Retrograde ejaculation is reported to occur in almost all patients undergoing TURP as the normal bladder neck mechanism which contracts to allow antegrade ejaculation is surgically resected. Counselling prior to surgery must include a discussion of the impact on sexual performance and also fertility. Erectile dysfunction (ED) may be associated with TURP either via thermal nerve injury or emotional stress and was reported in early studies at a rate of 4-40%. This has now been shown to be an overestimation (74,206).

The rate of ED in the AUA Cooperative study was found to be 13% in 1,000 men (80), however this must be compared to increases of around 20% of ED in untreated groups with BPH. Although ED is often quoted as a side effect of TURP, Kassabian concluded that TURP (or even any other surgical therapy) did not appear to have a long-term effect on erectile function or libido (74). Incontinence is infrequent and typically is a result of intra-operative damage to the external urinary sphincter. Large pooled analysis revealed rates of incontinence following TURP of around 1% (207).

There has been one randomized controlled trial (Veterans Affairs Cooperative Study Group, see above) comparing TURP to “watchful waiting” or reassurance (203). This demonstrated that TURP showed greater benefit with 66% of patients having a decrease in symptoms post TURP compared to 28% who were undergoing ‘watchful waiting’.

One significant modification to the standard TURP using monopolar cautery with glycine as an irrigant has been the use of bipolar cautery using normal saline as the irrigant. The latter has been termed bipolar transurethral resection in saline (TURIS). Glycine alters serum osmolality when absorbed through venous channels in the prostate as the system is under pressure which potentially leading to hyponatremia and also glycine directly itself has an impact on the nervous system. This syndrome is termed “TURP syndrome” and dictates that monopolar resections should be abandoned at around the one-hour mark or when significant venous breach occurs. The TURIS or bipolar technologies thus have the advantage of the ability to carry out resections for a longer time due to very few issues with absorption of saline systemically as opposed to glycine. Large series meta-analysis illustrated comparable efficacy and morbidity profiles when compared to monopolar TURP (207,208). A further modification of the bipolar technology is so called plasmakinetic vaporization where some data is emerging (209,210). This

vaporizes rather than resects the prostate tissue. Compared to TURP, plasmakinetic energies results in similar improvements to IPSS up to 12-month follow up (211).

LASER THERAPY FOR BPH – ENUCLEATION OR VAPORIZATION OF THE PROSTATE

There are several evolving therapies for BPH involving various lasers including Nd-YAG, Holmium, and now Thulium lasers. These laser energies may be utilized in various methods to resect, enucleate, or vaporize the prostate. Laser as an energy source has an advantage over standard electrocautery by being relatively bloodless and does not carry the risk of hyponatremia, which may rarely occur via absorption of irrigation fluid in a standard TURP (212).

Photoselective Vaporization of the Prostate (PVP)

The characteristic 532-nm wavelength laser is selectively absorbed by hemoglobin within prostatic tissue (213,214). Introducing this energy to the prostate results in selective vaporization of prostatic tissue, with effective hemostasis and relatively little tissue coagulation (1.5 – 0.3mm margin). Initially launched as a 60W prototype, the laser was ultimately introduced to the urology community as an 80W system that has been the predominant device used in clinical trials. This first generation used an Nd:YAG laser beam passed through a potassium-titanyl-phosphate (KTP) crystal, halving the wavelength (to 532nm), doubling the laser's frequency, and resulting in a green light. In 2006, the 120W lithium triborate laser (LBO) laser was introduced using a diode pumped Nd:YAG laser light that is emitted through an LBO instead of a KTP crystal, resulting in a higher-powered 532 nm wavelength while still using the same 70-degree deflecting, sidefiring, silica fiber delivery system. More recently, a 180W version has been released (215). This increase in energy corresponds with reduced lasering and operating time (216). Two-

year data from the GOLIATH trial illustrates that the 180W version provides durable symptom improvement that is comparable to traditional TURP (217).

Compared to TURP, PVP has been shown to have an improved side-effect profile, time of catheterization, hospital stay, and improvement in urinary flow rate (218,219). Clinically, the advantage of PVP is that the length of stay in hospital is usually under 24 hours and it can be performed on anticoagulated patients. Outcomes have demonstrated a reduced frequency and severity of clinical complications, however it was limited to smaller prostate sizes (215).

In summary, several laser wavelengths (Potassium titanyl phosphate [KTP], Holmium:Yttrium aluminum garnet [Ho:YAG], Thulium), and delivery systems (end-firing; side-firing; interstitial) are available for PVP, and each has particular characteristics and potential advantages (171,219). In current practice, the use of 532nm 180W PVP (Greenlight) lasers is becoming increasingly more common due to significantly reduced operative times.

Holmium:YAG Laser for Enucleation (HoLEP) or Resection of the Prostate (HoLRP)

This laser may be used to enucleate the prostate and remove the tissue in pieces (HoLEP) or to vaporise the tissue (HoLRP). HoLRP is an operation involving laser resection of the prostate tissue via an endoscope, similar to a standard TURP using electrocautery as outlined above. The fragments of prostate tissue are made small enough to irrigate out prior to detachment from the prostate (220). HoLEP again uses a Holmium laser but the laser acts like a finger would at an open prostatectomy, shelling out tissue until it floats in the bladder. The tissue is then morcellated and extracted. This technique may be safely used in large prostate glands (those weighing >100g) as an alternative to open prostatectomy as discussed below (212). Initial

studies have demonstrated that HoLEP improved flow rates by 56-119% and by TURP 96-127%, and symptom scores reduced in both groups by 60%. Further, these studies reported a reduced length of hospital stay, clot retention rates, the occurrence of hyponatremia, strictures but had a slightly higher risk of reoperation (221-223). Pooled data of recent randomized trials suggest HoLEP results in significantly improved maximal flow rate, IPSS, transfusion rate at a cost to operative time (224). Patients are usually kept in hospital a little longer with the Holmium:YAG compared to the PVP technique. However, the Holmium:YAG laser has a longer track record. The disadvantage is that treatment with the Holmium:YAG is quite a complex procedure to learn as it widely resects all the prostatic tissue. HoLRP with its inherent wavelength and laser properties is not photoselective for prostate tissue and as such causes more coagulation and necrosis and has not been popular as a therapeutic intervention.

Thulium Laser

A two-micron continuous-wave is produced with a wavelength of 2013nm. This wavelength is close to the water absorption peak in tissue. This provides several advantages including excellent hemostasis with minimal thermal injury to surrounding tissue. Tissue may be incised accurately or vaporized depending on the settings utilized. Initial reports in 2005 reported the use of a 50-Watt Thulium: YAG (Tm:YAG) laser (225). More recently an improved 120 W laser has been produced, allowing for up to 1.08g of vaporization per minute (226). With the high degree of accuracy of focal ablation, various resection techniques have been reported including: Tm laser resection of the prostate-tangerine technique (TmLRP-TT), Tm vaporization (ThuVaP), Tm vaporesction (ThuVaRP), Tm vapoenucleation (ThuVEP), Tm enucleation (ThuLEP). Combinations of the available techniques allow prostate removal rates to be increase to 2-3 grams per minute (227).

When compared to TURP, TmVaRP offered similar urinary symptom improvement however TURP was superior in improving max voiding velocity post operatively (228). Furthermore, no improvements in reduced blood loss or decreased length of hospital stay were observed (228). Similarly, a meta-analysis of four clinical trials comparing ThuVEP and HoLEP showed both lasers were effective in reducing BPH symptoms but found ThuVEP to have slightly reduced blood loss and shorter lasting urinary incontinence post procedure (229). This evidence largely suggests that the choice between TURP, HoLEP, and thulium laser is based on availability and surgeon experience.

Visual Laser Thermoablation of the Prostate (VLAP)

Alternate minimally invasive laser therapies such as VLAP rely on deep thermal coagulation of the prostate by Nd:YAG laser with later necrosis and sloughing of the prostate tissue (230). They are not photoselective for prostate tissue and do not vaporize the tissue as PVP lasers do. They require prolonged catheterization and have a failure rate of around 10% as reported by Chacko et al in a randomized trial in 2001 (231). Such therapies differ from debulking surgery and require a post-procedure period for resolution of symptoms with the advantages being lack of general or regional anesthesia. Durability and tolerability remain issues for such therapies with re-treatment rates between 10 and 49% (202). Certainly, further studies, using randomization, larger sample sizes, and comprehensive measures of outcomes and adverse events, are still needed to better define the role of laser techniques for treating benign prostatic obstruction (221).

OPEN SIMPLE PROSTATECTOMY

This is the oldest, most invasive therapy for BPH (232). This form of surgery was the standard for men with BPH for over a century however was often associated with complications and prolonged hospital

stays. The number of simple prostatectomies being performed has declined since the introduction of TURP and laser energies.

It is commonly done through a transvesical approach, but may be done retropubically. Early complications of this operation include hemorrhage, blood transfusion, sepsis, and urinary retention with the most common late complication being bladder neck stricture (2-3%) (200). TURP has lower perioperative morbidity but open prostatectomy produces equivalent, if not superior improvement with a similar or lower re-operation rate (233). Sexual dysfunction is not likely to be altered by the surgery (74,234) however ED is still quoted at 3-5% risk (200). Retrograde ejaculation occurs in 90% patients. Other complications of surgery such as deep vein thrombosis, myocardial infarction, and stroke are less than 1% (200).

SUMMARY OF INVASIVE SURGICAL TECHNIQUES

Over the past decade, significant advances have been made regarding the invasive management for BPH. Traditionally, TURP has been reserved for refractory or complicated BPH. However, recent advances in laser technologies have resulted in a marked uptake in the use of laser prostatectomy. Novel approaches utilizing laser energy allows for the enucleation, resection, or ablation of prostatic tissue. Multiple meta-analyses demonstrate equivocal efficacy when comparing TURP and laser prostatectomy. In light of this information, in patients where prostatectomy is indicated it is reasonable to proceed with either of the energy sources discussed above based on surgeon and patient preferences.

MINIMALLY INVASIVE SURGICAL THERAPIES (MIST)

Minimally invasive therapies for BPH have evolved in the past decade with the goal being to achieve

symptomatic improvement that is durable, without the morbidity associated with surgery or the long-term side effects or compliance issues associated with medical therapies (202). The aim of such treatments is to achieve results similar to TURP but with minimal anesthesia, hospitalization, and morbidity. An overview of earlier randomized controlled trials in 2000 by Tubaro et al (235) comparing minimally invasive and invasive modalities of treatment found re-treatment rates to be higher in the minimally invasive group. They concluded that at the time, none of the minimally invasive treatments were superior to TURP from a cost and benefit standpoint and that TURP remains the gold standard of treatment.

More recently, an increasing number of therapeutic options have been developed to improve durability without limitation to the minimally-invasive approach. Multiple ablative (thermo or chemical) or mechanical options have been introduced with early data available. Accordingly, current practice suggests a markedly increasing use of MIST, particularly in the younger patients (236). While the precise role of MIST is not clear, some view such treatments as in-between medical and TURP and we await long term data on all proposed therapies.

TRANSURETHRAL INCISION OF THE PROSTATE (TUIP)

A similar approach to a TURP is used except that no surgical debulking is undertaken. Between one and three incisions are made into the prostate at the level of the bladder neck back almost to the insertion of the ejaculatory ducts. This releases the “ring” of BPH tissue at the bladder neck, creating a larger opening. There is a reduced risk of morbidity such as hemorrhage. In some instances, ejaculation may be preserved in younger men, especially if one incision is made. The procedure only works if the tissue in the periurethral area is not too bulky, otherwise a “ball-valve” mechanism of adenoma may develop. Therefore, TUIP should be recommended to men with

smaller prostates (237). Laser may be used for incisions of the prostate, as well as standard electrocautery (212). Some studies have shown TUIP to have similar IPSS outcomes to TURP but lower urine peak flow rate. Understandably, TUIP has also been shown to give better outcomes in terms of ejaculatory function (238).

THERMO-ABLATIVE THERAPIES

Thermoablation is the principle underlying the several minimally invasive available treatments that have been introduced thus far (239) and these include transurethral microwave thermotherapy (TUMT), transurethral electrovaporization of the prostate (TUEVP), and transurethral needle ablation (TUNA). Collectively, these therapies have been shown to have similar or decreased efficacy when compared to TURP but have a slightly better morbidity profile at this stage. Longer follow up data will determine the true efficacy and risk profiles for these thermo-ablative therapies.

Transurethral Microwave Therapy (TUMT)

An intraurethral antenna emits microwave radiation and delivers heat to a targeted region of the prostate. Histologically, this results in well-controlled coagulative necrosis. A number of series have been published reporting outcomes following TUMT. Multiple studies have compared TUMT versus TURP, which have demonstrated the sustained effect of mild symptom improvement when compared to TURP. A recent review reported a reduced efficacy when compared to TURP with regards to IPSS improvement at 12 months (65% decrease compared to 77% with TURP) and urinary flow rate (70% increase compared to 119% with TURP) (240,241). Retreatment rates are high, ranging between 10-22% compared to 4-8% following TURP. Despite this limitation to efficacy, TUMT provides significant benefits when compared to TURP including improved sexual function, hospitalization, hematuria, transfusions rates (242).

Because of lower effectiveness compared to TURP, TUMT is considered a second line option at this stage (243).

Transurethral Electrovaporization of the Prostate (TUVP)

TUVP uses heat from a monopolar or bipolar high voltage electrical current to vaporize tissue (237). Theoretically this technique could have an ablative as well as coagulative effect. To date, a meta-analysis of randomized controlled trials comparing TUVP and TURP have shown no significant differences in IPSS, quality of life or post void residual volumes. Similar rates of complications have also been found however this is limited by short follow up durations (244,245). Furthermore, TUVP did not lead to a reduction in postoperative morbidity or shorter hospital stays (246).

Transurethral Needle Ablation (TUNA)

Radiofrequency ablation between two electrodes results in thermal ablation and resulting coagulative necrosis of tissue. Several randomized trials have been performed with only short-to-midterm follow up available. As with other forms of MIST, concerns regarding durability are present. A 5 year follow up demonstrated that 58% of patients had maintained symptom control, however 21% needed re-treatment (247). Meta-analytical data confirms an improved IPSS and urinary flow rate at one-year, however to a significantly lower magnitude when compared to TURP (248). Similar to TUMT and TUVP, TUNA has a favorable morbidity profile when compared to TURP.

MECHANICAL THERAPIES

Urolift

Prostatic urethral lift (PUL) is a novel procedure that is characterized by the placement of non-absorbable

implants within the prostatic urethra. When placed correctly, these implants provide anterolateral traction to the lateral lobes of the prostate without necessitating tissue ablation. Advantages of PUL are that it is a short, simple procedure that can be done under local anesthesia and has low complication rates. However, the presence of an obstructing median lobe poses a hurdle for procedure due to the inability to place an implant to the median lobe safely. This exclusion criteria prevents a large portion of men with BPH from undergoing this procedure. The BPH6 was a randomized controlled trial that prospectively compared the PUL with TURP. This study reported that PUL improves IPSS to 52% compared to 72% following TURP. Maximal urinary flow rates improved to a modest degree (41% compared to 144% following TURP). Interestingly the preservation of native prostatic tissue results in preserved erectile and ejaculatory function (249). Pooled analysis of available studies confirm these modest improvements in urinary and sexual function (250,251). Further, this procedure is well-tolerated and is performed in the outpatient setting under local anesthetic in a vast majority of cases. Morbidity is representative of typical MIST procedures with small proportions of patients reporting dysuria, urinary tract infection, and hematuria. Durability is among the main concern surrounding this procedure. Only three-year data has been published at present, reporting a modest IPSS improvement (252). Further comparative robust studies are required to determine the role of the PUL in current practice.

Intra-Prostatic Stents

In keeping with the principles of minimal invasion, a stent or coil is placed into the urethra at the point of maximal obstruction under local anesthesia, endoscopic and radiographic guidance. Stents may be temporary/biodegradable or permanent. Although effective in the short term, they do have a significant complication rate raising concerns over safety and large randomized controlled trials are needed to

establish their long-term efficacy and their true role in the management of BPH (204,253,254).

Transurethral Ethanol Ablation of the Prostate (TEAP)

Deep intra-prostatic injection of pure ethanol results in chemical ablation of the prostate. Of the limited studies available, 4 year follow up suggests sustained response in 73% of patient, with 23% requiring retreatment. More robust comparative data is required prior to more formal recommendations for the use of TEAP.

Fexapotide Trifluate – NX-1207

NX-1207 is injected into the transition zone of the prostate to ablate the tissue, but the precise mechanism by which NX-1207 acts has not been published to date. Trials of NX-1207 have shown a mean improvement of 5.7 points on IPSS score for men receiving one injection compared to placebo at mean 43 months follow up. When compared to men taking oral BPH medications, fewer in the NX-1207 group (8% vs 27%) required additional BPH intervention at 3 years (255). Long-term follow up of men receiving this chemical show durable reductions in symptom scores to 6.5-year follow-up (256). NX-1207 is well tolerated, with low rates of mild hematuria, dysuria and infection. No sexual dysfunction or incontinence has been reported for either agent.

Topsalysin - PRX-302

PRX-302 is a genetically modified bacterial pro-toxin that is activated by PSA within the prostatic tissue and forms transmembrane cellular pores that lead to apoptosis. Like TEAP and NX-1207, PRX-302 is injected into the transition zone of the prostate. PRX-302 results in a transient reduction in symptoms score that do not appear to be maintained at 12-month

follow-up (257). Similar to NX-1207, it is well tolerated, with low rates of mild hematuria, dysuria and infection. No sexual dysfunction or incontinence has been reported.

Botulinum Toxin subtype A (botox)

Botox is a toxin produced by the bacterium *Clostridium Botulinum*. Its mechanism of action for intraprostatic injections is poorly understood however theories include glandular necrosis and the blockage of alpha-adrenergic receptors resulting in smooth muscle relaxation (258). Phase 2 single arm studies have shown that intraprostatic botox has minimal side effects but has a re-treatment rate as high as 29% (185).

OTHER THERAPIES

Aquablation

Aquablation involves a transrectal ultrasound guided, robot-assisted, high velocity saline stream. This results in the ability to ablate glandular tissue without the requirement of heat. Real-time monitoring is available and allows the surgeon to ensure sparing of the prostatic capsule. Early studies have demonstrated its safety and feasibility. The WATER trial showed that aquablation was not inferior to TURP for improving IPSS scores at 6 months follow up with slightly improved rates of anejaculation (259). Longer follow up data from this study is needed to prove long term efficacy and assess long term complication rates.

Prostatic Artery Embolization (PAE)

PAE is performed by a trained interventional radiologist. Unilateral or bilateral prostatic arteries are injected with an embolic agent - which is typically ethanol-based. With increasing experience, technical success has increased to greater than 90%. A

metanalysis of 13 studies including 1,254 men found that PAE demonstrated a mean 16.2 increase in IPSS score and improved quality of life that remained statistically significant after 3 years follow up. Transient dysuria and urinary frequency were reported in 10% and 16% of men, respectively. Post embolization syndrome was reported in 3.6% of men and only three cases of major post-operative complications were recorded (260).

More recently, two-year follow up data from a randomized controlled trial of PAE vs TURP was published. Reduction in IPSS score was similar in both arms however TURP men showed better urinary flow, post void residual volume, reduced prostate volume but more erectile dysfunction. 21% of men who had PAE required subsequent TURP within the 2-year period. PAE adverse events were less frequent than TURP but distribution within the severity classes were similar (261).

Water Vapor Therapy - Rezum

Rezum uses radiofrequency to create thermal energy in the form of water vapor. This vapor is delivered transurethrally under cystoscopy to the prostate and causes instant cell necrosis through cell membrane disruption. It is frequently performed under local anesthetic in the outpatient setting. Two retrospective studies showed improvement in IPSS, urinary flow and post void residual volume at 6 and 12 months follow up (262,263). A randomized trial of Rezum vs sham procedure showed a mean improvement of 7 points on IPSS score and an improvement in quality of life in the Rezum group. Peak urinary flow rate was improved by 6.2ml/s in the rezum group and was sustained at 12 months (264). Morbidity is minimal and is in-line with those experienced following alternate MISTs (265).

Histotripsy

Histotripsy is the use of extracorporeal ultrasound energy that produces extreme pressure changes within the prostatic tissue. This pressure changes result in localized clusters of microbubbles which cause mechanical fractionation. Collapse of these microbubbles leads to cellular destruction and prostatic cavitation (266). The method of prostate injury allows the procedure to be monitored through ultrasound in a real-time setting. One safety and feasibility trial has been published to date reporting three cases of transient urinary retention, 1 case of minor anal abrasion, and one case of microscopic hematuria out of 25 men. No serious intraoperative complications occurred (267).

SUMMARY OF MINIMALLY INVASIVE THERAPIES

A myriad of minimally invasive therapies (MIST) has been developed to reduce the morbidity of surgical BPH management. Current evidence in MIST is characterized by improvements in symptom and urinary flow rates similar or slightly less than TURP with high rates of retreatment. Despite this, these procedures are very well tolerated and may be performed as an outpatient. Further, these therapies are highlighted by the significant reduced risk of sexual dysfunction. Some consider that MIST might be suitable in younger patients that are willing to accept less urinary improvement to preserve sexual function. Elderly or co-morbid men might also benefit given many of these procedures can be performed under local anesthetic or in the outpatient setting. However, the precise role for MIST has not become clear to date. It is clear that MISTs are emerging and will likely become a prevalent treatment option in the management of BPH.

MEASURING OUTCOMES AND EFFECTIVENESS OF TREATMENT

When considering the effectiveness of any treatment for BPH, one must consider the efficacy and tolerability of invasive or medical therapies (i.e., the effect on both subjective symptoms and urinary flow and incidence of adverse effects), the long-term effectiveness, the impact on daily life activities (quality of life) and the costs (268). Large scale randomized controlled trials provide information on the tolerability and efficacy of treatment options and evidence-based databases such as Cochrane reviews, may further analyze evidence-based data from multiple trials.

CONCLUSION

In conclusion, BPH is a common urological condition that is increasing in incidence in conjunction with the aging male population. If left untreated, BPH can lead to lower urinary tract obstructive symptoms that can significantly affect the quality of life of men.

As outlined in this chapter, the diagnosis of BPH begins with a detailed history of presenting complaint and interrogation of any lower urinary tract signs or symptoms. Questionnaires such as the IPSS score

can help quantify the severity of these symptoms along with a uroflowmetry and PVR scan. A urinalysis, serum creatinine, and serum PSA should be ordered to investigate for prostate cancer, UTI, and renal failure. Imaging with USS or CT is not indicated unless there is concurrent hematuria, UTI, or urolithiasis.

Several options are now available for the treatment of BPH. Non-surgical management consists of medications such as alpha-blockers, 5-alpha reductase inhibitors, and PDE5 inhibitors which are available as monotherapy or in combination. BPH refractory to medical management is treated with surgical management which includes invasive and minimally invasive procedures. TURP remains the most widely used procedure for surgical BPH management and simple prostatectomies are reserved for larger prostates, complicated BPH or if TURP cannot be performed. These two procedures form the gold standard of treatment. Laser treatments when available offer good patient outcomes and have potential benefits when compared to TURP. The decision for either of these modalities of treatment is still largely dependent on availability and surgeon experience. The majority of minimally invasive treatment options are still experimental however may have a potential benefit for carefully selected men.

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