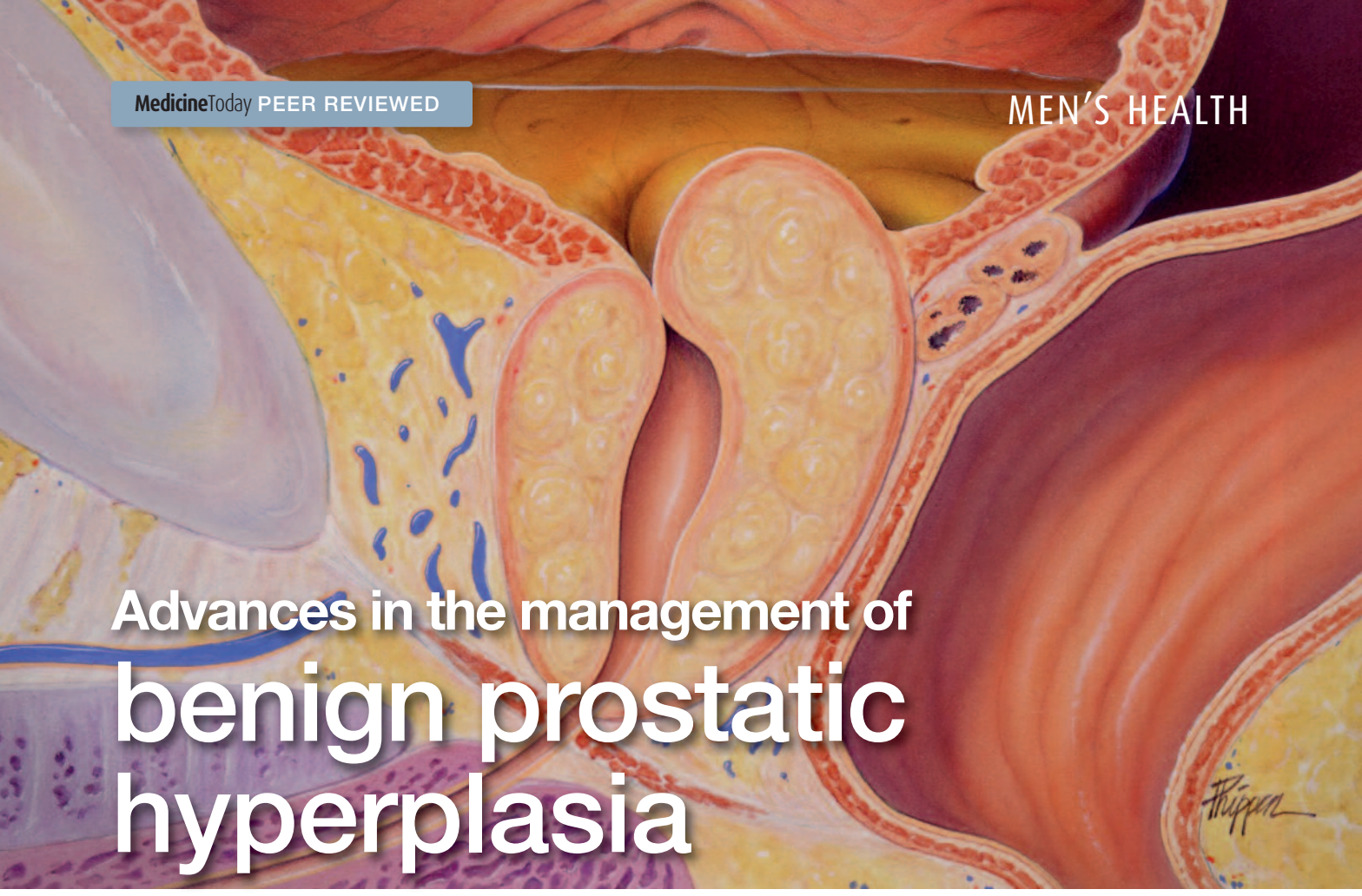

Advances in the management of benign prostatic hyperplasia

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In the modern approach to management of benign prostatic hyperplasia, GPs have a role to play in observation (watchful waiting), and in providing lifestyle advice and initiating medical therapy. The choice of therapy should be a shared decision between doctor and patient, and will depend on patient preference, degree of bother, and the severity and type of symptoms.

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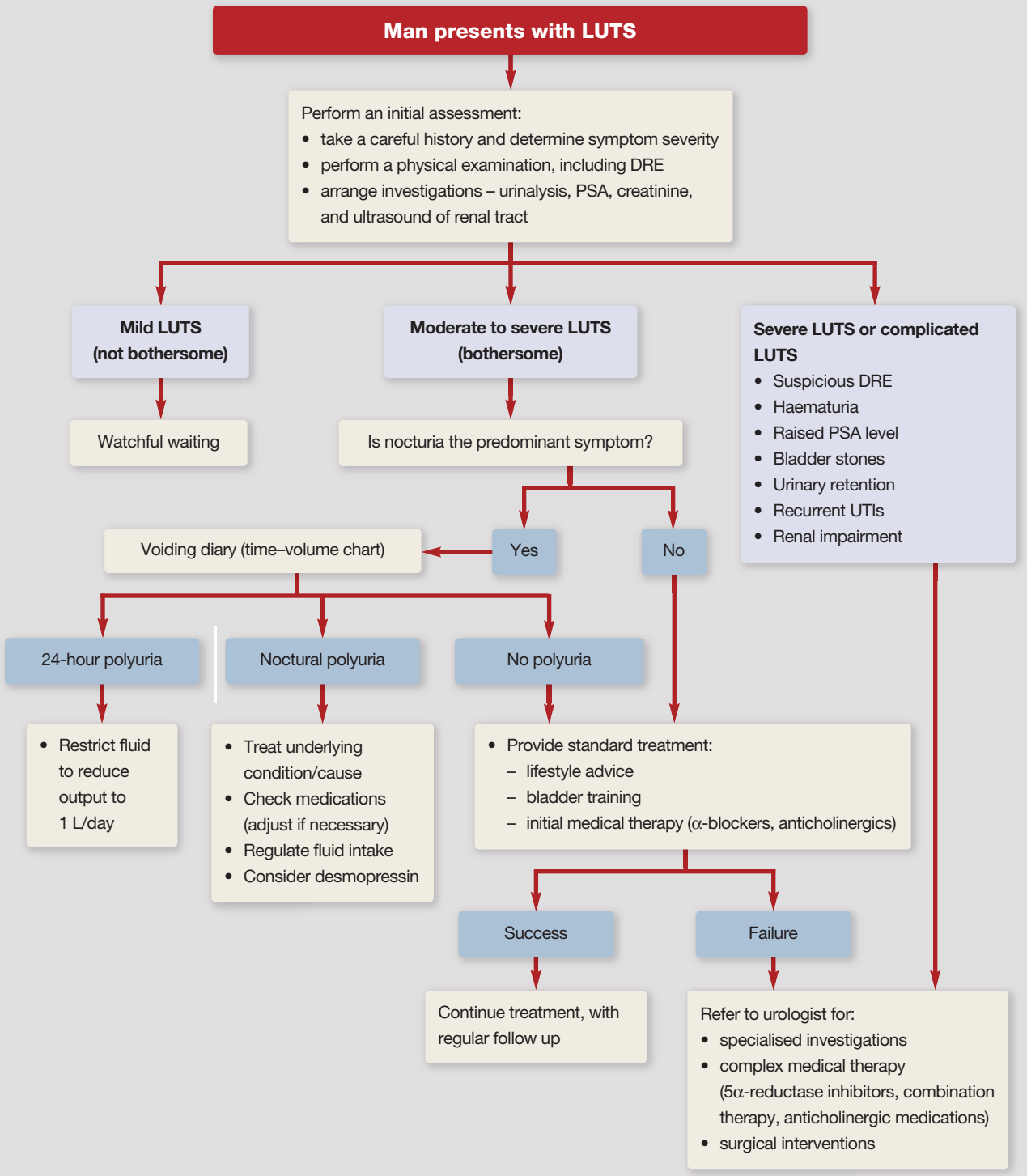
Over the past 10 years, the management of benign prostatic hyperplasia (BPH) has changed dramatically. Medical therapy is increasingly being utilised as more selective medications have become available and understanding of the natural history of the condition has improved. This is enabling us to risk-stratify patients and delay or avoid surgery all together. The benefits of combination medical therapy in reducing the long-term risk of urinary retention and the need for surgery have been demonstrated,[1,2] and the American Urological Association (AUA) has released new guidelines on the management of BPH supporting its use.[3] Furthermore, new surgical therapies have emerged in recent years, with laser treatment becoming widely available and showing results that are comparable to traditional transurethral resection of the prostate (TURP).

An approach to the assessment and management of lower urinary tract symptoms (LUTS) in general practice is presented in the flowchart on page 96.[4]

EPIDEMIOLOGY AND NATURAL HISTORY

BPH is characterised by cellular proliferation and impaired programmed cell death (apoptosis), resulting in prostate gland enlargement and bladder outlet obstruction that can give rise to LUTS. BPH is common among ageing men and its incidence increases with age. It has been estimated that 50% of all men over 40 years are affected by BPH; between 30% and 50% of these have bothersome LUTS.[5,6]

LUTS IN MEN: AN APPROACH TO ASSESSMENT AND MANAGEMENT*



ABBREVIATIONS: LUTS = lower urinary tract symptoms; DRE = digital rectal examination; PSA = prostate specific antigen; UTI = urinary tract infection.

* ADAPTED FROM REFERENCE 4: Roehrborn CG. Currently available treatment guidelines for men with lower urinary symptoms. *BJU Int* 2008; 102(Suppl 2): 18-23.

BPH: FACTORS PREDICTING SYMPTOM PROGRESSION

- Age >70 years
- Serum PSA level >2.0 ng/mL
- Prostate size >40 cm^3
- Severe urinary symptoms or bother
- International Prostate Symptom Score (I-PSS) >19
- Failure to respond to medical therapy
- History of acute urinary retention

CHOOSING THERAPY IN PATIENTS WITH LUTS: KEY POINTS

- Generally, therapy is tailored to the severity and type of urinary symptoms, and will depend on the degree of bother and presence of complications related to BPH. This should be a shared decision involving the patient and GP, and also the specialist if surgical therapy is being considered.
- Medical therapy is most suitable for patients who are experiencing mild to moderate symptoms and have at least some degree of bother.
- Treatment with 5α-reductase inhibitors, with or without α-blockade, seems to be better for men with large prostates, whereas treatment with an α-blocker alone seems to be better for men with smaller prostates.
- Combination medical therapy with an α-blocker plus anticholinergic may be the best therapeutic choice from the start in men with significant storage symptoms and a small prostate.
- Transurethral resection of the prostate (TURP), while still considered the gold standard treatment for BPH, is now being challenged by less invasive modalities such as laser enucleation or vaporisation of the prostate, which give very similar results with quicker recovery and possibly fewer side effects.

There are two broad categories of male LUTS:

- voiding (obstructive) symptoms – urinary hesitancy, weak stream, intermittency, straining to void, incomplete emptying
- storage (irritative) symptoms – urinary urgency, urge incontinence, frequency, nocturia.

Approximately two-thirds of men presenting with LUTS have a mixture of voiding and storage symptoms. Storage symptoms are usually due to poor compliance and bladder overactivity secondary to obstruction or to other, unrelated causes, such as infection, bladder stones, overactive bladder, malignancies (bladder, prostate) or neurological diseases (e.g. stroke, Parkinson's disease, multiple sclerosis).

No strong correlation has been demonstrated between prostate size, symptoms and urinary flow rates. However, it has been shown that men with larger prostate glands are more likely to experience further volume increases in prostate size, leading to an increase in severity of symptoms, a decrease in maximum flow rates and, ultimately, progression to acute urinary retention and subsequent prostate surgery.[7]

ASSESSMENT

A full history is mandatory for men presenting with LUTS. The nature and extent of urinary symptoms should be documented, as well as past genitourinary history. It is important to assess the severity and impact of symptoms because the degree of bother will largely influence the need for therapy. The International Prostate Symptom Score (I-PSS) is a useful means of quantifying these symptoms and their effects on the patient's quality of life.[8] Generally, a prostate symptom score of less than 8 is regarded as mild, 8 to 19 as moderate and 20 to 35 as severe. Factors that are predictive of symptom progression are listed in the box on this page.

A focused physical examination should be performed to rule out urinary retention and a digital rectal examination is necessary to assess prostate size and risk of cancer. A neurological examination of the perineum and lower limbs should also be conducted.

The PSA test is recommended in the assessment of men presenting with LUTS. The PSA level has been shown to correlate well with prostate size in men who do not have prostate cancer and therefore predicts the likelihood of symptom progression and the risk of urinary retention.[9] A serum PSA level of 1.5 ng/mL roughly equates to a prostate volume of 30 cm^3.[10] Furthermore, a PSA level greater than 1.5 ng/mL and a prostate volume greater than 30 cm^3 has been strongly associated with progression of urinary symptoms to retention and the need for prostate surgery. This information is beneficial in assisting treatment selection.

A urinalysis, looking for haematuria, proteinuria and pyuria, should be performed for men presenting with LUTS. The serum creatinine level should also be measured to exclude renal impairment. The other useful study (optional) is ultrasound of the renal tract to document the post-void residual volume and rule out chronic retention.

A voiding diary is particularly useful when nocturia is the predominant symptom and is helpful in identifying patients with nocturnal polyuria or excessive fluid intake, which are common in ageing men. The time and volume of every void as well as fluid intake should be documented over a period of 48 hours.

MANAGEMENT

After the initial assessment, the doctor should discuss treatment options, including the option of no treatment ('watchful

WATCHFUL WAITING

- Lifestyle changes:
  - fluid restriction
  - diet
  - avoidance of alcohol and caffeine
  - bowel management
- Bladder training
- Medication review
- Monitoring of urinary symptoms (6- to 12-monthly)
- PSA testing and ultrasound (yearly)
- Phytotherapy (not recommended but may be considered)

waiting'), with the patient, and explain the benefits and risks of each. The choice of therapy is a shared decision between the doctor and patient, and will depend on patient preference, degree of bother, and the severity and type of symptoms. Key points are summarised in the box on page 97.

Watchful waiting

Watchful waiting involves the monitoring of symptoms with periodic review (see the box on this page). If watchful waiting is selected, patients should be offered lifestyle advice to minimise the chance of urinary retention. This includes refraining from excess alcohol and caffeine, and also restricting fluid intake to regulate urine output. Certain medications (such as pseudoephedrine, antidepressants, antipsychotics and antihistamines), a cold environment or constipation can worsen symptoms and should be avoided.

Bladder training, a program of urinating on schedule, may be useful in men with predominantly storage symptoms. The program involves gradually increasing the amount of urine the bladder can comfortably hold (functional bladder capacity).

Expectant management for men with mild symptoms that cause little or no bother is safe because the risk of clinical progression is low. Patients should be reviewed at least annually with a PSA test and an ultrasound to check for progression. They should be warned of the small risk of urinary retention (long-term) and advised to return if their symptoms deteriorate.

Nocturia can significantly impact on a patient's quality of life. If nocturia is the predominant symptom then it is important to work out if it is due to 24-hour polyuria or nocturnal polyuria. The definition of 24-hour polyuria is urine output of more than 3 L over 24 hours and it is managed by fluid restriction to decrease output to 1 L per day. Nocturnal polyuria is diagnosed when more than one-third of the 24-hour output occurs at night. It is important to treat any underlying cause (e.g. sleep apnoea, diabetes mellitus, diabetes insipidus, renal failure, congestive cardiac failure), to avoid certain medications (e.g. diuretics) and to restrict evening fluid intake. In selected cases, it may be worth considering desmopressin use to reduce the urine output overnight.

Phytotherapy

Despite the widespread use of phytotherapy for BPH, there is no good evidence that it is any better than placebo. Even saw palmetto extract, the most commonly used phytotherapeutic agent, has failed to show a benefit in symptom score.[11] Improvement in nocturia has been shown in selected patients, but without any objective evidence of an improved flow. Use of phytotherapy is not recommended in the current International Consultation for Urological Diseases (ICUD) or AUA guidelines.[3,12]

MEDICAL THERAPY

For patients with bothersome moderate to severe urinary symptoms, between 5% and 17% will progress to surgery within four years (if untreated) and medical therapy is generally recommended.[1] The two major classes of drugs used to treat BPH are the α-adrenergic receptor antagonists ('α-blockers') and 5α-reductase inhibitors.

The α-blockers

The α-blockers act by relaxing the smooth muscle fibres of the bladder neck and prostate, thereby reducing the dynamic component of prostatic obstruction. These drugs have good long-term efficacy in terms of symptom improvement but they allow for ongoing prostatic growth and do not reduce the risk of progression to retention and the need for surgery. Symptom relief usually occurs within two weeks of initiating treatment.

The α-blockers currently available in Australia are alfuzosin, prazosin, tamsulosin and terazosin. The more selective drugs (alfuzosin and tamsulosin) allow single daily dosing and have a lower incidence of orthostatic hypotension but ejaculatory dysfunction is more common. The less selective drugs (prazosin and terazosin) have a higher incidence of hypotension, asthenia and dizziness; these agents require titration to the maximum tolerated dose. Floppy iris syndrome may occur with all the α-blockers; a patient must discontinue use before undergoing cataract surgery and resume treatment thereafter.

Cost, convenience, administration (single dose v. dose titration) and the likelihood of cardiovascular adverse events in the elderly population may be deciding factors when choosing one α-blocker over another.

The 5α-reductase inhibitors

The 5α-reductase inhibitors act by shrinking the prostate to relieve the static component of bladder outlet obstruction. They work through hormonal control by decreasing levels of prostatic intracellular dihydrotestosterone (the major growth-stimulatory hormone in BPH). This leads to a 20% to 30% reduction in prostate volume and an improvement in symptoms and urinary flow over a period of three to six months. The two drugs available in this class, dutasteride and finasteride, have similar efficacies.

Long-term use of 5α-reductase inhibitors has been shown to be safe and

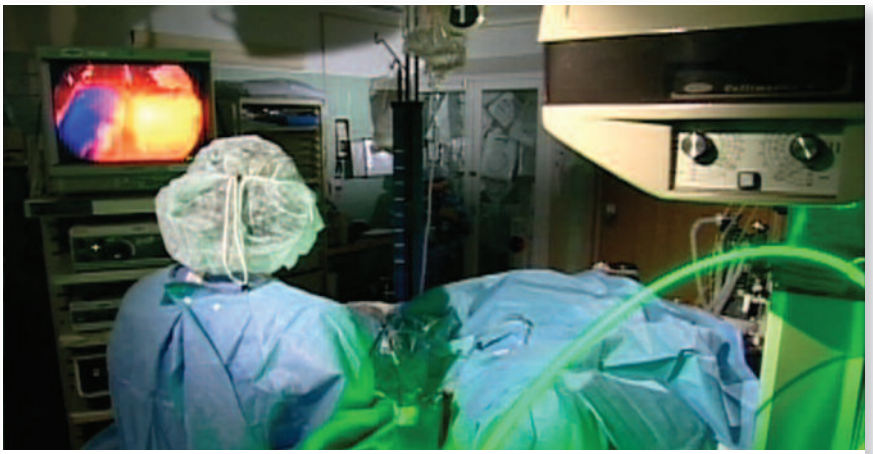


Figure. GreenLight laser surgery for BPH.

decreases the risk of symptom progression, urinary retention and surgery when taken as monotherapy or in combination with an α-blocker. However, they are only effective if the prostate gland is significantly enlarged (>40 cm^3) and should not be used in men without prostatic enlargement. The PSA level is typically halved when a 5α-reductase inhibitor is taken consistently over 12 months – if this is not observed then prostate cancer should be suspected. Consequently, it is important to perform a full urological evaluation, including a risk assessment for prostate cancer (PSA test and digital rectal examination), prior to initiating a 5α-reductase inhibitor.

Treatment with 5α-reductase inhibitors is associated with sexual adverse events (e.g. erectile dysfunction, decreased libido and decreased ejaculate volume).

Combination medical therapy

The effectiveness of combined medical therapy (an α-blocker and a 5α-reductase inhibitor) has been demonstrated. The Medical Therapy of Prostatic Symptoms (MTOPS) study compared the efficacy of doxazosin (an α-blocker), finasteride and a combination of both drugs against placebo.[1] Combination therapy was shown to be more effective than either mono - therapy in preventing disease progression, thus altering the natural history of BPH, significantly reducing the incidence of symptom progression and risk of acute urinary retention or need for surgical intervention. The greatest benefit was demonstrated in men with larger prostates (>40 cm^3), severe symptoms or higher PSA levels (>4.0 ng/mL), which correlated well with prostate size.

Medical therapy can prevent the clinical progression of BPH, and the combination of an α-blocker and a 5α-reductase inhibitor is more effective than either alone, particularly in high-risk groups (men with large prostates, higher PSA levels and severe symptoms). Combination therapy is generally well tolerated, despite an increased overall rate of adverse events compared with the monotherapies. The side effect profile is similar to those of the monotherapies combined.

A combined preparation of dutasteride (500 μg) and tamsulosin (400 μg) is available and was recently listed on the PBS.

Anticholinergics

Anticholinergic medications, including oxybutynin, solifenacin and tolterodine, may be useful for storage urinary symptoms that are secondary to bladder outlet obstruction. They can be used safely in conjunction with an α-blocker.

Common side effects of anticholinergic medications include dry mouth and constipation and urinary retention, which are due to their antimuscarinic properties. Before starting an anticholinergeric, a baseline bladder residual volume should be documented and the treatment avoided if the volume is greater than 200 mL.

SURGERY

Surgery is generally indicated for patients in whom medical therapy has failed and for patients who have severe LUTS or complications related to BPH. These include:

- urinary retention
- recurrent prostate bleeding (persistent gross haematuria)
- recurrent UTIs
- renal impairment due to bladder outlet obstruction resulting in dilatation of the upper urinary tract (bilateral hydronephrosis)
- bladder stones.

TURP

TURP is still considered the gold standard treatment if surgery is required. About 80% to 90% of patients undergoing this treatment experience significant and sustained improvement of their voiding symptoms.

The main side effect of the treatment is permanent retrograde ejaculation, which occurs in at least 70% of patients. The incidence of *de novo* erectile dysfunction is low (2% to 4%) and urinary incontinence is rare. Other complications include a small risk of urethral stricture. The likelihood that further TURP will be required in 10 years is 5% to 10%. There is a four-week period of convalescence after the operation.

Laser enucleation or vaporisation of the prostate

Various laser techniques have been developed as an alternative to TURP for the treatment of BPH.

GreenLight laser therapy (Figure) has been in use for over five years and vaporises a cavity through the prostate, similar to TURP. It is particularly haemostatic and is suitable for patients who are taking

PHOTO COURTESY AMS AUSTRALIA.

anticoagulation therapy. Initial dysuria is common but usually disappears after six to 12 weeks. Five-year results are similar to those after TURP. The length of hospital stay is usually less than 24 hours.

The Holmium:YAG laser is used to enucleate the prostate and the tissue is subsequently removed in pieces. This method has also been shown to give comparable results to TURP. Patients are usually kept in hospital a little longer for Holmium:YAG laser treatment than for GreenLight laser surgery. The Holmium:YAG laser has a longer track record, but it widely resects prostatic tissue so there is a higher incidence of retrograde ejaculation.

The Evolve laser is a new technique that uses dual wavelength technology and promises more rapid ablation and improved haemostasis. It uses a contact technique, thus reducing the risk of inadvertent bladder or ureteric injuries. Data are limited, but early results suggest similar efficacies to GreenLight laser therapy, with excellent haemostasis and improved safety.[13,14] The Evolve laser is new in Australia and has TGA approval for treating patients with BPH. It has been used for some time in Europe and Asia.

Transurethral incision of the prostate

In a patient who has a very small prostate, an incision through the prostate can be used instead of resection. This procedure has an excellent outcome and a lower chance of retrograde ejaculation (10% to 20%) than TURP.

Minimally invasive therapies

Other forms of treatment for patients with BPH include transurethral needle ablation of the prostate and transurethral microwave therapy. These are used selectively in specialised situations.

REFERRAL

Urological referral is indicated for patients in whom initial therapy has failed and for patients with complications related to BPH, including urinary retention, recurrent infections, high bladder residual volumes (>200 mL), bladder stones or renal impairment. Other reasons for referral include suspected prostate cancer, predominantly storage symptoms, severe bother, pain and haematuria.

Specialised investigations may include cystoscopy, prostatic biopsy, flow rate study, urodynamic assessment and CT scanning.

FUTURE DEVELOPMENTS

Possible future treatment of LUTS associated with BPH may involve injection of botulinum toxin type A into the prostate, which may alleviate urinary symptoms. This, however, is still quite expensive and under investigation. Results from studies of tadalafil on urinary symptoms are showing interesting but mixed results.

SUMMARY

Over the past 10 years, the management of men with BPH has changed dramatically. Medical therapy (including combination therapy) is increasingly being utilised, and new surgical therapies, such as laser treatment, have become widely available. In the modern approach to management of BPH, GPs have a role to play in observation (watchful waiting), and in providing lifestyle advice and initiating medical therapy. MT

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