Management of Benign Prostatic Hypertrophy-Related Urinary Retention
Current Trends and Perspectives
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The failure of prostate-directed treatment modalities to help all men or all symptoms has questioned the longstanding assumption that the prostate is at the root of all male urinary symptoms, and a correlation between urinary bladder function and prostate pathology has been recognized. Now, it is widely recognized that bladder dysfunction plays a role in some, if not most, of the benign prostatic hyperplasia-related symptoms and signs, and recent studies have suggested that pharmacotherapies that target the bladder, such as antimuscarinics, may improve storage urinary symptoms. Indeed, the current mainstays of overactive bladder syndrome pharmacotherapy are antimuscarinic agents with mixed actions, including musculotropic (calcium antagonistic) activity. Moreover, the combination therapy with alpha blocker and antimuscarinic agents is now suggested when bladder outlet obstruction related to benign prostatic hyperplasia coexists with overactive bladder symptoms. Combinational treatment, targeting to both decrease resistance to urine outflow through the prostatic urethra and increase bladder smooth muscle, may improve the bladder outlet surgery success rate, and perhaps it might reinforce the need to offer an additional trial without catheter in patients with benign prostatic hyperplasia who are likely to suffer from detrusor hypocontractivity. Currently, no clinical trial supporting the use of parasympathomimetic drugs in those with poor voiding and longstanding symptomatic benign prostatic hyperplasia exists in the literature; however, experimental studies present promising results.

INTRODUCTION
Urinary retention (UR), which can be acute or chronic, may have numerous causes that can be classified as obstructive, infectious and inflammatory, pharmacologic, neurological, etc. Urinary retention is most common among men, in whom prostate infarction, benign and malignant prostatic enlargement, or urethral strictures cause outlet obstruction. The main causes of UR in women are hypotonic bladder, dysfunctional voiding, and vaginal prolapse. In either sex, retention may be due to drugs (particularly those with anticholinergic effects, including many over-the-counter drugs), severe fecal impaction (which increases pressure on the bladder trigone), neurogenic bladder, and prior pelvic surgery resulting in bladder denervation. Excessive fluid intake, alcohol consumption, medication, sexual activity,
Urinary retention presents a major challenge in the care of older adults. The two main causes of UR in elderly include impaired bladder contractility and benign prostatic hyperplasia (BPH)-related bladder outlet obstruction.

**BENIGN PROSTATIC HYPERPLASIA**

**Epidemiology of Urinary Retention**
Both types of acute and chronic UR are among the most common and significant complications of long-term BPH. In fact, the rates of UR and its recurrence increase with increased prostate volume and baseline symptom severity retention. As shown in the Proscar Long-Term Efficacy and Safety Study, the highest rates of UR were recorded in men with a clinical diagnosis of BPH and a symptom score of 8 or greater. Interestingly, the rate of acute UR was 8-fold higher in those with a serum prostate-specific antigen (PSA) level higher than 1.4 ng/mL and threefold higher in those with a prostate volume higher than 40 mL. Age also is an important risk factor; in community-dwelling men, the incidence of UR increases from 0.4 per 1000 person-years for those 45 to 49 years old to 7.9 per 1000 person-years for those 70 to 83 years old. In men diagnosed with BPH, the UR risk increases with ageing dramatically. It is estimated that more than 1 in 10 men in their 70s will experience UR within the next 5 years. The risk increases to 1 in 3 for men in their 80s. In the absence of any other known etiologic factors, it is assumed that the higher rates of UR in older men are due to poor detrusor function.

**Pathophysiology and Diagnosis of Urinary Retention**
Acute UR is a sudden inability to empty the bladder, while chronic UR is an inability to empty the bladder completely during voiding that develops over time. The definitions of acute and chronic UR remain, however, empirical and subject to wide interpretation. Standardized criteria have not been established and many questions regarding both pathophysiology and accurate treatment remain unanswered. Age, previous retention episodes, lower urinary tract symptoms, chronic inflammation, serum PSA level, prostate size, and urodynamic variables appear to be the most important predisposing factors for the development of acute UR. Pathophysiology of acute UR remains poorly understood; however, UR is a consisting part of lower urinary tract symptoms, and similarly to other lower urinary tract symptoms (both irritative and obstructive), it may be caused by both static elements, such as bladder outlet obstruction, which often occurs as a consequence of prostatic enlargement, and by dynamic elements, such as a decrease in bladder smooth muscle tone or a spontaneous cessation of detrusor contraction.

Since acute UR is associated with severe discomfort, causing abdominal distension and severe pain, diagnosis in patients who cannot void, is obvious. On the contrary, chronic UR occurs silently and often remains undiagnosed until it progresses to complete UR, urosepsis, kidney failure, or overflow incontinence. Normally, a high postvoid residual urine volume measured on 2 separate occasions is posing the diagnosis of chronic UR. Urinary retention is determined by measuring the postvoid residual urine volume immediately after the completion of micturition, and a postvoid residual volume of greater than 100 mL is generally accepted as the criterion to define incomplete bladder emptying. Although residual urine volume can be measured with sufficient accuracy both invasively (by catheterization) and noninvasively (by transabdominal ultrasonography), the definition of significant postvoid residual urine itself is unclear. Firstly, the threshold volume defining a poorer outcome is uncertain. Moreover, residual urine volume measurement has significant intra-individual variability that limits its clinical usefulness, while it does not correlate well with other signs or symptoms of prostatism. In fact, while chronic UR shares the same symptoms with symptomatic BPH—such as a sense that the bladder does not empty...
completely, difficulty initiating urination, a weak or interrupted urinary stream, having to urinate multiple times to empty the bladder, dribbling of urine after completion of urination, urinary urgency or frequency, leakage of urine, and recurrent UTIs—the above symptoms exist also in the absence of high postvoid residual urine volumes. Despite the biologic range of postvoid residual variation, pathogenesis of chronic UR seems to imply both bladder obstruction and impaired detrusor contractility. Epidemiologic studies show that bladder outlet obstruction is common among elderly men, while the incidence of urinary retention dramatically increases with age as well. Pathophysiologically, the presence of bladder outlet obstruction is initially compensated for by detrusor hypertrophy. Over the course of time, pathological deposition and replacement of detrusor fibbers with collagen occur. In addition to impairing detrusor contractility and reducing bladder compliance, this process may also be implicated with denervation hypersensitivity of the bladder’s neuromusculature, a process which is yet to be accurately defined. Apart from the morphological changes of the bladder, chronic urinary tract obstruction can lead to permanent damage to the urinary tract. Progressive back pressure on the ureters and kidneys can occur and can cause hydrourereter and hydronephrosis. The ureter can then become dilated and tortuous, with the inability to adequately propel urine forward. Hydronephrosis can cause permanent nephron damage and kidney failure, while urine stasis along any portion of the urinary tract increases the risk of calculus formation, infection, and upper urinary tract injury. Initial management of UR includes bladder catheterization for prompt and complete decompression. If more than 700 mL of urine is emptied from the bladder, the indwelling urinary catheter is clamped for 30 to 60 minutes, and the bladder is emptied gradually to prevent compressed blood vessels dilatation and the impending persistent macroscopic hematuria.

Although the most usual cause of UR is bladder outlet obstruction, a vast range of conditions can also cause either acute or chronic UR; therefore, many investigations may be used to define the severity of urinary flow disruption and to establish the underlying cause. Testing that may be useful in the initial evaluation of UR, which includes clinical examination, laboratory tests, and imaging studies. Clinical examination includes a check for enlarged bladder, which in case of chronic UR will usually be nontender; a check for enlargement of the kidneys via bimanual palpation; and a digital rectal examination which should be carried out to look for evidence of prostatomegaly and signs of prostatic carcinoma. Extended bladder enlargement accompanied by lower abdominal discomfort/restlessness may indicate intermittent acute-on-chronic-retention. Urinalysis may reveal microscopic hematuria, proteinuria, glucosuria and infection. If the latter is suspected, then urine microscopy and culture should be carried out. Serum urea nitrogen, creatinine, and electrolytes can help assess kidney failure caused by lower urinary tract obstruction, while blood glucose should be checked in order to diagnose undetected or uncontrolled diabetes mellitus. There is controversy over PSA’s usefulness in the initial investigation of UR. On the one hand, it should be considered where there is a clinical suspicion of prostate cancer after digital rectal examination; however, on the other hand, for patients with UR suspicious of urinary tract infection, it is acceptable to omit PSA testing. Ultrasonography may detect bladder calculi, hydronephrosis, and upper urinary tract disease. Further investigations are usually done based on clinical findings and include magnetic resonance imaging or computed tomography, intravenous urography, cystoscopy, retrograde cystourethrography, uroflowmetry, cystometry, electromyography, urethral pressure profile, video urodynamics, and pressure flow studies of micturition.

Computed tomography of the abdomen and pelvis can determine the presence of a pelvic, abdominal, or retroperitoneal mass or malignant growth causing extrinsic bladder neck compression. In cases suspected of neurogenic bladder, magnetic resonance imaging or computed tomography of the brain is useful to detect intracranial pathologic processes such as tumor, stroke, or multiple sclerosis. Spinal magnetic resonance imaging can help
assess lumbosacral disk herniation, cauda equina syndrome, spinal tumors, spinal cord compression, and spinal multiple sclerosis. When bladder tumor and bladder or urethral calculi or strictures are suspected, cystoscopy, retrograde cystourethrography, or both may be helpful. Formal urodynamic study of lower urinary tract function is invaluable when investigating symptomatic BPH with acute UR. In contrast, chronic UR and repeated episodes of acute urinary retention suggesting intermittent acute-on-chronic-retention should give cause for concern. Patients presenting the above should proceed to a full urodynamic investigation before embarking on treatment. Evaluation of bladder function should be also offered to young patients with UR or those with a history of neurological disease or injury.(16)

Management of Urinary Retention

Specific clinical recommendations for management of acute UR are as follows: “In men with BPH, starting α-blocker treatment at the time of catheter insertion improves the probability of success when attempting to void without the catheter (level of evidence, B),” “Before considering surgical treatment for urinary retention from BPH, these men should undergo at least 1 trial of voiding without the catheter (level of evidence, C),” and “Long-term treatment with 5α-reductase inhibitors may prevent acute urinary retention in men with BPH (level of evidence, B).”(17) In fact, current medical therapy for the treatment of BPH-related lower urinary tract symptoms appears to reduce the risk of UR, and consequently, the overall number of BPH surgeries.(18) According to the current literature, estimated UR incidence rates in men with diagnosed BPH are ranging between 5 and 25 per 1000 person-years, while older estimates of occurrence of UR ranged from 4 to 15 to as high as 130 per 1000 person-years.(19) Despite the decrease in UR incidence, an important number of patients with BPH still develop UR during the 4 years of active treatment. It seems plausible that patients with UR who did not receive any medication for the BPH treatment may have a higher chance of successful trial without catheter (TWOC) than those who receive an α-blocker treatment.(5) Therefore, it is not clear whether patients with UR receiving medical therapy for BPH should be offered a TWOC by modifying their treatment (eg, by increasing the dose of α-blocker or changing the drug in case of finasteride treatment). Notably, studies performed before the advent of α-blockers showed that simple bladder drainage improves the chances of a successful TWOC.(20) Moreover, current guidelines offer little help to office urologists in deciding the exact time for the TWOC after the catheter placement and how many failed further TWOCs are needed to decide upon final treatment. In the United Kingdom, nearly 71% of urologists start their patients on α-blockers immediately after emergency catheterization, with 64% using a TWOC 2 days after starting them. One failed TWOC is an indication for surgical intervention for 72.8%, while a second TWOC is advocated by only 11.7%.(21) The most possible explanation for the very low number of the reported additional TWOC attempts is probably the established opinion that the majority of patients both with and without previous symptoms suggestive of outflow obstruction will have further retentions.(22) In part, these concerns are justified since the risk of recurrence was cited as 76% to 83%.(5) These data, however, have recently been challenged by the results of several observational studies showing that a number of patients presenting with UR regain spontaneously their ability to void. In fact, only 32% of patients with successful TWOC, or even less, will require prostatectomy within 8 to 24 months of follow-up, reinforcing the need to offer more than one TWOC in patients with a first episode of UR.(23) Evidence shows that the risk of a further episode of acute UR is higher when recurrence is close in terms of time to the previous episode of UR, suggesting that attempts of catheter removal in men with BPH-related UR should be scheduled in a longer time interval than 2 days.(24) To our knowledge, the time needed to obtain a successful TWOC is not known. It differs from patient to patient and depends on the underlying pathology; however, it should be probably extended. Increasing the period of drainage of the bladder before a TWOC improves the chances of success (44%, 51%, and 62% success at days 0, 2, and 7,
respectively.\(^{(20)}\) In contrast, it is estimated that the risk of recurrence when TWOC is performed within 1 week of the first episode is as high as 64%\(^{(25)}\). Despite the number of patients with successful TWOC and the improved odds of such intervention, when treating the patients with α-blockers, a significant proportion of patients presenting with acute UR will ultimately require a definite treatment. Surgical intervention is generally considered to be the endpoint for acute UR. Treatment-wise, transurethral resection of the prostate remains the reference standard for BPH. The final outcomes of the prostatectomies of patients with BPH and acute UR were found to be similar to those of treatment of the symptoms alone.\(^{(26)}\)

A specific clinical recommendation for management of chronic UR does not exist; however, it should be directed at reducing the residual volume, eliminating hydronephrosis (if present), and preventing urosepsis. The first step is to use indwelling or intermittent catheterization to decompress the bladder for up to a month, while reversing potential contributors to impaired detrusor function (fecal impaction and medications).\(^{(27)}\) At the end of this time interval, an attempt to remove the catheter (TWOC) should be performed in order to evaluate if patients regained their ability to void.\(^{(14)}\) Unfortunately, men with BPH-induced chronic UR are more likely not to be able to return to normal voiding. Factors associated with an unsuccessful TWOC are age higher than 75 years, a residual drained urine volume of larger than 1 L, and a detrusor contraction less than 35 cm H\(_2\)O.\(^{(28)}\) Whether α-blockers improve the probability of success when attempting to void without the catheter and if α-blockers are successful in preventing a further episode of UR in patients with chronic UR is doubtful.\(^{(29)}\) In fact, despite the α-blocker treatment, success rate remains inversely proportional to postvoid residual volumes: 77% to 85% of α-blocker-treated patients with UR in whom TWOC fails have larger postvoid residual volumes.\(^{(30)}\) Data also indicates that chronic UR patients treated with α-blockers who had a successful TWOC are more likely to require surgery treatment within a shorter period of follow-up when compared to patients with smaller postvoid residual volumes.\(^{(31)}\) However, bladder outlet surgery success rate is also inversely proportional to the degree of chronic UR; studies of the outcome of surgery in patients with chronic retention demonstrated that high postvoid residual volumes, old age, absence of instability, a maximal detrusor pressure of less than 20 cm H\(_2\)O, poor sensation, large retention volumes, and absence of voluntary detrusor contractions are associated with a poor surgical outcome and failure to void.\(^{(26,32,33)}\) Even when patients with chronic UR regain their ability to void after transurethral resection of the prostate, they still have persistent symptoms with impaired flow rates suggestive of detrusor underactivity.\(^{(34)}\) If the detrusor is incontractile after decompression by either pharmacotherapy or surgery, patients should be started on intermittent catheterization or an indwelling urethral catheter. Unfortunately, despite the benefits and proven feasibility of intermittent catheterization, most elderly patients choose indwelling catheterization instead.\(^{(35)}\) Prolonged use of indwelling catheter, however, is accompanied by several side effects and complications; urethral and/or suprapubic pain and bleeding occur in 69% of patients,\(^{(25,36)}\) while pain, bleeding, and infections associated with the prolonged use of indwelling catheter have a significant negative effect on the quality of life in 85.5% of patients.\(^{(36)}\) In addition, the cost implication of having an indwelling bladder catheter is enormous.\(^{(35)}\) Therefore, medical treatment, targeting to decrease resistance to urine outflow through the prostatic urethra and increase bladder smooth muscle, may improve the bladder outlet surgery success rate, and perhaps it might reinforce the need to offer an additional TWOC in those with poor voiding and longstanding symptomatic BPH.

### Medical Treatment of Chronic Urinary Retention

From a clinical point of view, the prostatic component of UR can be targeted through androgen blockade (eg, a 5α-reductase inhibitor) or by decreasing resistance to urine outflow through the prostatic urethra using α-adrenergoreceptors inhibition or both. The α1- and α2-adrenergoreceptors are present in the human
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prostate, though there is preponderance of α1-adrenoreceptor subtypes, which are thought to be responsible for prostate contraction. Since no strong relationship has been observed between the size of the prostate and obstructive symptoms, the α1-blockers inducing decrease of sympathetic tone seems to be more effective in reducing bladder outlet resistance and preventing UR recurrence. Several small studies have shown that α1-blockers improve the rate of successful TWOC. On the basis of these results, α1-blockers are used routinely before catheter removal and are even considered an appropriate treatment option in the American Urological Association guidelines.

On the other hand, the bladder component of UR can be targeted through parasympathomimetic drugs. There are few studies examining the role of parasympathomimetic drugs in the treatment of BPH-related chronic UR and residual urine in the literature to date. Two parasympathomimetic drugs—the nonselective acetylcholinesterase inhibitor distigmine and the muscarinic agonist bethanechol—have been studied in clinical trials, while the selective acetylcholinesterase inhibitor TAK-802 has been studied in experimental basis. Bethanechol is a parasympathomimetic choline ester that selectively stimulates muscarinic receptors (with further selectivity for M3 receptors) without any effect on nicotinic receptors. Experimental studies showed that bethanechol decreased residual urine volume in a dose-dependent manner; however, its effectiveness has not been proved in controlled trials. Although there was evidence of a pharmacological effect, when bethanechol was combined with prostaglandin E2, the therapeutic effect was limited compared with placebo. Unfortunately, bethanechol decreases the storage function by increasing voiding frequency, a fact that further deteriorates its potential clinical usefulness.

Since inactivation of cholinesterase leads to a sustained action of acetylcholine on cholinergic nerve endings, which results in improved detrusor contractions, distigmine bromide, a peripherally acting cholinesterase inhibitor, has been suggested to be helpful to patients with underactive detrusor to regain their ability to void. Interestingly, Tanaka and colleagues demonstrated both symptomatic and urodynamic improvement by oral distigmine bromide in patients with BPH suffering from detrusor hypocontractivity after transurethral resection of the prostate. Moreover, experimental studies in rats with bladder outlet obstruction showed that distigmine bromide restored voiding function and decreased residual urine volume, despite the presence of obstruction. Finally, combinational treatment with α-blockers has been proved to enhance detrusor contractility and improve voiding function in selected patients with BPH and underactive detrusor.

Model-based studies showed that treatment with the novel selective acetylcholinesterase inhibitor TAK-802 reinforces the bladder and voiding functions by increasing the bladder contractility without decreasing the storage function and preventing the bladder mass increase. Since TAK-802 was found to exhibit higher selectivity for muscarinic actions over nicotinic actions in comparison with other acetylcholinesterase inhibitors with a minimum side effect, it might be a more useful drug than either carbamate acetylcholinesterase inhibitors or muscarinic receptor agonists. Therefore, clinical trials are needed in order to assess the efficacy of TAK-802 in the treatment of patients with BPH and impaired detrusor contractility. Its efficacy to aid patients in achieving spontaneous voiding after recurrent episodes of acute UR, reducing UR risk, and preventing the first episode of UR should also be tested.

CONCLUSION

Urinary retention is one of the most usual and significant complications of long-term BPH. The risk is cumulative and increases with age. Moreover, recurrent urinary retention in
elderly often indicates a poor detrusor function, which represents a risk factor of both surgical and conservative therapy failure. Currently, there are no clinical trials supporting the use of parasympathomimetic drugs in patients with poor voiding and longstanding symptomatic BPH; however, experimental studies present promising results.

CONFLICT OF INTEREST
None declared.

REFERENCES