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Management of Urgency and Mixed Urinary Incontinence

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Abstract: Urinary incontinence (UI) is a prevalent disorder that significantly affects quality of life. This article reviews management of urgency and mixed UI by breaking the management algorithm down into observation, lifestyle and behavioral changes, pharmacologic therapy, and procedural management. Stress UI is best managed with mid-urethral slings and is covered in other chapters. Behavioral and pharmacologic management are equally efficacious for urgency UI, but procedural therapy is superior. Mixed UI is conventionally treated by first managing whichever UI subtype is most bothersome. The management of overflow UI is directed at its underlying etiology: detrusor underactivity or bladder outlet obstruction.
Key words: urinary incontinence, management lifestyle, pharmacology, surgery

Introduction

DEFINITION AND EPIDEMIOLOGY

Urinary incontinence (UI) is a bothersome disorder that significantly impacts patient quality of life. It is defined by the International Continence Society (ICS) as the "complaint of involuntary loss of urine" (symptom) and the "observation of involuntary loss of urine on examination" (sign).[1] There is little recent information on prevalence of UI, but it is known is known to be a common disorder, with 50% of American females reporting UI.[2]

This review will discuss up to date management of urgency urinary incontinence (UUI), mixed urinary incontinence (MUI), and overflow UI. Management of stress urinary incontinence (SUI) will be presented elsewhere.

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Management of UI

The management of UUI consists of 4 basic strategies: observation, lifestyle and behavioral modifications, medical management, and procedural management. Observation applies to all types of incontinence, while the other 3 management options vary depending on the type of UI.

OBSERVATION

Because UI is almost never a life-threatening issue, observation and management with incontinence aids is always an option for patients who do not desire or are not candidates for active management. Menstrual sanitary pads are frequently insufficient for women with UI, underscoring the

importance of using proper incontinence aids for these patients. In addition, women with large, frequent, or chronic UUI may suffer from skin irritation for which barrier ointments and other moisturizing lotions can help to protect from further skin breakdown. Finally, a thorough mobility assessment is recommended for patients with UUI, as attempts to rapidly get to a bathroom may be dangerous for those who are unsteady on their feet. Conversely, impaired mobility may increase UUI episodes and improving ambulation and access with a walker or bedside commode may decrease UI symptoms and improve patient quality of life. The Simon Foundation (https://simonfoundation.org/) and the National Association for Continence (https://www.nafc.org/) websites contain helpful information and resources.

UUI

Urgency UI is defined by the ICS as the "complaint of involuntary loss of urine associated with urgency" (symptom) and as the "observation of involuntary leakage from the urethral orifice associated with the individual reporting the sensation of a sudden, compelling desire to void" (sign).[1] Urgency UI is included in the syndrome known as overactive bladder (OAB), which is defined by the ICS as urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with UI (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable disease. UUI is associated with high degrees of bother due to the often unexpected, sudden, and large volume leakage that often occurs.

Treatments for UUI have historically been grouped into first, second, and third-line therapies.

FIRST LINE THERAPIES: LIFESTYLE AND BEHAVIORAL MODIFICATIONS

Lifestyle modifications including fluid management/fluid restriction and timed voiding/bladder training are the hallmarks of initial treatment for UUI and are considered just as effective as pharmacologic management. Historically, patients with UUI were counseled to limit bladder irritants such as caffeine, carbonated drinks, and alcohol, as consumption of these beverages was thought to correlate with worsening symptom severity, while cessation led to symptom improvement.[3] However, a recent systematic review challenges these common recommendations.[4] Investigators reviewed 110 articles including bladder irritants and found inconsistent associations between caffeine intake, alcohol, and dietary and UI and lower urinary tract symptoms (LUTS), although increased fluid intake was associated with urinary urgency/frequency. Therefore, health care providers should recommend dietary changes to improve UUI with caution.

There is evidence to suggest that those patients whose urgency is triggered by a full bladder may find timed voiding (toileting on a schedule) and fluid restriction to 60 to 80 oz fluid daily be beneficial.[5] Bladder training can also be helpful in the treatment of UUI and consists of controlled and deliberate timed voiding, where the patient uses distraction techniques to suppress urge sensations in between voiding times. The goal is to progressively increase the amount of time between voids and reduce the number of urgency episodes. Bladder training works on the premise that conscious efforts to suppress sensory stimuli will reestablish cortical control over a previously uninhibited bladder.

Pelvic floor muscle training (PFMT) is a reasonable treatment option for women with UUI. One randomized controlled trial compared lifestyle modifications, PMFT, and percutaneous tibial nerve stimulation (PTNS) in women with UUI and found a similar reduction in UUI episode in the 3 groups.[6]

SECOND LINE THERAPIES: PHARMACOLOGIC MANAGEMENT

Pharmacologic management of UUI includes anti-muscarinics, beta agonists, and vaginal estrogen. While vaginal estrogen therapy can be initiated while patients are trying lifestyle and/or behavioral modifications, the use of oral medications for UUI is typically recommended for women with insufficient improvement in their symptoms with conservative measures.

Vaginal estrogen is FDA-approved for the use of vulvar and vaginal atrophy and is frequently used for the treatment of OAB symptoms in postmenopausal women with physical exam evidence of genitourinary syndrome of menopause. The level of evidence that vaginal estrogen significantly improve UUI is low and should probably not be used alone is women with bothersome UUI. Several unproven theories exist regarding the etiology of vaginal estrogen on LUTS. Vaginal estrogen may improve LUTS though its effects on the vaginal epithelium leading to decreased vaginal irritation. Some data also suggest that vaginal estrogen may ameliorate OAB symptoms through a biochemical effect on the lower urinary tract nervous system. Indeed, one study evaluating urodynamic findings in patients with OAB found that detrusor overactivity decreased after the use of vaginal estrogen for 15 weeks.[7] Likewise, vaginal estrogen likely changes the urobiome, which may impact UUI.[8] Any formulation of vaginal estrogen (cream, tablet, ring) may improve UUI and OAB symptoms.

For many years, anti-muscarinic medications were the first choice for pharmacologic management of UUI; however, newer data indicates that even short term used of these medications is associated with dementia. We recommend health care providers do not routinely prescribe this class of medications if patients are candidates for beta-3 agonists or third-line therapies. Anticholinergic bladder medications include oxybutynin, darifenacin, fesoterodine, solifenacin, tolterodine, and trospium. Anti-muscarinic medications are believed to decrease urgency episodes by blocking acetylcholine stimulation of the muscarinic receptor during bladder storage. In general, anti-muscarinics are more effective than placebo in reducing UUI, but cure rates are low and inferior to third-line therapies.[9] Common side effects associated with anti-muscarinic medications include dry mouth, dry eyes, and constipation. The majority of patients discontinue taking anticholinergic medications within 1-year in part due to adverse effects. Given the relationship of anticholinergics and dementia, health care providers should recommend this class of medications cautiously to women with UUI. A recently published article demonstrated that patients older than 55 years old who were taking anti-muscarinic medications had a dose- and time-dependent risk of developing dementia.[10] Some data suggest an association with dementia with a little as three months of use. Trospium is the only anti-muscarinic medication that does not cross the blood-brain barrier. If one is going to recommend an anticholiergic medication for UUI in older patients, it should be considered.

Beta-3 agonists play an increasingly important role in the treatment of UUI. The most used beta-3 agonist is mirabegron, but other drugs are currently being investigated. Beta-3 agonists stimulate beta-3 receptors in the detrusor muscle to increase bladder relaxation, thereby allowing storage of a larger volume of urine without associated increased intra detrusor pressure. Mirabegron increases voided volumes and time between voids, thereby reducing UUI but does not alter the intensity of detrusor contractions when they occur. The evidence on the efficacy of mirabegron relative to anti-muscarinics is mixed, with some reporting that mirabegron is more efficacious than anti-muscar-

inic medications and others reporting similar efficacy between the two drug classes.[11,12] Side effects of mirabegron include slight increase in blood pressure and nasopharyngitis, but in general, the medication is better tolerated and has a higher 1-year adherence than anti-muscarinic medications. We recommend mirabegron over anticholinergic medications for most patients. Unfortunately, many payers do not cover mirabegron limiting access to many patients with UUI.

In patients with refractory UUI who do not respond to single drug therapy, combination pharmacotherapy with both an anti-muscarinic and beta-3 agonist can be considered. Combination therapy is more effective treatment than monotherapy with either anticholinergics or beta-3 agonists alone.[13] Mirabegron and solifenacin are a popular combination therapy option, but any anti-muscarinic medication can be utilized. Urinary retention is a side effect of these medications, so symptoms of retention and postvoid residuals should be monitored.

Ultimately, the decision to proceed with pharmacologic management should consider patient safety, medication tolerability, and individual preference. Pharmacologic management of UUI is associated with improved sleep quality and quality of life, but these benefits must be weighed against adverse effects and risk of dementia.

THIRD LINE THERAPIES: PROCEDURAL MANAGEMENT

Procedural management of UUI, commonly referred to as "third-line therapy" includes minimally invasive procedures such as PTNS, sacroneuromodulation (SNM), intradetrusor onabotulinum toxin A injections (BTX), and more invasive procedures such as augmentation cystoplasty and urinary diversion. These treatments should be considered in women who continue to experience bothersome UUI despite behavioral/lifestyle modifications and medical management or who are not candidates for beta-3 agonists and prefer to not incur the risk of dementia associated with anticholinergics.

PTNS involves the delivery of an electric current to the tibial nerve through a small needle placed 4 to 5 cm cephalad to the medial malleolus. The nerve is stimulated for 30 minutes once weekly for 12 weeks. One multi-center, double blind, randomized controlled trial found that in OAB patients randomized to PTNS versus sham therapy, 54.5% of those in the PTNS group reported moderately or markedly improved responses compared with 20.9% in the sham group.[14] A major drawback to PTNS is many patients find it cumbersome to return to the clinic once a week for 12 weeks. In response to this, implantable PTNS devices that would provide continuous stimulation are currently being evaluated.

SNM also delivers electrical impulses to the nervous system to improve UUI; however, stimulation is applied to the S3 nerve root rather than the tibial nerve. SNM involves implanting a permanent electrode or lead in the S3 foramen to allow for continuous stimulation of the S3 nerve root. The procedure is typically done in 2 stages, which allows the patient to test their satisfaction with the device before it is permanently implanted. In the first stage, a lead or wire electrode can be placed into the S3 foramen in the operating room (referred to as Stage I) or surgeon's office (percutaneous nerve evaluation) under local anesthesia. Patients undergo a 1-week trial period to evaluate the devices effectiveness. In general, patients who experience at least a 50% reduction in UUI proceed with full implant (Stage II) in the operating room. If the patient's symptoms do not improve by at least 50%, the lead is removed. The efficacy of SNM varies depending on the definition of success; a recent systematic review which included the original SNM device noted that 29% to 76% of patients

with SNM experienced at least a 50% improvement in their symptomatology, but only 43% to 56% were completely dry.[15] Complications are not common and range from surgical site infection to repeat surgery for lead or stimulator revision.

The original SNM device precluded patients from undergoing magnetic resonance imaging, which limited the utility of SNM in many older patients or those with neurological disorders, and required battery replacement every 3 to 5 year. Newer SNM devices from Axonics use improved technology, making them rechargable and magnetic resonance imaging compatible. The Axonics SNM device has a 15-year battery life in contrast to 3 to 5 years. Two-year outcome data in 129 patients with the Axonics device for UUI showed a response rate (> 50% reduction in UUI) of 93%. Importantly, responders actually had an 82% reduction in UUI 2 years after implantation.

Injection of onabotulinum toxin A (BTX) into the detrusor muscle is another third-line option for treatment of UUI. Intradetrusor onabotulinum toxinA injections are performed cystoscopically in the office with local anesthesia. While different dosages of BTX have been studied, 100 to 200 units of BTX are most commonly used for UUI in non-neuropathic patients to balance efficacy and adverse effects like urinary retention. 100 units of BTX are reconstituted into 10 mL of preservative-free 0.9% sodium chloride, which is then injected at ~10 sites throughout the detrusor muscle under cystoscopic guidance. Repeat BTX injection can be done when the patients UUI symptoms return with most patients going 6 to 12 months before needing retreatment. We still do not have a complete understanding of how BTX influences bladder function, but current evidence suggest that BTX acts through both afferent (via anti-inflammatory/antinociceptive mechanisms) and efferent (via inhibition of muscular contraction) avenues.[16,17] The major risks of BTX for the treatment of UUI are urinary retention and urinary tract infection, which are treated with clean intermittent catheterization (CIC) and antibiotics, respectively.

A multicenter randomized trial compared SNM and 200 units BTX for refractory UUI in women.[18] A small statistically significant difference favored BTX; however, the difference was not clinically meaningful leading the authors to conclude both treatments were efficacious. However, a recent systematic review that included seventeen randomized controlled trials found that SNM resulted in the greatest reduction of UUI episodes, and BTX had a higher number of complications.[19] Given the lack of clear superiority of one treatment over another, shared decision making between the patient and health care provider should guide this decision. Many health care providers are recommending third line therapies more commonly given their success in treating UUI and the risk of dementia associated with bladder medications.

MUI

MUI is defined by the ICS as complaints of both stress and UUI.[1] Mixed UI is the most challenging to treat and most bothersome for patients. Women who experience MUI are more bothered by their symptoms and suffer a more dramatic negative effect on their quality of life than women with only SUI or UUI. The etiology of MUI is equally challenging and may represent 2 separate disease processes or a spectrum of disease. In at least some women with SUI, concomitant UUI is secondary to the guarding reflex where urine enters the proximal urethra and induces a reflex-mediated uncontrolled bladder contraction.

Optimal management of MUI is unclear as there is no expert consensus or high quality data on how to approach treatment. Traditionally, health care providers sought to determine which UI subtype, SUI or UUI, was most bothersome to the patient and initiated therapy for the more bothersome subtype of UI. If the patient is unable to articulate which is more bothersome, and a primary etiology cannot be determined through history and physical exam alone, another strategy includes utilizing the results of urodynamic studies to guide management.

The initial management of MUI can include any of the lifestyle and behavioral modifications previously mentioned including weight loss, diet and fluid modifications, bladder training, and PFMT. The advantage of these conservative treatments are many are known to be effective in the treatment of both UI subtypes; however, they are often less effective than other therapies. For patients with urgency predominant MUI, medications for UUI may be an effective early strategy. Similarly, one can start with third line UUI treatments such as SNM or BTX. However, a systematic review concluded that while traditional UUI therapy can be effective for the urge component of MUI, SUI symptoms often persist.[20] In women with stress predominant MUI, both retropubic and transobturator slings have good success in patients with mixed incontinence.[21]

More recently, surgeon-scientists have focused treating both components of a woman's MUI simultaneously. A multicenter randomized trial of women with MUI investigated if the addition of pelvic floor muscle therapy to midurethral sling would result in greater symptom improvement, but did not find significant benefits to combined treatment.[22]

Another recent trial randomized women with MUI to retropubic midurethral sling with concomitant injection of BTX or placebo.[23] Similar to other sling studies, overall UI symptoms improved significantly in both groups; however, women receiving BTX reported less urgency severity and greater improvement in urgency symptoms at 3 months.

Overflow UI

Per the ICS, the definition of the symptom of overflow UI is the "complaint of urinary incontinence in the symptomatic presence of an excessively (over-) full bladder (no cause identified)."[1] Overflow incontinence is generally secondar to: (1) detrusor underactivity; (2) bladder outlet obstruction (BOO), (3) or both. The etiology of detrusor underactivity is varied and includes medication side effects, acute spinal cord trauma, chronic neuropathies, and myogenic pathologies. Similarly, BOO may be secondary to uncoordinated contraction of the striated urethral sphincter, a periurethral mass, pelvic organ prolapse, or iatrogenic obstruction from a prior sling. Treatment is ideally directed at the underlying etiology, however, facilitating bladder emptying is the common goal.

DETRUSOR UNDERACTIVITY

Detrusor underactivity is primarily treated with urinary catheterization regardless of the cause as there are no effective ways to increase detrusor contractility. Catheterization options include: indwelling urethral or suprapubic catheters or CIC. CIC is superior to indwelling catheterization due to lower complication rates, although infection rates are similar. Studies of pharmacologic options like bethanechol chloride and distigmine bromide fail to show a clinically significant improvement in symptoms when these medications are used[24] and therefore are not indicated in the management of detrusor underactivity. SNM described for the treatment of UUI can be an effective treatment for detrusor underactivity in the absence of BOO.

BOO

BOO is managed by treating the source of the obstruction. PFMT can be utilized to treat patients who suffer from dysfunctional voiding due to a nonrelaxing pelvic floor. Some have suggested using benzodiazepines and baclofen for voiding dysfunction cases that are refractory to more conservative management[25]; however, data on the use of these medications or alpha adrenergic blocker is women do not support their use. Obviously, any urethral masses that result in BOO should be excised and urethral carcinomas referred to urologic oncology. Similarly, BOO from stage III or IV prolapse can be alleviated with pessary or surgery. Finally, patients with obstruction secondary to prior sling should be offered sling release and urethralysis.

Conclusion

In conclusion, UUI and MUI dramatically impact the quality of life of millions of women every year. Fortunately, there are a wide range of effective treatments for UUI and MUI, and patients and health care providers can used shared decision making to determine the best option.

While certain therapeutics have been found to be more effective than others, there is no "one-size-fits-all" and the management strategy chosen must be individualized to fit each patient's goals, taking into account the risks, benefits and alternatives to each therapy recommended. Health care providers should use anticholinergic medications with great caution given their association with dementia

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