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Mixed Urinary Incontinence: What First?

Nazia Q. Bandukwala · Angelo E. Gousse

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Abstract Mixed urinary incontinence (MUI) is the involuntary loss of urine associated with the sensation of urgency and also with exertion, effort, sneezing, or coughing. The underlying cause of MUI is poorly understood. Without clearly understanding the pathophysiological and anatomical changes associated with MUI, treatment is often misdirected. This review presents an analysis of the most recent studies and pathophysiological mechanisms thought to be associated with MUI-related voiding dysfunction. A suggested algorithm is provided for the workup of these women with a review of medical and surgical treatment options used to treat MUI.

Keywords Female urology · Mixed urinary incontinence · Stress urinary incontinence · Urge urinary incontinence · Urodynamics

Abbreviations

MUI	Mixed urinary incontinence
SUI	Stress urinary incontinence
UUI	Urge urinary incontinence
DO	Detrusor overactivity
MUS	Midurethral sling
UTI	Urinary tract infection
ICS	International Continence Society
TVT	Transvaginal tape
TOT	Transobturator tape
ISD	Intrinsic sphincter deficiency
SNM	Sacral neuromodulation

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N. Q. Bandukwala · A. E. Gousse (✉)
Memorial Hospital Miramar, South Broward Hospital District, 1951 SW 172 Avenue, Suite 305, Miramar, FL 33029, USA
e-mail: agousse@aol.com
URL: http://www.bladder-health

Introduction

The International Continence Society (ICS)-International Urogynecological Association defines urinary incontinence as any involuntary loss of urine [1••]. Urinary incontinence is subcategorized into three groups according to the ICS: (1) stress urinary incontinence (SUI), which is defined as involuntary leakage of urine on effort or exertion or on sneezing or coughing; (2) urge urinary incontinence (UUI), which is the involuntary leakage of urine immediately preceded by urgency; and (3) mixed urinary incontinence (MUI) defined as the involuntary loss of urine associated with the sensation of urgency and also with exertion, effort, sneezing, or coughing [2]. There are other types of incontinence that are beyond the scopes of this paper including continuous urinary leakage seen in fistula patients, coital incontinence, and insensible urinary incontinence [3••].

Mixed urinary incontinence (MUI) is a term that applies to both urinary incontinence symptoms and urodynamic findings in the same individual [4]. MUI with a prevalence rate as high as 35 % in the nearly 15 million women with urinary incontinence is fairly common in everyday clinical practice [5, 6•]. Estimates of MUI vary. Studies from China report a rate as low as 6 % in Chinese women with urinary incontinence while other studies have found a prevalence rate as high as 61 % [6•, 7–9]. MUI affects women more than men and women of all ages. Multiple studies comparing health-related quality of life (HRQoL) have found that patients with MUI have a greater negative impact on quality of life than either SUI or UUI [6•, 10•, 11, 12].

Incontinence symptoms do not always reveal the true etiology behind an individual's incontinence. Symptomatology is often inconsistent with urodynamic findings, which are in turn often not reflective of MUI. Physical exam and urodynamic findings will often reveal either SUI or detrusor over-activity (DO) consistent with UUI [4]. These findings

were demonstrated in studies by Cardozo and Stanton. Fifty percent of women with mixed symptomatology were found to have only SUI and 40 % of women were found to have only detrusor over-activity during urodynamic testing [13]. Similar findings were reported by Sandvik who found that only half of the patients with MUI symptoms had an identifiable mixed condition [4, 9, 14].

There is an abundance of literature on MUI as well as many developing treatment options for MUI. However, we are still plagued with the same clinical problems today as nearly a decade ago. Conservative treatment aimed at the most bothersome component of a patient's MUI can improve subjective and objective measures on validated questionnaires, patient-reported symptom improvement, and urodynamic testing. The group of women that do not respond to traditional treatments poses a serious challenge that we have yet to effectively treat. Furthermore, while some studies are based on incontinence symptoms, others are based on urodynamic findings, which render effective comparison of the available results very difficult if not impossible [3••, 4]. The goal of this paper is to review the current literature on MUI and provide a MUI treatment algorithm for clinicians.

Pathophysiology

Parity, vaginal delivery, obesity, diabetes, constipation, family history, and increasing age predispose women to incontinence. Genetic differences in extracellular matrix proteins and androgen receptors may also play a role in the development of mixed urinary incontinence [15].

A separate theory behind the etiology of mixed urinary incontinence is attributed to two separate disease processes, which cumulatively contribute to more bothersome symptoms. Another theory describes behavioral changes in voiding habits in women with MUI. These women retrain the bladder by urinating more frequently to avoid leakage associated with SUI. The patient may rush to the restroom to urinate at the first sensation or first desire. This patterned behavior to avoid stress-induced leakage may lead to a "pseudo-urgency syndrome" [4, 16].

Anatomical changes corresponding to theories accounting for SUI include the following: alterations in the urethrovesical axis, intrinsic sphincter deficiency, hammock theory, and integral theory [10•]. It has also been postulated that accumulation of urine in the proximal urethra can lead to urethral relaxation and detrusor contraction. Additionally, urethral instability and fluctuation in urethral pressure lead to detrusor overactivity and change in the urethrodetrusor reflexes that can lead to a heightened micturition reflex [4].

Workup

Clinicians should focus on medical, neurological, and genitourinary history; explore symptoms in terms of duration, frequency, and most bothersome symptoms; and explore precipitants and treatments. Investigations include a urine dipstick, post void residual, voiding diary, and a thorough physical exam assessing rectal tone, tightness of the perineal body, vaginal mucosa, urethral mobility, and presence of prolapse. Anatomical changes leading to a lax pelvic floor have been found to contribute to MUI symptoms. Quality of life (QOL) questionnaires assessing the impact of urinary incontinence symptoms are useful tools utilized in evaluating MUI. These tools can aid physicians in their assessment and monitoring of a patient's progress posttreatment [3••, 15]. The 3 Incontinence Questions (3IQ), The Questionnaire for Female Urinary Incontinence Diagnosis (QUID), Stress and Urge Incontinence Quality of Life Questionnaire (SUIQQ), and the International Consultation on Incontinence Questionnaire-short form have received high grade A recommendations from the International Consultation on Incontinence and can be used to diagnose MUI [17].

Although a detailed history and physical exam are important in diagnosing patients with MUI, subjective symptoms are often a poor indicator of the final diagnosis. Secondary testing including cystourethroscopy and urine cytology to rule out pathologic conditions of the bladder are also recommended.

Urodynamics is an important tool in determining the underlying etiology of a patient's incontinence especially when symptomology is unclear or potentially misleading. The literature however has varying recommendations regarding urodynamics. Digesu et al. state the initial symptom and most bothersome component are more predictive of a patient's response to a particular treatment than urodynamics findings [18]. Conversely, detrusor overactivity (DO) can be detected on urodynamics in a significantly higher proportion of women with urge urinary incontinence as the predominant component and is helpful in providing guidance in the clinical scenario in which the symptomatic diagnosis is unclear [19]. Recently released SUFU and AUA guidelines on urodynamics state that urodynamics can be utilized to diagnose MUI but is not absolutely necessary to confirm the diagnosis of MUI given that it is a symptomatic diagnosis. The AUA guidelines specifically state that (1) clinicians may perform multi-channel filling cystometry when it is important to determine if altered compliance, DO, or other urodynamic abnormalities are present (or not) in patients with urgency incontinence in whom invasive, potentially morbid, or irreversible treatments are considered. (2) Clinicians may perform pressure flow studies (PFS) in patients with urgency incontinence after bladder outlet procedures or to evaluate for bladder outlet obstruction. (3) Clinicians should counsel patients with urgency incontinence

and mixed incontinence that the absence of DO on a single urodynamic study does not exclude it as a causative factor for their symptoms [20••, 21•, 22•].

Videourodynamics, which utilizes fluoroscopy, allows simultaneous assessment of structure and function and is the preferred method for evaluation of mixed symptomatology. Urodynamics is especially important in patients with MUI as it provides information on bladder compliance. Poorly compliant bladders with high pressures can lead to detrimental upper tract damage of the kidneys and ureters. Poor compliance can result from a variety of causes including neurological disease, prolonged catheter drainage, long standing obstruction of the urinary tract, radiation therapy, prior genitourinary surgeries, and interstitial cystitis. Urodynamics should therefore be performed in any patient at risk for poor bladder compliance. Anti-incontinence procedures and medications to correct MUI can risk damaging the upper tracts due to elevated bladder pressures [4]. Urodynamics is routinely performed in patients with MUI symptoms in the authors' clinical practice prior to proceeding with invasive procedures.

Treatment

MUI treatment is addressed in a stepwise fashion. MUI utilizes either monotherapy or a combination therapy of conservative management, pharmacotherapy, and surgery [10•]. Table 1 reviews the summary of evidence for treatment of MUI.

Conservative management includes lifestyle interventions such as weight loss and decreased fluid intake, bladder retraining, anti-incontinence devices such as pessaries, biofeedback, and pelvic floor muscle exercises (PFME). It is the responsibility of the physician to work with the patient in identifying which component of MUI is most bothersome—stress or urge. Based on this assessment, a physician can offer the appropriate initial treatment [10•]. See Fig. 1 for determining which is the most bothersome component.

Pharmacological therapy consists of topical hormone replacement; antimuscarinic drugs (oxybutynin, tolterodine, solifenacin, fesoterodine, darifenacin, trospium); Beta 3 adrenergic agonists (mirabegron); and serotonin/norepinephrine reuptake inhibitors [15, 30]. A typical clinical scenario in MUI patients on anticholinergic therapy is resolution of the urge component in 50–60 % of patients but little to no improvement in the stress component [4, 16].

Multiple trials have been conducted comparing anticholinergic therapy to placebo and surgery. The Mixed Incontinence Effective Research Investigating Tolterodine (MERIT) study, a multinational, double-blinded, placebo controlled trial, evaluated the efficacy of antimuscarinic therapy in patients with urge-predominant MUI. In total, 854 patients with MUI were studied, 634 (74.5 %) with UUI as their initial or predominant symptom. After 8 weeks of treatment 76 % in the drug group reported improvement compared with 53 % in the placebo group [4, 23]. Karram and Bhatia found no significant difference in cure rates in either the SUI or UUI component of 52 MUI patients treated with surgery or medical therapy [5]. Osman et al. compared patients with MUI who received anticholinergic versus either a Burch colposuspension or pubovaginal sling. Persistent UUI was seen in 43 % of patients who received anticholinergic therapy compared to 13 and 12 % in the Burch and sling groups [16].

Surgical treatment of urinary incontinence is planned according to the dominant component of urinary incontinence. If SUI is the dominant symptom, according to the AUA guidelines on surgical treatment of female stress urinary incontinence, one might offer pelvic floor muscle exercise with or without physical therapy and biofeedback, midurethral sling (MUS), peri-urethral bulking injections, or colposuspension. If the above fails, re-evaluate the patient and re-enter the algorithm at the appropriate stage. Consider second-line surgery for SUI if applicable [31]. Conversely, in cases of urge-predominant MUI, in accordance with the AUA/SUFU OAB guidelines, the patient may be offered behavioral and dietary adjustment with physical therapy, pharmacotherapy, intradetrusor botulinum toxin A injection, sacral neurostimulation, percutaneous tibial nerve stimulation, bladder augmentation, or urinary diversion in extreme cases [21•].

As mentioned earlier in this article, mixed symptomatology does not always correlate with a mixed condition. As shown in a handful of studies, surgical correction in patients who underwent either a Burch colposuspension, pubovaginal sling, tension free vaginal tape (TVT), or transobturator tape (TOT) procedure can lead to resolution of urge incontinence and urgency in a majority of patients with MUI symptoms. Scotti and colleagues demonstrated an overall resolution of urgency incontinence in 56.5 % of the 46 MUI patients after Burch colposuspension [32]. Langer and colleagues studied 127 women with MUI who underwent a Burch colposuspension, 33 % had preoperative UUI, and 55 % had urinary urgency. Only 9 % of the patients with preoperative UUI and 25 % of the patients with urgency were still complaining at 1 year postoperatively [33]. Another study by Serels et al. evaluated 36 patients with DO on urodynamics who underwent various pubovaginal sling procedures. Sling procedures included in situ vaginal wall slings, free swing vaginal wall slings, rectus fascia slings, cadaveric fascia slings, and synthetic slings. Preoperatively, 21 (58 %) patients had MUI. SUI was cured in 92 % of these patients with 75 % having resolution of their UUI [34]. Other studies by McGuire, Fulford, and Osman report resolution of urge incontinence in 69–83 % of their patients who had undergone a pubovaginal sling operation [4, 16] . A meta-analysis conducted in 2011 reviewed the effectiveness of mid urethral slings on mixed urinary incontinence. Six randomized trials (RCTs) and seven prospective studies were reviewed. The overall subjective cure from seven

Table 1 Summary of evidence for treatment of mixed urinary incontinence

Source	Study type	Type of urinary incontinence	No. of patients analyzed	Treatment mode	Summary statistics
Karram and Bhatia [5], 1989	Retrospective case cohorts	Mixed	52	Surgery vs conservative	
Osman [16] 2003	Randomized Trial	Mixed	75	Retropubic colposuspension/ traditional sling vs anticholinergic medication	Surgery more effective anticholinergic medication ($P<.05$)
Khullar et al [23], 2004	Randomized double-blind, placebo-controlled trial	Mixed	854	Anticholinergic medication	Extended-release tolterodine decreased weekly urge urinary incontinence vs placebo ($P<.001$); no difference stress urinary incontinence
Staskin and Te [24], 2006	Pooled studies with subanalysis	Overactive bladder, mixed	1041	Anticholinergic medication	
Kulseng-Hanssen et al [25], 2007	Prospective cohort	Mixed	1113	Mid-urethral slings	
Kulseng-Hanssen et al [26], 2008	Large prospective trial	Mixed	113	Mid-urethral slings	
Townsend et al [27], 2011	Large prospective cohort	Mixed	65,167	Behavioral	High caffeine intake worsened urinary incontinence vs caffeine intake (RR, 1.19; CI, 1.06–1.34)
Jain et al [28], 2011	Systematic review and meta analysis	Mixed	11 trials including 2693 patients	Mid-urethral slings	
Gormley et al [21•], 2012	AUA/SUFU guidelines	Overactive bladder	8 trials	Conservative, behavioral	
Abdel-Fattah, 2014 [29•]	Prospective randomized	Mixed	66	Midurethral sling surgery	Midurethral sling or transobturator tape has a 73.8 % reputed success at 3 years. Surgical management of MUI with primarily a stress component resulted in a 50 % cure of the urge and urge incontinence component.

Myers, Abdel-Fattah [3••, 29•]

prospective non-randomized studies that included patients with symptomatic±urodynamically proven MUI was found to be 56.4 %. The overall cure of urgency and the UUI component was 30–85 % at a follow-up of a few months to up to 5 years. Most of the studies described found this cure does not persist over time. The cure rate of SUI following MUS varies from 85 to 97 %. On meta-analysis of five RCTs that included women with MUI symptoms, the odds of overall subjective cure with TVT versus TOT tapes are similar at 6–33 months follow-up. This was true when a subgroup analysis was performed on women with MUI who did not demonstrate DO on UDS [28]. A more recent study in 2014 by Abdel Fattah et al. found that transobturator tape procedures are associated with a good (73.8 %) patient reported success rate at a minimum of 3 years of follow up in the surgical management of MUI in women with predominant SUI symptoms. Nearly half of the women reported cure of their urgency and UUI [29•]. A Cochrane review analysis of urethral bulking agents for SUI found limited benefit for MUI [35].

There are a few studies that address the etiology behind the resolution of MUI by fixing the SUI component; however, this resolution can be attributed to preoperative mixed symptomatology rather than a true MUI. Most studies suggest that women with stress-predominant MUI have significantly better cure rates than women with equal stress-urge and urge-predominant MUI. Women with urge-predominant MUI have more postoperative bother [4].

De Novo Urgency and Other Voiding Dysfunctions After Anti-Incontinence Therapy

Existing reports indicates that up to 40 % of patients develop voiding dysfunction after anti-incontinence procedures. Voiding dysfunction discussed here includes persistent or worsening urinary urgency, urethral obstruction, and de novo urgency.

Persistent urinary urgency is symptomatic urgency that does not resolve after anti-incontinence therapy. Persistent urgency can also be manifested with DO on UDS prior to surgery that continues post operatively. It is estimated to be up to 40 % after synthetic sling surgery and ranges from 13.6 to 74 % in women with a history of MUI. Postulated risk factors for persistent urgency are the presence of DO on preoperative urodynamics, increasing age, and increased baseline severity [36•]. These patients have the lowest satisfaction with the

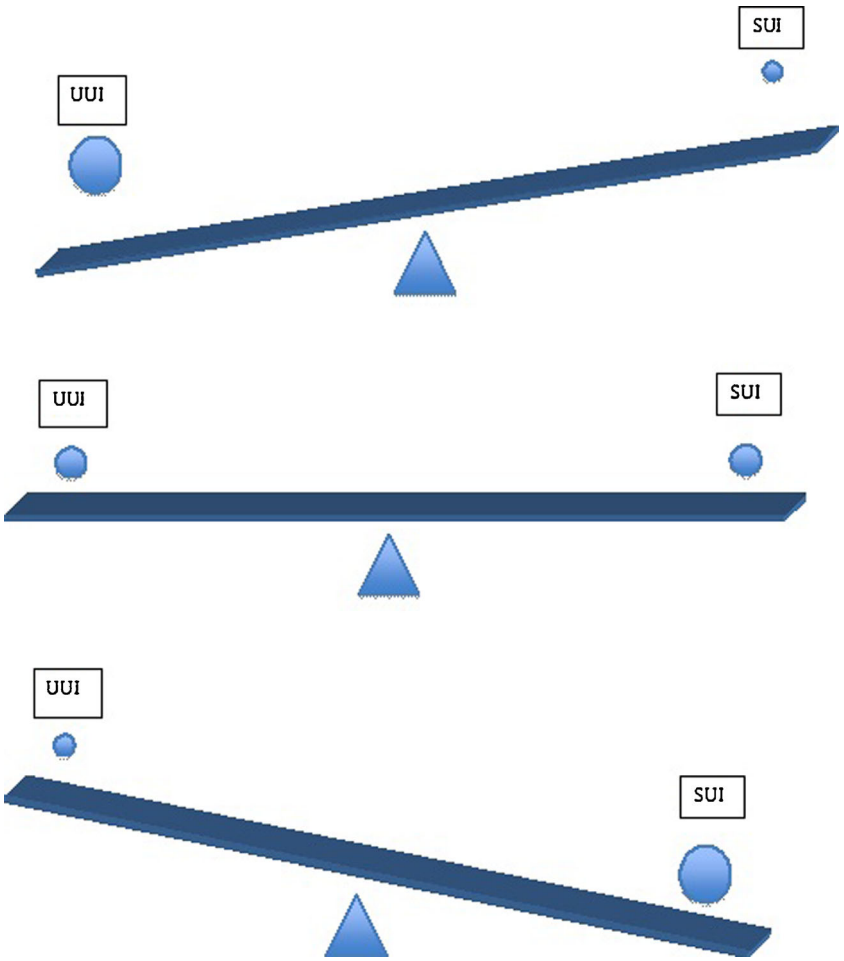

Fig. 1 Mixed urinary incontinence: which is the heavier component?

procedure and should be appropriately counseled on the data of persistent urgency and urgency incontinence preoperatively.

De novo urgency, on the other hand, is urinary urgency that develops after sling placement and includes new symptoms of frequency, nocturia, urgency, and or UUI. Contributing factors in the development of de novo urgency include postoperative urinary tract infection, urethral obstruction, perforation of the urinary tract and idiopathic urgency. Other theories include increased urethral resistance during voiding, denervation causing detrusor super-sensitivity and over-activity, failed repair of SUI, and intrinsic sphincter deficiency (ISD) [4]. The Ingleman-Sundberg procedure in which there is intentional division of the terminal branches of the pelvic nerves could also cause these symptoms. Urinary tract infections in a large Medicare study have been reported to be as high as 33.6 % in the first 3 months after sling placement [36•]. Urethral obstruction is uncommon with an incidence in the literature ranging from 1 to 19 %. Higher rates of urethral obstruction and repeat surgery have been reported following retropubic sling placement compared to transobturator sling placement [4, 36•, 37]. Urinary tract perforation is a rare complication and the estimated prevalence ranges from 0.5 to 24 % after sling placement. Higher rates are reported in retropubic sling placement with blind passage of trocars [38].

It is especially important to note that there is no preoperative urodynamic parameter that directly correlates with de novo urgency [4, 36•].

Evaluation of Postoperative Voiding Dysfunction

The normal healing process can take up to 6 weeks and it is prudent that the clinician and patient wait this time period postoperatively prior to performing further invasive tests and procedures. It is critical to rule out urinary retention in patients with postoperative voiding dysfunction. Urinary retention can be diagnosed via assessment of the post void residual (PVR). Some authors suggest that a PVR value greater than 60 mL may be suggestive of obstruction in a patient who has undergone a sling without a history of elevated residuals preoperatively [36•]. Evaluation should begin with a thorough history and physical exam. History can clarify the initial onset and bother of symptoms and differentiate between persistent and de novo urgency. A detailed history will also identify any irritative or obstructive voiding symptoms such as gross hematuria, dysuria, pain, urinary tract infections, incomplete emptying, hesitancy, dribbling, or decreased urinary stream. This is also an appropriate time to re-administer QoL and voiding questionnaires to determine any changes post operatively. Voiding diaries can also be helpful in assessing the severity of symptoms.

Physical examination should assess the anterior vaginal wall for the appearance and position of the bladder neck and proximal urethra. Palpation of this same region can also assess for mobility, scarring, pelvic prolapse, and sling extrusion. A catheter or urethral sound placed in the urethra can demonstrate the degree of urethral mobility and allow the examiner to assess for urethral stenosis or obstruction. Cystourethroscopy can rule out a foreign body such as sutures, stones or sling extrusion. Cystoscopy can also evaluate for any neoplasms.

Urodynamics can be done for the same indications mentioned in the workup section of MUI earlier in the body of this paper. Urodynamics can evaluate for any DO and or new altered compliance. Videourodynamics can evaluate the bladder neck for any obstruction. High-pressure low-flow voiding is suggestive of bladder outlet obstruction. While specific data points for females with obstruction on urodynamic testing are lacking, it has been stated that a detrusor pressure greater than 30 cm H_20 and peak flow less than 15 mL/s are suggestive of an obstructive voiding pattern. Blavias and Groutz proposed values of detrusor pressure greater than 20 cm H_20 and peak flow less than 12 mL/s as suggestive of female bladder outlet obstruction [4, 36•, 39]. A multimodal approach utilizing the aforementioned recommendations is advised in the evaluation of voiding dysfunction after anti-incontinence surgery.

Treatment of Postoperative Voiding Dysfunction

In cases of obstructive uropathy following an anti-incontinence surgery, treat the underlying cause. If there is excessive sling tension, the sling can be incised/excised or urethrolysis can be performed [36•].

If obstruction has been ruled out, treatment similar to idiopathic urgency including bladder-retraining exercises, pharmacotherapy, and limitation of bladder irritants is recommended. If conservative therapy fails, intradetrusor onabotulinumtoxin A injections or xylocaine mixed with steroids injected periurethrally have also been used to treat external sphincter spasticity and dysfunctional voiding [4]. Starkman et al. reported on the success of sacral neuromodulation (SNM) in the management of refractory overactive bladder after urethrolysis for bladder outlet obstruction. On retrospective review, six of eight patients that underwent SNM had a favorable response to SNM with three patients being dry and three patients having one to two urgency incontinence episodes per week [40].

Conclusion

High-quality evidence is lacking for the treatment of mixed urinary incontinence. There is no consensus as to which

component to treat first: urge or stress. Most clinicians opt to treat the most bothersome component. It is the authors' opinion when choosing treatment options, to start with conservative treatment of the urge component before considering surgical therapy for SUI. This can bypass un-needed surgery in a group of patients who respond to non-operative treatment.

There is no sound data suggesting which patients will have success or failure with each treatment option. We have provided a stepwise algorithm from our practice. Although this algorithm has not been validated, it has translated into effective clinical outcomes. There are many new treatment options in development for women with MUI including new pharmacologic agents including potassium channel agonists, calcium channel blockers, phosphdiesterase-5 inhibitors, and neurokinin receptor antagonists [15, 41, 42]. Randomized trials in women with mixed urinary incontinence are needed to validate these treatment options. Only then will we be able to improve the overall cure rates and offer sustained relief to those complex and challenging cases of MUI refractory to standard treatment options. In the meantime, it is best to start with non-operative and conservative treatment of the most bothersome component of a given individual's MUI.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Nazia Q. Bandukwala declares no potential conflicts of interest. Dr. Angelo E. Gousse is a consultant and investigator for Allergan.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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