Review

Mixed Urinary Incontinence: Diagnosis and Management

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Abstract

The evaluation and treatment of mixed urinary incontinence receives relatively little attention as compared to other forms of incontinence. Mixed incontinence, however, defined as the combination of stress and urgency incontinence, accounts for the largest proportion of incontinence, with an increased incidence in older women. The condition can be very challenging to manage due to the coexistence of multiple pathologies. Treating either component can worsen the other, which means careful discussion of the risks and benefits, in addition to considerations of multimodal treatment approaches are required. In the older adult population, where this condition confers a significant impact on quality of life, there are many special considerations when evaluating and treating patients. Evaluation requires a careful assessment of the impact on QOL and goals of care and may need to involve caregivers and/or family members in the discussion, in addition to considerations of more advance evaluation on an individual basis prior to invasive treatments. Conservative treatments including behavioral and lifestyle modifications and pelvic floor physical therapy should be the mainstay of first-line treatment for older women with MUI, while taking into careful consideration how cognitive and/or physical limitations may impact treatment. Pharmacologic therapy should include a consideration of vaginal estrogen replacement, however oral medications for urgency and overactive bladder have increased risks in older

women, which means more advanced treatments may want to be introduced sooner. There is really limited data on the use of third-line overactive bladder treatments in older women with mixed incontinence, however there may be some demonstrated benefits. Finally, when considering surgical interventions in this population, although the data demonstrate some benefit in mixed incontinence, providers may want to utilize a formalized assessment of frailty due to the increased morbidity associated with frailty in surgeries for incontinence.

Keywords

Mixed urinary incontinence; elderly; frailty; anticholinergics; mid-urethral sling; older adults

1. Introduction

Older adults are defined by the World Health Organization (WHO) as those 65 years of age or older and by the United Nations as 60 years of age or older [1, 2]. With the world's aging population, the number of older adults is projected to reach 1.5 billion by 2050 [3]. Likewise, urinary incontinence (UI), which is defined by the International Continence Society (ICS) as "an involuntary loss of urine" for any reason, is an incredibly common condition, particularly in older adults [4]. While about 20% of women of all ages suffer from UI, the incidence increases to over 75% of older female nursing home residents [5]. Additionally, WHO has identified UI as a public health priority, due to the substantial effects on the quality of life (QOL) of women, including physical, mental, and social [6]. In fact, the impact of UI on QOL in the elderly exceeds that of many other common comorbid conditions, including arthritis, diabetes, and stroke [7, 8]. Urinary incontinence in older women is associated with accelerating the decline in functional status, the risk of falls, the psychosocial burden, and the requirement for nursing home care [9, 10]. Therefore, the evaluation and management of UI, particularly in older women, is of substantial importance for providers.

Mixed urinary incontinence (MUI) is defined as complaints of both types of UI-stress and urgency- or involuntary loss of urine associated with urinary urgency and also with effort or physical exertion including sporting activities, sneezing, or coughing [11]. In older women, MUI is the most common type of UI, accounting for over 50% of all cases and occurring in estimated 1 in 3 of all older women [9, 12]. Mixed urinary incontinence, particularly, can be a challenging condition to manage, especially in older women. Due to the coexistence of multiple pathologies, treating either component of UI can worsen, or make more prominent, the symptoms of the other. Therefore, multimodal treatment approaches can be required, which can lead to greater morbidity, especially in the older population. Understanding the diagnosis and management options for this challenging condition, and special considerations in older patients, is paramount for providers to offer the most comprehensive care to this vulnerable population.

2. Detection, Diagnosis, and Evaluation

2.1 Detection

One critical barrier in diagnosis and evaluation of all UI in women is detection. Detection relies on the patient seeking medical care for their condition. Because of the sensitive nature of the topic,

it is understandable that there is a high prevalence of undiagnosed UI, especially in older women who may have particular embarrassment surrounding the topic. The rate of people with UI who do not seek medical care for their condition varies in the literature from 30 to 70%, which of course ultimately depends on the study population. A European questionnaire-based study found that 67% of women with UI reported not seeking care for their condition [13]. On the lower end of the spectrum, a study from the United Arab Emirates with the objective of determining the prevalence and sociodemograhpics of UI in their population found only 31% of women with UI sought medical advice [14]. This proportion was similarly low in a study of 1,000 community-dwelling older adults with UI from rural Pennsylvania, in which only 38% stated they reported UI to their physician [15]. Finally, in our own recent questionnaire-based study, we found that of 1,303 community-dwelling participants with overactive bladder (OAB) with or without urgency urinary incontinence (UUI), only 48% reported ever talking to a healthcare provider about their bladder symptoms, despite 95% reporting a visit to the doctor for any reason within the last year [16]. This suggests barriers to care for UI and lower urinary tract symptoms (LUTS) may exist that are distinct from overall access to healthcare.

A few studies have aimed to further understand the specific barriers to care for women with UI. Previous studies have demonstrated reasons for women not seeking care for UI included not knowing a provider well enough to feel comfortable discussing UI, worry about the costs of care, and fear of discussing sensitive topics with a male provider [14, 17, 18]. More recently, this has led to the development of the Barriers to Incontinence Care Seeking Questionnaire (BICS-Q) which includes questions about multiple factors that may impede seeking care including inconvenience, relationship (not knowing an appropriate provider or not feeling comfortable discussing this problem), site related (transportation issues, distance), cost, and fear [19]. While there is a paucity of literature regarding how different factors may impact older women seeking care for UI, specifically, one can infer that they may be uniquely impacted by these factors as well, particularly with increased co-morbid conditions, changing hormonal environments, medication exposures, functional differences, social supports, and psychosocial factors that may change and/or become greater impact as women age.

Few studies, however, have used the BICS-Q. The above-mentioned European questionnaire-based study found that the most frequent barriers to seeking care for UI included fear, long wait times, and long travel distances [13]. Additionally, authors found that patients with more severe UI on the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) scored higher on the BICS-Q, indicating that those with the most severe UI actually have a decreased probability of seeking care. While the BICS-Q is one tool for assessing these factors, it is not all-inclusive. It poorly assesses for other associated, and possibly confounding factors, including sociodemographics and other social determinants of health, societal differences, cultural beliefs, personality, differences in individual understanding of health, and personal experience surrounding health and illness, all of which ultimately contribute to reasons for not seeking medical care. One very important factor not assessed by the BICS-Q is the knowledge gap that exists around many health topics, particularly urinary, sexual, and women's health. Only a few studies and commentaries have discussed this important factor, noting that women may be unaware they should, or could, seek medical care for UI, the commonly held belief that UI is a "normal" part of aging, the belief that UI may resolve spontaneously, and that the most common source of knowledge regarding UI and other genitourinary issues is talking to family and friends [14, 20].

The Prevention of Lower Urinary tract Symptoms (PLUS) Network has developed multi-level conceptual frameworks for research regarding LUTS, which includes societal/community, institutional, interpersonal, and individual levels of a person's environment which may influence LUTS and vice versa [21]. Approaching urinary conditions within such frameworks is critically important, and this type of framework can be used to understand different barriers to women seeking medical attention for their urinary conditions, including UI. Moving forward, more research, understanding, outreach and education, both in the community and for providers, is needed to determine how best to increase detection of UI, particularly in vulnerable populations such as older women, as detection is the very first step in diagnosis, evaluation, and ultimately management of this challenging condition.

2.2 Diagnosis and Evaluation

The diagnosis of MUI can be particularly challenging for multiple reasons. The challenge is additionally compounded in older women in which there are special considerations of the risks and benefits of pursuing invasive testing. It is reasonable to assume the first opportunity for diagnosis for UI in older women is in the primary care setting. Incontinence history can and should be pursued in this setting, as a primary care provider is the most common healthcare professional seen by older women and is most likely the longest-standing patient-provider relationship, therefore providing a safe and comfortable environment for women to discuss sensitive issues. While more advanced evaluation can be pursued upon specialty referral, opening the door for patients to discuss UI, educating that there are safe and effective treatment options, and understanding how much UI effects a patient's QOL is a critical first step of diagnosis and evaluation. In a recent online survey-based assessment of 108 primary care providers in a large healthcare system, only 52% reported "very often" or "all of the time" screening for UI in women, despite that the majority (71%) correctly identifying the overall prevalence of UI in women in the United States [22]. This suggests that while primary care providers understand the burden of UI to women, they are not utilizing their patient interactions to screen for UI. This demonstrates a potential area for improving care for women with UI, particularly when considering the older population, who may not easily be able to travel to multiple specialty medical appointments. Additionally, it is important for primary care providers to screen for UI as it is paramount for them to rule out, evaluate, and/or manage other transient causes of UI, especially in the higher risk population of older women. This includes pharmacologic causes, infections, psychosocial factors, renal urine production, mobility issues, bowel issues, and neurologic causes.

While primary care providers can and should screen for UI, and even consider starting conservative treatments, in the case of true MUI, both the diagnosis and management tends to be more complex. Therefore, after establishing a diagnosis, degree of bother, and desire for treatment for UI, older women could benefit from a specialty referral as they may require advanced evaluation and a nuanced discussion of the risks and benefits of treatments.

2.2.1 History

The first step of evaluation is always a careful history. However, several studies have indicated that patient history is not always accurate as the sole determinant of UI type, which can be particularly challenging in a patient with MUI [23, 24]. Basic evaluation should include questions

regarding both the presence and severity of UI, in addition to the overall bother and burden to the patient. Assessing symptom bother and establishing expectations of potential outcomes is critical, especially in older women, such that the degree of bother can be adequately balanced with the risks associated with the available therapies for each individual patient [25]. Additionally, concomitant urinary symptoms and presence of other pelvic floor disorders should be assessed. Additionally, when assessing the older patient, it is even more important to consider other co-morbid conditions, the presence of other neurologic symptoms, history of radiation or trauma, gynecologic and obstetric history, and other pelvic surgeries or prior interventions for UI, as they may be more prevalent. Finally, it may be important for an older patient to come to an office visit with a loved one or caregiver with whom they feel very comfortable discussing these sensitive topics, as any cognitive impairment can make assessment of UI based on history more challenging, particularly MUI.

2.2.2 Physical Examination

Physical examination is a necessary and important component of the evaluation, even when the history obtained may seem "straightforward". The information gained from the overall general appearance of the patient can be incredibly valuable, particularly in older patients. For example, details including gait, mobility, stature, and fragility can be surrogates for assessing overall performance status and for any neurologic issues which may ultimately effect treatment options and discussions of outcomes. It is worth considering a formal assessment of frailty in the older population during assessment for UI, as there is surmounting evidence that the clinical phenotype of frailty predisposes this population to poorer surgical outcomes and increased post-operative complications [26-28]. Increasing literature suggests that a formal assessment of frailty may be beneficial in a urologic population specifically, especially when considering surgical interventions. The "Timed Up and Go Test" (TUGT), which relies on measuring the time for a patient to stand from a seated position and walk 10 feet, is a simple, and effective, measure of frailty [29-31]. In a prospective, single-center study in which the TUGT was measured for all patients presenting to a non-oncologic urology clinic over the age of 65, 30% of patients were categorized as "prefrail" and 15% as "frail" based on TUGT times [32]. However, there was no difference in the TUGT times for patients who did and did not undergo urologic surgeries, suggesting an opportunity to use frailty as a pre-operative consideration in surgical counseling and decision making.

Finally, performing a comprehensive pelvic exam is important for evaluation of UI. This should include an assessment of estrogen status, including presence of urethral prolapse or caruncle, labial adhesions, and overall tissue appearance and color. Additionally, assessments for both stress urinary incontinence (SUI) via supine cough stress test with a reasonably full bladder and pelvic organ prolapse using one blade of a vaginal speculum both with and without straining should be performed. Evaluation for occult SUI which occurs after anterior prolapse is reduced should be assessed as needed as well. Finally, in the cases of prior pelvic or vaginal surgery with synthetic grafts, an assessment for the presence of vaginal mesh extrusion should be thorough. Older patients, particularly, with changes in cognitive status or who had surgeries performed many years prior to evaluation may not remember all the details of prior surgery, such as whether a vaginal mesh was used or not, so a degree of suspicion in these cases must exist on the part of the provider.

2.2.3 Supplemental Evaluations

Aside from the above-mentioned history and physical examination, which are standard and should be performed in all women presenting with UI, there are several considerations for supplemental evaluations. In most patients, a urinalysis (UA) and post-void residual (PVR) volume measurement should be performed [25, 33]. However, beyond this, there is no universally agreed-upon standard for the evaluation for MUI with regards to adjunct studies including cystourethroscopy, urodynamic studies (UDS), radiographic studies, and other means to quantify symptoms (i.e. pad tests, validated questionnaires, voiding diaries). While these adjunct tests are generally not needed for the index patient with either SUI or OAB/UUI, in the case of MUI, they may be useful. However, the risks of invasive testing, especially in older patients should also be carefully considered.

Symptom Quantification. Voiding diaries can be a useful evaluation tool, as they provide diagnostic information, particularly in patients who may have difficulty describing or recalling their UI and urinary symptoms. They may also be therapeutic by allowing patients to understand their pattern of urination better. Voiding diaries can be considered, especially in older patients who may be higher risk for more invasive testing. In patients with impaired cognition, however, a voiding diary may be difficult to complete and/or interpret. Additionally, they are not a substitute for more formal bladder function testing, especially in complex diagnoses such as MUI.

There is no standard for using certain questionnaires when evaluating patients with MUI, and there are numerous validated questionnaires for assessing urinary symptoms. However, patient questionnaires may serve as an adjunct to patient history and can help better elucidate symptoms. Particularly in patients with MUI, using a validated questionnaire may help the patient grade the severity of each component of UI in an objective way. They can also be used to track response to treatments. Pad tests are generally reserved for academic purposes only, as they are tedious and cumbersome to complete.

Cystourethroscopy. While cystourethroscopy is not necessary in index patients, it should be considered especially to rule out other conditions in at-risk patients. Older women presenting with microscopic or gross hematuria should always get a cystoscopy, as being over the age of 60 automatically makes them high risk according to the risks stratification in the American Urologic Association (AUA)/ Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) guidelines on microhematuria [34]. This risk stratification is based on the risk of malignancy which increases with increasing age, and therefore must be evaluated in the older patient population. Additionally, cystoscopy should be strongly considered in the patient who has a history of previous anti-incontinence surgery, pelvic radiation or prior prolapse repair.

Imaging. Similar to cystourethroscopy, upper tract imaging should be pursued in certain patients with UI, particularly those with chronic urinary retention, severe prolapse, any element of neurogenic lower urinary tract dysfunction, or in the setting of an evaluation for microscopic or gross hematuria. Again, older patients are, by definition, high-risk, therefore in the setting of microhematuria, cross-sectional upper tract imaging with delayed phase is recommended [34].

Urodynamic Studies. In the work-up of MUI, multi-channel UDS is the adjunct testing with the most potential utility. Due to multiple studies which have demonstrated a poor correlation between UDS diagnosis and symptom-based diagnosis for MUI, utilizing UDS to assess MUI should be strongly considered [24, 35, 36]. One purpose of UDS in the evaluation of MUI is to help determine which UI component is the most predominant, which can be difficult to ascertain on history alone. The relationship between SUI, UUI, and the UDS diagnosis of MUI has been investigated in several studies [37, 38]. The sensitivity and specificity of UDS in the diagnosis of SUI alone is 78% and 84%, respectively; for UUI, 61% and 95%; and for MUI 68% and 79% [37]. In a recent review of UDS findings in women with UI, in those with clinical symptoms suggestive of MUI, the clinical diagnosis was confirmed by UDS (patients exhibited both detrusor overactivity [DO] with leakage and leakage with Valsalva or cough) in only 21% [39]. The proportion of women who reported symptoms suggestive of DO with UI, who did not demonstrate DO/UUI on UDS was 46%. Finally, 10% of women with clinical symptoms of MUI had normal UDS findings. These studies demonstrate that UDS and clinical symptoms do not always correlate, and if UDS is obtained, it should be used in conjunction with clinical history in the diagnosis of MUI to answer a clinical question.

There is a paucity of literature on UDS outcomes specifically in older adults. One small retrospective cohort of 53 women over the age of 80 hypothesized that urinary symptoms and UDS findings would poorly correlate in older patients [40]. Authors found that UDS resulted in a complete change in patient management in 43% of patients and helped confirm the diagnosis prior to treatment in 52%. Again, there was poor correlation between UDS finding of DO/UUI and clinical UUI, with only 29% of those with clinical UUI exhibiting DO and UI on UDS. Finally, the authors found that in only 5% of patients UDS was deemed not clinically useful, as it matched perfectly with the clinician's working diagnosis from clinical symptoms and non-invasive testing alone. While this cohort is small, it suggests the benefit of UDS in older women for diagnosis and appropriate counseling of management options. Because of the poor correlation between clinical symptoms and UDS findings, and the implication for treatment/surgical outcomes depending on UDS findings, the AUA/SUFU guidelines recommend additional evaluations, such as UDS, in patients being considered for surgical intervention who have clinical symptoms of MUI [25].

Despite the diagnostic utility of UDS in women with MUI, the risks in older adult patients must also be considered. Several observational studies have demonstrated that older age is a predictive factor for urinary tract infection (UTI) following UDS [41, 42]. Therefore, the SUFU best practice policy statement on antibiotic prophylaxis prior to UDS testing recommends antibiotic prophylaxis for UDS studies in patients older than 70 years of age [42]. This is due to the increasing prevalence of bacteriuria with age, such that 23 to 50% of women over the age of 80 have bacteriuria [43]. The best practice policy statement does recognize that frailty is likely a better marker than numerical age, however, there are no studies specifically on frailty and UDS as of yet. The previously discussed study on frailty and TUGT demonstrated that women with recurrent UTIs had the longest TUGT times, indicating the highest proportion of frail patients in this population [32].

In conclusion, although UDS testing is safe and can be beneficial, there are increased risks with the older adult population that should be carefully considered. Additionally, invasive testing should only be performed under the circumstances of considering more invasive options for either the stress or urgency component, when there is a particular question to be answered, and when that answer may lead to different management or counseling.

3. Management

It is generally recommended to determine which component of MUI is more bothersome to the patient or more predominant, and to pursue treatment of this component first. However, as previously discussed, this can be quite challenging. Aside from just the diagnostic difficulties with MUI, deciding on a management strategy and counseling patients appropriately can also be complex. Many of the treatment strategies for one component of MUI may exacerbate or even worsen the other component, and there is no perfect solution to fix both UUI and SUI simultaneously.

Additionally, special considerations in older patients of risks and benefits of treatment are of utmost importance. It is important to remember and to discuss with patients that UI compromises QOL but generally does not affect survival, therefore pursuing no treatment is an acceptable management strategy after appropriate counseling and excluding other conditions and etiologies [33]. This is particularly important when considering treatment in the older adult patient with cognitive difficulties such that they would not be able to perceive symptomatic improvement with treatments. Considering mobility limitations contributing to UI is also important, as correcting UI will not correct the underlying factors associated with limited mobility, and therefore may not result in a benefit to the patient. One special population are those in whom skin breakdown from incontinence-associated dermatitis (IAD) is a major concern. This is painful and significantly impacts QOL, can be associated with secondary infections, pressure ulcers, and can require advanced levels of care and even hospitalization for wound management [44]. Therefore, pursuing more aggressive treatment in these patients may be necessary. Regardless of the situation, when dealing with frail and/or older adult patients, the decision to pursue treatment and the specific management strategies can be complicated, and all options, risks, and benefits should be discussed thoroughly with the patient and caregivers. Along these same lines, it is critically important to establish goals of treatment for MUI with all patients, but particularly in the older adult population. In pursuing treatment, what is the measure of success for that patient? This may be using fewer pads, dryness, enabling certain social activities, becoming more independent, avoiding polypharmacy, or avoiding invasive surgical options. Every older adult patient with MUI should be assessed for goals of care as an individual because the measure of success may be different for each person. Therefore, having this discussion prior to invasive treatments is critically important [45].

3.1 Conservative Treatment Options

3.1.1 Behavioral and Lifestyle Modifications

Behavioral and lifestyle modifications are first-line therapy options for both OAB/UUI and SUI, and therefore should be first-line for patients with MUI as well [25, 33]. This is especially relevant in the older adult population, as behavioral modifications have essentially no adverse effects, and can offer a significant benefit in symptoms and QOL. It is important for patients to understand that these improvements may be gradual, as interventions rely on learning new skills and changing long-term habits around toileting [46].

Basic lifestyle modifications for the management of UI include type and timing of fluid intake and daily exercise. In a randomized-controlled trial of community-dwelling Japanese women comparing multidimensional exercise twice weekly for 3 months to control, there was significant improvements in the exercise group in all types of UI, including 40% cure rate of MUI at 3 months

[47]. The sustained cure of UI in this trial at 7 months was significantly associated with body mass index reduction, which is consistent with other trials suggesting that weight loss programs can improve UI episodes [48]. Other modifications such as decreasing fluid intake prior to sleep and changing the timing of diuretic medications can also be considered depending on the individual patient. However, special care should be taken prior to recommending fluid restriction in older and/or frail women as a long-term management strategy for UI, as it places them at higher risk for dehydration and other medical issues. While we often consider such interventions to be beneficial regardless of age due to their safety profile, lifestyle modifications may be inappropriate or impractical for the frail and/or older adult. There are no trials to our knowledge specifically on older women and the benefits of such lifestyle modifications for MUI.

Behavioral modifications aim to teach certain skills or change habits around voiding with the goal of improving continence. These include scheduled or timed voiding, delayed voiding, double voiding, and pre-emptive voiding. Some behavioral modifications have been designed specifically for the frail and/or older adult patient who may have cognitive or physical impairments and these can be used as a mainstay of treatment for UI in the very frail [49]. For example, prompted voiding can be utilized for nursing-home residents or those with caretakers, which increases patient requests for voiding attempts and self-initiation of toileting, and is a form of pre-emptive voiding to decrease the number of UI episodes [49]. Pre-emptive voiding can be utilized in conjunction with a voiding diary to better target voiding habits. Timed voiding can help reinforce behaviors and establish better voiding patterns, again to establish pre-emptive voiding [50, 51]. It is important to remember than cognitive impairment or functional limitations may limit the utility or preclude the use of certain behavioral interventions and may require the by-in from caretakers or staff in the case of nursing home residents which can therefore limit long-term benefit. In nursing home residents or those who need assistance, prompted voiding techniques and/or "wet checks" can be used and combined with lifestyle interventions whenever able [49, 52]. The evidence behind various behavioral modifications is variable and limited, especially in the frail and/or older adult population. However due to the safety as compared to more invasive treatments, these conservative measures are recommended.

3.1.2 Pelvic Floor Muscle Training

Pelvic floor muscle training (PFMT) is another conservative measure recommended for the management of MUI. In a recent Cochrane database review, despite the differences in interventions and study populations, PFMT was deemed better than no treatment for the management of MUI with no serious adverse events [53]. The benefits of PFMT include reduction of UI episodes, decreased pad usage, and improvements in QOL, with cure rates up to nearly 30% and improvement rates up to 80%. While PFMT has not been studied extensively in the frail and/or older adult population, it should certainly be offered to those who have sufficient cognitive and physical function to participate. One retrospective study comparing bother from UI between premenopausal and postmenopausal women using PFMT found success of PFMT did not differ between the two groups [54]. Although the study did not delineate outcomes by type of UI, there were a significant number of women with MUI included, especially in the postmenopausal group (58%). Another recent study comparing group versus individual PFMT in over 360 women 60 years of age or older,

in whom over 80% had MUI, found median reduction in UI episodes was 70% at one year in both groups [55].

Pelvic floor muscle training can and should be combined with other behavioral and lifestyle modifications as able. A recent randomized controlled trial of PFMT plus weight training versus PFMT alone in elderly women, showed a cumulative benefit in preventing all UI episodes with the combined treatment [56]. The follow up in this small study was only 1 month, and therefore limited conclusions on long-term management of UI with this strategy can be drawn. It is also worth noting this type of strategy would only work in a very high functioning older adult patient, who is not frail. Therefore, based on the evidence supporting its benefit, supervised PFMT should be offered as first-line treatment of MUI in women of all ages who have the appropriate functional status to participate.

3.2 Medical Therapy

Medical therapy should be considered in the frail and/or older adult woman with UI only following a complete evaluation, and a trial of more conservative therapies. As previously stated, pharmacologic therapy is not beneficial and should not be used in those who do not make toileting attempts or in the severely cognitively and functionally impaired, such that there will be no perceived benefit.

3.2.1 Vaginal Estrogen Replacement

Estrogen has important effects on the female lower urinary tract, and its depletion after menopause has been implicated as the etiology for various genitourinary conditions, including UI. The outcomes on vaginal estrogen replacement on UI have been somewhat inconsistent. A Cochrane review on the effects of estrogen for the treatment of UI in postmenopausal women included 34 trials on both vaginal and systemic estrogen replacement therapy [57]. Systemic estrogens resulted in worse UI over placebo, and this is not a recommended treatment strategy specifically for UI. However, the use of vaginal estrogen therapy versus placebo resulted in a reduction in UI episodes (RR 0.74, 95% confidence interval [CI] 0.64 to 0.86). Additionally, there were improvements in frequency, urgency, and nocturia with the use of vaginal estrogen over placebo. The administration of vaginal estrogen appeared to be safe, with no serious adverse events, and the most common side effects being vaginal bleeding (occurring in about one in four women treated) and breast tenderness (occurring in about one in five women treated). The use of vaginal estrogen specifically in MUI has not been well studied. However, in the postmenopausal woman with MUI and evidence of vaginal atrophy on physical examination, we believe that it is worth discussing utilizing a vaginal estrogen replacement as it may offer some benefit for UI episodes and has a safer side-effect profile as compared to some more invasive pharmacologic and surgical treatments.

3.2.2 Pharmacologic Treatment

Pharmacologic therapy for MUI relies on treatment of the urgency-component of MUI with oral anticholinergic or beta-3 adrenoceptor agonist medications. More aggressively treating the urgency component of MUI may be beneficial as the urgency and UUI tends to be the more bothersome UI component if all else is equal, with UUI having a greater effect on QOL as compared to SUI [58, 59]

This is likely due to the unpredictable nature of urgency and UUI, which leads to a perceived decrease in control over one's bladder condition.

There are limited trials on the use of oral anticholinergic or beta-3 agonists specifically in patients with MUI. The Mixed Incontinence Effectiveness Research Investigating Tolterodine (MERIT) trial was the first double-blind randomized controlled trial looking specifically at the use of an anticholinergic in patients with MUI [60]. The trial included 854 women with MUI randomized to 8 weeks of tolterodine 4mg daily versus placebo. Authors found that significantly more women in the treatment arm believed their condition was improved at 8 weeks versus the placebo arm (76% versus 55%, $p < 0.001$), with a decrease in number of daily UUI episodes, increase in voided volumes, and decrease in frequency and urgency. There was no decrease in SUI episodes, indicating that adequately controlling the urgency component of MUI can result in a sufficient perception of improvement of the overall condition.

A subgroup analysis of a multicenter trial also on tolterodine compared 239 patients with MUI to 755 patients with UUI only [61]. After 16 weeks, there were similar reductions in overall UI episodes (67% in MUI versus 75% in UUI only), and a similar proportion of patients were dry (39% MUI versus 44% UUI). The authors concluded that the treatment of MUI with tolterodine in this cohort was nearly unaffected by the presence of a stress component. Another secondary analysis of 4 pooled randomized controlled trials on solifenacin in women with MUI revealed similar findings [62]. Women in the treatment arm had significant improvements in UI as compared to placebo after 12 weeks, with 74% in the treatment arm stating their treatment was satisfactory. Finally, a recent post-hoc analysis using pooled data from two randomized controlled trials on mirabegron in 261 women with MUI observed a significant decrease in mean daily voids, UI episodes, and improvements in QOL with treatment [63].

While several trials have revealed that MUI can respond to oral anticholinergic or beta-3 agonist medications, there must be significant caution taken in using these medications in the older adult population. There is surmounting evidence on the association between anticholinergic medications and the increased incidence of dementia [64-67]. As such, SUFU released several guidance statements in a white paper regarding the use of these medications, which states chronic use (over 3 months) of anticholinergic medications for OAB is associated with a 10 to 65% increased risk of new-onset dementia [68]. There are several observational studies on exposure to anticholinergics for OAB which are focused on older populations, all of which have demonstrated an increased risk of dementia with the medication use, several which showed this risk increases with increasing exposure in a dose-dependent fashion [69]. Additionally, it is recommended that when pharmacologic therapy is needed, a beta-3 agonist is preferred, or at least an extended-release formulation of trospium, darifenacin, or fesoterodine which have properties that are favorable to limit central nervous system effects as compared to other medications [68]. Finally, it is important for prescribing providers to remember that polypharmacy is common in the older and/or frail patients, which places them at higher risk for adverse drug events, including impaired cognition [70]. It also may be difficult for the patient to recognize themselves that there is an impairment or change in cognition with medication use, therefore it may be important for family and caregivers to also be involved as needed in the monitoring for the effects [71]. Although there is demonstrated benefit to using oral medications in MUI, when considering their use in the older and/or frail patient population, there should always be shared decision making between patients, providers, and caregivers on the risks and benefits, and to use the preferred agents to limit risk whenever possible.

3.3 Procedural and Surgical Treatments

Beyond pharmacologic and conservative treatments for UI, there are numerous other procedural and surgical treatment options. These are namely third-line therapies for the treatment of UUI/OAB and anti-incontinence surgeries for SUI. Aside from the caveats in treating MUI with these more invasive options, which we will discuss more in depth below, the increased risks of invasive interventions in the frail and/or older patient should always be carefully considered.

3.3.1 Urologic Interventions in the Frail

There has been increasing attention in the literature on outcomes of surgery, even minor procedures, in the frail, and the associations between frailty and increased morbidity from surgery. Several recent studies have looked specifically at outcomes of urologic interventions in the frail and/or older adult. In a retrospective cohort study on mortality and functional outcomes of minor urologic surgeries in nursing home residents aged 65 and older, overall 1-year mortality after surgery was 50% [72]. Additionally, study participants had a decline in functional status after surgery, which was most pronounced in the participants with the highest functional status preoperatively. Finally functional decline at 1 year after surgery was associated with a decline starting 6 months prior to surgery, older age over 85 years, and a baseline cognitive impairment. Despite undergoing what were considered minor urologic procedures, this study demonstrated the patients have a high 1-year mortality and may experience a sustained decline in functional status following surgery.

Additionally, data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) were used to evaluate the association between frailty and postoperative discharge destination after common urology procedures [73]. In this study, overall 5.5% of urologic procedures resulted in a discharge to a skilled or assisted living facility, and this number increased to 9.8% in those who were designated as frail pre-operatively according to the NSQIP Frailty Index. This literature demonstrating associations between frailty and morbidity and mortality following urologic interventions is critically important to consider when offering more advanced and invasive treatments in older and/or frail women with MUI, and can ultimately aid in patient counseling for shared decision making.

3.3.2 Third-Line Treatments for Overactive Bladder

The rationale for using third-line treatments for OAB in women with MUI is the same as that for treating the urgency-component using pharmacologic treatments for OAB. The AUA/SUFU guidelines on non-neurogenic OAB state that third-line treatments for OAB should be offered in patients who are refractory to behavioral and pharmacologic therapies [33]. However, when treating older patients who may have more barriers to using optimal conservative or medical therapy due to the aforementioned reasons, the provider should be more flexible in progressing to third-line treatments for the urgency-component of MUI as needed [74]. Additionally, there is evidence that frail patients respond well to third-line OAB therapies. A recent prospective study of 45 patients (both men and women) over the age of 60 found that the 40% of the cohort who were frail according to TUGT times had similar improvements in their OAB symptoms and bother scores on validated questionnaires as those who were not frail [75]. Below we will discuss specific third-line OAB therapies and outcomes in older patients with MUI.

Percutaneous Tibial Nerve Stimulation. Percutaneous tibial nerve stimulation (PTNS) is treatment option for OAB which may offer adequate control of the urgency associated with MUI which limited morbidity, as the procedure is typically well tolerated with few side effects. The pooled objective and subjective success rate of PTNS for OAB in a meta-analysis is about 60%, which is quite comparable to oral medical therapy [76]. The main downside to PTNS is that it requires frequent office visits for treatment with weekly sessions of 30 minutes each for 12 weeks and then monthly maintenance sessions. This travel may be quite onerous to the older patient, and the ability of the patient to comply with this rigorous treatment schedule can ultimately limit benefits. The efficacy of PTNS specifically in frail and/or older women is unknown due to the paucity of literature in this patient population.

Furthermore, the effect of PTNS on patients with MUI is unknown and essentially unmeasured in the literature. There are however a few trials assessing PTNS in combination with other treatments for MUI. In one randomized, single-blinded trial on 24 women with MUI on the effects of PFMT alone versus in combination with PTNS, authors observed a subjective improvement as measured by the Patient Global Impression of Improvement (PGI-I) with combination treatment, but no differences on validated questionnaires in OAB or incontinence symptoms between groups [77]. Another recent retrospective analysis on women with MUI comparing those treated with transobturator tape (TOT) sling versus TOT with PTNS found statistically significant improvements in UDS parameters in the combined treatment group, as well as symptomatic and QOL improvements on validated questionnaires [78]. While the benefits of PTNS for MUI specifically are not clear, the use of PTNS for MUI especially for older patients may be considered, especially with the minimal risks and morbidity of the treatment in the appropriate patient.

Intradetrusor OnabotulinumtoxA Injections. Intradetrusor onabotulinumtoxA (Botox) injections are an effective treatment for OAB and UUI with multiple randomized controlled trials demonstrating decrease in UI episodes, frequency, urgency, and improvement in QOL after treatment [33]. Once again, however, the data regarding Botox injections for the treatment specifically of MUI are quite scarce. One small retrospective cohort study comparing women with UUI only versus those with MUI getting 100 U Botox injections found that the women with MUI had a significantly lower incidence of urinary retention after Botox requiring catheterization, with similar improvement in UI, suggesting that Botox monotherapy can be effective in those with MUI and that the presence of a stress component may be somewhat protective against retention [79].

More recently, there are trials on using Botox in conjunction with other treatments for MUI. In a prospective, double-blind trial 78 women with MUI who were planning to undergo a mid-urethral sling (MUS) were randomized to concurrently receive 100U Botox injections intraoperatively during MUS surgery or not [80]. At 3 months, improvement in overall UI as assessed on PGI-I was not different between groups. Additionally, there were no differences on multiple validated questionnaires regarding symptomatic improvement in UI between groups, although the Botox group reported less urgency. There were also no differences in adverse outcomes including UTI and urinary retention. This suggests that there may not be much utility in Botox as an adjunct for treating MUI in this setting. The only trial on the use of Botox for treatment of MUI specifically in elderly women 65 years or older was a recent single-center observational study to assess the efficacy and safety of combining Botox injection (doses ranged from 50-200 U) and polyacrylamide hydrogel (PAHG, Bulkamid) injection into one surgical procedure [81]. Fifty-five women with a median age of

75 years old were included in the trial, and after 12 months, 76% were cured or improved of both SUI (assessed by cough test) and UUI (subjective). The rate of urinary retention requiring catheterization was 22% and the rate of UTI in 30 days was 13%. Despite these adverse events, authors concluded this demonstrates a safe and effective way to manage elderly women with MUI without the morbidity of general anesthesia. However, in this study the authors did not elaborate on the dose of Botox chosen and reported only 2 (4%) of patients received repeat Botox injections over 12 months, which is drastically lower than the reinjection rates in other studies to maintain an effect [82].

While there is some limited evidence to support the use of Botox in women with MUI, there are several considerations when considering its use in the frail and/or older population, mainly due to the specific risks associated with the therapy. The most common adverse events following Botox injections are urinary retention requiring intermittent self-catheterization and symptomatic UTI. It should also be kept in mind that there is a need for repeated treatments which could be burdensome to an older patient. A recent multi-center retrospective study by the SUFU Research Network on the adverse effects of 100 U Botox injections for idiopathic OAB in a cohort of 278 patients with a mean age of 65 years found the urinary retention rate (defined as the need to initiate catheterization or PVR volume over 300 mL) following injection in women to be as high as 17% [83]. Additionally, 24% of women had one or more UTI following injection. These rates of adverse events, especially for urinary retention, are much higher than the previously reported <10% retention rate in the ROSETTA trial [84]. Another study compared outcomes of frail elderly, elderly, and younger patients (including both men and women) getting 100 U Botox injections for idiopathic DO and UUI [85]. While improvements in Patient Perception of Bladder Condition (PPBC) were similar among all groups, PVR volume was higher and rate of recovery of spontaneous voiding following urinary retention was slower in the frail elderly patients as compared to the other two groups, which remained true on multivariable regression even after adjusting for age, gender and other factors. Yet another study demonstrated that the rate of UTIs after Botox injections to be significantly higher among older women over 65 years old [86]. Therefore, although there is a small body of evidence for using Botox as monotherapy or as an adjunct in MUI, due to these higher rates of adverse events, careful patient selection and appropriate counseling are important prior to utilizing Botox in this population, and Botox injection is likely not the optimal treatment in older women who would be unable to catheterize themselves or with baseline elevated PVRs.

Sacral Neuromodulation. In multiple trials, sacral neuromodulation (SNM) has been shown to be an effective third-line therapy for patients with OAB with or without UUI. In the most recent outcomes from the ROSETTA trial comparing 200 U Botox injection to SNM for idiopathic OAB, at 2 years both therapies were found to have similar sustained reduction in the primary outcome of UUI episodes [87]. While there are no trials to our knowledge on SNM usage specifically in patients with MUI, the benefits of treating the urgency component of MUI with this modality should be theoretically similar to other treatments discussed. There have been however, a few studies on the use of SNM in frail and/or older patients. In an observational cohort on the use of SNM for OAB/UUI in patients over 65 years old (with a mean age of 76 years old), at 12 months nearly 30% were improved and 56% had complete cure in terms of UUI episodes, with overall improvements in frequency, urgency, and nocturia [88]. Additionally, a few studies have compared outcomes of SNM by age, with inconsistent results. A prospective observational study compared outcomes between

younger (age 40-64) and older (65 years and older) patients (majority women-83%) who underwent SNM for all indications (OAB, interstitial cystitis, or urinary retention) and found there was no difference between the age groups in improvement of UI episodes or other urinary symptoms at 26 weeks post-implant [89]. In contrast, an older, similar study, found that efficacy following permanent implantation defined as complete dryness from OAB/UUI was achieved in only 17% of older patients as compared to 40% of younger patients [90].

One consideration on the use of SNM in older patients is potentially their ability to operate the device and change programs as needed [74]. However, today a growing number of older adults in the United States own and operate cell phones, computers, tablets, and other devices daily. A recent survey found that 61% of adults over the age of 65 in 2021 owned and operated a smart phone, which has increased dramatically from only 13% 10 years prior [91]. Therefore, the concern for an older patient's ability to operate the smart programmer for a SNM device should be evaluated on an individual basis. Additionally, a caregiver or family member would be able to operate the device if needed for an older patient. It is, however, important to consider the cognitive status of a patient prior to device implantation. While impaired cognition could certainly affect a patient's ability to make adjustments in therapy after permanent implantation, which may limit the efficacy of the device, more importantly it could affect the ability of the provider to assess the efficacy during trial phase if the patient is unable to clearly articulate improvements. However, a recent retrospective review on the use of SNM in people over 55 years old found that a pre-existing diagnosis of cognitive impairment was not a predictor in going on to final implantation of the device, suggesting cognitive impairment should not exclude the use of this therapy in older patients [92]. Finally, implantation of the device is also more invasive than other third-line OAB treatments, and the risk of undergoing even this minor surgical procedure in a frail patient should be considered carefully. Therefore, although there is limited evidence on the use of SNM for MUI in older adults, it may be an appropriate choice in carefully selected patients after discussion of the risks, benefits, and alternatives.

3.3.3 Surgical Management of Stress Urinary Incontinence

The role of surgical intervention for SUI in the patient with MUI should always be approached with appropriate caution, as these procedures may aggravate pre-existing OAB with or without UUI or lead to de-novo storage symptoms. Despite these concerns, there have also been several studies showing the benefit of the surgical management for patients with MUI.

Bulking Agent Injections. Urethral injection of bulking agents remains an attractive option for the management of the stress component of MUI which is less invasive and with less morbidity as compared to the surgical treatments discussed in the following section. For this reason, bulking agent injection can be considered in frail and/or older patients, as many of these procedures can be performed in an office setting without general anesthesia. There have been a multitude of bulking agents available over the years, with little data comparing between agents in terms of efficacy or complications. The newest agent, PAHG (Bulkamid), is distinct from prior agents as it is a homogenous non-particulate gel made of 97% water, and appears to have fewer adverse events such as foreign body reactions and material migrations/extrusions which were associated with the particulate agents [93].

As such, much of the recent literature has focused on the use of PAHG, and many of the trials on PAHG injection includes women both of an older age (over 60 years old) and/or with MUI, including some longer-term outcomes. A recent retrospective review reported outcomes of 216 consecutive patients treated with either PAHG or Macroplastique (polydimethylsiloxane macroparticles suspended within polyvinylpyrrolidone hydrogel) with a mean age of 66 years old and included 36% with MUI (including preoperative DO in 25%) [94]. At 12-month follow up, 70% of patients declared themselves "improved" or "very improved", and 33% were completely dry. Additionally, the recently published 7-year outcomes following PAHG injection included 31% of women with MUI in the cohort and demonstrated the durability of treatment [95]. A total of 388 women with a mean age of 66 years, and after 7 years, 67% were improved or cured, however 20% required a secondary procedure for persistent UI. Complication rates were quite low, with a 4% rate of UTI and <1% rate of urinary retention. This is the largest trial with the longest-term outcomes for PAHG injection and demonstrates the durability of the treatment.

While these studies do demonstrate efficacy, they do not separately report outcomes on women with MUI. However, the largest series to look specifically at the use of PAHG in women in MUI included 150 women with a mean age of 68 years old [96]. While follow up was quite short at only 3 months, there was significant improvement in both subjective UI and pad weights, and improvements in all domains of QOL. The adverse outcomes, however, were higher in this study, with a 13% UTI rate after injection. Urethral bulking agents have also been used in conjunction with other therapies for elderly women with MUI, including Botox, as previously discussed, in addition to after prior failed surgeries for SUI [81]. Injection of bulking agents offers an effective and durable option for the management of MUI, which may offer older women the benefit of less morbidity, however more data are really needed in this space.

Sub-Urethral Sling Surgery. Sub-urethral sling surgery, either synthetic MUS or autologous pubovaginal sling (PVS), is the gold standard surgical treatment for women with SUI [25]. There are numerous studies on the use of slings in women with MUI that have demonstrated efficacy, however, the main concern is that the urgency and UUI can persist or worsen after surgery. One retrospective study of 927 women undergoing either synthetic MUS or autologous PVS included 78% of women with MUI in the cohort [97]. In women with MUI, 71% had improvement of their storage symptoms following surgery, 3% had worsening symptoms, and 26% remained unchanged. Additionally, urinary symptoms and outcomes for MUI following sling surgery tend to change over time. In one study of long-term outcomes of TVT in women with MUI, UUI resolved in 60% initially after surgery, however by 8 years, the cure rates for UUI declined to only 30% [98]. Another retrospective review on storage symptoms after TVT in a cohort of patients with MUI, the UUI resolved in 63% at a follow-up of 50 months [99]. Additionally, 58% of patients who required anticholinergic medication for their MUI symptoms were able to stop these medications after sling surgery. One of the largest observational studies with the longest-term outcomes for patients with MUI following TVT included 1,113 women followed for 10 years [100]. By 38 months after surgery, 11% of women had worsening UUI.

Several studies have attempted to determine risk factors for storage symptoms following SUI surgery, as urgency and UUI are strong predictors of patient dissatisfaction and failure. Numerous preoperative factors of MUI including urodynamic DO [101], particularly high-pressure DO [102, 103], clinical OAB [101, 103-105], and anticholinergic medication use [105, 106] have all been

identified as independent risk factors for urgency and/or UUI following surgery for SUI in various studies. Sling surgery can also be combined with other therapies for the treatment of MUI, including Botox injections [80] and PTNS [78], which have been discussed in the previous sections. However, a recent randomized clinical trial combining PFMT with MUS for the management of MUI was less successful [107]. Authors found that after 3 months both patients treated with the combination of PFMT and MUS and those treated with MUS alone had significant improvement in UI without any significant difference between groups.

Therefore, although most studies report that women with MUI have lower cure rates than women with pure SUI, sling procedures are an effective treatment for women with MUI and the presence of mixed symptoms does not preclude the use of sling surgery. However, sling surgery should not be offered as a "cure" for MUI, and patients should not hold this expectation, as the initial benefits to the urgency component seems to diminish over time and results are quite variable across studies depending on patient populations, outcome measures, and pre-existing conditions. Finally, it is imperative to assess storage symptoms preoperatively and counsel patients appropriately on what to expect in terms of their urgency/UUI following surgery.

When considering performing sling surgery in frail and/or older women, there are several important additional concerns. Although there is quite a large body of literature on the outcomes of slings, comparatively there is really a paucity of data on how advanced age and frailty may affect outcomes, especially in MUI. In a prospective comparison of 460 women, of whom 157 (34%) were elderly, who underwent MUS surgery consecutively with 26 month follow up, despite MUI being more common (up to 30%) in the elderly population, the cure rates after surgery were similar between the elderly and younger groups [108]. However, older women were more likely to have significant perioperative morbidity associated with MUS surgery as compared to younger patients, including pulmonary embolism, cardiac arrhythmias, deep vein thromboses, and pneumonia. Similarly, a study from Sweden using a national database of over 5,000 women who underwent MUS surgery found that the subjective cure rate at one year was lowest for women over the age of 75 (64%) as compared to 88% in those 55 to 64 years old. However, the estimated age-related probability of SUI cure, improvement, and satisfaction were not different between age groups on multivariable regression analysis, suggesting other factors aside from age may play a more important role in cure and satisfaction [109]. Along the same lines, several recent studies have examined the effect of frailty in women undergoing sling surgery. One study used NSQIP data to assess the prevalence of frailty among women undergoing sling surgery and to determine the effect of frailty on 30-day postoperative outcomes [110]. Authors found about 10% of all women undergoing sling surgery qualified as frail, and frailty was associated with increased hospital length of stay, increased likelihood of hospital readmission 30 days after surgery, and longer operative times. Likewise, in a study using data from 54, 112 Medicare beneficiaries 65 years or older who underwent sling surgery, 5.2% were found to be moderately or severely frail according to the Claims-Based Frailty Index [111]. The adjusted relative risk of all 30-day complications increased steadily with increasing frailty, with a 57% complication rate in the severely frail patients. A similar pattern was seen with 1-year mortality, which increased to 11% in the moderately and severely frailty patients. Additionally, frailty was associated with a need for repeat procedures for persistent incontinence or iatrogenic obstruction. Therefore, while we can see there are far fewer slings being performed in this frail and/or older patient population, the increase in morbidity and complications is exponential.

Finally, when considering surgery in the frail and/or older patient which confers a significant risk, it is critically important to ensure the surgical intervention offers an improvement in QOL. In a prospective observational cohort of 67 women with SUI undergoing TVT to assess impact on QOL, 31% were over the age of 70 and were compared to the a younger cohort under the age of 70 [112]. The older group reported similar improvements in QOL across multiple domains after surgery at 22 months, however, the hospital length of stay was 6 days in the older group, which suggests a significant immediate postoperative morbidity in this group. Finally, a prospective controlled trial randomized 69 women over the age of 70 to undergo immediate TVT surgery for SUI versus delaying surgery for 6 months as a control group, and found that women who underwent immediate sling surgery had significant improvements in QOL and increased patient satisfaction as compared to those who did not have surgery [113].

The decision to undergo a sling surgery for MUI in a frail and/or older woman should not be taken lightly. While the evidence supports the use of slings for the treatment of MUI, there are increased risks and lower cure rates regardless of age in this population. Additionally, older, frail women have significantly more immediate morbidity following surgery, even if there may be an ultimate improvement in QOL in terms of UI. In the end, there should be shared decision making between patients, providers, and family and/or caregivers on the risks and benefits of pursuing more invasive interventions for MUI on an individual basis.

4. Conclusions

In conclusion, MUI is a condition which impacts a larger proportion of older women and is associated with a significant negative impact on overall QOL. Additionally, due to the multiple pathologies associated with MUI, the condition can be challenging to detect, diagnose, and treat. Diagnosis of MUI in older women should start with routine screening and specialty referral for advanced evaluation as needed. While the literature is quite limited, there are numerous treatment options available for MUI which range from observation to invasive surgery, each with its own risks and benefits, with many unique considerations in the older patient. A careful discussion of these risks, in addition to a thoughtful assessment of goals of care should take place prior to undergoing any treatments, whether conservative or more invasive. Additionally, providers may want to consider a formal assessment of frailty in the older population prior to invasive treatments, as there is emerging data on the morbidity associated with frailty when undergoing surgeries for UI.

Author Contributions

Both authors were involved in the conceptualization, design, data acquisitor for, writing, editing and finalization of this paper.

Competing Interests

The authors have declared that no competing interests exist.

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