EAU Guidelines on the diagnosis and management of female non-neurogenic lower urinary tract symptoms: Part I - Overactive bladder, Stress Urinary Incontinence and Mixed Urinary Incontinence

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Abstract

Context: Female lower urinary tract symptoms (FLUTS) are a common presentation in urological practice. Thus far, only a limited number of conditions within female LUTS have been included in the EAU guidelines compendium. The new non-neurogenic female LUTS guideline expands the remit of the guidelines to include these symptoms and conditions.
Objective: This review articles summarises the diagnostic section of the non-neurogenic female LUTS guideline, as well as the management of female overactive bladder (OAB), stress urinary incontinence (SUI) and mixed urinary incontinence (MUI).
Evidence Acquisition: New literature searches were carried out, dated September 2021, and evidence synthesis conducted using modified GRADE criteria as outlined for all EAU guidelines. A new systematic review (SR)on OAB was carried out by the panel for purposes of this guideline.
Evidence Synthesis: The important considerations for informing guideline recommendations have been presented, along with a summary of all the guideline recommendations.
Conclusions: Non-neurogenic female LUTS are an important cause of urological dysfunction. The initial evaluation, diagnosis and management should be carried out in a structured and logical fashion based on best available evidence. This guideline serves to present this evidence to health care providers (HCP's) in an easily accessible and digestible format.
Patient Summary: In this report we summarise the main recommendations from the EAU non-neurogenic female LUTS guideline, which relates to symptoms and diseases of the female lower urinary tract (bladder and urethra). We cover recommendations related to diagnosis of these conditions, as well as the treatment of overactive bladder, stress urinary incontinence and mixed urinary incontinence.

1. Introduction

The EAU guidelines on non-neurogenic female lower urinary tract symptoms (FLUTS) has evolved from the previous guidelines on urinary incontinence (UI) [1], to incorporate the wider gamut of lower urinary tract symptoms affecting women that were previously not considered in the EAU guidelines compendium. The wider scope of the subject area has resulted in a re-structuring of the guidelines, that are now presented in a condition-based format.

Here we present a precis of the current version of these guidelines [2], specifically focusing on the sections relating to diagnostics, overactive bladder (OAB), stress urinary incontinence (SUI) and mixed urinary incontinence (MUI). The remaining topic areas will be covered in Part 2 of this publication. Information on epidemiology is not presented here, rather we consider the patient pathway from presentation through diagnostics, to the management of the specific symptom complexes. The best available evidence is summarised and the main recommendations from the full version of the guidelines presented in a concise and easily digestible format.

2. Evidence acquisition and methods

Due to the expansion of the scope of these guidelines, a new literature search was carried out with expanded terminology and criteria. The full details of the search strategy may be found online at https://uroweb.org/wp-content/uploads/2021-EAU-Non-neurogenic-Female-LUTS-Guidelines-Search-Strategy.pdf

The EAU Guidelines Office uses a modified GRADE approach to evaluate the relevant literature pertaining to each topic area. High quality systematic reviews (SR)s are referred, where available, and lower quality evidence evaluated where these are not available. For this guideline edition, new SRs on OAB and female bladder outlet obstruction (BOO) were carried out by the panel.

Evidence summary statements and assessment of the quality of available evidence is reinforced by certainty ratings (from very low to high). Recommendations are then produced based on these certainty ratings, benefit-to-harm balance as well as consideration of patient values and preferences, where feasible, to give an overall recommendation with a strength rating of ‘strong’ or ‘weak’. It must be noted that the balance between ‘strong’ and ‘weak’ recommendations relates to these three factors rather than purely the evidence base of the intervention. Our Panel recommendations are reinforced by the inclusion of patient representatives as part of the Panel, who provide valuable input into the discussion around ‘patient values and preferences’.

3. Evidence synthesis

3.1 Diagnostics

3.1.1 History and physical examination

The value of a thorough medical history and physical examination remains undisputed despite the lack of high-level evidence to support it, which is reflected in the Panel's strong recommendation. History of non-neurogenic FLUTS should include an attempt to differentiate and quantify storage, voiding and post-micturition symptoms, as well as sexual, gastro-intestinal and neurological symptoms. Urinary incontinence should be classified as urgency urinary incontinence (UUI), SU), MUI (detailing the most bothersome component) or other forms of UI, such as overflow or continuous UI. Any red flag symptoms should be elicited in all patients (pain, haematuria, neurological symptoms or associated dysfunction, previous pelvic surgery or radiotherapy). Smoking status, co-morbidities and body mass index should also be recorded.

Clinical examination should include abdominal and genito-urinary examination to assess for any palpable masses, pelvic floor muscle (PFM) tone and function, cough stress test for SUI, and vaginal oestrogenisation. A basic assessment for any pelvic organ prolapse (POP) should also be carried out.

3.1.2 Patient questionnaires

In general, questionnaires should be validated for the language in which they are being used and demonstrated to be sensitive to change [3]. The International consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms (ICIQ-FLUTS), Questionnaire for Urinary Incontinence Diagnosis (QUID), 3 Incontinence Questions (3IQ) and ICIQ-short form (ICIQ-SF) have potential to discriminate UI types in women [4-6]. The OAB-SF and B-SAQ have been developed to measure symptoms and bother in OAB. There is no evidence to indicate whether use of quality of life (QoL) or condition-specific questionnaires has an impact on outcome of treatment. The recommendation on use of questionnaires has been upgraded to 'strong' based on panel consensus.

3.1.3 Bladder diaries

The panel advocates consistent use of terminology in studies evaluating the tools variably described as micturition diary, frequency volume chart, bladder diary and voiding diary. Consensus terminology is now well-defined and should be widely accepted [7,8]. Moderate quality observational studies have demonstrated that bladder diaries have satisfactory reproducibility [9,10], feasibility, reliability, and validity [11,12], and even therapeutic benefit [13]. The optimum diary duration appears to be guided by a balance between accuracy and compliance, with durations between three to seven days routinely reported in the literature.

3.1.4 Urinalysis and urinary tract infections (UTI)s

UTIs are a common cause of FLUTS and pre-existing symptoms of FLUTS may be exacerbated by a UTI [14]. Urinalysis negative for nitrites and leucocyte esterase may

exclude bacteriuria in women [15], and treatment of asymptomatic bacteriuria was not shown to be beneficial in the elderly [16].

3.1.5 Post-void residual volume (PVR)

There does not seem to be any consensus on what constitutes a significant PVR in women without neurological disease, and most studies investigating the topic assess mixed populations. The panel therefore suggests the additional use of bladder voiding efficiency (BVE), where BVE = (voided volume (VV)/[VV]+PVR) × 100 [17]. The recommendations on PVR have been upgraded based on the potential harms possible where high PVR associated with UTI, upper tract dilatation and renal insufficiency is missed.

3.1.6 Urodynamics

The utility of urodynamics in the diagnostic workup of FLUTS is still unclear. Most of the evidence comes from observational studies, but a Cochrane review [18], SR and meta-analysis [19] and an randomised controlled trial (RCT) [20] have addressed the question in relation to SUI. Overall, pre-operative urodynamics made no difference to cure rates or complication rates.

The presence of pre-operative detrusor overactivity (DO) did not predict overall treatment failure following surgery for SUI [21], nor did DO have any predictive value for treatment response in studies on fesoterodine, onabotulinum toxin or sacral nerve stimulation for OAB symptoms [22-25].

Although pressure-flow studies are capable of discriminating BOO from detrusor underactivity (DU) as a cause of voiding dysfunction, *post-hoc* analysis of two high-quality surgical trials of tension-free vaginal tape (TVT), Burch colposuspension and autologous fascial sling, showed that no preoperative urodynamic parameter predicted postoperative voiding dysfunction in a selected population of women with low preoperative PVR volume [26,27].

There is no consistent correlation between the results of urethral function tests (e.g. urethral pressure profilometry) and subsequent success or failure of SUI surgery [21,28].

The recommendations on urodynamics have been formulated taking into consideration the inconsistency in the evidence on their predictive value, while recognising their utility in cases of diagnostic difficulty.

3.1.7 Pad testing

Two SRs have assessed the utility of pad testing for UI [29,30]. They have been shown to have high diagnostic accuracy, but variation in standardisation of parameters used (bladder volume and degree of provocation) reduces their utility in daily clinical practice. Tests of shorter duration and standardised exercise protocols have higher specificity but lower sensitivity, whereas tests of longer duration are more reproducible and sensitive, but standardising activity levels remains difficult. They may, therefore, be more useful in the research setting than in routine practice.

3.1.8 Imaging

In cases of suspected LUTS/UI caused by an upper urinary tract (UUT) anomaly or uretero-vaginal fistula, UUT imaging (intravenous urography or computed tomography) may be indicated [31].

Ultrasonography can be used to assess PFMs and their function, where indicated.

No consensus exists as to the relationship between OAB and increased bladder wall thickness (BWT) or detrusor wall thickness (DWT) [32], and there is no evidence that BWT/DWT imaging improves management of OAB. DWT was also not associated with any urodynamic parameters that may indicate BOO [33].

There is a large variation in magnetic resonance imaging (MRI)interpretation between observers [34] and little evidence to support its clinical usefulness in the management of LUTS/UI in general, although its utility for diagnosing urethral diverticula is recognised.

In general, there is no indication to carry out imaging investigations in the basic evaluation of FLUTS. The imaging component of video urodynamics is a special case, where the additional anatomical information obtained may be beneficial. Specific instances where imaging modalities add value will be discussed in the relevant disease sections.

Recommendations for the overall diagnosis of LUTS are provided in Table 1.

Please insert Table 1 here

BVE = bladder volume efficiency; ICS = International Continence Society; LUT(S) = lower urinary tract (symptoms); OAB = overactive bladder; PVR = post-void residual; SUI = stress urinary incontinence; UI = urinary incontinence; UTI = urinary tract infection; UUT = upper urinary tract.

3.2 Overactive Bladder

Overactive bladder is defined by the International Continence Society (ICS) as “urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of UTI or other obvious pathology” [35]. It is generally classified into wet and dry, based on the presence or absence of associated UI. As outlined in the diagnostics section, a thorough baseline assessment should be carried out to classify the type and severity of symptoms, elicit any signs of UI, associated POP, concomitant UTI, current anticholinergic burden, associated neurological dysfunction or genito-urinary symptoms of menopause.

3.2.1 Conservative management

Medication adjustment and containment:

There is no evidence to suggest that improving any comorbid medical condition improves OAB symptoms, although it is recommended practice to review any new medication that is associated with the development or worsening of OAB symptoms. Of the containment devices, pads have been shown to offer effective control of leakage [36] and indwelling or clean-intermittent catheterisation are also useful in select patients [37, 38].

Caffeine reduction:
A recent review of fourteen interventional and twelve observational studies reported that reduction in caffeine intake may reduce symptoms of urgency, but the certainty of evidence was low, with significant heterogeneity [39].

Modification of fluid intake:
One RCT showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI [40]. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving anticholinergics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [41].

Weight loss:
There is evidence that the prevalence of both UUI and SUI increases proportionately with body mass index [42], but this evidence base relates largely to SUI.

Smoking cessation:
The effect of smoking cessation on LUTS was described as uncertain in a health technology assessment review [43].

Behavioural and physical therapies:
Two SRs [44, 45] confirmed a positive effect on continence for prompted voiding in comparison to standard care [45]. Three SRs on the effect of bladder training (BT) compared to standard care confirmed that BT is more effective than no treatment in improving UUI [46, 43, 47]. A SR of 11 RCTs [48] in women with OAB compared the efficacy of pelvic floor muscle training (PFMT) vs inactive control, usual care, other lifestyle modification or other intervention. PFMT significantly reduced OAB symptoms (frequency and UUI) in five RCTs, while the remaining six reported no significant difference. Substantial heterogeneity in protocols precluded meaningful comparisons.

The results of studies of percutaneous tibial nerve stimulation (PTNS) in women with refractory UUI are consistent, showing that PTNS improves UUI in women without adequate improvement with, or who cannot tolerate, anti-muscarinic therapy [49, 50]. A SR commissioned by this panel (currently pre-publication) has found that PTNS techniques were more effective than antimuscarinics in reduction of UUI episodes (MD -0.67, 95% CI -1.31 to -0.02, p = 0.04, CoE is low) with no significant difference in reduction of mean symptoms score, frequency episodes, or urgency episodes.

3.2.2 Pharmacological management

Anticholinergic (antimuscarinic) drugs are currently the first-line pharmacological treatment for OAB, however the evaluation of cure or improvement of OAB is made harder by the lack of standard definitions. In general, SRs note that the overall treatment effect of drugs is usually small but larger than that of placebo (Table 2). A network meta-analysis of 128 RCTs comparing anticholinergics with placebo or other anticholinergics revealed that all anticholinergics, except imidafenacin, showed significant cure or improvement in OAB symptoms [51]. There is limited evidence that patients who do not respond to first-line anticholinergic treatment respond to a higher dose or a different anticholinergic agent [52, 53].

Please insert table 2 here

CI = confidence interval; IR = immediate release; NNT = number to treat; RR = relative risk; UI = urinary incontinence.

No single anticholinergic has been shown to have superior cure, improvement or QoL characteristics compared to others.

Three SRs assessing the clinical effectiveness of mirabegron [54, 55, 56] reported that mirabegron at doses of 25, 50 and 100 mg per day results in significantly greater reduction in UI episodes, urgency episodes and micturition frequency than placebo, with no difference in the rate of common adverse events [55]. One SR showed that mirabegron is as efficacious as most anticholinergics in reducing UUI episodes [57]. The most common adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%), with the overall rate similar to placebo. An RCT in patients who had inadequate response to solifenacin monotherapy 5 mg demonstrated that combination treatment with mirabegron 50 mg had a higher chance of achieving clinically meaningful improvement in UI as compared to dose escalation of solifenacin [58].

Two SRs of largely retrospective cohort studies showed a consistent association between long-term anticholinergic use and cognitive dysfunction [59, 60].

The association of LUTS with genitourinary syndrome of menopause (GSM) should be considered [61]. GSM is a new term that describes various menopausal symptoms and signs associated with physical changes of the vulva, vagina and LUT. These include mucosal pallor/erythema, loss of vaginal rugae, tissue fragility/fissures, vaginal petechiae, urethral mucosal prolapse, introital retraction and vaginal dryness. Evidence from a SR suggests benefit from vaginal oestrogen therapy in GSM [62].

3.2.3 Surgical management

Bladder wall injection of botulinum toxin A:

Data from a SR [63, 64] have shown that onabotA injections are more effective than antimuscarinics for cure of UUI (27% vs 13%), while resulting in higher rates of urinary retention (5% vs 0) and UTI (33% vs 13%).

Sacral nerve stimulation (SNS):
A 2018 review of trials including SNS with ≥ 6 months follow-up reported cure rates of 43–56% [65]. Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33–41% [66, 67]. A large RCT has reported similar efficacy between SNS and onabotA injections at two years, although satisfaction rates and treatment endorsement was higher with onabotA [68].

Augmentation/clam cystoplasty:
The evidence is of low quality and from mixed populations (including neurogenic DO), reporting about 58% continence and satisfaction rates at five years [69]. The risk of malignant transformation remains very low and almost exclusively occurs beyond ten years from the original cystoplasty [70].

Recommendation for the management of OAB are provided in Table 3.

Please insert table 3 here.

BT = bladder training; CISC = clean intermittent self catheterisation; ER = extended release; LUT(S) = lower urinary tract (symptoms); OAB = overactive bladder; PFMT = pelvic floor muscle training; PTNS = percutaneous tibial nerve stimulation; SNS = sacral nerve stimulation; UI = urinary incontinence; UTI = urinary tract infection; UUI = urge urinary incontinence.

3.3 Stress Urinary Incontinence

SUI is defined as involuntary loss of urine on effort or physical exertion. Broadly, it can be classified as uncomplicated or complicated SUI. Complicated SUI refers to SUI associated with previous surgery for incontinence or extensive pelvic surgery; history of pelvic irradiation; presence of anterior or apical POP; presence of voiding symptoms or neurogenic LUT dysfunction; or significant associated OAB/ UUI. Uncomplicated SUI occurs in the absence of these associated factors, but in cases where additional significant storage symptoms, especially OAB are present, a possible diagnosis of MUI should be considered.

The Panel recognises the role of urodynamics in evaluation of SUI and has incorporated a separate recommendation for these cases, as follows (Table 4):

Please insert table 4 here.

POP = pelvic organ prolapse; SUI = stress urinary incontinence.

3.3.1 Conservative management

Evidence from SRs and RCTs suggest that weight loss improves UI in obese women. A Cochrane SR compared PFMT with no treatment or inactive control treatment and found that women with SUI in the PFMT groups were eight times more likely to report cure (56% vs. 6%) [71].

3.3.2 Pharmacological management

Oestrogen therapy:
A Cochrane SR looked at the use of oestrogen therapy in postmenopausal women with 17 studies focusing on SUI [71] and reporting improvement in the short term. Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams.

Duloxetine:
A SR showed significant efficacy for duloxetine compared to placebo in women with SUI, but with increased risk of adverse events [73].

3.3.3 Surgical management

Concerns around the use of polypropylene mesh are legitimate and legislation surrounding its use varies between countries in Europe. The ESTER SR and network meta-analysis [74] is a high-quality review comparing the different surgical modalities for treatment of SUI. Individual rankograms for all surgical interventions were created, which give probabilities of an intervention being ranked 1 (the highest) to 9 (the lowest) for each outcome. A Surface Under the Cumulative Ranking (SUCRA) score is then given, which is a numerical representation of the overall ranking and presents a single number associated with each intervention. We report this figure for each intervention for comparative purposes (Table 5), while acknowledging the ESTER review is limited by only reporting a follow-up of one year.

Please insert Table 5 here.

MUS = mid urethral sling

Other considerations:

A Cochrane SR [75] on open colposuspension reported 70% subjective cure at five years. A sub-analysis from this review reported better effectiveness for autologous fascial slings compared to open colposuspension at one to five years.

Bulking agents were not included as a comparator in ESTER. A SR of 23 studies using Macroplastique© showed a 75% improvement with 43% dry rate at <6 months and a 64% improvement and 36% cure rate at >18 months [76]. In a more recent RCT comparing TVT to Bulkamid® the objective cure rates were 95% vs 64% [77].

A long-term cohort study of retropubic TVT showed an 89.9% objective cure rate and a 76.1% subjective cure rate at ten years. Overall, 82.6% of patients reported high satisfaction with surgery [78]. However, another ten-year follow-up study from an RCT reported 31.7% dry rate following TVT, and 50.8% following autologous fascial sling (AFS) [79]. A long-term prospective study on transobturator sling showed that, at 145 months, the objective and subjective cure rates were 78.9% and 62.6% respectively; with no significant deterioration in SUI cure rates over time [80].

The retropubic approach for MUS was associated with a significantly higher rate of bladder perforation than transobturator MUS (5% vs 0.2%), but groin pain was more frequent after transobturator MUS than retropubic MUS (6.3% vs 1.3%). The rate of tape/mesh exposure or extrusion between retropubic and transobturator MUS was similar (2.1% vs 2.4%; OR: 1.10) [73].

Adjustable compression device (ACT®) and artificial urinary sphincter (AUS) are used in selected patients in some countries but lack high quality studies to support their use. Other surgical modalities, such as Vesair® intravesical pressure-attenuating balloon, should only be offered as part of a well-regulated research trial.

Shared Decision-Making:

The panel recognise that a shared decision-making approach is paramount when any treatments are proposed but felt particular emphasis should be made for the topic area of surgical treatment for SUI. There are a number of different options available for patients which vary in both efficacy and safety profile. Consequently, the amount of information given to patients considering surgery for SUI is substantial. The panel would unequivocally advise adherence to the fundamental principles of the shared decision-making process which include:

- full participation from the patient
- delivery of factual information regarding benefits and risks of any particular treatment, if possible, adapted to the specific situation of the patient
- delivery of information about the experience and expertise of the HCP/ institution delivering the treatment, especially for highly-specialised procedures such as complex SUI and mesh removal surgery
- confirmation that the patient understands the information given
- clinician understanding and documenting individual patient preferences
- patient opportunity to consider and confirm any decisions made
- clinician assistance with implementation of the final decision

Recommendations for the management of SUI are provided in Table 6.

Please insert Table 6 here

ES = electrical stimulation; LUT(S) = lower urinary tract (symptoms); MUI = mixed urinary incontinence; PFMT = pelvic floor muscle training; SUI = stress urinary incontinence

3.4 Mixed Urinary Incontinence

The term MUI may refer to equal stress and urgency symptoms, stress-predominant symptoms, urgency-predominant symptoms, urodynamic stress urinary incontinence (USUI or USI) with DO or USUI with clinical urgency symptoms, but no DO [81]. The challenge of this broad definition is that it leads to inconsistencies when evaluating treatment options and outcomes

The role of urodynamics in MUI is unclear but establishing objective degrees of SUI and DO incontinence may help in counselling patients about the most appropriate initial treatment option.

3.4.1 Conservative management

PFMT appears less effective for MUI than for SUI alone, and the addition of BT may provide additional benefit [82].

3.4.2 Pharmacological management

Tolterodine and Solifenacin have been assessed in RCTs in MUI patients, with results showing improvement of the UUI component [83, 84, 85]. Duloxetine has also shown efficacy in improving incontinence and QoL in all MUI sub-groups in an RCT vs placebo [86]. However adverse event rates were high at 61.3% and the discontinuation rate was 15.7%.

3.4.3 Surgical management

Few RCTs on surgical management of SUI report separate outcomes for MUI subgroups. Post-hoc analyses show poorer results for participants with pre-operative urgency or DO, but these results are conflicting [87, 88]. In a study of 1113 women treated with transobturator TVT, SUI was cured equally in stress- or urgency-predominant MUI. However, women with stress-predominant MUI had significantly better overall outcomes than women with urgency-predominant MUI [89].

In contrast to studies examining older surgical methods, more recent studies (generally small case series) have reported that UUI symptoms improve in 30–85% of women with MUI after MUS surgery [90].

Recommendations for the diagnosis and management are provided in Table 7.

Please insert Table 7 here.

BT = bladder training; PFMT = pelvic floor muscle training; MUI = mixed urinary incontinence; UI = urinary incontinence.

4 Conclusion

Non-neurogenic FLUTS encompass a broad subject area, much of which has not been previously covered in the EAU guidelines compendium. This article provides an overview of the management pathway from general diagnostics in FLUTS, through to treatment of OAB, SUI and MUI. A related article will similarly outline the management of underactive bladder, female BOO, nocturia, POP relating to LUTS, urinary fistula and urethral diverticulum.

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