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REVIEW

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Open questions on lower urinary tract infections: Results of a Delphi consensus study

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Abstract

Background and Objective: This is a Delphi study that aims to explore expert consensus regarding open questions in current literature evidence on lower urinary tract infections (UTIs). This manuscript deals with adults and analyzed the most recent guidelines and meta-analysis on the topic.

Methods: A panel of leading urologists and urogynaecologists participated in a consensus-forming project using a Delphi method to reach consensus on gray zone issues on recurrent lower UTIns (rUTIs), asymptomatic bacteriuria (AB) in pregnant women, and catheter-associated UTIs (CAUTI) in adults. All the panelists were invited to participate the four phases consensus. Consensus was defined as ≥75% agreement. An ordinal scale (0–10) was used. A systematic literature review was analyzed for diagnostic workup and prevention of rUTIs, AB, and CAUTI.

Results: In total, 37 experts participated. All panelists participated in the four phases of the consensus process. Consensus was reached if ≥75% of the experts agreed on the proposed topic. Online meetings and a face-to-face consensus meeting was held in Milan in March 2023. Formal consensus was achieved for 12/13 items.

Conclusions: This manuscript is a Delphi survey of experts that showed interest on some debated points on rUTIs, AB in pregnancy, and prevention of CAUTI. There is still little data on nonantibiotic prevention of UTIs and CAUTI; quite old studies have been reported on AB in pregnancy. The emerging problem of antibiotic resistance is relevant and nonantibiotic prophylaxis may play a role in its prevention.

KEYWORDS
asymptomatic bacteriuria, catheter-associated urinary tract infections, lower urinary tract infections, urinary tract infections

1 | INTRODUCTION

Recurrent cystitis is defined as recurrences of uncomplicated and/or complicated cystitis, with a frequency of at least three episodes/year or two episodes in the last 6 months.[1] Recurrent UTIs negatively impact patient quality of life.[1,2]

In accordance with American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) guidelines on recurrent uncomplicated urinary tract infections (rUTIs) guidelines, in this study, the term UTI will refer to acute bacterial cystitis unless otherwise specified.[2]

Some open questions regarding asymptomatic bacteriuria (AB) in pregnancy and prevention of intermittent urethral catheterization (IC) infections have been explored.

A panel of experts analyzed the most recent guidelines[1–12] and 1a level of evidence papers on these topics with the aim to propose an answer to these gray zone urologic questions.

2 | MATERIALS AND METHODS

This paper followed Delphi consensus methodology.[13,14] A comprehensive literature review was performed as the initial step of the process. A panel of experts ($n = 37$) was assembled based on clinical and research expertise in UTIs and cystitis or as "opinion leaders" in this field. The panelists were urologists and urogynaecologists skilled in functional urology, neuro-urology, and urogynecology. The consensus was developed in four phases and all the panelists actively took part in this process.

A preliminary set of items was identified and discussed internally among the opinion leaders A final list of 13 points was created and finalized for an online survey. Items were chosen to identify open questions in the field of diagnosis and prevention of recurrent cystitis, rUTIs, IC infections, and AB in pregnant women.

Phase 1 was initiated in January 2022 with an online survey that was distributed to participants to discuss the different questions. Ten foundation questions pertained to the diagnosis and prevention of recurrent cystitis, three questions were selected for prevention in intermittent catheterization, screening and treatment of AB in pregnancy and prevention of antibiotic resistance respectively.

In Phase 2, an online meeting took place in February 2022. At the meeting, evidence from literature was presented and discussed in relation to each point of the survey. After each presentation, participants discussed the evidence and determined potential practice indicators. A practice indicator was defined as an actionable item that a health care professional would enact and/or recommend.

In Phase 3, a follow-up online survey was sent in November 2022. All the panelists were asked to rate the indicators on a 1–10 scale based on the following: (1) Potential for improvement in clinical practices; (2) impact on patient outcomes; and (3) feasibility of abstracting the data.

In Phase 4, an in-person meeting took place in Milan during the annual European Association of Urology congress in Milan (March 2023). Final consensus of the items was determined at this concluding meeting. Consensus was considered to be reached if ≥75% of the experts agreed on recommendations.[13]

The panel group was asked to review and discuss evidence obtained from literature on open questions in recurrent cystitis, AB and intermittent catheterization where international guidelines or 1a level of evidence papers do not give strong recommendations. A systematic literature search in the PubMed, EMBASE, Cochrane databases on diagnosis and prevention of recurrent cystitis, AB in pregnancy and intermittent catheterization in adults published from 2017 to March 2022 (5 years) and international guidelines (always considering the last updated version). Guidelines considered were: 2022 EAU,[1] 2022 the AUA/CUA/SUFU,[2] the UK National Institute for Health and Care Excellence (NICE) 2018 and 2023,[3,4] the Society of Obstetricians and Gynaecologists of Canada (SOGC),[5] the American Academy of Family Physicians (AAFP),[6] the Mexican College of Gynaecology and Obstetrics Specialists (COMEGO),[7] the Swiss Society of Gynaecology and Obstetrics (SSGO),[8] the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC),[9] and the Association of Scientific Medical Societies in Germany (AWMF).[10,11] The guideline of guidelines by Kwok et al.[12] has been also considered in this review.

The literature research was performed in several rounds. The MeSH terms used were cystitis, recurrent cystitis, asymptomatic bacteriuria, intermittent catheterization, diagnosis, prevention, prophylaxis, adult. Each combination search used the Boolean operators "or" and "and" when needed. Results were limited to English language. The international guidelines were hand searched to identify additional reports. The functional terminology used for the research was in accordance with the standardization one on the lower urinary tract promoted by the International Continence Society (ICS).[15] All the selected papers were screened for eligibility in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[16] Four authors

independently extracted the items from eligible reports and discussed any discrepancies. Levels of evidence were those according to the 2011 Oxford center of evidence-based medicine (http://www.cebm.net/explanation-2011-ocebm-levels-evidence)[17] or those expressed in the AUA/CUA/SUFU guideline.[2]

The final recommendations were approved by the unanimous consensus of the panel, expressed as expert opinions, and compared with the best practices recommendations available in the literature. The consensus panel met and discussed the outcomes of all these studies with the following aims:

1) analyze the current evidence on diagnosis and prevention in recurrent cystitis, AB in pregnancy and intermittent catheterization in adults to better face some items in a low recommendation "gray area,"
2) advance a "best practice recommendation" or expert opinions to counteract the occurrence of challenging clinical infections and suggest helpful methods to avoid them.

3 | RESULTS

Four authors identified 47 papers. Twenty-two papers fulfilled the inclusion criteria. One article was added by hand search as a guideline of guidelines outside the literature search.

The systematic search for evidence included 11 guidelines and 10 systematic reviews and meta-analysis published on indexed international journals. The panelists depicted the state of the art of "open questions" and gray areas in the fields of diagnosis and prevention of recurrent cystitis, AB in pregnancy, and intermittent catheterization in adults. The flow diagram is shown in Figure 1.

The survey items and level of consensus achieved are schematized in Table 1.

Results for each item are reported systematically as follows subdivided in three categories as follows: (1) recurrent cystitis; (2) AB in pregnancy; (3) intermittent catheterization.

3.1 | Recurrent cystitis/UTIs

Eleven items of this consensus were focused on different debated aspects of diagnosis and prevention in patients with recurrent cystitis.

Consensus has been reached for all the 11 points as specified as follows.

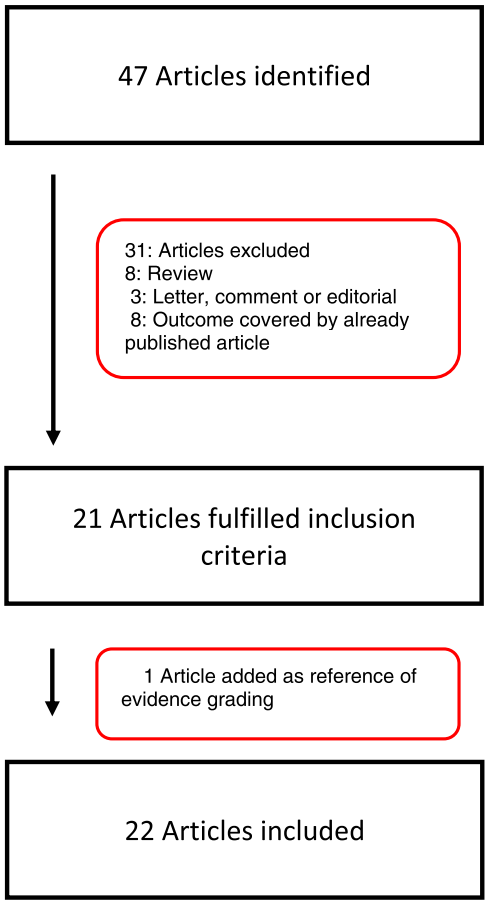

FIGURE 1 Flow diagram of systematic search for evidence with regard to studies stratifying the results.

3.1.1 | The diagnostic workup of a patient with rUTI should include a cystoscopy and/or a urinary tract imaging

Once diagnosed with urine culture, patients with rUTIs should be investigated for the presence of risk factors either in young and premenopausal women (sexual life, a mother with a history of UTI, history of UTI during childhood, blood group antigen secretory status), and in postmenopausal women (history of UTI before menopause, urinary incontinence, atrophy, pelvic organ prolapse, dysfunctional urination).[1] However, following the EAU, cystoscopy and/or urinary tract imaging should be performed in atypical cases (renal calculi, outflow obstruction, interstitial cystitis, or suspected urothelial cancer).[1] A physical examination including an abdominal and detailed pelvic examination should be performed to look for any structural or functional abnormalities.[2]

With a low level of evidence, the EAU guidelines report cystoscopy and imaging as not central in the diagnosis of rUTIs and they weakly recommend not to

TABLE 1 The survey items and level of consensus achieved.

Panelists: 37		Final evaluation											Consensus
Items		0	1	2	3	4	5	6	7	8	9	10	%
1	The diagnostic workup of a patient with rUTI should include a cystoscopy and/or a urinary tract imaging			1	1		2	2	3	7	3	18	84%
2	The diagnostic workup of a patient with recurrent cystitis should include a noninvasive urodynamic evaluation (frequency–volume chart/bladder diary, PVR and, if possible, a uroflowmetry)								1	10	4	22	92%
3	An extensive sexual history should be collected in patients with recurrent cystitis (number of partners, frequency, and type of intercourse, intravaginal or intrauterine contraceptives, use of spermicide)								2	5	2	28	95%
4	Lifestyle changes (water intake, timed voiding, voiding after sex) may contribute to a risk reduction of rUTIs							2	1	5	3	26	93%
5	The management of associated gastrointestinal symptoms may contribute to lower the risk of recurrent cystitis									7	1	29	95%
6	The role of lactobacilli in the recurrent cystitis prevention is relevant and proved							1	3	11	6	16	88%
7	The use of local vaginal estrogens therapy is advised in postmenopausal women with rUTIs					3		3	5	6	7	13	82%
8	In the noncomplicated recurrent cystitis prevention, the continuative or cyclic use of D-mannose is useful		1					1	3	5	4	23	90%
9	In the noncomplicated recurrent cystitis prevention, D-mannose can be used as monotherapy or in combination with lactobacilli and cranberry					1		1	5	4	3	23	90%
10	In the postcoital recurrent cystitis, a D-mannose prophylaxis may be useful	1			1	1	2	2	3	8	7	12	80%
11	A nonantimicrobic approach may lower the antibiotic resistance when treating rUTIs								2	4	2	29	95%
12	During pregnancy, a screening for bacteriuria should be routinary performed	1	1	2	3	3	4	1	3	7	1	11	67%
13	In the IC, a nonantibiotic prophylaxis may be useful		1		1		4		2	7	4	18	83%

Abbreviations: IC, intermittent urethral catheterization; PVR, postvoid residual; rUTI, recurrent urinary tract infection.

perform this diagnostic workup in women younger than 40 years of age and no risk factors.[1] This is aligned with the AUA/CUA/SUFU guideline statement (expert opinion) when not applicable to those with anatomic or functional abnormalities of the urinary tract.[2] The NICE guideline suggests to refer to urologist and perform further investigation, such as using ultrasound scanning in men with a rUTI and women with a recurrent lower UTI, where the cause is unknown, or a recurrent upper UTI.[4] AAFP,[6] COMEGO,[7] and SEIMC[9] guidelines do not routinely recommend cystoscopy or imaging. On the other hand, the SOGC[5] and the AWMF[10,11] suggest further investigations when hematuria or non-*Escherichia coli* culture are reported and SSGO[8] advice for cystoscopy if ≥3 UTIs/year and kidney contrast computed tomography (CT) if ≥2 pyelonephritis episodes/year.

Consensus: Panelists have a consensus on the use of cystoscopy and/or a urinary tract imaging in the diagnostic workup of patients with rUTIs.

Comment: Urine culture is mandatory for the identification of the microorganism responsible of the infection, but nothing is expressed on the underlying cause of the infection recurrency. Urinary tract ultrasound (or in atypical cases even CT or magnetic resonance imaging) and cystoscopy may have a fundamental role on the proper diagnosis of a rUTIs when anatomical or/and functional abnormalities are suspected. Ultrasound or cystoscopy can be useful to identify anatomical issues related to rUTIs even in younger patients without risk factors when the recurrency itself should be considered as an atypical phenomenon. This follows the AUA guidelines recommendation on patients who do not respond appropriately to treatment of uncomplicated rUTIs (i.e., poor symptomatic or microbiological response to initial treatment or rapid recurrence of infection, same organism repeatedly); these patients should be considered to have a complicated UTI, thereby necessitating further evaluation.[2]

3.1.2 | The diagnostic workup of a patient with recurrent cystitis should include a noninvasive urodynamic evaluation (frequency–volume chart/bladder diary, postvoid residual [PVR], and, if possible, a uroflowmetry)

Considering recurrency of UTI as an atypical event, a dysfunction should be investigated to rule out underlying anatomical or functional issues. All the guidelines and papers considered do not report any urodynamic recommendation for the diagnostic evaluation of rUTIs. However, the ICS and the International Urogynecological Association terminology papers suggest a frequency-volume chart/bladder diary along with urodynamics as tools for the proper diagnosis of any lower urinary tract dysfunction (LUTD).[18–21]

Consensus: Panelists have a consensus on the use of noninvasive urodynamic evaluation.

Comment: Useful clinical data may come from the frequency–volume chart/bladder diary in terms of number of micturition, the volume voided for at least 24 h (best for three not consecutive days) even adding information about fluid intake, pad usage, or eventual incontinence episodes. Urodynamics is the measurement of all the physiological parameters relevant to the function and any dysfunction of the lower urinary tract. First line urodynamic investigations involve an individual attending with a comfortably full bladder for free (no catheter) uroflowmetry and PVR measurement.[18–21] These functional exams may highlight LUTD associated with the recurrence of UTIs.

3.1.3 | An extensive sexual history should be collected in patients with recurrent cystitis (number of partners, frequency, and type of intercourse, intravaginal or intrauterine contraceptives, use of spermicide)

Sexual history is part of the patient history and should be investigated. The EAU guidelines mention sexual intercourse, use of spermicide and the presence of a new sexual partner as a young and premenopausal women risk factor associated with rUTIs.[1] The AUA recommends the collection of sexual history to find any related infectious triggers[2] as well as the NICE guidelines underline that urinary symptoms may be due to urethral inflammation post sexual intercourse, irritants, or sexually transmitted infection.[3,4] Although all the guidelines refer to sexual history as part of the anamnesis,[5–11] a specific recommendation has not been found.

Consensus: Panelists have a consensus on collecting an extensive sexual history.

Comment: Sexual history is important not only for young women but even for post-menopausal ones and men (who have sex with women and/or men). Investigation on some habits (such as multiple sexual partners, practice of anal intercourse or anal--vaginal intercourse, the use of sex toys) may play a role in assessing a possible cause of rUTIs.

3.1.4 | Lifestyle changes (water intake, timed voiding, voiding after sex) may contribute to a risk reduction of rUTIs

Data from literature review leaded to consider lifestyle changes as part of rUTIs prevention. Evidence on behavioral modifications is scarce. The EAU and NICE guidelines identify some avoidable risk factors such as insufficient hydration, habitual and postcoital delayed urination, wiping from back to front after defecation, douching, and wearing occlusive underwear.[1,3,4] The majority of guidelines made a weak recommendation for behavioral modifications for rUTI prevention (except AWMF[10,11]: strong recommendation).[12]

A low level of evidence (=3) is expressed regarding the water intake that should be increased in premenopausal women at high risk for recurrence who drink low volumes (<1.5 L) of fluid daily.[1,22,23] The AUA, NICE, COMEGO, and SSGO identified promising data on increased water intake as prevention of rUTIs but no conclusions had been drawn.[2–4,7,8] The AWMF strongly recommend to increase fluid intake.[11]

Timed voiding and voiding after sex are strategies that have been explored in the past. Bladder emptying is effective in patients with rUTIs, and its correction may play an important part in the management of UTI.[22,23]

Consensus: Panelists have a consensus on clinical relevance of behavioral modifications.

Comment: Conservative measures including increasing fluid intake, voiding education, a correct hygiene regimen, timed voiding and voiding after sex are the clinical mainstays for the management of rUTIs prevention before initiation of prophylactic drug treatment, although there is limited evidence available regarding these approaches.[1,24]

3.1.5 | The management of associated gastrointestinal symptoms may contribute to lower the risk of recurrent cystitis

The relationship between bladder and bowel function is complex and has implications for treating urinary infections and disorders.[25] Currently, the role of bladder

and bowel microbiota is under investigation and their crosstalk may impact on the incidence of UTIs.[26] When collecting patient's history, the AUA guidelines suggest that a focused investigation on any bowel symptoms such as diarrhea, accidental bowel leakage, or constipation should be performed.[2] Clinically, the bladder-bowel relationship could be evident through the presence of urinary symptoms in patients with bowel dysfunctions and bowel symptoms in patients with acute cystitis.[25] Scarce is the reference to gastrointestinal symptoms in the papers considered.[1–12]

Consensus: Panelists have a consensus on clinical relevance of managing gastrointestinal symptoms in patients with recurrent cystitis.

Comment: Although assessing gastrointestinal symptoms and treating them could be intuitively considered part of the clinical management in patients with rUTIs, guidelines do not report any recommendation. When proper, referral to a gastroenterologist is deemed.

3.1.6 | The role of lactobacilli in the recurrent cystitis prevention is relevant and proved

All guidelines agreed there is insufficient evidence for probiotics and *Lactobacillus* products.[2–12]

The European guidelines analyzed four meta-analyses and 10 relevant systematic reviews on the role of lactobacilli in the rUTIs.[1] Although literature discrepancies in the results due to different strains and different administration regimes, treatment durations, and patient populations, the EAU guidelines show a very high level of evidence (1b) for literature reporting probiotics containing *Lactobacillus rhamnosus* GR-1, *Lactobacillus reuteri* B-54 and RC-14, *Lactobacillus casei* Shirota, or *Lactobacillus crispatus* 1b CTV-05 in the treatment of vaginal flora restoration and prevention of rUTIs. However, the recommendation for their use is weak on the use of local or oral probiotics containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs. This is mainly due to low-quality studies on the route of admission, optimal dosage, and treatment duration for probiotic prophylaxis.[1] The AUA and the NICE guidelines do not recommend the use of *Lactobacillus* as a prophylactic agent for rUTIs given the current lack of data indicating benefit in comparison to other available agents.[2,3]

Consensus: Panelists have consensus on the role of lactobacilli as a prophylactic agent for rUTIs.

Comment: This point of the consensus was selected to underline the defensive role of some strains of microorganisms that could help in the rUTIs prevention. Although the current guidelines already suggest this approach, the recent improvement in the comprehension of microbiota may further endorse this kind of prophylaxis and clinicians should be educated on the topic.[26]

3.1.7 | The use of local vaginal estrogens therapy is advised in post-menopausal women with rUTIs

Vaginal estrogen replacement is strongly recommended for rUTI prevention by the EAU (in postmenopausal women),[1] SSGO,[8] and SEIMC[9] (especially in postmenopausal women or those with vaginal atrophy), whereas other guidelines made a weak to moderate recommendation.[2–7,10–12]

Considering the four meta-analyses reviewed by the EAU guidelines, this point reached a very high level of evidence (1b) considering that vaginal estrogens replacement has shown a trend towards preventing rUTIs in postmenopausal women. Thus, the EAU guidelines strongly recommend its use. The AUA guideline statement expresses a moderate recommendation (Level of evidence B) for the vaginal estrogen therapy to reduce the risk of future UTIs in peri- and postmenopausal women with rUTIs.[2]

Consensus: Panelists confirmed the guidelines.

Comment: According to the guidelines, the local use of estrogens is advisable in postmenopausal women with rUTIs. As a Cochrane review underlined, even though vaginal estrogens reduced the number of UTIs in postmenopausal women, type of estrogen used, and the treatment duration should be further investigated.[27]

3.1.8 | In the noncomplicated recurrent cystitis prevention, the continuative or cyclic use of D-mannose is useful

From our literature review, evidence on the prophylactic use of D-mannose for rUTIs is limited. Its use is debated. The SEIMC strongly recommends D-mannose due to its similar effectiveness to nitrofurantoin for this indication.[9,28] Similarly, The EAU,[1] SSGO,[8] and AWMF[10,11] also support D-mannose use (weak–moderate recommendations), while the NICE guidelines recommended for some nonpregnant women as a self-care treatment.[3,12]

The EAU guidelines mentioned four papers.[1] A meta-analysis including one randomized controlled trial (RCT), one randomized cross-over trial and one prospective cohort study reported that D-mannose is effective in the prevention of rUTIs with comparable efficacy to antibiotic prophylaxis.[1,29] Same papers were analyzed by

the AUA panel and found to be at high risk of bias.[2] Further studies on optimal dosage, treatment duration, and use modalities are needed.[30] The EAU guidelines level of evidence reported for D-mannose in reducing the number of UTI episodes is 2 and its use is recommended with a weak strength, because patients should be informed that further studies are needed to confirm the promising results of initial trials.[1]

Consensus: Panelists have consensus on the use of D-mannose in rUTIs prevention.

Comment: The use of D-mannose in preventing rUTIs is quite recent but sustained by promising results. D-mannose binds to the tip of type 1 pili and saturates the adhesin FimH, thereby preventing bacterial adhesion to the urothelium.[29,31] D-mannose can saturate the FimH and may prevent or attenuate the infection.[29]

3.1.9 | In the noncomplicated recurrent cystitis prevention, D-mannose can be used as monotherapy or in combination with lactobacilli and cranberry

Nonantibiotic rUTIs prevention approaches are currently spreading and under research. From the Section 3.1.6 of this paper, lactobacilli may contribute to contain the UTIs recurrence. Regarding the cranberry, supplementation was strongly recommended by the SOGC guidelines,[5] whereas others only provided a weak–moderate recommendation. The EAU guidelines report a high level of evidence (1a) and the use of cranberry products is weakly recommended with the need to inform patients that the quality of evidence underpinning this is low with contradictory findings.[1] The AUA guidelines report a conditional recommendation (Level of evidence C) for cranberry prophylaxis in women with rUTIs.[2] The AUA reported a single, very low quality study on the combination of D-mannose, *Lactobacillus paracasei* and cranberry.[29,30]

Consensus: Panelists reached the consensus on the use of D-mannose in monotherapy or in association with lactobacilli and cranberry.

Comment: Clinical practice is variegated given the absence of well powered randomized studies and lack of evidence in the guidelines. Intuitively, combination approaches may have synergic effects.

3.1.10 | In the postcoital recurrent cystitis, a D-mannose prophylaxis may be useful

Literature and guidelines report that antibiotic prophylaxis as continuous low-dose for longer periods or as postcoital administration is the most effective approach against rUTIs compared with placebo or no treatment without significant difference in the efficacy of the two approaches (Level of evidence 1b).[1–12,31–33] There is no consensus on which is the best antibiotic and the most proper regimen.[1] Therefore, the EAU guidelines strongly recommend postcoital prophylaxis when behavioral modifications and nonantimicrobial measures have been unsuccessful.[1]

Data on the use of D-mannose in postcoital recurrent cystitis are missing, but its efficacy in rUTIs has been reported as comparable to antibiotic prophylaxis.[1,28]

Consensus: Panelists have consensus on the possible role of D-mannose in preventing postcoital cystitis.

Comment: Propose a postcoital or continuous low-dose antibiotic prophylaxis is suggested only when nonantimicrobial measures have been ineffective. Promising results of D-mannose should be assessed even for postcoital recurrences given the possibility to avoid any antibiotics, reduce the dose or shorten the prophylaxis regimen. It should be kept in mind that postcoital or continuous low-dose antibiotic prophylaxis may expose to side effects and that patients should be counseled for that.

3.1.11 | A nonantimicrobic approach may lower the antibiotic resistance when treating rUTIs

Long-term and low-dose antibiotic use in the treatment of rUTIS can lead to alteration of normal intestinal flora and antibiotic resistance. Nowadays, antibiotic resistance is one of the major health problems worldwide; its increase will make it more difficult to treat future UTIs. Guidelines did not report any recommendation.

Consensus: Panelists reached a consensus on the utility of nonantimicrobic approach to reduce the spread of antibiotics resistance.

Comment: nonantibiotic rUTI prevention approaches, such as cranberry products, estrogens, lactobacilli, and D-mannose, have increasingly been the subject of research.[28]

3.2 | AB in pregnancy

Item 12: During pregnancy, a screening for bacteriuria should be routinary performed.

AB, generally defined as true bacteriuria in the absence of specific symptoms of acute UTI, is a common finding, and occurs in 2% to 15% of all pregnancies.[34] None of the guidelines reviewed reported this kind of recommendation. The literature review did not identify a standardized timed protocol for screening bacteriuria in pregnant women.

Consensus: Panelists did not reach the consensus.

Comment: Although a well-planned screening for bacteriuria has not been identified, it is mandatory to treat this condition when detected.

First referring to the EAU guidelines, it should be emphasized that the overall quality of the scientific evidence underpinning this item is low. Several RCT have been performed but most of them in the 60–80 s. The EAU guidelines performed a meta-analysis of the available evidence reporting that treatment of AB in pregnant women was beneficial (Level of evidence 1a), even though most of the studies are old. Thus, the weak recommendation is to treat AB in pregnant women with standard short course (2–7 days) treatment.[1]

The 2019 Cochrane review on the use of antibiotics in AB in pregnancy, reported that antibiotic treatment may be effective in reducing the risk of pyelonephritis and the risk of preterm birth and low birthweight. However, the authors clearly stated that the confidence in the effect is limited given the low certainty of the evidence. The authors further underlined the need to identify a low-risk group of women who are unlikely to benefit from treatment of AB.[34] Probably, considering behavioral modifications and nonantimicrobial measures as a first line approach may prevent from antibiotic exposure.

3.3 | Intermittent catheterization

Item 13: In the IC, a nonantibiotic prophylaxis may be useful.

The guidelines do not report any data on nonantibiotic prophylaxis in IC.[1–12] However, a weak recommendation is to not routinely use antibiotic prophylaxis to prevent clinical UTI in patients performing intermittent self-catheterization.[1]

Consensus: Panelists reached a consensus on the utility of nonantimicrobic prophylaxis in patients undergoing IC.

Comment: IC is a self-made maneuver that can occur multiple times per day. The routine use of antibiotics for such a common procedure in the healthcare setting would result in an increased usage of antimicrobials and in in the development of severe and multi-antimicrobial resistance. Behavioral modifications and nonantimicrobial measures as a first line approach may prevent from antibiotic therapy.

4 | DISCUSSION

Recurrent UTI is a highly prevalent, costly, and burdensome condition. Several international scientific associations systematically report the evidence on this topic trying to face with challenges in clinical practice.

Nowadays, guidelines offer the best clinical practice principles to clinicians highlighting some open questions that are under investigation. The role of this Delphi consensus was to identify these gray zones in the lower rUTIs management to achieve an expert opinion position.

Following the AUA suggestion, the definition of UTI maybe somewhat refined.[1] Although recurrency could not be considered a complication of UTIs, it could be defined as something "atypical"[1] that could require a more extensive diagnostic workup after urine culture has been done. Recurrency could be the effect of hidden morphological or functional dysfunction or even linked to wrong sexual or hygiene habits. This implies that the diagnostic workup of a patient with rUTI should include an extensive personal and sexual history and a cystoscopy and/or a urinary or tract imaging or a noninvasive urodynamic evaluation when anatomical or functional issues are suspected.

Behavioral modifications have only a weak recommendation in the guidelines, even though may play an important role when the patients with rUTIs are carefully educated by the physicians.

Gastrointestinal symptoms are listed as part of the patient history. Management of bowel dysfunction could be relevant in light of the recent findings on the microbiota crosstalk between urinary and gastrointestinal systems. Supplementation of lactobacilli is poorly investigated even though some strains may contribute to contain the UTIs recurrence.

Several open questions were analyzed in the field of nonantibiotic prophylaxis. The use of local vaginal estrogens therapy demonstrated a variegated level of recommendation among the guidelines and reviews. This panel of experts is aligned with the strong recommendation especially in postmenopausal women or those with vaginal atrophy. The role of D-mannose as monotherapy or in combination (lactobacilli or cranberry products) seems promising in the prevention of rUTIs for its opsonizing effect on bacteria but further studies are mandatory.

The nonantibiotic approach to rUTIs needs a better understanding of rUTI pathophysiology that will greatly aid to design more effective, mechanistically-based treatments effective in the prevention of the so called "collateral damage," the ecological adverse effects of antibiotic therapy.[2,34,35] The wide use of antibiotics is the cause of the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms. This risk has been reported for cephalosporin use that has been linked to subsequent infection with vancomycin-resistant enterococci, extended-spectrum beta-lactamase-producing

Klebsiella pneumoniae, β-lactam-resistant Acinetobacter species, and *Clostridium difficile*. Similarly, quinolone use has been linked to infection with methicillin-resistant *Staphylococcus aureus* and with increasing quinolone resistance in Gram-negative bacilli, such as *Pseudomonas aeruginosa*.[34] Multidrug resistance is an increasing prevalent condition and any type of preventive synergistic effect with antibiotics should be encouraged.

The Item 12 was the only one that did not reach the consensus. None of the papers reviewed indicate to routinary screen pregnant woman for AB. Although once diagnosed, a short course antibiotic treatment should be prescribed.

The role of nonantibiotic approach to rUTIs should be investigated both for AB and for intermittent self-catheterization.

Very few data are available on male rUTIs. Following the EAU, cystitis in men without involvement of the prostate is uncommon and should be classed as a complicated infection.[1] Therefore, treatment with antimicrobials penetrating the prostate tissue is needed in males with symptoms of UTI.[1] However, nonantibiotic prevention should not be underestimated in the management of these patients.

5 | CONCLUSIONS

There are some open questions on rUTIs, AB in pregnancy and IC that still need to be investigated. This Delphi consensus analyzed the available data and led to consensus statements that could be useful to better manage these clinical conditions. Lack of evidence is present on most of these topics and further studies are mandatory to lower antibiotic resistance and for a better tailoring of antibiotic and nonantibiotic treatments.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows. *Study conception and design*: Enrico Finazzi Agrò, Valerio Iacovelli. *Analysis and interpretation of results*: Vincenzo Ficarra, Umberto Vittorio Maestroni, Manuela Tutolo. *Draft manuscript preparation*: Enrico Finazzi Agrò, Valerio Iacovelli. All authors reviewed the results and approved the final version of the manuscript.

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ETHICS STATEMENT

Ethics of approval statement is not applicable to this article.

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REFERENCES

1. Bonkat G, Bartoletti R, Bruyère F, et al. European Association of Urology (EAU) Guidelines on Urological Infections. EAU Guidelines. Paoer presented at: EAU Annual Congress Amsterdam, The Netherlands. ISBN 978-94-92671-19-6. 2022.
2. Anger JT, Bixler BR, Holmes RS, Lee UJ, Santiago-Lastra Y, Selph SS. Updates to recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. *J Urol*. 2022;208(3):536-541.
3. National Institute for Health and Care Excellence. Urinary Tract Infection (Recurrent): Antimicrobial Prescribing. 2018. Accessed April 2021. https://www.nice.org.uk/guidance/ng112
4. National Institute for Health and Care Excellence. Urinary tract infections in adults. 2023. Accessed February 2023. https://www.nice.org.uk/guidance/qs90/chapter/Quality-statements
5. Epp A, Larochelle A, Urogynaecology Committee, Family Physicians Advisory Committee. Recurrent urinary tract infection. *Journal of Obstetrics and Gynaecology Canada*. 2010;32(11):1082-1090. (English, French).
6. Arnold JJ, Hehn LE, Klein DA. Common questions about recurrent urinary tract infections in women. *Am Fam Physician*. 2016;93(7):560-569.
7. Velazquez MDP, Nava LER, de Avalos DRL, et al. Clinical practice guidelines. Recurrent infection of the urinary tract in women. Colegio Mexicano de Especialistas en Ginecologıa y Obstetricia. *Ginecol Obstet Mex*. 2010;78:S437-S459.
8. Betschart C, Albrich WC, Brandner S, et al. Guideline of the Swiss Society of Gynaecology and Obstetrics (SSGO) on acute and recurrent urinary tract infections in women, including pregnancy. *Swiss Med Wkly*. 2020;150:w20236.
9. de Cueto M, Aliaga L, Alós JI, et al. Executive summary of the diagnosis and treatment of urinary tract infection: guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). *Enferm Infecc Microbiol Clin*. 2017;35(5):314-320. (English, Spanish).

10. Kranz J, Schmidt S, Lebert C, et al. The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uncomplicated urinary tract infections in adult patients: part 1. *Urol Int*. 2018;100(3):263-270.
11. Kranz J, Schmidt S, Lebert C, et al. The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uncomplicated urinary tract infections in adult patients. Part II: therapy and prevention. *Urol Int*. 2018;100(3):271-278.
12. Kwok M, McGeorge S, Mayer-Coverdale J, et al. Guideline of guidelines: management of recurrent urinary tract infections in women. *BJU Int*. 2022;130(suppl 3):11-22.
13. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol*. 2014;67:401-409.
14. Milholland AV, Wheeler SG, Heieck JJ. Medical assessment by a Delphi group opinion technic. *N Engl J Med*. 1973;288:1272-1275.
15. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology*. 2003;61:37-49.
16. Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd Edition. John Wiley & Sons; 2019.
17. Howick J, Chalmers I, Glasziou P. *Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document)*. Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
18. D'Ancona C, Haylen B, Oelke M, et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. *Neurourol Urodyn*. 2019;38(2):433-477.
19. Haylen BT, Chetty N. International Continence Society 2002 terminology report: have urogynecological conditions (diagnoses) been overlooked? *Int Urogynecol J*. 2007;18:373-377.
20. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International ContinenceSociety (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010;29:4-20; (*Int Urogynecol J*. 2010;21:5-26).
21. Haylen BT, Freeman RM, Swift SE, et al. An International Urogynecological Association (IUGA)/International ContinenceSociety (ICS) joint terminology and classification of complications related directly to the insertion of prostheses (meshes,implants, tapes) and grafts in female pelvic floor surgery. *Int Urogynecol J*. 2011;22:3-15.
22. Adatto K. Behavioral factors and urinary tract infection. *JAMA*. 1979;241(23):2525-2526.
23. Hooton TM, Vecchio M, Iroz A, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: A randomized clinical trial. *JAMA Int Med*. 2018;178(11):1509-1515.
24. Arlen AM. Dysfunctional voiders-medication versus urotherapy? *Curr Urol Rep*. 2017;18(2):14.
25. Kaplan SA, Dmochowski R, Cash BD, Kopp ZS, Berriman SJ, Khullar V. Systematic review of the relationship between bladder and bowel function: implications for patient management. *Int J Clin Pract*. 2013;67(3):205-216.
26. Salvatore S. Microbiota in incontinence and pelvic floor dysfunctions. In: Cardozo L, Rovner E, Wagg A, Wein A, Abrams P., eds. *Incontinence*. 7th Edition. International Continence Society; 2023.
27. Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev*. 2008; 2:CD005131.
28. Kranjčec B, Papeš D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol*. 2014;32:79-84.
29. Lenger SM, Bradley MS, Thomas DA, Bertolet MH, Lowder JL, Sutcliffe S. D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;223(2):265.e1-265.e13.
30. Kranz J, Schmidt S, Schneidewind L. Current evidence on nonantibiotic prevention of recurrent urinary tract infections. *Eur Urol Focus*. 2019;5(1):17-19.
31. Bouckaert J, Berglund J, Schembri M, et al. Receptor binding studies disclose a novel class of high-affinity inhibitors of the *Escherichia coli* FimH adhesin. *Mol Microbiol*. 2005;55(2): 441-455.
32. Nalliah S, Fong JSH, Yi Thor AY, Lim OH. The use of chemotherapeutic agents as prophylaxis for recurrent urinary tract infection in healthy nonpregnant women: a network meta-analysis. *Ind J Urol*. 2019;35(2):147-155.
33. Ahmed H, Davies F, Francis N, Farewell D, Butler C, Paranjothy S. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. *BMJ Open*. 2017; 7(5):e015233.
34. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2019;2019(11): CD000490.
35. Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis*. 2004;38: S341-S345.

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