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A global perspective on improving patient care in uncomplicated urinary tract infection: expert consensus and practical guidance

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ABSTRACT

Objectives: Uncomplicated urinary tract infections (uUTIs) are a common problem in female patients. Management is mainly based on empirical prescribing, but there are concerns about overtreatment and antimicrobial resistance (AMR), especially in patients with recurrent uUTIs.
Methods: A multidisciplinary panel of experts met to discuss diagnosis, treatment, prevention, guidelines, AMR, clinical trial design and the impact of COVID-19 on clinical practice.
Results: Symptoms remain the cornerstone of uUTI diagnosis, and urine culture is necessary only when empirical treatment fails or rapid recurrence of symptoms or AMR is suspected. Specific antimicrobials are first-line therapy (typically nitrofurantoin, fosfomycin, trimethoprim/sulfamethoxazole and pivmecillinam, dependent on availability and local resistance data). Fluoroquinolones are not first-line options for uUTIs primarily due to safety concerns but also rising resistance rates. High-quality data to support most non-antimicrobial approaches are lacking. Local AMR data specific to community-acquired uUTIs are needed, but representative information is difficult to obtain; instead, identification of risk factors for AMR can provide a basis to guide empirical antimicrobial prescribing. The COVID-19 pandemic has impacted the management of uUTIs in some countries and may have long-lasting implications for future models of care.
Conclusion: Management of uUTIs in female patients can be improved without increasing complexity, including simplified diagnosis and empirical antimicrobial prescribing based on patient characteristics, including a review of recent antimicrobial use and past pathogen resistance profiles, drug availability

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and guidelines. Current data for non-antimicrobial approaches are limited. The influence of COVID-19 on telehealth could provide an opportunity to enhance patient care in the long term.

1. Introduction

Uncomplicated urinary tract infections (uUTIs) are generally defined as infections of the bladder in non-pregnant women with no known functional or anatomical abnormalities or co-morbidities [1]. These are distinguishable from acute pyelonephritis (an infection of the upper urinary tract) and complicated urinary tract infections (cUTIs). The latter are a heterogeneous group of conditions and include those occurring in male patients and females with certain co-morbidities and abnormalities that impact urological function, and also include healthcare-associated and systemic infections [2].

It is well established that uUTIs are common in female patients of all ages, with an annual prevalence of ~11%, and are more common than cUTIs [2,3]. Up to 80% of females will experience at least one uUTI in their lifetime, and as many as 45% will have recurrent uUTIs [4–7]. Given their prevalence, uUTIs represent a substantial burden—without prompt and effective treatment, symptoms can be debilitating for several days and can impact work and daily routines [8–10].

The primary needs of patients with uUTIs are accurate and early diagnosis followed by timely symptom relief. Current guidelines recommend empirical prescribing of selected antimicrobial agents [1,11–15], which remains a largely effective approach for the acute episode. In young women experiencing a first episode of uUTI symptoms, urine culture is not recommended when a robust diagnosis can be reached by patient history-taking and other potential causes of symptoms can be excluded, which is important in order to minimise overdiagnosis and inappropriate treatment. Indeed, uUTIs are one of the most common conditions associated with antimicrobial prescribing [16,17], and previous antibiotic exposure is associated with an increased risk of antimicrobial resistance (AMR), which may therefore present a public-health challenge [18,19]. In particular, AMR of common uropathogens, e.g. *E. coli*, to therapies widely used for the management of uUTIs, such as fluoroquinolones, is increasing in many regions [20]. Fluoroquinolones also transiently suppress commensal intestinal Enterobacteriaceae, associated with the development of AMR, and resistant strains can then spread to unexposed household contacts of patients treated with fluoroquinolones for UTIs [21]. Consequently, there is a need for novel oral therapies with activity against resistant strains of uropathogens, including extended-spectrum β-lactamase-(ESBL)-producing *E. coli* that are becoming more prevalent worldwide [22–26].

The safety of antimicrobial therapy is also a major concern. In recent years, both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have published warnings regarding the use of fluoroquinolones for infections such as uUTIs [27–29]. In particular, potential severe adverse effects on multiple organ systems, mentation and glucose control have resulted in recommendations that these drugs should not be prescribed for uUTIs unless there are no other alternatives [1,11].

Recurrent uUTIs are a major issue for many women and are associated with multiple visits to various healthcare professionals [30] and often repeated antibiotic prescriptions, with an increased risk of potential side effects [31,32]. Some women may therefore prefer to avoid repeated courses of antibiotics and seek other treatment options [33].

To discuss current challenges and ways in which the management of females with uUTIs can be improved, an expert panel was convened by GlaxoSmithKline plc. that included urologists, obstetricians/gynaecologists, infectious diseases specialists, emergency medicine specialists, clinical microbiologists and primary care physicians. The panel members were chosen by a steering committee, with the aim of including specialists from several disciplines and representing a broad geographical spread (Europe, North America, Latin America and Asia). The panel met over 4 days to discuss the key issues, including diagnosis, treatment and prevention of uUTIs, current prescribing, guidelines and the problem of AMR. This paper summarises the outcomes from the meeting, including the key unmet needs (Table 1) that were identified.

2. Diagnosis of uncomplicated urinary tract infections

The discussions and conclusions of the expert panel regarding the diagnosis of uUTIs are summarised below and in Fig. 1.

2.1. Patient history-taking and symptoms

Certainty of a uUTI diagnosis is paramount to appropriate and effective treatment (and avoidance of overtreatment). In the experience of the group, the clinical workup for patients with suspected uUTI is often inadequate, with a less than thorough medical history/risk factor assessment, usually due to the limited time avail-

Table 1
Summary of unmet needs in the diagnosis and management of uncomplicated urinary tract infections (uUTIs)

Diagnosis	• A point-of-care test that can both identify the specific uropathogen present and provide antimicrobial susceptibility data without the need for urine culture
Treatment of acute uUTI episodes	• High-quality research regarding non-antimicrobial approaches • Simpler antimicrobial dosing regimens (single dose or once-daily doses)
Prevention of recurrent uUTIs	• Improved understanding of the vaginal, bladder and gut microbiomes and the impact of repeated courses or long-term antimicrobial therapy • High-quality research regarding non-antimicrobial prophylaxis
Guidelines	• Simpler guidelines that are easy to access and update, with greater use of digital media • Surveys to understand current challenges in different healthcare systems
Antimicrobial resistance (AMR)	• Immediate reductions in inappropriate fluoroquinolone prescribing • Surveillance data in the community to better understand local antibiograms and to inform appropriate prescribing
Clinical trial design	• Inclusion of patients with $<10^5$ CFU/mL bacteriuria, with appropriate subgroup analyses • Evaluation of non-microbiological outcomes for primary endpoints in studies of non-antimicrobial approaches
Novel methods of consultation	• Recommendations regarding virtual consultations should be included in management guidelines

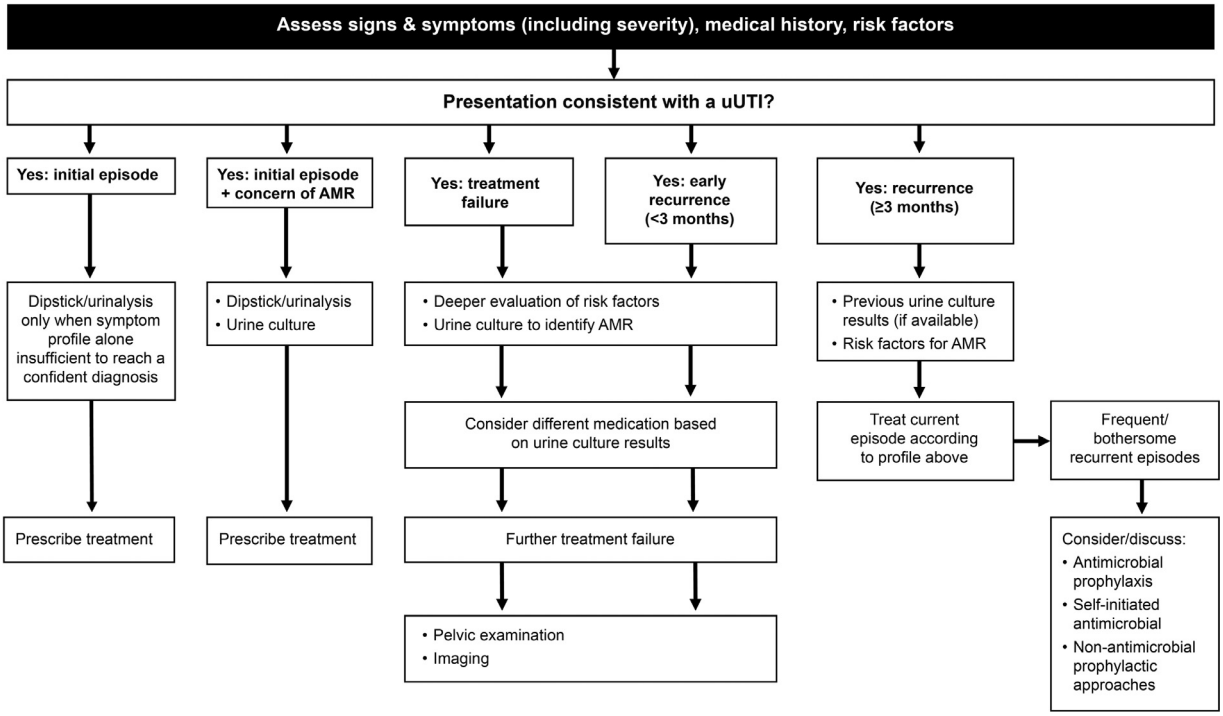

Fig. 1. Diagnostic algorithm. uUTI, uncomplicated urinary tract infection; AMR, antimicrobial resistance.

Table 2
Potential risk factors for uncomplicated urinary tract infections (uUTIs)

- Previous UTIs [35,130,131]
- Age at first UTI ≤15 years [35,132]
- Maternal history of UTIs [34,35,132]
- Childhood history of UTIs [34]
- Frequent sexual intercourse [1,34,35,131,132]
- Use of spermicides [34,35,130–132]
- New sexual partner within the preceding year [34,132]
- High-risk sexual intercourse [133]
- Constipation [133,134]
- Hormonal changes that can impact the microbiome, e.g. menopause [34,35]
- Diabetes mellitus [35]

able at a typical appointment. A list of suggested factors for discussion with patients that contribute to infection is presented in Table 2 and generally relate to a personal and/or family history of UTIs, sexual activity and hormonal changes, e.g. in postmenopausal women [34,35].

Symptoms remain the cornerstone of uUTI diagnosis (Fig. 1) [1,11–15]. However, it was agreed that symptoms of uUTIs are non-specific and can overlap with those of other conditions such as pyelonephritis, cUTIs, sexually transmitted infections (STIs), overactive bladder (OAB), urethral pain syndrome, interstitial cystitis/painful bladder symptoms, and menopausal symptoms in older women [1,36–39]. Symptoms strongly supportive of an uUTI diagnosis include dysuria, urgency and frequency—the greater number of symptoms present, the higher the likelihood of an uUTI [40,41]. Previous documented episodes of uUTI also increase the risk of a recurrent infection. It was also discussed that symptoms may not be sufficient in isolation to confirm a diagnosis of uUTI and could lead to overdiagnosis. However, the duration of symptoms and severity can guide a diagnosis and treatment decisions. There are validated scoring tools for the diagnosis of uUTI [Acute Cystitis Symptom Score (ACSS) and Urinary Tract Infection Symptom Assessment (UTISA) questionnaire] that can provide support for treatment decisions [42,43].

It is important to exclude conditions other than uUTIs as these may require further investigation and different treatment approaches. Differentiation from pyelonephritis or cUTI is critical, and the presence of symptoms such as fever, flank pain, nausea and vomiting can suggest the presence of these more serious infections [1]. Exclusion of diagnoses other than UTIs is also important as these typically do not require antimicrobial therapy; these include interstitial cystitis (e.g. pelvic pain, pressure and discomfort, daytime frequency and urgency) [39], OAB (e.g. frequency, urgency and nocturia, but symptoms are typically without sudden onset and urge urinary incontinence is often present) [36], urethral pain syndrome (e.g. dysuria, daytime frequency, urgency and suprapubic discomfort, but also hesitancy and urinary retention) [38], and genitourinary symptoms in older women that are related to the menopause (e.g. dysuria, urgency, nocturia and frequency) [37]. In sexually active women, concurrent vaginal discharge may indicate the presence of a STI [44] or vaginitis and reduce the probability of an uUTI [41]; however, further workup may be needed, including testing for a STI, pelvic examination and a urine culture. Additional indicators of a diagnosis other than uUTI include dysfunctional voiding and neurogenic bladder.

2.2. Point-of-care testing

There was some debate between members of the panel on the utility of urine dipsticks and urinalysis. Dipsticks are widely available, inexpensive and provide rapid results, and in some regions these are routinely employed as part of the workup alongside symptoms. However, they are typically not diagnostic of uUTIs in isolation—a negative test does not exclude infection—but can be used in a supportive context when the symptom profile alone is insufficient to achieve a confident diagnosis (nitrite test for bacteriuria and leukocyte esterase for pyuria) [40,41,45,46]. Conversely, if one or more symptoms are consistent with those of an uUTI and the patient has a prior history of UTIs, then a dipstick test is gen-

erally not considered necessary. The panel felt that the presence of bacteriuria/pyuria evidenced by dipsticks could lead to unnecessary reflex urine culture and/or overtreatment if results are not correctly interpreted in the context of symptoms.

2.3. Urine culture

Significant bacteriuria in a urine culture in the presence of suggestive signs and symptoms remains the gold standard for diagnosis of an uUTI. However, the panel agreed that urine culture and antimicrobial susceptibility testing should be conducted only under the following circumstances: (i) during an initial or recurrent episode if there is suspicion of a resistant uropathogen; (ii) if symptoms persist or worsen while on treatment; (iii) if infection recurs within 4 weeks of the initial episode; or (iv) when a diagnosis of uUTI is unclear (atypical symptoms). There was no consensus regarding a threshold for significant bacteriuria as published in guidelines—data suggest that the presence of *E. coli* as low as 10^2 CFU/mL in urine is predictive of *E. coli* colonisation in the bladder [47] and in combination with typical symptoms could still indicate active infection.

2.4. What is needed to improve the diagnosis of uncomplicated urinary tract infections?

The panel agreed that the most urgent need is for a point-of-care test that can both identify the specific uropathogen present and provide antimicrobial susceptibility data without the need for urine culture (Table 1). This could improve the appropriate use of antimicrobial therapy in women with uUTIs, with subsequent effects on AMR and public health. There are currently several tools in development aiming to provide this information within a few hours of urine testing [48–50].

3. Treatment of acute uncomplicated urinary tract infections

3.1. Antimicrobial therapy

With the primary aim of prompt symptom resolution, there was consensus that, if history-taking (with or without dipstick testing) provides a robust diagnosis of uUTI and excludes other conditions, empirical antibiotic treatment should be offered without ordering a urine culture. However, if symptom resolution is not achieved by the end of treatment or if a patient experiences a recurrent uUTI within the following 3 months, urine culture and antimicrobial susceptibility testing should be considered at this point [1,51]. Treatment may need to be changed according to these results, which can indicate that treatment failure may be related to inappropriate targeting of uropathogens or the presence of a resistant uropathogen.

It is generally accepted that existing therapies such as nitrofurantoin, fosfomycin and pivmecillinam are effective in the treatment of acute uUTI episodes in many patients [52–56]. Currently there are no specific recommendations for antimicrobial treatment selection in patients with ESBL- and carbapenemase-producing organisms, although it has been shown that in vitro these are largely susceptible to nitrofurantoin, fosfomycin and pivmecillinam [57–60]. Tolerability of these three therapies is generally favourable and historically resistance is low [17,18,52–56,61–64] although not negligible, according to recent reports [65,66]. Trimethoprim/sulfamethoxazole (TMP-SMX) is known to be effective but its use may be limited due to high rates of resistance worldwide [18,61,62,65–67].

3.2. Non-antimicrobial treatments

Antimicrobial and non-antimicrobial (symptomatic) treatments are not mutually exclusive and can be used simultaneously, although some patients may prefer the latter. However, the role of these interventions is currently unclear, but the concern of rising rates of AMR perhaps makes their use more appealing.

3.2.1. Analgesics/anti-inflammatories

Ibuprofen has been compared with antibiotics in two separate randomised controlled trials (RCTs). In the first RCT, 39% of patients in the ibuprofen group were symptom-free at Day 4 compared with 56% of patients in the fosfomycin group [68]. The median uUTI symptom duration was 1 day longer in the ibuprofen group and 31% of patients subsequently required antibiotics. Pyelonephritis was reported for five women receiving ibuprofen and one woman receiving fosfomycin. The second (non-inferiority) study compared ibuprofen with pivmecillinam in premenopausal women [69]. By Day 4, symptoms had resolved in 39% and 74% of patients randomised to ibuprofen and pivmecillinam, respectively. The median symptom duration was 6 days with ibuprofen versus 3 days with pivmecillinam, and 41% of patients in the ibuprofen group received antibiotics (within 14 days). Seven women in the ibuprofen group developed pyelonephritis compared with none in the pivmecillinam group [69].

The efficacy of diclofenac in women with uUTIs has been compared with norfloxacin [70]. Significantly more patients in the norfloxacin group than the diclofenac group experienced symptom resolution at Day 3 (80% vs. 54%; $P < 0.001$), and rescue antibiotic was required for 41% of women randomised to diclofenac at this timepoint. Six cases of pyelonephritis occurred in women receiving diclofenac compared with none receiving norfloxacin ($P = 0.03$) [70].

In the opinion of some, but not all, panel members, patients with mild-to-moderate symptoms may be initially treated with analgesics following consultation, and if they prefer to avoid antimicrobial therapies [1,71], but should be given a prescription for antimicrobial therapy in case symptoms do not resolve within 2–3 days. However, patients should be advised of the risk of pyelonephritis, analgesic use should be limited to a maximum of 3 days [71] and they should be told to contact their healthcare provider promptly should symptoms worsen.

3.2.2. Herbal preparations

A recent phase 3 RCT compared the effects of 7 days of treatment with either a herbal preparation (BNO 1045) or a single dose of fosfomycin in 659 women with acute uUTIs [72]. Between Days 1 and 38, 84% of patients in the BNO 1045 group did not take additional antibiotics versus 90% of patients in the fosfomycin group (the difference was within the prespecified non-inferiority margin). Symptom severity was comparable at baseline and substantially decreased in both groups over time to a similar extent. There were five cases of pyelonephritis in the BNO 1045 group and one in the fosfomycin group [72].

A preparation of uva ursi extract was compared with fosfomycin in another RCT conducted in Germany that enrolled 398 women with uUTI [73]. Although the uva ursi extract was associated with reduced use of antibiotics, symptom resolution was reported for significantly fewer women in this group relative to fosfomycin. Notably, there were eight cases of pyelonephritis in the uva ursi extract arm and two in the fosfomycin arm [73].

In a recently published RCT of 122 women with recurrent uUTIs, Bazheng powder (given for 4 weeks) was compared with either levofloxacin or amoxicillin/clavulanic acid (1 week of treatment followed by 3 weeks of placebo) [74]. Within 4 weeks, clinical cure of the acute episode was achieved by 90.2% of women

receiving the herbal preparation compared with 82.0% of women receiving antibiotics, which was not significantly different.

There was agreement that due to the small number of high-quality RCTs (and hence lack of systematic reviews) to support most non-antimicrobial approaches for the acute treatment of uUTIs, these interventions could be discussed alongside antimicrobial therapy, but no definitive recommendations made. Delaying antibiotics in women with only mild symptoms is possible if the patient finds it acceptable, but careful monitoring is required.

3.3. What is needed to improve the acute treatment of uncomplicated urinary tract infections?

The panel agreed that there is a need for additional high-quality research regarding non-antimicrobial approaches and also for simpler antimicrobial dosing regimens (single dose or once-daily doses) (Table 1).

4. Prevention of recurrent uncomplicated urinary tract infections

When considering patients with recurrent uUTIs, it is important to assess a patient's understanding of their symptoms; some may normalise these and not seek treatment immediately. Additionally, postmenopausal women may present differently and require a different diagnostic and treatment approach from younger women. In particular, symptoms may be confused with those of other conditions, e.g. menopause or OAB [36,37]. Identifying potential risk factors for recurrence (Table 2) is key to starting a dialogue regarding management strategies.

4.1. Antimicrobial prophylaxis

The panel agreed that if a patient presents again more than a few weeks after the initial episode and symptoms are suggestive of a uUTI, then a urine culture is not routinely indicated. However, results of cultures for previous episodes (as past resistance predicts current resistance) [75] and local resistance patterns should be used to guide empirical treatment (Fig. 1). Continuous or intermittent antimicrobial prophylaxis is an option for women with frequent bothersome recurrences, although the risk of side effects and AMR must be considered [31,51,76,77]. Self-initiated antimicrobial therapy may be considered for patients who have had previous uUTIs, have similar symptoms and can be relied on to contact their healthcare provider if symptoms do not improve. The duration of antimicrobial therapy should be as short as possible. Continuous prophylactic treatment is recommended for no longer than 12 months; for women whose recurrent infections are associated with sexual activity, single-dose prophylaxis before or after sexual intercourse can be effective [78,79]. In older patients it has been found that the risks of long-term antibiotic prophylaxis outweigh the benefits [80]. The impact of continuous antimicrobial exposure on the microbiome, or 'collateral damage', is largely unknown for some commonly used antimicrobial agents (with the exception of fluoroquinolones) [81,82] and further research is needed.

4.2. Non-antimicrobial approaches

There are a number of reasons for considering non-antimicrobial approaches for the prevention of recurrent uUTIs, including tolerability, safety, concerns of AMR, and patient choice. Women with recurrent uUTIs may prefer to avoid repeated courses of antimicrobials, with anxiety regarding side effects, occurrence of other infections, and fear that long-term use will diminish their effectiveness, leaving few treatment options when infections are severe [83,84]. Many women have therefore tried numerous alternative treatments in an attempt to prevent further episodes [3]. The panel agreed that these interventions should be discussed but no definitive recommendations made owing to the limited supportive evidence (Table 3). Counselling should include discussion of risk factors, e.g. sexual intercourse and use of spermicides. However, restricting sexual intercourse may not be desirable or practical for some patients. When discussing personal hygiene, it is important that the patient is educated regarding the potential impact of excessive cleaning of the vaginal region on the local microbiome.

A meta-analysis published in 2020 included data from seven RCTs assessing the effects of increased fluid intake on uUTI recurrence [85]. Rates of recurrence at 6 months and 12 months were both reduced with increased fluid intake, and although antibiotic usage decreased this was not statistically significant. However, the amount of fluid intake, as well as other constituents, e.g. water only versus cranberry solutions, varied widely between individual studies. Panel members felt that increased fluid intake was an acceptable measure if patients can tolerate it or there are no restrictions to this intervention. However, the optimal amount of fluid intake required has not been established.

Results of studies assessing the efficacy of cranberry juice in preventing recurrent uUTIs are conflicting, even when the daily quantity consumed and duration of intake were similar (Table 3) [86–88]. It should also be noted that placebos in these studies were fluid-based, which is a confounding factor. Capsules containing cranberry extract have been directly compared with trimethoprim prophylaxis for 6 months in women aged ≥45 years with recurrent uUTIs [89]. During the follow-up period, there was no significant difference between groups for the number of symptomatic antimicrobial-treated UTIs. However, in a separate study of premenopausal women, 12 months of treatment with cranberry extract was less effective than TMP-SMX in preventing uUTI recurrence [90].

Although the panel members had clinical experience of topical oestrogens for their postmenopausal patients, there are only two small RCTs published to date. In the first, an intravaginal oestriol cream significantly reduced the mean number of events relative to placebo [91]. In the second, the use of an oestradiol-releasing vaginal ring was associated with a significantly longer time to first UTI recurrence relative to no intervention after 36 weeks of treatment [92].

Two immunostimulants have been investigated for the prevention of recurrent UTIs. Some European and Latin American panel members use these for selected patients [1,15], but specialists in other parts of the world do not. The oral lyophilised form of *E. coli* lysate OM-89 (Uro-Vaxom©) is the most widely studied of these and in three trials there was a significant benefit observed with OM-89 versus placebo in the number of recurrent uUTIs at 6 months and 12 months [93–95]. A vaginal mucosal immunostimulant (Urovac©) has also been developed that is administered as a vaginal pessary. In three trials, when patients received both the initial and booster doses there was no benefit relative to placebo over the 20-week period [96–98]. However, in one study there was a significant benefit with immunostimulant therapy in the subgroup of patients with infections caused by *E. coli* [99]. Vaccines against uUTIs caused by *E. coli* are in early clinical development [100,101].

A single published study compared D-mannose with nitrofurantoin and no treatment for a duration of 6 months [102]. Six-month recurrence rates were significantly reduced with both active treatments relative to no intervention; there was no significant difference between D-mannose and nitrofurantoin. One study has reported that annual UTI recurrence rates were higher with methenamine hippurate compared with nitrofurantoin [103], but another found that methenamine hippurate was as effective as trimethoprim [104].

Table 3
Summary of evidence from randomised controlled trials (RCTs) for non-antimicrobial approaches for preventing uncomplicated urinary tract infection (uUTI) recurrence in women

Intervention	Published evidence	Key outcomes
Increased fluid intake		
Scott et al., 2020 [85]	Meta-analysis (7 RCTs of women with recurrent UTIs)	• Increased fluid intake vs. control: overall rate of recurrent uUTI: OR = 0.46 (95% CI 0.40–0.54); $P < 0.001$ • Increased fluid intake vs. control: ≤6-month rate of recurrent uUTI: OR = 0.13 (95% CI 0.07–0.25); $P < 0.00001$ • Increased fluid intake vs. control: 12-month rate of recurrent uUTI: OR = 0.72 (95% CI 0.39–1.35); $P = 0.31$
Cranberry-containing products		
Barbosa-Cesnik et al., 2011 [86]	• RCT (319 women aged 18–40 years with recurrent uUTIs) • Cranberry juice (8 oz daily) vs. placebo for 6 months	• Cranberry juice vs. placebo: 6-month rate of recurrent uUTIs: 19.3% vs. 14.6%; $P = 0.21$
Stapleton et al., 2012 [87]	• RCT (176 premenopausal women aged 18–45 years with recurrent uUTIs) • Cranberry juice (4–8 oz daily) vs. placebo for 6 months	• Cranberry juice vs. placebo: 6-month rate of recurrent uUTIs: HR = 0.78 (95% CI 0.43–1.41); $P = 0.41$
Maki et al., 2016 [88]	• RCT (373 women aged 20–70 years with recurrent uUTIs) • Cranberry juice (8 oz daily) vs. placebo for 6 months	• Cranberry juice vs. placebo: annualised incidence of recurrent uUTIs: RR = 0.62 (95% CI 0.42–0.92); $P = 0.017$
McMurdo et al., 2009 [89]	• RCT (137 women aged ≥45 years with recurrent uUTIs) • Cranberry extract capsules (500 mg daily) vs. trimethoprim for 6 months	• Cranberry extract vs. trimethoprim: 6-month rate of recurrent uUTIs: RR = 1.616 (95% CI 0.93–2.79); $P = 0.084$
Beerepoot et al., 2011 [90]	• RCT (221 premenopausal women with recurrent uUTIs) • Cranberry extract capsules (1000 mg daily) or TMP-SMX for 12 months	• Cranberry extract vs. TMP-SMX: 12-month rate of recurrent uUTIs: 78.2% vs. 71.1%; $P = 0.03$
Topical/intravaginal oestrogen		
Raz and Stamm, 1993 [91]	• RCT (93 postmenopausal women with recurrent UTIs) • Intravaginal oestriol cream vs. placebo for 8 months	• Intravaginal oestriol cream vs. no treatment: 8-month rate of recurrent UTIs: 0.5 vs. 5.9 episodes per patient year; $P < 0.001$
Eriksen, 1999 [92]	• RCT (108 postmenopausal women with recurrent UTIs) • Oestradiol-releasing vaginal ring for 36 weeks vs. no treatment	• Oestradiol-releasing vaginal ring vs. no treatment: 36-week rate of recurrent UTIs: 51% vs. 80%; $P = 0.008$
Immunostimulation		
Bauer et al., 2005 [93]	• RCT (453 women aged 18–65 years with recurrent uUTIs) • OM-89 (3 months of daily dosing plus boosters [a]) vs. placebo	• OM-89 vs. placebo: 12-month mean number of recurrent uUTIs: 0.84 vs. 1.28; $P = 0.0026$
Schulman et al., 1993 [94]	• RCT (166 women with recurrent UTIs) • OM-89 vs. placebo (daily for 3 months then no treatment for 3 months)	• OM-89 vs. placebo: 6-month number of recurrent UTIs: 99 vs. 155; $P < 0.0001$
Tammen et al., 1990 [95]	• RCT (120 patients with recurrent uUTIs) • OM-89 vs. placebo (daily for 3 months then no treatment for 3 months)	• OM-89 vs. placebo: 6-month number of recurrent UTIs: 50 vs. 104; $P < 0.001$
Uehling et al., 2003 [96]	• RCT (54 women with recurrent UTIs) • Vaginal immunotherapy containing suppository with boosters or vaginal immunotherapy containing suppository without boosters vs. placebo	• 6-month rate of freedom from UTIs: vaginal immunotherapy with booster, 55.6%; vaginal immunotherapy without booster, 22.2%; placebo, 22.2%; $P = 0.06$ for vaginal immunotherapy with booster vs. vaginal immunotherapy without booster and for vaginal immunotherapy with booster placebo
Hopkins et al., 2007 [97]	• RCT (75 women with recurrent UTIs) • Vaginal immunotherapy containing suppository with boosters or vaginal immunotherapy containing suppository without boosters vs. placebo	<u>All patients</u> • 20-week rate of freedom from UTIs: vaginal immunotherapy with booster, 46.0%; vaginal immunotherapy without booster, 25.0%; placebo, 16.7%; $P = 0.100$ for vaginal immunotherapy with booster vs. placebo; $P = 0.265$ for vaginal immunotherapy without booster vs. placebo <u>Patients with UTIs caused by *Escherichia coli*</u> • 20-week rate of freedom from UTIs: vaginal immunotherapy with booster, 72.5%; vaginal immunotherapy without booster, 57.0%; placebo, 30.0% $P = 0.0015$ for vaginal immunotherapy with booster vs. placebo; $P = 0.038$ for vaginal immunotherapy without booster vs. placebo
Uehling et al., 1997 [98]	• RCT (91 women with recurrent UTIs) • Vaginal immunotherapy containing suppository low and high dose vs. placebo	• 20-week rate of freedom from UTIs: combined dose vaginal immunotherapy 36% vs. placebo 27%; $P = 0.48$
D-mannose		
Kranjcec et al., 2014 [102]	• RCT (308 women aged >18 years with recurrent uUTIs) • D-mannose vs. nitrofurantoin vs. no treatment for 6 months	• D-mannose vs. no treatment: 6-month rate of recurrent uUTIs: RR = 0.239 (95% CI 0.146–0.392); $P < 0.0001$ • Nitrofurantoin vs. no treatment: 6-month rate of recurrent uUTIs: RR = 0.335 (95% CI 0.222–0.506); $P < 0.0001$ • No significant difference between D-mannose and nitrofurantoin
Methenamine hippurate		
Brumfitt et al., 1981 [103]	• RCT (99 women with recurrent UTIs) • Methenamine hippurate vs. nitrofurantoin for 1 year	• 12-month rate of patients remaining asymptomatic: methenamine hippurate vs. nitrofurantoin, 27% vs. 58% (95% CIs and statistical difference between groups not presented)
Brumfitt et al., 1983 [104]	• RCT (64 women with recurrent UTIs) • Methenamine hippurate vs. trimethoprim vs. topical povidone-iodine for 1 year	• 12-month rate of patients remaining asymptomatic: methenamine hippurate vs. trimethoprim vs. topical povidone-iodine, 28% vs. 45% vs. 53% (95% CIs and statistical difference between groups not presented)

(*continued on next page*)

Table 3 (*continued*)

Intervention	Published evidence	Key outcomes
Probiotics		
Stapleton et al., 2011 [105]	• RCT (100 premenopausal women aged 18–40 years with recurrent uUTIs) • Intravaginal *Lactobacillus* vs. placebo for 10 weeks	• *Lactobacillus* vs. placebo: 10-week rate of recurrent uUTIs: RR = 0.5 (95% CI 0.2–1.2)
Beerepoot et al., 2012 [106]	• RCT (252 postmenopausal women with recurrent UTIs) • TMP-SMX vs. oral *Lactobacillus* for 1 year	• *Lactobacillus* vs. TMP-SMX: mean 12-month rate of uUTI recurrence: 3.2 (95% CI 2.5–4.2) vs. 1.9 (95% CI 1.4–2.6); mean difference not presented
Herbal medicine		
Albrecht et al., 2007 [107]	• RCT (174 patients aged 18–75 years with recurrent UTIs) • Nasturtium + horseradish preparation vs. placebo for 90 days	• Nasturtium + horseradish preparation vs. placebo: mean ± S.D. 90-day UTI recurrence rate: 0.43 ± 0.78 vs. 0.77 ± 1.06; $P = 0.035$
Liu et al., 2019 [74]	RCcol2" valign="top">• T (122 women aged 18–75 years with recurrent uUTIs) • Bazheng powder vs. antibiotics for 4 weeks	• Bazheng powder vs. antibiotics: 6-month rate of recurrent UTIs: 9.1% vs. 14.0% (not significant)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk; S.D., standard deviation; TMP-SMX, trimethoprim/sulfamethoxazole.

[a] OM-89 or placebo capsules: one capsule daily during Months 1–3, no treatment in Months 4–6, one capsule daily for the first 10 days each of Months 7–9, and no treatment in Months 9–12.

Probiotic therapy with *Lactobacillus* has been compared with no treatment and with TMP-SMX in two separate studies. In the first, 10 weeks of treatment with intravaginal *Lactobacillus* reduced the recurrence of UTIs by 50% in premenopausal women [105]. In the second, oral *Lactobacillus* was compared with TMP-SMX treatment over a 1-year period in postmenopausal women. The difference in mean annual incidence between the groups did not meet the prespecified non-inferiority margin [106].

With respect to herbal medicine, one RCT compared a compound of horseradish and nasturtium with placebo and found that it was superior in terms of reducing the 90-day uUTI recurrence rate [107]. In a recently published RCT of 122 women, there was no significant difference in the rate of uUTI recurrence between Bazheng powder and antibiotics [74].

4.3. What is needed now for the prevention of recurrent uncomplicated urinary tract infections?

The panel agreed that there is an urgent need for better understanding of the vaginal, bladder and gut microbiomes and the impact of repeated courses or long-term antimicrobial therapy. Further high-quality research regarding non-antimicrobial approaches for prevention of recurrent uUTIs is warranted.

5. Antimicrobial availability and guidelines

5.1. Current antimicrobial use

Use of specific antibiotics varies between countries and regions and is significantly impacted by availability, guidelines, cost and local resistance epidemiology. However, fosfomycin, nitrofurantoin and pivmecillinam are consistently perceived as effective for the treatment of uUTIs and are typically first-line therapies (although pivmecillinam is not globally available) (Table 4).

The panel strongly agreed that fluoroquinolones should not be routinely used as first-line therapy for the management of uUTIs owing to safety concerns, in line with the warnings issued by the FDA and EMA [27–29]. Among individual panel members from the USA, Brazil, Italy, India, South Korea, China and Japan, increasing fluoroquinolone resistance was reported as a key issue in empirical prescribing for uUTIs. However, these agents remain as recommended treatments in uUTI guidelines, typically as second-line options (Table 4). Continued prescribing of these antimicrobials represents a significant challenge worldwide and is a particular problem in primary care. In an analysis of outpatient data in the USA, the majority of inappropriate fluoroquinolone prescriptions were for uUTIs [108]. Similarly, in a large retrospective cohort study of almost 50 000 women with UTIs managed in primary care, choice of first-line antibiotic was a fluoroquinolone in 20–39% of cases across Brazil, Italy, Belgium and Russia [109]. One panel member reported that in Japan, although it is widely accepted that fluoroquinolones should be reserved for severe infections, they are often still prescribed for uUTIs. Several antimicrobial stewardship interventions including education, clinical decision support tools, and audit and feedback have been successful in reducing outpatient fluoroquinolone prescribing. Further research is needed to facilitate the scale-up and sustainability of these interventions [110–113].

In some countries, e.g. India, fluoroquinolones can be purchased without a prescription. This, however, is a global problem: a recent systematic review that found non-prescription antimicrobial supply to patients with UTI symptoms was available in 68% of cases, with fluoroquinolones being the most frequently purchased agents [114]. Although the problem was estimated to be greatest in Latin America, parts of Africa and Asia, it was not uncommon in parts of Europe. Use of antibiotics without prescription is also prevalent in the USA [115].

With respect to current guidelines for the diagnosis and management of uUTIs, panel members agreed that there are a number of improvements that could be considered. A rapid evidence-based approach is needed as extensive literature reviews are time consuming and evidence difficult to distil; this delays updates to guidelines, which then do not reflect contemporary challenges in real-life clinical practice. A key point of discussion was the use of thresholds for AMR within guidelines that could impact treatment decisions. A key example is the cut-off of 20% local resistance to prescribing of TMP-SMX: this is largely arbitrary, although studies have consistently shown a link between in vitro resistance to TMP-SMX and clinical treatment failure [116–119]. It was therefore suggested that a core international guideline (with brief summaries for diagnosis and treatment) should be developed, with adaptation for local use, taking into account the availability of specific antibiotics, structure of healthcare systems and resistance rates within individual countries and regions, and specific patient risk groups.

For some of the experts, the COVID-19 SARS-CoV-2 pandemic has driven innovation in the management of patients with suspected uUTIs largely due to necessity, primarily with respect to telemedicine consultations (online or via telephone), where this is permitted; studies to date indicate that this approach can achieve successful outcomes with respect to symptom resolution [120]. Telemedicine has some advantages: better access to healthcare for some patients and greater convenience. However, telemedicine consultations have their disadvantages with respect to patients with suspected UTIs, most notably the inability to examine patients. In addition, it is more difficult, if not impossible, to obtain

Table 4
Current guidelines for antimicrobials in uncomplicated urinary tract infections (uUTIs)

Country	Fosfomycin	Nitrofurantoin	AMC	Cephalosporin [a]	Fluoroquinolones	Pivmecillinam	TMP-SMX
Argentina	1st line	1st line		1st line	Not to be used	Not available	Not recommended
Brazil	1st line	1st line	2nd line	2nd line	Not recommended	Not available	Not recommended
Canada	1st line	1st line	2nd line	1st line	2nd line	Not available	1st line
China	1st line	1st line	2nd line	1st line	2nd line	Not available	1st line (if resistance <20%)
Germany	1st line	1st line	2nd line	2nd line	2nd line	1st line	1st line (if resistance <20%)
India	Not recommended	1st line	Not recommended	2nd line	1st line	Not available	1st line
Italy	1st line	1st line	2nd line	2nd line	2nd line	Not available	1st line
Japan	2nd line	Not available	1st line	1st line	2nd line	Not available	Not covered by insurance
Mexico	1st line	1st line	2nd line	2nd line	Not to be used	Not available	Not recommended
South Korea	1st line	Only QD formulation available	2nd line	2nd line	2nd line	Not available	2nd line
Taiwan	2nd line		2nd line	1st line (1st generation)	2nd line	Not available	1st line
USA	1st line	1st line	2nd line	2nd line	3rd line	Not available	1st line (if resistance <20%)

AMC, amoxicillin/clavulanic acid; QD, once daily; TMP-SMX, trimethoprim/sulfamethoxazole.
[a] Includes cefdinir, cefpodoxime, cefalexin and cefuroxime.

urine samples for dipstick testing, culture and antimicrobial susceptibility testing. Innovation in access to home tests for patients is therefore needed.

5.2. Clinical trial design and regulatory criteria

Experts discussed the impact of regulatory criteria (primarily FDA and EMA) on clinical trial design for new treatments in patients with uUTIs and the relevance of the outcomes to clinical practice. The EMA requires the symptoms of dysuria, frequency and urgency as well as pyuria, while the FDA requires at least two of these three symptoms plus suprapubic pain and evidence of pyuria for trial enrolment. The panel members felt that the requirement for baseline $>10^5$ CFU/mL uropathogens excludes 30–50% of women with uUTIs, even though bacterial cell count is not correlated with symptoms, suggesting that the latter are not of interest in formal clinical trial research, which subsequently informs treatment practices. It was suggested that women with lower bacterial counts should be included and outcomes could be analysed by subgroup. The current criteria also render study designs and conduct difficult, and results may not be generalisable to a wider population. FDA guidelines require complete resolution of symptoms for a treatment to be considered effective, which may not be achievable or necessary in patients seen in clinical practice. Additionally, the primary endpoint of combined clinical and microbiological success cannot be used when evaluating non-antibiotic treatments.

5.3. What is needed now?

The panel agreed that simpler guidelines which are easy to access (e.g. via apps) and update would be most useful in clinical practice (Table 1). These could be targeted to different audiences, including family medicine, infectious diseases specialists, urologists and emergency medicine specialists. Multidisciplinary dialogue between healthcare providers involved in managing patients with uUTIs is also needed—surveys could be conducted to understand current challenges in different healthcare systems.

6. Treating uncomplicated urinary tract infections in an age of increasing antimicrobial resistance

It was agreed by all experts that there is a need for local surveillance data specifically for community-acquired uUTIs. However, given the therapeutic success of available antimicrobial agents, such information would currently be unlikely to substantially improve patient outcomes. A critical challenge in the near future is antimicrobial efficacy in the face of an increasing prevalence of ESBL-producing uropathogens in the community setting. Currently, levels are relatively low in North America and some parts of Europe but are much higher in Latin America and Asia [22,24–26,121]. Carbapenemase-producing uropathogens are also on the rise and represent a growing threat to effective antimicrobial therapy [122–124].

Table 5
Risk factors for antimicrobial resistance (AMR) in patients with uncomplicated urinary tract infections (uUTIs)

- Older age (>55 years) [19,125]
- Recurrent uUTIs [135]
- Chronic medical conditions [126]
- Recent antibiotic exposure (within previous 12 months) [18,19,75]
- Hospitalisation within previous 6 months [18]
- Recent travel to countries with high prevalence of AMR [127–129]
- Previous urine culture showing AMR within the previous 12 months [75]

The feasibility of resistance data collection within the community is problematic because: (i) the proportion of patients with uUTIs who have urine culture and susceptibility testing is low, it is a highly selected subgroup of patients, results of their urine cultures tend to be biased, and this precludes extrapolation to the population level; and (ii) the involvement of primary care providers would be needed to collect sufficient data, and this would add to workloads and costs. A surrogate measure to guide empirical prescribing in the treatment of uUTIs and in the absence of surveillance data is an awareness of risk factors for AMR in individual patients (Table 5). These include older age, the presence of chronic medical conditions, recent exposure to antibiotics, travel to areas of high AMR, and previous urine culture demonstrating AMR [19,75,125–129].

6.1. What is needed now?

The panel members agreed that a concerted effort to reduce inappropriate use of fluoroquinolones for the treatment of uUTI globally is urgently required. Surveillance data in the community to better understand local antibiograms and inform appropriate prescribing are also required, although these will be difficult to obtain. The experts agreed that recommendations regarding virtual consultations should now be included in management guidelines for patients with uUTIs.

7. Conclusions

The panel members agreed that management of uUTIs in women can be improved without increasing complexity. In partic-

ular, the diagnostic process can be simplified and consistent across healthcare systems. Antimicrobial agents remain the cornerstone of treatment and prevention for many cases, and more research is needed into the efficacy and safety of non-antimicrobial approaches. It is critical that fluoroquinolone use is minimised to reduce the risk of toxicity (already addressed in class labelling in Europe and the USA), to reduce resistance selection pressure and to preserve these agents for patients with severe infections. Better implementation of international guidelines in the context of local surveillance data is needed. Where this is lacking, improved identification of risk factors for AMR could facilitate appropriate empirical oral treatment in an environment where AMR in uUTIs is likely to increase. The impact of COVID-19 has changed the way physicians interact with patients in many countries, with both advantages and disadvantages. Improvements in virtual consultations could provide an opportunity to enhance patient care in the long term.

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