Consensus document

Diagnosis and treatment of urinary tract infection. Clinical guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

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ABSTRACT

Urinary tract infection (UTI) remains one of the most common infectious diseases encountered in the outpatient setting. Most patients are young healthy sexually active women with uncomplicated UTI. Most women do not require extensive evaluation and can be safely managed as outpatients with oral antibiotics. Antibiotic treatment is empirically established based on the local susceptibility pattern of *Escherichia coli*, which is the causative agent of more than 80% of these infections. Other major clinical problems associated with UTI include asymptomatic bacteriuria and patients with complicated UTI. Complicated UTIs are a heterogeneous group associated with conditions that increase the risk of acquiring infection or failing therapy. Distinguishing between complicated and uncomplicated UTI is important because it influences the initial evaluation, choice and duration of antimicrobial therapy. Diagnosis is especially challenging in the elderly and in patients with indwelling catheters. The increasing prevalence of resistant uropathogens, including extended-spectrum β-lactamases and carbapenemase-producing *E. coli* and *Klebsiella pneumoniae,* and other multidrug-resistant Gram-negative organisms, further compromises treatment of both complicated and uncomplicated UTIs.

The aim of these clinical guidelines is to provide a set of recommendations for improving the diagnosis and treatment of UTI in accordance with the latest published evidence and local resistance patterns.

Keywords:
Urinary tract infection
Asymptomatic bacteriuria
Acute cystitis

Acute pyelonephritis
Recurrent urinary tract infections
Catheter-associated urinary tract infection

Diagnóstico y tratamiento de las infecciones del tracto urinario. Guía de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)

RESUMEN
Las infecciones del tracto urinario (ITU) siguen siendo una de las enfermedades infecciosas más frecuentes del ámbito ambulatorio. La mayoría de infecciones del tracto urinario son infecciones no complicadas que se presentan en mujeres jóvenes, sexualmente activas. En la mayoría de los casos no se requieren pruebas diagnósticas complementarias y se pueden tratar ambulatoriamente de forma segura con antibióticos por vía oral. El tratamiento antibiótico se establece de forma empírica, de acuerdo con el patrón local de sensibilidad de *Escherichia coli,* que es el agente causal de más del 80% de estas infecciones. La bacteriuria asintomática (BA) y las ITU complicadas son otras formas de presentación de la ITU. Las ITU complicadas son un grupo heterogéneo de enfermedades que incrementan el riesgo de adquisición de la infección o de fracaso del tratamiento. La distinción entre ITU complicada y no complicada es fundamental para decidir la evaluación inicial del paciente, la elección del antimicrobiano y su duración. El diagnóstico es especialmente difícil en ancianos y en pacientes con sondaje permanente. El incremento de cepas resistentes a los antibióticos, especialmente *E. coli* y *Klebsiella pneumoniae,* productoras de betalactamasas de espectro extendido y de carbapenemasas y de otros gramnegativos multirresistentes, dificulta la elección del tratamiento de las ITU complicadas y no complicadas.

El objetivo de esta guía clínica es proporcionar recomendaciones basadas en la evidencia para mejorar el diagnóstico y tratamiento de las ITU de acuerdo con la última evidencia publicada.

Palabras clave:
Infecciones del tracto urinario
Bacteriuria asintomática
Cistitis aguda
Pielonefritis aguda
Infecciones recurrentes del tracto urinario
Infecciones urinarias asociadas con el sondaje vesical

Introduction

Justification and opportunity

Urinary tract infection (UTI) is one of the most common clinical problems in both the community and healthcare-associated settings. Community-acquired uncomplicated UTIs (uUTI) are particularly common among women, the vast majority of whom experience at least one episode of infection in their lifetime. A significant subset (25-40%) of women also develop recurrent urinary tract infections (rUTI), with multiple infections that recur over months, or years, in some cases[1,2]. Other relevant clinical problems associated with UTI include

asymptomatic bacteriuria (AB) and patients with complicated urinary tract infection (cUTI)[2–4]. Nosocomial UTI (generally a reflection of catheter-associated infections) constitutes about 20-30% of all hospital-acquired infections and are common sources of nosocomial bacteremia[2,4].

One of the most important factors impacting the management of UTI in recent years has been the emergence of antimicrobial resistance among uropathogens, particularly isolates causing community–acquired UTI. Numerous studies have been published examining rates of *in vitro* resistance among uropathogens in individual institutions or geographic areas. These studies include a variety of patient populations, such as inpatients, outpatients, and people with normal or abnormal urinary tracts. Taken together, these studies demonstrate that *in vitro* resistance is a significant problem, not only in nosocomial complicated UTI, where it has traditionally been recognized as such, but also in community-acquired, uncomplicated UTIs that have typically been simple to treat. Although at the moment antimicrobials can generally ensure the successful treatment or prevention of UTI, the emergence of antimicrobial resistance among uropathogens may soon limit our ability to do so[5–7].

The judicious use of antibiotics and novel non-antimicrobial-based products for preventing UTIs are important strategies to help slow the progression of resistance.

All the above reasons illustrate how variable and complex these infections are, which is why the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica) requested a panel of experts to provide an update on many of the issues involved, including the aetiology, microbiology, prevention, diagnosis, and treatment of various UTI syndromes. The related topic of prostatitis falls outside the scope of these guidelines.

Aims

The main objective of this Consensus Statement is to provide an ensemble of recommendations for improving the diagnosis and treatment of different UTI syndromes in accordance with the latest evidence published.

Methods

Two authors (CP, MC) coordinated the contributions of all other authors (infectious diseases specialists, internal medicine physicians and clinical microbiologists), who appear in alphabetical order. The present statement was written following SEIMC guidelines for consensus statements (www.seimc.org), as well as *Agree Collaboration* (www.agreecollaboration.org) recommendations for evaluating the methodological quality of clinical practice guidelines. Over various meetings, the authors selected a set of questions designed to form the basis of the document. Their recommendations are based on a systematic critical review of the literature including, when necessary, the opinion of experts, who are SEIMC members. Their recommendations have been adjusted according to the scientific evidence available (Appendix 1). All the authors and the coordinators of the statement have agreed on the contents and conclusions of the document. Before final publication, the manuscript was made available online for all SEIMC members to read and to make comments and suggestions.

Definitions

A UTI is defined as a combination of clinical features and the presence of bacteria in the urine. Acute uUTI includes episodes of acute cystitis (AC) or lower UTI, and acute pyelonephritis (APN) occurring in otherwise healthy individuals, most of whom are women with normally functioning urinary tract systems[1,2,8]. Complicated UTI refers to UTI in patients with underlying predisposing conditions, whether medical, functional, or anatomical, or who have been recently hospitalized, which increases the risk of initial infection and recurrence or reduces the effectiveness of therapy. The most commonly found predisposing conditions considered to render a UTI complicated include diabetes, neurogenic bladder, indwelling catheter use and urinary obstruction of any cause[2,4,8].

In lower UTI, the presence of a resistant microorganism alone is not a sufficient criterion for a UTI to be considered complicated, because, with appropriate antimicrobial therapy, the outcome of the illness ought not be affected. Nonetheless, the presence of risk factors for resistance encourages us to be cautious in the management of APN patients and not to discharge the patient early until the antimicrobial susceptibility results have been received.

Although many UTIs in men and the elderly are complicated, a patient who is male or elderly does not in itself necessarily make UTI complicated; some men and elderly individuals can be considered as having uUTI and be treated accordingly[9]. Distinguishing between uncomplicated and complicated UTI is therefore important because it influences the initial evaluation, the location of treatment (outpatient versus inpatient setting), and the selection and duration of antimicrobial therapy[2,10].

Asymptomatic bacteriuria (AB) is the occurrence of bacteria in the urine without causing symptoms. AB is common in the population group that experiences symptomatic UTI (sUTI), but is of clinical significance mainly in pregnant women or individuals who undergo invasive genitourinary procedures[3].

General considerations

Etiology

Most cases of uUTI are due to a single bacterial pathogen, with *E. coli* isolated in 75-95% of cases. Another 5% to 15% of cases may be due to *Staphylococcus saprophyticus* (which is mainly associated with uncomplicated AC), while the remaining cases are usually due to other Enterobacteriaceae such as *Proteus mirabilis* and *Klebsiella pneumoniae.* In uncomplicated APN, the causative agents are similar to those that cause uncomplicated AC; in over 80% of cases, the causative agent is *E. coli*[5,6,11].

The etiology of UTI is modified by factors such as age, sex, diabetes mellitus, urinary tract obstruction, spinal cord injuries (neurogenic bladder) and urinary catheterization, among others, which are all possible conditions of cUTI. The etiology of cUTI is usually more varied and less predictable than uUTI. Microorganisms rarely implicated in UTI in a healthy population are able to cause UTI in patients with anatomical, metabolic and immune disorders. Exposure to antibiotics and a history of hospitalization also determine differences in the etiologic profile. In rUTI, especially cUTI, while *E. coli* remains the main causal agent, there is a significant increase in the relative frequency of infection by *Proteus* spp, *Pseudomonas aeruginosa, K. pneumoniae, Enterobacter* spp, enterococci and even yeast. Furthermore, there is the possibility of mixed infections in which two or more organisms are involved at the same time[4–6,12].

Epidemiology and risk factors

The incidence of UTI is highest in young women, the vast majority of whom experience at least one infection during their lifetime[1,2]. Other groups at increased risk for UTI, as well as complications of UTI, include infants, pregnant women, the elderly, and individuals with diabetes, immunosuppression, spinal cord injuries, indwelling catheters or urologic abnormalities[2,8,10].

Proven risk factors for UTI in young women are previous episodes of cystitis, recent sexual activity, and the use of spermicidal agents during intercourse. The odds of UTI increase by a factor of 60 in the first 48 hours after sexual intercourse. Additional risk factors have been shown to be significant in specific subgroups of the population. Postmenopausal women, cystoceles, urinary incontinence, and prior urologic or genital surgery are significant risk factors for recurrent cystitis. In elderly women, the risk of UTI increases with age, particularly in those with impaired voiding, and is also higher in patients with diabetes.

The prevalence of UTI is low in adult men (0.1% or less) until the later years, when it rises. The increase in UTI frequency in older men is related to prostatic disease and the resultant instrumentation. Other risk factors for the development of UTI in men include insertive anal sex, lack of circumcision, and renal stone disease[2,8–10].

Clinical impact of resistance

In recent years, *E.coli* has shown increasing resistance to several first-line antibiotics and has become a worldwide problem[5,6]. Since the resistance patterns of *E. coli* strains causing uUTI demonstrate considerable geographic variability, specific recommendations for treatment may not be universally applicable to all countries. Recommendations of first-line treatment agents should be supported by up to date local epidemiological data[5–7,11].

In Spain the results of recent studies[6,7] indicate a high prevalence (>50%) of resistance of *E. coli* to aminopenicillins (ampicillin and amoxicillin) and co-trimoxazole (COT) (20-35%). Also, from the beginning of the 1990s we have witnessed a continuous increase in the resistance of uropathogens to fluoroquinolones (FQs), which currently ranges 10-30%. In the ARESC study 26.1% of *E. coli* strains were resistant to nalidixic acid, a marker of the potential future level of FQs resistance, 11.5% with high-level resistance and 14.6% with low-level resistance[5].

Rates of resistance to amoxicillin/clavulanate (AMC) and cefuroxime (CXM) have had a slow but steady increase, and currently 25% of the strains are resistant or intermediate to these antibiotics in retrospective studies[6,7]. Associated resistance involving β-lactams, COT and FQs is common[5,6].

Antibiotics employed specifically in UTI, such as fosfomycin (FOF) and nitrofurantoin (NIT) exhibited low levels of resistance and over 95% of *E. coli* strains isolated in both recurrent and non-recurrent UTI were susceptible[5,6].

In many laboratory-confirmed infections, resistance correlates with clinical and microbiological failure, but there are few studies examining clinical outcome in UTI with resistant organisms, since patients with resistant organisms are usually excluded from clinical trials. In two studies involving lower UTI, resistance to COT was associated with lower rates of bacterial eradication, higher rates of clinical failure and reconsultation than when susceptible organisms were involved[13,14].

In uncomplicated APN, Talan *et al*[15] observed that women infected with strains resistant to COT showed higher rates of bacteriological failure than those susceptible to COT (50% vs. 4%). These results indicate that in women with either APN or AC, infection with a COT-resistant organism predicts clinical failure if COT is used for treatment. There are insufficient data to determine how other antibiotics perform in women infected with resistant uropathogens.

In the case of COT, clinical and mathematical modelling studies consistently suggest a resistance prevalence of 20% as the threshold beyond which the agent is no longer recommended for empiric treatment of AC, although there is insufficient evidence of other antibiotics to recommend thresholds for alternative empiric agents. In addition, the recommended threshold of 10% fluoroquinolone resistance for using an alternative agent for APN is based on expert opinion, since there is no supporting evidence from controlled therapeutic trials[1].

The empiric choice of particular antibiotics to treat very common diseases such as UTI should also consider their ecological impact. The use of broad-spectrum antibiotics is associated with selection of multidrug-resistant (MDR) bacteria, *Clostridium difficile*-associated diarrhea and fungal vaginitis.

RECOMMENDATION

1. An antimicrobial agent is not recommended for empiric treatment of urinary tract infections if local resistance prevalence is over 20% for cystitis (B-II) or 10% for pyelonephritis (C-III).

What microbiological and clinical data should be used to guide empiric treatment of UTI?

To interpret microbiological data on resistance, it should be borne in mind that the data published in many retrospective and even prospective microbiological studies is likely to show bias, because microbiology laboratories tend not to receive many urine samples for uUTI (which are treated empirically as recommended and generally do well), but do receive a significant percentage of urine samples from recurrent and cUTI, where the most resistant bacteria are isolated. Extrapolating data from hospital or cUTI pathogens to uUTI pathogens has its limitations since resistance tends to be overestimated[16].

In a retrospective study conducted in Spain that included cases of cUTI and uUTI, rates of resistance to FQs for lower UTI were higher than in a prospective study, also conducted in Spain, which included only cases of uUTI[6,7], and resistance rates varied significantly by sex, age and geographic location, which may be partly related to different antibiotic prescription patterns across the various communities. In another Spanish study where a urine culture was requested for all suspicious cases of UTI, it was observed that for cUTI, resistance to FQs was 19.5% to ciprofloxacin (CIP) and 25.6% to nalidixic acid, while for uncomplicated UTI, it was 8.5% and 14.6% respectively; these differences were statistically significant. There were also significant differences of FQ resistance by sex, age and previous antibiotic treatment[17].

In a study involving women with uUTI confirmed by culture, it was found that resistance to trimethoprim (TMP) was much less frequent than had been predicted based on the global data of urine cultures sent to the laboratory, 14% versus 24-27%[14].

RECOMMENDATION

1. Studies of the susceptibility of uropathogens in the community tend to overestimate resistance rates. To guide empiric treatment, susceptibility and clinical data (type of UTI (uncomplicated versus complicated), sex, age and previous antibiotic therapy) should be considered (A-II).

Diagnosis

When is a urine culture necessary for the diagnosis of uncomplicated cystitis?

Enterobacteriaceae are the main bacteria isolated in AC, which has a characteristic clinical presentation[1,2,18]. A meta-analysis found that women with at least 2 symptoms of UTI (dysuria, urgency, or frequency) and no symptoms suggesting vaginitis or cervicitis, such as vaginal discharge or irritation, was more than 90% likely to have AC[19].

A urine culture is generally not required for suspected cases of uncomplicated AC because the constellation of symptoms is sufficiently diagnostic, the spectrum of causative organisms and antimicrobial susceptibility profiles are predictable and also because the culture results become available only after the therapeutic decisions need to be made. A randomized trial of management strategies in women with symptoms of AC found that obtaining a urine sample for dipstick testing or culture had no advantages associated with symptom scores or time to reconsultation when compared with immediate empiric therapy[20]. Thus, the current recommendation therefore is to initiate empiric treatment on the basis of symptoms alone and without a pre-therapy urine culture[18,20–24]. The choice of antibiotic is generally determined by the local susceptibility pattern of *E. coli* and the patient's history of antibiotic allergy[21–23].

In certain cases a pre-treatment urine culture may be indicated, in young women, for example, when the diagnosis is not clear from her history and physical examination, or in outpatients with rUTI, who have experienced treatment failure, or have cUTI[24,25], as previously defined. Although *E. coli* remains the most common pathogen isolated in complicated AC, it is found in only 50% of cases. Other Enterobacteriaceae, such as *Proteus* spp*, Klebsiella* spp, *Serratia* spp, *Providencia* spp, as well as *P. aeruginosa,* enterococci, staphylococci and fungi may also play an important role, depending on the underlying conditions[24,25]. Furthermore, the organisms that cause complicated AC are more likely to be resistant to the oral antimicrobials most frequently recommended for uncomplicated AC[10,24,25]. One fluoroquinolone-resistant, extended-spectrum beta-lactamase (ESBL)-producing strain in particular, *E. coli* sequence type 131 (ST131), has emerged globally as a major cause of UTI[10,26,27]. Culture data are especially important for switching therapy in patients who fail to respond to empiric therapy because of infection with a resistant uropathogen, and for switching when appropriate to narrower-spectrum agents[1,10,20,24,25].

Some authors consider all UTIs in postmenopausal women to be complicated, although it is reasonable to consider them uncomplicated if the woman is healthy, ambulatory, and not institutionalized[1]. Urine culture is also considered standard of care in pregnant women[1,3,19,22,24,25,28].

A routine post-treatment culture is not indicated for asymptomatic women following treatment for AC because the advantages of detecting and treating AB in healthy women has been demonstrated only for pregnant women and before urologic instrumentation or surgery.

Post-treatment culture only should be obtained if symptoms persist or recur soon after treatment[3].

RECOMMENDATIONS

1. In women with uncomplicated cystitis, empiric treatment should be initiated on the basis of symptoms alone. A urine culture is generally not necessary (E-I).
2. A pre-treatment urine culture should be obtained when the diagnosis is not clear from the history and physical examination, when the episode represents an early symptomatic recurrence, when there is reason to suspect antimicrobial resistance or the patient's therapeutic options are limited due to medication intolerance (A-II).
3. Routine post-treatment cultures are not indicated for asymptomatic women following treatment for cystitis (E-II) and should only be obtained if symptoms persist or recur soon after treatment (A-II).

Are blood cultures useful in the management of patients with acute pyelonephritis?

Blood cultures are considered to be an important tool for evaluating and managing patients with suspected bacterial infection, although, in the case of APN, detecting the implicated pathogen in a urine culture has a high diagnostic yield[29–31]. Several, mostly retrospective, studies have investigated the utility of blood cultures in patients with complicated and uncomplicated APN and they have all generally supported the conclusion that blood cultures have limited clinical value and seldom vary from urine culture results[29–33]. In a prospective study in a Spanish hospital, 25.2% of blood cultures from 583 women with uncomplicated APN were positive. Only 2.4% of isolates from a blood culture differed from those from the corresponding urine culture, and not a single case required a change of antimicrobial therapy based on blood culture results[32]. In a retrospective study of 246 patients with APN, there were 83 (31%) bacteremic patients. Positive blood cultures were concordant with urine cultures in over 95% of cases and there were no differences in clinical outcome between patients with or without bacteremia[33]. Studies performed on pregnant women with APN reached the same conclusions[34,35].

Discordant results have most frequently been observed in patients receiving antibiotic therapy[36,37]. A study including 800 patients with cUTI from whom both urine and blood cultures were obtained showed that 7% of patients had discordant culture results. Receiving antibiotic therapy at the moment of presentation was associated with a 10.1% risk of having a discordant culture result, compared with 5.4% without antimicrobial treatment. On the basis of these results, the authors recommended collecting both blood and urine cultures in patients receiving antibiotics at the time of hospitalization[36].

At present, there is no supporting evidence from randomized controlled trials to evaluate whether a routine blood culture improves the outcome for the management of APN. In the context of uncomplicated APN, blood cultures are rarely clinically useful and seldom vary from urine culture results[29–33]. Based on the evidence available, the indications for taking blood cultures may be limited to patients with complicated infections, those receiving antibiotics and those with signs of severe sepsis[32,36,37].

RECOMMENDATION

1. The available evidence suggests that there is no need to routinely take a blood culture from women with uncomplicated pyelonephritis (E-II). It seems reasonable, however, to obtain a

blood culture from patients with complicated infections, those receiving antibiotics or who have severe sepsis (B-II).

What number of bacteria in urine is considered significant for the diagnosis of UTI?

A microbiological diagnosis of UTI requires an appropriately collected specimen of urine from which one or more uropathogens meeting specific quantitative criteria are isolated.

A quantitative count of $\geq 10^5$ CFU/mL from voided midstream urine was initially proposed as the diagnostic criterion for defining significant bacteriuria as opposed to contamination[38,39]. Although this criterion is still of general importance for a diagnosis of UTI, there are several exceptions. It is now clear that there is no fixed bacterial count indicative of significant bacteriuria that can be applied to every kind of UTI and all circumstances.

A bacterial count indicating "significant" bacteriuria (the isolate is the likely pathogen) depends on a combination of factors, including the presence or absence of symptoms, the age and sex of the patient, the identity of the uropathogens, and the sampling method[24,38–42].

In patients with UTI symptoms, isolation of $\geq 10^5$ CFU/mL of urine in one sample carries a 95% probability of being true bacteriuria. However, in symptomatic women with pyuria, a lower midstream urine count ($\geq 10^2$ CFU/mL) has been associated with the presence of bladder bacteriuria. In such instances, therefore, a finding of $\geq 10^2$ CFU/mL may be indicative of UTI. In one prospective case-control study, "low count" bacteriuria was more frequent among young women with urinary tract symptoms than among asymptomatic controls and a stepwise increase in bacterial counts from 10^2 to 10^5 CFU/mL was significantly associated with increased incidence of symptoms and pyuria. The authors suggested that low-count bacteriuria reflects an early stage of UTI[42]. In daily clinical practice in most microbiology laboratories, the lower detectable limit is $\geq 10^3$ CFU/mL. A more recent study of healthy premenopausal women with uncomplicated AC confirmed that the presence of *E. coli* in midstream urine was highly predictive of bladder bacteriuria, even at very low counts, with a positive predictive value of 93% for growth of $\geq 10^2$ CFU/mL. In contrast, enterococci and group B streptococci isolated from midstream urine at counts of 10^2–10^5 CFU/ml, often with *E.coli,* were not found in catheterized samples obtained at the same time and were not predictive of bladder bacteriuria at any colony count[43].

In samples obtained by catheterization, in symptomatic women with lower non-catheter related UTI, also a count of $\geq 10^2$ CFU/mL identifies significant bacteriuria[24,41,44].

Counts of 10^2–10^3 CFU/mL are also acceptable in symptomatic males (because contaminants are unlikely to be present in voided urine), in patients already on antimicrobials, and also with organisms other than Enterobacteriaceae[24,41,44]. In bladder urine obtained by suprapubic aspiration, any number of bacteria is considered to be significant, although the count will usually be $\geq 10^3$ CFU/mL. Bladder urine may occasionally be contaminated from the urethra, and small numbers of bacteria may be found in aspirated urine from non-infected persons[24,41,44].

Colony counts of $\geq 10^4$ CFU/mL are indicative of bacteriuria in women with APN (sensitivity 90% and specificity 90%)[40,44,45].

In symptomatic patients with indwelling urethral, indwelling suprapubic or intermittent catheterization, UTI is defined microbiologically as the presence of $\geq 10^3$ CFU/mL of a bacterial species in a single catheter urine specimen or in a midstream voided urine

specimen from a patient whose urethral, suprapubic, or condom catheter has been removed in the previous 48 h[4].

Most UTI are caused by a single microorganism. Recovery of more than one microorganism may be a result of contamination during collection or may represent polymicrobial infection. A single microorganism is almost invariably present in patient with uncomplicated infection. Patients with cUTI (mainly in patients with indwelling long term urinary catheter) may have multiple organisms in their urine. As many as four or more different species may be recovered from patients indwelling long term urinary catheter. However, there is no standard definition for significant bacteriuria in polymicrobial infections. In the opinion of some experts, no more than two bacterial species should be identified in a urine specimen from a patient with cUTI. The microbiology laboratory should be alerted to the possibility of polymicrobial infection, but if this is not done, the specimen should be informed as "contaminated"[41].

In women, AB should not be diagnosed on the basis of a single urine culture. Two consecutive clean-voided specimens with the same uropathogen at counts of $\geq 10^5$ CFU/mL or one positive urine culture with a positive nitrite test in another sample are required for diagnosis. In men, bacteriuria is defined as a single urine specimen with a uropathogen isolated at a count of $\geq 10^5$ CFU/mL. For the microbiological diagnosis of patients with catheter-associated asymptomatic bacteriuria (CA-AB) and patients with condom catheters, a urine culture is considered positive when the bacterial count is $\geq 10^5$ CFU/mL. These criteria apply only to Enterobacteriaceae. Gram-positive organisms, fungi, and bacteria with fastidious growth requirements may not reach titers of 10^5/mL in patients with infection, but may fall within the 10^4 to 10^5/mL range[3].

RECOMMENDATIONS

1. Urine samples for culture should be collected in a manner that minimizes contamination (A-II).
2. For symptomatic women, a culture definition for cystitis is $\geq 10^2$ CFU/mL (A-I) of a uropathogen, and for pyelonephritis $\geq 10^4$ CFU/mL (A-II). In non-catheter-related cystitis, counts of $\geq 10^2$ CFU/ml are significant in urine samples obtained by catheterization (B-III).
3. In males with cystitis, a culture of $\geq 10^3$ CFU/mL is considered to be significant (A-III).
4. In women with cystitis, the concomitant isolation of enterococci or group B streptococci with an Enterobacteriaceae in a midstream urine culture has low clinical significance (A-I).
5. In patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization, symptomatic UTI is microbiologically defined as the presence of $\geq 10^3$ CFU/mL of a bacterial species in a single catheter urine specimen or a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 h (A-III).
6. In bladder urine obtained by suprapubic aspiration, any number of bacteria is considered to be significant (A-II).
7. In women with asymptomatic bacteriuria, two consecutive clean-voided specimens with the same uropathogen at counts of $\geq 10^5$ CFU/mL, or one positive urine culture with a positive nitrite test in another sample, are required for diagnosis (B-II). In men, bacteriuria is defined as a single uropathogen isolated at a count of $\geq 10^5$ CFU/mL (B-III).
8. Asymptomatic bacteriuria in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization is microbiologically defined as the presence of $\geq 10^5$ CFU/mL of

a bacterial species in a single catheter urine specimen or a midstream voided urine specimen from a patient whose urethral (A-III), suprapubic (A-III), or condom catheter (A-II) has been removed within the previous 48 h.

General aspects of antimicrobial therapy for the treatment of uncomplicated UTIs

The aim of antibiotic treatment of UTI is to inhibit growth and kill bacteria present in the urine, as well as in the bladder and kidney tissues in order to prevent complications, such as abscesses in the urinary tract or the spread of infection to the blood[46]. The primary goal of antibiotic treatment in uUTI is to eradicate the uropathogen rapidly and cure the infection[47]. The treatment of uncomplicated AC due to antibiotic-resistant *E. coli* generally results in the longer duration of local symptoms. Furthermore, in APN, it can progress to sepsis and many patients often need longer hospitalization[16].

Which pharmacokinetic/pharmacodynamics parameters of an antibiotic describe exposure-response relationships in general?

The major indicator of the effect of an antibiotic is the MIC, or minimum inhibitory concentration, which provides information about the antibiotic susceptibility of a pathogen. However, use of MIC values as the only marker of the efficacy of an antibiotic agent may be misleading, since the clinical outcome is determined by complex interactions between the three elements of antibiotic therapy: the host, the microorganism, and the drug. Over the last few years, it has become apparent that the pharmacokinetic (PK) and pharmacodynamic (PD) properties are the major determinants of *in vivo* efficacy of antimicrobial agents.

PK/PD represents the relationship between antimicrobial exposure and the effect of the antimicrobial agent on the microorganism (MIC value). Bacterial killing is best described by the indices incorporating the antimicrobial's PK/PD parameters and by the lowest concentration of antimicrobial required to prevent the growth of the target organism[48]. The PK/PD indices are the length of time a free drug concentration exceeds the *MIC (fT>MIC)* for β-lactams (time-dependent antibiotics); the ratio of the maximum plasma concentration of antibiotic to MIC (C_{max}/MIC) for aminoglycosides and FQs (concentration-dependent antibiotics); and the ratio of the area under the concentration-time curve at 24 hours to MIC (AUC/MIC) for glycopeptides, FQs and aminoglycosides (a combination of the two patterns). These indices can be calculated *in vivo* and *in vitro* using population modeling with Monte Carlo simulations (computer algorithms which give probability distributions through repeated random sampling) and are useful for predicting the probability of target attainment (PTA) at different index thresholds using different dosing regimens[49]. The PK/PD breakpoint is the MIC value considered necessary to achieve a PTA of 90%. The value of 90% for PTA is arbitrary, but is currently accepted. Nevertheless, in UTI, lower doses of antimicrobials have been used with good clinical success.

RECOMMENDATIONS

1. Bacterial killing is best described by indices incorporating the antimicrobial's PK and PD parameters and the minimum inhibitory concentration (MIC), the lowest concentration of the antimicrobial required to prevent the growth of the target organism (B-II).

Are urine-specific breakpoints necessary?

It is conventional not to adjust the breakpoints of most antibiotics used for UTI in order to reduce the complexity of multiple interpretive criteria. Moreover, it is not usually possible to distinguish isolates associated with lower versus upper UTI[50]. There are however some antibiotics, like NIT and FOF, which appear in the CLSI guidelines and are used to treat lower UTI only. In 2014, CLSI created a urine susceptibility breakpoint of ≤16 mg/L for the use of cefazolin in uncomplicated UTI due to *E. coli*, *Klebsiella* spp, and *P. mirabilis.* The cefazolin urine breakpoint can also be used to predict the susceptibilities of 7 oral cephalosporins, such as CXM[51].

EUCAST has published several antimicrobial breakpoints that are valid only for isolates from lower uUTI (such as cephalexin, TMP and NIT against Enterobacteriaceae), although none of these agents have breakpoints for isolates from systemic infections. FOF and CXM have separate breakpoints for oral and intravenous formulations, with the oral formulations being for lower uUTI only. In 2014, EUCAST introduced a urinary susceptibility breakpoint for AMC of ≤32 mg/L (amoxicillin concentration plus a fixed (2 mg/L) concentration of clavulanic acid) for uncomplicated UTI[52].

RECOMMENDATIONS

1. Specific susceptibility breakpoints for UTI isolates are recommended (B-III). EUCAST and CLSI have published several breakpoints that are valid only for isolates in uncomplicated urinary tract infections.

Is the antibiotic concentration in serum or urine the most important?

Since there are few PK/PD studies on UTI and its treatment, the relative importance of antimicrobial concentrations of broad-spectrum antibiotics in plasma or urine remains controversial[46,47]. Urinary concentrations of antimicrobial agents are often 100-150 fold higher than serum concentrations over a dosing interval, and human data indicates that urine concentrations are more closely associated with clinical outcome than serum concentrations for lower UTI[53,54]. For the treatment of APN, however, high serum and tissue concentrations of the antimicrobial agent are required[47]. The PK/PD targets for optimal antimicrobial activity in patients with APN have not been studied specifically; nevertheless, experimental data derived from a model of ascending UTI in mice suggested that, in kidney infections, the plasma PK/PD indices of efficacy characteristic of the different antibiotic classes correlate with antibacterial activity in kidney tissue and urine[46]. At least in the case of beta-lactams, it is clear that dosages that achieve effective concentrations in urine but not plasma are unable to reduce the bacterial burden in the kidneys[55].

In order to optimize dosing strategies in acute uncomplicated AC and APN, specific PK/PD indices for UTIs can be calculated from mean serum and peak urine concentrations and the AUC (tables 1 and 2). To take an example, for uncomplicated AC, fosfomycin trometamol (FT) (an antibiotic with concentration-dependent activity and a long post-antibiotic effect)[56] reaches urinary concentrations of >500 mg/L for at least 18-20 h after a 3 g dose. The C_{max}/MIC values (table 1) are at least ten times higher than the standard values that predict efficacy in concentration-dependent antibiotics (138 vs. 10 for aminoglycosides). Inconsistencies

between susceptibility and the predicted efficacy of antibiotics have already been reported. Indeed, CLSI and EUCAST-defined breakpoints for Gram-negative bacilli may overestimate susceptibility, two to fourfold higher than those estimated with PK/PD simulations[57]. Table 2 shows the MIC values at which the PTA is ≥90% for six antimicrobial agents used in the treatment of APN[58]. In sequential therapy, the dose and subsequent exposure to the active drug is considerably lower with oral antibiotics than with the previous parenteral treatment, with the available daily dose reduced by up to 80%. The commonly used oral dosing regimens for AMC (500/125 mg q8h, 875/125 mg q8h) and CXM (500 mg q8h) are expected to provide efficacy for organisms with MICs of up to 2 mg/L (for *f*T >MIC ≥40%) or 0.75 mg/L (for *f*T>MIC ≥65%), respectively[59,60]. However, for pathogens with higher MIC values (such as MIC of AMC of 4 or 8 mg/L), the adequacy of the proposed dosing regimen when switching to an oral formulation would be unacceptable. Although there are no specific articles for patients with APN that report higher failure rates compared with those infected with very susceptible strains, we have observed failure in cases like this when AMC was switched from the intravenous to the oral route.

RECOMMENDATIONS

1. Human data indicates that urinary concentrations are more closely associated with clinical outcomes than serum concentrations for lower UTI. For the treatment of pyelonephritis, however, high serum concentrations of the antimicrobial agent are required (A-III).
2. With beta-lactams, the efficacy of sequential therapy may decrease due to the significant reduction in exposure to the active drug when switching to oral formulations for pathogens with higher MIC values (C-III).

Asymptomatic bacteriuria

Is pyuria useful for diagnosing asymptomatic bacteriuria? Are urine rapid tests recommended for screening of asymptomatic bacteriuria?

AB is defined in section 2.3. Pyuria (the presence of ≥10 leukocytes/mm^3 in uncentrifuged urine) can be determined in patients with non-infectious inflammatory processes, and in patients with AB, it changes over time. Its presence however does not correlate with a higher incidence of sUTI, so that pyuria cannot be considered an adequate criterion for establishing a diagnosis of AB, and the presence or absence of pyuria does not help distinguish between symptomatic and asymptomatic UTI[3].

Detection of urine leucocytes or nitrites by urine test stripes for screening of asymptomatic bacteriuria has a low sensitivity and specificity[61], and are not recommended for the detection of AB.

RECOMMENDATION

1. Pyuria cannot be considered as an adequate criterion for the diagnosis of AB nor for indication for treatment in a patient with AB (A-II). Urine test stripes are not recommended for the detection of AB (A-II).

Asymptomatic bacteriuria in at-risk populations

Pregnant women

The incidence of AB in pregnant women is from 2–10%[62] and has clinical impact, so that it is critical to diagnose and treat it. There is a well-established association between AB and APN during pregnancy. APN increases the incidence of other maternal complications, such as sepsis, acute respiratory failure, acute renal failure and anaemia[63,64], and several studies have associated it with a greater risk of foetal complications, such as low birth weight infants and preterm labour[64–66].

Antibiotic treatment is effective in eradicating AB. A meta-analysis involving 14 randomized or quasi-randomized studies associated it with a significant 77% reduction in the risk of developing APN (OR, 0.23; 95%CI, 0.13-0.41)[67]. Table 3 describes the results of several studies on the treatment of AB during pregnancy[68–81].

In a recent study involving 4,283 pregnant women, only 248 (5.8%) had AB, 40 of whom were treated with NIT (100 mg/12 h for 5 days), 45 with placebo (every 12 h for 5 days) and 163 were left untreated. A significant association between AB and the risk of developing APN was confirmed, although not in relation to treatment, since the risk of APN did not differ between treated and untreated AB patients[81]. The methodological limitations of the study make it difficult to modify the current recommendations and encourage new studies to be performed[82]. Treating AB also reduces the risk of hospitalisation due to APN, from 3-4% before systematic screening was implemented, to 1.4% in the study performed by Hill *et al* in 2005[63].

The relationship between AB and the risk of preterm labour and low birth weight infants is less clear[66,78,81,83]. With regard to the risk of preterm labour in pregnant women treated for AB, two studies with some limitations proved that the risk was lower after treatment[78,83]. Two other meta-analyses[67,84] also noted that treatment resulted in less risk. However, another study[81] did not identify any differences with respect to the risk of preterm labour or low birth weight infants.

The ideal moment for systematic screening for AB has not yet been clearly determined. It seems reasonable to carry out systematic screening[85] between the 12th and 16th week of pregnancy, since there is a higher incidence of AB during this period[86]. Implementation of a systematic screening program reduced the incidence of APN by 67%[87].

There is a high recurrence rate for AB in adequately treated pregnant women (up to 30%), and the Spanish Society of Gynaecology and Obstetrics (SEGO) recommends performing monthly follow-up urine cultures until[85].

RECOMMENDATIONS

1. Systematic screening and treatment of AB is recommended for pregnant women (A-I) in order to reduce the risk of pyelonephritis (A-I), preterm labour and low birth weight infants (B-II). An initial urine culture between the 12th and 16th week of pregnancy is recommended (A-I).
2. A follow-up urine culture is recommended in order to verify that the bacteriuria has been eradicated (A-III). Subsequent monthly urine cultures until delivery are recommended (C-III).

Patients who must undergo urological procedures

For patients with AB who are scheduled to undergo urological procedures, mucosal bleeding is a critical criterion for identifying high- and low-risk patients, and consequently considering initiating prophylactic antibiotic treatment due to the risk of onset of bacteremia and sepsis[88].

High-risk urological procedures. For transurethral resections of the prostate (TURP), patients with AB prior to undergoing the procedure have a 60 per cent risk of developing bacteremia and a six to ten per cent risk of developing sepsis if they do not receive antibiotic prophylaxis[88]. Ad hoc[89] and retrospective randomized studies[90–93] proved that antibiotic treatment was effective in preventing bacteremia and sepsis. Antibiotic prophylaxis should be administered prior to performing a transrectal prostate biopsy, regardless of whether or not bacteriuria is present, given that in a recent meta-analysis[94], prophylaxis was seen to reduce the risk of bacteriuria, bacteremia, sUTI and hospitalisation.

After endourological or percutaneous procedures to treat ureterolithiasis, the presence of bacteriuria before the procedure constitutes a risk factor for bacteremia[95]. There is very little significant information about other urological procedures associated with a high probability of mucous bleeding (high risk), since antibiotic prophylaxis is common in clinical practice[96]. As for those cases where the patient requires the placement of a urethral catheter, some authors recommend prolonging treatment until it is removed, provided that it is temporary[88,89,97].

Low-risk urological procedures. According to a 2008 meta-analysis and European, American and SEGO guidelines, systematic screening and treatment of AB is not recommended. Although prophylaxis reduces the incidence of AB, it does not reduce that of postoperative sUTI[3,98,99].

In patients who underwent cystoscopy without the use of intravesical instillations or antibiotic prophylaxis, only 3.5% with bacteriuria and 1% without it ($p = 0.08$) developed sUTI[100]. No infectious complications were recorded in a study involving urodynamic procedures, although AB persisted in a third of the patients examined and 3.6% of women with no previous history of AB acquired infection[101]. The risk of infection, including symptomatic bacteremia, during replacement of long-term urinary catheters is very low, so that antibiotic prophylaxis is not recommended in this situation either[102,103].

RECOMMENDATIONS

1. Systematic screening for and treatment of AB is recommended prior to performing a TURP of the prostate (A-I) or any other high-risk urological procedure (A-II).
2. Screening and prophylaxis for AB is not recommended for patients scheduled to undergo low-risk urological procedures (A-I).
3. Antibiotic prophylaxis should be initiated immediately before performing the procedure (A-II) and may be prolonged only in patients with a short-term urethral catheter, until removal (C-III).

Premenopausal, non-pregnant women

The prevalence of AB in this population is from 3-5%[104]. Although UTI is more common in young patients with bacteriuria, treatment is not recommended for these cases, since studies showed absence of bacteriuria at the 1-year follow-up in 55% of treated and 36% of untreated women. The incidence of UTI was 36.7% and 35.5%, respectively. Furthermore, of the 88 women who did not have bacteriuria, 5% developed AB and 7% sUTI[105].

Treatment of AB is not recommended for women who suffer rUTI. In a randomized study involving 673 female patients, 26.9% of the treated group vs. 85.3% of the untreated group achieved microbiological eradication. In addition, the percentage of sUTI was significantly higher in the treated group[106]. Increased rates of resistance to AMC, COT and FQs

were also observed in the treated group at the three-year follow-up[107]. In another study, no association was detected between AB and higher mortality or impaired renal function at the 24-year follow-up[108].

RECOMMENDATIONS

1. Systematic screening for AB is not recommended for non-pregnant women under the age of 60 (E-I).
2. Treatment of AB in non-pregnant women under the age of 60 increases the risk of sUTI and rates of antibiotic resistance (B-I).

Diabetic women

In patients with diabetes mellitus, the incidence of AB is 3% in men and between 5 and 25% in women[109]. AB correlates with duration and complications of the disease, but not with recent metabolic control[110].

A randomized study revealed that antibiotic treatment of AB with COT or CIP increased microbiological eradication after 4 weeks; nevertheless, no differences in the incidence of sUTI or rate of hospitalisation for sUTI were reported. Furthermore, a greater number of adverse events were recorded in the treated group[111]. Treatment of AB is also ineffective in terms of long-term microbiological eradication[112], with an 80% relapse rate after pharmacological treatment is discontinued[113].

RECOMMENDATION

1. Systematic screening for and treatment of AB is not recommended for non-pregnant diabetic women (E-I).

Patients with urinary catheters

Short-term urinary catheter (<30 days). AB is common among patients with urinary catheters and is associated with a very low risk of severe infectious complications[114]. Although treating AB reduces its incidence, it does not reduce the prevalence of sUTI or severe complications, even in intensive care units (ICU) [115], and it does increase colonization with resistant microorganisms[3].

The AB episode tends to resolve spontaneously after catheter removal, especially in younger patients compared to elderly ones (74% vs. 4%). Treatment was only observed to reduce the incidence of sUTI in women when AB persisted 48 hours after removal of a short-term catheter[116].

Long-term urinary catheter (>30 days). For those who wear permanent urinary catheters and suffer an AB episode, appropriate consecutive antibiotic treatment vs. no treatment eradicates bacteriuria, albeit with immediate recurrence of the episode. In such cases, treatment does not reduce the number of infectious febrile episodes or improve the patient's clinical condition and is associated, in the case of recurrent episodes, with the replacement of the original bacteria by antibiotic-resistant strains[3,117–119]. Treatment of AB, therefore, is not recommended for patients with permanent urinary catheters. Asymptomatic candiduria is frequent and also does not require treatment.

Prophylaxis is not systematically recommended either during the removal or replacement of a catheter in order to reduce the risk of UTI[1]. Although there is some risk of

bacteremia associated with mobilization of the catheter, the episode would, in most cases, be transient and asymptomatic[102,103,120]. Based on our own experience, antibiotic treatment may be advisable during traumatic replacements associated with haematuria, since there have been some reports of episodes of symptomatic bacteremia.

RECOMMENDATIONS

1. Systematic screening for and treatment of AB is not recommended for patients with short-term (E-II) or long-term urinary catheters (E-I).
2. Treatment of AB in women is recommended only if AB persists 48 hours after removal of the catheter (B-I).
3. Systemic antibiotic prophylaxis is not recommended during catheter replacement, since the risk of onset of symptomatic bacteremia is low (E-II); nonetheless, it may be recommended in cases of traumatic replacement associated with haematuria (C-III).

Elderly persons residing in the community

The incidence of AB increases with age and is estimated to be between 10.8% and 16% in women and 3.6% and 19% in men over the age of 70[121]. In such patients, treating AB with antibiotics achieves greater control of bacteriuria at the six-month follow-up, but does not reduce the frequency of sUTI[122,123]. In randomized studies, treating AB did not reduce patient mortality either[124].

RECOMMENDATION

1. Systematic screening and/or treatment of AB is not recommended for elderly patients living in the community (E-II).

Elderly institutionalised subjects

There is a higher incidence of AB in elderly institutionalised patients, estimated at between 25% and 50% in women and 15% and 40% in men[121]. Although antibiotic treatment in elderly institutionalised patients with AB is associated with better initial microbiological control, this situation is transitory, and only 6% of treated patients continued without bacteriuria or displayed fewer sUTIs secondary to treatment after 24 months[125]. No associated benefits have been identified in terms of morbimortality. Moreover, the incidence of reinfection, adverse events or the isolation of resistant microorganisms during recurrent episodes is higher in the treated group[126].

RECOMMENDATION

1. Systematic screening and/or treatment of AB is not recommended for institutionalised elderly patients (E-I).

Patients about to undergo orthopaedic surgery

The incidence of preoperative AB prior to arthroplasty procedures is variable. However, the issue of whether or not it is worthwhile diagnosing and treating it in order to reduce the risk of surgical site infection is still a contentious one. In one study involving 510 cases planned for

joint replacement surgery, only 25 patients (5%) exhibited signs of UTI and there were no negative effects on the joint prosthesis[127]. In another study, preoperative AB was not linked to prosthetic joint infection (PJI)[128]; nonetheless, all patients included in both studies had received prophylactic treatment with CXM. In two further studies, preoperative treatment of AB did not reduce the incidence of PJI and the microbiological isolates obtained were different from the preoperative urine cultures[129,130].

In patients scheduled to undergo complex spinal fusion surgery, the evidence supporting the benefits of detecting and treating episodes of AB is weak. In one meta-analysis, despite the wide variety of source studies, AB was not considered to be a risk factor for infection after spinal surgery[131]. In a study with two consecutive cohorts, cohort A, where the presence of preoperative AB was not investigated, and cohort B, where preoperative AB was screened and treated in patients at risk of developing UTI (neurogenic bladder, urinary incontinence, indwelling catheter), rates of surgical wound infection among untreated and treated patients were 9.3% and 6.7% respectively ($p > 0.1$), and there was a significant decrease in the incidence of gram-negative infections (68.2% vs. 33.4%; $p < 0.04$)[132].

RECOMMENDATIONS

1. Systematic diagnosis or treatment of AB is not recommended for patients scheduled to undergo total hip or knee arthroplasty (A-I).
2. Screening and treatment of AB prior to performing instrumental spinal surgery is recommended for patients with urinary catheters, neurogenic bladders or urinary incontinence in order to reduce the risk of gram-negative surgical site infections (B-II).

Patients with spinal cord injury

The incidence of AB in patients with spinal cord injury is 50% among patients undergoing sphincterectomy or intermittent catheterisation, and 100% in patients with permanent or suprapubic urethral catheters[3], and the risk of sUTI is high (2.5 episodes/patient/year) due to the difficulty of emptying neurogenic bladders[133–136].

Treatment for AB did not reduce the incidence of sUTI and AB episodes tended to recur soon after antibiotic treatment and were associated with increased risk of selection of resistant microorganisms[137–140].

RECOMMENDATION

1. Systematic screening and treatment of AB is not recommended for patients with spinal cord injury treated with intermittent urinary catheterisation (E-II).

Transplant recipients

In renal transplant recipients, UTI is the most common infection, particularly in the first year after the transplant procedure[141–143]. AB is not considered a risk factor for sUTI[144]. The recommendations for the need to diagnose and treat AB are both controversial and variable; hence, the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines refuse to make any recommendation[145], whereas the ISDA guidelines[3], the American Society of Transplantation Infectious Diseases Community of Practice and others[142,146–149] recommend diagnosis and treatment in the first 3-6 months after the transplant due to the increased risk of onset of sUTI during this period, and the association with underlying urological abnormalities. A prospective randomized study assessed the impact of AB on cases of kidney transplants with at least one-

year post-transplantation follow-up and noted that 21% (9/43) of treated patients vs. 31% (14/45) of untreated patients developed sUTI ($p > 0.05$)[150]. Two recent ad hoc studies analysed the impact of AB one month after transplantation and identified only one sUTI episode among untreated patients and none in treated patients[141,151]. On the basis of these studies, as well as Spanish guidelines for UTIs and solid organ transplants (SOT) and a recent review, the screening and treatment of AB in kidney transplant recipients is recommended only in the first month after transplantation[110,143].

Although systematic treatment of asymptomatic candiduria has been recommended for patients with kidney transplants[152], the new 2016 Infectious Diseases Society of America (IDSA) guidelines recommend treatment only for high-risk patients, such as neutropenic patients and/or patients scheduled to undergo urological procedures. In carriers of urinary catheters, removal of the catheter should suffice[153]. Screening and treatment of AB has not yet been assessed for cases of SOT other than kidney transplants[3], and the guidelines for prevention of infections in hematopoietic stem cell transplants do not include recommendations for the screening and treatment of AB[154].

RECOMMENDATIONS

1. For kidney transplant patients, the screening and treatment of AB is only recommended in the first month after transplantation (B-III).
2. For cases of hematopoietic stem cell transplants and SOTs other than kidney transplants, no recommendations for the screening and treatment of AB can be made (C-III).
3. Systemic antifungal therapy for asymptomatic candiduria is not recommended for transplant patients, except for neutropenic patients or those scheduled to undergo urological procedures (D-III).

Orthotopic neobladder

AB is very common in this group of patients, with a prevalence of 57–81%[155]. Nevertheless, antibiotic treatment does not eradicate bacteriuria[156], but favours the selection of resistant microorganisms, thus supporting the recommendation not to systematically screen for or treat AB[155].

RECOMMENDATION

1. Systematic screening and treatment of AB is not recommended in patients with an orthotopic neobladder (D-III).

How long does it take to treat an asymptomatic bacteriuria?

Once indications for treatment have been determined, it is essential to determine its duration. The optimal duration of treatment of AB in pregnant women has not yet been defined. Table 4 describes studies comparing use of a single one-day dose vs. 4- to 7-day courses of antibiotic treatment for AB in pregnant women[157–170]. Although one-day and single-dose treatment regimens theoretically improve compliance and entail significant advantages, a meta-analysis published in 2015[171] that compared one-day treatment regimens (including single doses) with standard 4- to 7-day treatments concluded that eradication of bacteriuria was significantly higher in patients who received a 4- to 7-day course of treatment with the same antibiotic

(OR, 1.72), and similar when a single dose of FT 3 g was compared with a 5-day course of CXM[168] or a 7-day course of AMC or NIT[169,170].

In patients with AB scheduled to undergo urological procedures associated with a high risk of mucous bleeding, a single-dose therapy before the procedure (with a second postoperative dose if placement of a urethral catheter was involved) was as effective in preventing postoperative infections as prolonged preoperative treatment that continued until a negative urine culture was achieved. For cases where the patient requires placement of a urethral catheter, some authors recommend prolonging treatment until it is removed, provided that it is temporary[88,89,97].

Although a meta-analysis of antibiotic prophylaxis use in transrectal prostate biopsy proved that there was an increased risk of bacteriuria with single-dose versus multiple-dose antibiotic treatment (RR: 1.98; 95%CI: 1.18-3.33), the authors concluded that there was insufficient data to guarantee that a 3-day course of treatment was better than a 1-day treatment, that a multiple-dose regimen was better than a single-dose, or that the risk was related to route of administration of the prophylactic treatment[172].

RECOMMENDATIONS

For pregnant women with asymptomatic bacteriuria

1. Standard 4- to 7-day treatment regimens are better than short one-day treatments for eradicating bacteriuria (A-I). Only a single 3 g dose of FT offers similar results to the standard treatment regimen (A-I).

For patients scheduled to undergo high-risk urological procedures

1. The administration of a single-dose of an appropriate antibiotic is recommended immediately prior to the procedure (A-II).
2. Prolonging antibiotic treatment after these procedures is only recommended for patients with a short-term urethral catheter and until it has been removed (C-III).

Treatment for acute uncomplicated cystitis

What is the first-choice empiric antibiotic treatment recommended for acute uncomplicated cystitis?

Although there is considerable variation in susceptibility rates to antibiotics between countries, the rates of antimicrobial resistance associated with the antibiotics specifically employed against UTI (FOF, pivmecillinam and NIT), in both recurrent and non-recurrent UTI[173,174], are low in all countries of Europe. The latest European guidelines include the three antibiotics mentioned above as first-choice agents for therapy for uncomplicated AC in women[1,173,174]. Pivmecillinam is not currently available in Spain.

Fosfomycin trometamol. FOF, a phosphonic antibiotic, acts by inhibiting cell wall synthesis and has broad-spectrum bactericidal activity against staphylococci, enterococci, *Haemophilus* spp and most gram-negative enteric bacteria, including 95.5% of extended-spectrum beta-lactamase (ESBL)-producing *E. coli*[175,176].

In Spain, there is an intravenous formulation of FOF, disodium fosfomycin, and oral formulations, either calcium or tromethamine salts (also known as trometamol). FT is administered solely for treatment of uncomplicated AC in a single 3 g dose. It is absorbed best when taken before food[175]. It reaches high concentrations in the urine and maintains high levels for over 24 hours[175,176]. A recent open-label study estimated that fosfomycin calcium

(1 g administered three times daily for 2 days) provides comparable efficacy to treatment with a single 3 g dose of FT[177].

Several clinical studies have compared the clinical and microbiologic efficacy of FT with other first-line antimicrobials used against uncomplicated AC. The clinical efficacy of one (3 g) dose of FT (91% cure) is comparable to that of NIT (93%), COT (93%) and FQs (90%) in uncomplicated AC (table 5)[2]. The microbiological cure rate of FOF (80%) is lower than with comparable antibiotics, 82% versus 94%[1,21], although a recent meta-analysis of 27 trials found no difference in efficacy between FOF and other antibiotics for the treatment of cystitis, and also that FOF was associated with significantly fewer adverse reactions in pregnant women[178]. Furthermore, a recent randomized single-blind study found that one 3 g dose of FT was as effective as CIP at 500 mg twice a day for 5 days for the treatment of uncomplicated AC, as shown in table 6[179].

FOF is also useful for the treatment of MDR organisms. Several *in vitro* studies have demonstrated that FOF is active against vancomycin-resistant enterococci, methicillin-resistant *Streptococcus aureus,* and ESBL-producing gram-negative rods[1,175,176,180]. Two studies evaluated oral FT treatment for ESBL-producing *E. coli*-related lower urinary tract infection, either in the form of a single 3 g dose or once every other night for three nights. Treatment with FOF was associated with clinical cure in 75 out of 80 (93.8%) patients included in these two studies[180]. Observational studies also showed that FT can be effective in the treatment of UTI due to *K. pneumoniae* carbapenemase-producing Enterobacteriaceae as a 3 g dose repeated every 48 to 72 hours[175].

Finally, FOF appears to have minimal propensity for collateral damage. This assumption is supported by the high rate of *E. coli* susceptibility in regions where FOF is frequently used for uncomplicated AC in women[1].

Nitrofurantoin. NIT, a synthetic nitrofuran, was initially introduced in microcrystalline form. In 1967, a macrocrystalline form with improved gastrointestinal tolerance became available[175,181]. Nowadays, there are two basic presentations of NIT: the macrocrystalline form and as a mixture of microcrystalline and macrocrystalline forms (25 mg macrocrystals plus 75 mg monohydrate form)[175,181] blended in a patented dual delivery system, known in the USA as nitrofurantoin monohydrate/macrocrystals[182]. For UTI therapy, 50–100 mg of macrocrystalline nitrofurantoin is taken orally four times a day[175]. The dose for the mixed microcrystalline and macrocrystalline formulation is 100 mg twice daily[175,181]. The latter presentation is not commercially available in Spain.

NIT is active against more than 90% of *E. coli* strains causing UTI[175,181]. Resistance to NIT is uncommon, probably because of the multiple sites of action of the drug. However, *Proteus*, *Serratia* and *Pseudomonas* have natural resistance to NIT[175]. Enterococci, including those that are vancomycin-resistant, are susceptible to NIT. *S. aureus* and *S. saprophyticus* are usually susceptible[175]. Although it has been suggested that NIT could also be an option for treating AC produced by ESBL-producing bacteria[180], a recent study showed low clinical (69%) and microbiological success rates (68%)[183].

Absorption is improved when NIT is taken with food[175]. Serum concentrations are low or undetectable with standard oral doses, as are concentrations in prostatic secretions[175]. The antibiotic is eliminated predominantly through the urine, where the drug concentration easily exceeds the MIC for susceptible organisms. NIT should not be administered to patients with creatinine clearance <60 mL/min[175]. NIT has been used safely in pregnant women and children.

The established duration of therapy for NIT is 5-7 days[184]. Clinical efficacy studies show that there is an overall equivalence between NIT administered for 5 to 7 days and COT, CIP and single-dose FT, with a clinical cure rate for NIT of between 79% and 95%, and a microbiological cure rate of between 74% and 92%[1,175,181].

NIT is now considered a first-line therapeutic agent for acute uncomplicated AC because of the efficacy of the 5-day course of treatment and the small risk of collateral damage to normal human flora[1]. NIT should not be used to treat APN[1,2,175,181].

Fluoroquinolones. Several studies have demonstrated the efficacy of FQs in the treatment of UTI. Overall clinical and bacterial efficacy rates in studies are consistently high, although occasionally they have been <90% (table 5)[1]. A recent meta-analysis showed that FQs are the most effective therapy compared with other antimicrobials[185]. According to a Cochrane analysis, all FQs suitable for UTI therapy show the same effectiveness for this indication, although tolerability may vary[186]. Table 7 summarizes the dosages for different FQs. Single-dose FQ therapy may be an option for uncomplicated AC, but has lower effectiveness than 3-day regimens[1].

The main concern with respect to FQ use in AC is the appearance of resistance, not only among uropathogens, but also other organisms, including MRSA, that cause more serious and difficult-to-treat infections at other sites[1]. The IDSA guidelines therefore advise limiting the use of FQs to episodes of uncomplicated AC for which other UTI antimicrobials are unsuitable[1].

β-Lactams. In the IDSA guidelines, pivmecillinam was proposed as a first-line drug for empiric treatment of uncomplicated AC[1], although this drug is not licensed in Spain. Ampicillin and amoxicillin can no longer be recommended as empiric treatment, given the very high prevalence of antimicrobial resistance[1,2,187].

The most commonly used β-lactams for the treatment of lower UTI have been AMC and oral cephalosporins. Second-generation oral cephalosporins (CXM, cefaclor) show improved activity against *E. coli* compared to first-generation cephalosporins, but less activity than those of the third-generation (cefditoren pivoxil, cefixime, cefpodoxime proxetil and ceftibuten) [187]. In the ARESC study, the overall resistance patterns of *E. coli* isolates and all uropathogens to CXM were very similar to those for AMC[6]. Table 7 shows dosages for the most commonly used cephalosporins in our country for treatment of UTI. Most studies demonstrate that β-lactams (in 3-7 day regimens) generally have worse cure rates than FQs[1,21,185,187]. A recently published randomized controlled trial on cefpodoxime showed that it was inferior to CIP[188]. In addition, a recent meta-analysis showed that the efficacy of AMC was low compared to other antibiotics[185]. Possible explanations for this inferiority are that β-lactam use is associated with a lower rate of eradication of vaginal uropathogens and persistence of the reservoir of infection[1,21], or that is has low intracellular penetration, which could make intracellular uropathogens difficult to eradicate[189]. AMC may also be useful for treating patients with cystitis due to susceptible ESBL-producing Enterobacteriaceae[180]. In clinical practice, because it is a broad-spectrum drug, it is associated with increased risk of vaginal candidiasis[6].

The use of broad-spectrum cephalosporins has been associated with collateral damage, the most disturbing being ESBL resistance among gram-negative bacteria[1]. As a result, experts advise avoiding β-lactams for empiric therapy of uncomplicated AC, unless none of the recommended agents are appropriate.

Co-trimoxazole. (Trimethoprim-sulfamethoxazole 160/800 mg twice daily for 3 days) is a highly effective antimicrobial for the treatment of AC, with clinical and microbiological cure

rates ranging between 86% and 100% and between 85% and 100%, respectively (table 5)[1]. It involves less collateral damage than broad-spectrum cephalosporins or FQs[1] and is therefore recommended as a first-line agent in the IDSA guidelines when the rate of resistance is expected to be <20%. Previous data has shown that TMP (100 mg twice daily for 3 days) was equivalent to it in combination with sulfamethoxazole[1].

In Spain, however, the reported resistance patterns of *E. coli* to COT have varied from 27% to 34%[6,173,190] and it should not be used as empiric treatment. Nevertheless, COT is an excellent antimicrobial in cases known to be caused by susceptible strains of uropathogenic bacteria.

In conclusion, the choice of agent should be individualized on the basis of the patient's allergy and compliance history, prevalence of local community resistance, availability, cost, and ecological impact. If the first-line antimicrobial agents (FT or NIT) are not a good choice on the basis of one or more of these factors, FQs or β-lactams are reasonable alternatives, although it is preferable to minimize their use because of concerns about ecologically adverse effects (and efficacy in the case of β-lactams).

Regarding the duration of AC treatment, the effectiveness of short therapy has been only adequately studied in healthy (young and elderly) women with uncomplicated non-recurrent cystitis with short symptom duration. For patients with symptoms longer than 7 days, recent UTI (<1 month), with diabetes, renal insufficiency or immunosuppression or with a vaginal diaphragm, a longer course of antibiotic therapy (at least 7 days) is recommended. In men, the efficacy of a short course therapy has not been evaluated, and treatment has been traditionally administered for 7-14 days[191]. If FT is used, a 3 g dose should be administered on day one and four.

RECOMMENDATIONS

1. Due to minimal resistance and propensity for collateral damage, fosfomycin-trometamol (3 g in a single dose) and nitrofurantoin (for 5-7 days) are considered the first-choice drugs for therapy of uncomplicated cystitis (A-I).
2. Fluoroquinolones (ciprofloxacin, levofloxacin and norfloxacin) are highly efficacious in 3-day regimens (A-I), but should be considered as alternative antimicrobials because of their high propensity for collateral damage (B-III).
3. β-lactam agents, including amoxicillin-clavulanate, cefuroxime, ceftibuten, for 5 days, and cefixime for 3 days regimens, are appropriate choices for therapy when other recommended agents cannot be used (B-I). β-lactams generally have inferior efficacy and more adverse effects when compared with other UTI antimicrobials (B-I). Ampicillin and amoxicillin should not be used for the empiric treatment of uncomplicated cystitis, given the high incidence of antimicrobial resistance to these agents (E-I).
4. Co-trimoxazole is not recommended for empiric treatment in Spain, because the resistance rate in *E. coli* is greater than 20% (E-I). If the infectious organism is susceptible to co-trimoxazole, this agent is very effective therapy (A-I).
5. In men, and in women with symptoms longer than 7 days, recent UTI, diabetes, renal insufficiency, immunosuppression or with a vaginal diaphragm a longer course of antibiotic therapy (at least 7 days) is recommended (C-III).

Community-acquired acute pyelonephritis

In these guidelines, "complicated APN" refers to any episode occurring in patients with any conditions predisposing to poor outcomes, even if they receive appropriate antibiotics. These include: a) men, children, pregnant women and individuals aged ≥65; b) women with functional or anatomical urinary tract abnormalities that cause obstruction or voiding disorders, any sort of ureteral derivation or foreign body (including indwelling bladder catheters), polycystic kidney disease, single kidney, recent (within 1 month) instrumentation or urinary tract surgery, diabetes mellitus, renal insufficiency or transplantation, other immunosuppressed states or underlying diseases (liver cirrhosis, active malignancy, congestive heart failure), and c) severe sepsis.

What are the criteria for hospital admission in adult patients?

Any of the above conditions in association with complicated APN is a criterion for hospitalization. At the same time, circumstances that increase the risk of MDR microorganisms are also relevant for making decisions about the place of care. These include patients with the following conditions defining "healthcare-associated urinary tract infections" (HCA-UTI): a) receiving intravenous therapy, wound care or specialized nursing care at home in the 30 days prior to the episode; b) attending a hemodialysis ward or receiving intravenous chemotherapy in the 30 days before the episode; c) hospitalization in an acute-care hospital for 2 days or more in the 90 days before current hospitalization; d) residence in a nursing home or long-term care facility (LTCF); e) undergoing an invasive urinary procedure in the 30 days before the episode or having a long-term indwelling urethral catheter.

At least two well-designed controlled prospective trials[15,192] and a small randomized trial[193] have demonstrated that women under 60 with APN who tolerate oral intake, do not present severe sepsis, have no history of functional or anatomical abnormalities of the urinary tract or significant comorbidities and do have access to medical follow-up, can be safely managed as outpatients with appropriate oral antibiotics. Multiple studies[194–202] have consistently shown that women with mainly uncomplicated APN and pregnant women with otherwise uncomplicated non-bacteremic UTI can be safely discharged and treated with an appropriate oral antibiotic after an observation period of up to 24 h and 1-2 doses of parenteral antibiotics.

In pregnant women, two randomized trials compared outpatient and inpatient approaches[200,201] and found no difference in success between oral and intravenous regimens[203]. Some authors prefer hospital admission because pregnant women remain at an increased risk of respiratory failure (≈7%), acute renal dysfunction or preterm labour[63].

Finally, there are observational studies that indicate that patients with APN can be managed in a hospital-based home unit when intravenous antibiotics are required or daily control of an underlying disease is considered necessary[204].

Although advanced age is not commonly mentioned as a criterion for complicated APN[18], several retrospective studies have found that it is an independent predictor of mortality[205,206]. There is almost no evidence that male gender is an independent predictor of poor outcome, although it may still be justified to consider APN in men as complicated because of its higher association with urological abnormalities. There has also been some controversy concerning diabetics when there is no renal insufficiency or functional or anatomical abnormalities. Nonetheless, the association of diabetes with some severe complications and the frequent requirement for better metabolic control justifies retaining diabetes in the complicated category. There is little information regarding the prognostic role

of other underlying diseases, although immunosuppression, liver cirrhosis, malignancy, congestive heart failure and having an ultimately or finally fatal underlying disease have all been associated with poor outcomes in observational studies[205,207,208]. In several retrospective studies[206,209], leukocytosis ≥15,000-20,000/µL and serum C-reactive protein level of ≥15-20 mg/dL were also independent predictors of early clinical failure.

Lastly, community-onset HCA-UTI is associated with increased rates of MDR in *E. coli*, as well as a higher incidence of non-*E. coli* microorganisms, inappropriate empiric therapy and worse outcome[210,211], so that these patients may justify a particular approach, regardless of whether the infection is considered as complicated on other grounds. In addition, for patients who do not fulfill the HCA-definition, the presence of at least two specific risk factors from recent receipt of FQs or cephalosporins, recent hospitalization, transfer from another healthcare facility (including long-term care facilities), recent urinary catheterization, older age (>70 years), and a Charlson score higher than 3, may still place the patient at sufficient risk of ESBL-producing gram-negative enteric bacilli as to consider specific parenteral treatment until microbiological data are available[212]. Recent travel to highly endemic areas or previous infection/colonization with ESBL-producing Enterobacteriaceae should also be taken into account[212].

RECOMMENDATIONS

1. Women with uncomplicated APN and mild to moderate symptoms (fever <39 °C, no severe flank pain, no vomiting) can be treated as outpatients (A-II).
2. Women with uncomplicated APN but with social, mental or physical disabilities that might hinder adherence to a prescribed therapeutic regimen should be admitted to hospital (C-III).
3. Women with uncomplicated APN and severe symptoms (fever ≥39 °C, severe flank pain, vomiting) should be referred to an emergency room for evaluation, parenteral antibiotics and supportive measures (A-II). If, after 24 hours, there is improvement and good oral tolerance, the patient may be sent home with oral antibiotics (A-II).
4. Patients with complicated APN or healthcare-associated APN and those with risk factors for MDR Enterobacteriaceae should be admitted to hospital (A-II).
5. Pregnant women with otherwise uncomplicated APN and non-severe symptoms may be considered for treatment as outpatients if appropriate follow-up is assured (B-I). A normal abdominal ultrasonography is recommended before discharge (C-III).
6. Selected APN patients with no severe sepsis, no obstructive uropathy (as recorded by ultrasonography), no altered mental status, no metabolic abnormalities and who have a responsible caregiver at home, may be managed in a hospital-based home care unit (B-III).

What are the main therapeutic options for pyelonephritis in the different clinical situations, and which are not recommended for empiric treatment because of the high rate of resistance in our setting?

Aminoglycosides, beta-lactams, COT, and FQs have all been successfully used to treat patients with APN in prospective controlled trials[15,209,213–216].

Since *E. coli* would be involved in at least 65% of either uncomplicated or complicated cases of APN[32,207], the resistance rates of these microorganisms are of primary concern. However, there is little recent specific data on this issue in our country (2006 or later) for different subsets of patients with APN[6,7,190,207,210,211,217]. All these studies as well as recent

unpublished studies (tables 8 and 9) showed high rates of resistance to ampicillin (49%-66%), COT (21%-36%), CIP (15-30% in community-acquired infections), and AMC (14%-24%), regardless of gender or setting. In community-acquired uUTI, *E. coli* resistance to third-generation cephalosporins was consistently below 10%, although this rate exceeded 10% (10.2%-25%) in series that included febrile infections in men, complicated APN and healthcare-associated infections[207,210,211,218]. The prevalence of resistance to gentamicin (GEN) needs to be clarified; resistance rates range from 3.4% to 11% in community-acquired isolates[190,219] to as high as 18% in healthcare-associated isolates[211]. *E. coli* susceptibility to piperacillin-tazobactam (PIP-TAZ), ceftolozane-tazobactam, amikacin (AMK) and FOF is at least 95% in patients with community-acquired infections, and virtually 100% in the case of carbapenems. Up to 88% of ESBL-producing *E. coli* strains and about 40%-55% of ESBL-producing *K. pneumoniae* are non-resistant to PIP-TAZ (CMI ≤16 mg/L) [220], and there is some evidence that PIP-TAZ is appropriate for treating susceptible bacteremic ESBL-producing *E. coli* strains when the source is the urinary or biliary tract[221]. However, resistance to PIP-TAZ of up to 16% has been described for Enterobacteriaceae causing community-onset healthcare-associated bacteremic UTI[210]. *P. aeruginosa* and *Enterococcus* spp are a concern only in patients with community-onset HCA-UTI and, even in this context, frequencies have varied between 4% and 14% for *P. aeruginosa* and between 5% and 11% for enterococci[210,211].

An analysis of randomized controlled trials of doripenem, imipenem and levofloxacin (LVX), found a 31.8% rate of resolution for cUTI in patients who received inappropriate antibiotics, which was similar to the 28.6% observed in patients with uncomplicated infections who also received inappropriate therapy. These figures should be compared with the overall 80% microbiological eradication in patients who received appropriate therapy[222]. Although the presence of bacteremia does not seem to have clinical or prognostic significance in women with uncomplicated infections[31,32,35], it may still be associated with severe sepsis in patients with complicated APN[223]. Therefore, when selecting an appropriate antibiotic regimen for patients with APN, it is important to take into account the regular MIC breakpoints and serum PK/PD efficacy targets for the different antibiotic classes (table 2). The use of drugs such as NIT, which reach very low serum levels after regular oral dosages is discouraged[224], and some antibiotics with poor renal clearance (like tigecycline) have been less effective than others that achieve high urinary concentrations[225,226].

There is essentially no clinical experience about the use of FOF for the treatment of APN. FT at the usual dose of 3 g can obtain fosfomycin concentrations in plasma that remain above the MIC for susceptible *E. coli* for at least 12 h, but not necessarily 24 h, and the gastrointestinal tolerance of a higher dose (i.e. 3 g/12-24 h) administered over several days, as well as the risk of selecting resistant mutants may be of concern[227,228]. FOF sodium salt can be administered intravenously in sufficiently high doses (~24 g/d) to guarantee not only a time above the MIC of 100% for susceptible gram-negative bacilli, but also for it to have a chance of preventing selection of resistance in the kidneys.

The main concern about aminoglycosides continues to be toxicity, particularly renal injury, which makes them second-choice antibiotics[229]. There is no evidence that adding an aminoglycoside to a β-lactam improves survival, reduces therapeutic failure or prevents resistance[230,231], although in patients with infections caused by MDR microorganisms, combination therapy is associated with an increased rate of appropriate empiric therapy[232,233].

Management of patients with a history of hypersensitivity reactions to beta-lactams continues to be controversial. Two systematic reviews have found that there is a significantly increased risk of allergic reactions to first-generation cephalosporins and cefamandole among

penicillin-allergic patients, but not to CXM or third-generation compounds[234,235]. Based on this and additional observational evidence, several authors have suggested that CXM and third-generation cephalosporins can be safely administered to patients allergic to penicillins[236]. There is general agreement about the absence of cross-reactivity between aztreonam and other beta-lactams, except in those who have developed hypersensitivity to ceftazidime[237–239]. A systematic review of patients with a clinical history of Ig-E-mediated hypersensitivity to penicillins who were subsequently given a carbapenem estimated that the incidence of any type of hypersensitivity reaction was 4.3%, and of IgE-mediated reactions, 2.4%; true cross-sensitivity in those with a positive skin test for penicillin allergy was very low (0.3%)[240].

Once antibiotic susceptibility patterns are known, antibiotic treatment should be adjusted, particularly when broad-spectrum antibiotics are used empirically. Because of its low ecological impact, COT is preferred to FQs or third-generation cephalosporins. Daily recommended dosage in APN is shown in table 10.

RECOMMENDATIONS

1. In our setting, ampicillin, amoxicillin, amoxicillin-clavulanic acid, co-trimoxazole, fluoroquinolones, nitrofurantoin and fosfomycin-tromethamine are not recommended for the empiric treatment of acute pyelonephritis (A-III).
2. Parenteral antibiotic treatment is recommended as initial therapy for patients requiring hospital admission (A-III).
3. In patients with uncomplicated community-acquired acute pyelonephritis with no specific risk factors for ESBL-producing Enterobacteriaceae, empiric therapy with cefuroxime or a third-generation cephalosporin is recommended (A-II). For allergic patients, the alternatives are an aminoglycoside (B-I), aztreonam (B-II) or fosfomycin (C-III); a carbapenem is an acceptable option if the patient is closely monitored (C-III).
4. In community-acquired APN with specific risk factors for ESBL-producing Enterobacteriaceae (at least two risk factors without severe sepsis and one with it) or previous infection/colonization with ESBL, ertapenem is an acceptable option (C-II), although other carbapenems (B-II) or piperacillin-tazobactam (B-III) are alternatives. For patients with penicillin allergy, the alternatives are amikacin (B-I) or intravenous sodium fosfomycin (C-III); a carbapenem is an acceptable option if the patient is closely monitored (C-III).
5. In healthcare-associated APN, an antipseudomonal carbapenem is recommended (A-III) with ceftolozane-tazobactam or piperacillin-tazobactam as alternatives (C-III). For patients with severe sepsis, the addition of amikacin should be considered in order to increase the chances of providing appropriate empiric therapy against gram-negative bacilli (B-II). For patients allergic to penicillin, alternative treatments are aztreonam, amikacin or intravenous sodium fosfomycin +/- amikacin (C-III); a carbapenem is an acceptable option if the patient is closely monitored (C-III).
6. Anti-enterococcal coverage is recommended for patients with healthcare-related APN and severe sepsis or cardiac conditions at high risk of endocarditis (C-III).
7. When the antibiotic susceptibility pattern is known, treatment should preferably be adjusted to the drug with least ecological impact, such as co-trimoxazole (C- III).

What is the optimal duration of antibiotic therapy? Does it vary depending on the particular antibiotic administered?

Several randomized controlled trials have evaluated the efficacy of antimicrobial therapy of different durations in patients with APN. The patients included in the studies tended to be women with non-severe APN and fast clinical improvement. In a small comparative study in women with uncomplicated APN, a 2-week regimen of either oral ampicillin or COT was just as effective in terms of bacteriological eradication as a 6-week regimen with the same antibiotics[192]. Another small trial among women with uncomplicated APN treated for 48-72 hours with GEN or tobramycin, then with active oral antibiotics, found no clinical and microbiological differences between patients treated for 10 or 21 days[241]. In another larger unpublished study[242] that compared a single dose of ceftriaxone, followed by 400 mg/d of cefixime for either 7 or 14 days in women with uncomplicated APN, the rates of clinical and microbiological failure were similar. Recently, a double-blind randomized trial that compared ceftolozane-tazobactam (1.5 g/8 h) and LVX (750 mg), both given intravenously for 7 days for the treatment of patients with cUTI and APN[243], showed similar composite clinical and microbiological success rates. Five further trials involving quinolones demonstrated the following: 7 days of CIP performed better than 14 days of COT[15]; 7 days of either fleroxacin[244] or CIP[245] performed as well as 14 days with the same antibiotic, and 5 days of LVX at 750 mg/d was as efficacious as 10 days of CIP[246,247]. The only other antibiotics that have been tried in a 5-day regimen are aminoglycosides. In two small studies, netilmicin was as efficacious as CIP or parenteral β-lactams[219,248]. Clinical comparative trials published so far do not rule out the possibility that the optimal duration of antimicrobial therapy in patients with APN may depend on the particular class of antibiotic used. For uncomplicated APN, there is no reason to prolong LVX or CIP for more than 7 days, or third-generation cephalosporins (oral or parenteral) for more than 10 days. There are limited controlled studies of aminopenicillins such as AMC involving adults, although one randomized trial of children with APN showed good results in 10 days[249,250]. For COT, there is no controlled data to support using it for less than 14 days, although expert experience suggests that 10 days is enough for women who improve rapidly. Limited efficacy and toxicity data makes it advisable not to administer aminoglycosides for longer than 5 days.

There are no good quality studies for patients with severe or focal APN, or who respond slowly to antibiotic therapy. In this situation, most authors recommend a longer duration of antibiotic therapy.

RECOMMENDATIONS

1. In patients with uncomplicated acute pyelonephritis due to susceptible gram-negative enteric bacilli, 5 to 7 days of levofloxacin or ciprofloxacin is recommended (A-I).
2. In the case of third-generation oral or parenteral cephalosporins, a 7 to 10-day course is recommended (A-I). For amoxicillin-clavulanic acid and co-trimoxazole a 10-day course is recommended (A-III). For aminoglycosides, no more than a 5-day course is recommended (A-II).
3. For patients with severe or focal APN or slow response to appropriate antibiotics, a longer duration of therapy may be required (C-III).

What are the main indications for performing urological studies?

In patients with APN, urological studies are primarily aimed at diagnosing obstructive complications or abscess formation, which may require specific additional therapeutic

manoeuvres, such as drainage or prolonged antibiotic treatment. A diagnosis of APN on its own does not make it a priority, although it may be of additional interest in cases with doubtful or equivocal clinical symptoms. Currently, ultrasound imaging is the standard screening technique for detecting obstruction and may also be used to guide intervention, but it is quite insensitive for detecting an intrarenal abscess. Computerized tomography (CT) is the gold standard for establishing cause of obstruction and the nature and extent of intrarenal and extrarenal lesions. Magnetic resonance (MR) may be considered when exposure to ionizing radiation (pregnancy) or iodinated contrast (renal insufficiency, allergy) is contraindicated, although gas and calculi may produce voids that are difficult to interpret[251–253].

At least 95% of patients with uncomplicated APN cease to be febrile within 3 days of appropriate antibiotic therapy and follow an uneventful course with virtually no mortality[15,245,254]. In no more than 4% of such patients with an initial response to antibiotics would an ultrasound scan of the urinary tract reveal abnormalities that would eventually lead to a change of therapeutic approach[255,256]. Complicated APN on the other hand is associated with severe sepsis in about 25% of cases, septic shock in around 12%, and has a crude mortality of 6%–7%[207]. When fever persists after 72 h of appropriate antibiotic treatment or it fulfils the definition of complicated APN, ultrasonography may uncover urological abnormalities that can affect treatment in 25%–45% of patients[257]. Two studies of hospitalized patients with APN found a high rate of intrarenal abscesses (23.5%–39.5%) when sensitive imaging studies (CT or MR) were systematically performed[257,258]. Of note, patients were referred to the hospital after a mean of at least 3 days with symptoms and many were receiving antibiotics, which suggests that cases of initial clinical failure were overrepresented. In another study of hospitalized patients[259], abscesses were discovered by computed tomography in 17.7% of patients and were associated with hypotension, diabetes mellitus, acute renal failure and leukocytosis of more than 20,000/μL.

RECOMMENDATIONS

1. Urological studies are only recommended for patients with uncomplicated APN who continue with fever after 3 days of appropriate antibiotic treatment (A-III), for APN that fulfils the definition of complicated infection in these guidelines (including severe sepsis) (A-III) or for recurrent APN (C-III).
2. Urological study should also be considered when the clinical diagnosis is doubtful, either to confirm it or to rule out other processes (C-III).

Catheter-associated urinary tract infection

In these guidelines, catheter-associated UTI refers to infections occurring in those with indwelling or intermittent urethral, suprapubic or condom catheterization, as well as infections that develop within 72 hours of device removal. Regarding duration of catheterization, an indwelling urethral catheter is considered to be short-term when it remains in place for less than 30 days, and long-term when it is present for 30 days or more[4,260–267].

Most infections in patients with indwelling urinary catheters are usually asymptomatic and diagnosed when a specific quantitative count of a microorganism is isolated from urine in the absence of clinical signs or symptoms associated with the urinary tract. This clinical situation has been defined as catheter-associated asymptomatic bacteriuria (CA-AB).

Symptomatic infection (CA-UTI) is diagnosed when there is bacteriuria associated with symptoms or signs referable to the urinary tract. In recent years, multiple institutions have published guidelines for the diagnosis and management of CA-AB and CA-UTI, which differ in their clinical and epidemiological orientation[264–268].

The rate of acquisition of bacteriuria is 3% to 7% per day for patients with indwelling catheters, so that the prevalence of bacteriuria reaches around 50% and 100% after 2 weeks and one month of catheterization, respectively[260,263]. The incidence of bacteriuria associated with single and intermittent catheterization is significantly lower (~5% and ~50%, respectively) [263].

What is the etiology of UTI in patients with urinary catheters?

Initial infection, following insertion of a short-term catheter, is usually caused by a single organism, most often *E. coli* (32-39%) or other Enterobacteriaceae. *Enterococcus* spp (16-17%), *P. aeruginosa* (16-18%) or *Candida* spp may also be isolated[260–263,269]. Monomicrobial infection due to *E. coli* is also characteristic of patients with neurogenic bladders managed with intermittent catheterization[260,261].

In patients with long-term catheterization, the UTI is usually polymicrobial. In addition to the pathogens commonly isolated from patients with short-term catheters, other microorganisms, such as *P. aeruginosa*, Gram-positive bacteria and yeast are frequently found[114,260–262,270]. Urease-producing bacteria such as *P. mirabilis*, *K. pneumoniae*, *M. morganii* or *P. stuartii*[4] are also common in long-term CA-UTI and cause relapsing infections due to catheter blockage[260]. *C. albicans* is the most frequently isolated yeast, but other species such as *C. glabrata* and *C. tropicalis* may also appear[260–263]. Enterococci are frequently isolated, but these infections are rarely symptomatic. *S. aureus,* coagulase-negative staphylococci and *S. agalactiae* are uncommon causes of CA-UTI; the isolation of methicillin-resistant *S. aureus* or vancomycin-resistant *E. faecium* is extremely rare in our setting[261]. The etiology of community-acquired CA-UTI is similar to nosocomial UTI[263].

Data from the ENVIN study (2005-2010)[271] showed increasing rates of ciprofloxacin-resistant *E. coli* and *P. aeruginosa* strains (37%) and of imipenem-resistant *P. aeruginosa* isolates (36%)[272]. Bacteria causing CA-UTI are usually more resistant to antimicrobials due to frequent patient contact with the healthcare system and to the common use of antibiotic treatments for these infections[261–263,272].

RECOMMENDATIONS

1. In patients with short-term catheterization, UTI is usually monomicrobial and frequently caused by Enterobacteriaceae (B-II).
2. In patients with long-term catheterization, UTI is usually polymicrobial and frequently caused by antimicrobial-resistant bacteria (B-II).

What are the clinical and microbiological features for diagnosis of symptomatic CA-UTI?

Approximately 10-25% of patients with bacteriuria develop symptomatic UTI and between 1% and 5% develop bacteremia[114,262]. CA-UTI is most frequent among women, diabetic and old patients, those with urinary tract obstruction or haematuria due to catheterization, or when *Serratia* spp is isolated from the urine[261–263]. Bacteremia is an infrequent complication of

short-term catheterization and depends on the origin. While UTI causes 15-20% of nosocomial bloodstream infections, less than 5% of cases among ICU patients originate in the urinary tract[260,262]. In LTCFs, CA-UTI is associated with more than 50% of episodes of fever and is the most frequent cause of bacteremia[260].

The microbiological diagnosis of patients with CA-AB and CA-UTI is specified in section 2.3. A urine culture should be obtained before initiating therapy for patients with suspected CA-UTI. Urine specimens collected via a catheter are usually contaminated by biofilm bacteria, and more organisms and higher quantitative counts are isolated compared to bladder urine obtained after changing the catheter[273]. Thus, when the catheter has been in place for a prolonged period (>2 weeks), the catheter should be replaced and a urine specimen be collected for culture via the newly inserted catheter[4,260,261]. Urine specimens should never be obtained from a urine collection bag. Blood cultures should also be drawn if the patient has fever or other clinical signs of sepsis.

The clinical features of CA-UTI are non-specific. CA-UTI is usually asymptomatic and the most common symptomatic presentation is fever without localizing urinary findings and no identifiable alternative source. Urinary tract symptoms such as dysuria, frequency, or urgency are less frequent, but may occur with infection appearing after catheter removal[4,260,261]. There is little evidence in the literature about the clinical signs and symptoms of urinary infection in catheterized patients[268]. The usual localizing symptoms of lower UTI are useful for diagnosis of infection only in patients whose catheters have recently been removed.

The main risk factors associated with symptomatic infection are catheter obstruction or manipulation, complicated by haematuria, which usually precedes onset of fever or bacteremia[260]. Consensus criteria proposed for obtaining urine cultures and initiating empiric antimicrobial therapy for presumed CA-UTI in nursing home residents include fever, costovertebral angle tenderness, rigors, and new onset delirium, with no other obvious source[274,275]. No study has demonstrated that odorous or cloudy urine is clinically significant in catheterized patients, and so these findings should not be used to distinguish CA-AB from CA-UTI[4,260].

The classic symptoms of UTI are usually absent in patients with spinal cord injuries and neurogenic bladders. Signs and symptoms suggestive of UTI in these patient groups include fever, costovertebral or pelvic pain, incontinence, increased spasticity, autonomic dysreflexia, lethargy, malaise, and sense of unease[4,276,277]. Most of these symptoms and signs however have low sensitivity and specificity for diagnosing UTI or even identifying bacteriuria[278]. Finally, some patients may have typical signs of specific forms of UTI, such as urethritis, periurethral abscess, pyelonephritis, prostatitis and epididimitis[260,262].

RECOMMENDATIONS

1. If an indwelling catheter has been in place for >2 weeks, the catheter should be replaced before obtaining urine for culture (A-II).
2. Signs and symptoms compatible with CA-UTI include fever, rigors, altered mental state or malaise with no other identifiable cause, as well as focal signs in the urinary tract, such as flank or pelvic pain, costovertebral angle tenderness, and acute haematuria (A-III).
3. In catheterized patients, the presence of urinary symptoms is of limited value for differentiating CA-AB from CA-UTI (A-I). In patients, whose catheters have been removed, the presence of urinary symptoms is suggestive of symptomatic UTI (A-III).
4. In patients with spinal cord injuries, increased spasticity, autonomic dysreflexia, or a sense of unease are suggestive of CA-UTI (A-III).

5. In patients with indwelling catheters residing in LTCFs, the clinical criteria for obtaining urine cultures and initiating antimicrobial therapy include fever, costovertebral angle tenderness, rigors or new onset delirium with no other obvious source (A-II).
6. In catheterized patients, the presence or absence of odorous or cloudy urine should not be used to distinguish CA-AB from CA-UTI or as an indication for a urine culture or antimicrobial therapy (A-III).

Does the presence of pyuria indicate symptomatic UTI?

In catheterized patients, the presence of pyuria is a sensitive but non-specific finding for predicting CA-AB or CA-UTI. Indwelling catheters cause bladder irritation leading to inflammation and pyuria, even without bacteriuria. Significant pyuria (≥10 leukocytes/μl) accompanies bacteriuria in most patients with CA-UTI, and to a similar degree in CA-UTI and CA-AB, regardless of type of catheterization (indwelling or intermittent) or its duration (short-term or long-term)[4,260,261].

Pyuria is less frequent in patients infected with urease-producing bacteria[261]. The absence of pyuria in a catheterized patient, however, should suggest a diagnosis other than CA-UTI[4,260].

RECOMMENDATION
1. In catheterized patients, pyuria is not diagnostic of CA-AB or CA-UTI (A-II). The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI (A-III).

Is the Gram stain useful for guiding empiric antimicrobial treatment in CA-UTI?

The urine Gram stain test has the advantage of providing immediate microbiological information about the nature of the infecting bacteria or yeast and correlates well with the presence of significant bacteriuria. Sensitivity depends on the bacterial count, so that it is usually positive when it is $\geq 10^5$ CFU/mL[24]. As a general recommendation, it can be useful in patients with APN and cases of invasive UTI with severe infection when information is urgently needed about the microorganisms involved[24,262]. In catheterized patients, the urine Gram stain test is especially useful for guiding empiric therapy, since finding Gram-positive bacteria suggests the presence of enterococci, streptococci, or staphylococci, which is helpful for selecting an antimicrobial active against these microorganisms[261].

RECOMMENDATION
1. In catheterized patients, the urine Gram stain may be useful for guiding empiric antibiotic therapy in patients with severe UTI (B-III).

Should previous antibiotic use be considered for the selection of empiric therapy of CA-UTI?

Empiric antimicrobial treatment should provide adequate coverage against the most frequent microorganisms causing infection. Previous antimicrobial therapy received by the patient is associated with an increased risk of selection of resistant bacteria. To guide empiric therapy

of CA-UTI, it is essential to investigate the history of antibiotic use as well as previous colonization with, or infections caused by, MDR bacteria[261].

In recent years, an increasing prevalence of MDR *E. coli* and *K. pneumoniae* due to extended-spectrum beta-lactamases (ESBL) has been observed; these are no longer confined to the hospital setting, but appear at community level, and are especially common in LTCFs[212]. Many risk factors have been described for ESBL-producing bacteria. Two recent studies have developed predictive scores for the detection of community-acquired ESBL-producing Enterobacteriaceae[279,280]. It is noteworthy that both studies identified urinary catheterization (in the previous month) and therapy with beta-lactams or FQs (in the previous three months) as two of the most important risk factors, along with comorbidity, previous hospital admission and transfer from a LTCF. Previous antimicrobial therapy should, therefore, be taken into account to guide empiric antimicrobial therapy of CA-UTI. In Spain, the increasing detection of MDR carbapenemase-producing Enterobacteriaceae and *P. aeruginosa* as a cause of nosocomial UTI has further complicated this worrisome epidemiological situation[281].

RECOMMENDATION

1. In catheterized patients with suspected UTI, recent use of beta-lactams or quinolones should be investigated in order to evaluate the risk for MDR bacteria (B-II).

What is the empiric antimicrobial therapy for patients with CA-UTI?

Empiric antimicrobial therapy for CA-UTI should consider the clinical situation of the patient, the site of infection and local resistance patterns of infecting organisms[4,260–263,282]. Antimicrobial therapy is indicated for patients with symptomatic infection (pyelonephritis, prostatitis, epididymitis, bacteremia and so on) or clinical signs of sepsis[282]. As a general rule, broad-spectrum antimicrobials active against Enterobacteriaceae, *P. aeruginosa* and *E. faecalis*[264] should be used. Algorithms have been developed using clinical and microbiological factors (site and severity of infection, drug allergy, local patterns of resistance, urine Gram stain, etc.) for the selection of empiric therapy[261,263].

Critically ill patients with severe sepsis or hemodynamic instability should receive parenterally-administered broad-spectrum beta-lactam antibiotics active against MDR Enterobacteriaceae and *P. aeruginosa,* such as imipenem, meropenem or PIP-TAZ, due to the high rate of resistance to FQs in our setting[264,282]. If the patient has septic shock or there is suspicion of beta-lactam resistance, combination therapy with an aminoglycoside such as AMK should be used pending the results of cultures[261,263].

Antimicrobial therapy for invasive infections due to MDR Enterobacteriaceae (ESBL and carbapenemase producers) was recently reviewed in the SEIMC guidelines[212]; carbapenems are the drugs of choice for invasive infections caused by ESBL- and AmpC-producing Enterobacteriaceae, although PIP-TAZ may be considered a reasonable alternative for invasive UTIs caused by ESBL-producing *E. coli* due to increasing rates of resistance to carbapenems among Gram-negative bacteria and can be used as a carbapenem-sparing regimen[212]. PIP-TAZ is active in vitro against *E. faecalis*, most AmpC isolates and ESBL producers, as well as *P. aeruginosa.* Empiric coverage against Gram-positive bacteria such as *E. faecalis* and *S. aureus* should be considered following the results of the urine Gram stain[261]. When the susceptibility patterns of the causative organisms are known, directed therapy should be changed to narrow-spectrum antibiotics.

If the patient presents with symptoms of mild infection and a urinary origin is unlikely, antimicrobial therapy may be delayed pending urine culture results[260,282]. Treatment for CA-cystitis is similar to that of non-catheterized patients and narrow-spectrum antimicrobials (FT and NIT) should be used[1,261].

Finally, the urinary catheters of patients with CA-UTI should be removed whenever it is feasible to do so, or at least changed as soon as possible. A randomized controlled trial of long-term CA-UTI found that patients who underwent catheter replacement before initiating antimicrobial therapy had significantly higher clinical response rates and a lower incidence of bacteriuria and UTI within 28 days of therapy than those who did not[273].

RECOMMENDATIONS

1. Antimicrobial therapy is indicated for patients with symptomatic infection or clinical signs of sepsis (B-III).
2. Patients with symptomatic UTI and criteria for severe sepsis should be treated with parenteral broad-spectrum antibiotics adapted to the local resistance patterns of uropathogens (C-III). Imipenem, meropenem and piperacillin/tazobactam are the most active antimicrobials in our setting. If the patient has septic shock or resistance to beta-lactams is suspected, combination therapy with amikacin should be considered (C-III).
3. If the patient presents with symptoms of mild infection and a urinary origin is unlikely, antimicrobial therapy can be delayed until the urine culture results are known (C-III).

How long should antimicrobial therapy for CA-UTI last?

The wide spectrum of infections in patients with CA-UTI and the absence of trials with published outcomes of treatment for them make optimal duration of therapy an unresolved issue. Most authors recommend prolonged antimicrobial therapy of between 1 and 2 weeks[4,260,261].

However, in order to reduce toxicity and limit the spread of resistance, it is advisable to reduce the length of treatment, especially in mild infections and those that respond promptly to treatment. A randomized study conducted among women with catheter-associated lower UTI following removal of the catheter found similar resolution rates for single-dose and 10-day therapy with COT[116]. Another study of APN found similar clinical response rates for LVX (750 mg once daily for 5 days) and CIP (500 mg twice daily for 10 days), and a better microbiological response for LVX used to treat CA-UTI patients[247]. In patients with neurogenic bladders managed by intermittent catheterization, microbiological response to mild CA-UTI was significantly better in those who received CIP for 14 days rather than 3 days[283]. FT was found to be effective for treating catheterized patients with cUTI and/or infection caused by MDR bacteria; a 3 gr single-dose therapy and a longer 'off-label' course of FT (3 g every 48-72 h for 7-10 days) have been used for complicated infections[284], as well as for cystitis following catheter removal[261].

Antibiotic prophylaxis is not routinely recommended for catheter placement, removal, or replacement[4]. Traumatic long-term catheter manipulation may be associated with fever and haematuria; bacteremia may be a complication in 4-10% of these episodes[260,261,263]. These episodes of UTI secondary to catheter placement or removal generally obtain favourable responses after a short course (5-7 days) of antimicrobial therapy, provided that APN and prostatitis have been excluded[261].

Most experts recommend a short course of antimicrobial therapy (7 days) for patients with CA-UTI whose symptoms resolve promptly, and a longer course (10-14 days) for patients with APN, acute prostatitis, or those with delayed response, regardless of whether or not the catheter is removed. For selected patients, a shorter course of therapy might be as follows: 5 days LVX for mild UTI, and 3 days of antimicrobial therapy or single-dose FT for women with lower tract infection following catheter removal.

RECOMMENDATIONS

1. Seven days is the usual duration of antimicrobial therapy for CA-UTI patients with prompt resolution of symptoms, and patients with cystitis following urinary catheterization (A-III); 10-14 days of treatment is recommended for those with delayed response (A-III), regardless of whether the patient remains catheterized or not.
2. A 5-day course of levofloxacin may be considered for patients with mild CA-UTI (B-III). A 3-day course of antimicrobials (B-II) or a single-dose of fosfomycin trometamol (3 g) (C-III) may be considered for women who develop CA-UTI without upper urinary tract symptoms after removal of an indwelling catheter.
3. Antibiotic prophylaxis should not be administered to patients for catheter placement (E-I) catheter removal (D-I) or replacement (E-III) in order to prevent CA-UTI.

What are the most important measures for prevention of CA-AB and CA-UTI?

Recently published guidelines from multiple institutions and scientific societies have systematically reviewed recommendations for preventing infections associated with urinary catheterization[4,264,265]. It is noteworthy that these guidelines use different definitions for type of infection, strength of recommendation and the level of evidence of the recommendations. Furthermore, although it is important from a clinical point of view to differentiate between asymptomatic and sUTI, the outcomes of preventive measures have frequently been reported for CA-AB rather than CA-UTI[4,264,265,285,286].

Duration of catheterization is the most important risk factor for developing infection and the most important strategy for reducing ASB and UTI is to minimize indwelling catheter use. Catheterization should be used only for approved indications and for the shortest time possible. Several practices for limiting the use and duration of catheterization have been proposed. Alternate methods of catheterization, such as the condom catheter or suprapubic catheter, or intermittent catheterization, have been associated with a lower risk of infection and should be considered whenever possible. The aseptic technique during insertion of the catheter and maintenance of a closed drainage system are universal preventive practices, although there is no evidence about their efficacy during long-term catheterization.

In patients with long-term catheterization, there is no evidence of differential risk for CA-AB or CA-UTI with different catheter materials or antimicrobial-coated catheters. Antibiotic- or silver alloy-coated urinary catheters have been shown to prevent or delay the onset of CA-AB in short-term catheterization, although no decrease in the frequency of CA-UTI or any other clinical benefit has been demonstrated. Widespread use of these catheters in the hospital setting has been limited by their higher cost.

The use of systemic antimicrobials is associated with decreased frequency of CA-AB during the first days of catheterization, but no long-term clinical benefit has been shown and there is a greater risk of developing antimicrobial resistance. A recent meta-analysis found a

decreased frequency of sUTI among patients receiving antibiotic prophylaxis following short-term catheter removal[287], although no published guidelines have made other up-to-date recommendations for this specific situation. Routine catheter change is not recommended for patients with chronic indwelling urethral catheters, because it has not been shown to be beneficial for preventing infection. The catheter should only be changed when there is catheter obstruction, damage or malfunction, or before treatment for CA-UTI.

RECOMMENDATIONS

1. Indwelling catheters should be placed only when they indicated (A-III) and should be removed as soon as they are no longer required, in order to reduce the risk of CA-AB (A-I) and CA-UTI (A-II). Indwelling catheters should be inserted using the aseptic technique and sterile equipment (B-III) and a closed catheter drainage system should be maintained to reduce CA-AB and CA-UTI (A-II and A-III, respectively, for patients with short-term catheters; A-III and A-III, respectively, for patients with long-term catheters).
2. Appropriate alternatives to short- and long-term urethral catheterization should be considered for reducing CA-AB, such as condom catheterization (A-II and B-II, respectively) intermittent catheterization (C-I and A-III, respectively), and suprapubic catheterization (B-I for short-term catheterization). Alternatives for reducing CA-UTI are intermittent catheterization (C-III for short-term and A-III for long-term catheterization) and suprapubic catheterization (C-III for short-term catheterization)
3. In patients with short-term indwelling urethral catheterization, antimicrobial (antibiotic or silver alloy)-coated urinary catheters may reduce or delay the onset of CA-AB, but does not decrease the frequency of CA-UTI (B-II).
4. Systemic antibiotic prophylaxis should not be routinely used to reduce CA-AB or CA-UTI in patients with short-term (A-III) or long-term (A-II) catheterization because of the concern of selection of antimicrobial resistance.

Risk factors and prevention strategies for recurrent urinary tract infections (rUTI)

Recurrent UTI, defined as three episodes of UTI in the previous 12 months or two episodes in the previous six months, are common in women[191,288,289]. Distinguishing between relapse and reinfection is essential for determining an approach to diagnosis and therapy. *Relapse* represents 20% of rUTI and is due to the persistence and reappearance of the original infecting strain, generally within the first 2-3 weeks of an apparent cure. The various possible reasons for a relapse include short or inadequate antibiotic treatment, quiescent bacterial reservoirs of the causative organism due to coexistence of an underlying urological disease (renal calculi, the presence of a catheter that has not been withdrawn, or chronic prostatitis) which is diagnosed by performing a proper urological study.

Reinfection accounts for 80% of rUTI cases. These represent new UTIs caused by a different strain from the original one, although they may also be caused by the same strain persisting in the gastrointestinal tract. They occur mainly in sexually active young women, post-menopausal women and patients with certain urological disorders, such as urinary incontinence, cystoceles, patients with neurogenic bladders or a history of previous gynecological surgery. Reinfections usually occur later than relapses (usually more than two weeks after the initial UTI) and may be prevented by following some of the different strategies discussed in these guidelines.

Recurrent UTI in men is usually due to a urological abnormality (obstructive uropathy due to prostatic hypertrophy is the most common one) or to a chronic prostatitis and requires a different clinical approach and will not be discussed in this guideline.

What are the main risk factors of rUTI in premenopausal women?

The high frequency of rUTI in women has been associated with: a) anatomical factors, such as the shorter female urethra and its proximity to the vagina, which favors intestinal colonization with Enterobacteriaceae; b) genetic factors that determine increased adherence by Enterobacteriaceae to vaginal and uroepithelial cells, and explain why there is a family propensity to recurrent infection[191,288]. It has been demonstrated that the uroepithelial cells of patients who are non-secretors of ABO blood group antigens are more susceptible to enhanced adhesion of uropathogenic isolates than secretors. It has also been suggested that expression of the P blood group phenotype predisposes to recurrent pyelonephritis. The interleukin-8 receptor (CXCR1) is another genetic factor that may influence the development of UTI since CXCR1 expression is significantly lower in the pyelonephritis-prone children than in controls[191,288]; c) behavioral factors, with the main risk factor being frequency of sexual intercourse. A study published in 2000 demonstrated that there was a 9 times greater risk of rUTI with daily sexual intercourse[290]. Other behavioral factors associated with rUTI are intercourse before the age of 15 years, use of spermicidal creams (it reduces vaginal concentrations of lactobacilli), a recent change of sexual partner (which could lead to an increase in sexual activity) or recent antibiotic consumption[291]. In this group of patients, the presence of an underlying urological disease is rarely responsible for rUTI, so that a urological diagnostic test is not indicated if there is no suggestive medical history (UTI in infancy, haematuria with passage of blood clots, suspicion of neurogenic bladder, nephrolithiasis or relapse). Four different studies have demonstrated that, in the absence of the previous conditions, carrying out urological diagnostic tests has a low diagnostic yield and is not cost-effective[292–295].

RECOMMENDATIONS

1. In sexually active women, the main risk factor for rUTI is frequency of sexual intercourse (B-I).
2. In sexually active women with rUTI, it is not necessary to perform a urological study if there is no suspicion of underlying urological disease (A-II).

Are hygienic measures effective in preventing rUTI?

The traditional advice of high fluid intake, frequent urination, post-coital urination and maintaining hygienic habits after bowel movements often fails in patients with rUTI and there is in fact some evidence that these measures are not effective in women with rUTI[290,296]. This does not mean that they may not be useful for patients with isolated episodes of cystitis.

RECOMMENDATION

1. In women who fail to prevent rUTI with hygiene measures, it is not necessary to insist on their implementation (B-II).

Is acidification of the urine useful for preventing rUTI?

It has been suggested that ascorbic acid may be useful for acidifying the urine and preventing rUTI, although 2 g doses of vitamin C have not proved to be effective[297] due to rapid clearance, while more frequent dosing intervals (every 2-4 h) are unacceptable in daily practice[288,289].

Methenamine salts acidify the urine by producing formaldehyde. In a meta-analysis of 13 studies, methenamine hippurate, a preparation not available in Spain, reduced rates of rUTI (RR = 0.24) in patients with no urological abnormalities, although not in patients with urinary catheters or urinary tract disorders[298]. In 2011, it was declared to be carcinogenic, with a theoretical risk of causing tumours in the urinary tract. We agree therefore that this strategy should not be used for prolonged periods[289].

RECOMMENDATIONS

1. Vitamin C (ascorbic acid) in acceptable dosing intervals in regular clinical practice is not useful in the prevention of rUTI (B-II).
2. Although methenamine hippurate is useful for preventing rUTI (B-I), we do not recommend its use, given the potential carcinogenic risks (C-III).

When is it advisable to use prevention strategies?

In women with few UTIs per year (<3 per year) and patients who wish to take fewer antibiotics, self-treatment of cystitis with antibiotics previously prescribed by a physician can be used. Three studies showed that, in patients with sufficient intellectual capacity, self-diagnosed cystitis was correctly cured in approximately 90% of cases[299–301]. Clinical and microbiological cure rates using COT or FQs (ofloxacin, LVX) were above 90%. Only 6% of these patients subsequently required continuous antibiotic prophylaxis. Although patients who adopt this therapeutic strategy have more sUTIs than those who use continuous or post-coital antibiotic prophylaxis, self-administered antimicrobials reduce the symptoms quickly. This strategy is not recommended for patients at increased risk of sexually transmitted diseases, because it can delay the diagnosis and treatment of such infections.

In patients with rUTI, any of the following different strategies can be recommended: continuous or post-coital antibiotic prophylaxis, topical vaginal estrogens, cranberries, vaccines and D-Mannose. All these strategies have been shown to lead to a significant reduction in the incidence of recurrent urinary tract infections[191,288,289]. The choice of one or other strategy will depend on such aspects as the number of rUTI, its relation to sexual activity, menopausal state or not, individual preferences (e.g. reluctance to take antibiotics), possible side effects, risk of selection of resistance, previous strategy failure, and costs (some preparations are not financed by the Spanish Social Security System) [288].

Before any preventive strategy can be implemented, the most recent UTI must be eradicated. Most published studies apply preventive strategies for a period of 6 months.

RECOMMENDATIONS

1. In women with fewer than 3 UTIs per year, self-treatment of cystitis is a convenient and effective measure and also reduces the consumption of antibiotics associated with prophylaxis (B-II).

2. The administration of continuous (A-I) or post-coital (A-I) antibiotics, topical vaginal estrogens (A-I), cranberries (A-II) or D-Mannose (A-II) for a 6-month period reduces the frequency of rUTI to a greater or lesser extent.

What is the efficacy of continuous or post-coital antibiotic prophylaxis?

Numerous randomized, placebo-controlled studies have shown that continuous prophylaxis with a low dose of antibiotics significantly reduces rUTI[191,288,289,302,303]. It has been suggested that prophylactic action can occur by three mechanisms of action: reducing concentrations of uropathogenic Enterobacteriaceae in fecal and vaginal reservoirs, intermittent urine sterilization, and inhibition of bacterial adhesion to bladder mucosal cells by sub-inhibitory concentrations of antimicrobial agents. Table 11 shows the antibiotics mainly used and their dosages. In two meta-analyses of placebo-controlled trials[302,303], the administration of antibiotic prophylaxis for 6-12 months reduced clinical recurrence by 85% and microbiological recurrence by 78%, but increased the risk of oral and vaginal candidiasis. In six studies comparing two antibiotics, neither antibiotic showed superiority. After the meta-analyses were published, a randomized study with placebo, which administered 3 g of FT every 10 days for 6 months, similarly reduced the number of recurrences[304]. In elderly patients, this standard pattern is generally given weekly to facilitate compliance.

Given the presence of side effects, the risk of vaginal candidiasis, cost and the impact on resistance, the most recommended prophylactic options are FT, COT and NIT[44,191,288]. FQs should be reserved as the last option for prophylaxis, given their impact on resistance and the possibility of undesirable effects associated with them (*Clostridium difficile*-associated diarrhea). Continuous prophylaxis with a low dose of antibiotic to be taken every night is usually indicated for patients with frequent rUTI not clearly related to sexual intercourse, or when intercourse is very frequent. Most authors recommend administering antibiotic prophylaxis at night for a minimum of 6 months. If UTI recurs after cessation of prophylaxis, prolonged prophylactic therapy for 1 or 2 years or even longer, is recommended. This treatment strategy is effective in clinical practice, although there are no studies of its actual effectiveness[191,288,289]. The administration of low doses of COT or other agents for periods exceeding 5 years has proven to be effective and well tolerated.

NIT can cause neurotoxicity, pulmonary (acute hypersensitivity pneumonitis and chronic pulmonary fibrosis) and hepatotoxicity, particularly with prolonged exposure. Although the incidence of such adverse effects is low (0.13 to 0.0001% for pulmonary reactions and 0.0003% for hepatic reactions, clinical monitoring is recommended for the presence of respiratory and gastrointestinal symptoms[175,305,306]. Due to these side effects, recently the AEMPs (Spanish Drug Agency), has recommended to avoid prolonged treatment (>7 days) with NIT. No specific recommendations against the use for NIT in prolonged therapy (6 months) for prophylaxis for rUTI have been made by the FDA and the EMA (European Medicines Agency).

Increased resistance rates may have modified the effectiveness of these antibiotic regimens; however, monitoring the rectal or vaginal flora to detect the presence of resistant organisms does not predict the development of recurrence[288,289].

Post-coital prophylaxis is a useful therapeutic strategy for patients where UTI is related to sexual activity. Continuous prophylaxis, especially with 3 g FT administered every 7-10 days, is probably more comfortable for women with highly frequent sexual intercourse.

In placebo-controlled studies, post-coital administration of COT, FQs, NIT and cephalexin (table 11) reduced reinfection rates to percentages similar to those of continuous prophylaxis[191,288,302]. In the only comparative study, post-coital administration of CIP prophylaxis was as effective as continuous prophylaxis[307]. FQs should be reserved as the last prophylactic option, given their impact on resistance.

RECOMMENDATIONS

1. In women with rUTI, continuous or post-coital antibiotic prophylaxis administered for 6-12 months is highly effective for reducing recurrence (A-I).
2. The effectiveness of the different antibiotics used in prophylaxis (COT, NIT, trimethoprim, FQs and cephalosporins) is similar (B-II).
3. If UTI recurs after cessation of prophylaxis, it is recommended to restart the same prophylaxis regimen for a longer period (1-2 years) (C-III).
4. Due to its ecological impact, prophylaxis with FQs should be used only when no other preventive strategy is available (C-III).

What is the role of cranberries in preventing rUTI? Is antibiotic prophylaxis more effective than cranberries in the prevention of rUTI?

Cranberries are a traditional remedy for prevention of rUTI, but have neither the antimicrobial properties nor sufficient capacity to acidify the urine. However, cranberries inhibit the adhesion of uropathogens to urothelial cells mainly due to 2 mechanisms: Through their high fructose content, which inhibits enterobacterial type 1 fimbriae and proanthocyanidins (PAC) that inhibit the adhesion of P-fimbriated uropathogens[191,288,308]. It is difficult to summarize the literature because some of the studies are of poor quality, the dosages and administration methods vary, and some meta-analyses include patients with few episodes of UTI and so do not fulfill the criteria for rUTI[309]. In the first meta-analysis[310], which included only rUTI patients, cranberries administered for 6-12 months effectively reduced the incidence of UTI by 35%, except in patients with urinary catheterization (in this group only 10% of UTIs were caused by uropathogens with fimbriae). A more recent meta-analysis[311], which included 13 studies with 1,616 patients, observed an overall efficacy of 38%. When broken down by subgroups, efficacy was higher in women with rUTI (a 47% reduction in the rate of UTI) and children (63 %); cranberries, however, were not effective for patients with few UTIs.

Two randomized studies compared the efficacy of antibiotic prophylaxis using cranberries. In one, a similar efficacy to TMP was observed, but with fewer side effects[312]. Another recent study including 221 patients with frequent reinfection demonstrated that administration of low doses of COT (80/400 mg) was more effective than cranberries ($p < 0.02$), although in the cranberry group, antibiotic resistance rates did not increase[308].

The optimal dose of PAC is not yet clear. Although the French Agency for Food Safety recommends a minimum of 36 mg daily, it has been experimentally observed that 72 mg has greater capacity to inhibit adhesion[313]. In any case, in our country, most commercial preparations today contain more than 100 mg of PAC. The side effects of administering cranberries are few and mostly digestive.

RECOMMENDATIONS

1. Cranberries administered for 6-12 months are moderately effective in preventing new episodes of UTI in patients with rUTI (A-I); in patients with few UTIs, they are not effective (A-II).
2. Antibiotic prophylaxis is more effective than cranberries (A-I).
3. A 72 mg dose, or higher, of PAC is recommended (C-III).

What are the main predisposing factors in postmenopausal women?

rUTI is relatively common in postmenopausal women, with between 15-20% of women over 60 presenting recurrence. This percentage is higher among institutionalized patients.

One case-control study showed that anatomical or functional factors affecting the emptying of the bladder were the main factors associated with recurrence. Factors associated with rUTI were: urinary incontinence (41% vs. 9%, OR, 5.79), presence of a cystocele (19% vs. 0%), presence of post-void residual urine (28% vs. 2%), a history of UTI before menopause (OR, 4.85), non-secretion of ABO blood group antigens (OR, 2.9) and previous gynecological surgery[314]. The risk of recurrence was 6.9 times higher when diabetes mellitus was present[296]. Post-operative urinary obstruction leading to significant post-void residual urine should be suspected in patients who undergo surgery for urinary incontinence, followed by initiation of rUTI. A frequent cause of recurrence in post-menopausal women is the presence of post-void residual urine due to a neurogenic bladder, which may go unnoticed if urodynamic tests are not performed. This alteration is also frequently responsible for recurrence in patients with neurological disease. Among the elderly, residence in a nursing home, urinary catheterization and exposure to antimicrobials are other factors associated with rUTI[315]. In postmenopausal patients, less is known about the role of sexual habits. In a study involving 899 healthy women and 911 UTI patients, it was observed that patients with UTI were more often sexually active (OR, 1.42), had diabetes (OR, 2.78), a previous history of UTI (OR, 4.2) or urinary incontinence (OR, 1.36)[316].

In postmenopausal women with rUTI unrelated to urological disease, recurrence could also be related to low levels of vaginal estrogen. This would imply decreasing levels of vaginal glycogen and secondarily of *Lactobacillus* spp, thus promoting vaginal colonization with Enterobacteriaceae.[269]

RECOMMENDATIONS
1. In menopausal women without neurological diseases, the main risk factors for suffering rUTI are urinary incontinence, previous gynaecological surgery, presence of diabetes mellitus, a cystocele, residual urine and a history of rUTI before menopause (B-II).
2. The role of sexual activity is less relevant as a predisposing factor for recurrence in postmenopausal women (B-II).

What is the effectiveness of topical vaginal estrogens preventing rUTI?

A meta-analysis including 9 studies showed that administration of oral estrogens does not reduce rUTIs and increases cardiovascular and thromboembolic events and the risk of breast cancer[317]. Topical vaginal estrogens restore the vaginal flora, reduce vaginal atrophy, vaginal

pH and number of rUTIs. In this respect, some studies found that a topically applied intravaginal estriol cream reduced rUTI by 75-80%[317,318].

It is not known whether antibiotic prophylaxis is superior to topical estrogen. In a comparative study with nitrofurantoin, antibiotic prophylaxis was more effective[319], and in another, vaginal estrogen was more effective[317].

RECOMMENDATIONS

1. Oral administration of estrogen does not reduce rUTI (E-I).
2. Vaginal estrogen significantly reduces rUTI (A-II).
3. It is not known whether antibiotic prophylaxis is more efficacious than vaginal creams (C-II).
4. Vaginal estrogen administration is the prophylaxis of choice when associated with vaginal atrophy and should always be considered in all postmenopausal patients (C-III).

Are vaccines useful in the prevention of rUTI?

The intravaginal administration of vaccines using heat-inactivated pathogenic strains has a partial and transitory protective effect; between 5-28% women experience vaginal irritation after application[191,288,289].

Parenterally administered vaccines based on type 1 fimbriae looked promising almost 20 years ago, but so far there have been no clinical studies of humans[288].

Oral or intranasal vaccines using various bacterial extracts from uropathogenic strains are attractive. It has been suggested that they have multifactorial action. These vaccines stimulate innate immunity, activating the phagocytic activity of macrophages and cytokine production. Furthermore, they activate T helper cells that stimulate secretion of IgG and IgA in the mucosa associated lymphoid tissue (MALT) along the urinary mucosa, blocking bacterial adhesion[288].

The Uro-Vaxom (OM-89) vaccine, an extract of 18 different serotypes of urinary pathogens, is the most studied vaccine. In a meta-analysis that included five placebo-controlled studies, this vaccine showed a 40% reduction in rUTIs[320]. In another recent meta-analysis of 5 heterogeneous randomized studies, the efficacy of the vaccine was limited to a period of 6 month[321]s. This vaccine is not commercialized in Spain. There are no appropriate studies assessing the effectiveness of other similar vaccines commercialized in our country. Furthermore, there have been no studies to evaluate the indication for re-vaccinating patients following loss of effectiveness and the reappearance of rUTI after 6 months of exposure.

RECOMMENDATIONS

1. Oral and intranasal vaccines (OM-89) made from uropathogenic bacterial extracts are moderately effective in preventing rUTI (B-II).
2. There are no adequate studies assessing the effectiveness of other commercialized preparations (C-III).

Other prevention strategies

Intravaginal administration of probiotics like lactobacillus is an old and attractive option, although it is difficult to retain the organism in the vagina over a long period of time. Lactobacilli exert activity by maintaining a low vaginal pH, hampering the adhesion of uropathogens, secreting hydrogen peroxide (a microbicide) and stimulating the secretion of cytokines[191]. However, in a review of four randomized studies, only one showed a reduction in the number of rUTIs[322]. More appropriate studies are required before it can be recommended for application in daily clinical practice.

Other alternative strategies, of which there is limited experience or are difficult to apply, include intravesical hyaluronic acid instillation and use of avirulent strains of *E. coli.* D-mannose, a monosaccharide present in the Tamm-Horsfall glycoprotein that binds mainly to the type 1 fimbriae (or pili) of uropathogens, acts by preventing them from adhering to specific urothelial receptors. In a comparative prospective randomized study that included one hundred patients in each group, both D-mannose (2,000 mg/daily) and NIT (50 mg/daily) statistically reduced the number of rUTI compared to placebo group. Furthermore, there were no statistically significant differences in effectiveness between the D-mannose group and NIT at 6 months of follow-up (14.6% vs. 20.4% in recurrent UTI) [323].

It is currently unknown whether combinations of any of these strategies are more effective than when used individually.

RECOMMENDATIONS

1. There is insufficient evidence to recommend vaginal application of lactobacilli as a strategy for preventing rUTI (B-II).
2. D-mannose is effective in preventing rUTI (A-II). Its effectiveness is similar to nitrofurantoin for this indication (A-II).

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Annex 1

Level of scientific evidence	
I	Evidence obtained from ≥1 randomized clinical trial
II	Evidence obtained from ≥1 well-designed non-randomized clinical trial, or cohort studies, or case-control-studies, especially if they have been performed in more than one centre.
III	Evidence obtained from documents or opinions of experts, based in clinical experience or case series
Grades of recommendation	
A	Good evidence to recommend the use of a measure or practice
B	Moderate evidence to recommend the use of a measure or practice
C	Poor evidence to recommend the use of a measure or practice
D	Moderate evidence to discourage the use of a measure or practice
E	Good evidence to discourage the use of a measure or practice

Tables

Table 1

Serum and urine PK/PD indices of oral antibiotics against *E.coli* in acute uncomplicated cystitis

First choice	Dose (mg)	C_{max} (mg/L)	Fu (%)	Protein binding (%)	Urinary C_{max} (mg/L)	EUCAST breakpoints[52] (mg/L)	*E. coli* MIC$_{90}$ (mg/L)*	Urinary C_{max}/MIC$_{90}$
Fosfomycin tromethamol	3000 SD	22-32	32-43 (48h)	<5	4415	≤32	32	138
Nitrofurantoin	100 q12h	1	30-40	90	200	≤64	32	6.25

Alternatives								
Ciprofloxacin	500 q12 h	2-3	40-50	30	200	≤0.5	4	50
Cefuroximeaxetil	500 q12 h	4.4-9.9	32	40	160	≤8	8	20
Amoxicillin-clavulanic acid	500 /125 q8h	8/4	75/60	20/22	>500	≤32	16/8	31.25

Data from Mazzei et al[56].

Fu: Fraction unbound.

*MIC values of 781 isolates from female outpatients in Álava, aged between 15 and 65 years with acute urinary tract infections (Canut A, personal communication).

Table 2
Serum PK/PD indices for parenteral antibiotics against *E.coli* in acute pyelonephritis

				Probability of target attainment (PTA) ≥90%				
	Dose (mg)	**EUCAST breakpoints[16] (mg/L)**	***E. coli* MIC_{90} (mg/L) ***	**AUC_{0-24h}/MIC ≥125**	**% *f*T>MIC ≥50**	**% *f*T>MIC ≥70**	**% *f*T>MIC ≥40**	**C_{max}/MIC ≥10**
Ciprofloxacin	400 q12h	≤0.5	4	If MIC ≤0.12 mg/L				
Levofloxacin	500 q24h	≤1	2	If MIC ≤0.25 mg/L				
Ceftriaxone**	1,000 q24h	≤1	1			If MIC ≤0.5 mg/L		
Piperacillin-tazobactam	4,500 q6h	≤8	16/4		If MIC ≤4 mg/L			
Meropenem	1,000 q8h	≤2	1				If MIC ≤2 mg/L	
Gentamicin	5/kg q24h	≤2	4					If MIC ≤2 mg/L

Adapted from Frei et al[58].
*MIC values of 781 isolates from female outpatients in Álava, aged between 15 and 65 years with acute urinary tract infections (Canut A, personal communication).
**After improvement, the patient may be switched to oral cefixime (EUCAST breakpoint ≤1 mg/L). *f*T>MIC ≥70%, if MIC ≤0.25 mg/L (200 mg q12h). *f*T>MIC ≥70%, if MIC ≤0.06 mg/L (400 mg q24h).

Table 3

Treatment of asymptomatic bacteriuria during pregnancy

Reference (year)	**Design**	**Antimicrobial therapy**	**Bacteriological erradication** Number of patients with eradication of bacteriuria / total number of patients (%)		**Pyelonephritis** Number of patients with pyelonephritis / total number of patients (%)		
			Pregnant women with treated BA	Pregnant women with untreated AB	Pregnant women without AB	Pregnant women with AB	Pregnant women with untreated AB
Brumfitt W (1975)[68]	Randomized, placebo-controlled	Sulfonamide vs. placebo	----------	----------	3/150 (2)	4/67 (6)	55/179 (31)
Elder HA *et al* (1966)[69]	Randomized, placebo-controlled	Sulfasymazine vs. placebo	40/52 (76.9)	19/49 (38.8)	----------	----------	7/52 (13.5)
Elder EH *et al* (1971)[70]	Alternating, placebo-controlled	Tetracycline vs. placebo	100/133 (75.2)	47/145 (32.4	2/279 (0.7)	4/133 (3)	27/148 (18)
Foley ME *et al* (1987)[71]	Randomized	Sulphamethizole or nitrofurantoin vs. non-treatment	73/100 (73)	58/120 (48)	----------	3/100 (3)	3/120 (2.5)
Furness ET *al* (1975)[72]	Randomized	Methenamine mandelate or methenamine hippurate vs. non-treatment	----------	----------	150/5,030 (3)	23/139 (16.5)	17/67 (25.4)
Gold EM *et al* (1966)[73]	Randomized, placebo-controlled	Sulfadimethoxine or sulfadiazine vs. placebo	23/35 (65.7)	8/30 (26.6)	----------	0/35 (0)	4/30 (13.3)

Kincaid –Smith O, Bullen M (1965)[74]	Cohort, sequential	Sulphamethoxydiazine or sulphadimidine vs placebo	42/51 (82.3)	32/50 (64)	48/4,000 (1.2)	2/61 (3.3)	20/55 (36.6)
Little PJ (1966)[75]	Randomized, placebo-controlled	Sulphonamide or nitrofurantoin vs placebo	----------	----------	19/4,735 (0.4)	4/124 (3.2)	35/141 (25)
Pathak UN *et al* (1969)[76]	Placebo-controlled	Nitrofurantoin vs placebo	73/76 (96.1)	27/76 (35.5)	8/729 (1.1)	3/76 (4)	17/76 (22.4)
Williams GL *et al* (1969)[77]	Randomized	Sulphadimidine, nitrofurantoin or ampicillin vs non-treatment	----------	----------	----------	5/85 (6)	18/78 (23)
Wren BG (1969)[78]	Alternating	Nitrofurantoin, ampicillin, sulphafurazol, nalidixic acid vs non-treatment	70/83 (84.3)	3/90 (3.3)	----------	3/83 (3.6)	33/90 (37)
Savage *et al* (1967)[79]	Alternating, placebo-controlled	Sulfonamide vs placebo	----------	----------	7/496 (1.4)	1/93 (1.1)	26/98 (26)
LeBlanc AL, McGanity WJ (1964)[80]	Randomized, not blinded	Sulfamethizole and mandelamine or nitrofuradantoin or mandelamine alone vs non-treatment	----------	----------	22/1,143 (1.9)	3/69 (4.3)	8/41 (20)
Kazemier BM *et al* (2015)[81]	Cohort prospective Randomized, placebo-controlled	Nitrofurantoin vs non-treatment or placebo	----------	----------	24/4,035 (0.6)	1/40 (2.6)	5/208 (2.4)

Table 4

Comparative study of antibiotic treatment of asymptomatic bacteriuria in pregnancy (single dose versus short course of 4-7 days).

Same antimicrobial agent

Reference (year)	Design	Participants (1,378)	Antimicrobial therapy	Bacteriological eradication (%)	Recurrrent AB (%)	Side effects (%)
Anderton KJ *et al* (1983)[157]	Alternating	64	• Amoxicillin 3 g × 2 doses during 1 day • Amoxicillin 250 mg 3 times daily × 7 days	21/33 (63.6) 31/34 (91.2)	---------	1/33 (3) 1/34 (2.9)
Bailey RR *et al* (1983)[158]	Randomized	44	• Co-trimoxazole 1.92 g × 1 dose • Co-trimoxazole 0.96 g twice daily × 5 days	18/21 85.7) 20/20 (100)	7/24 (29.2) 2/18 (11.1)	0/24 (0) 0/20 (0)
Bailey RR *et al* (1986)[159]	Randomized	60	• Trimethoprim 600 mg × 1 dose • Trimethoprim 300 mg once daily × 5 days	27/30 (90) 24/30 (80)	6/30 (20) 5/30 (16.7)	1/30 (3.3) 0/30 (0)
Brumfitt W *et al* (1982)[160]	Randomized	54	• Amoxicillin 3 g × 2 doses during 1 day • Amoxicillin 250 mg 3 times daily × 7 days	19/29 (65.5) 16/24 (66.7)	1/29 (3.4) 1/24 (4.2)	3/29 (10.3) 4/24 (16.7)
Gerstner GJ *et al* (1987-89)[161,162]	Randomized	91	• Amoxicillin 3 g × 1 dose • Amoxicillin 750 mg 3 times daily × 4 days	41/53 (77.3) 23/37 (62.2)	11/46 (23.9) 9/29 (31)	2/53 (3.8) 5/37 (13.5)
Lumbiganon P *et al* (2009)[163]	Randomized	778	• Nitrofurantoin 100 mg × 2 doses during 1 day • Nitrofurantoin 100 mg twice daily × 7 days	281/371 (75.7) 319/370 (86.2)	---------	75/375 (20) 90/385 (23.4)
Masterton RG *et al* (1985)[164]	Randomized	102	• Amoxicillin 3 g ×1 dose • Ampicillin 500 mg 4 times daily × 7 days	33/39 (84.6) 20/23 (86.9)	---------	---------
Olsen L *et al* (1989)[165]	Randomized	41	• Sulfamethizole 2 g × 1 dose • Sulfamethizole 1 g twice daily × 6 days	8/15 (53.3) 20/24 (83.3)	7/15 (46.7) 11/24 (45.8)	3/15 (20) 6/24 (25)
Pregazzi R *et al* (1987)[166]	Randomized	44	• Amoxicillin 3 g, or ampicillin 3.5 g, or trimethoprim 320 mg, or sulfamethoxazole 1600 mg, or cephalexin 3 g, × 1 dose • The same antibiotics 2-4 times daily ×	12/22 (54.5) 19/22 (86.4)	8/22 (36.4) 6/22 (27.3)	4/22 (18.2) 6/22 (27.3)

			7days			
Reeves DS *et al* (1975)[167]	Alternating	100	• Sulfonamide sulfametopyrazine 2 g × 1 dose • Sulfadimidine 4 times daily × 7 days	37/49 (75.5) 25/40 (62.5)	---------	6/47 (12.8) 13/40 (32.5)

Different antimicrobial agents

Reference (year)	**Design**	**Participants (244)**	**Antimicrobial therapy**	**Bacteriological eradication (%)**	**Recurrrent AB (%)**	**Side effects (%)**
Bayrak O *et al* (2007)[168]	Randomized	90	• Fosfomycin trometamol 3 g × 1 dose • Cefuroxime Axetil 250 mg twice daily x 5 days	41/44 (93.2) 38/40 (95)	---------	1/44 (2.3) 2/40 (5)
Estebanez A *et al* (2009)[169]	Randomized	131	• Fosfomycin trometamol 3 g × 1 dose • Amoxicillin-clavulanate 500 mg/125 mg 3 times daily × 7 days	44/53 (83) 45/56 (80.3)	1/53 (1.9) 1/56 (1.8)	1/53 (1.9) 11/56 (19.6)
Thoumsin *et al* (1990)[170]	Randomized	23	• Fosfomycin trometamol 3 g × 1 dose • Nitrofurantoin 100 mg twice daily x 7 days	11/13 (84.6) 9/10 (90)	2/13 (15.4) 1/10 (10)	0/13 (0) 2/10 (20)

Table 5
Effectiveness and side effects of therapeutic regimens in acute uncomplicated cystitis[a]

Antibiotic	Dose, duration	Clinical efficacy % (range)	Microbiological efficacy % (range)	Common side effects
Fosfomycin trometamol	3-g single dose	91	80 (78-83)	Diarrhea, nausea, headache
Nitrofurantoin macrocrystals	50-100 mg qid, 5-7 days	93 (84-95)	88 (86-92)	Nausea, headache
Fluoroquinolones[b]	Dose varies, 3 days	90 (85-98)	91 (81-98)	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
Beta-lactams[c]	Dose varies, 3-5 days	89 (79-98)	82 (74-98)	Diarrhea, nausea, vomiting, rash, urticaria, vaginal candidiasis
Trimethoprim-sulfamethoxazole[d]	160/800 mg bid, 3 days	93 (90-100)	94 (91-100)	Rash, urticaria, nausea, vomiting, hematologic

bid: Twice daily; qid: Four times daily.
[a]Modified from Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update for the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e120, by permission of Oxford University Press.
[b]Data on fluoroquinolones applies to regimens of ciprofloxacin, levofloxacin, norfloxacin and ofloxacin.
[c]Data on beta-lactams is compiled from clinical trials examining second- and third-generation cephalosporins and amoxicillin-clavulanate (5 days).
[d]Efficacy data when resistance rate of *E. coli* to trimethoprim-sulfamethoxazole is <20%.

Table 6
Summary of the studies of antimicrobial therapy of acute uncomplicated cystitis in non-pregnant women, from January 2010 to June 2016

First author, year[ref]	Study design, Location	Study population	Study drugs (dosage, duration)	Follow-up			Adverse events[d] %	Quality assessment	Comments
				Early clinical cure[a]	Late clinical cure[b]	Bacteriological cure[c]			
Hooton, 2013[43]	Randomized, double-blind, noninferiority, clinical trial, United States	Women, aged 15-55 years with acute uncomplicated cystitis, 300 patients studied	Cefpodoxime 100 mg bid, 3 days	88%	82% - 71%	81%	23%	(++)	Cefpodoxime compared with ciprofloxacin did not meet criteria for noninferiority in achieving clinical cure in an intention-to-treat analysis. 40% of women in the cefpodoxime group and 16% in the ciprofloxacin group had vaginal *E. coli* colonization at first follow-up visit
			vs Ciprofloxacin 250 mg bid, 3 days	93%	93% - 83%	96%	20%		
Matsumoto, 2011[177]	Open label, observational study, Japan	Women, aged ≥ 20 ys, with acute cystitis. 48 patients studied, 64% were premenopausals	Fosfomycin calcium, 1 g tid, 2 days	92%	95.5%	96%	5%	(-)	A non-randomized trial with a small sample. Efficacy evaluated per protocol. No statistical comparisons among the different subgroups of the study. Dropout rate of 19%
Ceran, 2010[179]	Randomized, single-blind	Women, aged 18- 65 ys, with acute cistitis,	Fosfomycin trometamol	83%		83%	4%	(+)	A single 3 g dose of fosfomycin was as efficient as 5-day

	clinical trial, Turkey	142 patients studied	3 g single-dose vs Ciprofloxacin, 500 mg bid., 5 days	81%		81%	3%		ciprofloxacin. Small sample size. Not double-blinded.

bid: Twice daily; tid: Three times daily.
(++) High quality study. Little risk of bias. (+) Acceptable quality study, moderate risk of bias. (-) Poor quality study. High risk of bias.
a. Early clinical cure: Absence of urinary symptoms 5-9 days after the last dose of antimicrobials.
b. Late clinical cure: Absence of urinary symptoms 28-30 days after the last dose of antimicrobials.
c. Bacteriological cure: Absence of bacteriuria 7-10 days after the last dose of antimicrobial.
d. Adverse events were usually mild and did not involve interruption of study medication.

Table 7
Antimicrobial agents for the treatment of acute uncomplicated cystitis: Dosages and duration of therapy

Drug	Dosage	Duration (days)
Fosfomycin trometamol	3 g single dose	Single dose
Fosfomycin calcium[a]	1 g tid	2
Nitrofurantoin macrocrystals	50-100 mg qid*	5-7
Ciprofloxacin	250- 500 mg bid	3
Levofloxacin	250-500 mg once	3
Norfloxacin	400 mg bid	3
Ofloxacin	200 mg bid	3
Amoxicillin-clavulanate	500/125 mg tid	5
Cefuroxime axetil	250-500 mg bid	5
Cefaclor	250 mg tid	5
Cefixime	400 mg once	3
Cefpodoxime-proxetil	100 mg bid	3
Ceftibuten	400 mg once	5
Trimethoprim-sulfamethoxazole	160/800 mg bid	3
Trimethoprim[b]	100 mg bid	3

Data obtained from different studies[1,21,176,179,182,184,187].
bid: Twice daily; qid: Four times daily; tid: Thrice daily.
a. Dose and duration taken from reference[177].
b. Trimethoprim is commercialized in Spain as 160 mg tablets.
*Administer with meals. Manufacturer's labeling in Spain recommends 100 mg every 8 hours.

Table 8

Antibiotic resistance in community-acquired versus healthcare-associated non-nosocomial APN due to Enterobacteriaceae

Antibiotic	**Community adquired APN (n = 328)***	**Health-care associated APN (n = 61)***	**P**
Ampicilin	248 (75.6)	54 (88.5)	P = 0,029
Amoxicillin-clavulanic acid	73 (22.3)	27 (44.3)	P = 0,001
Piperacillin-tazobactam	59 (18)	27 (44.3)	P = 0,002
Cefuroxime	30 (9.2)	20 (33.3)	P <0,001
Cefotaxime	17 (5.3)	15 (24.6)	P <0,001
Imipenem	0 (0)	0 (0)	
Amikacin	8 (2.4)	2 (3.2)	NS (P = 1)
Ciprofloxacin	73 (22.4)	40 (65.6)	P <0,001
Cotrimoxazole	107 (32.6)	32 (52.5)	P = 0,005
Fosfomycin	9 (2.7)	8 (13.2)	P = 0,01

Data presented as absolute numbers (percentages). Data is from a tertiary hospital in Spain during 2014 (Vall d'Hebron University Hospital)[218].

*Data includes only Enterobacteriaceae (*E. coli*, *K. pneumoniae*, *Proteus* spp) representing the etiology of 91.3% of community-acquired APN and 65.6% of healthcare-associated APN.

Table 9

Antibiotic resistance in APN patients, taking into account all isolated microorganisms (n = 316) and *Escherichia coli* (n = 260), as well as complicated APN and sex

Antibiotic	Uncomplicated APN		Complicated APN			
	All microorganisms (n = 117)	*E.coli* (n = 110)	All microorganisms (n = 199)		*E. coli* (n = 150)	
			Women (n = 93)	Men (n = 106)	Women (n = 81)	Men (n = 69)
Amoxicillin-clavulanate	23 (19.7)	23 (20.9)	24 (25.8)	30 (28.3)	23 (28.4)	16 (23.2)
Piperacillin-tazobactam	2 (1.7)	2 (1.8)	3 (3.2)	4 (3.8)	2 (2.5)	1 (1.4)
Cefuroxime	13 (11.1)[a]	12 (10.9)[b]	20 (21.5)[a]	21 (20)	18 (22.2)[b]	9 (13)
Ceftriaxone	3 (2.6)	2 (1.8)	4 (4.3)	8 (7.5)	4 (4.9)	2 (2.9)
Imipenem	0	0	1 (1.1)	1 (0.9)	0	0
Gentamicin	9 (7.7)	8 (7.3)	6 (6.5)	16 (15.1)	5 (6.2)	9 (13)
Ciprofloxacin	18 (15.4)[c]	18 (16.4)[d]	24 (25.8)[c]	31 (29.2)	23 (28.4)[d]	18 (26)
Cotrimoxazole	36 (30.8)	36 (32.7)	38 (41)	37 (34.9)	36 (44.4)	23 (33.3)
Nitrofurantoin	13 (11.1)	12 (10.9)	9 (9.7)	16 (15.1)	7 (8.6)	6 (8.7)
Fosfomycin	5 (4.3)	2 (1.8)	6 (6.5)	5 (4.7)	5 (6.2)	1 (1.4)

[a]p = 0,04.

[b]p = 0,03.

[c]p = 0,01.

[d]p =0,04.

Data presented as absolute numbers (percentage). Data comes from a tertiary hospital in Spain between 2009 and 2014 (University Hospital of Álava).

Table 10

Daily dosages for adults with acute pyelonephritis and normal renal function

Antibiotic	**Dosage**	**Observation**
Amoxicillin-clavulanic acid*	1-2/0,25 g / 8 h iv 875-125 mg / 8 h oral	• Avoid in patients allergic to penicillins
Cefuroxime sodium	750-1,500 mg / 8 h iv	
Cefuroxime axetil*	0,5 g vo / 8-12 h oral	• Better absorption with meals
Ceftibuten*, cefixime*	0,4 g / 12-24 h oral	• Higher dose until improvement • Low dosage best suited for mild uPNA
Piperacillin-tazobactam	4 g-0.5 g / 6-8 h iv	Higher dose in severe sepsis or in *P. aeruginosa* Avoid in patients allergic to penicillins
Cefotaxime	1-2 g / 8 h iv	• Higher dose for patients with severe sepsis
Ceftriaxone	1-2 g / 24 h iv	• Higher dose for patients with severe sepsis
Ceftazidime, cefepime	1-2 g / 8 h iv	• Higher dose in severe sepsis or in *P. aeruginosa*
Ceftolozane-tazobactam	1-0.5 g / 8 h iv	
Aztreonam	1-2 g / 8 h iv	• Higher dose in severe sepsis or in *P. aeruginosa*
Ertapenem	1 g / 24 iv	
Imipenem	0,5 g / 6 h iv to 1 g / 8 h iv	
Meropenem	0,5-2 g / 8 h iv	• Higher dose in severe sepsis or in *P. aeruginosa*
Fosfomycin sodium	4-8 g / 8 h iv	
Gentamicin, tobramycin, netilmicin	3-5 mg/kg/d as a single daily dose	• Higher dose for patients with severe sepsis
Amikacin	15-20 mg/kg/d as a single daily dose	• Higher dose for patients with severe sepsis
Ciprofloxacin	200-400 mg /8- 12 h iv 500-750 mg / 12 h oral	• Higher dose in severe sepsis or in *P. aeruginosa*
Levofloxacin	500-750 mg /24 h oral or iv	• Higher dose in severe sepsis or in *P. aeruginosa*
Trimethoprim-sulfamethoxazole	160-800 mg / 12 h oral or iv	• Best suited for targeted therapy after improvement

iv: intravenous.

*Oral therapy may fail to eradicate the infection with susceptible isolates with MIC values near the breakpoint because PK/PD values are not attained. Higher doses are recommended.

Table 11
Prophylactic antibiotics for prevention of recurrent urinary tract infections

Continuous prophylaxis		**Post-coital prophylaxis**
Co-trimoxazole	40/200 mg once daily	40/200 mg once 80/400 mg once
Trimethoprim	100 mg once daily	100 mg once
Nitrofurantoin	50-100 mg once daily	50-100 mg once
Ciprofloxacin	125 mg once daily	125 mg once
Norfloxacin	200 mg once daily	200 mg once
Ofloxacin	--	100 mg once
Cefalexin	125-250 mg once daily	125-250 mg once
Cefaclor	250 mg once daily	--
Fosfomycin-trometamol	3 g every 7-10 days	--
Fosfomycin calcium	--	500 mg once

Due to its ecological impact, prophylaxis with fluoroquinolones should be used only when no other preventive strategy is available.