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Antimicrobial Original Research Paper

Clinical evaluation of guidelines and therapeutic approaches in multi drug-resistant urinary tract infections

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Antibiotic resistance represents a real health emergency worldwide, mostly due to the lack of new antibiotics active against multidrug-resistant *Enterobacteriaceae*. Considering the global epidemiological situation in several infections, including urinary tract infections (UTIs), some antibiotics, such as fluoroquinolones and trimethoprim/sulphamethoxazole, can no longer be used for empiric treatment due to high resistance rates. However, some old antibiotics maintain high microbiological activity against UTI pathogens: according to many recent guidelines, fosfomycin trometamol, nitrofurantoin and pivmecillinam are recommended for the first-line treatment of uncomplicated UTIs. This article provides an overview of the therapeutic management of UTIs, especially uncomplicated and recurrent cystitis, as well as complicated UTIs such as catheter-related UTIs, and UTIs in males, post-menopausal women and diabetic patients, based on the main international guidelines.

Keywords: urinary tract infections, fosfomycin trometamol, pivmecillinam, nitrofurantoin, quinolones, trimethoprim/sulphamethoxazole

Emerging issues in antibiotic therapy

The most relevant clinical issue concerning infections caused by Gram-negative strains (such as *Enterobacteriaceae*, *Pseudomonas aeruginosa or Acinetobacter spp.*) is resistance to the main antibiotic classes. This represents a real threat to both empiric and targeted treatments. According to the 2015 report by the European Centre for Disease prevention and Control (ECDC),[1] from 2012 to 2015 there was a significant increase in multidrug-resistant *Escherichia coli* and *Klebsiella pneumoniae* strains in at least one-third of participating countries, together with higher prescription of carbapenems. As a result, this trend was associated with the emergence of carbapenemase-producing strains, which caused endemic-epidemic foci in several European countries, worsening therapeutic management. The ECDC report shows that resistance to third-generation cephalosporins among *E. coli* (the most frequently isolated Gram-negative pathogen from blood and urine cultures and the main pathogen responsible for urinary tract infections [UTIs]) was observed in 5–10% of strains isolated in Belgium, the Netherlands and Nordic countries, in 10–20% of strains isolated in France, Spain, Portugal, U.K., Germany and Greece, and in 30–40% of strains isolated in Italy, Slovakia, Bulgaria and Romania. The majority of countries reporting resistance percentages of 25% or higher were located in southern and south-eastern Europe.[1] For *K. pneumonia*, 8.4% of strains isolated in Austria, 10–11% of strains isolated in Germany and U.K., 19–21% of strains isolated in Spain and Belgium, 30–41% of strains isolated in France and Portugal and ≥50% of strains isolated in Italy and Greece are resistant to third-generation cephalosporins.[1] Resistance to this antibiotic class is mediated by extended spectrum beta-lactamases (ESBLs) in 70–100% of strains isolated in Europe, meaning that carbapenems often represent the only active available antibiotics.

Resistance to carbapenems among *E. coli* in Europe is still low (<1%).[1] The rate of carbapenem-resistant *K. pneumoniae* (which is often also resistant to all available antibiotic classes except colistin, fosfomycin and tigecycline) is generally low in Europe (<5%), apart from in Romania (24.7%), Italy (33.5%) and Greece (61.9%).[1]

New epidemiological situations: long-term care facilities

Epidemiological data from ECDC are focused on invasive strains, isolated from blood or tissue of infected hospitalized patients. Although ECDC does not specify whether these are community-acquired or hospital-acquired infections, it is recognized that multidrug-resistant pathogens have been

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isolated primarily from patients with nosocomial infections.[2] However, in the last decade it has been demonstrated that both hospitals and long-term care facilities (LTCFs) represent reservoirs for multidrug-resistant strains and that mutual transmission will occur if adequate surveillance and control systems for colonized or infected patients would not be implemented. The HALT 2 (Healthcare-Associated Infections in Long-Term care facilities in Europe) 2013 trial is the most important survey performed in this setting. It showed that the prevalence of infections in European and Italian LTCFs was 3.4 and 3%, respectively. In particular, incidence rates of respiratory tract infections, UTIs and skin/wound infections were 38, 29 and 16%, respectively.[3] In Italy, the most frequently isolated pathogens in LTCFs, especially from urine, were *E. coli* (28%; resistant to third-generation cephalosporins in 46% of cases and to carbapenems in 8% of cases), *Proteus mirabilis* (14%, resistant to third-generation cephalosporins in 61% of cases and to carbapenems in 13% of cases), *K. pneumoniae* (10%, resistant to third-generation cephalosporins in 41% of cases and to carbapenems in 23% of cases) and *Pseudomonas aeruginosa* (7%, resistant to carbapenems in 38% of cases). According to the HALT 2 survey, the epidemiology of antibiotic resistance in LTCFs is similar to that reported by ECDC for *K. pneumoniae,* and worse for carbapenem-resistant *E. coli* (8% vs. <1%) and *P. aeruginosa* (38% vs. 10%).[3] These data have a relevant impact on the therapeutic management of the most frequent infections observed in LTCFs.

Inappropriate use of antibiotics: European situation

Antibiotic resistance represents a real health emergency worldwide, mainly due to the lack of new antibiotics active against carbapenemase-producing *Enterobacteriaceae*. At least 700,000 deaths/year could be attributable to antimicrobial resistance and this figure is increasing: the estimated number of deaths by antibiotic resistance-related deaths per year is projected to be 10 million worldwide by 2050 if adequate surveillance, control and prevention strategies are not implemented. One of the main risk factors associated with the spread of multidrug-resistant (MDR) strains is the selective pressure of antibiotics, amplified by their overuse or misuse. Other than antibiotic consumption in agriculture and zoology, an ECDC report[2] noted that global antibiotic use in Europe in 2012 was 21.5 defined daily doses (DDD)/1000 people/day. A 2015 U.K. Government report described the total amount of antibiotic consumption in human beings in Europe in 2013. Use was lowest in the Netherlands with 10.83 DDD/1000 people/day (rank 1) and among the highest in France at 30.14 DDD/1000 people/day (rank 26). Denmark was intermediate at 16.4 DDD/1000 people/day (rank 10), Germany at 15.79 DDD/1000 people/day (rank 7) and the U.K. (rank 16) at 21.46 DDD/1000 people/day. Penicillins, macrolides and fluoroquinolones are the most prescribed antibiotic classes.

In LTCFs, the rate of antibiotic consumption in the HALT 2 survey was 4% among the enrolled residents: treatment was started in 88% of documented infections (respiratory infections: 46% of cases; UTIs: 29% of cases; skin/wound infections: 12% of cases) and prophylactically in 12% of cases (half of these for preventing UTIs).[3] Despite the high prevalence of resistant strains, third-generation cephalosporins were the most prescribed antibiotics (26%), followed by fluoroquinolones (25%) and beta-lactams plus β-lactamase inhibitors (22%).[3] The Italian National Report on the use of drugs noted that systemic antibiotics were the second highest therapeutic cost in the first 9 months of 2015.[4] The most prescribed drugs were beta-lactams plus β-lactamase inhibitors, macrolides, fluoroquinolones and wide-spectrum penicillins.

Based on current global epidemiology, some antibiotics, particularly fluoroquinolones and trimethoprim/sulphamethoxazole, can no longer be used for empiric treatment of several infections, including UTIs, due to high resistance rates. In contrast, some old antibiotics, such as nitrofurantoin, pivmecillinam and fosfomycin trometamol, maintain a high microbiological activity against UTI pathogens.

Nitrofurantoin

Nitrofurantoin was approved by the U.S. Food and Drug Administration (FDA) in 1953 and has been used for more than 50 years. Many *E. coli* and *Citrobacter* spp. strains are susceptible to nitrofurantoin but activity against *Enterobacter* spp. and *Klebsiella pneumoniae* is moderate. However, *Proteus* spp., *Providencia* spp., *Morganella* spp., *Serratia* spp., *Acinetobacter* spp. and *Pseudomonas* spp. are generally resistant to nitrofurantoin. Nitrofurantoin has low activity against ESBL-producing *E. coli* (70% of susceptible strains).[5] Nitrofurantoin is mainly indicated for the treatment of UTIs in females because concomitant prostatitis cannot be ruled out in males and nitrofurantoin does not reach therapeutic levels in prostate tissue. Clinical trials have shown that nitrofurantoin is equivalent to trimethoprim/sulphamethoxazole, ciprofloxacin and amoxicillin/clavulanate (all administered for 3 days) when given for 5 or 7 days in the treatment of uncomplicated UTIs but less effective than comparators when administered for only 3 days. It should be noted that the four-times daily dosing required with nitrofurantoin is not ideal for achieving good patient compliance.[6] A recent systematic review and meta-analysis on the prophylaxis of recurrent UTIs in adult women showed that nitrofurantoin had similar efficacy to alternative prophylactic treatment options but a greater risk of adverse events (primarily gastrointestinal upset, peripheral neuropathy and headache).[7] Nitrofurantoin must not be used in patients with renal failure or glucose-6-phosphate dehydrogenase deficiency.[6]

Pivmecillinam

Pivmecillinam is an oral synthetic penicillin marketed in several European countries. After absorption, this pro-drug is metabolized to mecillinam via enzymatic hydrolysis. Mecillinam has a potent microbiological activity against *Enterobacteriaceae* but a moderate or

poor activity against other Gram-negative rod and Gram-positive bacteria. Recent *in vitro* studies showed that pivmecillinam had high activity against ESBL-producing *E. coli* (inhibition of 80–90% of tested strains). Clinical trials in infections caused by ESBL-producing strains are limited. Pivmecillinam has been used extensively in Nordic countries but it is not widely used in other countries. Nevertheless, this drug is indicated for the treatment of uncomplicated UTIs in Infectious Diseases Society of America (IDSA) and European Association of Urology (EAU) guidelines.[8,9] The adverse event profile of pivmecillinam is similar to that of other penicillins: the most common side effects being rash and gastrointestinal upset, including nausea and vomiting.[10]

Fosfomycin trometamol

Fosfomycin trometamol has a wide antibacterial spectrum, and is effective against both Gram-positive and Gram-negative strains. It is effective against the most relevant uropathogens, such as *E. coli*, *P. mirabilis* and *P. aeruginosa*. A microbiological and clinical review on fosfomycin including 17 studies on 5057 *Enterobacteriaceae* (4448 ESBL-producing strains), showed that 96.8% of ESBL-positive *Escherichia coli* strains were susceptible to fosfomycin; the susceptibility rate of ESBL-producing *Klebsiella pneumoniae* (608 strains) was 81.3%.[11] Despite its widespread oral use for the treatment of UTIs over previous years, fosfomycin maintains high microbiological activity against *Enterobacteriaceae*, including multidrug-resistant *Enterobacteriaceae* (resistant to beta-lactams, fluoroquinolones and trimethoprim/sulphamethoxazole, without any cross-resistance with other antibiotics).

A single 3-g dose rapidly achieves effective urinary concentrations lasting 1–3 days; furthermore, some trials suggest that it should be as affective as 5–7 days of cotrimoxazole or fluoroquinolone therapy.[12] One study evaluated fosfomycin trometamol for lower UTIs caused by ESBL *E. coli*. [13]: a 3-g, every 48 h, three-dose regimen was administered in more than half of the UTIs, the ones which were complicated; the investigators reported clinical and microbiologic success in 94% (49/52) and 79% (41/52) of patients, respectively. The only prospective study about ESBL-producing bacteria-related complicated UTI involved only 47 patients and showed no statistically significant difference between a 3-g, every 48 h, 3-dose regimen fosfomycin trometamol and carbapenems in terms of clinical and microbiological outcome.[14]

The most common side effects of fosfomycin are nausea, vomiting and diarrhoea, although the incidence of such side effects is low.

Trimethoprim/sulphamethoxazole

The combination of trimethoprim and sulphamethoxazole (cotrimoxazole) had been used for more than 3 decades for the treatment of patients with UTIs. It had represented the most frequently prescribed antibiotic for UTIs. Other indications include treatment of infections caused by *Pneumocystis jiroveci*, *Toxoplasma gondii*, *Stenotrophomonas maltophilia* and community-associated methicillin-resistant *Staphylococcus aureus*.[15] National and international guidelines recommend the use of trimethoprim/sulphamethoxazole for the treatment of uncomplicated UTIs, only when local resistance rates are <20%.[8,9,16–19] Even when effective, trimethoprim/sulphamethoxazole is associated with several adverse effects, including hematologic effects, drug hypersensitivity syndrome, hyperkalemia, neurologic, renal and reproductive abnormalities and decreased oxygen-carrying capacity).[15]

Fluoroquinolones

Due to their activity against Gram-negative pathogens, including uropathogens, the most representative quinolones (e.g. ciprofloxacin, ofloxacin and levofloxacin) are indicated for the short-term treatment (3 days) of UTIs.[20,21] However, an excessive use of both oral and parenteral fluoroquinolones for UTIs or other infections has increased the fluoroquinolone resistance rate among the most common uropathogens.[22] According to the ECDC 2015 report, resistance to fluoroquinolones among *Enterobacteriaceae* has reached a very high level (22.8% in *E. coli*, 29.7% in *K. pneumoniae*).[1] As a result, fluoroquinolones are no longer appropriate for empiric treatment of uncomplicated UTIs, as stated by the main national and international guidelines. Instead, fluoroquinolones are now usually recommended for the empiric treatment of UTIs only when local resistance rates are lower than 10%.[8,9,16–19] Several adverse events of fluoroquinolones have been described: tendinitis and tendon rupture, convulsions, hallucinations, depression, QT prolongation and torsade de pointes or *Clostridium difficile*-associated diarrhoea. A 2016 FDA Drug Safety Communication stated that oral and injectable fluoroquinolone antibiotics are associated with disabling and potentially permanent side effects. For this reason, the FDA stated that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated UTIs because the risk of serious side effects generally outweighs the benefits in these patients.[23]

The therapeutic management of urinary tract infections

There has been a marked increase in resistance to the most frequently used systemic antibiotics (e.g. beta-lactams plus β-lactamase inhibitors, trimethoprim/sulphamethoxazole and fluoroquinolones) in both the community and hospital settings over recent years, meaning that most of them are no longer suitable for the empiric treatment of UTIs. In addition, there is a lack of new antibiotics. However, some old antibiotics maintain high microbiological activity against uropathogens. Therefore, physicians need to implement specific therapeutic strategies for each patient, based on local epidemiology of resistance, availability of

active antibiotics and national and international guideline recommendations.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is characterized by the presence of bacteria in urine ($\geq 10^5$ colony forming units [CFU]/mL in urine culture], without any specific UTI symptoms (dysuria, pollachiuria, fever, etc.). Bacteriuria must be confirmed by a microbiological test of a second consecutive sample in female patients.[24] The prevalence of asymptomatic bacteruria varies between populations, from 1% in children to 100% in long-term catheterized patients and it is higher in the presence of anatomic or functional changes of urinary tract, in elderly patients and in female patients. Due to a bacterial colonization without mucosa invasion and inflammatory response, asymptomatic bacteriuria does not represent a real disease. Therefore, only selected cases should be screened and, eventually, treated. Based on clinical trials showing the effectiveness of treating asymptomatic bacteriuria in reducing complications in specific populations, screening is indicated in pregnant women, neutropenic patients and those undergoing surgical procedures involving the urinary tract (positioning or replacement of nephrostomy or stents or endoscopic procedures with a mucosal damage).

During pregnancy, untreated asymptomatic bacteriuria is associated with a high risk (up to 30%) of developing an acute pyelonephritis. However, a recent *Cochrane Collaboration* review showed that the clinical benefit of treating asymptomatic bacteriuria during pregnancy is uncertain both for women and foetus, highlighting the need for well-conducted, prospective randomized clinical trials.[25] Patients with asymptomatic bacteriuria who must undergo urological surgery are at high risk of post-surgical sepsis: in this group of patients, pre-surgical screening with a urine culture is recommended because the efficacy of the antibiotic treatment in preventing more severe post-surgical infections has been demonstrated.[26] Routine screening is not recommended in non-pregnant women, diabetic patients, elderly patients, kidney transplant recipients, catheterized patients (including intermittent catheterization, ureteral stent or urinary derivations) and patients with anatomic or functional change of the urinary tract. In these cases, asymptomatic bacteriuria usually resolves spontaneously and it is not associated with an increase in complications or mortality. However, antibiotics cannot prevent colonization of the urinary tract, can cause adverse events and contribute to the development of bacterial resistance.

When treatment is necessary, the agent chosen should be based on the antibiogram results and administered for at least 7 days (except fosfomycin trometamol, which is given as a single dose). Antibiotics that can be safely used for pregnant women are penicillins, and second- and third-generation cephalosporins, as well as fosfomycin trometamol. Conversely, fluoroquinolones and trimethoprim/sulphamethoxazole are contraindicated and nitrofurantoin should be avoided after 32 weeks of gestation. A control urine culture, performed after 2 weeks after the end of the treatment, is recommended for evaluation of treatment efficacy.

Uncomplicated cystitis

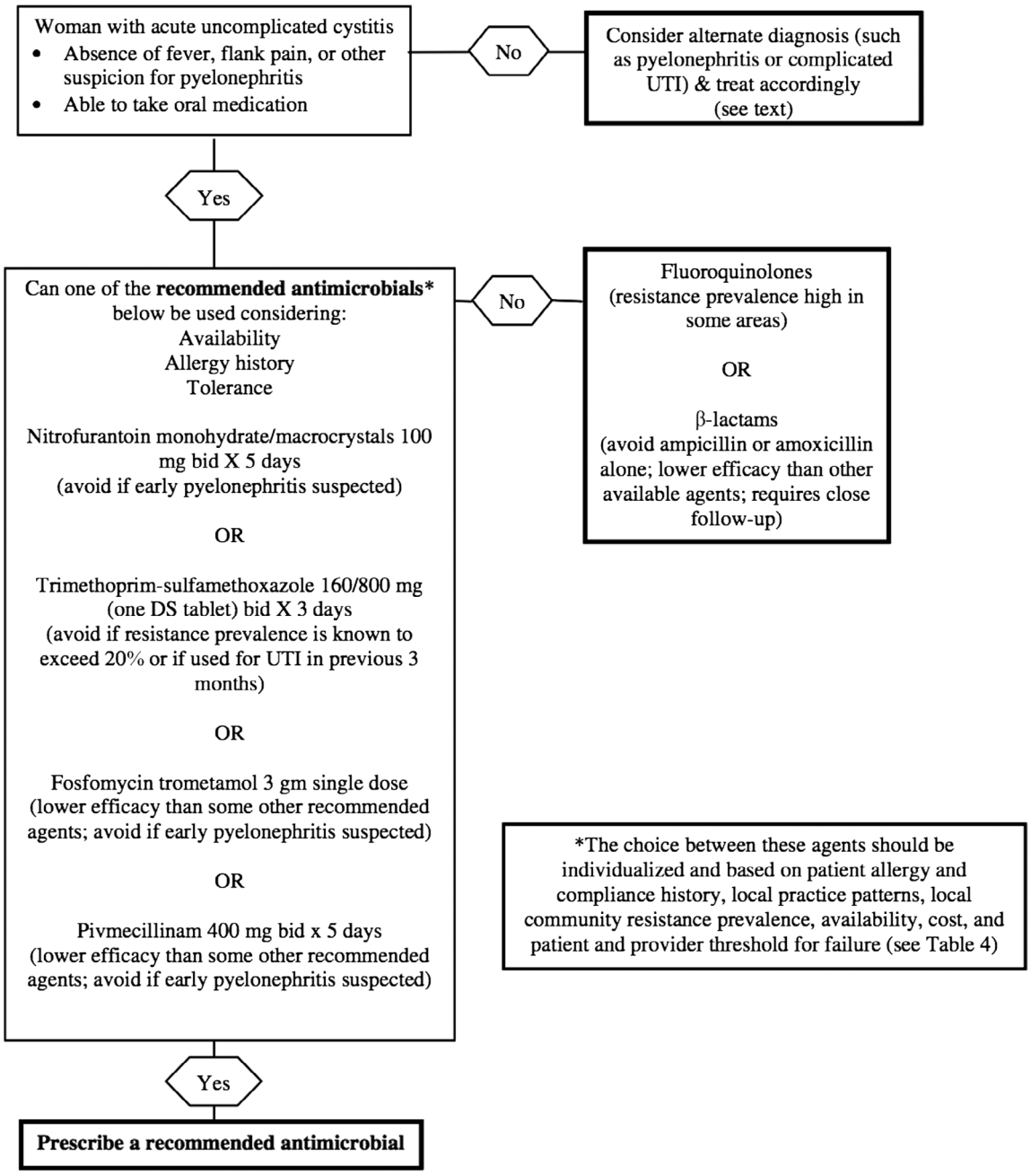
Uncomplicated cystitis is defined as a UTI in an otherwise healthy individual who does not have any risk factors for complications. UTIs in male patients are usually considered to be complicated because most occur concomitantly with anatomic or functional changes of urinary tract. The risk of developing cystitis in females is comparatively high, mainly due to the short urethra, and is further increased by sexual activity, delayed post-coital micturition, use of diaphragm or spermicidal gels or a history of recurrent UTIs.[27] Uncomplicated cystitis is the most frequent UTI (40%) and it is the second most common infection in the community setting in Europe, after respiratory tract infections. *E. coli* is the major causative pathogen (70–95%), followed by *Staphylococcus saprophyticus* (5–10%), *Enterobacteriaceae* (*Proteus mirabilis* and *Klebsiella* spp.) and *Enterococcus faecalis*.[28]

As far as the management of uncomplicated acute cystitis is concerned, a short course of antibiotics is strongly recommended due to the high efficacy and compliance associated with this approach, along with a lower risk of adverse and ecological events.

The IDSA 2010 guidelines on the treatment of uncomplicated UTIs recommend first-line treatment with nitrofurantoin, trimethoprim/sulphamethoxazole (if the resistance rate is <20%), fosfomycin trometamol or pivmecillinam (Table 1). The choice of agent should be based on several factors, including local factors such as drug availability and resistance patterns. Fluoroquinolones and beta-lactams (amoxicillin/clavulanate and oral cephalosporins) are considered second-choice agents.[8] The 'Guidelines on Urological Infections' published in 2017 by the EAU recommend fosfomycin trometamol 3 g as a single dose, pivmecillinam 400 mg every 8 h for 3–5 days, or nitrofurantoin 100 mg every 12 h for 5 days for the treatment of acute uncomplicated cystitis in adult female patients (Table 2). These guidelines indicate that ESBL-producing *E. coli* strains are generally susceptible to fosfomycin. Alternative drug regimens include trimethoprim/sulphamethoxazole (indicated only when *E. coli* resistance rates are <20%). Compared to the previous edition (2015), the most recent update did not recommend the use of fluoroquinolones because of the potential adverse events and the negative ecologic impact in terms of resistance. Beta-lactams plus β-lactamase inhibitors and oral cephalosporins are not indicated as first-line therapy and should be used as targeted therapy.[9]

The 'Société de Pathologie Infectieuse de Langue Française' guidelines, published in 2014, recommend first-line treatment with fosfomycin trometamol, due to

Table 1 IDSA recommendation for uncomplicated UTIs[8]



Note: This figure is not covered by the Open Access license of this publication. Gupta et al, International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clinical Infectious Diseases 2011;52(5):e103–e120, DOI: 10.1093/cid/ciq257, reproduced with permission of Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For permissions please email: journals.permissions@oup.com. Please visit: www.idsociety.org/Guidelines.

Table 2 EAU recommendation for uncomplicated cystitis[9]

Antimicrobial	Daily dose	Duration of therapy	Comments	LE	GR
First choice					
Fosfomycin trometamol	3 g SD	1 day	Recommended in women not men	1	A
Nitrofurantoin macrocrystal	100 mg bid	5 days			
Pivmecillinam	400 mg tid	3–5 days			
Alternatives					
Cephalosporins (e.g. cefadroxil)	500 mg tid	3 days	Or comparable	1b	B
If the local resistance pattern for E. coli is <20%					
Trimethoprim	200 mg bid	5 days	Not in the first trimester of pregnancy	1b	B
Trimethoprim/sulphamethoxazole	160/800 mg bid	3 days	Not in the last trimester of pregnancy		
Treatment in men					
Trimethoprim/sulphamethoxazole	160/800 mg bid	7 days	Restricted to men, fluoroquionlones can also be prescribed in accordance with local susceptibility testing	4	C

Note: bid, twice daily; SD, single dose; tid, three times daily.

Table 3 Recommendations of the Société de Pathologie Infectieuse de Langue Française for uncomplicated cystitis[16]

Treatment	Agent (s), dose and duration
First-line	Fosfomycin trometamol 3 g SD
Second-line	Pivmecillinam 400 mg bid for 5 days
Third-line	Fluoroquinolone SD; ciprofloxacin 500 mg or ofloxacin 400 mg
	Nitrofurantoin 100 mg tid for 5 days

Note: bid, twice daily; SD, single dose; SMX, sulphamethoxazole; tid, three times daily.

Table 4 Antibiotic prophylaxis regimens for recurrent uncomplicated cystitis

Long-term prophylaxis[9]

- fosfomycin trometamol 3 g, every 10 days
- nitrofurantoin 50 mg or 100 mg once daily*
- cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily (during pregnancy)**

Post-coital prophylaxis[17]

- nitrofurantoin 50–100 mg single dose
- trimethoprim/sulphamethoxazole 80/400 mg single dose
- ceftibuten 400 mg single dose
- cefixime 400 mg single dose

*There are recent warnings by governmental agencies about the long-term prophylactic use of nitrofurantoin because of rare but severe pulmonary and hepatic adverse effects.[14]

**Cephalosporins should not be used for longer periods to avoid selection of resistant strains.[14]

the low rate of resistance, very high microbiological eradication and clinical success rates, good safety and very high compliance (Table 3). Pivmecillinam is considered a second-choice drug, while fluoroquinolones and nitrofurantoin are reserved as third-choice agents. Amoxicillin/clavulanate, oral cephalosporins and trimethoprim/sulphamethoxazole are not indicated in uncomplicated cystitis.[16]

The guidelines proposed by the Italian Society of Urology in 2015 recommend fosfomycin trometamol and nitrofurantoin as first-line treatment for uncomplicated UTIs.[17] British guidelines, published in 2015, suggest that nitrofurantoin and trimethoprim/sulfamethoxazole should be considered as first choice, reserving fosfomycin trometamol as a second choice (this agent has been available in the UK since the second half of 2016), and fluoroquinolones when the resistance rate to trimethoprim/sulfamethoxazole is >20%.[18]

The Deutsch Interdisciplinary Society (AWMF) guidelines recommend fosfomycin trometamol, nitrofurantoin and pivmecillinam as a first-line treatment of uncomplicated UTIs.[19]

The use of antibacterial agents other than carbapenems for the treatment of ESBL-producing *Enterobacteriaceae*, such as nitrofurantoin, pivmecillinam and mostly fosfomycin trometamol, has a sparing effect on carbapenems, increasing use of which is causing a proliferation of carbapenemase-producing strains. Unfortunately, physicians do not always follow the guideline recommendations. A U.S. survey conducted over the period 2011 to 2014, including 1273 patients with acute cystitis, showed that fluoroquinolones were the most prescribed antibiotics (51.6%), followed by nitrofurantoin (33.5%) and trimethoprim/sulphamethoxazole (12.0%). Ciprofloxacin and levofloxacin were prescribed for 3 days in 29.0% of patients only; a similar situation was observed for trimethoprim/sulphamethoxazole which was prescribed for 3 days in only 16% of patients, and nitrofurantoin, administered for 3 days in 14% of cases only.[29] The most concerning aspects were the first-line use of fluoroquinolones and the long-term administration of all the antibiotics for the management of uncomplicated UTIs.

In summary, the following agents and regimens are recommended for empiric treatment of uncomplicated cystitis, where not contraindicated:

- fosfomycin trometamol 3 g orally (PO), single dose;
- nitrofurantoin 100 mg PO, every 12 h for 5 days
- pivmecillinam 400 mg PO, every 8 h for 3 days

Fosfomycin trometamol is the first-choice drug, due to the high rates of microbiological eradication and clinical success.[9,16,17] When the local resistance rate is <20%, the use of trimethoprim/sulphamethoxazole 160/800 mg every 12 h for 3 days is also feasible as an alternative option. Beta-lactams plus β-lactamase inhibitors and oral cephalosporins should not be used for a short period.[9,17]

Recurrent uncomplicated cystitis

Recurrent uncomplicated cystitis is characterized by two or more episodes of uncomplicated UTIs during the previous 6 months or three or more episodes during the previous 12 months. Recurrent uncomplicated UTIs affect 20–30% of women with a first episode of cystitis. The main risk factor is sexual activity, in particular when associated with the use of diaphragm or spermicidal gels or delayed post-coital micturition. Causative pathogens for recurrent UTIs and the therapeutic approach are the same as those for acute UTIs.[30] However, several strategies can be implemented to prevent further episodes. The most effective of these is behavioural prophylaxis, aimed at reducing or eliminating risk factors. Antibiotic prophylaxis is not routinely recommended because the preventive effect is limited to the period of drug administration. However, this may be appropriate in selected cases, especially when recurrent episodes are clearly related to sexual activity or if other behavioural strategies are ineffective. Antibiotic prophylaxis can be started in patients with negative urine cultures, at least 1–2 weeks after the end of a previous antibiotic therapy, and should be continued for at least 6 months or, depending on the clinical history of the patient, administered as a single post-coital dose. The choice of agent should be based on urine cultures and antibiogram results, taking into account that some antibiotics, such as fluoroquinolones or cephalosporins, are no longer routinely recommended due to their high risk of selecting resistant strains.[9,17] Table 4 shows the antibiotic prophylaxis

regimens for recurrent non-complicated cystitis.[9,17] The use of nitrofurantoin is not recommended for long-term prophylaxis because of a greater risk of adverse events than other treatments.[7] Post-coital prophylaxis should be considered to reduce the risk of UTI in pregnant women with a history of frequent UTIs before onset of pregnancy.[9] For example, Italian guidelines suggest nitrofurantoin, trimethoprim/sulphamethoxazole, ceftibuten and cefixime[17] (Table 4).

Several non-antibiotic prophylactic strategies (cranberry, oral immunoactive fractions of *Escherichia coli*, *Lactobacillus* by the oral or vaginal route, or topical oestrogens in post-menopausal women) have been proposed, but there is not sufficient evidence to recommend use of these in clinical practice.[9,17]

Catheter-related urinary tract infections

A catheter-related UTI is characterized by at least a positive urine culture with bacterial load $\geq 10^3$ CFU/mL in a catheterized patient with signs or symptoms of UTIs, after excluding other potential infectious sites (symptoms are often non-specific in a catheterized patient). Another important diagnostic parameter is the presence of piuria, which has a high negative predictive value. UTIs are the main nosocomial infections, generally associated with the urinary catheter. Several epidemiologic surveys showed that the urinary catheter is the most used nosocomial device, positioned in 15–25% of hospitalized patients and in at least 10% of subjects in LTCFs. The main risk factor for catheter-related UTIs is the duration of catheterization: it has been estimated that the risk of bacterial colonization increases by at least 3% for each day of catheterization, reaching 100% after 1 month. Bacterial colonization usually resolves after catheter removal but can cause infection in approximately 30% of cases.[31] A monomicrobial flora (predominantly *E. coli*, followed by *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *Enterococcus* spp. e *Staphylococcus* spp.) is usually observed during short-term catheterization (<1 month), whereas a polymicrobial etiology with typically non-urological pathogens, such as *Providencia stuartii* or *Morganella morganii,* is typical during long-term catheterization (>1 month).[32] A urine culture is strongly recommended. If a catheter has been in place for 2 weeks or more, it is recommended that it is removed before collection of urine samples. Table 5 shows the most suitable therapeutic options for the empiric treatment of catheter-related UTIs.[9,17] Removal or change of the urinary catheter before starting antibiotic treatment is recommended.[8]

Table 5 Therapeutic management of catheter-related urinary tract infections[9,17]

Initial empiric treatment, mild infections (cystitis)

- Amoxiclavulanate[3] 1 g, every 12 h for 7 days
- Cefixime[1] 400 mg, every 24 h for 7 days
- Ceftibuten[1] 400 mg, every 24 h for 7 days
- Levofloxacin[2] 500 mg, every 24 h for 7 days
- Ciprofloxacin[2] 500 mg, every 12 h for 7 days
- Ciprofloxacin[2] extended-release 1000 mg, every 24 h for 7 days
- Fosfomycin trometamol 3 g, every 72 h for 9 days

[1]First choice instead of penicillins in case of history of allergic reactions
[2]Empiric treatment only where local resistance is <10%
[3]EAU guidelines suggest that amoxicillin-clavulanic acid should not be used for empirical treatment of complicated UTI; amoxicillin plus an aminoglycoside is recommended instead

Treatment failure or severe infections, intravenous administration

- Ciprofloxacin[1,2] 400 mg, every 8–12 h for 14 days
- Piperacillin/Tazobactam[2] 4.5 g, every 8 h for 14 days
- Ceftazidime[2] 2 g, every 8 h for 14 days
- Meropenem[2,3] 1 g, every 8 h for 14 days
- Imipenem[2,3] 500 mg, every 6 h for 14 days

[1]Empiric treatment only where local resistance is <10%
[2]In case of urosepsis, consider a combination with amikacin 15 mg/kg, every 24 h, for the first 3–5 days, with adequate monitoring of the renal function
[3]Only in cases of suspected ESBL-producing pathogens: known colonization or previous infection by ESBL-producing strains

Urinary tract infections in males

Urinary infections in males generally occur in the presence of anatomic or functional changes of the urinary tract, obstruction (mainly due to benign prostatic hypertrophy) or instrumental procedures. About 20% of community UTIs affect male patients. The incidence of uncomplicated UTIs, without prostatic involvement or predisposing risk factors, is very low (<1/100 male patients aged 15–50 years).[33] Before starting empiric treatment, a urine culture is strongly recommended. *E. coli* is the main causative pathogen of UTIs in male patients, although the frequency of this pathogen is lower in males versus females, followed by other *Enterobacteriaceae* (*Proteus*, *Klebsiella* and *Enterobacter*), Enterococci and *Pseudomonas* spp. Due to the fact that a prostatic involvement cannot be excluded based on clinical presentation alone, the use of antibiotics reaching therapeutic concentrations in the prostatic tissue is recommended.[9,17] For this reason, the following regimens represent the most suitable therapeutic options for oral empiric treatment:

- trimethoprim/sulphamethoxazole 160/800 mg, twice daily
- levofloxacin 500 mg, once daily
- ciprofloxacin 500 mg, twice daily
- ciprofloxacin extended-release 1000 mg, once daily
- prulifloxacin 600 mg, once daily.

Few studies have evaluated the optimal treatment duration in male patients, but therapy is usually given for 14 days.[9,17] A urologic visit is recommended to evaluate the presence of predisposing risk factors, except for healthy young patients at first UTI that responds quickly to antibiotic treatment.[34]

There are few data on the use of fosfomycin trometamol in the treatment of male UTIs, mainly because its penetration into the prostatic tissue is not well known. A prospective uncontrolled study, performed in 26 men undergoing a transurethral resection of the prostate and taking a single dose of 3 g of fosfomycin trometamol as prophylaxis, showed a tissue antibiotic concentration

Table 6 Recommendation for antibiotic prophylaxis according to the urological procedures (modified from EAU guidelines[9])

	Procedure	Recommendation
Open surgery	Nephrectomy ± ureterectomy	AMP considered optional
	Adrenalectomy	
	Radical prostatectomy	
	Planned scrotal surgery, vasectomy, surgery for varicocele	AMP not recommended
	Prosthetic implants, artificial sphincter	AMP recommended
	Uretero-pelvic junction repair	AMP considered optional
	Partial bladder resection	
	Cystectomy with urine deviation	Single or one day dosage AMP recommended
Endoscopic procedures	Transurethral resection of the bladder; Transurethral resection of the prostate; Shock-wave lithotripsy; Ureteroscopy for stone management; Percutaneous and retrograde intra-renal stone management	AMP recommended
	Fulguration of small bladder tumours	AMP considered optional
Diagnostic procedures	Transrectal prostate biopsy	AMP recommended
	Cystoscopy	AMP not recommended
	Urodynamic study	AMP not recommended
	Diagnostic ureteroscopy	AMP considered optional

Note: AMP, antimicrobial prophylaxis.

above the minimum inhibitory concentrations (MICs) of pathogens.[35]

Urinary tract infections in post-menopausal women

The urinary tract of elderly people is at high risk of infection, with a 3-fold higher risk in women than in men. The lack of oestrogenic stimulus causes a reduction in the concentrations of *Lactobacillus* in the bacterial vaginal flora, resulting in an increase in vaginal pH, which favours the adhesion of Gram-negative pathogens to epithelium.[36] Other risk factors for UTIs in post-menopausal women include urinary or faecal incontinence, neurologic bladder or a clinically significant post void residual, dementia, permanent catheter, vaginal atrophy and deficit of cell-mediated immunity. Treatment recommendations for management of acute UTIs in these patients are the same as those for adult female patients.

Urinary tract infections in diabetic patients

Diabetes mellitus is a predisposing risk factor for UTIs, even though the risk is increased only in female patients. In females with diabetes, UTIs are often associated with severe complications (i.e. pyelonephritis, urosepsis). Treatment recommendations for acute UTIs in this setting are the same as for those in the general population. However, the efficacy of short-term treatment is not supported by statistically significant clinical data.

Surgical antibiotic prophylaxis

Oral perioperative antibiotic prophylaxis should be administered approximately 2–3 h before surgery whereas intravenous antibiotic prophylaxis should be given about 30–60 min before surgery, using the same dose as for treatment.[17] The prophylaxis strategy (dose and duration of therapy) should ensure that antibiotic concentrations above the MICs for pathogens are achieved in target tissues at all times during surgery. Administration for more than 24 h is generally not recommended, even in cases of *in situ* urinary devices (permanent catheter, stent, nephrostomy, etc.).

Table 6 shows recommendation for antibiotic prophylaxis for different urological procedures.[17] The EAU guidelines recommend second- and third-generation cephalosporins, aminopenicillins/beta-lactamase inhibitor, cotrimoxazole and fluoroquinolones.[9] It should be noted that these recommendations are based on studies conducted years ago, therefore, they do not take into account the most recent epidemiological data on bacterial resistance. For example, resistance to trimethoprim/sulphamethoxazole and fluoroquinolones among *Enterobacteriaceae* has significantly increased over recent years in Europe, making them unsuitable for surgical prophylaxis. Cefazolin is only active against methicillin-susceptible *Staphylococcus aureus*, not against Gram-negative strains. Third-generation cephalosporins (i.e. cefotaxime, ceftriaxone, ceftazidime) and fluoroquinolones should not be used for prophylaxis due to their negative ecological impact on bacterial resistance, especially ESBL-producing strains. Of note, fosfomycin trometamol is suggested by EAU guidelines[9] for surgical prophylaxis: this drug represents an effective and well-tolerated alternative option to aminopenicillins and fluoroquinolones.

An open prospective study evaluated the efficacy and safety of fosfomycin trometamol (3 g administered 3 h before and 24 h after the procedure) for the prevention of UTIs in 712 patients undergoing transurethral diagnostic or therapeutic procedures. Only 20 (3.2%) out of 618 enrolled patients had developed a UTI by day 2 after prophylaxis, while the rate on day 7 after prophylaxis was 3.6% (n = 22). Side effects occurred in 3.3% of patients.[37] A recent prospective randomized controlled trial included 300 patients undergoing transrectal ultrasound-guided biopsy of the prostate, prophylactically treated with oral fosfomycin (3 g dose administered the night before the procedure, n = 150) or oral ciprofloxacin (500 mg 60 min before the procedure, n = 150). The rate of UTIs was significantly lower in patients treated

with fosfomycin compared with ciprofloxacin (1.3% vs. 6.0%, respectively; $p = 0.032$). Urine cultures showed that 35.7% of the strains were resistant to fluoroquinolones.[38] Furthermore, a retrospective study compared 632 patients who received fosfomycin trometamol with 477 patients who received ciprofloxacin for antibiotic prophylaxis in transrectal prostate biopsy.[39] Compared with ciprofloxacin, fosfomycin trometamol was associated with a lower rate of symptomatic UTIs (1.6% vs. 12.9%, $p < 0.001$); rates of adverse events were similar in the two groups (0.6% vs. 0.4%, $p = 0.70$).[39] These studies confirm the therapeutic value of fosfomycin trometamol in the prophylaxis of urological procedures, including in male patients.

Conclusion

The progressive increase in bacterial resistance requires therapeutic strategies to be based on the local epidemiology of resistance. The treatment of UTIs, both in community and hospital settings, represents an important challenge in terms of costs and number of administered antibiotics. The most recent updates of national and international treatment guidelines base therapeutic recommendations for first-line regimens on epidemiological data as well as pharmacokinetic parameters, and clinical and safety data. In some epidemiological settings, such as LTFCs, the rate of ESBL-producing *Enterobacteriaceae* is particularly high. Stewardship programmes generally recommend a restriction on the use of carbapenems, which should be used only when no other suitable therapeutic options are available. Several clinical studies have re-evaluated the activity of old antibiotics, such as nitrofurantoin and fosfomycin trometamol, which maintain a good microbiological activity against multidrug-resistant uropathogens. According to the most recent guidelines, fosfomycin trometamol is recommended for the first-line treatment of uncomplicated and recurrent UTIs and as an alternative to fluoroquinolones in surgical prophylaxis during prostate biopsy. The antimicrobial activity and safety of this agent make it suitable both for empiric and target therapy of UTIs. Available data also suggest that fosfomycin is also effective and safe in off-label indications such as the treatment of complicated UTIs, but further clinical studies are needed to confirm these findings.

Contributors

CE conceived the paper, obtained funded, wrote the article in part, and revised the article. BD wrote the article in part and revised the article. MF conceived the paper, wrote the article in part, and revised the article.

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