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Clinical Management of an Increasing Threat: Outpatient Urinary Tract Infections Due to Multidrug-Resistant Uropathogens

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Urinary tract infections (UTIs) are among the most commonly treated bacterial infections. Over the past decade, antimicrobial resistance has become an increasingly common factor in the management of outpatient UTIs. As treatment options for multidrug-resistant (MDR) uropathogens are limited, clinicians need to be aware of specific clinical and epidemiological risk factors for these infections. Based on available literature, the activity of fosfomycin and nitrofurantoin remain high for most cases of MDR *Escherichia coli* UTIs. Trimethoprim-sulfamethoxazole retains clinical efficacy, but resistance rates are increasing internationally. Beta-lactam agents have the highest rates of resistance and lowest rates of clinical success. Fluoroquinolones have high resistance rates among MDR uropathogens and are being strongly discouraged as first-line agents for UTIs. In addition to accounting for local resistance rates, consideration of patient risk factors for resistance and pharmacological principles will help guide optimal empiric treatment of outpatient UTIs.

Keywords. urinary tract infection; cystitis; uropathogens; resistance.

Urinary tract infections (UTIs) are among the most common bacterial infections seen in the outpatient setting and are a frequent indication for antimicrobial use among otherwise healthy individuals [1]. UTIs can be classified based on clinical and epidemiological factors. This is important not only for understanding the pathogenesis of the infection but also for assessing the likelihood of multidrug resistance. Healthy premenopausal nonpregnant women who present with symptoms and physical examination findings compatible with acute cystitis generally meet the definition of having uncomplicated community-acquired UTIs. In many cases, these individuals do not need a urine culture performed as they have a very low likelihood of a resistant uropathogen [2]. Men who present with acute cystitis in the outpatient setting may have an uncomplicated infection, though predisposing anatomical and functional risk factors for infection should be considered, particularly related to the prostate. The likelihood of resistance can be higher among men, and a urine culture is warranted to help adjust whatever empiric therapy is chosen and to help inform management of future infections [3]. Any patient (regardless of sex) considered to be at risk of having a UTI due to a multidrug-resistant (MDR) uropathogen (generally considered nonsusceptible to ≥1 agent in ≥3 antibiotic classes, though definitions may vary by institution) should have a urine culture performed as part of the initial assessment in order to tailor the empiric therapy and inform empiric antimicrobial selection in the case of future occurrences [4]. Use of prior microbiological susceptibility data from the same patient within the past 2 years may also be helpful in choosing an active agent [5]. A more detailed discussion of diagnostic approaches to UTIs is outside the scope of this review but is well outlined by others [2].

CHANGING EPIDEMIOLOGY OF UROPATHOGENS

Studies of uncomplicated cystitis in women have consistently found that *Escherichia coli* accounts for 80%–90% of causative uropathogens, and the vast majority of *E. coli* are not MDR. There have been increases in the frequency of resistance to some antimicrobials in this female population, particularly trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones, and beta-lactams [6–8]. In other outpatient populations, regardless of sex, surveillance data suggest that clinicians are more frequently facing antimicrobial resistance among uropathogens [6]. For instance, the prevalence of MDR *E. coli* among outpatient isolates in the United States increased from 9% in 2001 to 17% in 2010 [6]. Particularly in complicated UTIs, active initial empiric therapy can improve patient outcomes. Thus, a critical appraisal of the UTI syndrome and likelihood of resistance based on surveillance data and patient risk factors is warranted at each patient encounter.

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RISK FACTORS FOR UTIs CAUSED BY MDR UROPATHOGENS

Defining the UTI syndrome is the first critical step in predicting the likelihood of resistance, and a risk profile needs to be constructed with the UTI syndrome in mind. Women with uncomplicated cystitis, by definition, should not have most of the exposures associated with an MDR organism. In this population, antimicrobial use, prior history of UTIs, recent international travel, and chronic medical conditions are factors associated with resistance that should be assessed [9, 10].

A common and preventable risk factor for MDR UTIs is prior use of antimicrobials. Recent studies have demonstrated that use of antimicrobials in the 4 weeks to 1 year preceding the index infection increases the probability of MDR in the index infection. Use of fluoroquinolones and antipseudomonal penicillins, as well as more cumulative days of treatment with any antimicrobial prior to UTI presentation, were most strongly associated with resistance [3, 11, 12].

In patients with a more complicated UTI syndrome, assessment of contact with the healthcare system or recent instrumentation should be conducted. Patients hospitalized for 48 hours, residing in a nursing home, or receiving hemodialysis in the previous 3 months were found to have greater rates of resistance [3]. Patients with complicating genitourinary factors, such as indwelling catheters, are also at risk for infection due to a MDR uropathogen [3]. Elderly patients are more likely to be immunocompromised, have comorbidities, and are hospitalized more frequently than younger patients and are more likely to develop infections with MDR pathogens [3]. For similar reasons, patients with diabetes are at risk of recurrent UTIs that, over time, pose more risk of resistance [3, 12]. While males are at lower risk of UTIs than females, males are at higher risk of a UTI with an MDR pathogen [3, 13, 14].

In addition to selecting an antimicrobial agent with activity against the predicted or identified uropathogen, the choice of agent may also be influenced by factors such as allergy history, drug interactions, and tolerability. As discussed in specific detail below, commonly used agents for cystitis—nitrofurantoin in particular—should not be used for invasive infections such as prostatitis or pyelonephritis. With a primary goal of evaluating oral options for empiric treatment of outpatient UTIs caused by MDR uropathogens, we conducted a review of the literature. Characteristics of oral antimicrobial agents discussed below are summarized in Table 1.

EVALUATION OF ORAL TREATMENT OPTIONS FOR MDR UROPATHOGENS

Fosfomycin Tromethamine

Fosfomycin remains one of the most active antimicrobials for treatment of outpatient UTIs and a viable option for MDR uropathogens. A recent study found an overall fosfomycin

Table 1. Characteristics of Oral Agents Used to Treat Urinary Tract Infections

Antimicrobial	Mechanism of Action	Pharmacokinetic Characteristics	Pharmacodynamic Characteristics	Standard Dosing Regimen for UTI	Resistance Rates for MDR Organisms (%)	Suggested Role in Empiric Therapy for UTI Caused by MDR Organism
Fosfomycin	Binds to and inhibits uridine diphosphate-*N*-acetyl-glucosamine-enol-pyruvyl-transferase, an enzyme involved in early stages of peptidoglycan synthesis [15]	38% renal elimination (unchanged); no dosage adjustments necessary in renal impairment or elderly populations	Bactericidal; inhibits bacterial cell wall synthesis [15]	3 g PO ×1 dose	5–40 [16, 17]	First line
Nitrofurantoin	Complex and unique; inactivates or alters bacterial ribosomal proteins and other macromolecules	90% renal elimination (30%–40% unchanged)	Bactericidal or static, depending on concentration; damages bacterial DNA	100 mg PO BID ×5 d	2–21 [6, 17]	First line
Trimethoprim-sulfamethoxazole	Sequentially inhibits steps in bacterial folate synthesis	Renal elimination (mostly unchanged); adjust dose when creatinine clearance < 30 mL/min	Bactericidal; inhibits folate synthesis	160/800 mg PO BID ×3 d	60–77 [3, 6, 18, 19]	Not recommended, depending on local resistance data and/or patient-specific risk of MDR infection
Fluoroquinolones	Inhibit bacterial DNA synthesis by inhibiting functions of DNA gyrase and topoisomerase IV	Renal elimination; dose adjustments in renal dysfunction (except moxifloxacin) [20]	Bactericidal; inhibit formation of topoisomerase II and IV	Varies depending on agent	49–72 [3, 6, 16]	Not recommended, depending on local resistance data
Beta-lactams	Inhibit peptidoglycan synthesis	Renal elimination; dose adjustments in renal dysfunction	Bactericidal; inhibit cell wall synthesis	Varies depending on agent	Not well characterized (72%–75% in non-MDR organisms) [18]	Not recommended due to high rates of resistance and poorer clinical outcomes

Abbreviations: BID, twice daily; MDR, multidrug resistant; PO, by mouth; UTI, urinary tract infection.

susceptibility rate of 94.4% for 323 consecutive nonduplicate Enterobacteriaceae (100% for *E. coli* [n = 150]; 95.5% for *Klebsiella* spp. [n = 44]; and 89.7% for other Enterobacteriaceae [n = 39]), Enterococci (90.6% [n = 64]), and *Pseudomonas aeruginosa* (76.9% [n = 26]) urine isolates from hospitalized patients [21]. Against 91 MDR or extended-spectrum beta-lactamase (ESBL)–confirmed uropathogens from the same isolate collection, fosfomycin was the most active (95% susceptibility) agent compared with 4 oral agents studied (nitrofurantoin, trimethoprim-sulfamethoxazole, ciprofloxacin, and ampicillin) [16]. Another study found similar rates of resistance to fosfomycin among community-acquired *E. coli* (5.7%) and ESBL-positive *E. coli* isolates (4.5%). However, for ESBL-positive *Klebsiella pneumoniae*, the frequency of resistance was higher at 42.4% [17].

Single-dose fosfomycin is well studied in community-acquired UTIs and continues to produce acceptable cure rates against nonresistant uropathogens [22]. Clinical cure rates in recent studies ranged from 87% to 93% [23, 24], and microbiological cure rates ranged from 80% to 83% [25, 26]. A retrospective study of 41 hospitalized patients with UTIs caused by MDR uropathogens and treated with fosfomycin demonstrated an overall microbiological cure rate of 59% [27]. Patients with microbiological failure had significantly more solid organ transplants and ureteral stents, suggesting more complicated UTIs. In general, fosfomycin is well tolerated, causing fewer adverse events than other agents in multiple studies [23, 25].

It should be noted that limited data are available to guide dosing in complicated or MDR UTIs. Consequently, the optimal course of therapy is not fully established. Two nonrandomized studies examined a regimen of 3 doses, administered every other day [28, 29]. Clinical cure rates were 94%–95%, but in ESBL-positive *E. coli*, microbiological cure was only achieved in 79% of cases. This regimen was generally well tolerated, with 5% of patients reporting mild to moderate diarrhea (for which 1 patient discontinued the study), and 2 additional patients reported other mild adverse events. Given the low resistance of most uropathogens to fosfomycin, it is possible that a longer course of therapy could result in higher clinical and microbiological cure rates in complicated UTIs (including those due to MDR uropathogens) than are currently observed after a single dose for uncomplicated UTIs. In the context of increasing resistance to other antimicrobial agents and the danger of ecological adverse effects when broader-spectrum agents are used, further empiric assessment of this possibility is warranted.

A significant barrier to the use of fosfomycin is the fact that it is not routinely tested in clinical microbiology laboratories since automated machines use broth dilution methods that are not recommended by Clinical and Laboratory Standards Institute (CLSI) for this agent. Thus, clinicians need to either ask their microbiology laboratory for specific (disk diffusion) testing (which often results in a delay in receiving results) or use fosfomycin empirically based on existing susceptibility data. The latter approach can be reasonably successful for *E. coli* isolates (since most are susceptible, even among hospital isolates) but has to be done with caution when treating other gram-negative species since CLSI interpretive criteria exist only for *E. coli* and *Enterococcus faecalis* urine isolates [21, 30]. Some epidemiologic data have suggested that susceptibility to routinely tested agents like ciprofloxacin or TMP-SMX can be used as a marker for likely susceptibility to fosfomycin, but it is not uniform [5].

Nitrofurantoin

Nitrofurantoin is a first-line agent in the treatment of uncomplicated UTIs [31]. It is not used in complicated UTIs due to lack of systemic or tissue accumulation. It was previously contraindicated in patients with a creatinine clearance (CrCl) of <60 mL/min, limiting its use in patients with renal dysfunction and the elderly. However, the American Geriatrics Society updated the Beers criteria in 2015 and now supports its use in patients with CrCl as low as 30 mL/min [32]. Nitrofurantoin is available in 2 dosage forms: microcrystals and macrocrystals. Currently only macrocrystal capsules are manufactured; they come in 2 forms under the trade names of Macrobid (nitrofurantoin monohydrate/macrocrystals) and Macrodantin. The twice-daily monohydrate/macrocrystal formulation, which is most commonly used to treat UTIs, delays the uptake of nitrofurantoin into the intestines.

At this time, there is minimal resistance to nitrofurantoin, favoring its use as a first-line agent. In a study that analyzed the prevalence of MDR organisms and drug susceptibility between 2001 and 2010 from outpatient urinary *E. coli* isolates across the United States, only 2.1% of MDR isolates were found to be resistant to nitrofurantoin [6]. For MDR *E. coli* specifically, the increase in resistance was only 1.0%–1.4% during this time period. This was considerably less than the increase in resistance to TMP-SMX, ciprofloxacin, and amoxicillin/clavulanate. One study that evaluated 134 ESBL *E. coli* urine isolates found 79.1% were susceptible to nitrofurantoin [17]. In a study that looked at *E. coli* resistance rates at urology clinics in the Netherlands, nitrofurantoin was active against 95% of isolates [33]. However, it is notable that antimicrobial resistance varied by region due to antimicrobial use and prescribing patterns.

In a study that compared a 7-day course of nitrofurantoin to a single dose of fosfomycin, clinical cure was achieved in 80% of both treatment groups. Bacteriological cure was achieved in 86% of cases treated with nitrofurantoin [23]. In another study of women with uncomplicated cystitis, both overall clinical cure (84% [nitrofurantoin] vs 79% [TMP-SMX]) and early (5–9 days after therapy) microbiological cure (92% [nitrofurantoin] vs 91% [TMP-SMX]) rates following a 5-day course of nitrofurantoin were equivalent to those for patients treated with a 3-day course of TMP-SMX [34].

There is a need for more systematic collection of nitrofurantoin outcomes data for treatment of UTIs caused by MDR pathogens since current resistance patterns favor the use of this drug. However, its reduced efficacy in complicated UTIs and longer duration of therapy may be factors that limit nitrofurantoin's clinical use and efficacy.

Trimethoprim-Sulfamethoxazole

TMP-SMX has a broad spectrum of antimicrobial activity, including both gram-positive and gram-negative pathogens. It is an important first-line antimicrobial in the treatment of uncomplicated UTIs. However, a recent study demonstrated that rates of resistance have significantly increased over the past decade, from 19% to 26% [6]. Surveillance data suggest that resistance currently ranges from 16% to 36% globally [3, 6, 33, 35, 36]. Substantial geographic and age-associated differences exist, with highest resistance demonstrated in parts of Europe and in younger women. However, a majority of studies show resistance consistently at or above the accepted 20% threshold in the community [31, 33, 35]. Studies that looked at in vitro activity against MDR uropathogens found resistance to be between 60% and 77% [3, 6, 16, 18, 19].

Despite increasing resistance, one large retrospective analysis of Veterans Affairs (VA) records showed TMP-SMX to be the second most-frequently prescribed antimicrobial in outpatient UTIs, used in 27% of cases [37]. Clinical outcomes data were not available, but a univariate analysis showed TMP-SMX to be associated with early recurrence; however, this effect did not remain significant in multivariate analysis. Prospective studies have shown clinical cure rates of 87%–88% [38, 39] and microbiological cure rates of 82%–83% [26, 39]. One study that compared outcomes of patients with either TMP-SMX-susceptible or TMP-SMX-resistant isolates found that in patients with TMP-SMX–resistant pathogens, only 54% achieved clinical cure and 42% achieved microbiological cure [39].

Based on emerging resistance and outcomes data over the last several years, it can be concluded that TMP-SMX is no longer appropriate for empiric first-line oral therapy of outpatient UTIs suspected of being caused by MDR uropathogens. Clinicians considering treatment with TMP-SMX should carefully review an ambulatory patient's individual risk of MDR pathogenesis in addition to considering local resistance patterns prior to prescribing. In patients with UTIs caused by MDR pathogens, choosing an agent concordant with previous uropathogen microbiologic data may increase the chance of providing active empiric therapy [5].

Fluoroquinolones

Fluoroquinolones have a broad spectrum of activity and cover many common gram-negative and gram-positive pathogens. [20]. They are frequently used antimicrobials; over the last decade, their use has resulted in increasing rates of resistance. Three recent studies demonstrated a significant increase in rates of resistance to fluoroquinolones, rising from 1%–4% to 6%–15% [6, 8, 35]. Rates also differ by geographic region [33]. With few exceptions, resistance rates in the community consistently remain below 20% [3, 6, 33, 36]. It is important to note, however, that MDR bacteria have demonstrated much higher rates of resistance, ranging from 49% to 72% [3, 6, 16].

Many studies have found that the fluoroquinolones are among the most popular class of drugs for UTIs. A VA study found that ciprofloxacin was the most-prescribed antimicrobial for outpatient UTIs, used in 62.7% of cases [37]. Considering increasing resistance and high use, it is particularly important to critically review the use of this antimicrobial class. A number of recent prospective studies have assessed outcomes of fluoroquinolones in outpatient UTIs [38, 40]. Clinical cure rates are consistently reported in 93%–97% of treated patients. Microbiological cure rates, when assessed in patients with nonresistant pathogens, show similar success [40]. Unfortunately, limited data are available with regard to outcomes of fluoroquinolones on MDR uropathogens.

Fluoroquinolones remain effective for outpatient UTIs caused by susceptible uropathogens, though data are lacking for efficacy in MDR strains. In the context of rapidly increasing rates of resistance, care is needed to ensure continued efficacy and to minimize the potential for collateral damage. Of note, a recent safety alert from the US Food and Drug Administration advised that the use of fluoroquinolones should be reserved for patients without alternative treatment options for certain uncomplicated infections (ie, sinusitis, bronchitis, uncomplicated UTIs). This alert was in response to a safety review that showed an association with "disabling and potentially permanent serious side effects" involving tendons, muscles, joints, nerves, and the central nervous system (http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm500665.htm). This strategy of reserving fluoroquinolones as an alternative treatment for uncomplicated UTIs is consistent with current treatment guidelines.

Beta-Lactams

Oral beta-lactam antimicrobials used to treat outpatient UTIs may include ampicillin, amoxicillin, amoxicillin-clavulanate, and orally available cephalosporins such as cefpodoxime. These agents may be used as alternative options when first-line agents cannot be used (ie, allergy to first-line agents). Poor efficacy data and high worldwide resistance rates account for their status as nonpreferred options [31]. In practice, cefpodoxime may sometimes be used as a convenient intravenous-to-oral transition for patients initially treated with intravenous third-generation cephalosporins. According to CLSI M100-S25 guidance, cefazolin susceptibility results predict those for the oral cephalosporins cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef when used to treat

uncomplicated UTIs due to *E. coli*, *K. pneumoniae*, and *Proteus mirabilis*. However, it may be advised to test cefpodoxime, cefdinir, and cefuroxime individually as some isolates may remain susceptible even if reported to be cefazolin resistant.

Beta-lactam resistance can be attributed to patient lack of adherence to the full antimicrobial course or ecological changes to bacteria. Isolates resistant to ampicillin are more likely to become resistant to amoxicillin/clavulanate, with studies showing nearly 75% of *E. coli* isolates resistant to amoxicillin/clavulanate and nearly 72% resistant to cephalosporins [18]. Cefpodoxime resistance is an area that needs further study, but it has been shown that resistance to third-generation cephalosporins is less than that to amoxicillin/clavulanate [36]. Clinical outcome data following treatment with beta-lactams are inferior to those of other agents [40]. Because of resistance rates being higher than for other agents, treatment failure and reinfection are concerns.

CONCLUSIONS AND RECOMMENDATIONS

Outpatient UTIs are one of the most common bacterial infections among women. Recent data have shown that an increasing number of MDR isolates cause outpatient UTIs, making them more difficult to treat and cure. Risk factors for UTIs caused by MDR uropathogens include previous antimicrobial use, hospital exposure, complicating genitourinary factors, age, recurrent UTIs, and male sex.

Consistent with the Infectious Diseases Society of America guidelines, which recommend fosfomycin and nitrofurantoin as first-line agents for uncomplicated UTIs, these 2 agents also appear to remain efficacious for UTIs caused by MDR uropathogens. Published surveillance data demonstrate low resistance rates and reasonable clinical success rates. Patient outcomes continue to be positive after treatment with TMP-SMX, but evolving resistance to this agent should warrant caution when empirically treating patients with MDR risk factors. Despite continued positive outcomes with fluoroquinolones among susceptible uropathogens, in the interest of minimizing continued resistance and collateral damage, these agents should be reserved for more serious infections. Avoidance of beta-lactams is still recommended due to poor clinical outcomes and widespread resistance among MDR pathogens. Finally, in the absence of active oral agents, outpatient UTIs may need to be managed with intravenous agents.

One difficulty of empiric management of UTIs is the overall lack of susceptibility data in the absence of routine patient urine cultures. Nevertheless, clinicians should carefully consider patient risk factors, previous microbiology, and local resistance patterns, when data are available, to help guide appropriate empiric treatment of outpatient UTIs.

Notes

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