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Treating uncomplicated urinary tract infections in a drug resistant era

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Introduction

Among common infections managed in the outpatient setting, few conditions have treatment guidelines, antibiotic selection strategies, or diagnostic protocols that have changed or evolved as rapidly as those for urinary tract infections (UTIs).[1] Changing resistance patterns observed with common urinary pathogens have altered the empirical approach to antibiotic selection for UTIs.[1] In the past, decisions regarding antimicrobial therapy have been made on patient characteristics and the most likely pathogens. The emergence of drug-resistant *E. coli* strains has complicated the management of infections including UTIs. Recently, there have been significant increases in the resistance to trimethoprim-sulfamethoxazole (TMP-SMX) among outpatient *E. coli* isolates.[2] As a result, uncomplicated community-acquired UTIs, which have traditionally been easily treatable, are now therapeutic challenges. This article will review the problem of antimicrobial resistance in acute uncomplicated UTI, focusing on TMP-SMX resistance, and outline recommendations for empirical treatment of uncomplicated UTI in a period of evolving antimicrobial resistance.

Epidemiology

Symptomatic UTIs are among the most common bacterial infections. Urinary tract infections are the leading cause of gram-negative bacteremia in patients of all ages, and are associated with a high risk of morbidity and mortality, especially in the elderly.[1] It is estimated that UTIs result in nearly 8 million office visits each year in the United States, with an additional 1 million visits to emergency departments.[1,3] However, assessing the accurate incidence of UTI is difficult, because UTIs are not reportable diseases in the United States.[3] Although accurate diagnosis depends on both the presence of symptoms and a positive urine culture, uncomplicated UTIs in the outpatient setting are usually diagnosed without the benefit of a culture making it difficult to determine its exact frequency.[3]

Symptomatic UTIs are very common among sexually active women and far more common among women than men. An estimated 1 in 3 women will have at least 1 UTI by 24 years of age and 40% to 50% of women will experience at least 1 UTI during their lifetime.[3] As both sexes age, the incidence of bacteriuria increases from less than 5% in young adult women and less than 0.1% in young adult men to at least 20% of women and 10% of men older than age 65.[2]

Microbiology

The microbial etiology of urinary tract infections is well-established and has been reasonably consistent for several decades.[4] *E. coli* remains the predominant uropathogen isolated in acute community-acquired uncomplicated infections, followed by *Staphylococcus saprophyticus* with *Klebsiella, Proteus, Enterococcus,* and *Pseudomonas* species seen less commonly.[1,4] The etiology of UTI is also affected by underlying host factors such as

Table 1. Percent incidence of urinary tract pathogens in uncomplicated and complicated UTIs[2]

Pathogen	Uncomplicated	Complicated
Escherichia coli	70-95	40-55
Klebsiella spp	2-6	10-17
Enterobacter spp	0-2	5-10
Proteus mirabilis	2-4	5-10
Pseudomonas aeruginosa	0-1	2-10
Enterococcus spp	2-5	1-20
Staphylococcus saprophyticus	5-20	—

UTIs=urinary tract infections

age, diabetes, spinal cord injury, or catherization.[4] Consequently, complicated UTI has a more diverse etiology than uncomplicated UTI.[4] The incidence of urinary pathogens in uncomplicated versus complicated UTIs is shown in Table 1.

Emerging Resistance Patterns

Historically, empiric therapy has proven clinically successful for UTIs. Until recently, high cure rates could be expected because a predictable group of urinary pathogens have manifested a low degree of resistance to most antibiotics selected on an empiric basis.[1] However, a number of recent studies have highlighted evolving changes in antimicrobial resistance patterns to *E. coli*.[1] Penicillin-based antibiotics were once a mainstay of UTI treatment, but current resistance rates among E. coli (approaching 40% in many regions) have limited their effectiveness.[1] Nonetheless, nitrofurantoin and the fluoroquinolones have retained in vitro activity against most *E. coli* isolates that cause uncomplicated UTIs.

The most substantial change in resistance prevalence has occurred with TMP-SMX. Resistance to TMP-SMX among uropathogens in the community was relatively infrequent in the United States during the early 1990s.[5] McCarty and colleagues[6] conducted a multicenter trial of low-dose ciprofloxacin compared with standard-dose ofloxacin and TMP-SMX for the treatment of acute uncomplicated UTIs in women. They reported only a 7% prevalence of TMP-SMX resistance among the E. coli isolates.

The rates of resistance did not increase to levels that may compromise clinical effectiveness until the mid-1990s. Gupta and colleagues[7] conducted a cross-sectional survey of urine isolates from a sample of outpatient women in western Washington State who had an uncomplicated UTI over a five-year period (1992-1996). They found that the prevalence of TMP-SMX resistance among *E. coli* isolates was 9% in 1992, but had increased to 18% by 1996, the last year of the study.

More recently, Gupta and colleagues[8] used a national laboratory database to assess the rates of resistance among uropathogens that were recovered from female outpatients both nationally and within 9 geographic regions in the United States. Almost all *E. coli* isolates that were recovered from female outpatients were susceptible to nitrofurantoin and to the fluoroquinolones that were tested. In contrast, 33%-40% of *E. coli* isolates were resistant to ampicillin and 16%-18% were resistant to TMP-SMX. There was significant variation in resistance to TMP-SMZ in relation to geographic region, ranging from a high of 22% in the western United States to a low of 10% in the Northeast ($p<.001$).

Burnam and colleagues[9] conducted a retrospective review of outpatients with *E. coli* UTIs during the first 6 months of 1998 to determine the rate of TMP-SMX resistance. The study was conducted within the Denver public health care system and was followed by a prospective phase to confirm the rate of TMP-SMX resistance. The rates of resistance were similar in both phases (24% vs. 23% in the retrospective and prospective phases, respectively). A summary of the in vitro susceptibility of *E. coli* from several United States studies of UTIs is shown in Table 2.

Clinical Outcomes and TMP-SMX Resistance

Resistance rates in the United States vary from region to region, and knowledge of local resistance rates are important factors when determin-

Table 2. In vitro susceptibility of *Escherichia coli* in the U.S.

Year	Study Site	Study Sample	Isolates (#)	TMP-SMX (%)	Nitrofurantoin (%)	Fluoroquinolones (%)
1990s[6]	U.S.	OP women, 18-93 yo	545	93	N/A	100.0[†]
1995[5]	WA State	OP women, university	499	89	99.4	99.8
1996[7]	WA State	OP HMO women, 18-50 yo	580	82	99.8	99.8[‡]
1998[9]	Denver	OP women, 17-42 yo	811[*]	76-77	92.0	97[§]
1998[8]	U.S.	OP women, 15-50 yo	63,196	82	99.0	99[‡]

TMP-SMX=trimethoprim-sulfamethoxazole, U.S.=United States, OP=outpatient, WA=Washington, HMO=health maintenance organization
[*]Retrospective phase n=681, prospective phase n=130. [†]ciprofloxacin and ofloxacin. [‡]ciprofloxacin. [§]levofloxacin

ing initial antibiotic therapy.[2] Potential confusion arises when the reported resistance levels are related to the blood concentration of antibiotic and not the urine concentration.[1] As a rule, antibiotics used for UTIs are concentrated in the urine and have higher urine levels than blood levels.[1] Therefore, isolates that are reported resistant to an antibiotic by laboratory testing actually may be eradicated by the antibiotic in the in vivo environment.[1]

The outcomes associated with treating a UTI by using an agent to which the pathogen is resistant have not been studied extensively.[5] However, at least two treatment trials have examined bacteriologic outcomes of acute uncomplicated UTI among women with uropathogens resistant to the study drugs.[5] Masterton and Bochsler[10] conducted a randomized trial comparing a high-dose formulation of amoxicillin-clavulanate and 7-day therapy with TMP-SMX for women with uncomplicated UTIs in the United Kingdom. Of 135 women randomly assigned to TMP-SMX, 12% had an uropathogen resistant to the drug. Bacterial eradication at day 14 was achieved in 50% of women (7 of 14) with an uropathogen resistant to TMP-SMX, compared with 86% (106 of 123) of all women in the TMP-SMX group.

More recently, McCarty and colleagues[6] found that the bacterial eradication rate was 50% (5 of 10) and the clinical cure rate was 60% (6 of 10) among women with an uropathogen resistant to TMP-SMX who had been randomly assigned to TMP-SMX treatment. Although these studies are limited by small sample sizes and therefore are not definitive, it seems that the failure rate in the setting of TMP-SMX resistance is greater than that for cases of uncomplicated UTIs caused by susceptible strains, which is documented in the literature as approximately 5%.[5]

On the basis of these data, the effect of TMP-SMX resistance on clinical outcomes can be estimated depending on the level of resistance in the community.[5] In a setting with no TMP-SMX resistance, bacterial eradication and clinical cure rates with a 3-day course of TMP-SMX are expected to approach 93% and 95%, respectively.[11] Assuming a 50% bacterial eradication rate and a 60% clinical cure rate among women treated with TMP-SMX in the setting of a TMP-SMX resistant pathogen, the expected effect of a resistance prevalence of 10% in a population of 100 women is relatively small.[5] However, the cure rates would be lower than those expected with a 3-day regimen of a fluoroquinolones among fluoroquinolones-susceptible cases of UTI.[11] At 20% TMP-SMX resistance, the expected cure rates are even lower. Table 3 summarizes the estimated impact of TMP-SMX resistance on bacterial eradication rate and clinical success rate.

Current Treatment Options

The antimicrobial agents used to treat uncomplicated community-acquired UTIs include the ß-lactams, TMP-SMX, nitrofurantoin, fosfomycin, and the fluoroquinolones.[5] All of these agents achieve high urinary concentrations, usually greatly exceeding the expected serum levels.[5] The aminopenicillins, ampicillin and amoxicillin, and most cephalosporins are rapidly excreted in the urine and

Table 3. Impact of TMP-SMX resistance on microbiological and clinical outcomes in patients with uncomplicated UTI[5*]

TMP-SMX Resistance Rate (%)	Expected Bacterial Eradication Rate (%)	Expected Clinical Success Rate (%)
0	93	95
10	89	92
20	84	88
30	80	85

[*] Adapted from reference 5. TMP-SMX = trimethoprim-sulfamethoxazole.

attain high urinary concentrations.[5] However, because of increasing in vitro resistance the ß-lactams are no longer recommended for empirical UTI therapy.[11] In certain settings, such as pregnancy or when enterococci is suspected, ampicillin and amoxicillin may still be an appropriate choice for acute UTI.[11]

Trimethoprim with or without SMX, has been the mainstay of therapy for UTI for the past 20 years. The combination of TMP and SMX is synergistic against a variety of organisms, including aerobic gram-negative rods such as *E. coli*.[5] After a single oral dose of one double-strength tablet (TMP, 160 mg; SMX, 800 mg), the peak urine concentrations are approximately 35 times higher for TMP and 3 to 4 times higher for SMX than serum concentrations.[5]

Nitrofurantoin is one of the oldest urinary anti-infective agents in use. It appears to be associated with lower cure rates (85%) than other first-line agents (90-95%).[12] The macrocrystalline formulation requires frequent dosing every six hours.[5] A modified monohydrate-macrocrystal form delays gastric uptake and allows twice-daily dosing.[5] Both the macrocystalline formulation and the twice daily formulation are prescribed for 7 days.[12] Nitrofurantoin is 90% renally excreted with a very high urine concentration making it an effective urinary antimicrobial agent.[5] However, it does not achieve high serum concentrations and is therefore not recommended for the treatment of acute pyelonephritis.[12]

Fosfomycin tromethamine is a phosphonic acid bactericidal agent with activity against many common uropathogens, including *E. coli, Citrobacter* spp, *Enterobacter* spp, *Klebsiella* spp, *Serratia* spp, and *Enterococcus* spp.[12] It achieves very high concentrations in the urine and persists in the urine for more than 24 hours.[5] Fosfomycin is indicated for the treatment of acute uncomplicated cystitis and is administered in 1 single dose of 3 g.[12]

The first fluoroquinolones widely used for the treatment of UTIs were norfloxacin, ciprofloxacin, ofloxacin, and levofloxacin.[5] All of these fluoroquinolones have excellent bioavailability and achieve high urinary concentrations.[5] Henry and colleagues[13] recently conducted a multicenter, prospective, randomized study to compare the efficacy and safety profile of once-daily extended-release ciprofloxacin 500 mg with conventional ciprofloxacin 250 mg BID, each administered orally for 3 days in uncomplicated UTI. They concluded that the extended-release ciprofloxacin (Cipro XR®) 500 mg given once daily for 3 days was as effective and well tolerated as conventional ciprofloxacin 250 mg given twice daily for 3 days. The pharmacokinetic characteristics of selected antimicrobial agents used in the treatment of uncomplicated UTI are shown in Table 4.

Evidence Based Treatment Recommendation

Recently, the Infectious Diseases Society of America (IDSA) developed evidence-based practice guidelines for antimicrobial treatment of acute uncomplicated cystitis and acute pyelonephritis in women. These guidelines are based in part on the rate of resistance to TMP-SMX in the geographic region of each individual practitioner.[11] The guidelines recommend TMP-SMX for 3 days as the current standard of therapy if the TMP-SMX resistance rate in the community is <20%.[11] In communities known to have a higher prevalence of resistance (>20%) to TMP-SMX, the IDSA recommends the use of a fluoroquinolone for 3 days or another alternative. Other alternatives

Table 4. Pharmacokinetic characteristics of agents used to treat community-acquired urinary tract infections[5]

Drug	Oral Dose (mg)	Serum C_{max} (mcg/mL)	Urine C_{max} (mcg/mL)	Half-life (h)
Amoxicillin	250	3.5-5.0	305-865	0.7-1.4
	500	5.5-11.0	772	
Cephalexin	250	9	830	0.5-1.2
	500	15-18	1100	
TMP-SMX	160/80	1-2/40-60	75/190	8-15/7-12
Nitrofurantoin*	100	<2	50-150	0.3
Fosfomycin	3000	26	1053-4415	5.7
Ciprofloxacin	250	0.8-1.9	>200	3-5
	500	1.6-2.9	350	
Levofloxacin	500	5.7	521-771	6-8

C_{max}=peak concentration, TMP-SMX = trimethoprim-sulfamethoxazole.
*Either formulation of nitrofurantoin.

include 7-day treatment with nitrofurantoin or single-dose treatment with fosfomycin. Empiric treatment with ß-lactam antimicrobials is not recommended. Table 5 summarizes the recommendations from the IDSA guidelines.

More recently, a primary care consensus report was published regarding UTI risk stratification, clinical evaluation, and evidence-based antibiotic therapy.[1] There recommendations differ from those developed by the IDSA in that they recommend fluoroquinolones as the drug of choice for uncomplicated UTI in women.[1]

Conclusion

Evolving changes in drug resistance have dramatically altered the approach to empiric therapy of UTI.[2] Although beta-lactams, sulfa-based antibiotics, and fluoroquinolones each have their place in the treatment of UTI, their roles are rapidly changing, with fluoroquinolones emerging as initial drugs of choice for uncomplicated UTI.[2] Antibiotic agents, especially TMP-SMX, which has been a mainstay of therapy cannot be considered the treatment of choice in areas in which *E. coli* resistance to TMP-SMX surpasses 20%.[1] However, rates of resistance of *E. coli* to TMP-SMX vary significantly according to geographic region, ranging from a high of 22% in the western United States to a low of 10% in the Northeast. Therefore, TMP-SMX remains a reasonable first-line choice for empirical therapy in the northern and eastern states, although it may no longer be appropriate in western and southwestern states.[8]

References

1. Primary Care Consensus Reports. Urinary tract infection: risk stratification, clinical evaluation, and evidence-based antibiotic therapy-year 2003 update. Atlanta (GA): American Health Consultants; 2003.
2. Hospital Medicine Consensus Reports. Complicated urinary tract infection: risk stratification, clinical evaluation, and evidence-based antibiotic therapy-year 2003 update. Atlanta (GA): American Health Consultants; 2003.
3. Brown P, Foxman B. Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. Infect Dis Clin North Am 2003 Jun;17(2):227-41.
4. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. Am J Med 2002 Jul;113 Suppl 1A:14S-19S.
5. Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. Ann Intern Med 2001;135:41-50.
6. McCarty JM, Richard G, Huck W, Tucker RM, Tosiello RL, Shan M, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Am J Med 1999;106:292-299.
7. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. JAMA 1999;281:736-738.
8. Gupta K, Sahm DF, Mayfield D, Stamm WE. Antimicrobial resistance among uropathogens that cause com-

Table 5. IDSA guidelines for acute uncomplicated urinary tract infections[11]

Resistance Rate	Antimicrobial Agent	Dosage (mg)	Frequency	Duration (days)
TMP-SMX resistance <20%	TMP-SMX	160/800	BID	3
	TMP	200	BID	3
TMP-SMX resistance >20%	Ciprofloxacin	250	BID	3
	Ciprofloxacin extended-release*	500	QD	3
	Norfloxacin	400	BID	3
	Ofloxacin	200	BID	3
	Levofloxacin	250	QD	3
	Nitrofurantoin	100	BID	7
	Amoxicillin-clavulanic acid	250	QID	7
	Fosfomycin	3000	1 dose	1
	Amoxicillin†	500	TID	7-10

IDSA=Infectious Disease Society of America, TMP-SMX = trimethoprim-sulfamethoxazole, BID=twice daily, QD=once daily, TID=three times daily.
*Drug of choice for uncomplicated UTI by the Primary Care Consensus Reports. †Only for known enterococcus infection.

munity-acquired urinary tract infections in women: a nationwide analysis. Clin Infect Dis 2001;33:89-94.
9. Burman WJ, Breese PE, Murray BE, Singh KV, Batal HA, MacKenzie TD, et al. Conventional and molecular epidemiology of trimethoprim-sulfamethoxazole resistance among urinary *Escherichia coli* isolates. Am J Med 2003;115:358-364.
10. Masterton RG, Bochsler JA. High-dosage co-amoxiclav in a single dose versus 7 days of co-trimoxazole as treatment of uncomplicated lower urinary tract infection in women. J Antimicrob Chemother 1995 Jan;35(1):129-37.
11. Warren JW, Abrutyn J, Hebel R, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Disease Society of America (IDSA). Clin Infect Dis 1999;29:745-58.
12. Nicolle LE. Urinary tract infection: traditional pharmacologic therapies. Dis Mon 2003;49(2).
13. Henry DC, Bettis RB, Riffer E, Haverstock DC, Kowalsky SF, Manning K, et al. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. Clin Ther 2002;24 (12):2088-2104.

Correction
Rosuvastatin (Crestor®): A New Statin for the Treatment of Dyslipidemia

The number of patients listed for the STELLAR Trial in the October Issue should be 2,431 not 12,569.

Daptomycin (Cubicin™) is the first of a new class of antibiotics called cyclic lipopeptide antibacterial agents. It works by binding to bacterial membranes causing a rapid depolarization of the membrane potential which leads to inhibition of protein, DNA, and RNA synthesis resulting in bacterial cell death. It has been approved for the treatment of complicated skin and skin structure infections caused by susceptible strains of Gram-positive organisms including MRSA.

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