Increasing Antimicrobial Resistance and the Management of Uncomplicated Community-Acquired Urinary Tract Infections

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Community-acquired urinary tract infections (UTIs) are among the most common bacterial infections in women. Therapy for these infections is usually begun before results of microbiological tests are known. Furthermore, in women with acute uncomplicated cystitis, empirical therapy without a pretherapy urine culture is often used. The rationale for this approach is based on the highly predictable spectrum of etiologic agents causing UTI and their antimicrobial resistance patterns. However, antimicrobial resistance among uropathogens causing community-acquired UTIs, both cystitis and pyelonephritis, is increasing. Most important has been the increasing resistance to trimethoprim–sulfamethoxazole (TMP–SMX), the current drug of choice for treatment of acute uncomplicated cystitis in women.

What implications do these trends have for treatment of community-acquired UTIs? Preliminary data suggest that clinical cure rates may be lower among women with uncomplicated cystitis treated with TMP–SMX when the infecting pathogen is resistant to TMP–SMX. Women with pyelonephritis also have less bacterial eradication and lower clinical cure rates when treated with TMP–SMX for an infection that is resistant to the drug. Therefore, in the outpatient setting, identifying risk factors for TMP–SMX resistance and knowing the prevalence of TMP–SMX resistance in the local community are important steps in choosing an appropriate therapeutic agent. When choosing a treatment regimen, physicians should consider such factors as in vitro susceptibility, adverse effects, cost-effectiveness, and selection of resistant strains. Using a management strategy that takes these variables into account is essential for maintaining the safety and efficacy of treatment for acute UTI.

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Uncomplicated community-acquired urinary tract infections (UTIs) are among the most common infections in women, accounting for more than 8 million office visits per year in the United States as well as significant morbidity and health care costs (1). Current management of these infections is usually empirical, without the use of a urine culture or susceptibility testing to guide therapy. The rationale for this approach is based on the narrow and predictable spectrum of etiologic agents that cause acute cystitis and their susceptibility patterns (2). However, as with many community-acquired infections, antimicrobial resistance among the pathogens that cause community-acquired UTIs is increasing (3–6). As the problem of antimicrobial resistance becomes more widespread, the use of narrow-spectrum, inexpensive antimicrobial agents becomes less feasible, affecting both the cost of and access to health care for patients. In addition, such infections as uncomplicated community-acquired UTI, which have traditionally been readily treatable, are now becoming therapeutic challenges.

Perhaps the most significant change in resistance among uropathogens has been the increase in the prevalence of resistance to trimethoprim–sulfamethoxazole (TMP–SMX), the current drug of choice in the United States for empirical therapy for uncomplicated UTI in women. In addition, TMP–SMX resistance has been associated with concurrent resistance to other antibiotics, resulting in multidrug-resistant uropathogens (7, 8). However, although several reports have focused on changing patterns of in vitro resistance of uropathogens to TMP–SMX, the clinical significance of this resistance has not been well studied. Therefore, implications for health care providers are not yet clear. This review highlights the problem of antimicrobial resistance in acute uncomplicated community-acquired UTI, focusing on TMP–SMX resistance, and summarizes the few available data regarding clinical outcomes associated with in vitro resistance. Finally, we outline recommendations for empirical treatment of uncomplicated UTI in a period of evolving antimicrobial resistance.

Etiologic Agents in Uncomplicated Community-Acquired UTIs

Although susceptibility patterns have changed, the spectrum of agents causing community-acquired UTI has remained relatively constant. *Escherichia coli* accounts for 75% to 90% of cases; *Staphylococcus saprophyticus* accounts for 5% to 15% (particularly in younger women); and enterococci and non–*E. coli* aerobic gram-

Table 1. **Pharmacokinetic Characteristics of Selected Antimicrobial Agents Used To Treat Community-Acquired Urinary Tract Infections***

Antimicrobial Agent	Oral Dose	Peak Serum Concentration	Peak Urine Concentration	Serum Half-Life	Reference
	mg	*μg/mL*		*h*	
Amoxicillin	250	3.5–5.0	305–865	0.7–1.4	12–14
	500	5.5–11.0	772		
Cephalexin	250	9	830	0.5–1.2	12, 15
	500	15–18	1100		
TMP–SMX	160/80	1–2/40–60†	75/190	8–15/7–12	12, 16
Nitrofurantoin‡	100	<2	50–150	0.3	12, 17
Fosfomycin	3000	26	1053–4415	5.7	18
Ciprofloxacin	250	0.8–1.9	>200	3–5	12, 19
	500	1.6–2.9	350		
Levofloxacin	500§	5.7	521–771	6–8	12, 20

* Data compiled from references listed and from reference 21. TMP–SMX = trimethoprim–sulfamethoxazole.
† Steady-state concentration.
‡ Either formulation.
§ 250-mg dose is recommended for urinary tract infection.

negative rods, such as *Klebsiella* species and *Proteus mirabilis*, account for the remaining 5% to 10% (2, 9). Although less well studied, the spectrum of agents causing uncomplicated pyelonephritis is similar to that causing acute cystitis (10, 11).

Pharmacologic Issues

The antimicrobial agents used to treat uncomplicated community-acquired UTIs include the β-lactams, TMP–SMX, nitrofurantoin, fosfomycin, and the fluoroquinolones. All of these agents achieve high urinary concentrations, usually greatly exceeding the expected serum levels (**Table 1**). Of note, susceptibility breakpoints from the National Committee for Clinical Laboratory Standards are based on serum rather than urine concentrations of these antimicrobial agents, except for nitrofurantoin and fosfomycin, which are exclusively used for treatment of cystitis (12).

The aminopenicillins, ampicillin and amoxicillin, and most cephalosporins are rapidly excreted into the urine and attain high urinary concentrations (**Table 1**) (12–15). The peak serum and urinary concentrations of amoxicillin are higher than those achieved with a similar dose of ampicillin (12). In the 1970s, ampicillin was commonly used for treatment of acute cystitis. However, because of increasing in vitro resistance, as well as lower efficacy and more adverse effects than are seen with other available UTI antimicrobial agents, the β-lactams in general are no longer recommended for empirical UTI therapy (1). In certain settings, such as during pregnancy or when enterococci are suspected, ampicillin or amoxicillin may still be an appropriate choice for acute UTI (1).

The combination of TMP and SMX has been shown to be synergistic against a variety of organisms, including such aerobic gram-negative rods as *E. coli* (16). This combination has been used for treatment of UTI for more than two decades, although the commonly used 3-day regimen has not been formally approved by the U.S. Food and Drug Administration. After a single oral dose of one double-strength tablet (TMP, 160 mg; SMX, 800 mg), the peak urine concentrations are approximately 35 and 3 to 4 times higher, respectively, than serum levels (**Table 1**). Trimethoprim also concentrates in prostatic tissue at levels 2 to 3 times higher than those found in serum (12).

Nitrofurantoin is one of the oldest urinary anti-infective agents in use. The macrocrystalline formulation requires frequent dosing (every 6 hours); however, a modified monohydrate–macrocrystal form delays gastric uptake and allows twice-daily dosing. Nitrofurantoin is used primarily for treatment of cystitis because it does not attain appreciable serum levels (**Table 1**). It is 90% renally excreted, and therefore the urine concentration is very high, making it an effective urinary anti-infective agent for most gram-positive and gram-negative uropathogens (17).

Fosfomycin tromethamine is a phosphonic acid derivative that is newly licensed for treating uncomplicated

cystitis caused by *E. coli* or *Enterococcus faecalis* (18). It is not approved for use for cystitis caused by *S. saprophyticus* or for treatment of pyelonephritis. It achieves very high concentrations in the urine and persists in the urine for more than 24 hours (**Table 1**).

The fluoroquinolones each have individual pharmacodynamic properties (12, 19, 20). The first fluoroquinolones widely used for treatment of UTI, namely norfloxacin, ciprofloxacin, ofloxacin, and levofloxacin, all have excellent bioavailability and achieve high urinary concentrations (**Table 1**). Their penetration into prostatic and renal tissue is also excellent. Some of the newer fluoroquinolones, such as sparfloxacin and trovafloxacin, are not excreted in high urinary concentrations and thus should not be used for treatment of uncomplicated pyelonephritis or complicated UTI. The fluoroquinolones also have a significant postantibiotic effect against gram-negative organisms (12).

In Vitro Susceptibility Data

Many recent studies have reported the resistance profiles of uropathogens to antimicrobial agents commonly used to treat UTI (3–8). Much of this in vitro data comes from laboratory-based surveys that often do not define the sex, age, clinical syndrome, or location (inpatient vs. outpatient) of the patients from whom the urine specimens are collected. Therefore, the reported rates of resistance may vary depending on whether the study sample consists primarily of outpatients with uncomplicated UTIs or patients with complicated nosocomial UTIs. The data presented here focus on studies that clearly define the study sample as women with uncomplicated community-acquired UTI.

Although susceptibility profiles vary by each specific organism and antimicrobial combination, some general trends have clearly emerged. Resistance of *E. coli* and other uropathogens to β-lactams, such as ampicillin, and the first-generation cephalosporins has continued to increase in the past decade and now approaches 40% in most studies (3, 6). Most gram-negative uropathogens are still susceptible to the combination of amoxicillin–clavulanate, but the expense and gastrointestinal side effects of this drug make it a less desirable choice for empirical treatment of uncomplicated UTI (2). Moreover, it has been suggested that the failure rate with this drug is high when the uropathogen is resistant to ampicillin but susceptible to amoxicillin–clavulanate (22). Nitrofurantoin and the fluoroquinolones have retained in vitro activity against most *E. coli* isolates that cause uncomplicated community-acquired UTI (>99% in most studies) (**Table 2**). However, nitrofurantoin is less active against non–*E. coli* gram-negative rods (3, 6) and inactive against *Proteus* and *Pseudomonas* species. The fluoroquinolones have had consistently high activity against essentially all gram-negative uropathogens seen in women with uncomplicated community-acquired UTI but are active against only 60% to 70% of enterococci, depending on the study (3, 6). Both nitrofurantoin and the fluoroquinolones retain good in vitro activity against *S. saprophyticus* (6), although increased failure rates have been reported with the use of single doses of fluoroquinolones to treat *S. saprophyticus*–related UTIs (1).

As mentioned, the most substantial change in resistance prevalence has been to TMP–SMX. Resistance to TMP–SMX among uropathogens in the community was relatively infrequent in the United States in the early 1990s (**Table 2**). At that time, McCarty and colleagues (9)

Table 2. **In Vitro Susceptibility of *Escherichia coli* from U.S. Studies of Urinary Tract Infection***

Reference	Study Site	Year	Study Sample	*Escherichia coli* Isolates	TMP–SMX Resistance	Nitrofurantoin Resistance	Fluoroquinolone Resistance (Drug)
				n	← % →		
9	United States	Early 1990s	Outpatient women, 18–93 years of age	545	7	NA	0 (ciprofloxacin and ofloxacin)
2	Washington State	1995	Outpatient university women	499	11	0.6	0.2 (multiple)
3	Washington State	1996	Outpatient HMO women, 18–50 years of age	580	18	0.2	0.2 (ciprofloxacin)
4	California	1997	Outpatient university women	208	15	0	0 (ciprofloxacin)
6	United States	1998	Outpatient women, 15–50 years of age	63 196	18	1	1 (ciprofloxacin)

* HMO = health maintenance organization; NA = not available; TMP–SMX = trimethoprim–sulfamethoxazole.

Table 3. **In Vitro Susceptibility of *Escherichia coli* from Non-U.S. Studies of Urinary Tract Infection***

Reference	Study Site	Year	Study Sample	*Escherichia coli* Infection	TMP–SMX Resistance	Nitrofurantoin Resistance	Fluoroquinolone Resistance (Drug)
				n	← % →		
23	Netherlands	1991	Outpatients	938	12	7	0 (norfloxacin)
24	United Kingdom	1992	Outpatients	1493	19	6	1 (ciprofloxacin)
25	France	1995	Patients with community-acquired infection	47	13	NA	0 (norfloxacin)
26	Israel	1995	Outpatients	611	31	NA	4 (ciprofloxacin)
27	Belgium	1995–1996	Outpatient women	128	17	1	1 (ofloxacin)
28	Trinidad	1995	Outpatients	385	17	11	1 (norfloxacin)
29	Bangladesh	1996–1997	Outpatients	179	60	NA	18 (ciprofloxacin)
30	Spain	Not specified	Outpatients	504†	32†	NA	13 (norfloxacin)
7	Canada	1998	Outpatients	1681	19	0.1	1 (ciprofloxacin)

* NA = not available; TMP–SMX = trimethoprim–sulfamethoxazole.
† Data include all isolates, 84% of which were *E. coli*.

conducted a multicenter trial of low-dose ciprofloxacin compared with standard-dose ofloxacin and TMP–SMX for treatment of acute uncomplicated cystitis 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 might compromise clinical effectiveness until the mid-1990s (**Table 2**). We conducted a cross-sectional survey of urine isolates from a well-defined sample of outpatient women in western Washington State who had acute uncomplicated cystitis. We found that the prevalence of TMP–SMX resistance among *E. coli* was 9% in 1992 but had increased to 18% by 1996, the last year of the study (3). Of interest, in a California student health sample, Dyer and coworkers found that the prevalence of UTI isolates resistant to TMP–SMX was lower in 1997 than in 1994 (15% vs. 32%, respectively) (4). They postulated that the high rate of resistance in the earlier years discouraged the use of TMP–SMX and thus resulted in a lower rate of resistance to this drug by 1997. Larger, nationwide laboratory surveys have demonstrated a prevalence of TMP–SMX resistance of approximately 18% among isolates collected in 1998 (6) and in 2000 (8). The latter survey (8) showed that 7.1% of *E. coli* urinary isolates from all patient groups combined were resistant to three or more drugs, the most common phenotype being resistance to TMP–SMX, ampicillin, and cephalothin.

Table 3 summarizes in vitro resistance data from studies of community-acquired UTI that were conducted outside the United States (7, 23–30). The studies included here are limited to those that clearly defined the isolates as coming from an outpatient sample. Most of these studies did not separate the susceptibility data by sex, and therefore the resistance rates shown, while predominantly based on isolates from women, include some urine isolates from men as well. These studies clearly demonstrate the variation in TMP–SMX resistance by geographic region. Resistance rates in Canada and northern Europe are similar to those reported in the United States, whereas rates in southern Europe, Asia, and Latin America are substantially higher. Rates of resistance to the fluoroquinolones and nitrofurantoin also varied greatly by geographic region and were, in general, higher than the rates reported in U.S. studies.

Clinical Outcomes Associated with UTIs Resistant to TMP–SMX

In vitro resistance is expected to correlate with clinical and bacteriologic response to therapy in most infections. However, because most antimicrobial agents used to treat UTIs can achieve high urinary concentrations, in vitro resistance may not translate into therapeutic failure. The outcomes associated with treating a UTI by using an agent to which the infecting organism is resistant have been studied very little, and all of these studies have been secondary analyses with small numbers of patients. In fact, most treatment trials exclude patients with uropathogens resistant to the antimicrobial agents being studied. However, at least three treatment trials have examined bacteriologic outcomes of acute uncomplicated cystitis among women with uropathogens resistant to the study drugs. In a multicenter randomized trial of two β-lactam agents, cefcanel daloxate and amoxicillin, Nicolle and associates (31) found that 52 of 73 women (71%) infected with a uropathogen resistant

to the study drug they received had bacterial eradication by the 6- to 8-day follow-up visit, compared with 258 of 308 women (84%) infected with a susceptible uropathogen ($P = 0.013$). Bacteriologic outcomes at days 28 to 35 did not differ between the two groups (31). Clinical cure rates were not reported.

With regard to TMP–SMX resistance, Masterton and Bochsler (32) conducted a randomized trial comparing a high-dose, single-sachet formulation of amoxicillin–clavulanate and 7-day therapy with TMP–SMX for women with acute uncomplicated cystitis in the United Kingdom. Of the 135 women randomly assigned to TMP–SMX, 12% had a uropathogen resistant to the drug. Bacterial eradication at day 14 was achieved in 50% of women (7 of 14) with a uropathogen resistant to TMP–SMX, compared with 86% (106 of 123) of all women in the TMP–SMX group. The study did not report clinical cure rates or other outcomes in the resistant group. More recently, McCarty and colleagues (9) found that the bacterial eradication rate was 50% (5 of 10) and the clinical cure rate was 60% (6 of 10) among women with a uropathogen resistant to TMP–SMX who had been randomly assigned to TMP–SMX treatment. All of the women with clinical failure also had bacteriologic failure (9). Although these studies are limited by small sample sizes and are therefore not definitive, it seems that the failure rate in the setting of TMP–SMX resistance is greater than that for cases of acute uncomplicated cystitis caused by susceptible strains, which is well documented in the literature as approximately 5% (1, 9).

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. 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 (1, 9). Assuming a 50% bacterial eradication rate and a 60% clinical cure rate among women treated with TMP–SMX in the setting of infection with a uropathogen resistant to the drug, the expected effect of a resistance prevalence of 10% in a population of 100 women is relatively small (**Table 4**). However, the cure rates would be lower than those expected with a 3-day regimen of a fluoroquinolone among fluoroquinolone-susceptible cases of cystitis (1, 9). At 20% TMP–SMX resistance, the expected cure rates with TMP–SMX approach the cure rates expected with a 7-day regimen of nitrofurantoin in a nitrofurantoin-susceptible sample (33). Thus, this model supports the Infectious Diseases Society of America (IDSA) guidelines in recommending an alternative agent for treatment of uncomplicated cystitis when the TMP–SMX resistance prevalence is at least 20%. If the threshold for failure of therapy is very low (because of other patient variables), then the use of a fluoroquinolone could be considered even at the level of 10% TMP–SMX resistance.

Table 4. **Estimated Impact of Trimethoprim–Sulfamethoxazole Resistance on Microbiological and Clinical Outcomes Patients in Given Trimethoprim–Sulfamethoxazole for Acute Uncomplicated Cystitis***

Trimethoprim–Sulfamethoxazole Resistance	Expected Bacterial Eradication Rate	Expected Clinical Success Rate
← % →		
0	93	95
10	89	92
20	84	88
30	80	85

* The estimated bacterial eradication and clinical cure rates among patients with infections susceptible to trimethoprim–sulfamethoxazole are based on references 1 and 9, respectively. The model assumes a 50% bacterial eradication rate and a 60% clinical success rate among patients with an infection resistant to trimethoprim–sulfamethoxazole (9).

Risk Factors for Resistance

Because poorer outcomes are possible when TMP–SMX is used to treat UTIs caused by an organism resistant to the drug, it would be useful to be able to predict which patients are most likely to have a resistant uropathogen. However, there is a paucity of information in this important area. Two studies published in the past year have addressed this issue. Wright and colleagues (34) conducted a retrospective case–control study of patients with acute UTI being seen in an emergency department. Case-patients were defined as women who had a urine culture positive for a coliform resistant to TMP–SMX, whereas control patients had a urine culture positive for a coliform susceptible to TMP–SMX. The medical records of the 448 study patients (67 case-patients and 381 controls) were reviewed for potential risk factors, such as age; sex; history of UTI; the presence of diabetes, cancer, or a chronic neurologic or urologic disorder; residence in a long-term care facility; recent hospitalization; and recent antimicrobial use.

Although several of these factors were associated with having a uropathogen resistant to TMP–SMX in a univariate analysis, only diabetes, recent hospitalization, current use of any antibiotic, and current or recent use of TMP–SMX remained significantly associated as independent predictors in the multivariate model. Not surprisingly, the strongest risk factor for resistance was current or recent (within the past 3 months) use of TMP–SMX (odds ratio, 5.1 [95% CI, 2.2 to 11.5]). As the authors point out, diabetes has been linked to antibiotic-resistant uropathogens in some studies but not in all (34). When the patients who were recently hospitalized were excluded, in order to focus on community-acquired UTI, diabetes was no longer an independent risk factor for resistance, suggesting that more frequent hospitalization rates among diabetic patients may be one of the mechanisms by which this population acquires resistant uropathogens.

A second study conducted in the United Kingdom also used a case–control design to examine risk factors for trimethoprim-resistant UTIs among 265 patients (52 case-patients and 213 controls) in the community with a urine culture positive for a gram-negative rod (35). Use of trimethoprim within the past 6 months was strongly associated with resistance (odds ratio, 2.5 [CI, 1.2 to 5.3]). Recent use of other antibiotics or corticosteroids, recent hospitalization, and diabetes were not associated with resistance. Estrogen exposure in the form of oral contraceptive pills or estrogen replacement therapy within the past 6 months was also associated with resistance, although the potential mechanisms for this finding were not elucidated.

It is likely that current or recent use of trimethoprim or TMP–SMX increases the chance that a patient with acute cystitis will have an organism resistant to these agents. However, actual causality and the temporal associations between these variables remain to be elucidated. Furthermore, the effects of such conditions as diabetes, use of other antimicrobial agents, travel to areas with high rates of TMP–SMX resistance, and exposure to strains colonizing children in daycare or to a household member with recent antibiotic exposure all deserve further study. Several earlier studies have suggested that fecal colonization with *E. coli* resistant to trimethoprim or TMP–SMX is increased among persons who recently traveled to Mexico (36), among children attending daycare centers (37), and among family members of patients who had recently received a diagnosis of and treatment for a UTI caused by a trimethoprim-resistant *E. coli* strain (38). The duration of persistence of these resistant strains in the fecal reservoir, with or without antimicrobial exposure, and the likelihood that these strains would produce subsequent UTIs are not clear.

Acute Uncomplicated Pyelonephritis

Uncomplicated community-acquired pyelonephritis is a more serious and invasive disease than cystitis, and collection of a urine specimen for culture and sensitivity testing is always recommended before initiating therapy. A recently published treatment trial suggests that the trends in resistance occurring in cystitis strains also pertain to pyelonephritis (10). This study compared a 7-day course of ciprofloxacin with a 14-day course of TMP–SMX for outpatient oral treatment of acute uncomplicated pyelonephritis in women. Patients could receive one dose of intravenous therapy (ciprofloxacin in the ciprofloxacin group and ceftriaxone in the TMP–SMX group) if the treating physician deemed it necessary. The prevalence of resistance to TMP–SMX among the 255 uropathogens studied was 18.4%, compared with less than 1% for ciprofloxacin. Of interest, the rate of TMP–SMX resistance among *E. coli* strains varied considerably by geographic region, with a low of 7% in the eastern United States and a high of 32% in the western United States. The bacteriologic cure rate 4 to 11 days after therapy in the TMP–SMX group was 96% (73 of 76) among women with a uropathogen susceptible to TMP–SMX compared with 50% (7 of 14) among women with a uropathogen resistant to TMP–SMX ($P < 0.001$). The clinical cure rate was also significantly lower among women treated with TMP–SMX who had a resistant uropathogen (6 of 17 [35%]) than among women who had a susceptible uropathogen (76 of 83 [92%]) ($P < 0.001$). Among patients with a uropathogen resistant to TMP–SMX, 5 of 5 who received an initial intravenous dose of ceftriaxone had bacteriologic cure, compared with 2 of 9 who received only oral TMP–SMX. However, the clinical cure rates did not differ significantly between the groups. Thus, a high prevalence of TMP–SMX resistance and lower bacteriologic and clinical efficacy among patients treated with TMP–SMX in the setting of a uropathogen resistant to

TMP–SMX are important issues to consider in the management of pyelonephritis.

Management Strategies Based on Current Knowledge

Clearly, the susceptibility patterns of uropathogens causing acute uncomplicated UTI are changing, reducing the safety and effectiveness of empirical therapy for affected patients. To complicate matters, this change is not uniform from region to region or within different patient groups. The IDSA recently published evidence-based guidelines for treatment of acute UTI that tried to take these factors into account. The recommendations suggest that the TMP–SMX resistance level in the practitioner's region be considered when empirical therapy is selected (1). However, most communities lack surveillance systems to monitor resistance rates among community-acquired UTI isolates and to correlate those rates with age, sex, clinical syndrome, and comorbid conditions, all of which are essential for accurately identifying the resistance prevalence among isolates from acute uncomplicated UTIs.

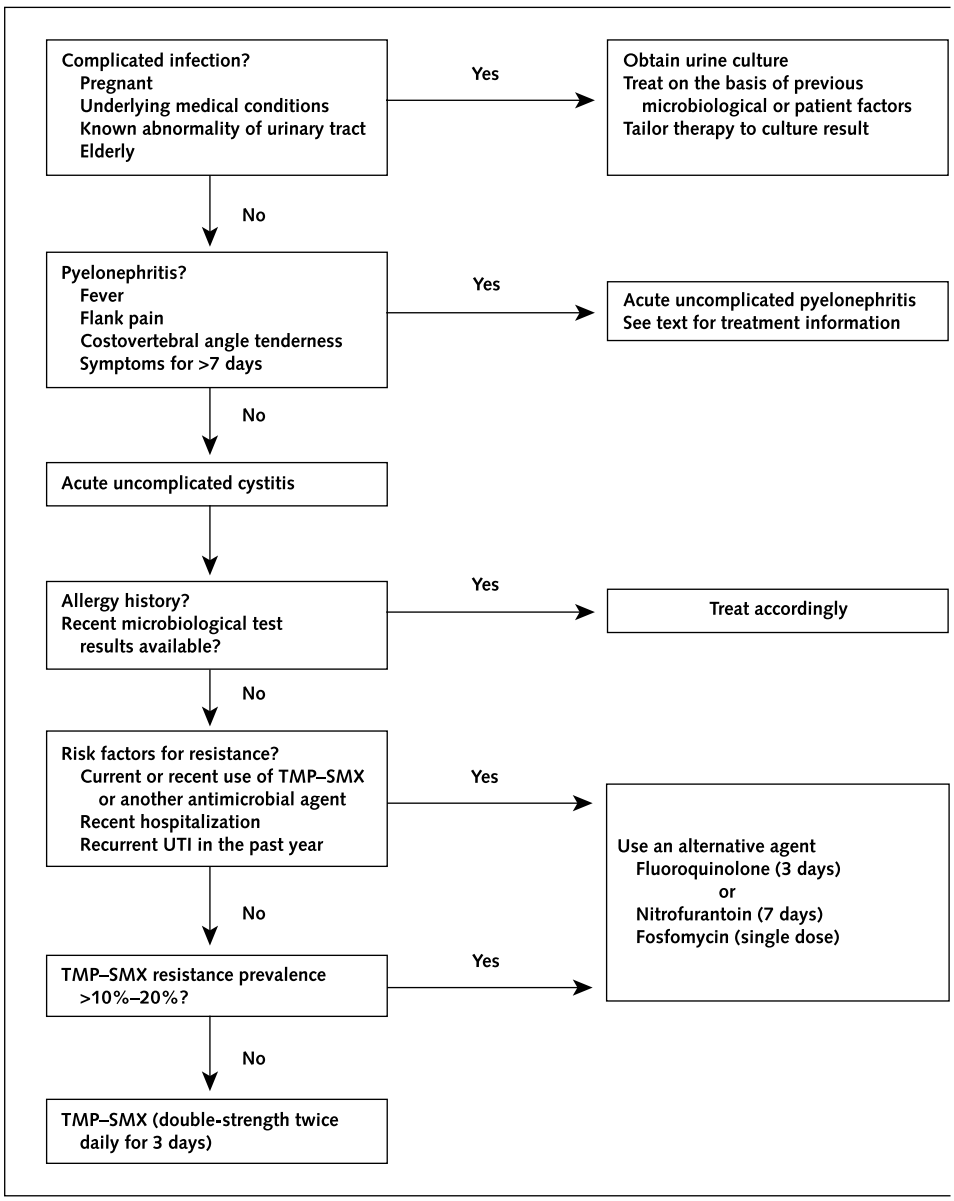
Given these circumstances, what strategies can an individual practitioner use to ensure that empirical UTI therapy remains safe and effective? An important initial step is to characterize the patient as having cystitis or pyelonephritis and complicated or uncomplicated UTI (**Figure**). Community-dwelling, nonelderly women who have dysuria, frequency, or urgency without flank pain or fever, and who are otherwise healthy, are not pregnant, and have no known abnormalities of the urinary tract, are considered to have acute uncomplicated cystitis. In most instances, such patients can be treated empirically, without obtaining a pretherapy urine culture. Patients who do not fall into this category or those in whom the diagnosis is not clear should have a urine culture, and therapy should be tailored accordingly. In addition, patients in whom empirical therapy fails should have a urine culture and susceptibility testing to guide further therapy.

After uncomplicated cystitis is established as the diagnosis, specific patient factors, such as severity of symptoms, allergic history, results of recent microbiological tests (if available), and risk factors for resistance need to be considered (**Figure**). Accessibility to medical care should also be considered. Culture results from previous UTIs may also be helpful, since studies have shown that most women with recurrent UTI are reinfected with the same organism even months later. This organism is often a single uropathogenic strain that resides in the vaginal and fecal reservoir between recurrent episodes of UTI (39). Although the risk factors for TMP–SMX resistance are not yet well delineated, it would seem prudent to expect a higher rate of resistance among women who have used any systemic antibiotic, but especially TMP–SMX, within the past 6 months or among those who have recently been hospitalized.

Finally, data on the prevalence of resistance in the relevant geographic region should be considered, if available. If the TMP–SMX resistance is less than 10% to 20% among strains causing uncomplicated community-acquired UTI, TMP–SMX is the drug of choice for therapy. If the local TMP–SMX resistance prevalence exceeds 20%, alternative antimicrobial agents should be considered. However, the choice of the optimal alternative agent can be difficult and is not clear-cut. A 3-day course of a fluoroquinolone is the alternative regimen with the greatest efficacy (equivalent to a 3-day regimen of TMP–SMX); however, important concerns include both the increased drug cost and the consideration that widespread use of fluoroquinolones for uncomplicated UTI may promote quinolone resistance in the community and hasten the emergence of resistance to these drugs (40, 41). Regarding cost, in one study, the overall cost per treatment episode for a fluoroquinolone was equivalent to that of TMP–SMX and less than that of amoxicillin or nitrofurantoin because the latter drugs had higher rates of side effects and treatment failures. Therefore, the initial procurement cost of a fluoroquinolone may be mitigated by overall improved outcomes (42). Other agents, such as fosfomycin (single dose) or nitrofurantoin (5- to 7-day regimen) would also be reasonable options for therapy among women in whom TMP–SMX is not appropriate, although the expected cure rates (on the basis of currently available data) are lower with these agents and single-dose fosfomycin is more expensive than a 3-day fluoroquinolone regimen (43). Additional data on the clinical effectiveness and side effects of 5 to 7 days of nitrofurantoin would be useful. Once again, such patient factors as allergic history, previous results of microbiological tests, and severity of illness should all play a role in this decision.

In a woman with nausea, vomiting, abdominal pain, dysuric symptoms, and costovertebral angle tenderness

Figure. **Strategy for management of uncomplicated community-acquired urinary tract infections (*UTI*) in women.**



TMP–SMX = trimethoprim–sulfamethoxazole.

on examination, pyelonephritis should be considered (**Figure**). Women whose cystitis symptoms are present for more than 7 days or are accompanied by fever may also have upper urinary tract involvement (44). If the patient meets the criteria for uncomplicated UTI outlined previously, has a temperature less than 38.3 °C, and has no nausea or vomiting, she can be treated as an outpatient with oral therapy. Outpatient therapy is also safe and effective in many women with higher temperatures and gastrointestinal symptoms after hydration and initial treatment in an observation unit (10). According to the IDSA guidelines, a fluoroquinolone is the drug of choice for outpatient treatment of acute uncomplicated pyelonephritis. If the infecting pathogen is known to be susceptible, TMP–SMX can be used as an alternative agent. If the patient is allergic to fluoroquinolones and the susceptibility of the pathogen is not known, we suggest an intravenous dose of ceftriaxone in

conjunction with oral TMP–SMX. In at least one study, this strategy resulted in improved outcomes in the setting of a pathogen resistant to TMP–SMX (10). Finally, if a Gram stain of the urine reveals gram-positive cocci, amoxicillin–clavulanate, amoxicillin alone, or amoxicillin plus an initial dose of gentamicin should be considered.

Patients with pyelonephritis who have underlying medical conditions, are more severely ill, or are unable to take oral therapy should be admitted for intravenous antimicrobial therapy. In this setting, a fluoroquinolone, an aminoglycoside with ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside are recommended. Once again, if the Gram stain suggests enterococci, use of ampicillin–sulbactam with or without an aminoglycoside should be considered. Therapy should be modified once the infecting organism and its susceptibility pattern are known and can be switched to an oral formulation (usually a fluoroquinolone) after the patient has defervesced.

Community-acquired UTIs, whether cystitis or pyelonephritis, that occur in the setting of underlying medical conditions, pregnancy, or long-term use of an indwelling urinary catheter, or in men, are most often considered to be complicated. Therapy for these infections must be tailored to the individual patient circumstances. Previous results of microbiological tests, allergy history, severity of illness, and potential drug interactions with other medications all need to be considered. For complicated cystitis that is suitable for outpatient therapy, a 7-day course of a fluoroquinolone is a reasonable regimen (barring a contraindication), given the low rates of resistance to these agents in the community. Patients with complicated pyelonephritis should be hospitalized and treated with intravenous antibiotics, as outlined previously.

CONCLUSIONS

The rate of in vitro resistance to TMP–SMX and to some β-lactams among community-acquired uropathogens is increasing in many areas. Preliminary data suggest that the increase in TMP–SMX resistance is associated with poorer bacteriologic and clinical outcomes when TMP–SMX is used for therapy. Further research on which factors best predict resistance and at what level in vitro resistance truly has clinical implications is needed. In addition, surveillance data that combine results of in vitro susceptibility tests with epidemiologic and clinical patient characteristics are needed for a more accurate estimate of resistance rates among women with uncomplicated infection. In the meantime, the management strategy presented here is intended as a guide for clinicians in a period of evolving resistance.

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