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Trends in Antimicrobial Resistance among Urinary Tract Infection Isolates of *Escherichia coli* from Female Outpatients in the United States

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The Infectious Diseases Society of America advocates trimethoprim-sulfamethoxazole (SXT) as initial therapy for females with acute uncomplicated bacterial cystitis in settings where the prevalence of SXT resistance does not exceed 10 to 20%. To determine trends in the activities of SXT, ampicillin, ciprofloxacin, and nitrofurantoin among urine isolates of *Escherichia coli* from female outpatients, susceptibility testing data from The Surveillance Network (TSN) Database-USA (n = 286,187) from 1995 to 2001 were analyzed. Resistance rates among *E. coli* isolates to ampicillin (range, 36.0 to 37.4% per year), SXT (range, 14.8 to 17.0%), ciprofloxacin (range, 0.7 to 2.5%), and nitrofurantoin (range, 0.4 to 0.8%) varied only slightly over this 7-year period. Ciprofloxacin was the only agent studied that demonstrated a consistent stepwise increase in resistance from 1995 (0.7%) to 2001 (2.5%). In 2001, SXT resistance among *E. coli* isolates was >10% in all nine U.S. Bureau of the Census regions. At institutions testing ≥100 urinary isolates of *E. coli* (n = 126) in 2001, ampicillin (range, 27.3 to 98.8%) and SXT (range, 7.5 to 47.1%) resistance rates varied widely while ciprofloxacin (range, 0 to 12.9%) and nitrofurantoin (range, 0 to 2.8%) resistance rates were more consistent. In 2001, the most frequent coresistant phenotypes were resistance to ampicillin and SXT (12.0% of all isolates; 82.3% of coresistant isolates) and resistance to ampicillin, ciprofloxacin, and SXT (1.4% of all isolates; 9.9% of coresistant isolates). Coresistance less frequently included resistance to nitrofurantoin (3.5% of coresistant isolates) than resistance to ciprofloxacin (15.8%), SXT (95.7%), and ampicillin (98.1%). In conclusion, among urinary isolates of *E. coli* from female outpatients in the United States, national resistance rates to SXT were relatively consistent (14.8 to 17.0%) from 1995 to 2001 but demonstrated considerable regional and institutional variation in 2001. Therapies other than SXT may need to be considered in some locations.

There are an estimated 150 million urinary tract infections per annum worldwide (26). In the United States, urinary tract infections result in approximately 8 million physician visits per year (30). Urinary tract infections are the most common bacterial infections in women and account for significant morbidity and health care costs (4, 26). A limited and predictable spectrum of organisms cause urinary tract infections in young, otherwise healthy females. Among both outpatients and inpatients, *Escherichia coli* is the primary urinary tract pathogen, accounting for 75 to 90% of uncomplicated urinary tract infection isolates (4, 21). *Staphylococcus saprophyticus*, *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., and *Enterobacter* spp. are pathogens less commonly isolated from outpatients.

The currently recommended empirical antimicrobial regimen for treating acute uncomplicated bacterial cystitis in otherwise healthy adult nonpregnant females is a 3-day course of double-strength trimethoprim-sulfamethoxazole (SXT) in settings where the prevalence of SXT resistance is <10 to 20% (1, 30). Investigators studying the economic impact of SXT and ciprofloxacin therapies have presented data supporting the empirical use of SXT when the local rate of resistance to SXT does not exceed 22% (14). Alternative therapy for uncomplicated urinary tract infections in settings with >10 to 20% SXT resistance may include a fluoroquinolone, nitrofurantoin, or fosfomycin (30).

The Infectious Diseases Society of America also recommends that physicians obtain information on local resistance rates and that ongoing surveillance be conducted to monitor changes in susceptibility of uropathogens (30). Surveillance at the institutional and regional level is particularly important given that previous studies have reported that the activity of SXT against urinary isolates of *E. coli* can vary considerably by geographic region (6, 25). The prevalence of SXT resistance among urinary pathogens appears considerable in the United States, and it seems inevitable that SXT will eventually need to be replaced by alternative therapies, at least in some areas (5–7, 11, 26).

In vitro studies specifically describing the antimicrobial susceptibilities of urinary isolates of *E. coli* from female outpatients are limited (5–7, 9, 12, 18). In these studies, SXT resistance increased from 7 to 9% in 1989 to 1992 (5, 7, 18, 28) to 17 to 18% in 1995 to 1999 (5–7, 12). Fluoroquinolone resistance was ≤1% in each of the aforementioned studies, and nitrofurantoin resistance was reported to be ≤2% on national and regional levels in the United States. The 1998 SENTRY surveillance program, reporting on isolates of *E. coli* collected from 26 U.S. centers, found the overall prevalence of SXT

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resistance to be 23.3% (17), very similar to the resistance rate found a year earlier (25.2%) by the same surveillance program (11).

The present study was conducted to determine national, regional, and institutional in vitro susceptibilities for ampicillin, ciprofloxacin, nitrofurantoin, and SXT among urine isolates of *E. coli* from female outpatients from across the United States in 2001. In addition, the rate of change in susceptibilities to these four commonly tested antimicrobial agents over 7 years, from 1995 to 2001, was also determined.

MATERIALS AND METHODS

Antimicrobial susceptibility testing results. The Surveillance Network (TSN) Database-USA (Focus Technologies, Herndon, Va.) was used as the source of antimicrobial susceptibility testing results for this study. TSN Database-USA is a real-time database that can be queried and that electronically assimilates antimicrobial susceptibility testing and patient demographic data from a network of hospitals in the United States (24). The number of laboratories participating in TSN Database-USA increased from 43 in 1995 to 58 in 1996, 122 in 1997, 186 in 1998, 232 in 1999, 258 in 2000, and 270 in 2001. Laboratories are included in TSN based on factors such as hospital bed size, patient population, geographic location, and antimicrobial susceptibility testing methods used (24). Susceptibility testing of patient isolates is conducted on site by each participating laboratory as a part of their routine diagnostic testing. Only data generated using Food and Drug Administration-approved testing methods with MIC results interpreted according to NCCLS recommendations (20) are included in TSN. In addition, a series of quality control filters (i.e., critical rule sets) are used to screen susceptibility test results for patterns indicative of testing error; suspect results are removed from analysis for laboratory confirmation.

The antimicrobial susceptibility testing results included in the analysis were restricted to the first urine isolate of *E. coli* submitted per calendar year by female outpatients of all ages. Data from patients in nursing facilities were not included. Urine specimen sources other than clean catch (e.g., catheterized urine or catheter tip cultures) were excluded from the analysis. Ampicillin, ciprofloxacin, nitrofurantoin, and SXT susceptibility data were analyzed nationally from 1995 to 2001 and in 2001 for the nine U.S. Bureau of the Census regions and for institutions (n = 126) testing ≥100 isolates of *E. coli* from unique female outpatients. All isolates were tested against all four antimicrobial agents. Additional analyses were performed to determine levels of coresistance and coresistant phenotypes for isolates tested in 2001.

TABLE 1. Antimicrobial susceptibilities of *E. coli* urinary isolates from female outpatients in the United States from 1995 to 2001

Antimicrobial and yr[a]	% of isolates		
	Susceptible	Intermediate	Resistant
Ampicillin			
1995	63.1	0.5	36.4
1996	62.5	0.6	36.9
1997	63.2	0.8	36.0
1998	62.3	0.7	37.0
1999	61.8	0.8	37.4
2000	62.7	0.6	36.7
2001	62.1	0.9	37.0
Ciprofloxacin			
1995	99.2	0.1	0.7
1996	99.3	0	0.7
1997	99.1	0	0.9
1998	98.8	0	1.2
1999	98.3	0	1.7
2000	97.8	0	2.2
2001	97.4	0.1	2.5
Nitrofurantoin			
1995	99.1	0.5	0.4
1996	98.8	0.5	0.8
1997	98.9	0.5	0.6
1998	98.8	0.6	0.6
1999	98.7	0.7	0.6
2000	98.7	0.7	0.6
2001	98.3	1.0	0.7
SXT			
1995	85.2	0	14.8
1996	83.7	0	16.3
1997	84.0	0	16.0
1998	83.0	0	17.0
1999	83.1	0.1	16.8
2000	83.4	0.1	16.5
2001	83.8	0.1	16.1

[a] 1,653 isolates were tested in 1995; 10,937 isolates were tested in 1996; 22,748 isolates were tested in 1997; 45,509 isolates were tested in 1998; 64,815 isolates were tested in 1999; 82,460 isolates were tested in 2000; 58,065 isolates were tested in 2001.

RESULTS

Ampicillin, ciprofloxacin, nitrofurantoin, and SXT susceptibilities for urine isolates of *E. coli* from female outpatients during the years 1995 through 2001 are presented in Table 1. Ampicillin susceptibility (yearly range, 61.8 to 63.2%), SXT susceptibility (yearly range, 83.1 to 85.2%), ciprofloxacin susceptibility (yearly range, 97.4 to 99.3%), and nitrofurantoin susceptibility (yearly range, 98.3 to 99.1%) were generally unchanged or decreased marginally over the 7 years studied. Ciprofloxacin was the only agent studied that demonstrated a consistent stepwise increase in resistance from 1995 (0.7%) to 2001 (2.5%). Resistance rates to ampicillin (range, 36.0 to 37.4% per year), SXT (range, 14.8 to 17.0%), and nitrofurantoin (range, 0.4 to 0.8%) varied only slightly over this 7-year period.

In 2001, significant regional variations in resistance rates for ampicillin (range, 29.4 [New England region] to 43.5% [West South Central region]), SXT (range, 11.8 [East North Central region] to 21.8% [West South Central region]), and ciprofloxacin (range, 1.3 [West North Central region] to 6.0% [South Atlantic region]) were observed (Fig. 1). Nitrofurantoin resistance rates were the most regionally consistent, with a narrow range from 0.4% (New England region) to 0.9% (South Atlantic region).

All 126 institutions in 2001 that tested ≥100 urinary isolates of *E. coli* had nitrofurantoin resistance rates of 0 to 5% (Fig. 2). The majority (>90%) of institutions also reported resistance rates of 0 to 5% for ciprofloxacin. Resistance to nitrofurantoin ranged from 0 to 2.8% and from 0 to 12.9% for ciprofloxacin. Resistance rates for ampicillin and SXT, however, varied widely across the institutions studied. Institutions most commonly (35%) had ampicillin resistance rates of between 36 and 40%, with an overall range of 27.3 to 98.8% resistant. Approximately 46% of the 126 institutions reported SXT resistance rates between 11 and 15%, with a range of 7.5 to 47.1% resistant.

Among the 58,065 isolates that were studied from 2001, the majority (n = 34,846; 60.0%) were susceptible to all four agents. Resistance to a single agent (n = 14,793; 25.5% of all isolates) was predominantly attributable to ampicillin (n = 13,219; 89.4%), followed by resistance to only SXT (n = 1,300; 8.8%), ciprofloxacin (n = 151; 1.0%), or nitrofurantoin (n = 123; 0.8%) (data not shown).

The coresistance analyses are summarized in Table 2. Concurrent resistance to ampicillin and SXT was the most preva-

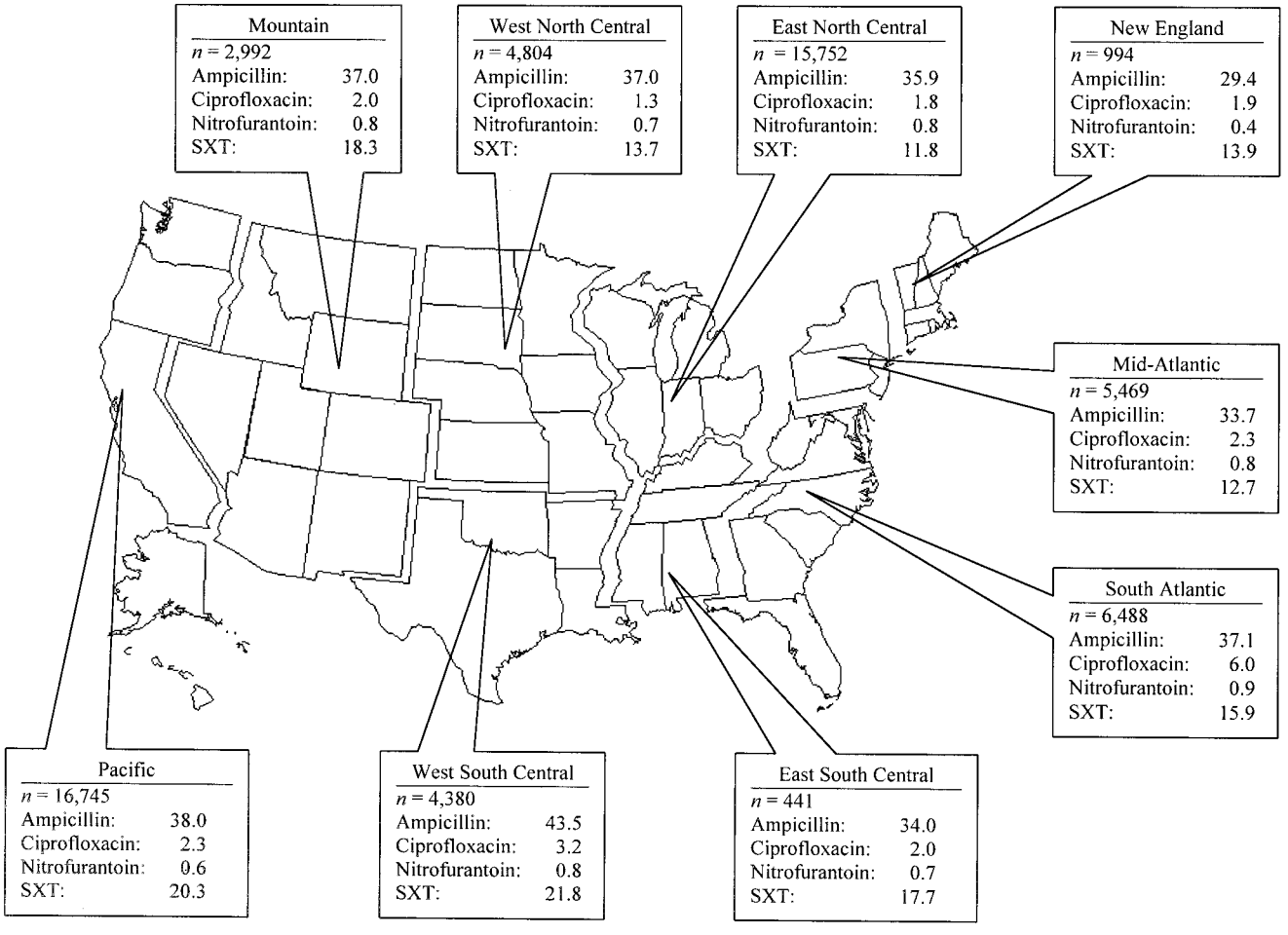

FIG. 1. Antimicrobial resistances (percent) among urinary isolates of *E. coli* in the nine U.S. Bureau of the Census regions in 2001.

lent coresistance phenotype (12.0% of all isolates; 82.3% of all coresistant isolates), followed by resistance to ampicillin, ciprofloxacin, and SXT (1.4% of all isolates; 9.9% of coresistant isolates). Ciprofloxacin (2.5%) and nitrofurantoin (0.7%) resistances, although rare overall in 2001, were for each agent more commonly found in isolates resistant to at least one other class of antimicrobial agent than among isolates susceptible to the other three agents studied. There were 8,426 isolates of *E. coli* (14.5% of all isolates) with a coresistant phenotype: 82 isolates (0.1% of all isolates) were resistant to all four agents.

DISCUSSION

Recent regional and national studies in the United States have reported resistance to SXT among urinary isolates of *E. coli* to be approaching or to exceed 20% (4–7, 11–13, 17, 23, 25). Given that *E. coli* is the principal pathogen in urinary tract infections, particularly among outpatients, resistance to SXT in *E. coli* is an important indicator of whether SXT should continue to be used empirically. The present study of 286,187 urine isolates of *E. coli* from female outpatients across the United States confirms that resistance to SXT is approaching 20% nationally but also that this rate (14.8 to 17.0%) changed only marginally in the 7 years studied, from 1995 to 2001 (Table 1). Previous studies documented significant increases in SXT resistance over the decade preceding 1995, from rates of <10% to the present levels of approximately 16 to 20% (4, 5, 7, 9, 12, 13, 23, 25, 28).

In 2001, all regions of the United States had SXT resistance rates that exceeded 10%. In five of the nine regions, resistance was >15%, and in two regions, resistance exceeded 20%. Resistance to SXT exceeded 10% in >90% of institutions and was >20% in approximately 45% of institutions (Fig. 2). A recent report suggesting that the dissemination of a single clonal group may have accounted for nearly half of the SXT-resistant isolates of *E. coli* from community-acquired infections in women in three geographically diverse communities (California, Michigan, and Minnesota) implies that rapid changes in susceptibility rates may be possible (15). The report of Manges et al. (15) is interesting given that urinary tract infections are generally considered to be the result of infection by endogenous fecal flora (11).

Approximately 14% of all isolates in 2001 were coresistant to at least ampicillin and SXT (Table 2). Two previous studies have also reported coresistance in urinary isolates of *E. coli* (25, 31). Zhanel et al. demonstrated a correlation between

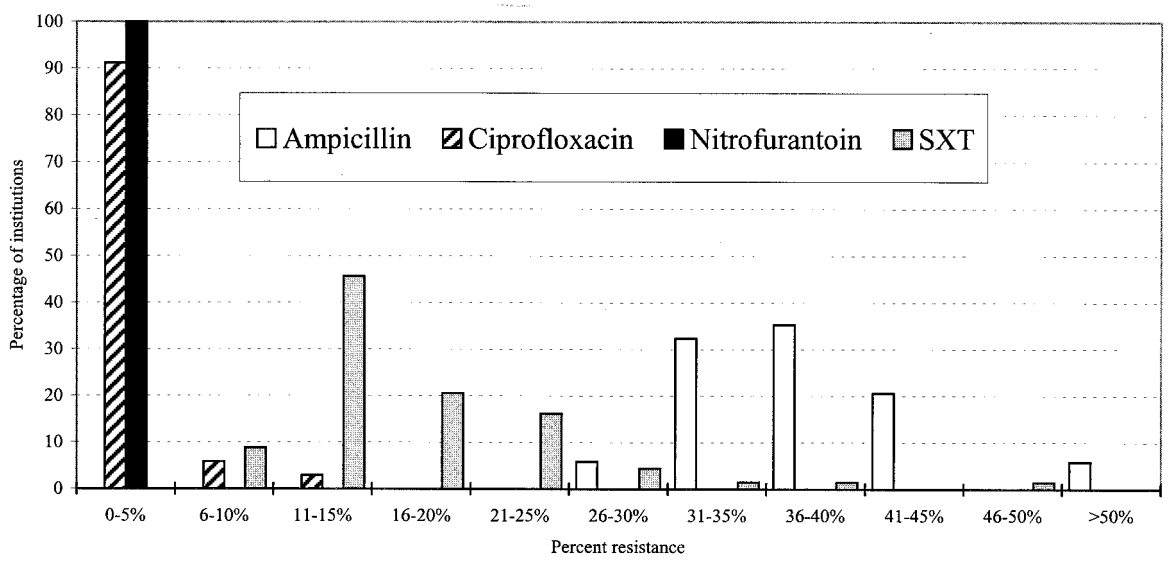

FIG. 2. Antimicrobial resistances at 126 institutions in the United States testing 100 or more urinary isolates of *E. coli* against four antimicrobials in 2001.

ampicillin and SXT resistances in *E. coli*, as well as reporting maximal rates of ampicillin (90%) and SXT (100%) resistance for ciprofloxacin-resistant *E. coli* (31). Specifically, the study (31) found that 80% of SXT-resistant *E. coli* isolates were concurrently ampicillin resistant, while nitrofurantoin resistance appeared unrelated to ampicillin, SXT, or ciprofloxacin resistance, an observation confirmed by the present study. Sahm et al. reported that in the United States in 2000, 7.1% of urinary isolates of *E. coli* were multidrug resistant (MDR) (resistant to three or more of the following drugs: ampicillin, cephalothin, ciprofloxacin, nitrofurantoin, and SXT) and that among the MDR isolates, 97.8% were resistant to ampicillin, 92.8% were resistant to SXT, 86.6% were resistant to cephalothin, 38.8% were resistant to ciprofloxacin, and 7.7% were resistant to nitrofurantoin (25).

Most antimicrobials used to treat urinary tract infections, including SXT, can achieve high urinary concentrations. Nevertheless, preliminary data suggest that clinical cure rates may be lower among outpatient women with uncomplicated urinary tract infections (cystitis and pyelonephritis) treated with SXT when the infecting pathogen is resistant to SXT (4, 16, 19, 22, 27). For example, in a study of women with acute uncomplicated pyelonephritis, Talan et al. reported that ≤50% of patients infected with SXT-resistant isolates were clinically or microbiologically cured (4 to 11 days posttherapy) when treated with SXT compared with a >90% clinical and microbiological cure rate in women who received SXT for SXT-susceptible isolates (27). Similarly, Raz et al. demonstrated that 5 to 9 days following cessation of SXT therapy, microbiological cure rates for women with uncomplicated urinary tract infections were twice as high among patients infected with SXT-susceptible pathogens (86%) than among patients infected with SXT-resistant strains (42%) (22). Clinical cure rates 5 to 9 days following SXT therapy were similar to microbiological cure rates for patients infected with SXT-susceptible (88%) and SXT-resistant (54%) isolates in the study conducted by Raz et al. (22).

TABLE 2. Coresistant phenotypes (n = 8,426) among 58,065 *E. coli* urinary isolates tested against ampicillin, ciprofloxacin, nitrofurantoin, and SXT in 2001

Coresistant phenotype	No. of coresistant isolates	% of coresistant isolates	% of all isolates
Ampicillin, SXT	6,938	82.3	12.0
Ampicillin, SXT, ciprofloxacin	836	9.9	1.4
Ampicillin, ciprofloxacin	241	2.9	0.4
SXT, ciprofloxacin	114	1.4	0.2
Ampicillin, SXT, nitrofurantoin, ciprofloxacin	82	1.0	0.1
Ampicillin, nitrofurantoin	79	0.9	0.1
Ampicillin, SXT, nitrofurantoin	70	0.8	0.1
Ampicillin, nitrofurantoin, ciprofloxacin	22	0.3	<0.1
Ciprofloxacin, nitrofurantoin	20	0.2	<0.1
Nitrofurantoin, SXT, ciprofloxacin	14	0.2	<0.1
SXT, nitrofurantoin	10	0.1	<0.1

It has been suggested that fluoroquinolones are a logical choice for empirical therapy of uncomplicated urinary tract infections (29). The data presented in this study appear to validate this supposition; however, the widespread use of fluoroquinolones for such a common infection raises concerns regarding the possibility of accelerated development of resistance (30). Also, the present study noted ciprofloxacin to be the only agent that demonstrated a stepwise, >3-fold increase in resistance from 1995 (0.7%) to 2001 (2.5%) (Table 1). Given that fluoroquinolone resistance among gram-negative bacteria is found predominantly among MDR isolates suggests that fluoroquinolone resistance will be maintained and perhaps accelerate even if other antimicrobials are used (2). While fluoroquinolones have maintained an excellent level of activity against commonly occurring uropathogens, the ability of these organisms to acquire fluoroquinolone resistance, its linkage

with SXT and β-lactam resistances (25), and the presence of MDR isolates in every clinically important gram-negative species are important considerations. A gradual decrease in the susceptibility of *E. coli* to fluoroquinolones (approximately 1% per annum) has also been reported by the U.S. arm of the SENTRY surveillance program, with no change in susceptibility to nitrofurantoin (11, 17). Increasing fluoroquinolone resistance among urinary *E. coli* has also been documented in studies conducted outside the United States (3).

The rate of resistance to nitrofurantoin (0.4 to 0.8%) remained low across the United States from 1995 to 2001, with rates similar to those published in earlier studies (5, 7). Nitrofurantoin is bactericidal in urine at therapeutic doses, and its multiple mechanisms of action appear to have enabled it to retain potent activity against *E. coli* despite nearly 50 years of use (19). The consistent and high-level susceptibility of *E. coli* to nitrofurantoin may be influenced by nitrofurantoin's narrow spectrum of activity, limited indication (treatment of acute cystitis), narrow tissue distribution (low or undetectable serum concentrations), and limited contact with bacteria outside the urinary tract (8).

The results of our laboratory-based investigation must be interpreted in light of the following considerations. The management of acute uncomplicated urinary tract infections has changed dramatically in the past few years. Attempts to manage reimbursable medical costs have led to a decrease in physician orders for routine urine cultures and subsequent susceptibility testing for patients with acute cystitis. Because the treatment of acute cystitis in otherwise healthy adult females is now largely empirical, isolates that are tested in laboratory-based studies may be predominantly from patients for whom previous antimicrobial treatment failed or from patients with other underlying risk factors. Therefore, traditional surveillance data, such as those studied here and elsewhere, may bias towards an overreporting of resistance in patients with acute uncomplicated cystitis (26). Performing patient-based studies would be an optimal alternative but would be costly and likely not practical for regional and national data assimilation.

The consistently high prevalence of resistance to SXT (14.8 to 17.0% per annum) from 1995 to 2001 and an increasing pattern of resistance to ciprofloxacin require ongoing surveillance to identify further changes among urinary tract isolates of *E. coli*. Resistance to ciprofloxacin (2.5% in 2001), although still relatively low, appears to be increasing in a stepwise manner and was higher than reported in previous U.S. surveillance studies (5, 7, 11). An increase in fluoroquinolone prescribing practices for uncomplicated urinary tract infections in recent years may be contributing to this observation, according to a report by Huang et al. (10). The in vitro activities of ciprofloxacin and nitrofurantoin found in the present study suggest that they would provide adequate alternative therapy in locations where SXT use is no longer prudent because of elevated (>10 to 20%) rates of resistance.

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