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Multidrug-Resistant Urinary Tract Isolates of *Escherichia coli:* Prevalence and Patient Demographics in the United States in 2000

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Concurrent resistance to antimicrobials of different structural classes has arisen in a multitude of bacterial species and may complicate the therapeutic management of infections, including those of the urinary tract. To assess the current breadth of multidrug resistance among urinary isolates of *Escherichia coli,* the most prevalent pathogen contributing to these infections, all pertinent results in The Surveillance Network Database—USA from 1 January to 30 September 2000 were analyzed. Results were available for 38,835 urinary isolates of *E. coli* that had been tested against ampicillin, cephalothin, ciprofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole. Of these isolates, 7.1% (2,763 of 38,835) were resistant to three or more agents and considered multidrug resistant. Among the multidrug-resistant isolates, 97.8% were resistant to ampicillin, 92.8% were resistant to trimethoprim-sulfamethoxazole, 86.6% were resistant to cephalothin, 38.8% were resistant to ciprofloxacin, and 7.7% were resistant to nitrofurantoin. The predominant phenotype among multidrug-resistant isolates (57.9%; 1,600 of 2,793) included resistance to ampicillin, cephalothin, and trimethoprim-sulfamethoxazole. This was the most common phenotype regardless of patient age, gender, or inpatient-outpatient status and in eight of the nine U.S. Bureau of the Census regions. Rates of multidrug resistance were demonstrated to be higher among males (10.4%) than females (6.6%), among patients >65 years of age (8.7%) than patients ≤17 (6.8%) and 18 to 65 (6.1%) years of age, and among inpatients (7.6%) than outpatients (6.9%). Regionally, the rates ranged from 4.3% in the West North Central region to 9.2% in the West South Central region. Given the current prevalence of multidrug resistance among urinary tract isolates of *E. coli* in the United States (7.1%), continued local, regional, and national surveillance is warranted.

Urinary tract infections (UTIs) result in approximately 8 million physician visits and more than 100,000 hospital admissions per year in the United States (9). The vast majority of UTIs arise in female outpatients, many of whom are treated empirically by physicians if their symptoms suggest acute uncomplicated bacterial cystitis (4, 5, 9). The pathogens causing UTIs are almost always predictable, with *Escherichia coli* the primary etiologic agent among both outpatients and inpatients (2–6, 10). Guidelines recently published by the Infectious Diseases Society of America (IDSA) recommend trimethoprim-sulfamethoxazole (SXT) as initial therapy for women with acute uncomplicated bacterial cystitis, but only in communities where the prevalence of SXT resistance is less than 10 to 20% (9).

The prevalence of *E. coli* resistant to SXT worldwide varies considerably in published reports, with current estimates ranging from approximately 18 to 50% (1–6, 10). The most recently published SXT resistance rates for *E. coli* isolated from UTIs in North America range from 18 to 25% (3, 4, 6, 10), suggesting that SXT would soon cease to be a first-line therapeutic option in some locales if the IDSA recommendations for initial empiric therapy are followed (4). Ampicillin resistance rates of *E. coli* isolated from UTIs are generally higher than those for SXT and are reported to be approaching 40% in North America (3, 4, 6, 10). The aforementioned surveillance studies notwithstanding, only limited data describing multidrug resistance among UTI isolates exist (10). A single study has demonstrated a correlation between ampicillin and SXT resistance in *E. coli*, as well as reporting maximal rates of ampicillin and SXT resistance for ciprofloxacin-resistant *E. coli* (10).

The goal of this study was to define the current prevalence and phenotypes of multidrug-resistant (MDR) *E. coli* among UTI isolates in the United States and to investigate associations between patient demographic parameters and multidrug resistance. Because the data are current, we used The Surveillance Network (TSN) Database—USA to obtain results from UTI isolates of *E. coli* tested against selected antimicrobials from 1 January to 30 September 2000.

MATERIALS AND METHODS

TSN is a repository of isolate-specific antimicrobial test results collected from more than 200 nationally accredited clinical laboratories across the United States via the Internet and a network of computer interfaces. It reflects current testing in U.S. laboratories and contains the data upon which clinical decisions are made. Laboratories are included in the network based on factors such as hospital bed size, patient population, geographic location, and antimicrobial susceptibility testing methods used (8). Susceptibility testing of patient isolates is conducted on site by each participating laboratory as part of their routine diagnostic testing. Proprietary susceptibility testing methods used by laboratories submitting results to TSN include Vitek (bioMerieux, St. Louis, Mo.), MicroScan (Dade-Microscan, Sacramento, Calif.), Sceptor and Pasco MIC/ID (Becton Dickinson, Sparks, Md.), and Etest (AB Biodisk, Solna, Sweden), as well as manual broth microdilution MIC and disk diffusion. The majority of results (74.2%) analyzed in this study were produced by the Vitek and MicroScan automated methods. For quality control purposes, only data generated according to recommendations established by the National Committee for Clinical Laboratory Standards

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TABLE 1. Antimicrobial susceptibility results for 123,691 *E. coli* urinary tract isolates as reported to TSN 1 January to 30 September 2000[a,b]

Antimicrobial agent	Total no. of isolates	% Isolates (no.) classified as[c]:		
		Susceptible	Intermediate	Resistant
Ampicillin	122,519	60.1 (73,598)	0.8 (986)	39.1 (47,935)
Cephalothin	49,667	70.4 (34,943)	14.0 (6,960)	15.6 (7,764)
Ciprofloxacin	107,342	96.2 (103,251)	0.1 (77)	3.7 (4,014)
Nitrofurantoin	105,595	98.1 (103,621)	0.9 (966)	1.0 (1,008)
SXT[d]	123,691	81.4 (100,673)	–[e]	18.6 (23,018)

[a] Isolates were included from both upper and lower urinary tract specimens.
[b] 31.4% (38,835 of 123,691) of isolates were tested against all five antimicrobial agents.
[c] Categories of susceptibility defined using NCCLS criteria (7).
[d] Trimethoprim and sulfamethoxazole tested in a ratio of 0.5/9.5 (7).
[e] No intermediate interpretive category exists by NCCLS criteria.

(NCCLS) (7) were included. In addition, TSN database uses a series of quality control filters (i.e., critical rule sets) to screen all susceptibility test results for patterns indicative of testing error and removes suspect isolate results from analysis until laboratory confirmation is provided.

From 1 January to 30 September 2000, TSN database included data for 123,691 UTI isolates of *E. coli* tested against at least one of the following antimicrobials: ampicillin, cephalothin, ciprofloxacin, nitrofurantoin, and SXT. All five antimicrobials were tested against 31.4% of these isolates (38,835 of 123,691). Data were drawn from specimens submitted by 202 geographically distributed medical institutions participating in TSN at the time of this study. NCCLS breakpoints were used to categorize isolates as susceptible, intermediate, or resistant (7). Multidrug resistance was defined as resistance to three or more of the antimicrobials tested. Demographic data describing patient age, gender, inpatient or outpatient status, and geographic location were also analyzed. Resistance by geographic location was analyzed by allocating the institutions participating in TSN to their appropriate U.S. Bureau of the Census regions and then comparing results for each of the nine regions. The nine U.S. Bureau of the Census regions are as follows: Pacific (Washington, Oregon, California, Alaska, and Hawaii), Mountain (Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona, and New Mexico), West North Central (North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, and Missouri), West South Central (Oklahoma, Arkansas, Texas, and Louisiana), East North Central (Wisconsin, Michigan, Illinois, Indiana, and Ohio), East South Central (Kentucky, Tennessee, Alabama, and Mississippi), New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, and Connecticut), Mid-Atlantic (New York, Pennsylvania, and New Jersey), and South Atlantic (Maryland, Delaware, West Virginia, Virginia, Washington D.C., North Carolina, South Carolina, Georgia, and Florida).

Given the number of isolate results included in the analysis of multidrug resistance ($n = 38,835$), statistical analysis of the data was not performed, as even subtle differences in percent resistance (<1%) to an antimicrobial agent for any of the demographic parameters would be reported as highly significant ($P < 0.001$).

RESULTS

The overall rates of resistance for the 123,691 *E. coli* isolates analyzed are provided in Table 1. Of the agents tested, nitrofurantoin (1.0%) and ciprofloxacin (3.7%) demonstrated the lowest rates of resistance, and ampicillin (39.1%) demonstrated the highest. The rate of SXT resistance among the *E. coli* isolates was 18.6%. By region in the United States, resistance rates ranged as follows: SXT, 11.6 to 23.9%; ampicillin, 29.1 to 45.7%; cephalothin, 11.4 to 23.9%; ciprofloxacin, 0.5 to 6.1%; and nitrofurantoin, 0.7 to 1.4% (data not shown). Rates of resistance to all five agents were highest in the West South Central region and lowest in New England, with the exception of cephalothin, which was not reported to TSN by participating laboratories in the New England region (data not shown).

The three most common antimicrobial susceptibility testing methods, Vitek, MicroScan, and disk diffusion, accounted for 95.2% of all results. The results for all methods were highly similar (data not shown): for example, SXT resistance ranged from 17.1 to 20.6% by test method. The resistance rates remained essentially unchanged when the results for all isolates ($n = 123,691$) were compared with those for isolates tested against all five antimicrobials simultaneously ($n = 38,835$): for example, the ampicillin resistance rates were 39.1% ($n = 123,691$) and 38.8% ($n = 38,835$). Similarly, the SXT resistance rates were 18.6% ($n = 123,691$) and 18.9% ($n = 38,835$).

Among the 38,835 isolates that were tested against all five antimicrobials, the majority (55.9%) were susceptible to all the agents studied (Table 2) and 20% were resistant to a single agent, predominantly ampicillin. MDR isolates accounted for 7.1% ($n = 2,763$) of the 38,835 isolates. The majority of MDR isolates ($n = 2,146$; 77.7%) were resistant to three antimicrobials, and these accounted for 5.5% of all isolates. Isolates were also identified that were resistant to four agents ($n = 555$; 20.1% of MDR isolates; 1.4% of all isolates) and all five agents ($n = 62$; 2.2% of MDR isolates; 0.2% of all isolates). All MDR phenotypes that were identified are listed in Table 3, with concurrent resistance to ampicillin, cephalothin, and SXT accounting for 57.9% of the MDR isolates. Resistance to ampicillin was a component of 97.8% (2,701 of 2,763) of the MDR isolates. Similarly, 92.8 ($n = 2,591$), 86.6 ($n = 2,393$), 38.8 ($n = 1,071$), and 7.7% ($n = 212$) of MDR isolates were resistant to SXT, cephalothin, ciprofloxacin, and nitrofurantoin, respectively. Of ciprofloxacin-resistant ($n = 1,437$) and nitrofurantoin-resistant ($n = 343$) isolates, 74.5 and 61.8% were MDR, in contrast to ampicillin-resistant ($n = 15,063$) and SXT-resistant ($n = 5,736$) isolates, of which 17.9 and 35.2% were MDR (Table 2).

Rates of antimicrobial resistance to individual agents and the percentage of isolates demonstrating an MDR phenotype were stratified by patient demographic characteristics and are

TABLE 2. Resistance to one or more antimicrobials among 38,835 *E. coli* urinary tract isolates tested against all five antimicrobials as reported to TSN 1 January to 30 September 2000

No. of agents to which isolates were resistant	Total % of isolates (no.)	% Isolates (no.) resistant to:				
		Ampicillin	Cephalothin	Nitrofurantoin	SXT	Ciprofloxacin
0	55.9 (21,701)					
1	20.0 (7,778)	77.4 (6,022)	8.4 (652)	1.0 (79)	11.4 (884)	1.8 (141)
2	17.0 (6,593)	96.2 (6,340)	40.8 (2,691)	0.8 (52)	58.8 (3,877)	3.4 (225)
3[a]	5.5 (2,146)	97.4 (2,090)	83.5 (1,792)	3.8 (82)	92.7 (1,990)	22.6 (484)
4[a]	1.4 (555)	98.9 (549)	97.1 (539)	12.3 (68)	97.1 (539)	94.6 (525)
5[a]	0.2 (62)	100 (62)	100 (62)	100 (62)	100 (62)	100 (62)

[a] 7.1% (2,763 of 38,835) of isolates were resistant to three or more antimicrobials and defined as MDR.

TABLE 3. Antimicrobial resistance phenotypes of 2,763 MDR *E. coli* urinary tract isolates as reported to TSN 1 January to 30 September 2000

Antimicrobial resistance phenotype	No. of isolates	% MDR isolates	% Total isolates[a]
Ampicillin, cephalothin, SXT	1,600	57.9	4.1
Ampicillin, cephalothin, ciprofloxacin, SXT	487	17.6	1.3
Ampicillin, ciprofloxacin, SXT	316	11.4	0.8
Ampicillin, cephalothin, ciprofloxacin	103	3.7	0.3
Ampicillin, cephalothin, ciprofloxacin, nitrofurantoin, SXT	62	2.2	0.2
Cephalothin, ciprofloxacin, SXT	45	1.6	0.1
Ampicillin, cephalothin, nitrofurantoin	38	1.4	0.1
Ampicillin, cephalothin, nitrofurantoin, SXT	30	1.1	0.1
Ampicillin, nitrofurantoin, SXT	23	0.8	0.1
Ampicillin, ciprofloxacin, nitrofurantoin, SXT	16	0.6	<0.1
Ampicillin, cephalothin, ciprofloxacin, nitrofurantoin	16	0.6	<0.1
Ampicillin, ciprofloxacin, nitrofurantoin	10	0.4	<0.1
Cephalothin, ciprofloxacin, nitrofurantoin, SXT	6	0.2	<0.1
Cephalothin, ciprofloxacin, nitrofurantoin	5	0.2	<0.1
Ciprofloxacin, nitrofurantoin, SXT	5	0.5	<0.1
Cephalothin, nitrofurantoin, SXT	1	<0.1	<0.1

[a] The total number of isolates was 38,835.

summarized in Table 4. Ciprofloxacin resistance was approximately twice as common among *E. coli* isolates from males (7.6%) as among those from females (3.2%) and increased with patient age to 7.1% in patients >65 years old. A trend toward higher rates of ciprofloxacin resistance among inpatients (5.0%) than outpatients (3.2%) was also evident. The ampicillin resistance rates decreased by more than 15% among patients aged ≤17 years (46.5%) compared with those 18 years and older (≤39.0%). A similar trend correlating cephalothin resistance with patient age was not identified. Nitrofurantoin resistance was approximately twice as common among males (1.4%) as among females (0.8%) and was highest (1.5%) among patients >65 years old. A trend toward lower rates of resistance with increasing patient age was evident for SXT, with 22.7% of isolates from patients ≤17 years old being resistant compared with 17.3% for patients >65 years old.

The most common MDR phenotype overall (Table 3)—resistance to ampicillin, cephalothin, and SXT—was also individually the most prevalent among males and females, patients ≤17, 18 to 65, and >65 years old; and inpatients and outpatients (data not shown). Trends toward higher rates of MDR *E. coli* among males (10.4%), patients >65 years old (8.7%), and inpatients (7.6%) were evident (Table 4) and became increasingly pronounced when MDR isolates resistant to four and five agents were considered in isolation from those resistant to three agents (data not shown).

Table 5 depicts the prevalence of single-drug resistance and multidrug resistance and the most prevalent MDR phenotype by region in the United States. Single-drug resistance demonstrated a narrow range (18.3 to 23.5%) by region, with <5% between the highest and lowest rates. The range of MDR rates also varied by <5% but was twice as common in the West South Central region (9.2%) as in the West North Central region (4.3%). By geographic region, resistance to ampicillin, cephalothin, and SXT was the most prevalent MDR phenotype in all eight regions for which cephalothin data were reported.

DISCUSSION

The recent IDSA guidelines suggest that in communities with SXT resistance rates of ≥10 to 20% among UTI pathogens, alternative antimicrobial agents should be considered as

TABLE 4. Patient demographic characteristics for 38,835 MDR *E. coli* urinary tract isolates as reported to TSN 1 January to 30 September 2000

Patient category	Total no. of isolates	% Isolates resistant to:					% MDR isolates (no.)
		Ampicillin	Cephalothin	Nitrofurantoin	SXT	Ciprofloxacin	
Gender							
Female	32,999	38.6	14.3	0.8	18.7	3.2	6.6 (2,189)
Male	4,642	39.3	18.5	1.4	20.1	7.6	10.4 (485)
Age							
≤17 yr	5,144	46.5	14.3	0.8	22.7	0.6	6.8 (350)
18–65 yr	19,468	39.0	13.7	0.5	18.3	2.7	6.1 (1,193)
>65 yr	12,029	33.2	15.8	1.5	17.3	7.1	8.7 (1,047)
Location							
Inpatient	7,936	40.2	17.5	1.0	17.5	5.0	7.6 (605)
Outpatient	30,522	38.4	14.0	0.7	19.2	3.2	6.9 (2,105)

[a] Of the 38,835 isolates tested against all five antimicrobials, demographic data was not available for all isolates: gender was not reported for 1,194 isolates, age was not reported for 2,194 isolates, and patient location was not reported for 377 isolates.

TABLE 5. Prevalence of single-drug and multidrug resistance among 38,835 *E. coli* urinary tract isolates tested against all five antimicrobials by geographic region (as reported to TSN 1 January to 30 September 2000)

Region	% Single-drug resistance	% Multidrug resistance	Most prevalent MDR phenotype
East North Central	22.7	5.8	Ampicillin, cephalothin, SXT
East South Central	23.5	6.0	Ampicillin, cephalothin, SXT
Mid-Atlantic	19.4	7.8	Ampicillin, cephalothin, SXT
Mountain	19.1	6.6	Ampicillin, cephalothin, SXT
New England	–[a]	–	–
Pacific	19.9	8.4	Ampicillin, cephalothin, SXT
South Atlantic	19.9	6.7	Ampicillin, cephalothin, SXT
West North Central	21.4	4.3	Ampicillin, cephalothin, SXT
West South Central	18.3	9.2	Ampicillin, cephalothin, SXT
All regions	20.0	7.2	Ampicillin, cephalothin, SXT

[a] Cephalothin results were not reported by laboratories in the New England region participating in TSN; thus, no phenotype comparisons were possible for this region.

first-line treatment for acute uncomplicated bacterial cystitis in women (9). Inherent in these recommendations is the need to perform regular surveillance to ensure that the activities of SXT and alternative agents are maintained and that emerging resistance trends, such as multidrug resistance, are identified. Further, it must also be appreciated that substantial geographic variations may exist in SXT resistance, as well as in the resistances to other antimicrobials, and therefore surveillance data must be available at the institutional, regional, and national levels. In addition, patient demographic data is a useful supplement to susceptibility data in helping to identify patient groups at higher risk of being infected with resistant organisms, such as MDR *E. coli*. Recent North American studies (3, 4, 6, 10) and studies performed in other countries (1, 2) have not addressed the issues of regional variation in antimicrobial resistance, emerging resistance trends such as multidrug resistance, and patient demographic associations with antimicrobial resistance in any detail.

Given that the majority of therapy for UTIs is empiric and that urinary tract pathogens are demonstrating increasing antimicrobial resistance, continuously updated data on antimicrobial susceptibility patterns would be beneficial to guide empiric treatment. The purpose of the present study was to describe the susceptibility profiles and patient demographics of isolates of *E. coli* from a representative sampling of all regions in the United States, with specific attention to the prevalence of MDR isolates. To accomplish this, antimicrobial susceptibility test results submitted to TSN in 2000 were used. The overall rates of resistance to ampicillin (39.1%) and SXT (18.6%) found in this study were significant and similar to those reported by the North American arm of the SENTRY surveillance program for 1997 (6) and by a recent Canadian national surveillance study (10). All three studies indicated substantial increases in rates of resistance to ampicillin and SXT compared with the rates reported from 1992 to 1996 (3, 4).

The rate of resistance to nitrofurantoin (1.0%) remained low across the United States in 2000 and was similar to rates (<2%) published for isolates tested from 1992 to 1996 (4). The low rate of ciprofloxacin (3.7%) resistance is noteworthy given its more than 13 years of continued use in the United States; however, resistance was slightly higher (<2.2%) than reported in previous North American surveillance studies (3, 4, 6, 10). Ciprofloxacin has maintained a high level of activity against UTI isolates of *E. coli* compared with other commonly used agents, such as ampicillin and SXT (4). The current data also demonstrated that a ciprofloxacin-resistant phenotype without concurrent resistance to other classes of antimicrobials is uncommon (1.8%) (Table 2). Previous work performed by Canadian investigators described a correlation between resistance to ampicillin and resistance to SXT and ciprofloxacin in *E. coli* but did not describe MDR phenotypes or patient demographics (10). Specifically, the study found increased rates of ampicillin resistance among SXT-resistant (79.6%) and ciprofloxacin-resistant (90.0%) *E. coli* isolates. In addition, all ciprofloxacin-resistant *E. coli* isolates were reported to be SXT resistant (10). Nitrofurantoin resistance appeared unrelated to concurrent ampicillin, SXT, or ciprofloxacin resistance (10). The present study, conducted in the United States, expanded upon these observations by describing the prevalence of resistance to SXT and other agents among *E. coli* isolates with MDR phenotypes. Resistance to ampicillin, SXT, cephalothin, ciprofloxacin, and nitrofurantoin were components of 97.8, 92.8, 86.6, 38.8, and 7.7% of MDR isolates, respectively.

The prevalence of resistant isolates was lower among females than males for all agents under study (Table 4). This trend likely reflects the tendency for males to present more often with complicated UTIs, which may be associated with more antimicrobial-resistant pathogens. Previous studies have described isolates from females only (3, 4), have not reported gender (6), or have not elaborated upon gender differences (10). With regard to patient age, the prevalence of isolates resistant to ampicillin or SXT was higher among isolates from patients ≤17 years old than among older patients. Levels of resistance to cephalothin and nitrofurantoin appeared relatively consistent irrespective of patient age. For ciprofloxacin, the prevalence of resistant isolates was highest among patients >65 years old (7.1%); however, among this patient demographic, rates of ciprofloxacin resistance were less than one-half those of ampicillin, cephalothin, and SXT. Previous studies describing associations between patient age and antimicrobial resistance with which to compare the current data are unavailable.

To better understand and respond to increasing antimicro-

bial resistance, the recent IDSA guidelines recommended that communities establish routine mechanisms to assess local resistance rates among UTI pathogens and that standard regimens for empiric therapy be reassessed periodically in light of changing susceptibility patterns. Physicians should be aware of current antimicrobial susceptibility patterns for *E. coli* and other UTI pathogens in their local communities, as antimicrobial susceptibilities change over time and vary geographically. Although the IDSA did not address the areas of multidrug resistance and patient demographics specifically, these data indicate that such knowledge could be useful in determining an alternative antimicrobial for empiric therapy.

Regional variability in resistance to single and multiple agents, the increases in ampicillin and SXT resistance among urinary pathogens over time (1–4, 6, 10), the predictability of the organisms causing acute bacterial cystitis, and evidence that the in vitro susceptibilities of common UTI pathogens are an important consideration for empiric therapy of UTIs emphasize the value of local, regional, and national surveillance programs (4, 5, 9). Because antimicrobial resistance patterns are continually evolving, properly designed and conducted regional surveillance studies will continue to be essential to ensure the provision of safe and effective empiric therapy. Clearly, the current prevalence of multidrug resistance among urinary tract isolates of *E. coli* in the United States (7.1%) suggests that monitoring these phenotypes is important and should be a consideration as the guidelines for the empiric treatment of UTIs evolve.

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