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A Canadian National Surveillance Study of Urinary Tract Isolates from Outpatients: Comparison of the Activities of Trimethoprim-Sulfamethoxazole, Ampicillin, Mecillinam, Nitrofurantoin, and Ciprofloxacin

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Ampicillin, trimethoprim-sulfamethoxazole, mecillinam, nitrofurantoin, and ciprofloxacin mean resistance rates for 2,000 urinary tract isolates collected from outpatients across Canada in 1998 were 41.1, 19.2, 14.7, 5.0, and 1.8%, respectively. For *Escherichia coli* isolates alone ($n = 1,681$) comparable rates were 41.0, 18.9, 7.4, 0.1, and 1.2%, respectively. The majority of *E. coli* isolates resistant to ampicillin, trimethoprim-sulfamethoxazole, or ciprofloxacin were susceptible (MIC, <16 μg/ml) to mecillinam.

Ampicillin and trimethoprim-sulfamethoxazole (SXT) resistance among urinary tract isolates has recently been reported with an increased frequency in Canada and the United States (1–3, 5, 11; R. Davidson, J. Fuller, T. Mazzulli, S. Porter-Pong, A. McGreer, and D. E. Low, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-34, 1998; T. Mazzulli, M. Skulnick, G. Small, D. E. Low, W. Marshall, D. Hoban, G. G. Zhanel, and S. Finn, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-38, 1998; G. G. Zhanel, A. S. Gin, A. Kabani, D. J. Hoban, and L. E. Nicolle, Abstr. 36th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-17, 1996). *Escherichia coli* remains the principal causative pathogen of urinary tract infections in both outpatients and inpatients (4–6, 13; Davidson et al., 38th ICAAC; Mazzulli et al., 38th ICAAC). As many as 30 and 50% of *E. coli* isolates from urinary tract infections of outpatients and inpatients, respectively, have been reported to be resistant to ampicillin (3, 5, 10; Davidson et al., 38th ICAAC; Mazzulli et al., 38th ICAAC). Reports of the prevalence of *E. coli* resistant to SXT vary considerably, with values ranging from 9% to more than 40% (3, 11; Mazzulli et al., 38th ICAAC). Presently, SXT is frequently the treatment of choice for uncomplicated urinary tract infection in Canada and the United States (4, 5). Nitrofurantoin, β-lactams such as amoxicillin, and fluoroquinolones such as ciprofloxacin are also prescribed to treat urinary tract infections of outpatients (4, 5). Reported SXT resistance rates in urinary tract isolates suggest that a reevaluation of first- and second-line therapies may be necessary.

A recent pilot study conducted at a single clinical microbiology laboratory serving a tertiary-care teaching hospital in Canada reported significant resistance to the first- and second-line therapies SXT and ampicillin for 258 urinary tract isolates (11). The goal of the present study was to assess the activity of relevant antibiotics against urinary tract isolates obtained from outpatients at other centers across Canada to determine if similar resistance patterns existed.

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From January to September 1998, 10 tertiary-care hospital microbiology laboratories (listed in the appendix) from across Canada each collected, for study, bacterial isolates from 200 consecutive outpatients with urinary tract infections. All isolates were deemed significant urinary tract pathogens by individual laboratory criteria and identified to the species level by each laboratory's existing protocols. Isolates were transported to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) on Amies charcoal swabs. Only one isolate per patient was accepted. Upon receipt, isolates were cultured by the coordinating laboratory, stocked in skim milk, and stored at −70°C awaiting reference antibiotic susceptibility testing. Elementary demographic information was also compiled for each isolate.

Susceptibilities to ampicillin (Sigma Chemical Company, St. Louis, Mo.), SXT (Sigma Chemical Company), mecillinam (Leo Pharma Inc., Ajax, Ontario, Canada), nitrofurantoin (Procter & Gamble Inc., Cincinnati, Ohio), and ciprofloxacin (Bayer Inc., Toronto, Ontario, Canada) were determined using the National Committee for Clinical Laboratory Standards (NCCLS) M7-A4 broth microdilution method (7). Cation-adjusted Mueller-Hinton broth (Ca^{2+}, 25 μg/ml; Mg^{2+}, 12.5 μg/ml) microdilution panels were prepared by the coordinating laboratory to contain antimicrobial doubling dilution concentrations appropriate for each agent tested (7, 8). Each final panel well volume was 100 μl with a bacterial inoculum of 5×10^5 CFU/ml (7). Panels were read following 16 to 20 h of incubation at 35°C in ambient air (7). The MIC was defined as the lowest concentration of antimicrobial inhibiting visible growth (7). The ampicillin, SXT, nitrofurantoin, and ciprofloxacin re-

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sistance breakpoints used were those published by the NCCLS (8). The mecillinam susceptibility and resistance breakpoints used were <16 and ≥16 μg/ml, respectively. Resistance rates were compared using analysis of variance calculations, with statistical significance defined as a P value of <0.05.

The 2,000 urinary tract isolates from outpatients included 1,681 (84.1%) *E. coli* isolates, 75 (3.8%) *Klebsiella pneumoniae* isolates, 56 (2.8%) *Enterococcus* sp. isolates, 51 (2.6%) *Proteus mirabilis* isolates, 27 (1.4%) *Staphylococcus saprophyticus* isolates, 17 *Enterobacter cloacae* (1.9%) isolates, 14 *Pseudomonas aeruginosa* (0.7%) isolates, 10 β-hemolytic streptococcus group B (0.5%) isolates, and 69 (3.5%) isolates of other organisms, including 9 coagulase-negative staphylococcus, 8 *Citrobacter freundii*, 8 *Enterobacter aerogenes*, 7 *Staphylococcus aureus*, 6 *Citrobacter koseri*, 5 *Staphylococcus epidermidis*, 4 *Morganella morganii*, 4 *Serratia marsescens*, 2 *Acinetobacter baumanii*, 2 *Acinetobacter lwoffi*, 2 *Citrobacter amalonaticus*, 2 *Citrobacter diversus*, 2 *Enterobacter agglomerans*, 2 *Flavobacterium odoratum*, 2 *Klebsiella oxytoca*, 2 *Providencia stuartii*, and 2 *Pseudomonas fluorescens* isolates. The 2,000 isolates were collected from 1,643 (82.1%) female and 357 (17.9%) male outpatients. The mean age for all outpatients was 43.2 years (range, 3 months to 97 years).

The mean rates of resistance (for all 2,000 isolates) to ampicillin, SXT, mecillinam, nitrofurantoin, and ciprofloxacin were 41.1% (range, 35.5 to 47.0%), 19.2% (range, 17.0 to 21.5%), 14.7% (range, 12.5 to 16.5%), 5.0% (range, 4.0 to 6.0%), and 1.8% (range, 1.5 to 2.0%), respectively. Significant differences ($P > 0.05$) in resistance rates between results from the 10 study centers were not detected (data not shown).

Susceptibilities to each antibiotic are presented in Table 1 as MIC ranges, MICs at which 50% of the isolates tested were inhibited (MIC_{50}s) and MICs at which 90% of the isolates tested were inhibited (MIC_{90}s). Considering all isolates, there were significantly ($P < 0.05$) lower rates of resistance to mecillinam than to either ampicillin or SXT, while ciprofloxacin and nitrofurantoin resistance rates were both significantly ($P < 0.05$) lower than those for ampicillin, SXT, and mecillinam (Table 1). For the 1,681 isolates of *E. coli*, the mean rates of resistance to ampicillin, SXT, mecillinam, ciprofloxacin, and nitrofurantoin were 41.0, 18.9, 7.4, 1.2, and 0.1%, respectively (Table 1). The mecillinam resistance rate for *E. coli* was significantly ($P < 0.05$) lower than those of ampicillin and SXT, while there were again significantly ($P < 0.05$) lower rates of resistance to ciprofloxacin and nitrofurantoin than to ampicillin, SXT, and mecillinam (Table 1). MIC and resistance rate data are also provided in Table 1 for *K. pneumoniae*, *Enterococcus* spp., *P. mirabilis*, and *S. saprophyticus*.

The activities of antibiotics against ampicillin-, SXT-, and ciprofloxacin-resistant *E. coli* are depicted in Table 2. Against ampicillin-resistant, SXT-resistant, and ciprofloxacin-resistant *E. coli*, the rates of resistance to nitrofurantoin were lowest. Concurrent resistance to mecillinam (MIC, ≥16 μg/ml) among ampicillin-, SXT-, or ciprofloxacin-resistant *E. coli* was present in less than 15% of isolates. Ampicillin and SXT did not demonstrate activity against ciprofloxacin-resistant *E. coli* (Table 2).

Table 2 also displays the distributions of the MICs of the different antibiotics for ampicillin-, SXT-, and ciprofloxacin-resistant *E. coli*. MICs for ampicillin-resistant isolates were generally from 128 to >512 μg/ml. The MICs for mecillinam-resistant isolates were not densely clustered around a single value, as MICs ranged from 16 to >512 μg/ml (data not shown). The MICs for ciprofloxacin-resistant isolates were evenly distributed from 4 to >16 μg/ml (Table 2). The MICs for nitrofurantoin-resistant isolates clustered around the resistance breakpoint at 128 μg/ml (Table 2). The MICs for SXT-resistant isolates were clustered in small numbers around the resistance breakpoint of 4 μg/ml; however, for the majority of resistant isolates the MICs of SXT were higher, being ≥64 μg/ml (Table 2).

TABLE 1. In vitro activities of antibiotics tested against 2,000 urinary tract isolates from outpatients

Isolate(s) (n) and antibiotic	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	% Resistant[a]
All (2,000)				
Ampicillin	4	>512	≤0.5–>512	41.0
Ciprofloxacin	≤0.03	0.12	≤0.03–32	1.8
Mecillinam	4	64	≤0.5–>512	14.7
Nitrofurantoin	16	32	≤2–>512	5.0
SXT	0.12	>64	≤0.06–128	19.2
E. coli (1,681)				
Ampicillin	4	>512	≤0.5–>512	41.0
Ciprofloxacin	≤0.03	≤0.03	≤0.03–32	1.2
Mecillinam	1	16	≤0.5–>512	7.4
Nitrofurantoin	16	32	≤2–>512	0.1
SXT	0.12	>64	≤0.06–128	18.9
K. pneumoniae (75)				
Ampicillin	32	128	8–>512	65.6
Ciprofloxacin	≤0.03	0.12	≤0.03–32	1.3
Mecillinam	1	64	≤0.5–>512	17.8
Nitrofurantoin	64	128	4–512	18.7
SXT	0.12	0.5	≤0.06–128	8.0
Enterococcus spp. (56)				
Ampicillin	≤0.05	1	≤0.5–256	4.5
Ciprofloxacin	1	>16	≤0.03–32	19.6
Mecillinam	256	512	1–>512	90.1
Nitrofurantoin	8	16	4–64	0
SXT	0.06	32	≤0.06–128	17.9
P. mirabilis (51)				
Ampicillin	1	64	≤0.5–>512	11.9
Ciprofloxacin	0.03	0.06	≤0.03–0.25	0
Mecillinam	64	256	≤0.5–>512	76.5
Nitrofurantoin	128	128	4–128	76.5
SXT	0.12	>64	≤0.06–128	17.5
S. saprophyticus (27)				
Ampicillin	≤0.05	32	≤0.5–32	15.8
Ciprofloxacin	0.25	0.5	0.06–0.5	0
Mecillinam	8	32	≤0.5–32	48.1
Nitrofurantoin	8	16	4–32	0
SXT	≤0.06	2	≤0.06–2	0

[a] Resistance breakpoints used were those defined by NCCLS M100-S9 (8). They are as follows: for ampicillin, ≥32 μg/ml; for ciprofloxacin, ≥4 μg/ml; for nitrofurantoin, ≥128 μg/ml; and for SXT, ≥4/76 μg/ml. The mecillinam resistance breakpoint used was ≥16 μg/ml.

Enterobacteriaceae (*E. coli*, *K. pneumoniae*, and *P. mirabilis*) were the most common among the pathogens isolated in this study, followed by gram-positive cocci (*Enterococcus* spp. and *S. saprophyticus*). These data are consistent with recently published studies (3; Mazzulli et al., 38th ICAAC). All previous reports as well as the present study have documented that *E. coli* is the principal pathogen responsible for urinary tract infections of outpatients (3, 5; Mazzulli et al., 38th ICAAC).

The present study demonstrated that the prevalence of ampicillin (41.0%) and SXT (19.2%) resistance among urinary tract isolates recently collected from outpatients in Canada was high. These data are consistent with recently published reports (1–3, 5, 11; Davidson et al., 38th ICAAC; Mazzulli et al., 38th ICAAC; Zhanel et al., 36th ICAAC) and suggest that the prevalence of ampicillin and SXT resistance among urinary

TABLE 2. In vitro activities and MIC distributions of five different antibiotics tested against ampicillin-, SXT-, and ciprofloxacin-resistant isolates of *E. coli*

E. coli isolate group (*n*) and antibiotic	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	% Resistant[a]	No. of isolates inhibited by MIC (μg/ml) of:														
					≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	>512
Ampicillin-resistant (689)																				
Ampicillin	512	>512	32–>512	100					0	0	0	0	0	0	11	18	46	190	204	220
Ciprofloxacin	≤0.03	≤0.03	≤0.03–32	2.0	643	9	3	6	0	14	0	0	5	2	7					
Mecillinam	4	64	≤0.5–>512	14.8					75	75	35	287	115	27	5	12	19	9	21	9
Nitrofurantoin	16	16	4–128	0.2							0	9	149	473	48	9	1	0	0	0
SXT	0.5	>64	≤0.06–128	35.7		155	71	79	100	26	12	6	5	0	8	4	223			
SXT-resistant (317)																				
Ampicillin	256	>512	2–>512	79.6					0	0	26	18	20	0	0	5	18	74	69	86
Ciprofloxacin	≤0.03	0.25	≤0.03–32	6.3	282	0	3	3	0	9	0	1	3	7	9					
Mecillinam	4	64	≤0.5–>512	15.1					82	36	27	83	41	10	0	7	8	8	7	8
Nitrofurantoin	16	32	≤2–64	0							4	3	57	180	68	5	0	0	0	0
SXT	>64	>64	4–128	100		0	0	0	0	0	0	4	6	8	5	8	286			
Ciprofloxacin-resistant (20)																				
Ampicillin	512	512	4–512	90					0	0	0	2	0	0	0	0	0	2	16	0
Ciprofloxacin	16	>16	4–32	100	0	0	0	0	0	0	0	1	3	7	9					
Mecillinam	2	16	≤0.5–16	10					3	4	3	3	5	2	0	0	0	0	0	0
Nitrofurantoin	16	32	2–32	0							4	0	0	7	9	0	0	0	0	0
SXT	>64	>64	8–128	100		0	0	0	0	0	0	0	1	0	0	0	19			

[a] Resistance breakpoints used were those defined by NCCLS M100-S9 (8). They were as follows: for ampicillin ≥32 μg/ml; for ciprofloxacin, ≥4 μg/ml; for nitrofurantoin, ≥128 μg/ml; and for SXT, ≥4/76 μg/ml. The mecillinam resistance breakpoint used was ≥16 μg/ml.

tract isolates from outpatients is increasing. The data also support recommendations made in previous studies (1, 3, 11; Davidson et al., 38th ICAAC; Mazzulli et al., 38th ICAAC) that suggest nitrofurantoin or ciprofloxacin may be more effective than SXT or amoxicillin in the empiric treatment of urinary tract infections of outpatients. However, the clinical relevance of SXT-resistant *E. coli* and its association with clinical failure is presently unknown (4, 5).

The activity of ampicillin against urinary tract isolates from outpatients in general as well as against SXT-resistant (79.6% resistance) and ciprofloxacin-resistant (90.0% resistance) *E. coli* isolates, specifically, was shown to be limited (Table 2). These data, in addition to other recent reports, highlight the continued deterioration of ampicillin activity against urinary tract pathogens, especially against isolates with concurrent resistance to other antibiotics (3, 11; Davidson et al., 38th ICAAC). SXT resistance was common among all isolates tested, and rates of SXT resistance for ampicillin-resistant *E. coli* (35.7% resistance) and ciprofloxacin-resistant *E. coli* (100% resistance) were high. These data confirm reports of increasing SXT resistance (3, 11; Davidson et al., 38th ICAAC; Mazzulli et al., 38th ICAAC). Nitrofurantoin and ciprofloxacin demonstrated excellent in vitro activity against both ampicillin- and SXT-resistant *E. coli* (Table 2).

Mecillinam, a β-lactam antibiotic that was introduced into clinical use in the United States and Canada in 1985, was also tested in this study, as it has previously demonstrated notable activity against gram-negative urinary tract pathogens (9, 11; Mazzulli et al., 38th ICAAC). Mecillinam's mechanism of action against *E. coli* and, presumably, other gram-negative bacilli differs from those of other β-lactam antibiotics in that its primary target is penicillin-binding protein 2, an enzyme critical to the establishment and maintenance of bacillary cell shape (9, 10). Mecillinam demonstrated a level of activity superior to the activities of both ampicillin and SXT ($P < 0.05$) against all isolates tested, and ampicillin-, SXT-, and ciprofloxacin-resistant *E. coli* demonstrated low levels of resistance to this drug (Table 2). Mecillinam, administered as its prodrug pivmecillinam, has been reported to be an effective agent for the treatment of uncomplicated urinary tract infections of outpatients (6). The observations that mecillinam demonstrated activity superior to that demonstrated by SXT, the current antibiotic of choice for the treatment of uncomplicated urinary tract infections of outpatients (4, 5), and was active against ciprofloxacin-resistant *E. coli* indicate that its role in the treatment of urinary tract infections needs to be reassessed.

In conclusion, increasing resistance to both ampicillin and SXT is being reported for urinary tract isolates in both Canada and the United States (1, 3, 5, 11; Mazzulli et al., 38th ICAAC; Zhanel et al., 36th ICAAC) and suggests that a reevaluation of first- and second-line therapies for the treatment of urinary tract infections of outpatients may be necessary.

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APPENDIX

The members of the Canadian Urinary Isolate Study Group and their participating laboratories were P. Kibsey, Victoria General Hospital, Victoria, British Columbia, Canada; D. L. Roscoe, Vancouver General Hospital, Vancouver, British Columbia, Canada; A. P. Gibb, Calgary Laboratory Services, Calgary, Alberta, Canada; R. Rennie, University of Alberta Hospitals, Edmonton, Alberta, Canada; J. Blondeau, Royal University Hospital, Saskatoon, Saskatchewan, Canada; G. K. M. Harding, St. Boniface General Hospital, Winnipeg, Manitoba, Canada; G. G. Zhanel and D. J. Hoban, Health Sciences Centre, Winnipeg, Manitoba, Canada; J. Dubois, Universitaire de Sante de l'Estrie, Sherbrook, Quebec, Canada; V. Loo, Montreal General Hospital, Montreal, Quebec, Canada; and M. Laverdiere, Maisonneuve-Rosemont, Montreal, Quebec, Canada.

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