Community-acquired antibiotic resistance in urinary isolates from adult women in Canada

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BACKGROUND: There are currently limited data regarding the prevalence of antimicrobial-resistant organisms causing community-acquired urinary tract infections among adult women in Canada. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended first-line empirical antibiotic treatment, unless resistance of *Escherichia coli* to TMP-SMX exceeds 20%.
OBJECTIVE: To assess current levels of TMP-SMX-resistant *E coli* in community-acquired cases of urinary tract infection in adult women.
METHOD: Assessment of urine culture reports obtained from 21 laboratories across Canada, submitted by family physicians for women aged 16 years and older.
RESULTS: In 2199 adult women with a positive urine culture, 1079 (49.1%) of pathogens isolated were resistant to at least one antibiotic and 660 (30.0%) were multidrug-resistant (resistant to two or more antibiotics). TMP-SMX resistance was seen in 245 of 1613 (15.2%) *E coli* isolates (95% CI 13.5 to 17.0). This proportion was higher in women 50 years of age and older (155 of 863 isolates [18.0%]; P=0.001), in British Columbia (70 of 342 isolates [20.5%]) and in Ontario (62 of 370 isolates [16.8%]) when compared with eastern provinces (65 of 572 isolates [11.4%]; P=0.001). Fluoroquinolone-resistant *E coli* occurred in 107 of 1557 (6.9%) isolates (95% CI 5.7 to 8.2), with the highest level found in British Columbia (54 of 341 isolates [15.8%]; P=0.001).
CONCLUSION: TMP-SMX continues to be appropriate as first-line empirical treatment of acute cystitis in adult women in Canada, as resistance remains below 20%. However, TMP-SMX resistance is higher in older women and in some provinces. The level of fluoroquinolone-resistant *E coli* is highest in British Columbia.

Key Words: *Antibiotic resistance; Primary care; Uropathogens*

Une antibiorésistance non nosocomiale dans les isolats urinaires de femmes canadiennes

HISTORIQUE : Les données sur la prévalence des organismes résistants aux antimicrobiens provoquant des infections urinaires non nosocomiales chez les femmes du Canada sont limitées. Le triméthoprim-sulfaméthoxazole (TMP-SMX) est le traitement antibiotique empirique de choix recommandé, à moins que la résistance de l'*Escherichia coli* au TMP-SMX soit supérieure à 20 %.
OBJECTIF : Évaluer les taux courant d'*E coli* résistant au TMP-SMX en cas d'infections urinaires non nosocomiales chez les femmes.
MÉTHODOLOGIE : L'évaluation des résultats de cultures urinaires obtenues dans 21 laboratoires du Canada, soumises par les médecins de famille de femmes de 16 ans et plus.
RÉSULTATS : Chez 2 199 femmes ayant une culture urinaire positive, 1 079 (49,1) des pathogènes isolés étaient résistants à au moins un antibiotique et 660 (30,0 %) étaient multirésistants (résistants à au moins deux antibiotiques). On observait une résistance au TMP-SMX dans 245 des 1 613 (15,2 %) isolats à l'*E coli* (95 % IC 13,5 à 17,0). Cette proportion était plus élevée chez les femmes de 50 ans et plus (155 isolats sur 863 [18,0 %]; P=0,001), en Colombie-Britannique (70 isolats sur 342 [20,5 %]; P=0,001) et en Ontario (62 isolats sur 370 [16,8 %]) par rapport aux provinces atlantiques (65 isolats sur 572 [11,4 %]; P=0,001). On observait un *E coli* résistant à la fluoroquinolone dans 107 des 1 557 (69,9 %) isolats (95 % IC 5,7 à 8,2), le taux le plus élevé s'observant en Colombie-Britannique (54 des 341 isolats [15,8 %]; P=0,001).
CONCLUSION : Le TMP-SMX continue de convenir comme traitement empirique de choix de la cystite aiguë chez les femmes du Canada, car la résistance demeure inférieure à 20 %. Cependant, la résistance au TMP-SMX est plus élevée chez les femmes plus âgées et dans certaines provinces. Le plus haut taux d'*E coli* résistant à la fluoroquinolone s'observe en Colombie-Britannique.

A three-day course of trimethoprim-sulfamethoxazole (TMP-SMX) is recommended as first-line empirical treatment for acute cystitis in adult women in North America, where resistance of *Escherichia coli* to TMP-SMX is less than 20% (1,2). TMP-SMX resistance has increased over time (3,4), with a resulting shift toward the use of other antibiotics for acute cystitis, including fluoroquinolones (5,6). There is concern that this may promote the more rapid emergence of fluoroquinolone-resistant uropathogens and reduce the effectiveness of fluoroquinolones in treating more serious infections (7,8).

Trying to determine the rate of TMP-SMX resistance in community-acquired cases of acute cystitis has been problematic. Widely varying rates of resistance have been reported in different countries (9) and from different regions within the same country (4). In Canada, a study of outpatients attending tertiary care hospitals found that 19% of *E coli* isolates were resistant to TMP-SMX; however, the study included men and children (10). Two other community-based studies found that 8% (11) and 11% (12) of *E coli* isolates were resistant to TMP-SMX. We conducted a national study of community-acquired

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TABLE 1
Antibiotic resistance in urine isolates from adult women across Canada with community-acquired urinary tract infections

Characteristic	n	Any resistance	%
Total	2199	1079	49.1
Age			
16–49 years	928	392	42.2
50–64 years	409	204	49.9
≥65 years	862	483	56.0*
Region			
British Columbia	451	238	52.8
Western provinces†	367	186	50.7
Ontario	498	246	49.4
Eastern provinces‡	802	361	45.0§

**P<0.001; †Saskatchewan and Manitoba; ‡New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland; §P=0.045*

urinary tract infections to update TMP-SMX resistance rates and determine whether resistance was sufficiently high in some regions to warrant changes to empirical treatment recommendations.

METHODS

Canadian laboratories providing microbiology services were contacted by mail in 2004. Some laboratories had participated in a previous study (12), while others were identified from Health Canada and Internet listings of commercial laboratories. A faxback form was provided to indicate interest in participation or a request for additional information. Two follow-up reminder letters were sent to nonresponders.

Each laboratory was asked to provide 100 recent urine culture and susceptibility reports positive for significant bacterial growth by their usual criteria. They were asked to limit reports to those submitted from family physicians' offices, and to exclude nursing homes, hospitalized patients and hospital outpatient departments. Only one report per patient was included. The culture report provided the patient age, sex, and city and province of residence. Where no patient address was provided, the laboratory address was used. Patient names were removed from reports. The organism, colony count and antibiotic susceptibility was determined from the reports. Organisms with intermediate susceptibility were considered susceptible. The analysis was limited to adult women 16 years of age and older.

Categorical variables were described using frequencies and compared with χ^2 testing (STATA Release 6.0, StataCorp, USA). A wide range of oral and parenteral antibiotic susceptibilities were reported. Antimicrobial resistance were determined to be 'any resistance' (resistance to at least one antibiotic reported) or 'multidrug resistance' (resistance to two or more antibiotics reported). In assessing regional differences, the analysis was limited to four antibiotic classes (ampicillin, TMP-SMX, fluoroquinolones and nitrofurantoin). Multiple logistic regression was used to control for age and other differences between regions. Ethics approval was obtained from the Mount Sinai Hospital Research Ethics Board.

RESULTS

Of the 43 laboratories contacted, 21 (48.8%) provided urine culture reports for 2199 women from across Canada (Table 1). All cultures were obtained in 2004. The majority of reports were from Ontario, Nova Scotia and British Columbia. No reports were received from Alberta. Because of the small numbers of isolates from some provinces, adjacent provinces were grouped together into regions to examine regional variations in resistance. Quebec was excluded from the regional analysis because too few reports were received. Community-based laboratories provided all of the reports from Ontario, while hospital laboratories provided all of the reports from the eastern provinces. The mean age of women was 55.2 years (range 16 to 100 years), with most women older than 50 years of age.

The most common organisms isolated were *E coli* (1634 [74.3%]), *Klebsiella pneumoniae* (156 [7.1%]), *Proteus mirabilis* (82 [3.7%]) *Enterococcoccus* species (70 [3.2%]) and *Staphylococcus saprophyticus* (20 [0.9%]). The remaining 237 (10.8%) isolates included *Acinetobacter*, *Citrobacter*, *Enterobacter* and group B streptococcus. Almost one-half of isolates were resistant to at least one antibiotic, while 660 (30.0%) were multidrug-resistant. Ampicillin resistance was most common (842 of 2107 isolates [40.0%]), followed by resistance to TMP-SMX (293 of 2069 isolates [14.2%]), cefazolin (121 of 1314 isolates [9.2%]), nitrofurantoin (187 of 2124 isolates [8.8%]) and fluoroquinolones (130 of 2069 isolates [6.3%]).

Resistance increased with age, and there was a trend toward higher levels of antibiotic resistance in the western provinces (P=0.045). Multidrug resistance was highest in British Columbia (170 of 451 [37.7%]) compared with the rest of Canada (465 of 1667 isolates [27.9%]; P<0.001). After adjusting for differences in patient age and organism distribution among the regions, antibiotic resistance remained higher in British Columbia (adjusted OR 1.30, 95% CI 1.03 to 1.63) than in other regions, as did multidrug resistance (adjusted OR 1.60, 95% CI 1.28 to 1.99).

E coli antibiotic resistance

There were 610 of 1634 (37.3%) *E coli* isolates resistant to at least one antibiotic and 415 of 1634 (25.4%) resistant to two or more antibiotics. Ampicillin resistance was reported in 512 of 1615 isolates (31.7%; 95% CI 29.4 to 34.0), 245 of 1613 isolates (15.2%; 95% CI 13.5 to 17.0) were resistant to TMP-SMX, 107 of 1557 isolates (6.9%; 95% CI 5.7 to 8.2) were resistant to fluoroquinolones, 53 of 1025 isolates (5.2%; 95% CI 3.9 to 6.7) were resistant to cefazolin, and 22 of 1614 isolates (1.4%; 95% CI 0.9 to 2.1) were resistant to nitrofurantoin. Because the level of ciprofloxacin-resistant *E coli* (100 of 1385 [7.2%]) was similar to overall fluoroquinolone resistance (P=0.71), the latter was used in further analyses to make use of all available data.

Regional variations in *E coli* antibiotic resistance were found for TMP-SMX and fluoroquinolones (Table 2). TMP-SMX resistance reached the 20% threshold (suggested by the Infectious Diseases Society of America for consideration of alternative first-line agents for empirical treatment [1]) in British Columbia, and approached this level in Ontario. TMP-SMX-resistant *E coli* were also more common in women 50 to 64 years of age (52 of 291 [17.9%]) and in those 65 years of age and older (103 of 572 [18.0%]) when compared with younger women (90 of 750 [12.0%]; P=0.004). Adjusting for age differences among regions did not affect the results. TMP-SMX resistance remained higher in British Columbia (adjusted OR 1.94, 95% CI 1.34 to 2.81) and Ontario (adjusted OR 1.61, 95% CI 1.10 to 2.35) than in the eastern provinces.

TABLE 2
Regional variations in *Escherichia coli* antibiotic resistance in community-acquired urinary tract infections in Canada

Resistance	British Columbia	Western provinces	Ontario	Eastern provinces	P
Any resistance, n (%)	143 of 342 (41.8)	105 of 269 (39.0)	146 of 371 (39.4)	189 of 592 (31.9)	0.01
Multidrug resistance, n (%)	102 of 342 (29.8)	55 of 269 (20.5)	92 of 371 (24.8)	150 of 592 (25.3)	0.07
Antibiotic-specific resistance, n (%)					
Ampicillin	113 of 342 (33.0)	84 of 269 (31.2)	132 of 371 (35.6)	159 of 573 (27.8)	0.07
TMP-SMX	70 of 342 (20.5)	35 of 269 (13.0)	62 of 370 (16.8)	65 of 572 (11.4)	0.001
Fluoroquinolones	54 of 341 (15.8)	7 of 216 (3.2)	26 of 368 (7.1)	17 of 572 (3.0)	<0.001
Nitrofurantoin	8 of 342 (2.3)	1 of 269 (0.4)	5 of 371 (1.4)	8 of 572 (1.4)	0.24

TMP-SMX Trimethoprim-sulfamethoxazole

TABLE 3
Changes in community-acquired *Escherichia coli* antibiotic resistance between 2002 and 2004

	Previous study (2002) (12)	Current study (2004)	P
TMP-SMX, n (%)			
Any resistance	20 of 183 (10.9)	245 of 1613 (15.2)	0.12
Age group			
16 to 49 years	12 of 116 (10.3)	90 of 750 (12.0)	0.61
50 years or older	8 of 67 (11.9)	155 of 863 (18.0)	0.21
Region			
Western Canada	9 of 49 (18.4)	105 of 611 (17.2)	0.83
Eastern Canada	11 of 132 (8.3)	127 of 942 (13.5)	0.10
Fluoroquinolone, n (%)			
Any resistance	2 of 178 (1.1)	107 of 1557 (6.9)	0.001*
Age group			
16 to 49 years	0 of 107 (0.0)	22 of 712 (3.1)	0.10*
50 years or older	2 of 71 (2.8)	85 of 845 (10.1)	0.06*
Region			
Western Canada	0 of 52 (0.0)	61 of 557 (11.0)	0.006*
Eastern Canada	1 of 124 (0.8)	43 of 940 (4.6)	0.052*

**Fisher's exact test. TMP-SMX Trimethoprim-sulfamethoxazole*

Regional variations in fluoroquinolone resistance were also seen, with significantly higher levels of resistance in British Columbia (P<0.001). Fluoroquinolone resistance increased with age, with 22 of 712 (3.1%) *E coli* isolates resistant to fluoroquinolones in women 16 to 49 years of age, 20 of 283 (7.1%) isolates in women 50 to 64 years of age, and 65 of 562 (11.6%) isolates in women 65 years of age and older (P<0.001). Resistance ranged from a low of 1.1% (three of 267) in women 16 to 49 years of age in eastern provinces to a high of 24.3% (36 of 148) in women 65 years of age and older from British Columbia (P<0.001; Fisher's exact test). Results were similar when the analysis was repeated using ciprofloxacin instead of all fluoroquinolones. After controlling for age, fluoroquinolone resistance remained higher in British Columbia than elsewhere in Canada (adjusted OR 3.88, 95% CI 2.57 to 5.84).

Although culture reports came from 18 different communities in British Columbia, 80% came from two communities. The rate of fluoroquinolone-resistant *E coli* was lower in the two communities (38 of 278 [13.7%]) than in the remaining 16 communities combined (16 of 63 [25.4%]; P=0.02), indicating that the high rate of fluoroquinolone resistance in British Columbia was not due to a few communities with high resistance levels. To exclude the possibility that nursing home residents had been included, the analysis was repeated excluding women 65 years of age and older. Fluoroquinolone-resistant *E coli* was also higher in women younger than 65 years of age in British Columbia (18 of 193 [9.3%]) than in the western provinces (three of 138 [2.2%]), Ontario (15 of 273 [5.5%]) and the eastern provinces (four of 346 [1.1%]; P<0.001).

To assess whether *E coli* resistance rates were increasing, the results were compared with a previous study (Table 3) (12). Women 50 to 64 years of age and those 65 years of age and older were combined due to small numbers in the earlier study. There were no significant differences by age or region in TMP-SMX-resistant *E coli* between the two time periods, although there was a trend toward increased TMP-SMX resistance overall. There was a significant increase in fluoroquinolone-resistant *E coli* overall and by region.

DISCUSSION

The Infectious Diseases Society of America has recommended TMP-SMX for the first-line empirical antibiotic treatment of acute cystitis, unless the level of TMP-SMX-resistant *E coli* in an area exceeds 20% (1). While the clinical relevance of this threshold has been questioned (8), treatment failure is more common in women with TMP-SMX-resistant *E coli* (13). The present study found that 15% of *E coli* isolates from adult women with community-acquired urinary tract infections in Canada are currently resistant to TMP-SMX. As a result, no changes in prescribing recommendations for Canadian physicians are needed at present.

There were some areas of the country and some age groups where *E coli* TMP-SMX resistance was higher. The level of TMP-SMX-resistant *E coli* in British Columbia was 20%. This was not due to differences between British Columbia and other regions in terms of population age. TMP-SMX-resistant *E coli* was also common in women 65 years of age and older. The levels of TMP-SMX in these two groups are at, or are approaching, the threshold suggested by the Infectious Diseases Society of America for considering alternatives to TMP-SMX in the empirical treatment of acute cystitis. Ongoing monitoring will be needed to determine whether resistance levels increase further in these groups.

However, it is unclear whether TMP-SMX resistance in Canada has increased in community-acquired urinary tract infections in adult women. A study by Zhanel et al (10) found that 19% of *E coli* isolates were TMP-SMX-resistant, but the sample included men and children. Separate results for adult women by age groups were not reported. A 1997 study of urinary tract isolates from family physicians' offices in southern Ontario found that 8.2% of *E coli* were TMP-SMX-resistant, but the age and sex of the population was not described (11). A comparison of the current study with our previous study of adult women (12) found some increase in TMP-SMX resistance, although the change was not statistically significant. In addition, there were differences in how cultures were obtained in the two studies.

In our previous study (12), urine cultures were obtained from clinically diagnosed cases of acute uncomplicated cystitis, whereas the current study used pooled urine cultures submitted to laboratories without clinical information. A study of all urinary tract infections in women seen in general practice found that 27% had complicating factors (14). The occurrence of TMP-SMX-resistant *E coli* was two to three times more likely in these women. A study based in New Zealand (15) also found lower levels of TMP-SMX resistance in clinically assessed cases of uncomplicated urinary tract infection compared with pooled community laboratory specimens. Thus, the suggestion of higher TMP-SMX resistance in the present study may also have been due to the use of pooled cultures.

The increase in the rate of fluoroquinolone-resistant *E coli* between the two time periods was significant. The level of fluoroquinolone-resistant *E coli* was 7%. This is higher than the levels of 1% to 1.8% reported in previous Canadian studies (10-12). We found that 10% of *E coli* isolates were fluoroquinolone-resistant in women older than 65 years of age, and this level was found to be 16% in British Columbia. While we were not able to rule out that some nursing home patients were included in the sample, fluoroquinolone resistance was higher in British Columbia even in younger women.

Reasons for the high level of fluoroquinolone resistance in British Columbia were not identified. However, prescriptions for fluoroquinolone antibiotics in British Columbia increased by 44% between 1996 and 2000 (16). Because prior fluoroquinolone exposure is a risk factor for fluoroquinolone resistance (17), changes in prescription practices in British Columbia in community-acquired urinary tract infections may have contributed to the higher level of resistance. If confirmed, prescribing restrictions may be needed to prevent further increases in fluoroquinolone-resistant *E coli*.

Resistance of *E coli* to nitrofurantoin has remained low over the years (8) and was also uncommon in the current study. However, physicians prescribe antibiotics empirically in acute cystitis before knowing the causative organism. We found that 9% of all isolates were resistant to nitrofurantoin overall. Greater use of this antibiotic has been suggested to limit fluoroquinolone use (8), but additional research has been recommended to address questions about overall effectiveness and safety (1,2,8). Other alternatives include beta-lactam antibiotics, although they are generally considered to be less effective (2,8).

The major limitation of the present study was the use of pooled laboratory specimens. However, this method has also been used in other studies that have provided estimates of antibiotic resistance levels in *E coli* (4,10,11). Although the use of pooled laboratory specimens may overestimate resistance levels (15), this provides greater confidence in the conclusion that the level of TMP-SMX-resistant *E coli* in acute cystitis seen by family physicians in Canada is significantly less than 20%.

CONCLUSIONS

TMP-SMX continues to be an appropriate first-line empirical antibiotic treatment for acute uncomplicated cystitis in adult women in Canada, as resistance levels remain below 20%. The level of fluoroquinolone-resistant *E coli* in community-acquired urinary tract infections should be monitored, and the apparent high levels of fluoroquinolone resistance in British Columbia should be confirmed to determine whether prescribing restrictions are warranted. Future studies should use urine cultures from clinically confirmed cases of acute uncomplicated cystitis to avoid overestimating resistance rates.

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