Escherichia coli antimicrobial susceptibility profile and cumulative antibiogram to guide empirical treatment of uncomplicated urinary tract infections in women in the province of Québec, 2010–15

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Objectives: Empirical treatment of uncomplicated urinary tract infections (UTIs) in women should be based on local susceptibility data. We aimed to generate regional and provincial cumulative antibiograms combining data from different laboratory information systems and determine the impact of basic patient characteristics on susceptibility results.

Methods: All positive urine samples for Escherichia coli obtained from women aged 18–65 years old in outpatient settings between 1 April 2010 and 31 March 2015 from four hospitals in Quebec, Canada, were included. The cumulative antibiogram for ciprofloxacin, nitrofurantoin and trimethoprim/sulfamethoxazole was calculated. A clinically significant difference in susceptibility profile was defined as factor(s) that lowered the susceptibility proportion below 80%.

Results: A total of 36293 positive urine cultures were analysed. In the last year of the study, the proportion of susceptibility for ciprofloxacin, nitrofurantoin and trimethoprim/sulfamethoxazole was 90.3%, 95.4% and 81.9%, respectively. The susceptibility proportion was <80% for trimethoprim/sulfamethoxazole in the Montreal region (73.4%; 95% CI 71.1%–75.9%), whereas it remained >80% for the other regions. A significant decrease in susceptibility with time was identified for ciprofloxacin (92.1%–90.3%, P<0.001) and nitrofurantoin (97.1%–95.4%, P<0.001). Increasing age, recent hospitalization and site of collection were associated with an increase in resistance for certain antibiotics.

Conclusions: Overall, all first-line antimicrobials remain acceptable choices for empirical treatment of uncomplicated UTIs in women in Quebec. The regional variability in susceptibility data within a single province emphasizes the importance of local susceptibility data to inform the development of empirical treatment guidelines for UTIs.

Introduction

Urinary tract infections (UTIs) are the most prevalent bacterial infections encountered in adult primary care throughout the world. Women are known to be more prone to UTI than men, with a 50% chance of a UTI in their lifetime.1,2 Most cases of community-acquired cystitis in adult women are caused by Enterobacteriaceae, with Escherichia coli being the most frequently isolated microorganism.1,3–7 Empirical treatment for cystitis is often prescribed without a urine culture or before urine culture results are available. According to treatment guidelines, empirical treatment choices should be based on local or regional susceptibility data.1,6–10 Studies on the susceptibility profile of community-acquired urinary isolates of E. coli have rarely been done using a large study population from multiple hospital centres.11,12 In Canada, most antimicrobial resistance surveillance systems have focused on healthcare-associated isolates.5,11,13 Local information about the susceptibility profile of E. coli is seldom available to prescribers, forcing them to rely on provincial, national or international data and guidelines. The IDSA treatment guidelines recommend
fosfomycin, nitrofurantoin, pvmecillinam or trimethoprim/sulfa-
methoxazole for empirical treatment of acute uncomplicated
pyelitis.1,14 Fluoroquinolones and β-lactams are recommended
only if the previous antibiotics cannot be prescribed.

Although local susceptibility data are not always made avail-
able to physicians, the data are present in each hospital’s micro-
biology laboratory information system (LIS). In the province
of Quebec, laboratories have different LISs and pooling the data
to produce a provincial antibiogram has been challenging.
However, the last few years have seen some hospitals in the prov-
ince acquiring infection control software (Nosokos; Nosotech,
Rimouski, Canada) that allows them to track nosocomial infec-
tions and transmit data to the provincial public health authorities.
This software also uses a dictionary that can convert the data
from each hospital into a common terminology.

The objective of this study was to generate regional and provin-
cial cumulative antibiograms combining data from different LISs
and determine the impact of basic patient characteristics on sus-
cceptibility results.

Methods

Study population

All urine samples obtained in a community setting, positive for E. coli at
>10^5 cfu/L from 1 April 2010 to 31 March 2015 (5 hospital fiscal years)
were included. Community acquisition was defined as samples taken
from patients in emergency departments, in hospital outpatient clinics
and community clinics. Specimens collected from urinary catheters were
excluded when that information was available in the hospital’s LIS. Other
exclusion criteria included cultures from long-term care facilities and nurs-
ing homes, prior hospitalization in the last 30 days and cultures that were
collected more than 2 days after arrival to the emergency department.
Samples with more than two different bacterial species were considered
contaminated and were excluded from the analysis. For our main objective,
adult women were defined as women that were between 18 and
65 years of age at the time of sample collection.

Four hospitals that use Nosokos were selected to represent different
regions of the province: The McGill University Health Center (MUHC; large
urban); The Centre Hospitalier Universitaire de Québec (CHUQ) and l’Hôpital
de l’Enfant-Jésus de Québec (CHA) (smaller urban); and l’Hôpital régional du
CSSS Rimouski–Neigette (CHRR; remote/rural). Two different LISs are in use in
these hospitals: Cerner Millennium PathNet General Laboratory (Cerner
Corporation, Kansas City, USA) (one hospital) and TD-LIMS (Technidata,
Montbonnot, France) (three hospitals). For each isolate, the following infor-
mation was available: age of patient, sex of patient, patient’s prior admission
date, sample collection date and susceptibility testing interpretation for all
antimicrobials tested by each laboratory (susceptible, intermediate or resist-
ant). Isolates were identified and submitted for susceptibility testing by each
laboratory using their routine methods. For all laboratories, identification of
E. coli was mostly done by usual phenotypic testing15 or use of the Vitek2
system (bioMérieux, France). Susceptibility testing was also mostly done by
the Vitek2 system using appropriate panels or a disc diffusion method follow-
ing CLSI guidelines and breakpoints.16,17 Every laboratory in Quebec participates
in the provincial external quality control programme.

Analysis

Antimicrobials of interest were ciprofloxacin, nitrofurantoin and trimethop-
prim/sulphamethoxazole. Pvmecillinam and fosfomycin were not included
in this study because the first one is not available in Canada and suscep-
tibility testing for the second was not routinely done throughout the study
period. The proportion of susceptible isolates was calculated as the
number of susceptible isolates for a given antimicrobial divided by the
total number of isolates that were tested for the same agent. Duplicates
were considered as more than one isolate per patient per administrative
year. According to the CLSI guidelines,18 only the first isolate was retained.
When more than one E. coli was reported for a given specimen, only the
first one—as randomly listed in the LIS—was kept.

A two-sample test of proportion was used to compare susceptibility
percentages obtained between two groups. A χ^2 for trend test was per-
formed to ascertain year-to-year changes of susceptibility proportions.
All analyses were performed using STATA statistical software, version
14.0 (StatCorp, TX, USA).

Ethics

Ethics approval was obtained from every participating health centre’s ethics
committee prior to the beginning of this study (no. MP-CUSM-14-412-PED).

Results

The initial database included 100 080 E. coli isolates from urine
cultures. Two strains of E. coli were reported in the same sample
254 (2.5%) times. There were 12 141 (12.1%) duplicate isolates from the
same year that were removed. Finally, 140 (0.1%) speci-
mens were considered contaminated and were removed, leaving
85 255 (85.2%) E. coli isolates from one unique specimen per
patient per fiscal year. From these, 69 684 were from females
and, of those, 36 293 were from females between 18 and
65 years, not hospitalized in the previous year. Other demo-
graphic variables are presented in Table 1.

Table 1. Demographic and epidemiological characteristics of 85 255
patients with a urinary isolate of E. coli in the province of Quebec from 2010
to 2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>69 684 (81.7)</td>
</tr>
<tr>
<td>male</td>
<td>11 755 (13.8)</td>
</tr>
<tr>
<td>unknown</td>
<td>3816 (4.5)</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
</tr>
<tr>
<td>&lt;18 years old</td>
<td>8925 (10.5)</td>
</tr>
<tr>
<td>18–65 years old</td>
<td>44046 (51.6)</td>
</tr>
<tr>
<td>&gt;65 years old</td>
<td>32 284 (37.9)</td>
</tr>
<tr>
<td>No history of recent hospitalization</td>
<td>81 240 (95.3)</td>
</tr>
<tr>
<td>Financial year</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>15 167 (17.8)</td>
</tr>
<tr>
<td>2011</td>
<td>15 795 (18.5)</td>
</tr>
<tr>
<td>2012</td>
<td>16 983 (19.9)</td>
</tr>
<tr>
<td>2013</td>
<td>18 235 (21.4)</td>
</tr>
<tr>
<td>2014</td>
<td>19 075 (22.4)</td>
</tr>
<tr>
<td>Study population</td>
<td>36 293 (42.6)</td>
</tr>
</tbody>
</table>
Cumulative antibiograms for community-acquired *E. coli* from adult women are presented in Table 2. Overall, all three antibiotics analysed remain active against 80% of the isolates tested. Nitrofurantoin appears to be the most active agent with an overall proportion of susceptibility 95% over the 5 years, compared with only 82% for trimethoprim/sulfamethoxazole. There is evidence that susceptibility decreased with time. When compared with 2010, the 2014 susceptibility proportions are lower for ciprofloxacin (from 92.1% to 90.3%, \( P \) for trend \( \leq 0.001 \)) and nitrofurantoin (from 97.1% to 95.4% \( P \) for trend \( \leq 0.001 \)).

There is some variability in the annual susceptibility profile of each antibiotic by laboratory, but the 20% threshold of resistance is crossed only in the case of trimethoprim/sulfamethoxazole at the MUHC in Montreal. The proportion of susceptibility for trimethoprim/sulfamethoxazole at MUHC varied from 78.1% in 2010 to 73.4% in 2014 (\( P \) for trend = 0.007). Other increasing resistance proportions by hospitals are presented in Table 2.

The impact of age, site of collection and recent hospitalization on the proportion of susceptibility was ascertained and results are presented in Table 3. The only factor that increases the resistance percentage of an antimicrobial above the 20% cut-off is recent hospitalization for trimethoprim/sulfamethoxazole (77.3% susceptibility; 95% CI = 74.8%–79.7%). Nonetheless, there is a significant decrease in ciprofloxacin susceptibility when recently hospitalized patients (84.8% susceptibility; 95% CI = 82.6%–86.7%) are compared with women who were not (91.3% susceptibility; 95% CI = 91.0%–91.6%). Age also affects susceptibility proportions. When compared with the group aged 18–24 years old, an increase in age is statistically associated with higher resistance percentages for ciprofloxacin and nitrofurantoin. This increase is more important for ciprofloxacin where the susceptibility percentage is 94.4% in 2014.

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**Table 2.** Susceptibility profile of 36293 isolates of *E. coli* isolated from urine samples of women aged 18–65 years old in the province of Quebec from 2010 to 2015, by laboratory

<table>
<thead>
<tr>
<th>Laboratory and fiscal year (number of isolates)</th>
<th>Percentage susceptibility (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ciprofloxacin</td>
</tr>
<tr>
<td><strong>All laboratories (36293)</strong></td>
<td></td>
</tr>
<tr>
<td>2010 (6057)</td>
<td>92.1 (91.4–92.8)</td>
</tr>
<tr>
<td>2011 (6507)</td>
<td>92.5 (91.8–93.1)</td>
</tr>
<tr>
<td>2012 (7323)</td>
<td>91.4 (90.8–92.1)</td>
</tr>
<tr>
<td>2013 (8001)</td>
<td>90.7 (90.1–91.3)</td>
</tr>
<tr>
<td>2014 (8405)</td>
<td>90.3 (89.7–91.0)</td>
</tr>
<tr>
<td><strong>CHA (13627)</strong></td>
<td></td>
</tr>
<tr>
<td>2010 (2363)</td>
<td>92.9 (91.7–93.9)</td>
</tr>
<tr>
<td>2011 (2491)</td>
<td>93.0 (91.9–94.0)</td>
</tr>
<tr>
<td>2012 (2697)</td>
<td>92.4 (91.4–93.4)</td>
</tr>
<tr>
<td>2013 (2961)</td>
<td>91.7 (90.6–92.6)</td>
</tr>
<tr>
<td>2014 (3115)</td>
<td>91.4 (90.4–92.4)</td>
</tr>
<tr>
<td><strong>CHRR (2558)</strong></td>
<td></td>
</tr>
<tr>
<td>2010 (482)</td>
<td>94.2 (91.7–96.1)</td>
</tr>
<tr>
<td>2011 (483)</td>
<td>94.0 (91.5–95.9)</td>
</tr>
<tr>
<td>2012 (521)</td>
<td>94.6 (92.3–96.4)</td>
</tr>
<tr>
<td>2013 (525)</td>
<td>91.4 (88.7–93.7)</td>
</tr>
<tr>
<td>2014 (547)</td>
<td>92.5 (90.0–94.6)</td>
</tr>
<tr>
<td><strong>CHUQ (13797)</strong></td>
<td></td>
</tr>
<tr>
<td>2010 (2056)</td>
<td>93.0 (91.8–94.7)</td>
</tr>
<tr>
<td>2011 (2326)</td>
<td>92.6 (91.4–93.6)</td>
</tr>
<tr>
<td>2012 (2766)</td>
<td>91.7 (90.6–92.7)</td>
</tr>
<tr>
<td>2013 (3252)</td>
<td>91.6 (90.6–92.5)</td>
</tr>
<tr>
<td>2014 (3397)</td>
<td>91.0 (89.9–91.9)</td>
</tr>
<tr>
<td><strong>MUHC (6311)</strong></td>
<td></td>
</tr>
<tr>
<td>2010 (1156)</td>
<td>88.2 (86.2–90.0)</td>
</tr>
<tr>
<td>2011 (1207)</td>
<td>90.7 (88.9–92.3)</td>
</tr>
<tr>
<td>2012 (1339)</td>
<td>87.5 (85.6–89.2)</td>
</tr>
<tr>
<td>2013 (1263)</td>
<td>86.2 (84.1–88.0)</td>
</tr>
<tr>
<td>2014 (1346)</td>
<td>85.3 (83.3–87.2)</td>
</tr>
</tbody>
</table>

*χ² test for trend from 2010 to 2014, \( P < 0.05 \).

Trimethoprim alone was tested in 2010.
women aged 18–24 years old compared with 86.3% in the group aged 55–65 years old. As for the site of collection, there is a slight increase in trimethoprim/sulfamethoxazole resistance when specimens are collected in the emergency department (81.3% susceptibility; 95% CI = 80.3%–82.3%) compared with outpatient clinics (82.5% susceptibility; 95% CI = 82.1%–83.0%).

### Discussion

This study shows that by using healthcare-associated infection software one is able to pool individual laboratory data relatively easily to generate regional cumulative antibiograms. Using these cumulative antibiograms, we were able to see the high proportion of *E. coli* susceptibility to nitrofurantoin. This could be explained by the fact that nitrofurantoin is actually not prescribed much in Quebec, as shown in the Public Health Agency of Canada’s *Human Antimicrobial Drug Use Report 2012/2013*. According to the report, in Quebec, nitrofurantoin is the least prescribed drug (18.19 prescriptions/1000 inhabitants) of the three drugs studied, compared with 90.9 prescriptions/1000 inhabitants for ciprofloxacin and 22.25 prescriptions/1000 inhabitants for trimethoprim/sulfamethoxazole. Some authors have also argued that the many mechanisms of action of nitrofurantoin would reduce the ability of *E. coli* to develop resistance and could explain why susceptibility remains high. Although nitrofurantoin cannot be used for the treatment of pyelonephritis and in patients with kidney failure, its use should be encouraged in the context of a low level of resistance and limited ecological collateral damage.

In the context of increasing antimicrobial resistance, this study allowed us to confirm that, overall, the targeted antimicrobials remained acceptable choices as empirical treatment for uncomplicated cystitis in Quebec. Nonetheless, the rate of *E. coli* resistance to trimethoprim/sulfamethoxazole in Montreal emphasizes the importance of obtaining local susceptibility profiles, as there may be clinically significant variation between different regions of a single province. The actual impact that these results will have on clinical practice is hard to predict. The threshold of 20% resistance is often cited in the literature as the maximum proportion of isolates that can be resistant to an agent without compromising empirical treatment success, but it is based on expert opinion and mathematical models. In any case, these results could encourage physicians from the region of Montreal to order urine cultures before prescribing trimethoprim/sulfamethoxazole, particularly if women were recently hospitalized.

Studies similar to ours have confirmed that age, gender, recent hospitalization and geographical location are risk factors that influence resistance in urine cultures. Toner *et al*. showed that male gender, increasing age and hospitalization status modified the susceptibility of uropathogens to empirical treatment in the UK. *E. coli* showed increased resistance to fluoroquinolones, amoxicillin and trimethoprim/sulfamethoxazole, while carbapenems and nitrofurantoin remained effective treatments for UTIs. Kumar *et al*. analysed similar risk factors such as age and sex in hospitalized patients rather than community-acquired infections and showed the increasing resistance of uropathogens in women to fluoroquinolones and trimethoprim/sulfamethoxazole; however, nitrofurantoin was not examined. Zhanel *et al*. found that age, gender and geographical location were risk factors for antibiotic resistance in outpatient isolates of *E. coli*. The authors showed that the use of fluoroquinolones, trimethoprim/sulfamethoxazole and nitrofurantoin were still optimal in Canada. However, their study included only 280 isolates from Canada that had been collected between 2003 and 2004. Moreover, they did not stratify Canada’s data into provinces or regions confirming the importance of our present results. Sanchez *et al*. had a comparable surveillance study in the USA with similar resistance results for the treatment of outpatient UTI with nitrofurantoin,
trimethoprim/sulfamethoxazole and ciprofloxacin. However, their data were not stratified by regions, while our data show that there can be potentially clinically significant differences in resistance percentages within a single province. Our study had the advantage of using readily available data without the need for complex procedures for data collection. It would theoretically be possible to automate the process so that cumulative antibiogram data would be generated and made available periodically for every region in the province. In addition, the use of LIS data and software could be particularly interesting for the implementation of other surveillance programmes for the emergence of resistance in community-acquired infections, as there are generally few surveillance programmes for this setting.

There are a few limitations to this study. First, there were no clinical data available. This means that there was no way to differentiate from uncomplicated UTI. Because there is no recommendation to systematically collect a urine specimen from patients with uncomplicated UTI, this could have caused an increase in the resistance proportions calculated and resistance for uncomplicated cases might be lower. Moreover, there was no way to account for the probable inclusion of pregnant women with asymptomatic bacteriuria. This could also have had an impact on the susceptibility data reported. Second, because all isolates were not sent to a central laboratory for identification and susceptibility testing, it is possible that some isolates were misidentified or had incorrect susceptibility testing interpretations. Nonetheless, because E. coli in urine are easy to identify and test for resistance and, with >35,000 isolates included in this analysis, it is unlikely that this had a major impact on the pooled results. A third limitation is that because we were using passively collected data, there was some missing information about gender. As these isolates represented <5% of specimens, it is unlikely that this would have significantly modified the pooled susceptibility percentages. Another limitation is that, although it was possible to manage duplicate patients within one laboratory with Nosokos, it is still possible that the same patient had a urine sample analysed in more than one laboratory and thus provided duplicate information. Beside the two laboratories from Quebec City, it is very unlikely that this situation occurred in the other two laboratories given the large distance that separates them. Finally, although we tried to restrict our analyses to isolates that represented community-acquired infections, it is possible that some isolates were from women who had been hospitalized in another hospital in the 30 days prior to sample collection. Some of these women may even have received antibiotics in the weeks prior to their UTI. These factors could potentially have increased the proportion of resistance that we have calculated.

Conclusions
This study confirmed that, overall, ciprofloxacin, nitrofurantoin and trimethoprim/sulfamethoxazole can still be used as the empirical, first-line treatment for uncomplicated cystitis in adult women in Quebec. Given our data, trimethoprim/sulfamethoxazole might need to be used more cautiously in the Montreal region. Nitrofurantoin might emerge as a more appealing alternative in the context of increasing resistance.

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Transparency declarations
None to declare.

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References
Cumulative antibiogram of community-acquired *E. coli*


