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

Gaelle Delisle1, Caroline Quach1,2, Marc-Christian Domingo3,4, Alexandre A. Boudreau4,5, Marie Gourdeau4,5, Harold Bernatchez6 and Christian Lavallée7*

1Research Institute, McGill University Health Centre, McGill University, 1001 Boulevard Décarie, Montréal, Québec H4A 3J1, Canada; 2Epidemiology, Biostatistics & Occupational Health, McGill University, 1001 Boulevard Décarie, Montréal, Québec H4A 3J1, Canada; 3Institut national de santé publique du Québec, 20045 Chemin Ste-Marie, Sainte-Anne-de-Bellevue, Québec H9X 3R5, Canada; Département de microbiologie- Infectiologie et d’Immunologie, Université Laval, 2325 Rue de l’Université, Ville de Québec, Québec G1V 0A6, Canada; 5CHU de Québec, Université Laval, 11 Côte du Palais, Ville de Québec, Québec G1R 2J6, Canada; 6CISSS Bas-St-Laurent, 150 Avenue Rouleau, Rimouski, Québec G5L 5T1, Canada; 7CIUSSS de l’Est-de-l’Île-de-Montréal, Université de Montréal, 5415 Boulevard l’Assomption, Montréal, Québec H1T 2M4, Canada

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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.1,3,6–7 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...
Cumulative antibiogram of community-acquired \textit{E. coli}

fosfomycin, nitrofurantoin, pivmecillinam or trimethoprim/sulfamethoxazole for empirical treatment of acute uncomplicated cystitis.\textsuperscript{1,14} Fluoroquinolones and \(\beta\)-lactams are recommended only if the previous antibiotics cannot be prescribed.

Although local susceptibility data are not always made available to physicians, the data are present in each hospital's microbiology 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 province acquiring infection control software (Nosokos; Nosotech, Rimouski, Canada) that allows them to track nosocomial infections 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 provincial cumulative antibiograms combining data from different LISs and determine the impact of basic patient characteristics on susceptibility results.

Methods

\textbf{Study population}

All urine samples obtained in a community setting, positive for \textit{E. coli} at \(>10^7 \text{ cfu/L}\) 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 nursing 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 information 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 resistant). Isolates were identified and submitted for susceptibility testing by each laboratory using their routine methods. For all laboratories, identification of \textit{E. coli} was mostly done by usual phenotypic testing\textsuperscript{15} 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 following CLSI guidelines and breakpoints.\textsuperscript{16,17} Every laboratory in Quebec participates in the provincial external quality control programme.

\textbf{Analysis}

Antimicrobials of interest were ciprofloxacin, nitrofurantoin and trimethoprim/sulfamethoxazole. Pivmecillinam and fosfomycin were not included in this study because the first one is not available in Canada and susceptibility 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,\textsuperscript{16} only the first isolate was retained. When more than one \textit{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 \(\chi^2\) for trend test was performed to ascertain year-to-year changes of susceptibility proportions. All analyses were performed using STATA statistical software, version 14.0 (StatCorp, TX, USA).

\textbf{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).

\textbf{Results}

The initial database included 100080 \textit{E. coli} isolates from urine cultures. Two strains of \textit{E. coli} were reported in the same sample 2544 (2.5\%) times. There were 12141 (12.1\%) duplicate isolates from the same year that were removed. Finally, 140 (0.1\%) specimens were considered contaminated and were removed, leaving 85255 (85.2\%) \textit{E. coli} isolates from one unique specimen per patient per fiscal year. From these, 69684 were from females and, of those, 36293 were from females between 18 and 65 years, not hospitalized in the previous year. Other demographic variables are presented in Table 1.

\begin{table}[h]
\centering
\begin{tabular}{lrr}
\hline
\multicolumn{1}{c}{\textbf{Characteristics}} & \multicolumn{1}{c}{\textbf{Number (\%)}} \\
\hline
\textbf{Gender} & & \\
\quad female & 69684 (81.7) \\
\quad male & 11755 (13.8) \\
\quad unknown & 3816 (4.5) \\
\hline
\textbf{Age category} & & \\
\quad <18 years old & 8925 (10.5) \\
\quad 18–65 years old & 44046 (51.6) \\
\quad >65 years old & 32284 (37.9) \\
\hline
\textbf{No history of recent hospitalization} & & \\
\quad No & 81240 (95.3) \\
\hline
\textbf{Laboratory} & & \\
\quad CHA & 28831 (33.8) \\
\quad CHRR & 7416 (8.7) \\
\quad CHUQ & 32611 (38.3) \\
\quad MUHC & 16397 (19.2) \\
\hline
\textbf{Financial year} & & \\
\quad 2010 & 15167 (17.8) \\
\quad 2011 & 15795 (18.5) \\
\quad 2012 & 16983 (19.9) \\
\quad 2013 & 18235 (21.4) \\
\quad 2014 & 19075 (22.4) \\
\hline
\textbf{Study population} & & 36293 (42.6) \\
\hline
\end{tabular}
\end{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 <0.001) and nitrofurantoin (from 97.1% to 95.4%, \( P \) for trend <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

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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>ciprofloxacin</th>
<th>nitrofurantoin</th>
<th>trimethoprim/sulfamethoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>All laboratories (36293)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 (6057)</td>
<td>92.1 (91.4–92.8)</td>
<td>97.1 (96.6–97.5)</td>
<td>83.1 (81.2–84.3)</td>
</tr>
<tr>
<td>2011 (6507)</td>
<td>92.5 (91.8–93.1)</td>
<td>97.4 (96.9–97.7)</td>
<td>82.3 (81.2–83.3)</td>
</tr>
<tr>
<td>2012 (7323)</td>
<td>91.4 (90.8–92.1)</td>
<td>96.3 (95.8–96.7)</td>
<td>82.8 (81.9–83.7)</td>
</tr>
<tr>
<td>2013 (8001)</td>
<td>90.7 (90.1–91.3)</td>
<td>95.6 (95.1–96.0)</td>
<td>82.7 (81.8–83.5)</td>
</tr>
<tr>
<td>2014 (8405)</td>
<td>90.3 (89.7–91.0)</td>
<td>95.4 (94.9–95.8)</td>
<td>81.9 (81.0–82.7)</td>
</tr>
<tr>
<td>CHA (13627)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 (2363)</td>
<td>92.9 (91.7–93.9)</td>
<td>97.2 (96.4–97.8)</td>
<td>b</td>
</tr>
<tr>
<td>2011 (2491)</td>
<td>93.0 (91.9–94.0)</td>
<td>97.5 (96.8–98.0)</td>
<td>83.8 (81.7–85.7)</td>
</tr>
<tr>
<td>2012 (2697)</td>
<td>92.4 (91.4–93.4)</td>
<td>95.9 (95.1–96.6)</td>
<td>85.8 (84.5–87.1)</td>
</tr>
<tr>
<td>2013 (2961)</td>
<td>91.7 (90.6–92.6)</td>
<td>95.8 (95.0–96.5)</td>
<td>84.2 (82.9–85.5)</td>
</tr>
<tr>
<td>2014 (3115)</td>
<td>91.4 (90.4–92.4)</td>
<td>95.5 (94.8–96.2)</td>
<td>84.9 (83.6–86.2)</td>
</tr>
<tr>
<td>CHRR (2258)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 (482)</td>
<td>94.2 (91.7–96.1)</td>
<td>99.4 (98.2–99.9)</td>
<td>90.2 (87.2–92.7)</td>
</tr>
<tr>
<td>2011 (483)</td>
<td>94.0 (91.5–95.9)</td>
<td>96.7 (94.6–98.1)</td>
<td>89.0 (85.9–91.7)</td>
</tr>
<tr>
<td>2012 (521)</td>
<td>94.6 (92.3–96.4)</td>
<td>97.5 (95.8–98.7)</td>
<td>87.1 (84.0–89.9)</td>
</tr>
<tr>
<td>2013 (525)</td>
<td>91.4 (88.7–93.7)</td>
<td>96.8 (94.9–98.1)</td>
<td>85.7 (82.4–88.6)</td>
</tr>
<tr>
<td>2014 (547)</td>
<td>92.5 (90.0–94.6)</td>
<td>97.4 (95.7–98.6)</td>
<td>87.9 (84.9–90.5)</td>
</tr>
<tr>
<td>CHUQ (13797)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2010 (2056)</td>
<td>93.0 (91.8–94.7)</td>
<td>97.6 (96.8–98.2)</td>
<td>84.3 (82.6–85.8)</td>
</tr>
<tr>
<td>2011 (2326)</td>
<td>92.6 (91.4–93.6)</td>
<td>98.0 (97.3–98.5)</td>
<td>82.8 (81.2–84.3)</td>
</tr>
<tr>
<td>2012 (2766)</td>
<td>91.7 (90.6–92.7)</td>
<td>97.2 (96.5–97.8)</td>
<td>83.3 (81.9–84.7)</td>
</tr>
<tr>
<td>2013 (3252)</td>
<td>91.6 (90.6–92.5)</td>
<td>96.8 (96.1–97.3)</td>
<td>83.5 (82.2–84.8)</td>
</tr>
<tr>
<td>2014 (3397)</td>
<td>91.0 (89.9–91.9)</td>
<td>96.2 (95.5–96.8)</td>
<td>81.3 (80.0–82.6)</td>
</tr>
<tr>
<td>MUHC (6311)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 (1156)</td>
<td>88.2 (86.2–90.0)</td>
<td>95.2 (93.8–96.4)</td>
<td>78.1 (75.6–80.5)</td>
</tr>
<tr>
<td>2011 (1207)</td>
<td>90.7 (88.9–92.3)</td>
<td>96.3 (95.0–97.3)</td>
<td>76.5 (74.0–78.9)</td>
</tr>
<tr>
<td>2012 (1339)</td>
<td>87.5 (85.6–89.2)</td>
<td>94.7 (93.4–95.8)</td>
<td>74.0 (71.6–76.3)</td>
</tr>
<tr>
<td>2013 (1263)</td>
<td>86.2 (84.1–88.0)</td>
<td>91.7 (90.0–93.1)</td>
<td>75.2 (72.7–77.6)</td>
</tr>
<tr>
<td>2014 (1346)</td>
<td>85.3 (83.3–87.2)</td>
<td>91.9 (90.4–93.3)</td>
<td>73.4 (71.1–75.9)</td>
</tr>
</tbody>
</table>

\( a \) \( \chi^2 \) test for trend from 2010 to 2014, \( P \leq 0.05 \).

\( b \) Trimethoprim alone was tested in 2010.
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 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,

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 79.79 prescriptions/1000 inhabitants for ciprofloxacin and 22.25 prescriptions/1000 inhabitants for trimethoprim/sulfamethoxazole.

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.
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 complications 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 isolated 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.

Nosotech extracted the data for this project, but had no input into the design of the study, the analysis of the data or the production of this manuscript.

References

Cumulative antibiogram of community-acquired *E. coli*


