Differences in antimicrobial susceptibility in *Escherichia coli* from Canadian intensive care units based on regional and demographic variables

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PRS Lagacé-Wiens, MR DeCorby, PJ Baudry, DJ Hoban, JA Karlowsky; the CAN-ICU study group, GG Zhanel. Differences in antimicrobial susceptibility in *Escherichia coli* from Canadian intensive care units based on regional and demographic variables. Can J Infect Dis Med Microbiol 2008;19(4):282-286.

OBJECTIVES: *Escherichia coli* resistance to antimicrobials varies according to many factors. *E coli* isolates from Canadian intensive care units (ICUs) were studied to determine the distribution and demographics associated with antimicrobial resistance in this population.
METHODS: The Canadian National Intensive Care Unit (CAN-ICU) study characterized pathogens isolated in Canadian ICUs from July 2005 to June 2006. *E coli* susceptibility to 10 antimicrobials was determined and a multivariate logistic regression model was designed to determine whether region, sex, isolation from a sterile site and age (younger than 30 years) were significantly associated with susceptibility to the tested antimicrobials, to multidrug resistance or pan-susceptibility.
RESULTS: Four hundred ninety-three *E coli* isolates, representing 12.6% of all isolates collected in the CAN-ICU study were examined. Susceptibilities were highest for meropenem and tigecycline (100%), cefepime (98.2%), piperacillin-tazobactam (97.0%), ceftriaxone (93.1%) and gentamicin (92.3%), and lowest for cefazolin (76.7%), trimethoprim-sulfamethoxazole (75.7%) and the fluoroquinolones (ciprofloxacin, 78.3%; and levofloxacin, 78.9%). In the multivariate model, fluoroquinolone resistance was lowest in patients younger than 30 years of age. Cefazolin and ceftriaxone susceptibility was lowest in Nova Scotia. Susceptibility to all tested antimicrobials was lowest in Nova Scotia and British Columbia. Isolation from a sterile site was associated with trimethoprim-sulfamethoxazole, piperacillin-tazobactam and multidrug resistance.
CONCLUSIONS: *E coli* antimicrobial susceptibility varies across Canadian ICUs. Age, region and site of infection should be considered when prescribing empirical antimicrobial therapy. For infections caused by or suspected to be caused by *E coli*, fluoroquinolones, cefazolin and sulfonamides should be avoided due to low susceptibilities. Local antimicrobial prescribing practices, in particular the liberal use of fluoroquinolones and cephalosporins, and inadequate infection control practices are likely reducing susceptibility rates.

Key Words: Escherichia coli; *Gram-negative; ICU; Infection; Resistance; Treatment*

Les différences de susceptibilité antimicrobienne de l'*Escherichia coli* aux unités de soins intensifs canadiennes d'après des variables régionales et démographiques

OBJECTIFS : La résistance de l'*Escherichia coli* aux antimicrobiens varie selon de nombreux facteurs. Des isolats d'*E. coli* provenant d'unités de soins intensifs (USI) canadiennes ont fait l'objet d'études pour déterminer la répartition et la démographie de la résistance antimicrobienne au sein de cette population.
MÉTHODOLOGIE : L'étude CAN-ICU aux unités de soins intensifs canadiennes a caractérisé les pathogènes isolés dans les USI canadiennes entre juillet 2005 et juin 2006. Les auteurs ont déterminé la susceptibilité de l'*E. coli* aux 11 (10) antimicrobiens et ont conçu un modèle de régression logistique multivariée pour déterminer si la région, le sexe, l'isolement d'un foyer stérile et l'âge (moins de 30 ans) s'associaient de manière significative à la susceptibilité aux antimicrobiens à l'étude, à la multirésistance ou à la pan-susceptibilité.
RÉSULTATS : Les auteurs ont examiné 493 isolats d'*E. coli*, représentant 12,6 % de tous les isolats prélevés pour l'étude CAN-ICU. Les susceptibilités les plus élevées étaient reliées au méropénem et à la tigécycline (100 %), au céfépime (98,2 %), à la pipéracilline-tazobactam (97,0 %), à la ceftriaxone (93,1 %) et à la gentamicine (92,3 %), et les plus faibles, à la céfazoline (76,7 %), au timéthoprim-sulfaméthoxazole (75,7 %) et aux fluoriquinolones (ciprofloxacine, 78,3 %, et lévofloxacine, 78,9 %). Dans le modèle multivarié, la résistance aux fluoriquinolones était la plus faible chez les patients de moins de 30 ans. C'est en Nouvelle-Écosse que la susceptibilité à la céfazoline et au ceftriaxone était la plus faible. La susceptibilité la plus faible à tous les antimicrobiens vérifiés s'observait en Nouvelle-Écosse et en Colombie-Britannique. L'isolement d'un foyer stérile s'associait au timéthoprim-sulfaméthoxazole, à la pipéracilline-tazobactam et à la multirésistance aux médicaments.
CONCLUSIONS : La susceptibilité antimicrobienne à l'*E. coli* varie selon les USI canadiennes. Il faudrait tenir compte de l'âge, de la région et du foyer d'infection avant de prescrire une thérapie antimicrobienne empirique. Dans le cas des infections causées par l'*E. coli* ou qu'on présume être causées par l'*E. coli*, il faudrait éviter les fluoroquinolones, la céfazoline et les sulfamides en raison de leur faible susceptibilité. Selon toute probabilité, les pratiques locales de prescription d'antimicrobiens, notamment l'utilisation libérale de fluoroquinolones et de céphalosporines, et les pratiques inadéquates de contrôle de l'infection réduisent les taux de susceptibilité.

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Received for publication September 6, 2007. Accepted May 30, 2008

Escherichia coli is the most commonly isolated, clinically relevant Gram-negative organism in Canadian intensive care units (ICUs), and is a common pathogen in ICUs worldwide (1-3). *E coli* can be responsible for urinary tract, wound, sterile site, respiratory tract and gastrointestinal infections. Furthermore, clinical isolates of *E coli* resistant to first-line agents is increasing; multidrug-resistant isolates – concurrent resistance to agents from two or more different antimicrobial classes – are common (2,4-6). Appropriate empirical antimicrobial choice must take into account local resistance patterns and other demographic variables such as patient age, site and severity of infection, sex, as well as previous antimicrobial use, stay in hospitals or personal care homes, and colonization with antimicrobial-resistant organisms (2,7). The purpose of the present study was to identify demographic and regional factors associated with susceptibility to antimicrobials commonly used as empirical therapy for infections caused by *E coli* in Canadian ICUs.

METHODS

Isolates

E coli isolates were obtained as part of the Canadian National Intensive Care Unit (CAN-ICU) study. The CAN-ICU study collected isolates between July 2005 and June 2006 from 19 clinical microbiology laboratories at hospitals with ICUs in eight provinces across Canada. However, broader geographical regions (British Columbia and Alberta [three hospitals], Saskatchewan and Manitoba [four hospitals], Ontario [five hospitals], Quebec and New Brunswick [four hospitals] and Nova Scotia [three hospitals]) were selected for the purpose of statistical analysis. Each laboratory was requested to collect up to 300 consecutive pathogens from blood, urine, tissue/wound and respiratory specimens submitted to the laboratory from ICU patients. Only one isolate of *E coli* per patient per site was accepted. Isolates had to be deemed clinically significant by the referring laboratory's current specimen workup protocol. In the case of urine specimens, a midstream urine specimen or a catheter urine specimen was considered significant if colony counts exceeded 1×10^8/L in the absence of significant contaminating flora, exceeded 1×10^7/L in the presence of symptoms compatible with urinary tract infection and in the absence of contaminating flora or if these criteria were not met, the specimen was considered to be significant if a special request was made for identification and susceptibility by the clinician. All urinary isolates from invasive procedures were considered significant. Demographic information collected with each isolate included patient age, sex and site of infection. Information on previous antimicrobial use, hospitalization duration and underlying medical conditions was not available. Isolates were shipped on Starswab II swabs (Starplex Scientific Inc, Canada), subcultured onto sheep blood agar (Oxoid Company, Canada) and stocked at –80°C in skim milk until batch antimicrobial susceptibility testing was performed.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) recommendations for broth microdilution testing of Enterobacteriaceae (8). Susceptibilities to cefazolin, cefepime, ceftriaxone, gentamicin, ciprofloxacin, levofloxacin, meropenem, piperacillin-tazobactam, tigecycline and trimethoprim-sulfamethoxazole were determined. Antimicrobials were obtained from either Sigma-Aldrich Ltd (Canada) or from the pharmaceutical manufacturer in the case of proprietary antimicrobials. Susceptibility breakpoints and determination of extended-spectrum beta-lactamase-producing (ESBL) phenotype for *E coli* were according to the CLSI recommendations (8). Because the CLSI-defined breakpoints for susceptibility did not exist for tigecycline, the Food and Drug Administration breakpoints (2 mg/L or less, susceptible; 4 mg/L, intermediate; 8 mg/L or greater, resistant) were used.

Statistical analysis

Univariate analysis using the χ^2 test (or the Fisher's exact test where required) was undertaken to identify relationships between isolates for each of the following response variables: susceptibility to each of the antimicrobials, pan-susceptibility (isolates susceptible to all antimicrobial classes tested) and multidrug resistance (resistance to two or more of the antimicrobial classes tested); and the following variables: region of origin, sex, age (30 years or younger) and isolation from a sterile site (blood, cerebrospinal fluid or synovial fluid). Relationships in which $P\leq0.20$ in the univariate analysis were included in a multivariate nominal logistic regression model to determine independent explanatory variables. A full multiple logistic regression analysis was initially performed using the potential explanatory variables identified in the univariate analysis for each antimicrobial, and then a backward selection was performed so that all factors remaining in the model were statistically significant at a 5% level ($P\leq0.05$). Each response variable (ie, antimicrobial) was analyzed separately. Statistical analysis was undertaken using JMP software version 7.0 (SAS Institute [USA]).

RESULTS

Of 4092 total organisms, 493 (12%) *E coli* isolates were collected from the CAN-ICU study, making it the second most common organism isolated from patients in Canadian ICUs after *Staphylococcus aureus* (16.6% of 4092 isolates). Regional distribution by specimen type is outlined in Table 1. The

TABLE 1
Source of specimens by region studied

	Region, n (%)				
Source, n (total %)	BC/AB	SK/MB	Ontario	QC/NB	Nova Scotia
Blood/CSF, 72 (14.6)	10 (11.0)	10 (13.2)	32 (21.5)	12 (14.3)	8 (8.6)
Urine, 243 (49.3)	26 (28.6)	32 (42.1)	67 (45.0)	42 (50.0)	76 (81.7)
Wounds, 56 (11.4)	22 (24.2)	8 (10.5)	13 (8.7)	9 (10.7)	4 (4.3)
Respiratory, 122 (24.7)	33 (36.3)	26 (34.2)	37 (24.8)	21 (25.0)	5 (5.4)
Total n (% specimens)	91 (18.5)	76 (15.4)	149 (30.2)	84 (17.0)	93 (18.9)

AB Alberta; BC British Columbia; CSF Cerebrospinal fluid; MB Manitoba; NB New Brunswick; QC Quebec; SK Saskatchewan

TABLE 2
Per cent susceptibility, and the minimum inhibitory concentrations required to inhibit the growth of 50% (MIC_{50}) and 90% (MIC_{90}) of 493 *Escherichia coli* isolates in the Canadian National Intensive Care Unit study

Antimicrobial	% Susceptible	% Intermediate	% Resistant	MIC_{50}, mg/L	MIC_{90}, mg/L
Cefazolin	76.7	6.5	16.8	2.0	>128.0
Cefepime	98.3	0.8	0.9	≤1.0	≤1.0
Ceftriaxone	93.1	3.7	3.2	≤1.0	8.0
Ciprofloxacin	78.3	0.6	21.1	≤0.06	>16.0
Gentamicin	92.3	4.5	3.2	0.50	2.0
Levofloxacin	78.9	0.0	21.1	≤0.06	16.0
Meropenem	100.0	0.0	0.0	≤0.12	≤0.12
Piperacillin-tazobactam	97.0	1.0	2.0	2.0	8.0
Tigecycline	100.0	0.0	0.0	0.25	0.5
Trimethoprim-sulfamethoxazole	75.7	0.0	24.3	≤0.12	32.0

TABLE 3
Percentage of *Escherichia coli* isolates susceptible to selected antimicrobials by explanatory variables deemed significant in the multivariate logistic regression model

	Antimicrobial (number, % susceptible)							
Variable (isolates, n)	CFZ	CRO	CIP	LVX	TZP	SXT	MDR*	Susc†
Region (493)	P<0.001	P<0.001	P=0.049	P=0.038	NS§	NS	NS	P<0.001
BC/AB (91)	87.9	98.9	68.1	69.2	95.6	69.2	26.4	55.0
SK/MB (76)	86.8	98.7	82.9	84.2	96.0	75.0	17.1	67.1
Ontario (149)	83.9	92.6	76.5	76.5	96.0	79/8	20.8	63.1
QC/NB (84)	92.9	96.4	79.8	79.8	98.8	74.5	16.7	70.2
Nova Scotia (93)	31.2	80.6	86.2	87.1	98.9	80.6	20.4	21.5
Age ≤30 years (493)	NS	NS	P=0.006	P=0.007	NS	NS	NS	NS
Yes (77)	72.7	93.5	90.9	90.9	94.8	74.0	16.9	58.4
No (416)	77.4	93.0	76.0	76.7	97.4	76.0	21.2	55.1
Sterile site isolate (493)	NS	NS	NS	NS	P=0.009	P=0.012	P=0.024	NS
Yes (72)	76.4	93.1	76.7	76.4	91.7	63.9	30.6	54.2
No (421)	76.7	93.1	78.6	78.6	97.9	77.7	18.8	55.8

**Multidrug-resitant (MDR) to two or more antimicrobial classes tested; †Susceptible (Susc) to all antimicrobials tested; §Nonsignificant (NS) association (statistically) between susceptibility to the antimicrobial and demographic variable at the 0.05 level in the multivariate model. AB Alberta; BC British Columbia; CFZ Cefazolin; CIP Ciprofloxacin; CRO Ceftriaxone; LVX Levofloxacin; MB Manitoba; NB New Brunswick; QC Quebec; SK Saskatchewan; SXT Trimethoprim-sulfamethoxazole; TZP Piperacillin-tazobactam*

mean age of patients infected with *E coli* was 57.1 years; 15.6% of *E coli* isolates were from patients 30 years of age and younger and 49.3% were from males; 49.3% of isolates were from the urinary tract, 24.7% from respiratory sources, 14.4% from blood and 11.4% from wounds, drains and abscesses. A single isolate was from cerebrospinal fluid. Isolates were not obtained from Newfoundland, Nunavut, the Northwest Territories, Yukon or Prince Edward Island. However, hospitals in Nova Scotia provide ICU care to residents of Prince Edward Island and hospitals in Alberta, Manitoba, Quebec and Saskatchewan provide ICU care to residents of the Yukon, Nunavut and the Northwest Territories.

The minimum inhibitory concentrations required to inhibit the growth of 50% and 90% of organisms, as well as the percentage of isolates susceptible to the antimicrobials are provided in Table 2. A multidrug-resistant phenotype was found in 20.5% of *E coli* isolates, and 55.6% were susceptible to all antimicrobial classes tested (aminoglycosides, beta-lactam/beta-lactamase inhibitor combinations, cephems, penems, fluoroquinolones, folate pathway inhibitors and glycylcyclines). Susceptibilities were highest for meropenem and tigecycline (100%), cefepime (98.3%), piperacillin-tazobactam (97.0%), ceftriaxone (93.1%) and gentamicin (92.3%), and lowest for cefazolin (76.7%), trimethoprim-sulfamethoxazole (75.7%) and the fluoroquinolones (ciprofloxacin, 78.3%; and levofloxacin, 78.9%). Eighteen (3.7%) of the isolates were phenotypically confirmed ESBL-producers. Eight (44.4%) were from urine, five (27.8%) from blood, three (16.7%) from wounds and two (11.1%) from respiratory specimens.

Univariate statistical analysis revealed no relationship (P>0.20) between meropenem or tigecycline susceptibility and any of the demographic variables. The multivariate model (Table 3) revealed that fluoroquinolone susceptibility was higher in patients younger than 30 years of age. Cephalosporin resistance varied significantly by region, with rates highest in Nova Scotia. Susceptibility to all antimicrobials tested was least common in Nova Scotia, British Columbia and Alberta. Isolation from a sterile site was associated with trimethoprim-sulfamethoxazole, piperacillin-tazobactam and multidrug resistance. In the full multivariate model, sex was not independently associated with any antimicrobial susceptibility and neither gentamicin nor cefepime susceptibility was associated with any of the explanatory variables.

DISCUSSION

Low susceptibility of ICU *E coli* isolates to cefazolin, fluoroquinolones and trimethoprim-sulfamethoxazole was not unexpected given the wide use of these and other closely related (eg, cephalexin) antimicrobials in the community, predominantly for urinary tract infections. In particular, the dramatic increase in fluoroquinolone resistance has been observed in many settings (9-12). Our observations suggest that first generation cephalosporins, trimethoprim-sulfamethoxazole and fluoroquinolones should not be used as single agents in patients suspected of having infections caused by *E coli* in Canadian ICUs due to susceptibility rates below 80%. Low fluoroquinolone susceptibility is of particular concern because they are commonly used as empiric therapy for serious infections in the ICU.

In the multivariate model, region was significantly associated with susceptibility to cephalosporins, the lowest susceptibility rate being in Nova Scotia (Table 3). Additionally, fluoroquinolone susceptibility was lowest in British Columbia and varied significantly from region to region (P=0.049 for ciprofloxacin and P=0.038 for levofloxacin). Discrepancies among antimicrobial susceptibility across Canada are likely to be multifactorial, combining antimicrobial use patterns, infection control policies and other unmeasured demographic variables (length of stay, severity of illness, procedures performed and type of care) as described in other regions (7,10,11,13). The observation of higher resistance to cephalosporins in Nova Scotia may reflect a true observation, but may also be an artifact of the collection dates or specimen source. Samples were not randomly collected throughout the year of study, and a disproportionate number of specimens (81.7%) were from urine cultures compared with other sites (Table 1). As such, clonal spread of a resistant isolate during an oversampled period of time or over-representation of urine specimens may also explain our findings. Low rate (3.7%) of ESBL production suggests that this mechanism of resistance is not playing a major role in oxyimino-cephalosporin resistance in Nova Scotian or Canadian ICUs, which contrasts with ICUs in other countries (2,3,5). An in-depth discussion of these ESBL-producing strains and their role in the Canadian ICU setting has been published elsewhere (14). Our findings suggest that oxyimino-cephalosporins (eg, cefepime and ceftriaxone) remain good empirical treatment choices for suspected *E coli* infections in ICUs across most of Canada, except possibly in Nova Scotia where ceftriaxone susceptibility rate was the lowest (80.6%).

The association between age and fluoroquinolone susceptibility has been demonstrated previously and is likely due to increasing exposure to fluoroquinolones over time and avoidance of fluoroquinolone use in children (10). This suggests that fluoroquinolones as empirical therapy may be appropriate in younger ICU patients, if indicated, but in routine pediatric practice, it is best avoided in children because of toxicity concerns.

Isolation from a sterile site was associated with resistance to piperacillin-tazobactam, trimethoprim-sulfamethoxazole and multidrug resistance. Because our data did not include information on length of stay in the ICU, this may reflect the higher likelihood that bacteremia caused by invasive isolates is often a delayed event and the pathogens are more likely to have been acquired within the nosocomial setting. (2,3,5,15).

Cefepime, meropenem, gentamicin and tigecycline susceptibility were not significantly associated with any demographic variable in the multivariate model. Interestingly, sex was not a predictor of susceptibility to any of the antimicrobials tested after adjusting for other factors in the multivariate model. This contradicts the findings of other studies (13), but this previous study included both community and hospital isolates, and sex may be less predictive of antimicrobial resistance in the ICU setting.

Our study had some limitations. We could not collect patient information such as length of stay, previous antimicrobial exposure and underlying disease. Although of great interest for the prediction of antimicrobial resistance, the effect of these variables could not be determined with our data. Furthermore, because we could not determine which of the infections caused by *E coli* in the ICU were acquired in the community, hospital or ICU, our data must be interpreted as representing an analysis of these infections in all-comers to the ICU. Also, our isolates reflect only information from the 19 centres studied and only during the study period. Therefore, our data may not reflect the antimicrobial susceptibility patterns of all ICUs in Canada. Finally, multivariate logistic regression models may reduce the number of isolates that fall within a demographic subcategory of interest and, therefore, reduces the power required to identify significant differences. However, the present study does provide valuable information about the factors predicting antimicrobial susceptibility of *E coli* in Canadian ICUs, such as patient age, site of infection and region.

ACKNOWLEDGEMENTS: The authors thank the following individuals and microbiology laboratories for their contributions – Dr P Kibsey (Victoria General Hospital, Victoria, British Columbia); Dr DL Roscoe (Vancouver General Hospital, Vancouver, British Columbia); Dr RP Rennie (University of Alberta Hospitals, Edmonton, Alberta); Dr E Thomas (Regina General Hospital, Regina, Saskatchewan); Dr JM Blondeau (Royal University Hospital, Saskatoon, Saskatchewan); Dr GKM Harding (St Boniface General Hospital, Winnipeg, Manitoba); Drs DJ Hoban/GG Zhanel (Health Sciences Centre, Winnipeg, Manitoba); Dr Z Hussain (London Health Sciences Centre, London, Ontario); Dr C Lee (St Joseph's Hospital, Hamilton, Ontario); Dr C Main (Hamilton HSC, Hamilton, Ontario); Dr S Poutanen (Mount Sinai Hospital, Toronto, Ontario); Dr F Chan (Children's Hospital of Eastern Ontario, Ottawa, Ontario); Dr M Laverdiere (Maisonneuve-Rosemont, Montreal, Quebec); Dr V Loo (Montreal General Hospital, Montreal, Quebec); Dr M Kuhn (South East Health Care Corporation, Moncton, New Brunswick); Ms Y Yaschuk (St John Regional, St John, New Brunswick); Dr Kevin McVarish (Cape Breton Regional Hospital, Sydney, Nova Scotia); and Dr R Davidson (Queen Elizabeth II Health Sciences Centre, Halifax and Dartmouth General, Halifax, Nova Scotia).

FUNDING: The CAN-ICU study was funded in part by the University of Manitoba, the Public Health Agency of Canada, Ortho-McNeil (USA) and Wyeth (Canada).

CONFLICTS OF INTEREST: Dr Hoban and Dr Zhanel have received research funds from Janssen-Ortho Inc (Canada), Merck Frosst (Canada), Pfizer (Canada), Abbott (Canada) and Wyeth (Canada), as well as speaker or board fees from Bayer Canada, Abbott, Wyeth, Ortho-McNeil (USA) and Janssen-Ortho Inc.

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