

Canadian patterns of antimicrobial resistance: Overview of current trends related to hospital pathogens

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Selection of appropriate empirical antibiotic therapy is dependent on many factors, not the least of which is an understanding of antimicrobial resistance rates in the patient population that is undergoing treatment. Resistance rates may vary by geographical location, institution, hospital ward or unit, and even body site of infection. The present paper reviews the currently available Canadian data regarding resistance rates for some of the most common hospital-acquired pathogens, including *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Enterobacter* species, *Staphylococcus aureus* and *Enterococcus* species. Current data suggest that the rates of extended-spectrum beta-lactamases among *E coli* and *Klebsiella* species remain relatively low across Canada. There are very little data on the epidemiology of ampC cephalosporinases among Gram-negative organisms, although combined American and Canadian data suggest that ceftazidime resistance rates for *Enterobacter* species range from 17.1% to 24.8%. The increased use of fluoroquinolones has led to an increase in resistance rates among most Gram-negative organisms. In the late 1990s, ciprofloxacin resistance rates for *P aeruginosa* were reported to be approximately 20%. For the Gram-positive organisms, methicillin resistance rates for *S aureus* have been reported to be as high as 10% and vancomycin resistance rates for *Enterococcus* species have been reported to be less than 1%. Additional data that are representative of all regions of Canada are needed. Continued surveillance, antibiotic stewardship, and adherence to good infection prevention and control measures will lead to a better understanding of the epidemiology of antimicrobial resistance in Canadian hospitals, as well as help to control its spread.

Key Words: Antimicrobial resistance; Hospital pathogens; Surveillance

Much has been written about the epidemiology and potential impact of antibiotic resistance. Although it is recognized as a major global health threat, its impact may be greatest in the hospital setting because it tends to house the most vulnerable patients as well as the most resistant organisms. Several studies involving hospitalized patients with a variety of different infectious disease syndromes have shown that early, effective antimicrobial therapy improves outcomes, including reduced mortality and length of hospital stay (1,2). In these studies, initial therapy is considered to be adequate if, based on culture data, it covers all of the infecting pathogens, the pathogens were susceptible to the antibiotic(s) used for treatment, dosing was appropriate and combination therapy was used, if needed (3). It therefore stands to reason that increasing

**La résistance aux antimicrobiens au Canada :
Aperçu des tendances actuelles concernant les
agents pathogènes dans les hôpitaux**

Le choix d'un traitement antibiotique empirique, approprié dépend de nombreux facteurs, dont, et non pas le moindre, la compréhension des taux de résistance aux antimicrobiens chez les patients soumis à ce type de traitement. Les taux de résistance peuvent varier selon les lieux géographiques, les établissements, les salles de malades ou les services dans les hôpitaux et même les foyers d'infection dans l'organisme. Le présent article passe en revue les données actuellement disponibles au Canada sur les taux de résistance de certains des agents pathogènes le plus souvent mis en cause dans les infections nosocomiales, notamment *Escherichia coli*, les espèces *Klebsiella*, *Pseudomonas aeruginosa*, les espèces *Enterobacter*, *Staphylococcus aureus* et les espèces *Enterococcus*. D'après les données actuelles, les taux de résistance aux bêta-lactamases à spectre étendu parmi les espèces *E. coli* et *Klebsiella* resteraient relativement faibles partout au Canada. Par ailleurs, l'on dispose de très peu de données sur l'épidémiologie des céphalosporinases de type AmpC parmi les micro-organismes gram-négatifs, même si, d'après des données américaines et canadiennes, les taux de résistance à la ceftazidime parmi les espèces *Enterobacter* varieraient de 17,1 % à 24,8 %. L'utilisation accrue des fluoroquinolones a entraîné une augmentation des taux de résistance chez la plupart des germes gram-négatifs. À la fin des années 1990, les taux de résistance de *P. aeruginosa* à la ciprofloxacine se situaient aux alentours de 20 %. Quant aux germes gram-positifs, les taux de résistance de *S. aureus* à la méthicilline s'élèveraient jusqu'à 10 %, mais les taux de résistance des espèces *Enterococcus* à la vancomycine seraient inférieurs à 1 %. Il faut donc poursuivre la collecte de données qui soient représentatives de toutes les régions du Canada. Une surveillance continue, une utilisation judicieuse des antibiotiques ainsi que le respect des mesures de prévention des infections et de lutte contre ces maladies nous permettront de mieux comprendre l'épidémiologie de la résistance aux antimicrobiens dans les hôpitaux au Canada et ainsi de mieux combattre leur transmission.

antibiotic resistance may result in an increased risk of ineffective initial therapy.

Because resistance rates may vary significantly from one geographical area to another, from institution to institution, from hospital unit or ward to hospital unit or ward, and even by body site of infection, one must have an understanding of the resistance issues in the particular patient population and setting in which one is working. As well, unless the surveillance network collecting and reporting the data accounts for these and other factors that may affect the information provided, it is extremely difficult to compare the results presented in different studies. Therefore, although an attempt is made to review the most recently published Canadian resistance data within the hospital setting, one must be cautious in generalizing

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the information available and in comparing the results presented in different studies.

Due to the paucity of data available for some organisms and the limited scope of the present review, not all issues of antimicrobial resistance are discussed. An attempt is made to highlight some features of the most common resistance issues encountered in the hospital setting. One must keep in mind not only the rates of resistance for a given organism, but also the frequency with which a given organism is isolated. Data from several studies have shown that Gram-positive organisms account for approximately two-thirds of nosocomial bloodstream infections, while Gram-negative organisms account for the remaining one-third (4). Within these groups, *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa* and *Enterobacter* species make up the majority of the Gram-negative organisms, while coagulase-negative staphylococci, *Staphylococcus aureus* and *Enterococcus* species make up the majority of the Gram-positive organisms. A broad overview of the susceptibility patterns for these key organisms (with the exception of coagulase-negative staphylococci) is presented.

EXTENDED-SPECTRUM BETA-LACTAMASE-PRODUCING *E COLI* AND *KLEBSIELLA* SPECIES

The production of extended-spectrum beta-lactamase-producing *E coli* and *Klebsiella* species (ESBLs) (Ambler class A) was first reported in the early 1980s (5). Since that time, more than 200 variants of these enzymes have been described worldwide. The genes that code for these enzymes are usually found on plasmids and are often associated with resistance to other classes of agents. The minimum inhibitory concentrations (MICs) for these organisms are only modestly increased (1 µg/mL to 8 µg/mL) and they are usually, but not always, inhibited by beta-lactamase inhibitors. Mulvey et al (6) reported the rates of ESBLs in a recently published survey of 29,323 *E coli* and 5156 *Klebsiella* species collected from 12 tertiary care centres across Canada from October 1999 to September 2000. Seventy-four (0.26%, range 0% to 1.79%) *E coli* and 42 (0.81%, range 0% to 3.25%) *Klebsiella* species were found to be ESBLs. These rates compare favourably with those reported from the United States, where different studies have found that 2% to 10% of *E coli* and 5% to 15% of *Klebsiella* species are ESBLs (7,8). Because there were no comparable Canadian data before the study by Mulvey et al, it is difficult to determine whether rates are stable or changing. Although data for only a small subset of non-ESBLs were presented, it does appear that ESBLs are more likely to be resistant to other classes of agents, including fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole.

ampC CEPHALOSPORINASES AND THIRD-GENERATION CEPHALOSPORIN RESISTANCE IN ENTEROBACTERIACEAE

Very little Canadian data are available on the epidemiology of ampC (Ambler class C) cephalosporinases among Gram-negative organisms. This mechanism of resistance is an intrinsic property of numerous Gram-negative bacilli and is usually expressed at low levels. However, it is inducible, particularly by cephamycins and carbapenems, and may occur during therapy, resulting in stable derepression and hyperproduction. The level of resistance tends to be high, with MICs of 8 µg/mL or greater. The clinical significance of this resistance is unmistakable, as evidenced by patients failing therapy with all penicillins,

cephalosporins, beta-lactam/beta-lactamase inhibitor combinations and monobactams. In vitro resistance of *Enterobacter* species and certain other enterobacteriaceae to ceftazidime and other third-generation cephalosporins is often used as a marker of this type of resistance in vitro (7). The SENTRY surveillance program in North America, which included both Canadian and American centres, recently published data on the rates of ceftazidime resistance among *Enterobacter* species from bloodstream infections (9). Of 1575 isolates collected between 1997 and 2002, resistance to ceftazidime ranged from 17.1% in 2002 to 24.8% in 1998. The activity of cefepime, the only other agent for which activity against *Enterobacter* species was reported, remained at approximately 99% or greater. Although the provinces of Alberta, Manitoba, Nova Scotia, Ontario and Quebec were represented throughout all six years of the study, the resistance rates for the Canadian centres specifically could not be determined. Earlier studies have shown that prior exposure to a third-generation cephalosporin is a major risk factor for infection with a ceftazidime-resistant organism (10).

FLUOROQUINOLONE-RESISTANT *P AERUGINOSA*

Fluoroquinolones have become extremely popular in the treatment of *P aeruginosa* infections because of their good safety profiles and proven efficacy. However, with their increasing use both in the hospital setting and in the community, increasing resistance has emerged. In a survey of 6783 *P aeruginosa* isolates collected from five to eight centres in Canada between 1997 and 1999, ciprofloxacin resistance remained stable at 19.0% to 20.1% (11). In the same survey, ciprofloxacin resistance rates among *P aeruginosa* isolates collected from 26 to 28 centres in the United States (28,870 isolates) were 20.2% to 24.6% (11). Resistance rates among other antipseudomonal agents were as follows: ceftazidime, 15.3% to 19.8%; imipenem, 8% to 17%; tobramycin, 5.85% to 8.6%; and piperacillin/tazobactam, 4.4% to 6.8%. Some have shown that the trend toward increasing fluoroquinolone resistance among *P aeruginosa* is associated with the overall increasing use of fluoroquinolones, while others have suggested that it is a result of the use of specific members of this class of agents (12-15).

METHICILLIN-RESISTANT *S AUREUS*

The first Canadian methicillin-resistant *S aureus* (MRSA) isolate was reported in 1981 (16). Since that time, many surveys of MRSA rates in Canadian hospitals have been conducted. One of the most recent and comprehensive data sets comes from the Canadian Nosocomial Infection Surveillance Program, which was established in 1994. Data from 22 to 34 hospitals from nine provinces found that the overall MRSA rate (based on 4507 infected and/or colonized patients) in Canadian hospitals in 1999 was approximately 6%, an increase of more than 5% over the rate from 1995 (17). The greatest increase in MRSA occurred in Ontario, Quebec and the western provinces. Subsequent studies have reported rates of 8.3% in 2000 and 10% in 2003 (Health Canada, unpublished data; 18-20). In the United States, the National Nosocomial Infection Surveillance program has reported MRSA rates of greater than 50% in several hospitals across the country (21). Since the early 1990s, there have been several reports of community-acquired MRSA in Canada (22). These patients may bring the organism with them when they enter hospitals and, thus, become a potential source for spread if they are not identified early and if appropriate infection control measures

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are not implemented. To date, there have been no published reports in Canada of vancomycin-resistant *S aureus*.

that adequately explains why Canada has been spared the rise in VRE that has been seen in the United States.

VANCOMYCIN-RESISTANT ENTEROCOCCUS SPECIES

Enterococci tend to be intrinsically resistant to a number of antibiotics. Even for those agents that are considered to be active against enterococci, the MICs tend to be at or near the break points. The emergence of vancomycin-resistant enterococci (VRE) has raised concerns because of the limited options for therapy. Fortunately, in Canada, the rates of VRE have remained relatively low, with most data suggesting rates of less than 0.2% (17-19). In contrast, VRE rates in the United States continue to rise, with rates as high as 25% being reported in some centres (22). Despite the low rates in Canada, several VRE outbreaks have been reported in at least three different centres in Ontario, Saskatchewan and Quebec, and thus, the importance of these organisms should not be underestimated (19,23,24). The use of third-generation cephalosporins and vancomycin has been correlated with the prevalence of VRE in the hospital setting (25,26). To date, no study has been published

SUMMARY

The Canadian data available for surveillance of antimicrobial resistance within the hospital setting are limited. In the past 10 years, the Canadian Nosocomial Infection Surveillance Program has been addressing this issue, and with time, a more detailed analysis of prevalence rates and trends over time should become available. It is well recognized that several factors may be driving antimicrobial resistance, not the least of which are the overuse and misuse of antibiotics. It must be kept in mind, however, that because resistance genes may cluster together on the same plasmid or transposon, the use of one class of drugs may not only select for resistance to itself, but it may also select for resistance to totally unrelated agents (27). Time will tell whether we will be spared the alarming trends of increasing resistance seen elsewhere in the world. Continued surveillance, coupled with antibiotic stewardship, and infection prevention and control measures, remains key to our ability to understand and control resistance within our hospitals.

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