

# The threat of the emergence of antimicrobial-resistant Gram-positive pathogens in Canada

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**DE LOW, BM WILLEY, AJ MCGEER.** The threat of the emergence of antimicrobial-resistant Gram-positive pathogens in Canada. *Can J Infect Dis* 1994;5(Suppl C):9C-14C. Since the early 1980s, much attention has been focused on the emergence of resistance in nosocomially acquired Gram-negative pathogens. However, in the 1990s we are witnessing in North America the development and spread of multiple resistance in Gram-positive pathogens in the hospital setting as well as in the community. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci are now endemic in many urban centres in the United States, although less so in Canada. In some states, penicillin-resistant *Streptococcus pneumoniae* in the community setting has gone from rates of less than 5% in 1988 to 50% in 1994, including resistance to third-generation cephalosporins and carbapenems. Although these same pathogens have now been identified in Canada, we may still be in a position to limit or prevent their spread.

**Key Words:** Antimicrobial resistance, Gram-positive bacteria, Methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*

## Menace de nouveaux pathogènes Gram positifs résistants aux antimicrobiens au Canada

**RÉSUMÉ :** Depuis le début des années 1980, l'émergence d'un phénomène de résistance manifesté par des pathogènes nosocomiaux Gram négatifs a fait passablement de bruit. Or, l'Amérique du Nord des années 1990 assiste au développement et à la propagation de pathogènes Gram positifs multi-résistants tant dans les établissements de santé que dans la communauté. Les *Staphylococcus aureus* méthicillino-résistants et les entérocoques résistants à la vancomycine sont désormais endémiques dans plusieurs centres urbains des États-Unis, et à un degré moindre, au Canada. Dans certains états, le taux de *Streptococcus pneumoniae* dans la communauté est passé de 5 % en 1988 à 50 % en 1994, y compris une résistance aux céphalosporines de troisième génération et aux carbapénèmes. Bien que ces mêmes pathogènes aient été identifiés au Canada, nous pourrions être en position de limiter ou de prévenir leur propagation.

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THE INTRODUCTION OF PENICILLIN 50 YEARS AGO WAS FOLLOWED rapidly by the identification of penicillinase-producing staphylococci. After just 10 years of penicillin use, 73% of *Staphylococcus aureus* isolates from in-patients at the Boston City Hospital were penicillin-resistant (1). This is one of the earliest illustrations that one of the consequences of the introduction of any new antimicrobial agent is the development of bacterial resistance to its action (2,3). Such resistance may arise by a mutation that reduces target affinity or allows the overproduction of a drug modifying enzyme. However, the introduction into a bacterium of foreign DNA encoding for resistance may bypass the need for endogenous mutational events. This DNA may be introduced into the chromosome by transformation and recombination or may be integrated into the bacterial cell on plasmids, which may be transferable from one organism to another by conjugation, transduction or transformation (4,5). In this article we review the emergence of methicillin-resistant *S aureus* (MRSA), multiply resistant *Enterococcus* species and penicillin-resistant *Streptococcus pneumoniae* (PRSP), and discuss the threat they may pose in Canada.

#### METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

Soon after methicillin became available, resistance to it was reported in *S aureus*. This resistance was not the result of destruction of the antibiotic by a beta-lactamase (6). It was subsequently found that the resistant strains had a newly acquired resistance gene, *mecA*, that encoded for a penicillin binding protein (PBP), PBP-2a (7,8). PBP-2a is able to maintain cell wall integrity during growth and division when native enzymes (PBPs) needed for assembly of the cell wall are inactivated by beta-lactam antibiotics. The spread of staphylococcal clones carrying the *mecA* gene has resulted in the worldwide dissemination of MRSA (9). Outbreaks reported in the United States in the 1970s were confined primarily to large, tertiary care teaching hospitals (10,11). However, in the 1980s some community hospitals and rehabilitation and extended care facilities experienced an increasing prevalence of MRSA colonization and/or infection (11-13). For instance, the prevalence of MRSA increased dramatically in Veterans' Administration medical centres between 1975 and 1984 (14). MRSA continues to be endemic in many of these facilities.

In Canada, the prevalence of MRSA remains low relative to other countries, but varies in different provinces, cities and hospitals. A point prevalence survey to determine MRSA colonization rates at three university-affiliated tertiary care facilities in downtown Toronto found that none of 1219 patients were colonized with MRSA (personal communication). McArthur et al (15) surveyed 20% of residents in each of 132 long term care facilities in Ontario for colonization with MRSA. One or more MRSA colonized residents were identified in eight of 132 facili-

ties (6.1%, 95% confidence level 1.9 to 10.2%). Only two facilities had previously recognized the presence of MRSA. Taylor et al (16) at the University of Alberta Hospitals found that the majority of MRSA isolates from hospitalized patients was community acquired and that most were isolated from residents of one aboriginal community. A study done by Embil et al (17) reviewed the experience with five tertiary care teaching hospitals on the Canadian prairies, and found similar results. Patients usually had MRSA identified at admission: in only one of five centres was the majority of isolates acquired nosocomially. Patients with MRSA present at admission were more frequently aboriginal. It appears that in Canada the major reservoirs for MRSA may be outside the hospital setting.

Can MRSA be controlled once introduced into a hospital? Boyce (18) reviewed 46 published outbreaks and found that early implementation of control measures was associated with success in eradication. All 11 hospitals with 20 or fewer cases were successful in eradicating MRSA compared with only 71% with 20 to 39 cases and 10% with 40 or more cases. In Sarnia, Ontario 21 patients with MRSA were identified in a secondary care hospital between March 1990 and January 1991 (19). The reservoir was suspected to be in nursing homes in the community. A survey of all hospital patients and nursing home residents in Sarnia was carried out, and those found to be colonized with MRSA were treated. All subsequent admissions from other institutions were screened for MRSA and treated if colonized. Since the institution of these policies no further outbreaks have occurred as of January 1994 (personal communication). Policies requiring admission screening of patients at risk for MRSA colonization (eg, admitted from an area where MRSA is endemic) may control the spread of this organism in Canada.

#### MULTIPLY RESISTANT ENTEROCOCCUS SPECIES

The enterococcus is an important nosocomial pathogen despite its low virulence: in National Nosocomial Infections Surveillance System (NNIS) hospitals, enterococci are the third most common pathogen associated with nosocomial bloodstream infections and the second most commonly isolated nosocomial pathogen overall (20-23). This is due to the organism's ubiquitous nature, its inherent antimicrobial resistance, and its ability to acquire multiple resistance traits.

Acquired high-level resistance to the aminoglycosides was first reported in the 1970s. By the mid-1980s many reports had documented high-level aminoglycoside resistance in both *Enterococcus faecalis* and *Enterococcus faecium* (24-26). Resistance to beta-lactams has also dramatically increased during the past decade (27-30). This resistance is usually a result of an increase in the amount of low affinity PBPs synthesized by the cell (31). However, high-level ampicillin resistance may also occur due to the acquisition of

a beta-lactamase gene (32,33). High-level vancomycin-resistant strains were first detected in 1986. Since then they have spread at an alarming rate (34-37). Outbreaks have been reported both in teaching and community hospital settings (36-41). In NNIS hospital intensive care units, the prevalence of vancomycin resistant enterococci (VRE) has increased from less than 1% to more than 10% in the three years from 1990 to 1992 (42). In New York City, the first isolate of VRE was identified in September 1989. Reports of VRE then increased almost exponentially, with 38 hospitals reporting 361 isolates by October 1991 (36).

Studies of the genetics and mechanisms of glycopeptide resistance in enterococci have suggested three classes of resistance: A, B and C. All classes have genes that encode for a cell wall precursor with a reduced affinity for glycopeptide antibiotics (43). Isolates with resistance to high levels of vancomycin (minimum inhibitory concentration [MIC] 256 µg/mL or greater) and to teicoplanin (MIC 16 µg/mL or greater) have been classified as phenotypic class A. This is the most prevalent phenotype. It is encoded for by the *vanA* gene, which may be transferred between strains on plasmids and transposons. Class B strains are resistant to vancomycin, with MICs ranging from 16 to 1024 µg/mL, but are susceptible to teicoplanin (MIC less than 8.0 µg/mL). This type of resistance is encoded for by the *vanB* gene, which is also transferable. Class C resistance, found in *Enterococcus gallinarum* and *Enterococcus casseliflavus*, comprises constitutive low-level resistance to vancomycin (MIC 4.0 µg/mL or greater, or 32 µg/mL or less) and susceptibility to teicoplanin (43-45). This type of resistance is chromosomal, intrinsic and nontransferable. The study of the rapid spread of glycopeptide-resistant enterococci in Europe and the United States suggests that dissemination occurs not only by clonal spread of individual strains, but also by the horizontal spread of resistance determinants from strain to strain (36,40,46). The rapid worldwide emergence of vancomycin resistance in enterococci more than 35 years after the introduction of this antibiotic probably reflects selective pressure due to its increased use (47,48). For instance, Ena et al (48) found that the rate of vancomycin use at a university hospital increased from 5.7 g/1000 patient days in 1981 to 21 g/1000 patient days in 1991.

In Canada, both high-level aminoglycoside-resistant and beta-lactamase-negative ampicillin resistant enterococci have been reported (49,50). There has been only one case report of a beta-lactamase-producing *E. faecalis* isolate (51). The first vancomycin-resistant isolate of *E. faecium* was described by Kibsey et al (52). This organism was isolated from two patients in an intensive care unit. Both patients were immunocompromised and had received broad spectrum antimicrobial therapy.

The emergence and dissemination of multiply resistant enterococci is resulting in infections for which there are no uniformly effective therapeutic options.

The possibility that the *vanA* gene will transfer into other Gram-positive organisms such as MRSA and/or PRSP is of even greater concern. The transfer of vancomycin resistance from enterococci to *S. aureus* has already been accomplished in vivo in the laboratory (53). VRE are readily detectable in the laboratory if appropriate antimicrobial testing practices are employed (54,55). Once identified, control of the spread of this organism will require strict adherence to infection control practices and the institution of a surveillance program to identify colonized patients and health care workers. Otherwise what has happened in the United States, and in particular in New York City, could easily occur in Canada (36).

### PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

Of equal concern is the rapid emergence of PRSP in North America. In 1967, the first patient infected with a PRSP strain with intermediate resistance to penicillin (MIC 0.1 to 1.0 µg/mL) was reported from Australia (56). Subsequently, other strains were identified in New Guinea and Australia (57,58). In 1977 in South Africa, outbreaks of the first strains that were highly penicillin-resistant (MIC 2 µg/mL or greater) were reported (59), as was the first multiply resistant strain (resistant to penicillin, tetracycline, erythromycin, clindamycin, trimethoprim-sulphamethoxazole and chloramphenicol) (59,60). PRSP infection in the United States was initially reported in 1974 (61), and the first resistant Canadian isolates were described in the mid-1970s (62). Before 1987, in the United States only 5% of pneumococci demonstrated intermediate resistance and less than 1% were highly resistant (63). The last two Canadian surveillance studies, performed in the 1980s, found less than 1.5% of isolates to have intermediate resistance and none to be highly resistant (64,65). Recently, however, disturbingly high rates of PRSP (more than 50%) have been identified in Spain and Hungary (66,67), and several reports from the United States document increases in the number of PRSP. From 1987 to 1992, the proportion of *S. pneumoniae* strains submitted to the Centers for Disease Control and Prevention that were highly resistant to penicillin increased from 0.02% to 1.3% (68). In community surveys in Kentucky and Tennessee in 1993 it was found that 65% and 39%, respectively, of *S. pneumoniae* strains were PRSP, and of these 65% and 30%, respectively, were highly resistant to penicillin (69).

Resistance to penicillin in clinical isolates of *S. pneumoniae* is due to the development of PBPs that have greatly decreased affinity for the antibiotic (70-72). In those isolates that have the highest levels of resistance to penicillin, there have been reductions in the affinity of at least four of the five high molecular weight PBPs (73). Low affinity forms are believed to have arisen by localized interspecies recombinational events that re-

place parts of the PBP gene with the corresponding parts of the homologous genes of closely related species (74). That is, the *S pneumoniae* has acquired PBP genes from other streptococci that are resistant to penicillin. Thus, the evolution of resistance in *S pneumoniae* is somewhat different from that in MRSA or enterococci. The *mecA* and *vanA* genes are highly conserved, and their spread occurs either by clonal dissemination of a strain carrying them (as usually occurs with MRSA), or by their transfer from strain to strain on a plasmid or transposon (as occurred with enterococci in New York City) (75,76). Although clonal dissemination of strains of PRSP has occurred (77), the transformation and recombination events that transfer penicillin resistance to *S pneumoniae* are not uncommon, and the emergence of PRSP may be due to the repeated new development of low affinity PBPs (78).

In Canada there has been a recent increase in reports of PRSP. In an unselected sample of 2642 isolates of *S pneumoniae* collected from across Canada, 252 (9.5%) were found to be resistant to penicillin by the oxacillin screen test. Of the resistant isolates, 39 were from blood cultures, four from sterile fluids and 209 from the respiratory tract. One hundred and twenty-seven of these were from Ontario, 31 from British Columbia, 34 from Alberta, 27 from Saskatchewan, 13 from Manitoba, 10 from Quebec, eight from the Maritimes and two from Yukon. Of the 146 isolates available for antimicrobial susceptibility testing, 37 exhibited high level resistance (penicillin MIC at least 2.0 µg/mL) and 109 had intermediate levels of resistance (penicillin MIC 0.12 to 1.0 µg/mL). Among the 99 isolates serotyped, 17 different serotypes were represented. The four predominant serotypes were: 23F (10), 9A (10), 9V

(seven) and 6B (six) (personal communication).

The appearance of PRSP in Canada has several important implications. First, if rates of resistance in a community become greater than 3%, then first-line low-cost antimicrobials for empirical therapy (ie, penicillin) may have to be replaced with more costly agents. Second, beta-lactams other than penicillin have reduced activity against PRSP isolates, thereby potentially limiting the use of a whole class of antimicrobials (79,80). Finally, alternative antimicrobials to penicillin for the treatment of invasive infections due to high-level resistant *S pneumoniae* are not as effective as penicillin for penicillin-susceptible strains, so that therapy for patients with these infections may be compromised (81,82). Effective alternative antimicrobials for invasive disease due to PRSP in nonmeningitis cases are ceftriaxone and cefotaxime.

## CONCLUSIONS

There are several strategies to try to combat the problem of emerging antimicrobial resistance. One approach is to reduce selective pressure for the development of resistance by more prudent use of antimicrobials. Equally important is the need for better surveillance to determine the frequency of antimicrobial resistance so that studies can be designed to determine the important factors in the emergence, persistence and transmission of drug-resistant organisms. Ongoing transmission of organisms being introduced may then be controlled. As Cohen (3) noted, "unless currently effective antimicrobial agents can be successfully preserved and the transmission of drug-resistant organisms curtailed, the post-antimicrobial era may be rapidly approaching".

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