The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance

Research

Recherche

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Abstract

Background: To better understand the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in Canadian hospitals, surveillance has been conducted in sentinel hospitals across the country since 1995. We report the results of the first 5 years of the program.

Methods: For each newly identified inpatient with MRSA, medical records were reviewed for demographic and clinical data. Isolates were subjected to susceptibility testing and molecular typing by pulsed-field gel electrophoresis.

Results: A total of 4507 patients infected or colonized with MRSA were identified between January 1995 and December 1999. The rate of MRSA increased each year from a mean of 0.95 per 100 *S. aureus* isolates in 1995 to 5.97 per 100 isolates in 1999 (0.46 per 1000 admissions in 1995 to 4.12 per 1000 admissions in 1999) ($p < 0.05$). Most of the increase in MRSA occurred in Ontario, Quebec and the western provinces. Of the 3009 cases for which the site of MRSA acquisition could be determined, 86% were acquired in a hospital, 8% were acquired in a long-term care facility and 6% were acquired in the community. A total of 1603 patients (36%) were infected with MRSA. The most common sites of infection were skin or soft tissue (25% of MRSA infections), pulmonary tissues (24%) and surgical sites (23%); 13% of the patients were bacteremic. An epidemiologic link with a previously identified MRSA patient was suspected in 53% of the cases. Molecular typing indicated that most (81%) of the isolates could be classified as related to 1 of the 4 Canadian epidemic strains of MRSA.

Interpretation: There has been a significant increase in the rate of isolating MRSA in many Canadian hospitals, related to the transmission of a relatively small number of MRSA strains.

In the past few decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has been recognized as an important nosocomial pathogen worldwide.[1–5] The emergence and rapid spread of this organism has created important new challenges for infection prevention and control services in hospitals and other health care facilities. Interestingly, there appears to be significant variability in the epidemiology and prevalence of MRSA in different parts of the world and even in different regions of a country.[3]

MRSA was first reported in Canada in 1981.[6] Since then, the organism has been identified in many Canadian health care facilities,[7–9] and one report has documented the rapid interprovincial spread of a single clone of MRSA.[10] Community-acquired MRSA has also been described, particularly for Aboriginal communities in the Prairie provinces.[11,12] However, nationwide data describing the incidence and epidemiology of MRSA in Canada were not available before 1995. In that year, national surveillance for MRSA was started in sentinel hospitals participating in the

Canadian Nosocomial Infection Surveillance Program (CNISP). Preliminary results of this surveillance have indicated a significant increase in the number of patients infected or colonized with MRSA in each of the past few years.[13,14] This report summarizes the results of the first 5 years of surveillance (1995 to 1999).

The CNISP is a collaborative effort involving sentinel hospitals across the country, which participate as members of the Canadian Hospital Epidemiology Committee (a subcommittee of the Canadian Infectious Diseases Society), and the Centre for Infectious Disease Prevention and Control, Health Canada. Surveillance for MRSA started in January 1995 and is continuing. From 1995 to 1999 the number of participating sites increased from 22 to 34, with widespread geographic representation. Hospital sites in every province except Prince Edward Island participate in the surveillance. Most (30 [88%]) of the hospital sites are tertiary care teaching hospitals, representing 90% of the university-affiliated teaching medical centres in the country. Twelve hospitals are also affiliated with long-term care facilities, and 5 are pediatric hospitals.

Methods

Surveillance for MRSA was based on laboratory testing. When MRSA was isolated from an inpatient for the first time, the hospital's infection control practitioner reviewed the patient's medical records to obtain demographic and clinical information, including age, sex, prior admissions to hospital in the previous year, hospital service at the time the MRSA was first detected, and the reason for which the culture that yielded MRSA was obtained. All sites and tissues from which MRSA was isolated were recorded. The presence of infection caused by MRSA was determined according to standard definitions used in infection surveillance.[15] MRSA colonization was defined as the presence of MRSA without any clinical signs or symptoms of infection. An attempt was made to determine whether the MRSA had been acquired in a hospital, a long-term care facility or the community, according to the infection control practitioner's best judgement. For MRSA colonization or infection to be defined as having been acquired in hospital, there had to be no evidence that the organism was likely to have been present at the time of admission, or there had to be evidence that it was likely to have been acquired during a previous admission. For those cases in which colonization or infection was thought to have been acquired in hospital, an attempt was made to determine whether there was an epidemiologic link with any other known MRSA patients in the facility (e.g., roommate, patients who had undergone the same procedures as the affected patient, or health care workers).

MRSA isolates were sent to a central laboratory, where the identity of the organism was confirmed according to standard procedures. Resistance to oxacillin was confirmed by growth on an oxacillin agar screening plate (Mueller-Hinton agar supplemented with 4% sodium chloride and oxacillin 6 µg/mL) incubated at 35°C for 24 hours.[16] Additional antimicrobial susceptibility testing was done by broth microdilution in accordance with the guidelines of the National Committee for Clinical Laboratory Standards.[16]

All isolates were confirmed as MRSA by detection of the *mecA* gene by polymerase chain reaction, as previously described.[17]

Isolates were typed by pulsed-field gel electrophoresis after extraction of DNA and digestion of the extract with *Sma*I. Electrophoretically generated DNA profiles were digitized into the GelCompar computer software program for analysis. Cluster analysis was performed by the unweighted pair-group method on the basis of arithmetic averages, and DNA relatedness was calculated on the basis of the Dice coefficient.[18,19] Isolates were considered to be genetically related if their macrorestriction DNA patterns differed by fewer than 7 bands and the Dice coefficient of correlation was 75% or greater.[18,19]

Categorical variables were compared with either the Fisher exact test or the χ^2 test. The extended Mantel-Haenszel χ^2 test for trend was used to determine changes in proportion over time. Differences for which p was less than 0.05 were considered statistically significant.

Results

During the 5 years of surveillance, a total of 4507 new patients with MRSA were identified in the participating hospitals. Of these, 36% (1603) were infected with MRSA. The mean incidence rate of MRSA increased in each of the surveillance years, rising from 0.46 cases per 1000 admissions in 1995 to 4.12 per 1000 admissions in 1999 (range of rates in participating hospitals over the surveillance period 0.1 to 16.3 per 1000 admissions) ($p = 0.002$) (Table 1). MRSA infection rates also increased, from 0.25 infections per 1000 admissions in 1995 to 1.11 infections per 1000 admissions in 1999 ($p < 0.001$). Most of the increase in MRSA cases occurred in Ontario and Quebec, although there was also a significant increase in the country's western provinces (Fig. 1). The rates increased from 0.6 to 6.5 per 1000 admissions in Ontario ($p = 0.003$) and from 0.2 to 4.9 per 1000 admissions in Quebec ($p = 0.008$).

Overall, 59% (2667 of 4507) of the patients were male. The median age was 71 years (range less than 1 to 101 years). In 63% of cases (2797 of 4507), the patients were 65 years of age or older, whereas in only 4% (193 of 4507) were the patients less than 20 years of age. Patients 21 to 64 years of age were more likely to have had an MRSA infection than were those over 65 years of age (relative risk [RR] 2.7, 95% confidence interval [CI] 2.4–3.1; $p < 0.001$); conversely, patients over 65 years of age were more likely to have been colonized without infection (RR 1.9, 95% CI 1.6–2.1; $p < 0.001$). In 3% of cases (144) the patients were of Aboriginal origin; 105 (73%) of these people resided on reserves, particularly in the western provinces of Manitoba, Alberta, and British Columbia.

In 1995, 71% (135) of the 191 cultures that eventually yielded MRSA were obtained for clinical indications (i.e., an infection was suspected), 20% (39) were obtained as part of MRSA screening or surveillance, and 9% (17) were obtained as part of outbreak investigation. However, by 1999, the initial culture yielding MRSA was obtained for a clinical indication in only 37% (718) of the 1939 cases ($p < 0.001$), whereas specimens were obtained for screening and

outbreak investigation in 54% (1039) and 9% (182) of cases respectively. The most common sites from which MRSA was recovered in colonized and infected patients are summarized in Table 2.

A determination of where the MRSA had been acquired was made in 78% of the cases (3515 of 4507) cases. MRSA was thought to have been acquired in hospital in 86% of these cases (3008 of 3515), in a long-term care facility in 8% (288) and in the community in 6% (219). Cases from Alberta and Manitoba were more likely to have been acquired in the community than were cases from other provinces (RR 4.9, 95% CI 3.8–6.3; $p < 0.001$). Of the 3008 cases thought to have been acquired in hospital, 23% (692) were thought to have been acquired on a surgical service, 22% (662) on a medical service and 13% (391) in a critical care unit. Patients in a critical care unit were more likely to have had an MRSA infection (RR 1.5, 95% CI 1.4–1.6; $p < 0.001$) than were patients elsewhere in the hospital.

The proportion of hospital-acquired cases thought to have been acquired in the "index" hospital (i.e., the hospital that initially identified the patient with MRSA) was 86% (2587 of 3008). The rate of cases thought to have been acquired in the index hospital increased from 0.91 per 1000 admissions in 1997 to 2.81 per 1000 admissions in 1999 ($p = 0.02$). An epidemiologic link between the index case and another patient in the hospital was identified for slightly more than half (53%) of the hospital-acquired cases (1594 of 3008). In most of the epidemiologically linked cases (88%; 1403 of 1594), the identified link was a stay in the same hospital room or on the same nursing unit. An epidemiologic link was more likely to be identified in 1999 than in 1995 (960 of 1844 [52%] v. 76 of 187 [41%]; RR 1.6, 95% CI 1.2–2.5; $p < 0.001$).

Antimicrobial susceptibility testing of 2663 MRSA isolates from across the country revealed uniform resistance to the β-lactam antibiotics. Resistance rates for other antimicrobial agents were as follows: erythromycin and clindamycin, 94% each; ciprofloxacin, 89%; trimethoprim-sulfamethoxazole, 56%; tetracycline, 33%; rifampin, 3%; fusidic acid, 3%; and mupirocin, 2%. None of the isolates were found to have reduced susceptibility to vancomycin. Isolates recovered from patients in provinces west of Ontario were more likely to be resistant to tetracycline than were those recovered in Ontario, Quebec or the Atlantic provinces (72% v. 11%; $p < 0.01$). No other regional differences in susceptibility profiles were identified. There were also no temporal changes in antibiotic susceptibility profiles over the 5 years.

A total of 1831 isolates, consisting of all of those from the period 1995 to 1997 and a subset of those from 1998 and 1999, were typed by pulsed-field gel electrophoresis. Fifty-six distinct DNA profiles were obtained. However,

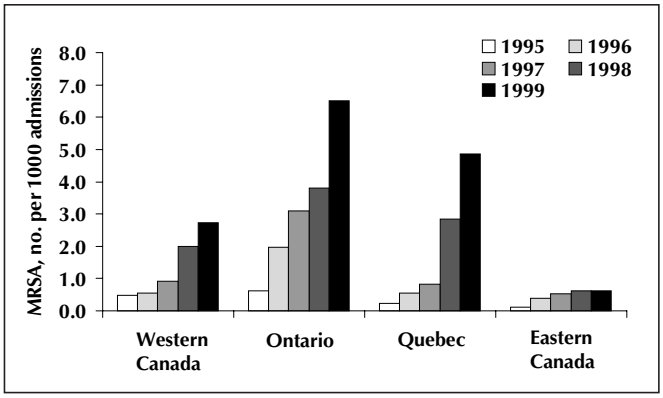

Fig. 1: Rates of methicillin-resistant *Staphylococcus aureus* (number per 1000 admissions) in hospitals participating in the Canadian Nosocomial Infection Surveillance Program from 1995 to 1999.

Table 1: Incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) in sentinel Canadian hospitals, 1995–1999

Year	No. of patients with MRSA	No. per 1000 admissions	No. per 100 000 patient-days	No. per 100 *S. aureus* isolates
All cases of MRSA*				
1995	194	0.46	5.84	0.95
1996	468	1.07	12.68	1.97
1997	779	1.67	19.57	3.07
1998	1082	2.50	24.49	3.90
1999	1984	4.12	42.95	5.97
Overall	4507	2.03	22.59	3.46
MRSA infections				
1995	105	0.25	3.15	0.51
1996	205	0.46	5.45	0.85
1997	334	0.72	8.46	1.33
1998	424	0.98	9.55	1.52
1999	535	1.11	11.62	1.62
Overall	1603	0.76	8.00	1.23

*Infections and colonizations.

most of the isolates (81%; 1483 of 1831) could be grouped into 1 of 4 "epidemic" strains of MRSA, which have previously been designated as Canadian epidemic strains (CMRSA-1, CMRSA-2, CMRSA-3 and CMRSA-4).[14] Each of these MRSA clones could be distinguished by its electrophoretic DNA profile and caused significant disease in patients from numerous hospital sites in 3 or more geographic regions of the country. CMRSA-1 was the most prevalent strain in Ontario, CMRSA-2 was the most prevalent strain in Quebec and CMRSA-3 was the most prevalent strain in provinces of western Canada. The DNA profiles were not associated with colonization or infection status, site of MRSA acquisition or antimicrobial susceptibility profile.

Interpretation

Since MRSA was first identified nearly 40 years ago, this organism has become prevalent in many countries around the world. However, for most of the past 2 decades, the epidemiology of MRSA in Canadian hospitals has been different from that described in the United States and many European countries. In the United States, for example, MRSA became endemic in many hospitals throughout the 1980s and early 1990s, with rates as high as 40% of all *S. aureus* isolates.[2] In contrast, until relatively recently, MRSA was not thought to be endemic in any Canadian health care facility. This study describes the results of a prospective nationwide surveillance program for MRSA in a large sample of Canadian hospitals. The results indicate a significant increase in MRSA rates in many parts of the country over the 5-year period 1995 to 1999. The largest increase occurred in hospitals in Ontario and British Columbia, but there have also been substantial increases in Alberta and Quebec. Part of this increase may be related to more frequent screening for asymptomatic MRSA in high-risk patients.[20] However, it is important to note that there has also been a fourfold increase in MRSA infection rates, in addition to the increase in identification of MRSA colonized patients.

In this study most of the patients with MRSA were older adults receiving care on medical or surgical units. Our surveillance was not designed to identify risk factors for MRSA acquisition, but risk factors that have previously been associated with acquisition of MRSA in hospitals have included prolonged stay, broad-spectrum antimicrobial therapy, admission to an intensive care unit, older age and proximity to other patients with MRSA.[21–23]

Although there have been recent reports indicating an increase in community-acquired MRSA in the United States,[24,25] our data suggest that MRSA remains largely a hospital-acquired pathogen in Canada. Less than 15% of cases were thought to have been acquired outside of a hospital setting, and the rate of community-acquired MRSA did not change during the 5 years of surveillance (data not shown). Neither age nor infection or colonization status was associated with whether MRSA was nosocomial or acquired in the community (data not shown). However, cases from Manitoba and Alberta were more likely to have been acquired in the community than were cases from other provinces. Many of these patients were Aboriginals, which concurs with previously reported findings.[8,11,12]

The frequent identification of an epidemiologic link between cases and the results of molecular typing by pulsed-field gel electrophoresis indicate that acquisition and transmission of MRSA were common occurrences in the participating hospitals. These surveillance results also indicate that MRSA has spread between institutions, with transmission of certain strains to several hospitals in geographically separate regions of the country. Such rapid, widespread dissemination within Canada of an epidemic strain of MRSA has previously been described.[10] However, in the absence of an outbreak, the spread of multiple clones of MRSA has been reported more often.[7,26] It is therefore remarkable that 81% of the Canadian MRSA isolates belonged to 1 of only 4 DNA types (designated Canadian epidemic MRSA strains).[14] It is not known what factors determine the ease of transmission of different strains of MRSA, but several phenotypic and genotypic properties have been associated with epidemic strains of MRSA.[27]

Because a substantial number of hospitals participated in the surveillance and because most of the teaching medical centres in the country were represented, we believe that the results of this study are an accurate indication of MRSA in Canadian tertiary care hospitals. Moreover, the results obtained from Ontario CNISP hospitals are consistent with those from all Ontario hospitals, as reported by the province's Laboratory Proficiency Testing Program,[20] which indicates that CNISP results may also reflect the epidemiology of MRSA in many nonteaching hospitals in Canada. However, more broadly based surveillance with a representative sample of health care facilities would be necessary to obtain results that could be generalized to nonteaching hospitals in all regions of the country.

Patients, physicians and hospital administrators should be concerned about increases in illness and death associated with MRSA, as well as the organism's impact on health care

Table 2: Sites of MRSA infection and colonization

Site	No. (and %) of cases*			
	Infection		Colonization	
Nose	0		1889	(43)
Surgical site	431	(23)	168	(4)
Other skin or soft tissue	474	(25)	1517	(34)
Respiratory tract	454	(24)	467	(11)
Urinary tract	177	(9)	254	(6)
Bloodstream	250	(13)	0	
Other†	122	(6)	106	(2)

*Some patients had MRSA at more than one site; each site of infection or colonization was counted as a separate case.
†Other sites of infection or colonization included catheter exit site (49 patients), intravascular catheter tip (49), conjunctiva (32), bone (9), cerebrospinal fluid (9) and pleural fluid (1).

costs and the risks of emergence of further antibiotic resistance. MRSA strains are virulent and capable of causing serious disease. It has been reported that among hospital inpatients colonized with MRSA, 30% to 60% will eventually experience a significant MRSA infection, such as a wound infection, pneumonia or bacteremia.[22] In this surveillance project, slightly more than one-third of the patients had an MRSA infection, including 13% who were bacteremic. Several studies have documented that MRSA infections are associated with greater mortality rate and length of hospital stay,[28–32] and that after adjustment for comorbidities methicillin resistance is a significant independent risk factor for death.[29,30]

MRSA is typically resistant to multiple classes of antibiotics. Therefore, treatment options for the management of serious MRSA infections are limited. The current medication of choice is vancomycin. Higher rates of MRSA in Canadian health care facilities would lead to increased use of vancomycin, which is in turn associated with the emergence of vancomycin resistance in enterococci and MRSA.[33–35] Although *S. aureus* with reduced susceptibility to vancomycin has not yet been identified in Canada, it is likely just a matter of time before this occurs. Higher rates of MRSA and a concomitant increase in the use of vancomycin would promote earlier emergence of vancomycin resistance.

The continued spread of MRSA in health care settings poses a serious risk to the health of patients. The associated costs of treating MRSA infections and of controlling outbreaks present an enormous burden on health care resources. Epidemic modelling has indicated that, if little is done now, MRSA rates will continue to rise exponentially in Canadian hospitals during the next 5 to 10 years.[36] The results of our study suggest an urgent need to implement better infection prevention and control measures to limit transmission of MRSA in hospital settings in Canada. Hospitals and countries that have implemented stringent infection control measures have been successful in limiting the spread of MRSA.[3,37,38] We believe there is currently an opportunity to effectively intervene and limit further spread of MRSA in Canadian health care facilities, but this opportunity will not exist indefinitely.

Competing interests: None declared.

Contributors: Dr. Simor participated in developing the initial study concept and design, supervised the conduct of the study, participated in data analysis and was the primary author of the manuscript. Ms. Ofner-Agostini participated in study design and data analysis and contributed to writing the manuscript. Dr. Bryce participated in study design and contributed to writing the manuscript. Ms. Green participated in study design and revision of the manuscript. Dr. McGeer participated in developing the initial study concept and design, participated in the conduct of the study and data analysis and contributed to writing the manuscript. Dr. Mulvey participated in the conduct of the study, reviewed the laboratory results and contributed to writing the manuscript. Ms. Paton participated in developing the initial study concept and design, helped to coordinate the conduct of the study and participated in analyzing the data and revising the manuscript.

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