The emergence of methicillin-resistant *Staphylococcus aureus* as a community-acquired pathogen in Canada

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The majority of strains of *Staphylococcus aureus* encountered in the community setting are sensitive to methicillin, with methicillin-resistant *S aureus* (MRSA) encountered most frequently in the hospital setting. However, there has been a significant increase in the occurence of infections caused by community-acquired methicillin-resistant *S aureus* (CA-MRSA) in different areas of the world during the last 10 years. In light of this, it was considered timely to review the steadily increasing reports of CA-MRSA and examine the threat of this newly emerging pathogen and its consequences from a Canadian perspective. The emergence of CA-MRSA is a recent phenomenon, raising considerable concern because this type of *S aureus* would cause infections difficult to treat in the outpatient setting and would markedly increase the need for vancomycin hydrochloride therapy.

Staphylococci are amongst the most hardy of the nonspore forming bacteria and can survive significant adverse environmental conditions. They can be easily cultured from dessicated clinical material, even after several months, are relatively heat-resistant and can tolerate high salt concentrations. *S aureus* is one of the most prevalent of this genus and has been a recognized pathogen in humans for centuries (1). The natural history of colonization of this bacterium with respect to the life cycle of humans is remarkable (2,3). Shortly after birth, many neonates become colonized through human or inanimate contact, often on the skin, umbilical stump or gastrointestinal tract. As the years progress, children and adults become colonized and can become carriers — either intermittent or chronic. The usual reservoir is the anterior nares, although other sites such as the groin, axillae and perineal area have been described as well. Approximately 20% to 40% of the adult population may be colonized at any given time, depending on a number of local and epidemiological factors. On an individual basis, about 30% of the adult population will be chronic carriers, 50% will be intermittent carriers and another 20% do not seem to become colonized. If the mucous membranes or the skin barrier are breached from trauma or surgical intervention, *S aureus* may enter the soft tissues and establish an invasive infection. Given this background and the virtual absence of a non-human reservoir, it is readily apparent why *S aureus* continues to be a major human pathogen that infects both healthy hosts in the community setting as well as compromised hosts in the hospital setting.

Methicillin resistance is chromosomal in origin and is conferred by a specific penicillin-binding protein (PBP) called PBP 2' (or PBP 2a) that possesses reduced affinities for binding to β-lactam antibiotics (4,5). PBP 2' is encoded by the *mecA* gene, which is carried by a large mobile genetic element that is integrated on the chromosomes of MRSA strains, designated staphylococcal cassette chromosome *mec* (SC*Cmec*) (6,7). Most MRSA infections are acquired nosocomially and most strains of MRSA are resistant to multiple antibiotics, including clindamycin hydrochloride, erythromycin, trimethoprim/sulfamethoxazole and the tetracyclines. In the late 1960s and early 1970s, the prevalence of MRSA was less than 5% in most hospital settings worldwide. A decade later, the prevalence had increased to as high as 40% in many hospitals in the United States and Europe (8,9). The first MRSA isolate was reported in Canada in 1981 (10), since this time, it has been reported in both acute care and long term care facilities (11,12). Recent data from the Canadian Nosocomial Infection Surveillance Program (CNISP) (a collaborative effort between the Laboratory Centre for Disease Control, Health Canada and the Canadian Hospital Epidemiology Committee, which is a subcommittee of the Canadian Infectious Diseases Society), has revealed that the proportion of *S aureus* isolates that are resistant to methicillin reported in the respective microbiology laboratories has increased from 0.95 per 100 isolates (0.46 per 1000 admissions) in 1995 to 3.8 per 100 isolates (1.67 per 1000 admissions) in 1997, to 5.97 per 100 isolates (4.12 per 1000 admissions) in 1999, and to 8.1 per 100 isolates (5.3 per 1000 admissions) in 2000 (13). The occurrence of MRSA varied across the country: 26% were from Western Canada, 70% were from Central Canada and 4% were from Eastern Canada.

A significant increase in the occurence of infections caused by CA-MRSA among groups of patients with no apparent connection to hospitals has been reported in different areas of the world during the past 10 years. In 2001, Chambers (14) reviewed the published reports of MRSA colonization and infection among individuals who lacked traditional risk factors. Conducting a Medline search for the period of 1976 through 1990, he identified 10 articles in which the key words

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'methicillin-resistant *Staphylococcus aureus*' and 'community' appeared in the title. By contrast, for the period of 1991 through 1999, he identified 39 articles, 21 of which were published from 1996 through 1999. Since 1999, there has been an exponential increase in these reports from around the world. Some of the countries that have reported cases to date include Australia (15,16), New Zealand (17), the United Kingdom (18), Canada (19) and the United States (14, 20).

In early reports, community isolates of MRSA had affected persons with known risk factors for colonization, including contact with health care facilities, a history of recent hospitalization, close contact with a person who had been hospitalized or previous usage of antimicrobial therapy (21,22). In the 1980 to 1981 outbreak of community-acquired MRSA infections in Detroit, approximately two-thirds of the patients affected were injection drug users (23,24). Recent hospitalization, defined as within four months (which may not have been long enough, given that hospital-acquired MRSA colonization may last years), was not a predictor of MRSA infection in drug users. The source of the Detroit outbreak was not definitively identified, but frequent needle sharing was speculated to be the mode of transmission. In turn, patients (and probably health care workers who become colonized with MRSA as a consequence of their exposure to colonized patients) in a hospital or other health care setting, can then transmit MRSA strains to close associates and family members by direct contact. A recent study of two daycare centres in Dallas, Texas, each of which had an index case of MRSA infection, revealed that 3% and 24% of children in the respective centres were colonized (25). Of the children colonized, 40% had had no contact with a healthcare facility or a household member who had been hospitalized within the two years leading up to colonization, which suggests that sustained transmission and colonization of MRSA in children were occurring in the community. Another study from Chicago (26) found a 25-fold increase in the number of children admitted to the hospital with MRSA infection who lacked an identifiable risk factor for prior colonization. These MRSA strains, presumably transmitted and acquired in a community setting, were susceptible to multiple antibiotics, in contrast to the hospital-acquired strains, which were multiply antibiotic resistant.

In 1999, the Centers for Disease Control and Prevention reported the deaths of four children in apparently unrelated cases of infection with virulent CA-MRSA in Minnesota and North Dakota (27). The cases of CA-MRSA infection in the children from Minnesota and North Dakota were alarming in that these children also had none of the risk factors commonly associated with MRSA and the infections were extremely virulent. The strains isolated from these four children were resistant to all of the β-lactams but susceptible to gentamicin sulfate, erythromycin, clindamycin hydrochloride and vancomycin hydrochloride. The deaths of these children, caused by CA-MRSA strains, focused attention on the threat of latent dissemination of highly virulent CA-MRSA strains in the community setting. Among children in the United States, the sites most frequently reported to be affected have been skin and soft tissues (28,29). Recent data, however, suggest that CA-MRSA may be becoming a more common cause of infection in other sites, including the external and middle ear. A recent study (29,30) describing the spectrum of disease in children with CA-MRSA in south Texas reported otitis externa among patients without identifiable risk factors for infection with this organism.

Recent studies have identified a novel genetic element, designated SCCmec type IV, in CA-MRSA isolates (31-33). It differs from other types of SCC*mec* in that it is very small and does not have multiple antibiotic resistance determinants. This methicillin resistance cassette has been found in isolates from diverse geographic locations, including Chicago, New Jersey, New York City, Japan and France. The relatively small size of SCC*mec* type IV suggests that it may spread easily among S *aureus* isolates. The recombinases are wild type in the type IV SCC*mec*, possibly explaining its apparent movement. SCC*mec* type IV has also been found in at least four different genomic backgrounds, suggesting a relative ease of transfer compared to types I, II and III. Its spread also appears to be clonal, as exhibited by a common pulsed-field gel electrophoresis pattern (32). Infections with these isolates have ranged from overwhelming sepsis to necrotizing pneumonia to skin and soft tissue infections; the SCC*mec* type IV element is not in itself a virulence factor (33). Baba and colleagues (33) have recently sequenced the entire genome of one CA-MRSA isolate obtained from North Dakota in 1998. The sequence analysis identified a type IVa SCC*mec* element and 19 virulence genes, including enterotoxins C and H and the *Panton-Valentine leukocidin* (*pvl*) gene. In addition, high levels of enterotoxin B and C production have been demonstrated from a recent analysis of CA-MRSA strains, which together with toxic shock syndrome toxin-1 cause nearly all of the staphylococcal toxic shock syndrome cases (34). In addition to the enterotoxins C and H, the *pvl* gene, which is normally present in only 2% to 3% of all S *aureus* isolates (35) and is associated with severe necrotizing soft tissue infections and necrotizing pneumonia (32), has been found in an increasing number of CA-MRSA strains with type IVa SCC*mec* (36).

The first report of community acquired MRSA in Canada was in 1990, when Taylor and colleagues (37) reported a multi-strain cluster of MRSA from a First Nations community in central Alberta. The authors thought that the MRSA was a hospital-acquired strain that had spread through the community, with transmission facilitated by overcrowding and poor living conditions. Embil and collegues (19) reported an association of community-acquired MRSA from Western Canada that was associated with rural residence, younger age and First Nations people. These two studies called attention to the potential endemicity of CA-MRSA in First Nations communities in Canada and were reviewed recently in this *Journal* (38). A small cluster of 15 CA-MRSA infections, predominantly of the soft tissues, was reported from a small rural village in southern Manitoba and was relatively drug susceptible (39). There are several other anecdotal reports of severe soft tissue infections from CA-MRSA arising in Western Canada (author's unpublished observations), and it is possible that the overall prevalence of this emerging pathogen has been underestimated.

The emergence of CA-MRSA has the potential to be a major threat with serious implications for the epidemiology of and therapy for S *aureus* infections. While particular vigilance is required in the First Nations populations in Canada, there is also a need to begin surveillance for these strains in all Canadian populations. If the number of infections with CA-MRSA isolates increases significantly, physicians may need to change their treatment of presumptive S *aureus* infections, relying on clindamycin hydrochloride and vancomycin hydrochloride instead of on the β-lactams.

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