ORIGINAL ARTICLE

Clinical characteristics of pediatric patients hospitalized with methicillin-resistant *Staphylococcus aureus* in Canadian hospitals from 2008 to 2010

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Methicillin-resistant *Staphylococcus aureus* (MRSA) infections were uncommon in children in Canada until the 1990s. Using a standardized case report form, treating physicians reported children hospitalized due to MRSA infections in Canadian hospitals through the Canadian Pediatric Surveillance Program in a 24-month period (2008 to 2010). Of 155 cases reported, 70% were ≤4 years of age and approximately one-third had an underlying medical condition. The most common clinical infections involved skin and soft tissue (69%), the lower respiratory tract (12%), and bone and joint (10%). Almost one-third had had contact with the health care environment in the previous year and 18% had a known household member with MRSA. Initial therapy with a beta-lactam alone occurred in 65%, while 22% included vancomycin. No child in this cohort died but 14% required admission to the intensive care unit. Of 143 reports of individual isolates, 93% were reported susceptible to trimethoprim-sulfamethoxazole, 63% to clindamycin and 50% to mupirocin.

The present study involved only children hospitalized with MRSA infections. It may not be representative of the children treated as outpatients nor children in selected areas of Canada where MRSA infections may be more endemic. Further targeted surveillance to identify risks and treatment practices in these populations may be important.

Key Words: *Infections in hospitalized children; Methicillin-resistant* Staphylococcus aureus*; MRSA; Pediatrics*

Les caractéristiques cliniques des patients d'âge pédiatrique hospitalisés en raison d'un staphylocoque doré méthicillinorésistant dans des hôpitaux canadiens de 2008 à 2010

Jusque dans les années 1990, l'infection par le staphylocoque doré méthicillinorésistant (SARM) était peu courante chez les enfants du Canada. Au moyen d'un formulaire de déclaration de cas standardisé, des médecins traitants ont signalé les enfants hospitalisés à cause d'une infection par le SARM dans les hôpitaux canadiens par l'entremise du Programme canadien de surveillance pédiatrique au cours d'une période de 24 mois (2008 à 2010). Des 155 cas déclarés, 70 % avaient quatre ans ou moins, et environ le tiers présentait un problème de santé sous-jacent. Les infections cliniques les plus courantes touchaient la peau et les tissus mous (69 %), les voies respiratoires inférieures (12 %) ainsi que les os et les articulations (10 %). Près du tiers avait eu des contacts avec le milieu de la santé au cours de l'année précédente, et dans 18 % des cas, un membre de la famille était atteint d'une SARM connue. Chez 65 % des patients, le traitement initial se limitait à une bêta-lactamine, tandis que dans 22 % des cas, il incluait la vancomycine. Aucun enfant de cette cohorte n'est décédé, mais 14 % ont dû être hospitalisés aux soins intensifs. Des 143 déclarations d'isolats individuels, on a signalé que 93 % étaient susceptibles au triméthoprim-sulfaméthoxazole, 63 % à la clindamycine et 50 % à la mupirocine.

La présente étude portait seulement sur les enfants hospitalisés à cause d'une infection par le SARM. Elle n'est peut-être pas représentative des enfants traités en consultations externes ou des enfants de certaines régions du Canada où les infections par le SARM sont peut-être plus endémiques. Il serait peut-être important de poursuivre une surveillance ciblée pour déterminer les risques et les pratiques thérapeutiques au sein de ces populations.

Staphylococcus aureus is a major pathogen associated with skin and soft tissue infections (SSTIs) as well as invasive disease, particularly necrotizing pneumonia, fasciitis, osteomyelitis and sepsis. Once readily sensitive to methicillin-based β-lactams, methicillin-resistant *S aureus* (MRSA) has emerged over the past several decades as a significant cause of morbidity and mortality. The prevalence of methicillin-sensitive *S aureus* infections has remained relatively constant; however, rates of community-associated MRSA (CA-MRSA) have increased since the beginning of the 21st century (1,2). While adding to the burden of community-associated infection, MRSA is also associated with increased morbidity and mortality in children with underlying conditions such as cancer and cystic fibrosis (3-5).

Historically, strains responsible for health care-associated MRSA (HA-MRSA) were associated with higher rates of multidrug resistance than strains responsible for CA-MRSA. The diagnosis of HA-MRSA, based on previous associations with an acute care facility or with indwelling devices, was predictive and empirical antibiotic therapy could be guided by historical risk factors (6,7). In children, robust risk factors that differentiate risk of CA-MSRA from HA-MRSA are few (8-12). Recurrent skin infections, a history of skin infections in household members and/or lower trunk disease versus upper trunk disease appear to be risks for CA-MRSA (13). The risk of MRSA versus methicillin-sensitive *S aureus* SSTIs has been shown in some studies to depend on race and socioeconomic status. These risks, however, vary with the geographical distribution of the patient populations studied and may not be applicable across national boundaries where differences in health care provision and insurance models exist (1,9-11).

The Canadian Paediatric Surveillance Program (CPSP) undertook active timely surveillance for hospitalized children <18 years of age with MRSA infections. This surveillance aims to describe the clinical spectrum of these infections as well as identify characteristics associated with MRSA infections requiring hospitalization.

METHODS

Case definition

A case was defined as a hospitalized child, <18 years of age, who presented with or developed symptomatic MRSA infection that was laboratory confirmed from a clinical sample. Cases of MRSA isolated

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TABLE 1
Case demographics*

Characteristic	Total n=155
Male sex	89 (57)
Age	
<1 month	18 (12)
1–12 months	37 (24)
1–4 years	50 (32)
5–9 years	18 (12)
10–15 years	22 (14)
≥16 years	10 (6)
Place of residence	
Urban	116 (75)
Rural	31 (20)
Residents per houshold	
≤4	81 (52)
≥5	44 (28)
Known household member with MRSA	28 (18)
Known household member in health care	8 (5)
Previous MRSA hospitalization	17 (11)
Hospital, surgical or dialysis admission in past 12 months	47 (30)
Catheterization or percutaneous line in past 12 months	14 (9)
Underlying chronic medical condition	49 (32)
Prematurity	3 (2)
Eczema	9 (6)
Asthma	4 (3)
Cystic fibrosis	4 (3)
Neurological or neuromuscular disorder	12 (8)
Congenital abnormality/syndrome	10 (6)
Crohn disease	1 (1)
Not defined	6 (4)
Skin condition	23 (15)
Piercing/tattoo	9 (6)
Illicit drug use/homelessness	4 (3)
Daycare attendance in past year	19 (12)
Contact sports participation in past year	4 (3)

*Data presented as n (%). *Total percentages may not equal 100% because of unreported or unknown data. The denominator for percentage calculations is the total of cases minus the total of unknown or unreported cases for each particular data. MRSA Methicillin-resistant* Staphylococcus aureus

from a surveillance culture or as an incidental finding were excluded.

Case ascertainment

Through established methodology of the CPSP, an average of 2500 pediatricians and pediatric subspecialists were actively surveyed on a monthly basis to submit cases meeting the definition from September 2008 to August 2010. For each hospitalized case of MRSA, the physician was asked to complete a non-nominal case report form detailing the patient's demographic data, previous history, clinical presentation on admission, site of culture isolate, preceding antimicrobial therapy, antibiotic susceptibility of clinical isolates and outcome (including hospital length of stay, intensive care unit length of stay, discharge to rehabilitation facility and death). Using the information available to them, the reporting physicians were asked to report whether the case had been classified, based on local institutional guidelines, as CA-MRSA or HA-MRSA. Duplicate submissions, based on same institution and admitting date, for the same case presentation were merged into a single record. Monthly 'nil reports' were also received from physicians.

Ethics approval

Ethics approval was granted by the Research Ethics Board of the Children's Hospital of Eastern Ontario, Ottawa, and by the Public Health Agency of Canada Research Ethics Board.

RESULTS

A total of 262 hospitalized children with MRSA were identified during the two-year study period. Eighty-four cases were excluded either because they were colonized and did not experience clinical infections, or the completed case reports were not submitted. Twenty-three cases were duplicate reports of the same patient presentation. In total, 155 hospitalized patients with MRSA infections were eligible for analysis. Of these, 91 (59%) cases were reported from tertiary children's hospitals and the remaining 64 (41%) were reported from community hospitals that admit both adults and children. Physicians reported that 133 (85.8%) cases were CA-MRSA and 22 (14.2%) were HA-MRSA.

Demographic and previous history

As shown in Table 1, more than one-half of patients with MRSA were male (57%). The mean (± SD) age of MRSA cases was 4.6±5.5 years with a median of 1.8 years. There was no difference in mean age between male and female subjects. Overall, 107 (69%) had no underlying minor or major medical conditions.

Central (Quebec and Ontario) and far Western (Alberta and British Columbia) regions of Canada reported the highest proportions of cases. Quebec reported 45 (29%) of the MRSA cases, followed by Alberta with 30 (19%) cases and Ontario and British Columbia reporting 26 (17%) and 22 (14%) cases, respectively. There were no reported cases from the Yukon or Nunavut. The majority (116 [75%]) of children lived in urban areas. Eighty-one (52%) patients lived in households of four persons or less. Children had known household MRSA contacts in 28 (18%) cases. There was a history of previous hospital admission in 47 (30%) cases and 17 (12%) patients had previously been hospitalized for MRSA infection. The presence of an underlying chronic medical condition was reported for 49 patients (32%); however, major systemic or congenital disorders (cystic fibrosis, Crohn disease, chronic neurological or congenital syndromes) were present for 27 (17%) patients. All of the children with a history of eczema presented with a SSTI and all children with a history of cystic fibrosis or bronchiectasis presented with respiratory infections. The patient with Crohn disease presented with an intra-abdominal abscess.

Health outcomes

The mean and median length of hospital stay in 154 reported cases was 14.5 and seven days, respectively (range one to 197 days). Twenty-one (14%) children required admission to an intensive care unit, with a mean and median length of stay of 27.7 and 8.5 days, respectively (range one to 197 days). Of the 143 patients for whom outcome information was available, 137 (96%) were recovering at the time of discharge while six (4%) patients were transferred to a rehabilitation facility. There were no deaths. Of the patients who were transferred to a rehabilitation facility, one had survived a motor vehicle collision and experienced a traumatic brain injury, one was born prematurely at 32 weeks and another had congenital myasthenia gravis. Two of the remaining three patients requiring rehabilitation had been hospitalized for joint infections.

Clinical characteristics

SSTI was the most common clinical presentation, occurring in 107 (69%) patients (Table 2). Ten (6%) of the SSTIs were accompanied by bone and joint (n=4), respiratory (n=2) or bloodstream (n=5) infections. There were 16 cases of cervical adenitis.

Respiratory tract infections were reported in 19 (12%) patients, including seven cases of empyema. Five of the empyema cases were in children between five and 12 months of age and none had an underlying medical condition.

Bone and joint infections were present in 16 (10%) patients. As well, there were three (2%) newborns with conjunctivitis: two younger than seven days of age and one 18 days of age. Other uncommon clinical presentations included a urinary tract infection in a patient with spina bifida and meningitis.

A total of 190 positive MRSA cultures were obtained from the 155 patients. MRSA was most commonly isolated from the skin. MRSA was isolated from the respiratory tract (sputum, endotracheal secretions, pleural tissue or chest tube drainage) in 24 cases (15%), from blood in 20 (11%) cases and from cerebrospinal fluid in two (1%) cases.

Coinfection with another pathogen, isolated within 72 h of MRSA infection, was reported in 33 (21%) cases. A positive test for viruses (five respiratory syncytial virus [RSV], three influenza, three varicella, four enterovirus/rhinovirus, and two herpes simplex virus – one patient was positive for both RSV and entero/rhinovirus) was reported in 16 (10%) patients. Eight cases with concomitant respiratory virus isolation (three RSV, three influenza and three entero/rhinovirus [one patient positive for both RSV and entero/rhinovirus]) presented with pneumonia including two infants 27 and 48 days of age, respectively. Three infants with empyema harboured viruses: one with RSV, one with rhinovirus and one had both RSV and rhinovirus identified by nucleic acid testing. A four-year-old girl with empyema was positive for H1N1 influenza.

Infection control precautions and therapy

Of the 151 patients for whom admission isolation status was reported, 51 (34%) were cared for with special precautions only after MRSA was identified. One patient who had MRSA in joint aspirate and blood was not isolated.

Antimicrobials most frequently used before the confirmation of MRSA diagnosis were cefazolin in 38 (25%) cases, vancomycin in 36 (23%) cases and clindamycin in 23 (15%) cases. A cephalosporin of any kind was prescribed in 72 (46%) of all cases. Twenty-three (25%) SSTI cases were treated empirically with a cephalosporin alone. Vancomycin, trimethoprim-sulfamethoxazole (TMP-SMX) or clindamycin was used as empirical therapy before MRSA identification in 48 (45%) of the 95 SSTI cases. All patients with fasciitis or myositis received vancomycin before MRSA identification.

MRSA antimicrobial susceptibilities

The majority of isolates with reported antibiotic susceptibilities were sensitive to TMP-SMX (Table 3). Ninety-three of 147 (63%) isolates were sensitive to clindamycin. The rate of resistance to TMP-SMX and clindamycin did not differ according to clinical presentation or tissue source of positive MRSA culture (data not shown). The majority of isolates with reported susceptibilities to ciprofloxacin and erythromycin were resistant, with only 16 (34%) and 23 (17%) being sensitive, respectively. Of 28 isolates in which mupirocin susceptibilities were reported, 14 (50%) were resistant, while 15 of 27 (56%) isolates were resistant to fusidic acid.

DISCUSSION

The present report is the first to describe the clinical characteristics of a large cohort of children hospitalized with MRSA infection in Canada. A Canadian Nosocomial Infection Surveillance Program laboratory-based study has identified an increase in CA-MRSA as a proportion of MRSA cases over time from 1995 until 2007 (6). In that study, CA-MRSA comprised 62% of MRSA in the years 2004 to 2007. In the present cohort, we could not verify the designation of CA-MRSA versus HA-MRSA; however, the majority appeared to be CA-MRSA.

TABLE 2
Frequency of clinical presentation in methicillin-resistant *Staphylococcus aureus* hospitalized pediatric cases

Clinical presentation	Total n=155*
Skin and soft tissue	107 (69)
Cellulitis	63 (41)
Boils	36 (23)
Abscess/adenitis (noncervical)	28 (18)
Superinfected eczema	5 (3)
Cervical abscess/adenitis	16 (10)
Fasciitis	2 (1)
Myositis	2 (1)
Wound/surgical site	2 (1)
Respiratory tract	19 (12)
Pneumonia	12 (8)
Pneumonia with empyema	7 (5)
Bone and joint	16 (10)
Osteomyelitis	13 (8)
Septic arthritis	7 (5)
Bacteremia	13 (8)
Otitis	5 (3)
Conjunctivitis	3 (2)
Mastoiditis	2 (1)
Meningitis	2 (1)
Urinary tract infection	1 (<1)

*Data presented as n (%). *Sum may equal more than 155 because some patients presented with infection of more than one body system*

In the present study, most of the children were previously healthy. Underlying medical conditions were reported in 49 (32%) patients with 11% having eczema, prematurity or asthma. Notably, 11% of children in the present cohort had a previous hospitalization for MRSA and 30% had contact with health care environments in the previous year (Table 1). Whether these represented acquisition of MRSA in health care settings is not known, but is suggestive.

Eighteen per cent of children in the present cohort had a known household member with MRSA. Within the cohort, 12% were younger than one month of age and only one of the 11 neonates had a family member known to be colonized with MRSA. In this age group, acquisition may have occurred during the birthing process or later through close contact with a colonized caregiver. A number of studies have identified MRSA carriage rates in pregnant women by recto-vaginal swab to be between 1% and 10% (14-17). Concordance rates between MRSA strains carried by mother-infant pairs have been reported to be between 31% and 68% (18,19). In the present study sample, however, the carriage rate of the mothers may not have been known because the practice of routinely testing women at delivery is not common in Canadian facilities.

Guidelines for treatment of simple cutaneous abscesses due to MRSA suggest that if uncomplicated, incision and drainage should be the primary treatment modality and antimicrobial therapy may not be required (20,21). The Canadian guidelines indicate that for moderate to severe disease, regardless of the presence of purulence, empirical therapy should include coverage for MRSA and group A streptococci (20). The Infectious Diseases Society of America guidelines for the management

TABLE 3
Reported antimicrobial susceptibility of methicillin-resistant *Staphylococcus aureus* isolates

	Antimicrobial susceptibility							
	Trimethoprim-sulfamethoxazole	Clindamycin	Ciprofloxacin	Erythromycin	Rifampin	Mupirocin	Fusidic acid	Doxycycline
Susceptible	133 (93)	93 (63)	16 (34)	23 (17)	80 (86)	14 (50)	12 (44)	27 (59)
Resistant	10 (7)	54 (37)	31 (67)	115 (83)	13 (14)	14 (50)	15 (56)	19 (41)
Total, n	143	147	47	138	93	28	27	46

Data presented as n (%) unless otherwise indicated. The totals reflect the number of isolates for which there was reported susceptibilities

of SSTI suggest that β-lactams are the first line of therapy for individuals with nonpurulent cellulitis, whereas empirical coverage for MRSA should be added for patients with purulent or complicated cellulitis (21). In this sample, the majority of children (65%) with SSTIs were treated empirically with β-lactams, while 21% were treated with clindamycin, 22% with vancomycin and 8% with TMP-SMX, suggesting that the index of suspicion for MRSA may still be low in some parts of Canada.

The MRSA isolates reported in the present study were not typed; however, susceptibility patterns were reported. In the present cohort, reported susceptibility to TMP-SMX was 93% while only 63% of isolates were susceptible to clindamycin. The recent Canadian Ward Surveillance Study analyzed isolates collected from tertiary hospitals from across Canada between 2007 and 2009 and documented that 28% of HA-MRSA and 86% of CA-MRSA isolates, respectively, were susceptible to clindamycin (7). Other pediatric MRSA isolates tested as part of a surveillance study conducted by the Canadian Nosocomial Infection Surveillance Program between 1995 and 2007 also indicated a significant level of clindamycin resistance (43% to 62%) (6). Infectious Diseases Society of America guidelines consider clindamycin monotherapy suitable only in areas where clindamycin resistance is low (<10%) (21). United Kingdom guidelines also indicate that clindamycin cannot be assumed to be active against MRSA (22). The reported resistance rates for clindamycin of 30% in the present study support this recommendation.

The strength of the present study was the large number of reports from diverse areas of the country including cases that might not be identified by a study limited to major academic hospital centres. There are notable limitations. The data were collected in a retrospective fashion by pediatricians; however, they would have been directly involved in the management of the patient. Additionally, the classification of cases as health care versus community associated could not be verified. Being a voluntary program, not all cases were reported and no cases were reported from Nunavut or the Yukon. Thus, this cohort does not include all hospitalized children with MRSA infections and may not represent areas of the country that may have a different epidemiology. For example, this may not reflect the Aboriginal populations or northern parts of Canada, or in communities where MRSA infections may be primarily managed in outpatient settings. Although clinical characteristics and demographic information were collected, this surveillance was not designed to identify risk factors for MRSA infection. The patterns of antimicrobial resistance were determined from laboratory reports on patient charts and the strains were not submitted for testing.

In summary, we report a 'snapshot' of children hospitalized with MRSA in Canadian hospitals between 2008 and 2010. Most children were generally healthy before their hospitalization while 17% had underlying neurological or congenital disorders requiring chronic care. The clinical outcome for these children was good, with no deaths reported. Greater than 90% of MRSA isolates are reportedly still susceptible to TMP-SMX; there is a reported rate of 30% of clindamycin resistance. Further attempts to study MRSA infections in populations not represented in this cohort may be warranted.

CONFLICTS OF INTEREST: None to disclose.

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