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Characterization of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Canadian Hospitals from 2007-2016

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REVISED ABSTRACT

Background: As part of the CANWARD surveillance study, we compared the epidemiology of community-associated (CA) and healthcare-associated (HA)-MRSA genotypes in Canadian hospitals. **Methods:** Between 2007 and 2016, 1963 MRSA were collected from patients attending tertiary-care medical centres across Canada. Susceptibility testing was performed by broth microdilution in accordance with CLSI guidelines. Isolates were characterized by *spa* typing and PCR of the Panton-Valentine leukocidin (PVL) gene. **Results:** The annual proportion of MRSA genotypes is shown below:

MRSA Type	Study Year										P-value*
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	
All MRSA (% of all *S. aureus*)	26.1	27.0	21.0	21.2	19.3	18.2	20.1	20.2	19.3	16.9	<0.0001
HA-MRSA (% of all MRSA)	79.2	69.1	65.5	58.7	59.7	54.4	57.2	56.1	50.7	43.8	<0.0001
CMRSA1 [USA600]	2.3	1.1	0	1.8	0.6	4.0	0.6	3.2	0.7	2.7	0.7374
CMRSA2 [USA100/800]	64.9	56.3	58.6	49.8	55.8	43.2	48.4	46.5	46.5	40.2	<0.0001
CMRSA3/6	10.6	8.8	4.7	3.1	0.6	0	3.8	1.9	0	0	<0.0001
CMRSA4 [USA200]	0	0.4	0	0.9	0	0.8	0.6	0	0.7	0	1
CMRSA5 [USA500]	1.0	1.5	0	1.3	1.3	2.4	0	1.3	0.7	0	0.5792
CMRSA8	0	0.7	1.7	1.8	1.3	4.0	3.8	3.2	2.1	0.9	0.2254
CMRSA9	0.3	0.4	0.4	0	0	0	0	0	0	0	1
CA-MRSA (% of all MRSA)	20.8	30.9	34.5	41.3	40.3	45.6	42.8	43.9	49.3	56.2	<0.0001
CMRSA7 [USA400]	6.5	5.5	8.2	6.7	7.8	12.0	8.2	5.1	11.1	11.6	0.1033
CMRSA10 [USA300]	13.2	22.1	23.7	31.4	28.6	27.2	27.7	31.8	29.3	33.9	<0.0001
Other	1.0	3.3	2.6	3.1	3.9	6.4	6.9	7.0	9.0	10.7	<0.0001

*P-value determined by Fisher's exact test comparing 2007 vs. 2016 data.

PVL was detected in 78.4% of CA-MRSA and 1.7% of HA-MRSA. Resistance rates (CA vs HA) were 60.8 vs 94.8% to ciprofloxacin, 69.3 vs 93.4% to clarithromycin, 13.4 vs 65.2% to clindamycin and 0 vs 9.4% to trimethoprim-sulfamethoxazole. MRSA were 100% susceptible to linezolid and 99.9% susceptible to daptomycin and vancomycin. **Conclusions:** The most frequent CA-MRSA genotype was USA300 (CMRSA10) while USA100/800 (CMRSA2) was the predominant HA-MRSA genotype. Despite an overall decrease in the numbers of MRSA, the proportion of CA-MRSA in Canadian hospitals has risen significantly between 2007 and 2016.

BACKGROUND

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) account for an increasing proportion of MRSA isolates in hospitals and long-term care facilities across North America. While skin and soft tissue infections are the most common infections caused by CA-MRSA, invasive disease such as bacteremia associated with sepsis and necrotizing pneumonia can occur. The individuals most often affected by CA-MRSA typically lack established risk factors for MRSA acquisition/infection. CA-MRSA differ from healthcare-associated MRSA (HA-MRSA) in that they are generally more susceptible to a variety of non-beta-lactam antimicrobial agents. Of particular concern, however, is the emergence of isolates with reduced susceptibility or heterogeneous resistance to vancomycin, an important antimicrobial for the empiric treatment of severe infections. In addition, the majority of CA-MRSA strains harbor virulence determinants such as the Panton-Valentine leukocidin (PVL) as well as other toxins that may contribute to the increasing morbidity and mortality associated with CA-MRSA infections.

The purpose of this study was to compare the demographics, antimicrobial susceptibilities and molecular epidemiology of community-associated and healthcare-associated MRSA genotypes in Canada from 2007 to 2016, inclusive.

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MATERIALS & METHODS

Methicillin-Resistant *S. aureus* Isolates

1963 isolates of MRSA were collected between 2007 and 2016 as part of the ongoing CANWARD surveillance study assessing antibiotic resistance in Canadian hospitals. Isolates were received from tertiary-care medical centres (12 in 2007, 10 in 2008, 15 in 2009, 14 in 2010, 15 in 2011, 12 in 2012, 15 in 2013 and 13 in each of 2014, 2015 and 2016) that were geographically distributed in a population-based fashion in 8 of the 10 Canadian provinces. All *S. aureus* were identified at the originating centre using local site criteria. Resistance to methicillin was confirmed at the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) using the CLSI-approved disk diffusion method with cefoxitin, as well as by growth on MRSA*select* chromogenic media.

Antimicrobial Susceptibility Testing

The *in vitro* activities of cefazolin, clarithromycin, clindamycin, ciprofloxacin, daptomycin, levofloxacin, linezolid, moxifloxacin, telavancin, tigecycline, trimethoprim-sulfamethoxazole and vancomycin were determined by broth microdilution in accordance with CLSI guidelines (M7-A10, 2015). MIC interpretive standards were defined according to CLSI breakpoints (M100-S27, 2017). The following interpretive breakpoints (FDA) were used: telavancin susceptible, ≤1 μg/ml; tigecycline susceptible, ≤0.5 μg/ml.

Molecular Characterization of MRSA

MRSA status was confirmed by real-time PCR of the *mecA* and *nuc* genes (McDonald et al. 2005. J. Clin. Microbiol. 43:6147-6149). This triplex PCR assay included primers for the detection of the *lukF-PV* and *lukS-PV* genes encoding the Panton-Valentine leukocidin (PVL) toxin (McDonald et al. 2005. J. Clin. Microbiol. 43:6147-6149).

MRSA strains were characterized by staphylococcal protein A (*spa*) typing as previously described (Golding et al. 2008. Can. J. Infect. Dis. Med. Microbiol. 19:273-281). For the purpose of this study, community-associated (CA)-MRSA and healthcare-associated (HA)-MRSA were defined genotypically (ie. on the basis of their *spa* type) and not epidemiologically as per CDC criteria for distinguishing CA-MRSA from HA-MRSA, because epidemiologic information was not available. There has previously been shown to be good correlation between *spa* types and Canadian epidemic PFGE strain types CMRSA1-10 (Golding et al. 2008. Can. J. Infect. Dis. Med. Microbiol. 19:273-281), allowing for classification of strains as either CA-MRSA or HA-MRSA. Any MRSA with a *spa* type associated with a CMRSA7 (USA400) or CMRSA10 (USA300) genotype were labeled as CA-MRSA. MRSA with infrequent *spa* types or those without an equivalent Canadian epidemic PFGE type (such as the USA700, USA1000 and USA1100 strains) were also considered to be community-associated. All other *spa* types corresponding to a characterized epidemic type (eg. CMRSA1 [USA600], CMRSA2 [USA100/800], CMRSA4 [USA200], CMRSA5 [USA500], CMRSA3/6, CMRSA8, CMRSA9, etc.) were labeled as HA-MRSA.

CONCLUSIONS

1. Overall, MRSA rates decreased during the 10-year study period (*P*<0.0001). Of the MRSA strains from Canadian hospitals, 37.0% and 63.0% were identified by *spa* typing as CA-MRSA and HA-MRSA, respectively. The prevalence of CA-MRSA increased significantly from 20.8% in 2007 to 56.2% in 2016 while HA-MRSA decreased from 79.2% to 43.8% during this same period (*P*<0.0001).
2. CA-MRSA genotypes CMRSA7 (USA400) and CMRSA10 (USA300) represented 7.7% and 24.9% of all MRSA, respectively. The prevalence of CMRSA10 (USA300) increased significantly from 13.2% in 2007 to 33.9% in 2016 (*P*<0.0001).
3. CMRSA2 (USA100/800) was the predominant HA-MRSA genotype, accounting for 53.6% of all MRSA and 85.0% of HA-MRSA.
4. The majority (78.4%) of CA-MRSA were PVL(+) whereas 98.3% of HA-MRSA were PVL(-).
5. Although the annual proportion of CMRSA7 (USA400) strains did not change significantly over the study period, the proportion of PVL(-) [versus PVL(+)] CMRSA7 (USA400) increased from 16.0% in 2007 to 76.9% in 2016 (*P*=0.0004).
6. CA-MRSA strains were more susceptible to clarithromycin, clindamycin, fluoroquinolones and trimethoprim-sulfamethoxazole than HA-MRSA.
7. 0.7% of CA-MRSA had a vancomycin MIC of 2 μg/ml compared to 2.1% of HA-MRSA (*P*=0.01). Intermediate resistance (MIC 4 μg/ml) to vancomycin was observed in two MRSA with a PVL-negative CMRSA2 (USA100/800) genotype and one PVL-positive CMRSA10 (USA300) genotype. MRSA were 100% susceptible to linezolid and telavancin and 99.9% susceptible to daptomycin and vancomycin.

RESULTS

Figure 1. Proportion of *S. aureus* strains identified as MRSA.

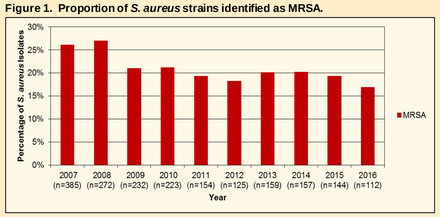

Figure 2. Proportion of MRSA strains identified as CA-MRSA or HA-MRSA.

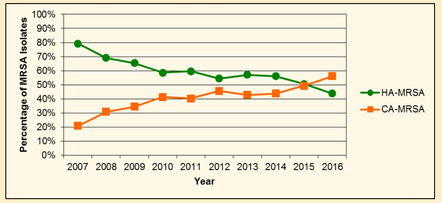

Figure 3. Distribution of PVL(+) and PVL(-) CA-MRSA and HA-MRSA.

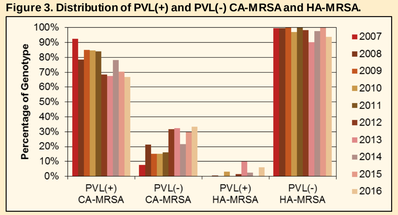

Figure 4. Distribution of CA-MRSA and HA-MRSA PFGE epidemic types.

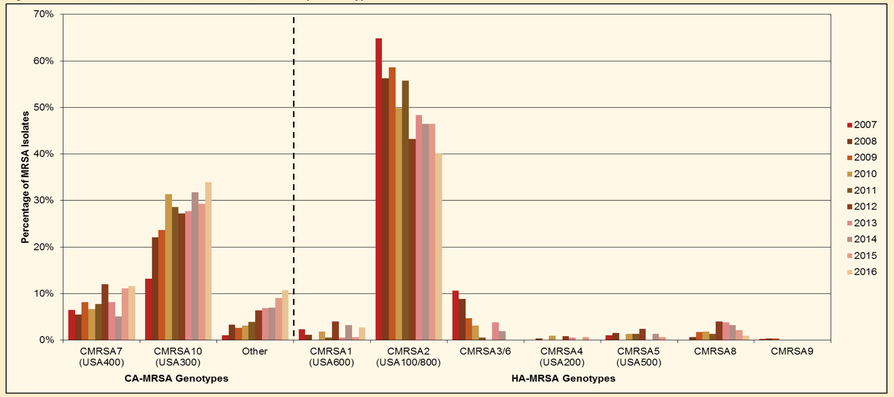

Table 1. Demographics of patients with MRSA infections.

Characteristic	CA-MRSA (n=726)	HA-MRSA (n=1237)	Total (n=1963)
Sex, n (%)			
Male	426 (58.7)	734 (59.3)	1160 (59.1)
Female	300 (41.3)	503 (40.7)	803 (40.9)
Mean age, years	42.8	64.6	56.5
Median age (range)	45 (1-95)	68 (1-105)	60 (1-105)
Age group, n (%)			
≤ 17	113 (15.6)	28 (2.3)	141 (7.2)
18-64	494 (68.0)	483 (39.0)	977 (49.8)
≥ 65	119 (16.4)	726 (58.7)	845 (43.0)
Region, n (%)			
West	402 (55.4)	348 (28.1)	750 (38.2)
Ontario	244 (33.6)	421 (34.0)	665 (33.9)
Quebec	43 (5.9)	362 (29.3)	405 (20.6)
Maritimes	37 (5.1)	106 (8.6)	143 (7.3)
Hospital ward type, n (%)			
Emergency room	225 (31.0)	183 (14.8)	408 (20.8)
Clinic/office	119 (16.4)	166 (13.4)	285 (14.5)
Intensive care unit	130 (17.9)	231 (18.7)	361 (18.4)
Medical/surgical ward	252 (34.7)	657 (53.1)	909 (46.3)
Infection site, n (%)			
Bloodstream	257 (35.4)	444 (35.9)	701 (35.7)
Respiratory tract	181 (24.9)	532 (43.0)	713 (36.3)
Urinary tract	6 (0.8)	48 (3.9)	54 (2.8)
Wounds/IV sites	282 (38.9)	213 (17.2)	495 (25.2)

Table 2. Comparison of antibiotic resistance rates among CA-MRSA and HA-MRSA.

Antibiotic	CA-MRSA (n=726)						HA-MRSA (n=1237)						All MRSA (n=1963)					
	MIC$_{50}$	MIC$_{90}$	MIC Range	% of Isolates per Category			MIC$_{50}$	MIC$_{90}$	MIC Range	% of Isolates per Category			MIC$_{50}$	MIC$_{90}$	MIC Range	% of Isolates per Category		
				S	I	R				S	I	R				S	I	R
Cefazolin	16	64	≤0.5 - >128	-	-	100[a]	128	>128	≤0.5 - >128	-	-	100[a]	64	>128	≤0.5 - >128	-	-	100[a]
Ciprofloxacin	16	16	≤0.06 - >16	38.2	1.0	60.8	>16	>16	0.25 - >16	5.2	0	94.8	>16	>16	≤0.06 - >16	17.4	0.4	82.2
Clarithromycin	32	>32	0.12 - >32	30.1	0.6	69.3	>32	>32	≤0.03 - >32	6.3	0.3	93.4	>32	>32	≤0.03 - >32	15.1	0.4	84.5
Clindamycin	≤0.12	>8	≤0.12 - >8	86.6	0	13.4	>8	>8	≤0.12 - >8	34.7	0.1	65.2	≤0.25	>8	≤0.12 - >8	53.8	0.1	46.1
Daptomycin	0.25	0.5	0.12 - 2	99.9	-	0.1	0.25	0.25	0.06 - 4	99.9	-	0.1	0.25	0.5	0.06 - 4	99.9	-	0.1
Levofloxacin	4	8	0.12 - 32	43.4	0	56.6	>32	>32	0.12 - >32	2.9	0	97.1	>32	>32	0.12 - >32	14.1	0	85.9
Linezolid	2	2	0.5 - 4	100	-	0	2	4	≤0.12 - 4	100	-	0	2	4	≤0.12 - 4	100	-	0
Moxifloxacin	2	2	≤0.06 - 16	39.7	8.8	51.5	8	>16	≤0.06 - >16	5.3	0.4	94.3	8	>16	≤0.06 - >16	18.0	3.5	78.5
Telavancin[b]	0.06	0.06	0.015 - 0.12	100	-	-	0.06	0.06	0.015 - 0.12	100	-	-	0.06	0.06	0.015 - 0.12	100	-	-
Tigecycline	0.25	0.25	≤0.03 - 0.5	100	-	0	0.25	0.5	0.06 - 2	98.7	-	1.3	0.25	0.5	≤0.03 - 2	99.2	-	0.8
TMP-SMX	≤0.12	≤0.12	≤0.12 - 2	100	-	0	≤0.12	0.5	≤0.12 - >8	90.6	-	9.4	≤0.12	≤0.12	≤0.12 - >8	94.1	-	5.9
Vancomycin	1	1	0.5 - 4	99.9	0.1	0	1	1	≤0.12 - 4	99.8	0.2	0	1	1	≤0.12 - 4	99.9	0.1	0

[a]Based on cefoxitin disktest. [b]Data available from 2013-2016.

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