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Characterization of Methicillin-Resistant *Staphylococcus aureus* in Canadian Hospitals from 2007-2017

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Introduction

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 and 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 potential for emergence of isolates with reduced susceptibility 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 2017, inclusive.

Materials and Methods

Methicillin-Resistant *S. aureus* Isolates

2078 isolates of MRSA were collected between 2007 and 2017 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, 13 in each of 2014, 2015 and 2016 and 14 in 2017) 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 ceftaroline, ceftobiprole, ciprofloxacin, clarithromycin, clindamycin, daptomycin, doxycycline, linezolid, moxifloxacin, telavancin, tigecycline, trimethoprim-sulfamethoxazole and vancomycin were determined by broth microdilution in accordance with CLSI guidelines (1). MIC interpretive standards were defined according to CLSI breakpoints (2). For tigecycline, MIC interpretation was based on the FDA package insert label (susceptible breakpoint ≤0.5 μg/mL). Ceftobiprole MICs were interpreted using EUCAST breakpoints (susceptible ≤2 μg/mL; resistant >2 μg/mL).

Molecular Characterization of MRSA

MRSA status was confirmed by real-time PCR of the *mecA* and *nuc* genes (3). This triplex PCR assay included primers for the detection of the *lukF-PV* and *lukS-PV* genes encoding the Panton-Valentine leukocidin (PVL) toxin (3).
MRSA strains were characterized by staphylococcal protein A (*spa*) typing, and Canadian epidemic PFGE strains types were inferred by *spa* repeat pattern analysis as previously described (4). For the purpose of this study, community-associated (CA)-MRSA and healthcare-associated (HA)-MRSA were defined genotypically based on the inferred epidemic strain type because epidemiologic information was not available. Any MRSA with a *spa* type associated with a CMRSA7 (USA400) or CMRSA10 (USA300) genotype were categorized 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 or CMRSA9) were labeled as HA-MRSA.

Results

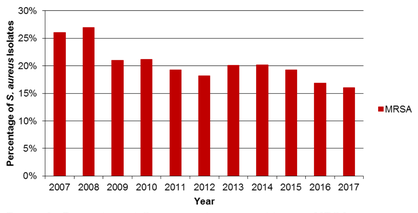


Figure 1. Proportion of *S. aureus* strains identified as MRSA

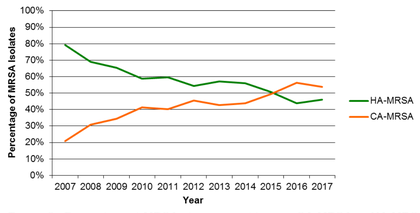


Figure 2. Proportion of MRSA strains identified as CA-MRSA or HA-MRSA

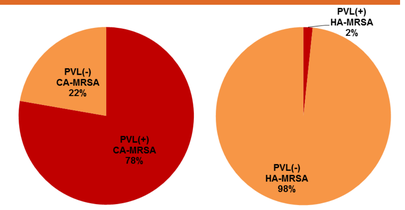
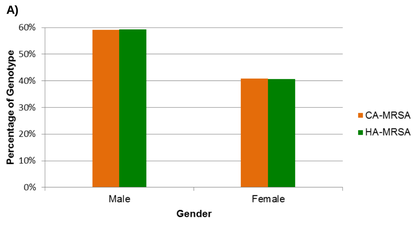
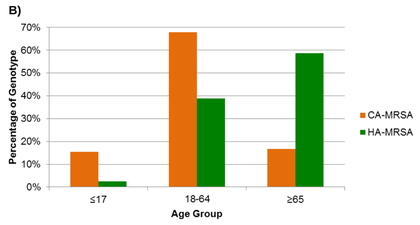


Figure 3. Distribution of PVL(+) and PVL(-) CA-MRSA and HA-MRSA





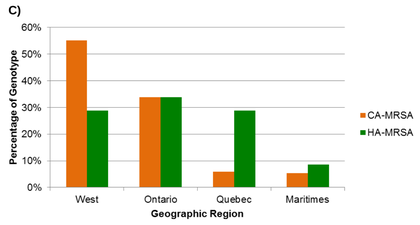


Figure 4. Demographics of patients with MRSA infections

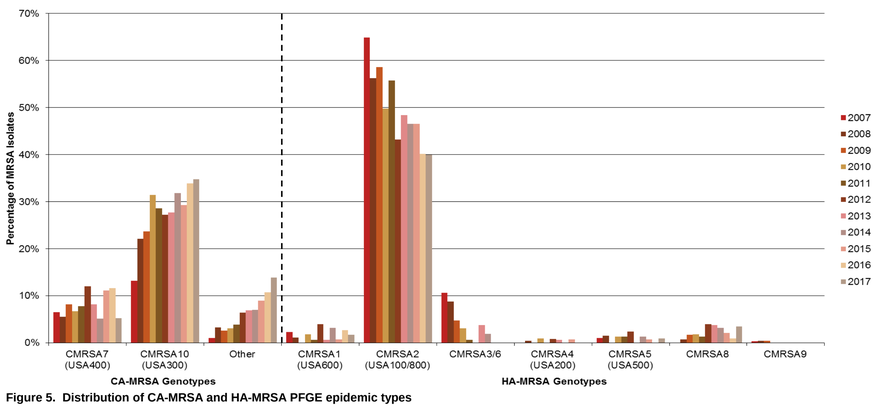


Figure 5. Distribution of CA-MRSA and HA-MRSA PFGE epidemic types

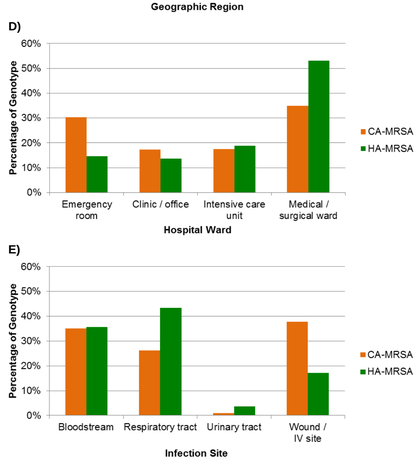


Table 1. Comparison of antibiotic resistance rates among CA-MRSA and HA-MRSA

CA-MRSA (n=788)

Antibiotic	MIC_{50}	MIC_{90}	MIC Range	% of Isolates per Category		
				S	I	R
Cefoxitin	-	-	-	-	-	100[a]
Ceftaroline	0.5	0.5	0.06 - 2	99.8	0.2	0
Ceftobiprole	1	1	0.5 - 2	100	-	0
Ciprofloxacin	16	16	≤0.06 - >16	38.1	0.9	61.0
Clarithromycin	32	>32	0.12 - >32	29.6	0.5	69.9
Clindamycin	≤0.12	>8	≤0.12 - >8	86.6	0	13.4
Daptomycin	0.25	0.5	0.12 - 2	99.9	-	0.1
Doxycyline	≤0.12	0.25	≤0.12 - 16	98.7	1.1	0.2
Linezolid	2	2	0.5 - 4	100	-	0
Moxifloxacin	2	2	≤0.06 - 16	39.3	9.0	51.7
Telavancin[b]	0.06	0.06	0.008 - 0.12	100	-	-
Tigecycline	0.25	0.25	≤0.03 - 0.5	100	-	0
TMP-SMX	≤0.12	≤0.12	≤0.12 - 4	100	-	0.1
Vancomycin	1	1	0.5 - 4	99.9	0.1	0

HA-MRSA (n=1290)

MIC_{50}	MIC_{90}	MIC Range	% of Isolates per Category		
			S	I	R
-	-	-	-	-	100[a]
1	1	0.12 - 2	99.2	0.8	0
1	2	0.25 - 4	99.6	-	0.4
>16	>16	0.25 - >16	6.1	0	93.9
>32	>32	≤0.03 - >32	6.9	0.3	92.8
>8	>8	≤0.12 - >8	35.8	0.1	64.1
0.25	0.5	0.06 - 4	99.9	-	0.1
≤0.12	1	≤0.12 - 16	96.9	1.0	2.1
2	4	≤0.12 - 4	100	-	0
8	>16	≤0.06 - >16	6.1	0.4	93.5
0.06	0.06	0.015 - 0.12	100	-	-
0.25	0.5	0.06 - 2	98.6	-	1.4
≤0.12	0.5	≤0.12 - >8	90.9	-	9.1
1	1	≤0.12 - 4	99.8	0.2	0

All MRSA (n=2078)

MIC_{50}	MIC_{90}	MIC Range	% of Isolates per Category		
			S	I	R
-	-	-	-	-	100[a]
0.5	1	0.06 - 2	99.5	0.5	0
1	2	0.25 - 4	99.7	-	0.3
>16	>16	≤0.06 - >16	18.2	0.3	81.5
>32	>32	≤0.03 - >32	15.5	0.4	84.1
≤0.25	>8	≤0.12 - >8	55.1	0.1	44.8
0.25	0.5	0.06 - 4	99.9	-	0.1
≤0.12	1	≤0.12 - 16	97.7	1.0	1.3
2	4	≤0.12 - 4	100	-	0
8	>16	≤0.06 - >16	18.7	3.7	77.6
0.06	0.06	0.008 - 0.12	100	-	-
0.25	0.5	≤0.03 - 2	99.1	-	0.9
≤0.12	≤0.12	≤0.12 - >8	94.3	-	5.7
1	1	≤0.12 - 4	99.9	0.1	0

[a]Based on cefoxitin disk test [b]Data available from 2013-2017

Conclusions

1. Overall, MRSA rates decreased during the 11-year study period (*P*<0.0001). Of the MRSA strains from Canadian hospitals, 37.9% and 62.1% 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 53.9% in 2017 while HA-MRSA decreased from 79.2% to 46.1% during this same period (*P*<0.0001).
2. CA-MRSA genotypes CMRSA7 (USA400) and CMRSA10 (USA300) represented 7.6% and 25.4% of all MRSA, respectively. The prevalence of CMRSA10 (USA300) increased significantly from 13.2% in 2007 to 34.8% in 2017 (*P*<0.0001). A significant increase also occurred among non-epidemic strain types, attributed in part to increases in USA700, USA1000 and USA1100 genotypes (*P*<0.0001).
3. CMRSA2 (USA100/800) was the predominant HA-MRSA genotype, accounting for 52.8% of all MRSA. Between 2007 and 2017, however, the prevalence of CMRSA2 (USA100/800) decreased significantly from 64.9% to 40.0% (*P*<0.0001).
4. The majority (77.7%) of CA-MRSA were PVL(+) whereas 98.3% of HA-MRSA were PVL(-).
5. CA-MRSA strains were more susceptible to clarithromycin, clindamycin, fluoroquinolones and trimethoprim-sulfamethoxazole than HA-MRSA.
6. 0.8% of CA-MRSA had a vancomycin MIC of 2 μg/mL compared to 2.0% of HA-MRSA (*P*=0.03). 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 99.7% susceptible to ceftobiprole, 99.9% susceptible to daptomycin and vancomycin and 100% susceptible to linezolid and telavancin.

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References

1. CLSI. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically.* 11th edition. CLSI standard M07. Wayne, PA: CLSI; 2018.
2. CLSI. *Performance standards for antimicrobial susceptibility testing.* 28th edition. CLSI supplement M100. Wayne, PA: CLSI; 2018.
3. McDonald RR *et al*. 2005. J Clin Microbiol 43:6147-6149.
4. Golding GR *et al*. 2008. Can J Infect Dis Med Microbiol 19:273-281.