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Characterization of Community- and Healthcare-Associated Methicillin-Resistant Staphylococcus aureus (MRSA) in Canadian Hospitals from 2007-2014

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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 2014, 1707 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:

				Study	/Year				P-value*
MRSA Type	2007	2008	2009	2010	2011	2012	2013	2014	
All MRSA (% of all S. aureus)	26.1	27	21	21.2	19.3	18.2	20.1	20.2	0.0019
HA-MRSA (% of all MRSA)	79.2	69.1	65.5	58.7	59.7	54.4	57.2	56.1	< 0.0001
CMRSA1 [USA600]	2.3	1.1	0	1.8	0.6	4	0.6	3.2	0.5598
CMRSA2 [USA100/800]	64.9	56.3	58.6	49.8	55.8	43.2	48.4	46.5	0.0001
CMRSA3/6	10.6	8.8	4.7	3.1	0.6	0	3.8	1.9	0.0004
CMRSA4 [USA200]	0	0.4	0	0.9	0	0.8	0.6	0	1
CMRSA5 [USA500]	1	1.5	0	1.3	1.3	2.4	0	1.3	1
CMRSA8	0	0.7	1.7	1.8	1.3	4	3.8	3.2	0.0019
CMRSA9	0.3	0.4	0.4	0	0	0	0	0	1
CA-MRSA (% of all MRSA)	19.7	27.6	31.9	38.1	36.4	39.2	35.8	36.9	< 0.0001
CMRSA7 [USA400]	6.5	5.5	8.2	6.7	7.8	12	8.2	5.1	0.6925
CMRSA10 [USA300]	13.2	22.1	23.7	31.4	28.6	27.2	27.7	31.8	<0.0001
Unique	1	3.3	2.6	3.1	3.9	6.4	6.9	7	0.0004
*P-value determined by Fisher's	exact test c	omparing 2	2007 vs. 20	14 data.					

PVL was detected in 86.8% of CA-MRSA and 1.6% of HA-MRSA. Resistance rates (CA vs HA) were 67.1 vs 95.7% to ciprofloxacin, 73.2 vs 93.5% to clarithromycin, 12.7 vs 65.4% to clindamycin and 0 vs 10.3% 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 2014.

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 nonbeta-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 2014, inclusive.

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MATERIALS & METHODS

Methicillin-Resistant S. aureus Isolates

1707 isolates of MRSA were collected between 2007 and 2014 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 2014) 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 MRSASelect 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-A9, 2012). MIC interpretive standards were defined according to CLSI breakpoints (M100-S23, 2013). The following interpretive breakpoints (FDA) were used: telavancin susceptible, $\leq 1 \mu g/ml$; tigecycline susceptible, $\leq 0.5 \mu g/ml$.

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, communityassociated (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 while 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. MRSA with a spa type not associated with one of the known Canadian epidemic types were labeled as unique (non-CMRSA).

- while HA-MRSA decreased from 79.2% to 56.1% during this same period (P<0.0001)
- 2007 to 31.8% in 2014 (P=0.0001).
- and 84.3% of HA-MRSA.
- 2007 to 75.0% in 2014 (P=0.004).
- trimethoprim-sulfamethoxazole than HA-MRSA.
- 99.9% susceptible to daptomycin and vancomycin.

CONCLUSIONS

1. Overall, MRSA rates decreased during the study period (P=0.0019). Of the MRSA strains from Canadian hospitals, 31.0% and 65.3% were identified by spa typing as CA-MRSA and HA-MRSA, respectively. The prevalence of CA-MRSA increased significantly from 19.7% in 2007 to 36.9% in 2014

2. CA-MRSA genotypes CMRSA7 (USA400) and CMRSA10 (USA300) represented 7.1% and 23.9% of all MRSA, respectively. The prevalence of CMRSA10 (USA300) increased significantly from 13.2% in

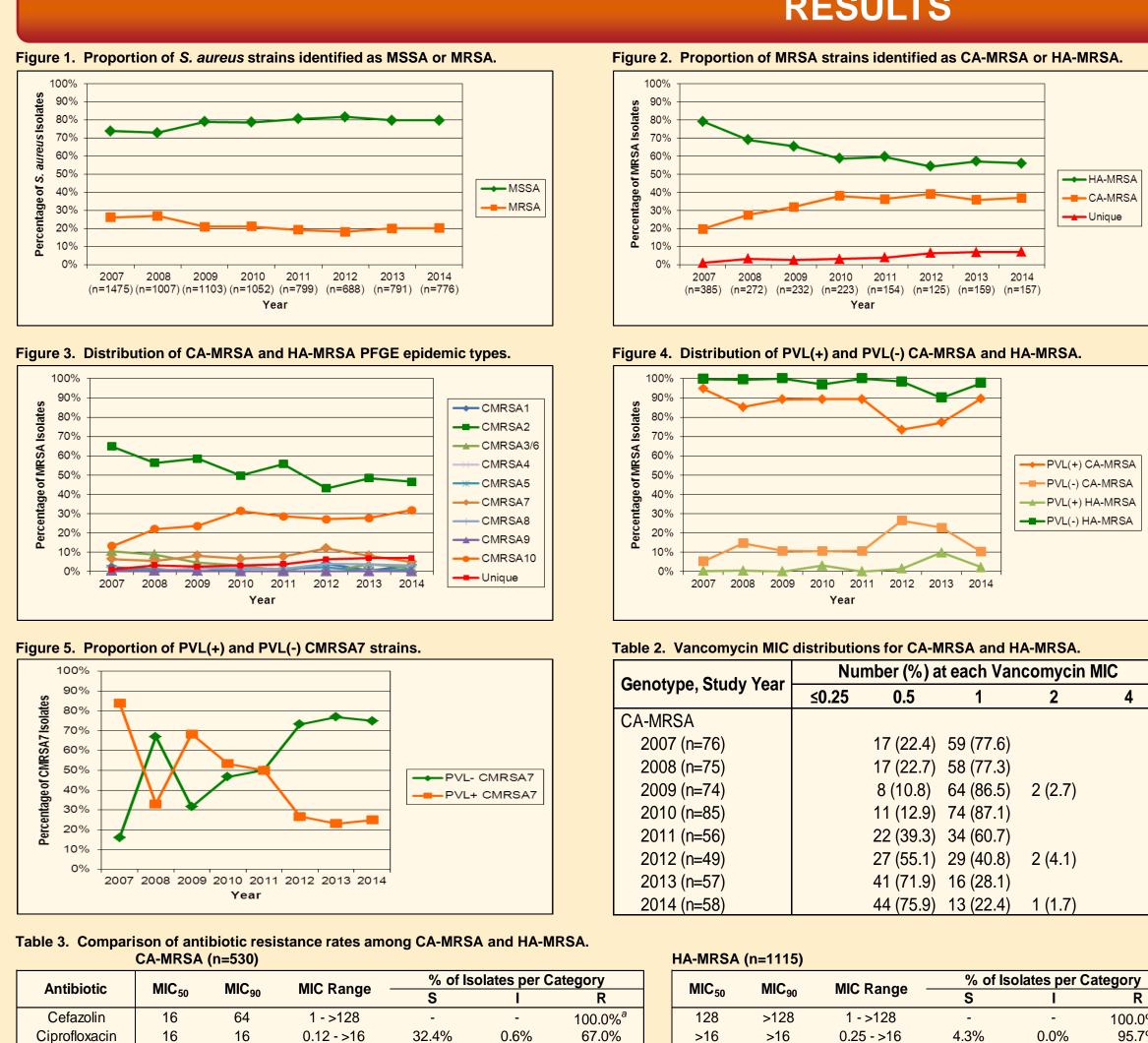
CMRSA2 (USA100/800) was the predominant HA-MRSA genotype, accounting for 55.1% of all MRSA

4. The majority (86.8%) of CA-MRSA were PVL(+) whereas 98.4% 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

CA-MRSA strains were more susceptible to clarithromycin, clindamycin, fluoroquinolones and

0.9% of CA-MRSA had a vancomycin MIC of 2 μ g/ml compared to 2.3% of HA-MRSA (*P*=0.05). Intermediate resistance (MIC, 4 µg/ml) to vancomycin was observed in one MRSA with a PVL-negative CMRSA2 (USA100/800) genotype. MRSA were 100% susceptible to linezolid and telavancin and



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>16

≤0.25

0.25

4

0.03

0.25

≤0.12

^aBased on cefoxitin disk test. ^bData available from 2013-2014.

Clarithromycin

Clindamycin

Daptomycin

Levofloxacin

Linezolid

Moxifloxacin

Telavancin^c

Tigecycline

TMP-SMX

Vancomycin

>16

>8

0.5

0.06

0.25

≤0.12

≤0.25 - >16

≤0.25 - >8

0.12 - 2

0.12 - 32

1 - 4

≤0.06 - 16

0.03 - 0.12

≤0.03 - 0.5

≤0.12 - 2

0.5 - 2

26.2%

87.3%

99.8%

40.0%

100.0%

33.7%

100.0%

100.0%

100.0%

100.0%

0.6%

0.0%

-

0.0%

-

9.5%

-

-

-

0.0%

73.2%

12.7%

0.2%

60.0%

0.0%

56.8%

-

0.0%

0.0%

0.0%

RESULTS

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Table 1. Demographics of p	atients with MR	SA infections.	
Charaotoriotia	CA-MRSA	HA-MRSA	Total
Characteristic	(n=530)	(n=1115)	(n=1707)
Sex, n (%)			
Male	312 (58.9)	659 (59.1)	1002 (58.7)
Female	218 (41.1)	456 (40.9)	705 (41.3)
Mean age, years	42.2	64.9	57
Median age (range)	44 (1-95)	68 (1-105)	61 (1-105)
Age group, n (%)			
≤ 17	79 (14.9)	22 (2.0)	114 (6.7)
18-64	374 (70.6)	437 (39.2)	849 (49.7)
≥ 65	77 (14.5)	656 (58.8)	744 (43.6)
Region, n (%)			
West	313 (59.0)	307 (27.5)	640 (37.5)
Ontario	170 (32.1)	381 (34.2)	583 (34.2)
Quebec	20 (3.8)	337 (30.2)	364 (21.3)
Maritimes	27 (5.1)	90 (8.1)	120 (7.0)
Hospital ward type, n (%)			
Emergency room	179 (33.8)	165 (14.8)	361 (21.1)
Clinic/office	92 (17.3)	146 (13.1)	251 (14.7)
Intensive care unit	88 (16.6)	222 (19.9)	317 (18.6)
Medical/surgical ward	171 (32.3)	582 (52.2)	778 (45.6)
Infection site, n (%)			
Bloodstream	189 (35.7)	410 (36.8)	618 (36.2)
Respiratory tract	128 (24.1)	477 (42.8)	622 (36.4)
Urinary tract	2 (0.4)	45 (4.0)	48 (2.8)
Wounds/IV sites	211 (39.8)	183 (16.4)	419 (24.6)

comycin MIC distributions for CA-MRSA and HA-MRSA.											
Study Voor	Number (%) at each Vancomycin MIC				Construes Study Veer	Number (%) at each Vancomycin MIC					
, Study Year	≤0.25	0.5	1	2	4	Genotype, Study Year	≤0.25	0.5	1	2	4
						HA-MRSA					
=76)		17 (22.4)	59 (77.6)			2007 (n=305)	5 (1.6)	22 (7.2)	274 (89.8)	4 (1.3)	
=75)		17 (22.7)	58 (77.3)			2008 (n=188)		18 (9.6)	161 (85.6)	8 (4.3)	1 (0.5)
=74)		8 (10.8)	64 (86.5)	2 (2.7)		2009 (n=152)		14 (9.2)	131 (86.2)	7 (4.6)	
=85)		11 (12.9)	74 (87.1)			2010 (n=131)		9 (6.9)	116 (88.5)	6 (4.6)	
=56)		22 (39.3)	34 (60.7)			2011 (n=92)		13 (14.1)	79 (85.9)		
=49)		27 (55.1)	29 (40.8)	2 (4.1)		2012 (n=68)		18 (26.5)	50 (73.5)		
=57)		41 (71.9)	16 (28.1)			2013 (n=91)		37 (40.7)	54 (59.3)		
=58)		44 (75.9)	13 (22.4)	1 (1.7)		2014 (n=88)	3 (3.4)	32 (36.4)	52 (59.1)	1 (1.1)	

		MIC Range	% of Isolates per Category				
WIIC 50	WIC 90	Mic Kange	S	I	R		
128	>128	1 - >128	-	-	100.0% ^a		
>16	>16	0.25 - >16	4.3%	0.0%	95.7%		
>16	>16	≤0.25 - >16	6.1%	0.4%	93.5%		
>8	>8	≤0.25 - >8	34.5%	0.1%	65.4%		
0.25	0.25	0.06 - 1	100.0%	-	-		
>32	>32	0.12 - >32	2.9%	0.0%	97.1%		
2	4	≤0.12 - 4	100.0%	-	0.0%		
8	>16	≤0.06 - >16	4.5%	0.4%	95.1%		
0.06	0.06	0.03 - 0.12	100.0%	-	-		
0.25	0.5	0.06 - 2	98.6%	-	1.4%		
≤0.12	8	≤0.12 - >8	89.7%	-	10.3%		
1	1	≤0.25 - 4	99.9%	0.1%	0.0%		

All MRSA (n=1707)

МС	MIC	MIC Banga	% of Isolates per Category			
MIC ₅₀	MIC ₉₀	MIC Range	S		R	
64	>128	1 - >128	-	-	100.0% ^a	
>16	>16	0.12 - >16	16.0%	0.3%	83.7%	
>16	>16	≤0.25 - >16	14.4%	0.4%	85.2%	
≤0.25	>8	≤0.25 - >8	52.8%	0.1%	47.1%	
0.25	0.5	0.06 - 2	99.9%	-	0.1%	
>32	>32	0.12 - >32	14.1%	0.0%	85.9%	
2	2	≤0.12 - 4	100.0%	-	0.0%	
8	>16	≤0.06 - >16	16.7%	3.1%	80.2%	
0.06	0.06	0.03 - 0.12	100.0%	-	-	
0.25	0.5	≤0.03 - 2	99.1%	-	0.9%	
≤0.12	≤0.12	≤0.12 - >8	93.3%	-	6.7%	
1	1	≤0.25 - 4	99.9%	0.1%	0.0%	