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Comparison of Community-Associated (CA) and Healthcare-Associated (HA) Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Canada: Results from CANWARD 2008

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ABSTRACT (Revised)

Background: CA-MRSA differ from HA-MRSA in their genotypic and phenotypic characteristics. In this study we compared the demographics, antimicrobial susceptibilities and molecular epidemiology of CA- and HA-MRSA in Canada.
Methods: In 2008, 272 MRSA were collected from patients attending hospital clinics (HC), emergency rooms (ER), medical/surgical wards (MSW) and intensive care units (ICU) in 10 hospitals across Canada. Susceptibilities to β-lactams, ciprofloxacin (CIP), clarithromycin (CLR), clindamycin (CLD), trimethoprim/sulfamethoxazole (SXT) and vancomycin (VAN) were determined by CLSI broth microdilution. Typing of isolates was conducted using *spa* typing and the Panton-Valentine leukocidin (PVL) gene was detected by PCR.
Results: Of the 272 MRSA, 75 (27.6%) were CA-MRSA and 187 (68.8%) were HA-MRSA. Isolates (CA vs. HA) were obtained from patients in ER (46.7 vs. 16.6%), MSW (30.7 vs. 54.0%), HC (8.0 vs. 9.1%) and ICU (14.8 vs. 20.3%). MRSA (CA vs. HA) were isolated from wound/IV sites (36.0 vs. 13.9%), blood (49.3 vs. 36.9%), respiratory specimens (14.7 vs. 41.7%) and urine (0.0 vs. 7.5%). CA-MRSA belonged to epidemic types CMRSA10/USA300 (80.0%) and CMRSA7/USA400 (20.0%); HA-MRSA epidemic types included CMRSA2/USA100/800 (81.9%), CMRSA3 or CMRSA6 (12.8%), CMRSA1/USA600 (1.6%), CMRSA5/USA500 (1.6%), CMRSA8 (1.1%), CMRSA4/USA200 (0.5%) and CMRSA9 (0.5%). PVL was detected in 64/75 (85.3%) CA-MRSA and 1/187 (0.5%) HA-MRSA. Resistance rates (CA vs. HA) were 69.3 vs. 96.8% to CIP, 73.3 vs. 94.1% to CLR, 20.0 vs. 72.7% to CLD and 0.0 vs. 15.0% to SXT.
Conclusions: CA-MRSA represented 27.6% of all MRSA. CA-MRSA were significantly more susceptible to CIP, CLR, CLD and SXT than HA-MRSA. 85.3% of CA-MRSA were PVL(+) while 99.5% of HA-MRSA were PVL(-). CA-MRSA is an emerging pathogen in Canadian hospitals.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing in prevalence in Canada, the United States and throughout the world, and is well recognized as a leading cause of nosocomial infections. In the past decade, MRSA has also emerged as a significant community-associated (CA) pathogen capable of causing disease in young, otherwise healthy individuals lacking traditional risk factors for MRSA acquisition/infection. Several reports have documented CA-MRSA infections among aboriginals, military recruits, intravenous drug users, correctional facilities, homeless persons, amateur and professional sports teams, daycares and schools. Of particular concern is that CA-MRSA strains, in addition to skin and soft tissue infections, may be associated with severe invasive disease including necrotizing pneumonia, bacteremia and septic shock, resulting in increased morbidity and mortality.
Recently, CA-MRSA genotypes have begun to replace healthcare-associated (HA)-MRSA in the hospital setting. These CA-MRSA strains differ from their healthcare-associated counterparts in their microbiological, epidemiological and molecular characteristics.

PURPOSE

The purpose of this study was to compare the demographics, antimicrobial susceptibilities and molecular epidemiology of community-associated and healthcare-associated methicillin-resistant *Staphylococcus aureus* genotypes in Canada.

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MATERIALS AND METHODS

Methicillin-Resistant *S. aureus* Isolates

272 isolates of MRSA were collected between January and December 2008, inclusive, as part of the ongoing CANWARD study assessing antibiotic resistance in Canadian hospitals. Isolates were received from 10 sentinel hospital sites that were geographically distributed in a population-based fashion in major cities in 7 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, tigecycline, trimethoprim-sulfamethoxazole and vancomycin were determined by broth microdilution in accordance with CLSI guidelines (M7-A7, 2006). MIC interpretive standards were defined according to CLSI breakpoints (M100-S18, 2008). The following interpretive breakpoint (FDA) was used for 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 also included primers for the detection of the *lukF-PV* and *lukS-PV* genes encoding the components of 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 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).

CONCLUSIONS

27.6% and 68.8% of MRSA strains from Canadian hospitals were identified by PFGE as CA-MRSA and HA-MRSA, respectively.

CA-MRSA belonged to PFGE types CMRSA10 (USA300) [80.0%] and CMRSA7 (USA400) [20.0%].

CMRSA2 (USA100/800) was the predominant PFGE type among HA-MRSA [81.9%]. Other PFGE types identified among HA-MRSA included CMRSA3/6 [12.8%], CMRSA1 (USA600) [1.6%], CMRSA5 (USA500) [1.6%], CMRSA8 [1.1%], CMRSA4 (USA200) [0.5%] and CMRSA9 [0.5%].

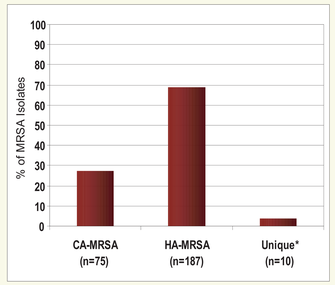
The majority (85.3%) of CA-MRSA were PVL(+). 14.7% of CA-MRSA and 99.5% of HA-MRSA were PVL(-).

CA-MRSA strains were more susceptible to clarithromycin, clindamycin, fluoroquinolones and trimethoprim-sulfamethoxazole than HA-MRSA.

Intermediate resistance (MIC, 4 μg/ml) to vancomycin was observed in one HA-MRSA strain. No MRSA were resistant to daptomycin, linezolid or tigecycline.

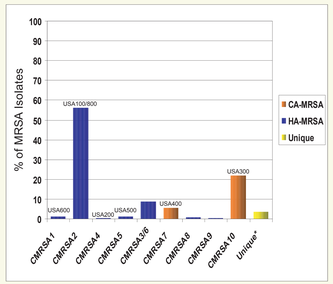
RESULTS

Figure 1. Proportion of MRSA strains identified as community-associated or healthcare-associated by PFGE (n=272).



Unique, Non-CMRSA PFGE type.

Figure 2. Distribution of community-associated and healthcare-associated PFGE epidemic types among MRSA from Canadian hospitals (n=272).



Unique, Non-CMRSA PFGE type.

Figure 3. Distribution of community-associated and healthcare-associated MRSA strains by patient gender (n=262).

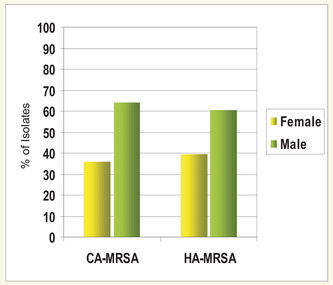


Figure 4. Distribution of community-associated and healthcare-associated MRSA strains by patient age (n=262).

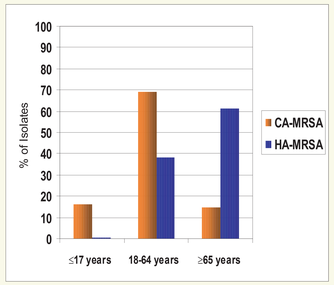


Figure 5. Distribution of PVL(+) and PVL(-) community-associated and healthcare-associated MRSA strains (n=262).

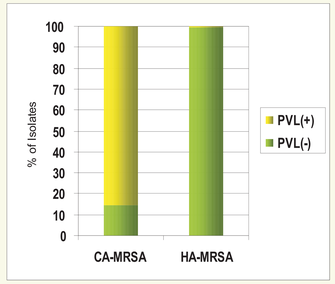
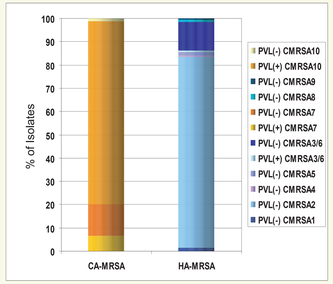


Figure 6. Distribution of PVL(+) and PVL(-) community-associated and healthcare-associated PFGE epidemic types (n=262).



CMRSA1 (USA600); CMRSA2 (USA100/800); CMRSA4 (USA200); CMRSA5 (USA500); CMRSA7 (USA400); CMRSA10 (USA300).

Figure 7. Distribution of PVL(+) and PVL(-) community-associated and healthcare-associated MRSA strains by hospital ward type (n=262).

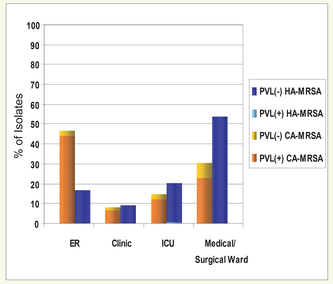


Figure 8. Distribution of PVL(+) and PVL(-) community-associated and healthcare-associated MRSA strains by specimen type (n=262).

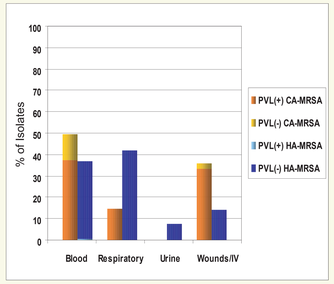


Table 1. Comparison of antibiotic resistance rates among community-associated and healthcare-associated MRSA strains.

Antibiotic	CA-MRSA (n=75)						HA-MRSA (n=187)						All MRSA (n=272)					
	MIC_{50}	MIC_{90}	MIC Range	% of Isolates per Category[a]			MIC_{50}	MIC_{90}	MIC Range	% of Isolates per Category[a]			MIC_{50}	MIC_{90}	MIC Range	% of Isolates per Category[a]		
				S	I	R				S	I	R				S	I	R
Cefazolin	16	64	2 - 256	-	-	100.0[b]	256	256	2 - 256	-	-	100.0[b]	128	256	2 - 256	-	-	100.0[b]
Ciprofloxacin	16	32	0.25 - 32	30.7	0.0	69.3	32	32	0.5 - 32	3.2	0.0	96.8	32	32	0.25 - 32	12.9	0.0	87.1
Clarithromycin	64	64	0.25 - 64	25.3	1.3	73.3	64	64	0.03 - 64	5.9	0.0	94.1	64	64	0.03 - 64	14.0	0.3	85.7
Clindamycin	0.12	16	0.12 - 16	80.0	0.0	20.0	16	16	0.12 - 16	27.3	0.0	72.7	16	16	0.12 - 16	44.5	0.0	55.5
Daptomycin	0.25	0.5	0.12 - 1	100.0	0.0	0.0	0.25	0.25	0.06 - 1	100.0	0.0	0.0	0.25	0.25	0.06 - 1	100.0	0.0	0.0
Levofloxacin	8	8	0.12 - 32	32.0	0.0	68.0	64	64	0.25 - 64	3.7	0.0	96.3	64	64	0.12 - 64	13.6	0.0	86.4
Linezolid	2	2	1 - 2	100.0	0.0	0.0	2	2	0.12 - 4	100.0	0.0	0.0	2	2	0.12 - 4	100.0	0.0	0.0
Moxifloxacin	2	2	0.06 - 8	32.0	0.0	68.0	8	32	0.06 - 32	3.7	0.0	96.3	8	32	0.06 - 32	13.6	0.0	88.4
Tigecycline	0.25	0.25	0.12 - 0.5	100.0	0.0	0.0	0.25	0.5	0.12 - 0.5	100.0	0.0	0.0	0.25	0.5	0.12 - 0.5	100.0	0.0	0.0
TMP-SMX	0.12	0.12	0.12 - 2	100.0	0.0	0.0	0.12	8	0.12 - 16	85.0	0.0	15.0	0.12	8	0.12 - 16	89.7	0.0	10.3
Vancomycin	1	1	0.5 - 1	100.0	0.0	0.0	1	1	0.5 - 4	99.5	0.5	0.0	1	1	0.5 - 4	99.6	0.4	0.0

[a] S, susceptible; I, intermediate; R, resistant.
[b] Based on cefoxitin disk test.

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