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Vancomycin and Daptomycin MIC Creep in *Staphylococcus* spp. in Canada – Analysis of 4642 *S. aureus* and 497 *S. epidermidis* isolates from 2007 – 2010

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ABSTRACT

Background: We analysed the vancomycin (Van) and Daptomycin (Dap) MIC of *S. epidermidis*, MRSA and methicillin-susceptible *S. aureus* (MSSA) isolates obtained from across Canada between 2007 and 2010 to determine if MICs increased during this time period.

Methods: Clinically significant isolates were collected from January 2007 to December 2010 as part of the ongoing national CANWARD surveillance study. Susceptibility testing was performed by broth dilution for all isolates. MRSA was identified using *mec*A PCR and *spa* typing was performed to identify community (CA) or hospital (HA) acquired MRSA. Annual differences between MICs in *S. epidermidis*, *S. aureus* and subgroups were analysed using linear regression applied to geometric means and logistic regression was used to calculate trend in isolates with MIC ≥1μg/mL and ≥2μg/mL.

Results: A significant increase in MIC to Van was observed in *S. aureus* using geometric mean analysis (p<0.01). Further analysis showed that the geometric mean Van MIC increased in MSSA (p<0.0001) and CA-MRSA (p=0.026) but not HA-MRSA (p=0.1). A significant decrease in Van and Dap MIC over time was observed for *S. epidermidis* (p <0.01). No MIC creep for Dap was seen in *S. aureus* or its subgroups. MSSA isolates with Van MIC ≥1μg/mL increased significantly from 72.3% to 83.1%, (p <0.01). CA-MRSA isolates with Van MIC ≥1mg/mL increased in prevalence from 77.0% to 87.1% (p = 0.03). Strains with vancomycin MIC of ≥2 mg/mL occurred in: MSSA 0.6% (20/3512), MRSA 2.4% (27/1110), CA-MRSA 0.7% (2/308), HA-MRSA 3.3% (25/758), MSSE 34.8% (143/411) and MRSE 50.0% (38/76). HA-MRSA isolates with Van MIC ≥2 mg/mL increased in prevalence from 1.4% to 4.6% (p = 0.05).

Conclusions: Van MIC creep was noted in *S. aureus* between 2007 and 2010 by geometric mean MIC analysis. The increase was only significant in MSSA and CA-MRSA subgroups. HA-MRSA isolates with MIC ≥2 mg/mL increased over time. No MIC creep was noted with Dap in *S. aureus* or its subgroups. A reduction in MIC for both Dap and Van was noted between 2007 and 2010 in *S. epidermidis*.

BACKGROUND

Although vancomycin creep remains a controversial phenomenon, it has been observed in in several published studies and *Staphylococcus aureus* strains with increased MICs to vancomycin have been shown to be associated with worse outcomes compared to more susceptible strains (1,2). Similar vancomycin creep has been studied in coagulase-negative staphylococci, but not yet documented (3). A similar low-level daptomycin MIC creep has been suggested in some studies, but remains to be deemed relevant (4). The factors involved in the development of reduced susceptibility to vancomycin and subsequent "glycopeptide MIC creep" are not entirely elucidated, but recognition of the phenomenon is important since it may be a precursor to hVISA (heterogenous vancomycin intermediate *Staphylococcus aureus*) and VISA (5).

MATERIALS & METHODS

Isolates were obtained as part of the CANWARD study between 2007 and 2010. Tertiary care hospital laboratories from 8 provinces across Canada participated. Isolates were from inpatient medical and surgical wards, intensive care units, emergency departments and outpatient clinics. Minimum inhibitory concentration for vancomycin and cefoxitin (to screen for MRSA) were determined using the CLSI microbroth dilution method according to CLSI documents M07-A7/A8 and M100-S21. Isolates with cefoxitin MIC ≥ 8 μg/mL were confirmed to be MRSA using *mecA* PCR and typed into health-care and community lineages using *spa* typing. The overall change in vancomycin MIC was evaluated using linear regression analysis of the geometric mean MIC while differences between the proportion of isolates with any given MIC were evaluated using logistic regression.

RESULTS

TABLE 1: Vancomycin MIC distributions for *S. aureus*, MRSA, CA-MRSA, HA-MRSA, MSSA and *S. epidermdis* during the study period.

S. aureus M IC (μg/mL)	2007 (%) (n =1455)	2008 (%) (n=997)	2009 (%) (n=1097)	2010 (%) (n=1035)	*P* value (GMA)	*P* value (MIC≥1)	*P* value (MIC≥2)
≤0.5	342 (23.5)	157 (15.8)	138 (12.6)	159 (15.4)	**<0.001**	**<0.001**	0.44
1	1103 (75.8)	827 (83.0)	943 (86.0)	867 (83.8)			
≥2	10 (0.7)	13 (1.2)	16 (1.5)	9 (0.9)			
MSSA MIC (μg/mL)	2007 (%) (n=1091)	2008 (%) (n=735)	2009 (%) (n=871)	2010 (%) (n=821)			
≤0.5	302 (27.6)	123 (17.2)	116 (13.3)	139 (17.0)	**<0.001**	**<0.001**	0.83
1	783 (71.8)	608 (82.7)	748 (85.9)	679 (82.7)			
≥2	6 (0.6)	4 (0.5)	7 (0.8)	3 (0.4)			
MRSA MIC (μg/mL)	2007 (%) (n=364)	2008 (%) (n=262)	2009 (%) (n=226)	2010 (%) (n=214)			
≤0.5	40 (11.4)	34 (13.0)	22 (9.7)	20 (9.4)	0.075	0.40	0.12
1	320 (87.9)	219 (83.6)	195 (86.3)	188 (87.9)			
2	4 (1.1)	9 (3.5)	9 (4.0)	6 (2.8)			
CA-MRSA MIC (μg/mL)	2007 (%) (n=74)	2008 (%) (n=75)	2009 (%) (n=74)	2010 (%) (n=85)			
≤0.5	17 (23)	17 (22.7)	8 (10.8)	11 (12.9)	**0.03**	0.03	0.57
1	57 (77.0)	58 (73.3)	64 (86.5)	74 (87.1)			
≥2	0 (0)	0 (0)	2 (2.7)	0 (0)			
HA-MRSA	2007 (%) (n=290)	2008 (%) (n=187)	2009 (%) (n=152)	2010 (%) (n=129)			
≤0.5	23 (7.9)	17 (9.1)	14 (9.3)	9 (7.0)	0.125	0.91	**0.05**
1	263 (90.7)	161 (86.1)	131 (86.2)	114 (88.4)			
≥2	4 (1.4)	9 (4.8)	7 (4.6)	6 (4.7)			
S. epidermidis MIC (μg/mL)	2007 n=133	2008 n=86	2009 n=102	2010 n=174			
≤0.5	4 (3.1)	0	4 (3.9)	43 (24.7)	**<0.001***	**<0.001***	**<0.001***
1	80 (60.2)	32 (37.2)	53 (51.0)	95 (54.6)			
≥2	49 (36.8)	54 (62.8)	46 (45.1)	36 (20.7)			

GMA: Geometric mean analysis, *Statistically significant reduction in MIC

TABLE 2: Daptomycin MIC distributions for *S. aureus*, MRSA, CA-MRSA, HA-MRSA, MSSA and *S. epidermdis* during the study period.

S. aureus M IC (μg/mL)	2007 (%) (n =1455)	2008 (%) (n=997)	2009 (%) (n=1097)	2010 (%) (n=1035)	*P* value (GMA)
≤0.12	926 (63.6)	517 (51.8)	755 (68.9)	557 (53.8)	0.94
0.25	453 (31.1)	416 (41.7)	320 (29.2)	466 (45.0)	
≥0.5	76 (5.2)	64 (6.4)	22 (2.0)	12 (1.2)	
MSSA MIC (μg/mL)	2007 (%) (n=1091)	2008 (%) (n=735)	2009 (%) (n=871)	2010 (%) (n=821)	
≤0.12	719 (65.9)	400 (54.3)	638 (73.2)	481 (58.6)	0.63
0.25	326 (29.9)	295 (40.1)	215 (24.7)	332 (40.4)	
≥0.5	46 (4.2)	40 (5.5)	18 (2.1)	8 (1.0)	
MRSA MIC (μg/mL)	2007 (%) (n=364)	2008 (%) (n=262)	2009 (%) (n=226)	2010 (%) (n=214)	
≤0.12	207 (56.9)	117 (44.6)	117 (51.8)	76 (35.5)	0.06
0.25	127 (35.9)	121 (46.2)	105 (46.5)	134 (62.6)	
≥0.5	30 (8.2)	24 (9.1)	4 (1.8)	4 (1.9)	
CA-MRSA MIC (μg/mL)	2007 (%) (n=74)	2008 (%) (n=75)	2009 (%) (n=74)	2010 (%) (n=85)	
≤0.12	43 (58.1)	34 (45.3)	34 (45.9)	25 (29.4)	0.16
0.25	23 (31.1)	31 (41.3)	40 (54.1)	60 (70.6)	
≥0.5	8 (10.8)	10 (13.3)	0	0	
HA-MRSA	2007 (%) (n=290)	2008 (%) (n=187)	2009 (%) (n=152)	2010 (%) (n=129)	
≤0.12	164 (56.6)	83 (44.4)	83 (54.6)	51 (39.6)	0.30
0.25	104 (35.9)	90 (48.1)	65 (42.8)	74 (57.4)	
≥0.5	22 (7.6)	14 (7.5)	4 (2.6)	4 (3.1)	
S. epidermidis MIC (μg/mL)	2007 n=133	2008 n=86	2009 n=102	2010 n=174	
≤0.12	110 (82.7)	32 (37.2)	90 (88.2)	161 (92.6)	**<0.001***
0.25	23 (17.3)	51 (59.3)	12 (11.8))	11 (6.3)	
≥0.5	0	32 (3.5)	0	2 (1.1)	

GMA: Geometric mean analysis, *Statistically significant reduction in MIC

CONCLUSIONS

By assessment of geometric means, MICs for vancomycin in *S. aureus* increased between 2007 and 2010 in this study of Canadian isolates. When stratified by methicillin resistance, the increase in MIC was noted only in methicillin-sensitive strains. The observation of vancomycin creep in MSSA with stable MICs in MRSA has been described in other studies (6). However, when MRSA were stratified for health-care associated and community associated strains, a small but statistically significant MIC creep was noted in the CA-MRSA strains.

The prevalence of MRSA isolates with MICs ≥ 2μg/mL, which are known to be associated with poorer outcomes (1,2), significantly increased only in HA-MRSA strains during the study period. This finding supports a creep in vancomycin MIC among these isolates. Significant increases in isolates with MIC ≥ 1μg/mL were also observed in *S. aureus,* MSSA, and CA-MRSA. The relevance of this is unclear, as poor outcomes have not been correlated with such isolates. However, they may forebode the emergence of higher MICs.

No creep in daptomycin MIC was observed for *S. aureus* in this study. However, a trend may be emerging in MRSA isolates by geometric mean analysis. A similar low-level daptomycin MIC creep has been observed by others (4) and should be monitored as daptomycin use increases.

Geometric mean vancomycin and daptomycin MIC for *S. epiderimidis* declined over time, an observation that has not previously been made and is of uncertain significance.

REFERENCES

1. Gould IM. Clinical relevance of increasing glycopeptide MICs against *Staphylococcus aureus*. Int J Antimicrob Agents. 2008. 31 Suppl 2:1-9.
2. Steinkraus G et. al. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001-05. J Antimicrob Chemother. 2007 Oct;60(4):788-94.
3. Ahlstrand E et. al. Glycopeptide resistance in coagulase-negative staphylococci isolated in blood cultures from patients with hematological malignancies during three decades. Eur J Clin Microbiol Infect Dis. 2011 Apr 5.
4. Sader HS et. al. Evaluation of vancomycin and daptomycin potency trends (MIC creep) against methicillin-resistant Staphylococcus aureus isolates collected in nine U.S. medical centers from 2002 to 2006. Antimicrob Agents Chemother. 2009 Oct;53(10):4127-32.
5. Appelbaum PC. Reduced glycopeptide susceptibility in methicillin-resistant *Staphylococcus aureus* (MRSA). Int J Antimicrob Agents. 2007 Nov;30(5):398-408.
6. Wang G, et. al. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol. 2006 Nov;44(11):3883-6.

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