

Vancomycin MIC Creep in *Staphylococcus aureus* in Canada: Analysis of 3587 Isolates from 2007 – 2009

P. R. S. LAGACÉ-WIENS, M. DECORBY, K. NICHOL, H. ADAM, J. KARLOWSKY, G. G. ZHANEL AND D. HOBAN

Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Canada

ABSTRACT

Background: We analyzed the vancomycin (Van) MIC of MRSA and methicillin-susceptible *S. aureus* (MSSA) isolates obtained from across Canada between 2007 and 2009 to determine if Van MICs increased during this time period.

Methods: Clinically significant isolates were collected from January 2007 to December 2009 as part of the national CANWARD surveillance study. Susceptibility testing was performed by microdilution for all isolates. Strict quality control was used to minimize lot to lot variability. MRSA was identified using *mecA* PCR and *spa* typing was performed to identify community (CA) or health-care (HA) associated MRSA. Annual differences between Van MICs in *S. aureus* and subgroups were analyzed using statistical comparison of geometric means using ANOVA, student's t test or Fisher's exact test.

Results: Overall, a significant increase in MIC to Van was observed in *S. aureus* using geometric mean analysis ($p < 0.0001$). From 2007 - 2009, *S. aureus* isolates with Van MIC ≥ 1 mg/L increased from 76.4% to 87.5%. Subgroup analysis showed that the geometric mean MIC increased in MSSA ($p < 0.0001$) and CA-MRSA ($p = 0.039$) but not HA-MRSA ($p = 0.39$). Furthermore, isolates with MIC ≥ 2 mg/L increased from 0.7 to 1.5% ($p = 0.026$) and was observed primarily in HA-MRSA.

Conclusions: A significant Van MIC creep in *S. aureus* has occurred in Canada between 2007 and 2009. The overall increase was only significant in MSSA and CA-MRSA subgroups. However, within HA-MRSA, an increase in isolates with Van MIC = 2 mg/L ($p = 0.04$) was noted. These isolates have been shown to adversely affect patient outcomes and prevalence should be closely monitored.

BACKGROUND

Vancomycin creep has been observed in the United States and the United Kingdom 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). 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 (3).

MATERIALS & METHODS

Isolates were obtained as part of the CANWARD study between 2007 and 2009. 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-S20. Isolates with cefoxitin MIC ≥ 8 mg/L 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 ANOVA analysis of the geometric mean MIC while individual differences between the proportion of isolates with any given MIC between 2007 and 2009 were evaluated with the Pearson χ^2 or Fisher's exact test.

RESULTS

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

Vancomycin MIC (mg/L)	2007 (%) (n=1477)	2008 (%) (n=1007)	2009 (%) (n=1103)	P value (2007 vs 2009)
0.25	48 (3.2)	5 (0.5)	0 (0)	0.12
0.5	300 (20.3)	154 (15.3)	138 (12.5)	<0.0001
1.0	1119 (75.8)	835 (82.9)	949 (86.0)	<0.0001
2.0	10 (0.7)	12 (1.2)	16 (1.5)	0.0258
4.0	0 (0)	1 (0.1)	0 (0)	n/a

MSSA	2007 (%) (n=1092)	2008 (%) (n=735)	2009 (%) (n=871)	P value (2007 vs 2009)
0.25	43 (3.9)	5 (0.7)	0 (0)	0.65
0.5	259 (23.7)	118 (16.5)	116 (13.3)	<0.0001
1.0	784 (71.8)	608 (82.7)	784 (90.0)	<0.0001
2.0	6 (0.6)	4 (0.5)	7 (0.8)	0.245

MRSA	2007 (%) (n=385)	2008 (%) (n=272)	2009 (%) (n=232)	P value (2007 vs 2009)
0.25	5 (1.3)	0 (0)	0 (0)	0.094*
0.5	41 (10.6)	36 (13.3)	22 (9.5)	0.321
1.0	335 (87.0)	227 (83.5)	201 (86.6)	0.447
2.0	4 (1.0)	8 (2.8)	9 (3.9)	0.020*
4.0	0 (0)	1 (0.4)	0 (0)	n/a

CA-MRSA	2007 (%) (n=74)	2008 (%) (n=75)	2009 (%) (n=74)	P value (2007 vs 2009)
0.5	17 (23)	17 (22.7)	8 (10.8)	0.048
1.0	57 (77.0)	58 (73.3)	64 (86.5)	0.14
2.0	0 (0)	0 (0)	2 (2.7)	0.25*

HA-MRSA	2007 (%) (n=290)	2008 (%) (n=187)	2009 (%) (n=151)	P value (2007 vs 2009)
0.25	5 (1.7)	0 (0)	0 (0)	0.12*
0.5	18 (6.2)	17 (9.1)	14 (9.3)	0.24
1.0	263 (90.7)	161 (86.1)	130 (86.1)	0.14
2.0	4 (1.4)	8 (4.3)	7 (4.6)	0.04*
4.0	0 (0)	1 (0.5)	0 (0)	n/a

*Fisher's Exact test

FIGURE 2: Geometric means in 2007, 2008 and 2009 for CA-MRSA and HA-MRSA.

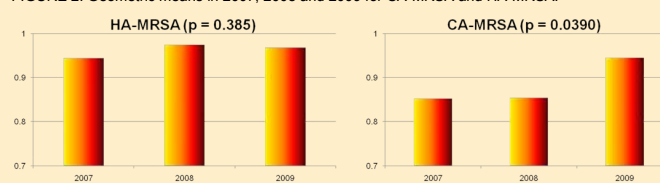
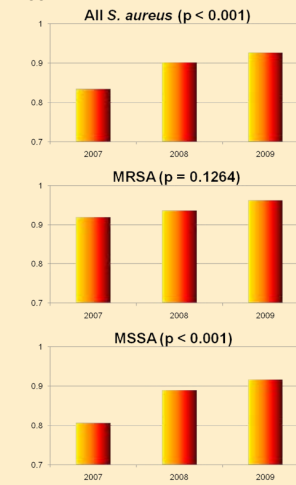


FIGURE 1: Geometric means (in mg/L) in 2007, 2008 and 2009 for all *S. aureus*, MRSA and MSSA.



CONCLUSIONS

MICs for vancomycin in *S. aureus* increased between 2007 and 2009 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 (4). 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 most significant change in MIC distribution for all *S. aureus* and for MSSA during the study period was a reduction in isolates with a MIC of 0.5 mg/L and a concomitant increase in isolates with a MIC of 1 mg/L. Nevertheless, statistically significant changes in the proportion of isolates with MICs of 2 mg/L occurred in the pooled *S. aureus* population as well as in MRSA and HA-MRSA isolates. This is particularly worrisome because isolates with MIC of 2mg/L have been associated with worse outcomes (1,2).

The prevalence of MRSA isolates with MICs ≥ 2 mg/L both statistically and clinically significantly increased by nearly 4 fold from 1% to 3.9% during the study period.

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