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Ceftaroline (CPT) and Cefazolin (CFZ) MIC Increase is Associated with Vancomycin (VAN) MIC Increase in Methicillin-resistant *Staphylococcus aureus* (MRSA) but not Methicillin-susceptible *Staphylococcus aureus* (MSSA). Analysis of 727 Vancomycin-susceptible MRSA and 2888 MSSA Isolates from the CANWARD Study for a Seesaw Effect.

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ABSTRACT

Background: The seesaw effect, whereby MRSA strains with decreased susceptibility to VAN appear to have increased susceptibility to β-lactam antimicrobials has been previously reported. These observations have pertained primarily to isogenic VAN intermediate *S. aureus* (VISA) strains that were either provoked to develop increased VAN MICs or that develop increased MICs in vivo during long-term VAN therapy. The purpose of this study was to explore the relationship between VAN MICs and CFZ and CPT MICs in a large population of clinical *S. aureus* isolates to determine if this relationship is observed at a population level.

Methods: We determined the MIC by broth microdilution to CFZ, CPT and VAN for 727 MRSA and 2888 MSSA strains recovered from hospitals across Canada as part of the CANWARD study. Relationships between VAN MIC and both the CPT and CFZ geometric mean(GM) MICs were explored using ANOVA with Tukey HSD Test.

Results: In MRSA isolates, MIC_{GM} CFZ and CPT increased significantly with increasing VAN MIC from 0.5 µg/mL to 2 µg/mL (see tables). No relationship between VAN MIC and β-lactam MIC was observed in MSSA.

Conclusions: A seesaw effect was not evident in this natural population of *S. aureus*. In fact, increased VAN MIC was associated with increased β-lactam MIC in MRSA isolates while there was no association in MSSA isolates. This suggests that the seesaw effect may not occur at a population level in the absence of long-term vancomycin pressure or that it is only relevant in isolates with high vancomycin MICs (e.g., ≥ 4µg/mL). The relationship of increasing β-lactam MICs in isolates with higher vancomycin MIC in MRSA isolates only deserves further study.

BACKGROUND

A seesaw effect, whereby susceptibility to β-lactam antimicrobials increases as glycopeptide susceptibility decreases has been reported in a small number of isogenic MRSA strains with a vancomycin intermediate phenotype (1,2), a few case reports (2) as well as a limited number of clinical blood culture isolates (3). The mechanism for the seesaw effect is not known, but has been proposed to be due to differential expression of *pbp2* and *pbp4* in strains with elevated vancomycin MICs (2). It has also been suggested that this effect could be used therapeutically to improve outcomes or to reduce the emergence vancomycin resistance (3). In this study, we evaluated the correlation between vancomycin MIC and cefazolin and ceftaroline MICs in a large collection of MSSA and MRSA strains from across Canada to minimize potential contribution of clonal characteristics.

MATERIALS & METHODS

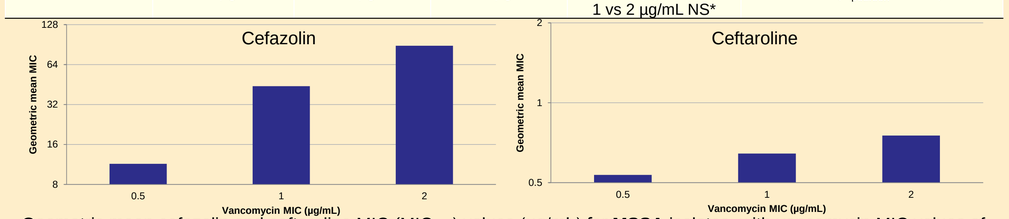
Isolates were collected as part of the CANWARD 2009-2012 studies. 15 Canadian centers in 8 provinces contributed clinically relevant isolates. All *S. aureus* isolates submitted during this period were included. Susceptibility testing to cefazolin, ceftaroline and vancomycin was performed by broth dilution using M100-S24 and M07-A10 CLSI recommendations (4,5). MRSA was identified by mecA PCR.

To assess the relationship between vancomycin MIC and cefazolin and ceftaroline MICs, the geometric mean cefazolin and ceftaroline MICs were compared among isolates with vancomycin MICs of 0.5 µg/mL, 1 µg/mL or 2µg/mL using ANOVA with post-hoc Tukey HSD and linear correlation of $\log_2$MIC by Pearson correlation. Six isolates with a vancomycin MIC of 0.25 µg/mL were excluded because meaningful statistical analysis was not possible. P values less than 0.05 were considered significant.

RESULTS

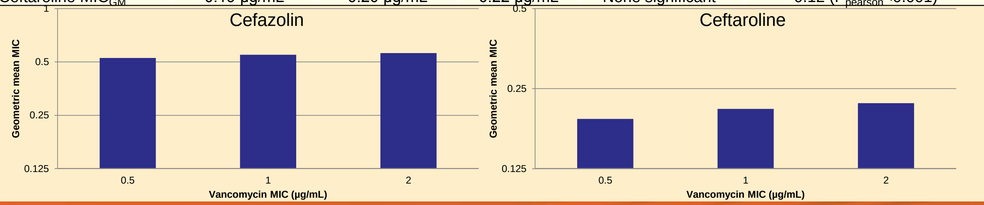
Geometric mean cefazolin and ceftaroline MIC (MIC_{GM}) values (µg/mL) for **MRSA** isolates with vancomycin MIC values of 0.5 µg/mL, 1 µg/mL or 2 µg/mL. *NS = not significant at p ≤ 0.05

	Vancomycin MIC				
MRSA (n=727)	0.5 µg/mL (n=17)	1 µg/mL (n=576)	2 µg/mL (n=134)	P value (Tukey HSD)	Coefficient of correlation
Cefazolin MIC_{GM}	11.4 µg/mL	44.0 µg/mL	88.7 µg/mL	0.5 vs 1 µg/mL<0.01 0.5 vs 2 µg/mL<0.01 1 vs 2 µg/mL NS*	0.33 ($P_{pearson}$<0.001)
Ceftaroline MIC_{GM}	0.53 µg/mL	0.64 µg/mL	0.75 µg/mL	0.5 vs 1 µg/mL<0.05 0.5 vs 2 µg/mL<0.01 1 vs 2 µg/mL NS*	0.21 ($P_{pearson}$<0.001)



Geometric mean cefazolin and ceftaroline MIC (MIC_{GM}) values (µg/mL) for **MSSA** isolates with vancomycin MIC values of 0.5 µg/mL, 1 µg/mL or 2 µg/mL. *No differences between MICs significant at p ≤ 0.05.

	Vancomycin MIC				
MSSA (n=2888)	0.5 µg/mL (n=828)	1 µg/mL (n=2048)	2 µg/mL (n=12)	P value (Tukey HSD)	Coefficient of correlation
Cefazolin MIC_{GM}	0.53 µg/mL	0.55 µg/mL	0.56 µg/mL	None significant*	0.08 ($P_{pearson}$<0.001)
Ceftaroline MIC_{GM}	0.19 µg/mL	0.20 µg/mL	0.22 µg/mL	None significant*	0.12 ($P_{pearson}$<0.001)



CONCLUSIONS

A seesaw effect was not observed in this large natural population of clinical *S. aureus* isolates.

Mean geometric MIC values of both beta-lactams increased with each incremental increase in vancomycin MIC for MRSA, but not MSSA. The increase from vancomycin MIC of 0.5 to 1 µg/mL and 0.5 to 2 µg/mL was most significant.

Ceftaroline and cefazolin MIC values had strong positive correlations with vancomycin MIC in both MRSA and MSSA, However the magnitude of the effect was very small in MSSA and significance achieved because of large sample numbersand this increase was not significant by ANOVA with Tukey HSD.

The reason for discrepancies in seesaw effects reported by our group and others remains unclear. Possible explanations may include deferential effects at higher vancomycin MICs, as our study did not include strains with MIC values of 4 µg/mL or greater, contributions of isogenic/clonal strains, requirement for ongoing glycopeptide pressure or different mechanisms of increased vancomycin MIC.

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REFERENCES

1. Werth BJ, Steed ME, Kaatz GW, Rybak MJ. Antimicrob Agents Chemother. 2013;57(6):2664-8.
2. Ortwine JK, Werth BJ, Sakoulas G, Rybak MJ. Drug Resist Updat. 2013; 16(3-5):73-9.
3. Barber KE, Ireland CE, Bukavyn N, Rybak MJ. Infect Dis Ther. 2014; 3(1):35-43.
4. CLSI. *Methods for Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Eighth Edition.* CLSI document M07-A10. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
5. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement.* CLSI document M100-S25. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.