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Enhanced Activity of Daptomycin and Vancomycin Combined with Imipenem or Oxacillin Against Community-Acquired MRSA Isolates

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AMENDED ABSTRACT

Objectives: To study glycopeptides and lipopeptides in combination with potent antistaphylococcal beta-lactams against community-acquired MRSA (CA-MRSA). CA-MRSA has emerged as a serious clinical therapeutic problem because of limited orally administered treatment options, recognized virulence (Panton-Valentine leukocidin) and ubiquitous presentations in outpatient practice in the USA and worldwide. Serious invasive cases needing hospitalization require prompt selection of bactericidal, parenteral agents. We report drug combinations with enhanced killing activity.

Methods: Following CLSI susceptibility (S) test screening of >100 CA-MRSA, vancomycin (MIC_{50}, 1 mg/L), daptomycin (MIC_{50}, 1 mg/L: CA-MHB) and imipenem (IPM; MIC_{50}, 0.5 mg/L) each had potential treatment utility as well as oxacillin (OXA; MIC_{50}, 16 mg/L) in combination. Ten strains with USA300 PFGE patterns (three USA300-0114) or variations were selected for checkerboard synergy/interaction tests. Interpretations used FICA calculations. The control beta-lactam was OXA and internal organism control was *S. aureus* ATCC 29213 (MSSA).

Results: All drugs tested alone were consistent with expected results for a MRSA except IPM where contemporary USA300 CA-MRSA MIC values ranged from only 0.03 to 1 mg/L (S levels by CLSI and US-FDA breakpoints). Combinations of IPM with daptomycin and vancomycin clearly indicated enhanced inhibition (and killing; data not shown) for 9 of 10 strains (synergy [SYN] or partial SYN [PSYN]). Similarly, OXA with daptomycin or vancomycin demonstrated SYN or PSYN at concentrations easily achievable in vivo. The control MSSA strain interaction results varied from indifference (daptomycin or vancomycin) to PSYN (daptomycin/OXA).

See Table 2.

Conclusions: Carbapenem (IPM) MIC results for CA-MRSA strains endemic in USA remain low (0.03-1 mg/L; MIC_{50}, 0.5 mg/L) and combinations with either daptomycin or vancomycin demonstrate enhanced inhibition (SYN or PSYN) and bactericidal activity. No antagonism was observed and these combinations should be considered for severe cases of CA-MRSA infections and studies should be expanded to endemic hospital-acquired MRSA.

INTRODUCTION

Community-acquired or -associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as a serious clinical therapeutic problem because of limited orally administered treatment options, recognized virulence (Panton-Valentine leukocidin[PVL]) and ubiquitous presentations in outpatient practice, especially in the United States (USA). Severe invasive cases needing hospitalization require prompt selection of bactericidal parenteral agents. We report drug combinations with enhanced bactericidal activity against this pathogen. In this study, a glycopeptide and a lipopeptide were examined in combination with potent anti-staphylococcal beta-lactams tested against CA-MRSA by the broth microdilution checkerboard technique.

MATERIALS AND METHODS

Following Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) susceptibility test screening of more than 100 CA-MRSA, vancomycin (MIC_{50}, 1 mg/L), daptomycin (MIC_{50}, 0.25 mg/L; in MHB at 50 mg/L calcium) and imipenem (MIC_{50}, 0.5 mg/L) had potential treatment utility as well as oxacillin (MIC_{50}, 16 mg/L) in combination. Ten strains with USA300 PFGE patterns (three USA300-0114) or variations (seven strains) were selected for checkerboard synergy/interaction tests. These strains also had PVL (+) and SCC*mec*IV (+) results. Interpretations of synergy test results used standard FICA calculations. The control beta-lactam for interaction categorization was oxacillin and internal organism control was *S. aureus* ATCC 29213 (methicillin-susceptible).

The strains selected had daptomycin MIC results at the upper-end of the normal MIC population distribution, one isolate with a non-susceptible result (MIC, 2 mg/L).

RESULTS

- All drugs tested alone produced in vitro results consistent with expected patterns for MRSA except imipenem where contemporary USA300 CA-MRSA strain imipenem MIC values that ranged from only 0.03 to 1 mg/L (susceptible levels by CLSI and USA-FDA breakpoints); see Table 1.
- Combinations of imipenem with daptomycin and vancomycin clearly indicated enhanced inhibition (and killing, data not shown) for 9 of 10 CA-MRSA strains (synergy or partial synergy). This included a significant reduction of the daptomycin MIC values.
- Oxacillin with daptomycin or vancomycin demonstrated partial or complete synergy at concentrations achieved in vivo.
- The control methicillin-susceptible *S. aureus* strain had interaction results that varied from indifferences (daptomycin or vancomycin/imipenem) to partial synergy (daptomycin/oxacillin; data not shown), a pattern consistently observed before.

Table 1. MIC results for the 10 USA300 CA-MRSA strains used in the synergy tests.

	MIC (mg/L):			
Antimicrobial agent	50%	90%	Range	% susceptible
Daptomycin	1	1	1-2	90.0
Vancomycin	1	1	1	100.0
Imipenem	0.5	1	0.03-1	100.0[a]
Oxacillin	16	32	8-32	0.0

a. Note all USA300 strains are imipenem-susceptible; daptomycin tested at 25 mg/L calcium.

Table 2. Drug interaction or synergy categories for testing of 10 USA300 CA-MRSA with daptomycin or vancomycin combined with imipenem or oxacillin.

	Interaction category (occurrences):				
Combination	Synergy	Partial Synergy	Additive	Indifferent	Antagonism
Daptomycin/oxacillin	7	3	0	0	0
Daptomycin/imipenem	4	5	0	1	0
Vancomycin/oxacillin	1	9	0	0	0
Vancomycin/imipenem	9	0	0	1	0

CONCLUSIONS

- Carbapenem (imipenem) MIC results for CA-MRSA strains endemic in USA remain low (0.03-1 mg/L; MIC_{50}, 0.5 mg/L) and combinations with either daptomycin or vancomycin demonstrated significantly enhanced inhibition (complete or partial synergy) and bactericidal activity.
- No antagonism was observed and these parenteral combinations should be considered for severe cases of CA-MRSA infections and studies should be expanded to endemic hospital-acquired methicillin-resistant *S. aureus* disease, also potentially having modestly elevated lipopeptides MICs (≥1 mg/L).

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