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Comparative Activity of Various Antibiotics alone & in Combination against High Inocula Methicillin-Resistant *Staphylococcus aureus* with Reduced Susceptibilities to Vancomycin

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Objectives

Methicillin-resistant *Staphylococcus aureus* (MRSA) is endemic worldwide, with increasing vancomycin (V) heteroresistance. Many new antibiotics (abx) developed are active against MRSA but the optimal chemotherapy is not well defined in endocarditis & osteomyelitis (high inocula infections).

We aim to examine the utility of various abx alone & in combination (combi) at high inocula for potential clinical use against a variety of well characterized MRSA with vancomycin heteroresistance.

Methods

Bacteria: Ten well-known MRSA clones (ST239 V-intermediate, UK-EMRSA-15, ST30 community-associated (CA) & ST8 USA300 CA) were selected for the study.

Antimicrobial Agents: Daptomycin, linezolid, rifampicin, tigecycline and vancomycin were employed for the study.

Susceptibility Studies: Minimum inhibitory concentrations (MIC) of the isolates were determined according to the CLSI broth-dilution method.[1]

Time-kill studies (TKS): TKS were performed with approximately 8 log CFU/ml at baseline with the above antimicrobial agents alone & in combination against the test isolates at maximally achievable clinical, unbound concentrations. **(Table 1)** The experiment was conducted for 24h in a shaker water bath set at 35° C. Samples were obtained from each flask in duplicate at various time intervals and the bacterial population was determined by quantitative culture.

Table 1. Simulated tissue/serum concentrations of various antimicrobial agents

Antimicrobial agent	Maximum clinical achievable FREE drug concentration (mg/L)	Corresponding maximum clinical dose
Daptomycin	5	6mg/kg q24h
Linezolid	19	600mg q12h
Rifampicin	2	600mg q12h
Tigecycline	2	100mg q12h
Vancomycin	12	20mg/kg q12h

Results

Susceptibility studies: The various MICs for the 10 isolates are shown in **Table 2**.

TKS: In single antibiotic TKS, most drugs did not exhibit any killing activity in all 4 strains although P alone exhibited bactericidal activity against all strains (>=3 log decrease from baseline inocula) until 8h before regrowth occurred at 24h. Synergistic antibiotic combinations (> 2 log decrease from baseline) were variable between the four tested strains. **(Table 3)**

Table 2. MICs of various antimicrobials for the 10 MRSA isolates
There are currently no CLSI standards for susceptibility testing to *Staphylococcus aureus

Antibiotic / Strain No.	Daptomycin (mg/L)	Linezolid (mg/L)	Rifampicin (mg/L)	Tigecycline (mg/L)	Vancomycin (mg/L)
311	0.5	2	≤0.06	0.06	1
312	0.5	≥16	≤0.06	≥8	1
313	0.5	8	≤0.06	≥8	2
314	0.5	2	≤0.06	0.5	1
315	8	≥16	≤0.06	0.5	2
316	≥16	2	≤0.06	0.25	4
317	4	2	≤0.06	0.25	2
318	1	4	≤0.06	0.5	2
319	2	2	0.12	0.5	2
320	8	≤0.06	≤0.06	0.5	4

Table 3. Bactericidal combinations depicted with a tick for the 10 MRSA isolates

Strain no. / Antibiotic/ combinations	311	312	313	314	315	316	317	318	319	320
Daptomycin	√									
Linezolid		√								
Rifampicin						√				
Tigecycline						√				
Vancomycin							√			
Linezolid + Rifampicin	√									
Daptomycin + Tigecycline		√						√	√	
Daptomycin + Rifampicin			√							
Daptomycin + Vancomycin			√							
Tigecycline + Rifampicin								√		

Conclusion

Combi therapy may be useful against MRSA infections with reduced susceptibilities to vancomycin based on the encouraging *in vitro* activity. However, 2-drug abx combi may not be sufficient to totally eradicate the infection.

Our approach may be used to identify abx combi that can be used for long-term adjuvant antibiotic therapy in clinical situations like osteomyelitis. Further research is warranted.

1. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-First Informational Supplement.* CLSI document M100-S21. Wayne, PA: Clinical Laboratory Standards Institute; 2011