Bacteremia due to Methicillin-Resistant *Staphylococcus aureus*

New Therapeutic Approaches

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KEYWORDS

• Methicillin • *Staphylococcus aureus* • MRSA • Bacteremia • Vancomycin • Daptomycin • Ceftaroline • Endocarditis

KEY POINTS

- Vancomycin, optimally dosed, remains the initial antibiotic of choice for the treatment of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endocarditis due to isolates with vancomycin minimum inhibitory concentration $\leq$2 mg/mL. Daptomycin is an effective, although more costly alternative, and ceftaroline appears promising.
- Treatment options for persistent MRSA bacteremia or bacteremia due to vancomycin-intermediate or vancomycin-resistant strains include daptomycin, ceftaroline, and combination therapies.
- There is a critical need for high-level evidence from clinical trials to allow optimally informed decisions in the treatment of MRSA bacteremia and endocarditis.

INTRODUCTION

Resistance of *Staphylococcus aureus* to the first semisynthetic penicillin, methicillin, was reported within a year of its introduction into clinical medicine, mirroring the rapid identification of penicillin resistance less than a decade earlier. Methicillin-resistant *S aureus* (MRSA) subsequently increased in prevalence, but was largely confined to hospital settings until its emergence in the community in the last decade of the 20th century.

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The progressive emergence of MRSA led to the widespread use of vancomycin and, inevitably, reports of reduced susceptibility emerged, beginning with strain MU80 (vancomycin minimum inhibitory concentration [MIC] of 8 μg/mL) isolated in 1996 from the wound infection of a Japanese child receiving prolonged therapy with this glycopeptide antibiotic. This emergence represented the first identified vancomycin-intermediate *S aureus* (VISA; MIC 4–8 μg/mL) and was followed by the recognition of the emergence of heterogeneous intermediate reduced susceptibility (hVISA) strains, each resulting from cell wall alterations with sequestration of the glycopeptide. The first fully vancomycin-resistant (VRSA) strain (MIC >32 μg/mL) was identified in 2002, an occurrence that has fortunately remained rare.

This evolutionary history, together with the recognition of the frequent failure of vancomycin treatment of MRSA infections regardless of the MIC of the isolate, provides unequivocal evidence of the need for newer more effective therapies and therapeutic approaches (Tables 1 and 2).

GLYCOPEPTIDES AND SEMISYNTHETIC LIPOGLYCOPEPTIDES

Vancomycin

Optimization of vancomycin administration is a critical factor in improving outcomes of patients with MRSA infection, and recent information provides insight into this issue.

Table 1
Pharmacokinetic/pharmacodynamics profile of anti-infective agents for methicillin-resistant *Staphylococcus aureus*

Agent	MIC Breakpoint for *S aureus* (μg/mL)	PK-PD Indices Associated with Efficacy	Activity Against *S aureus*	% Protein Bound	Half-Life (h)	Excretion
Vancomycin	≤2	AUC/MIC	Bactericidal	50	5–11	80%–90% renal
Daptomycin	≤1	AUC/MIC	Bactericidal	90	8–9	89% renal, 6% feces
Ceftaroline	≤1	T > MIC	Bactericidal	20	2.7	88% renal, 6% feces
Dalbavancin	≤0.12	AUC/MIC	Bactericidal	93	346	33% renal, 20% feces
Oritavancin	≤0.12	AUC/MIC	Bactericidal	85	245	<5% renal, <1% feces
Telavancin	≤0.12	AUC/MIC	Bactericidal	90	6.6–9.6	76% renal, <1% feces
Tedizolid	≤0.5	AUC/MIC	Bacteriostatic	70–90	12	20% renal, 80% feces
Linezolid	≤4	AUC/MIC	Bacteriostatic	31	4–5	30% renal, 9% feces
Tigecycline	≤0.25	AUC/MIC	Bacteriostatic	71–89	42	33% renal, 59% feces

Abbreviations: AUC, area under the plasma concentration curve; T > MIC, time of drug concentration above MIC.

Data from Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc; 2015; July 20, 2015; Micromedex Healthcare Series (Internet database). Greenwood Village, CO: Thomson Micromedex.