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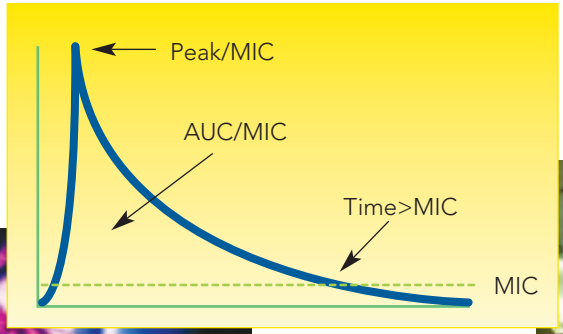
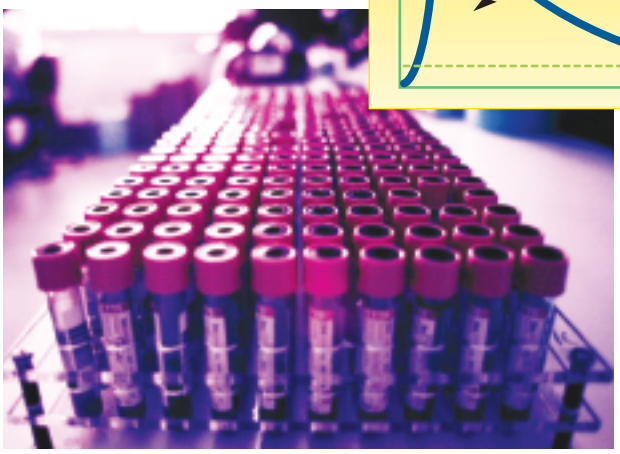
Gram-Positive Antibiotic Selection: PK/PD Considerations

CME Opportunity
From the 2006 MRSA
Education Summit





Antibiotic levels in various tissue

Pharmacokinetic profiles in relation to MIC

Optimal dosing strategies

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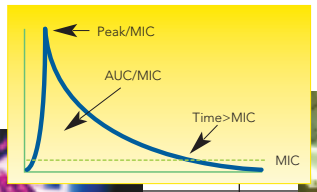

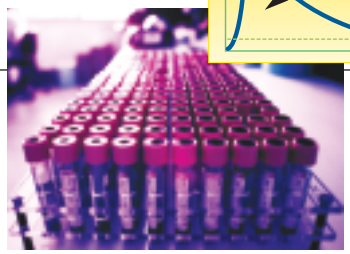

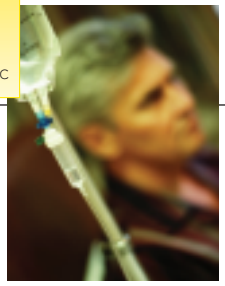

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Gram-Positive Antibiotic Selection: PK/PD Considerations

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Needs Statement

Staphylococcus aureus continues to challenge best practices of infection management. This may be attributed to several factors, including the ability of *S aureus* to elaborate virulence factors and toxins, along with the emergence of resistance mechanisms that undermine the success of traditional antibiotic agents. This monograph will provide insight into the pharmacokinetic (PK) and pharmacodynamic (PD) principles of antistaphylococcal agents that can facilitate appropriate antibiotic selection and lead to greater success in managing *S aureus* infections.

Accreditation Statements

Physician: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Kentucky College of Medicine and the International Society of Microbial Resistance. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this educational activity for a maximum of *1.0 AMA PRA Category 1 Credit*™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

The University of Kentucky Colleges of Pharmacy and Medicine present this activity for educational purposes only. Participants are expected to use their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected because of recognized expertise in their field.

Pharmacy:
The University of Kentucky College of Pharmacy is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

This activity has been assigned ACPE #022-999-06-006-H04 and will award 1.0 contact hour (0.1 CEUs) of continuing pharmacy education credit in states that recognize ACPE providers. Statements of credit will indicate hours and CEUs based on successful completion of a posttest (score 70% or higher) The college complies with the Criteria for Quality for continuing education programming.

Learning Objectives

At the completion of this activity, participants should be able to:

1) Cite the emerging challenges in antibiotic selection for management of MRSA infections
2) Summarize important pharmacodynamic attributes to clinical efficacy
3) Describe key pharmacokinetic properties of new antibiotics for MRSA
4) List antibiotics in late-stage development

Target Audience

This educational program is intended for physicians, pharmacists, and other healthcare professionals who manage the care of patients with MRSA infections, or who are at risk for MRSA infections.

Disclosure of Financial Interest

All faculty members participating in continuing medical education programs sponsored by the University of Kentucky Colleges of Pharmacy and Medicine Continuing Education Office are expected to disclose any real or perceived conflict of interest related to the content of their presentations. Faculty disclosures are listed above.

Estimated Time of Completion

This activity should take approximately 1.0 hour to complete.

Method of Participation

There are no fees for participating in and receiving credit for this activity. The participant should read the objectives and monograph, answer the multiple-choice post-test, and complete the answer sheet with registration and evaluation and mail to:
Continuing Education Office, Attn: Distance Education, Colleges of Pharmacy and Medicine, University of Kentucky, 1 Quality St, 6th Floor, Lexington, KY 40507-1428.
Certificates will be mailed to participants approximately 4 weeks after receipt of the mailed or faxed submissions. This credit is valid through January 23, 2008.

Support Statement

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Joint Sponsorship Statement

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Gram-Positive Antibiotic Selection: PK/PD Considerations

Staphylococcus aureus continues to challenge the best practices of infection management. This challenge can be attributed to several factors, including the emergence of resistance mechanisms that undermine the success of traditional antibiotic agents and the ability of *S aureus* to elaborate virulence factors and toxins. Insight into the pharmacokinetic (PK) and pharmacodynamic (PD) principles of antistaphylococcal agents can facilitate appropriate antibiotic selection and lead to greater success in managing *S aureus* infections.

The Methicillin-Resistant *Staphylococcus aureus* Problem

S aureus is responsible for a growing number of healthcare-associated methicillin-resistant *S aureus* (HA-MRSA) and community-acquired (CA-MRSA) infections. In a recent study of more than 3 million isolates collected from 1998 to March 2005, *S aureus* was the most frequent isolate identified in nosocomial infections, and the second most common pathogen in outpatient infections after *Escherichia coli*.[1] Gram-positive pathogens, including *S aureus*, have been the most common nosocomial pathogens since the late 1990s.[1-4]

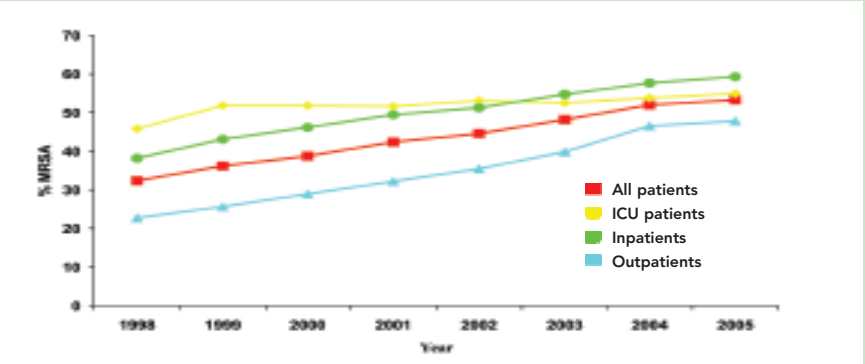
S aureus is a frequent cause of pneumonia, including ventilator-associated pneumonia,[5] complicated skin and soft tissue infections (cSSSIs), surgical site infections,[6] bacteremia, septic arthritis, toxic shock syndrome, osteomyelitis, and endocarditis.[3,7] Approximately 1% of hospitalizations are related to some type of *S aureus* infection.[7,8]

In the past 20 years, rates of MRSA have steadily increased in healthcare and community settings, forcing a shift in the clinical approach to gram-positive infections. The national average inpatient rate of MRSA infection accounts for 43% of *S aureus* infections and more than 125,000 hospitalizations annually.[7] Treatment of MRSA has been further confounded by *S aureus* with reduced sensitivity to vancomycin, even among those with no prior vancomycin exposure.[9,10]

Between 1998 and 2005, mean MRSA rates were highest among ICU patients (53%), followed by non-ICU inpatients (46%) and outpatients (31%) (Figure 1).[1] In the most recent survey by the National Nosocomial Infections Surveillance System, MRSA prevalence among patients in intensive care units (ICUs) in 2003 was 60%.[4] Risk factors for HA-MRSA infection include recent or prolonged history of antibiotic use, recent hospitalization, ICU stay, immunocompromised status, renal failure, and exposure to long-term care facilities.[3,6,11] Methicillin resistance has been independently associated with increased mortality,[12,13] length of hospitalization,[14,15] and hospital costs.[12,13-16] The impact of methicillin resistance on mortality, however, is still debated.[17]

The prevalence of CA-MRSA infections is also on the rise[1,11] and is predominately associated with skin and skin structure infections.[11,18] Notable outbreaks have been reported in otherwise healthy patient populations, including children, military recruits, persons in prisons, members of high school and professional sports teams, postpartum women, and men who have sex with men.[11] CA-MRSA infections can be mild or severe, and can include furuncles, impetigo, scalded skin syndrome, necrotizing soft tissue infections, septic arthritis, osteomyelitis, pneumonia, endocarditis, and toxic shock syndrome.[9,11] In contrast to HA-MRSA, community pathogens express unique toxin and resistance profiles[11,18]; however, recent evidence suggests that community strains have become increasingly prevalent in healthcare settings,[11,19] supporting the prediction that community and nosocomial strains might merge over time.[11]

Figure 1. MRSA Trends: Cumulative Data From 1998 to March 2005



Reprinted with permission from Styers et al, 2006.[1]

MRSA Colonization Rates

Approximately one third of the general population is colonized with staphylococci, of which 1% is MRSA.[8,20] Colonization is a risk factor for infections,[21] including skin[22] and surgical site infections.[14] In long-term care facilities, colonization has been associated with poor mobility and functional status, skin wounds, invasive devices such as nasogastric tubes or intravenous (IV) catheters, antibiotic therapy, and prior MRSA colonization.[23]

Genetic Mechanism of Methicillin Resistance

Resistance to methicillin is encoded by the *mecA* gene, which is carried on cassettes of varying size and is sometimes flanked by and cotransmitted with non–beta-lactam resistance genes. *MecA* confers resistance by producing penicillin-binding protein-IIa with low affinity for beta-lactam antibiotics.[3,24,25]

A distinct mobile genetic element called the staphylococcal cassette chromosome *mec* (SCC*mec*) conveys the *mecA* gene horizontally. Historically, HA-MRSA strains have been found to contain the SCC*mec* type I, type II, or type III genotype, while CA-MRSA strains have expressed the type IV SCC*mec* genotype (Table 1).[24,25] SCC*mec* type IV is smaller and less likely to be associated with non–beta-lactam antibiotic resistance determinants compared with HA-MRSA types II and III.[24,25] A common SCC*mec* type IV CA-MRSA isolate found between 2000 and 2002 in children in and around Memphis, Tennessee, was notable for clindamycin susceptibility and erythromycin resistance.[26] Similar resistance patterns have been reported in Houston, Texas.[19] Mapping the *mecA* gene cassette and toxin profiling are now among the preferred methods of distinguishing CA-MRSA from HA-MRSA.

Table 1. HA-MRSA and CA-MRSA Genotypes and Sources

Type	Size (kb)	Source	Ribotype
I	34.3	Hospital	Conserved
II	53	Hospital	Conserved
III	66.9	Hospital	Conserved
IV	21-24	Community	Variable

Adapted from Daum et al, 2002.[25]

Toxin Production by MRSA

Toxins produced by *S aureus* contribute to the organism's virulence and are associated with several syndromes such as necrotizing pneumonia[27] and severe soft tissue infections[6,28] that could have devastating consequences. Major toxin categories include the exfoliative toxins A and B (associated with impetigo, bullous impetigo, and scalded skin syndrome), and a family of enterotoxins associated with necrotizing pneumonia, epidemic furunculosis, and toxic shock syndrome.[11] Toxic shock syndrome toxin-1 and staphylococcal enterotoxin B cause toxic shock syndromes associated with menstrual and surgical site infections, respectively.[6,19,29] The pore-forming staphylococcal toxins include alpha-hemolysin and a family of leukotoxic proteins that combine in aggregates of two protein pairs to form pores in the membranes of human neutrophils, monocytes, macrophages, and red blood cells. In this family, the Panton-Valentine leukocidin toxin is associated with dermonecrosis, commonly associated with CA-MRSA strains. In addition, coagulase enzyme might assist *S aureus* in averting host immunity by causing localized clotting.[25] Despite the association of various toxin types with severe infectious processes, the direct relationship between the presence of toxin genes and severity of infection remains elusive.[30]

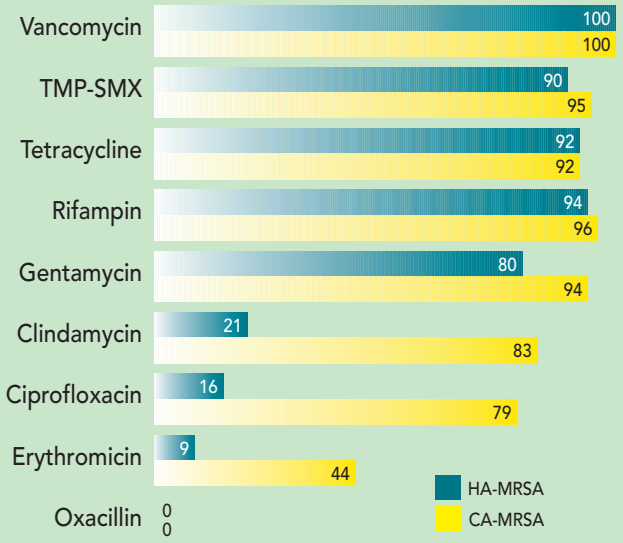
Antibiotic Options and Selection

Several antibiotics are currently available to treat MRSA infections. These include older products (vancomycin, tetracyclines, clindamycin, and trimethoprim-sulfamethoxazole [TMP/SMX]), plus the more recent additions linezolid, daptomycin, and tigecycline.[6,11,31] The clinician is faced with a challenging balancing act when deciding between narrow- and broad-spectrum antibiotics for empiric therapy. Narrow-spectrum antibiotics more precisely target antibiotic-sensitive organisms without applying selective pressure that can lead to the emergence of resistance. Alternatively, withholding coverage against resistant organisms might result in the delay of effective treatment and increase morbidity and mortality.[32] Despite the availability of numerous antibiotic options, a recent study of outpatient antibiotic prescriptions revealed that 73% of MRSA-infected patients receive ineffective initial treatment.[33] The local susceptibility profile and the possibility of multidrug resistance must be considered for suspected MRSA infections, and these factors should be weighed against a policy of sparing antimicrobials (eg, vancomycin, linezolid, daptomycin, or tigecycline) to retain efficacy against resistant organisms.

Resistance Patterns

MRSA sensitivities to antibiotics vary by geographic region and pathogen origin (community vs health-care setting). Approximate resistance to various agents is as follows: fluoroquinolones (30%-90%), erythromycin (90%-95%), clindamycin (75%-83%), ketolides (82%-98%), tetracycline (18%-82%), quinupristin-dalfopristin (4%-31%), rifampin (10%-60%), gentamycin (75%-93%), TMP/SMX (16%-65%), oxazolidinones (0%-1%), and daptomycin (1%-5%).[3,19,34-38] Differences in susceptibility based on whether the MRSA strain is of community or healthcare origin have also been noted (Figure 2), and physicians should rely on local resistance patterns to guide empiric treatment decisions. Recent attention has also been drawn to inducible clindamycin resistance. Isolates reported as resistant to erythromycin but susceptible to clindamycin likely have inducible clindamycin resistance and require additional testing using the D-test.[31] Strains that exhibit inducible resistance are associated with high rates of clindamycin resistance during therapy.[39]

Figure 2. Susceptibility Patterns for CA-MRSA and HA-MRSA



TMP-SMX = trimethoprim sulfamethoxazole; CA-MRSA = community-acquired MRSA; HA-MRSA = healthcare-associated MRSA.
Adapted from Kowalski et al.[38]

Recent evidence suggests that reduced sensitivity to vancomycin should also be considered when treating MRSA. The failure rate of vancomycin has been shown to increase with rising vancomycin minimal inhibitory concentration (MIC), even within the concentration range typically considered to be sensitive to vancomycin.[10,40-42] Organisms that persisted despite vancomycin treatment in vivo were associated with resistance to bactericidal action of the drug in vitro.[10] Strains that are not susceptible to vancomycin have been characterized as vancomycin-intermediate *S aureus* (VISA; MIC 4-8 mcg/mL) or vancomycin-resistant *S aureus* (VRSA; MIC >32 mcg/mL) isolates. An additional resistance category, heteroresistant vancomycin-intermediate *S aureus* (hetero-VISA) describes isolates that are fully susceptible to vancomycin when tested using a standard inoculum load (10^5 colony-forming unit [CFU]/mL), but reveal a subpopulation of intermediate sensitivity clones (MICs from 8-16 mcg/mL) when tested under high inoculum conditions. Heteroresistance observed in MRSA isolates[43] is associated with slower clearing of MRSA bacteremia,[44] and has recently also been associated with heteroresistance to daptomycin.[45] Although the clinical significance of the latter has not been evaluated, a recent retrospective report from the Centers of Disease Control (CDC) confirms that reduced susceptibility to vancomycin predicts daptomycin resistance in *S aureus* isolates.[46] In 2006, the Clinical and Laboratory Standards Institute (CLSI) lowered vancomycin susceptibility ranges in light of mounting evidence of clinical vancomycin failures. Current US Food and Drug Administration (FDA) concentration ranges have not changed (Table 2).

Table 2. Current Ranges for Vancomycin-Susceptible, Intermediate, and Resistant *S aureus*

	VSSA	VISA	VRSA
New CLSI	≤2 mcg/mL	4-8 mcg/mL	≥16 mcg/mL
Current FDA	≤4 mcg/mL	8-16 mcg/mL	≥32 mcg/mL

VSSA = vancomycin-susceptible *S aureus*; VISA = vancomycin-intermediate *S aureus*; VRSA = vancomycin-resistant *S aureus*; CLSI = Clinical and Laboratory Standards Institute; FDA = US Food and Drug Administration.

Although rare, *S aureus* resistance to linezolid has been reported; typically this is associated with point mutations in multiple copies of the 23S ribosomal RNA.[47] Resistance to daptomycin has also been reported during therapy for bacteremia.[37] Diagnostic manufacturers must use the FDA ranges, while clinical laboratories can use either the CLSI or FDA ranges.

Antibiotic Considerations

Mechanism of Action

The mechanism of action for antibiotics used to treat *S aureus* and MRSA infections can be divided into several broad categories.

Inhibition of cell wall synthesis. Vancomycin inhibits bacterial cell wall synthesis by binding to pentapeptide substrates, thereby preventing cross-linking functions in the final stages of membrane synthesis.[48] Similar to beta-lactams, which inhibit cell wall synthesis by binding to penicillin-binding proteins, these agents tend to be less effective against pathogens in stationary phases of the growth curve.

Protein synthesis inhibition. Linezolid employs a unique mode of protein synthesis inhibition: it blocks the formation of the bacterial 70S initiation complex by binding the 50S ribosomal subunit.[49] This site of inhibition differs from the inhibition of protein synthesis by clindamycin and tetracyclines (doxycycline, minocycline, and tigecycline), which interfere with the elongation cycle of protein synthesis.

Bacterial membrane disruption. Daptomycin acts at the level of bacterial cell membranes and causes depolarization of membrane potential through an ionophore-like mechanism and disruption of metabolic activity.[50]

MICs and pathogen killing. MICs and the minimum bactericidal concentration (MBC) are in vitro measures of an antibiotic activity profile.[29,51,52] As reported by the microbiology laboratory, these values can serve as a starting place for clinical decision making. The MBC is defined as the lowest antibiotic concentration that kills 99.9% (greater than 3 $\log_{10}$ decline) of organisms after an 18- to 24-hour incubation. The MIC is the lowest concentration of drug that prevents visible growth in the same time period (through either pathogen killing or by arresting growth). Recent evidence suggests that the MBC[41] and MIC[40] for vancomycin have increased in recent years, offering insight into the declining clinical effectiveness of vancomycin.[9]

Although useful as a way to categorize antibiotic activity across chemical classes, MIC and MBC values paint an incomplete picture and are but two of several important properties that must be considered to design a successful antimicrobial treatment plan.[51,53] By definition, antibiotics with bactericidal activity can achieve a greater than 3-$\log_{10}$ decline in in vitro bacteria count within 24 hours; this is typically seen when the MBC is ≤4 times the MIC.
In contrast, antibiotics that do not achieve a 3-$\log_{10}$ reduction or exhibit an MBC >4 times the MIC are considered bacteriostatic. Tolerance occurs when the MBC is >32 times the MIC.[29,53] It is common for bacteriostatic drugs to demonstrate bactericidal killing with a longer time of exposure, but with little dependence on concentration.[51]

In reality, however, antimicrobials might be bactericidal against some organisms and bacteriostatic against others (Table 3).[54]

Table 3. Antimicrobials: Bacteriostatic or Bactericidal

	Bacteriostatic	Bactericidal	Postantibiotic Effect (*S aureus*) (h)
TMP/SMX	NA	Usually	NA
Clindamycin	Usually		7.1
Vancomycin	*Enterococcus* sp	*Staphylococcus* sp *Streptococcus* sp	1-2
Linezolid	*Staphylococcus* sp *Enterococcus* sp	*Streptococcus* sp	1-3
Daptomycin	NA	All	5-10
Tigecycline	NA	Usually	3-4

NA = not applicable.

The debate over bactericidal and bacteriostatic mechanisms is largely academic. Theoretical advantages of bactericidal drugs include rapidly decreased bacterial load, faster resolution of infection, decreased host immunologic activation, lower risk of relapse, and reduced risk for the development of resistance.[53] Conversely, possible advantages of bacteriostatic drugs include inhibition of toxin production and less immune-related toxicity from the rapid release of cell wall components associated with rapid cell lysis.[55,56] Bacteriostatic agents inhibit protein synthesis during fast and slow phases of growth, whereas the bactericidal action of cell-wall–synthesis inhibitors is most effective during the rapid growth phase.[56]

A distinct clinical benefit to bactericidal therapy over bacteriostatic therapy for most infections is intuitive rather than based on rigorous research.[54] Regardless, many clinicians are inclined to think of bactericidal drugs for endocarditis, meningitis, osteomyelitis, and infections in neutropenic hosts.[56] Bactericidal agents have been favored in the treatment of endocarditis because of the concern for high bacterial concentrations in a relatively avascular site of infection. The traditional preference has been for a beta-lactam or vancomycin, alone or with an aminoglycoside,[54,56] but daptomycin has recently been approved by the FDA for the treatment of right-side endocarditis.[37] Some argue that cell-wall–active antibiotics (active only against replicating organisms) are suboptimal against bacteria in cardiac vegetations, which are in a dormant state.[56] Success in treating *S aureus* endocarditis with bacteriostatic agents linezolid[57] or clindamycin,[56] however, has also been reported. Interestingly, a recent comparative trial of linezolid vs vancomycin in febrile neutropenia[58] showed equivalent overall clinical responses, casting doubt on the notion of a clear advantage for bactericidal vs bacteriostatic mechanism.

Sub-MIC and Postantibiotic Effects

The lowest concentration of a drug that has some morphologic or ultrastructural impact on an organism is called the minimum antibiotic concentration (MAC). The MAC is usually lower than the MIC; therefore, MAC is considered a sub-MIC effect. Some drugs, especially bacteriostatic drugs, will have high MIC/MAC ratios, that is, they exert significant changes in bacteria at very low drug concentrations.[51] In light of the recent interest in *S aureus* toxins and pathogenesis of serious infection,[11] MAC effects may be a factor in agent selection. In vitro studies confirm that clindamycin or linezolid inhibit toxin production at sub-MIC concentrations,[59,60] and a recent case report confirms that linezolid or clindamycin, but not vancomycin, are effective in reducing toxic shock syndrome toxin-1 production by *S aureus* isolates from patients successfully treated with linezolid for toxic shock syndrome due to *S aureus*.[61] Sub-MIC effects for daptomycin[62] have also been reported.

Postantibiotic effects (PAE) include any persistent suppressive effects that occur after abbreviated exposure to therapeutic concentrations of a drug. PAE can be assessed by several methods, including centrifugation and washing for removal of the drug.[51] Vancomycin has a 2-hour PAE,[53,63] and linezolid exhibits mean maximal PAE against methicillin-susceptible *S aureus* (MSSA) and MRSA of 2.2 hours in vitro.[49] The PAE of daptomycin is approximately 6 hours,[62,63] whereas tigecycline has a 3- to 4-hour PAE against MRSA.[64]

Pharmacokinetic Considerations: Half-Life, Blood Levels and Tissue Distribution, Protein Binding, and Route of Administration

Beyond the characteristic in vitro actions of an antibiotic on a pathogen, clinical efficacy depends on the ability to achieve effective concentrations at the site of infection. Serum concentrations of

Table 4. Bioavailability and Dosing Considerations for Anti-MRSA Therapy

	Oral Bioavailability	Half-life (h)	Adult Dosing	Protein Binding (%)
TMP/SMX	T >63% S = 100%	T = 8-10 S = 10	160/800 mg q12h	T = 44% S = 70%
Clindamycin	90%	2-3	300 mg q6h PO 600 mg q12h IV	90%
Vancomycin	<5%	3-13	15 mg/kg q12h IV	55%
Linezolid	100%	5	600 mg q12h IV or PO	31%
Daptomycin	NA	8	4 mg/kg IV QD	92%
Tigecycline	NA	27-42	100 mg initial dose IV 50 mg q12h IV	71%-89%

PO = by mouth; IV = intravenous.
Adapted from Stevens et al, 2005,[6] Bamberg et al, 2005,[31] Cubicin prescribing information,[68] Zyvox package insert,[74] Tygacil package insert.[75]

antibiotic comprise free and bound portions. High levels of protein-bound drug allow for a long serum half-life, whereas high concentrations of unbound drug and smaller molecular size contribute to favorable tissue penetration of free drug. Effective dosing schedules should reflect the optimal use of these kinetic parameters (Table 4).

Vancomycin

Peak serum concentrations of vancomycin are 25 to 40 mcg/mL. Vancomycin penetrates most body tissues achieving levels in abscesses that are approximately 100% of serum levels; 75% in ascitic, pericardial, and synovial fluid; 15% to 20% in lung epithelial lining fluid; 30% to 50% in bile; and 1% to 37% in inflamed meninges.[53] Vancomycin exhibits approximately 55% binding to serum proteins.[53] Available in oral, intramuscular (IM), or IV formulations, vancomycin is most often used for *S aureus* infections through the IV route owing to low oral bioavailability and pain with IM injection. Vancomycin must be administered slowly over 1 hour to avoid adverse infusion-related effects, and is usually dosed every 12 hours in patients with normal renal function.

Although recent guidelines suggest that increasing the vancomycin dose might improve the clinical outcome,[5] a recent study in healthcare-associated pneumonia found no clinical benefit of achieving higher vancomycin trough concentrations, or area under the curve (AUC), on patient mortality.[65] In a similar study, the clinical response for patients who achieved high vancomycin trough levels (>15 mcg/mL) for the treatment of MRSA infections (respiratory tract, blood, wound, and urinary tract infections) was still lower when the isolate MIC was >2 mcg/mL.[66] Both studies found an increased risk of renal toxicity with higher vancomycin exposure, suggesting that the potential benefit of pharmacokinetic dose adjustment to address rising MICs might be offset by a higher side effect profile.

Linezolid

Linezolid is approved for the treatment of gram-positive pneumonia and cSSSIs. The C_{max} of linezolid 600 mg IV every 12 hours at steady state is 15 to 20 mcg/mL, approximately two thirds of which is free drug. Lung epithelial lining fluid penetration was roughly 4 to 8 times that of plasma following multiple 600-mg doses in healthy volunteers, indicating good lung penetration.[49] In patients with severe ventilator-associated pneumonia, clinical improvement was observed with mean lung concentrations that approximate plasma values.[67] In humans, mean blister penetration is 104% that of serum (range, 80%-130%). In uninfected patients receiving two perioperative 600-mg doses of linezolid, bone, fat, and muscle penetration was rapid, with 37% penetration into fat and 95% penetration into muscle.[49]

Approved for use in adults (600 mg q12h) and children (10 mg/kg q8h), linezolid is available in IV and oral formulations. The oral formulation is 100% bioavailable,[49] allowing a direct transition between IV and oral therapy without a dose adjustment. Oral linezolid can be administered with or without food.

Daptomycin

Daptomycin is approved for use in gram-positive cSSSI (4 mg/kg) and bacteremia, including right-side endocarditis (6 mg/kg) in patients aged 18 years and older. In healthy adults, the C_{max} at steady state is 58 mcg/mL at 4 mg/kg intravenous once daily and 99 mcg/mL at 6 mg/kg once daily.[68] Reversible protein binding occurs, mostly to albumin at 92%. The half-life of daptomycin at 4 mg/kg once daily is 8 hours.[68] Daptomycin tissue penetration into blister inflammatory fluid is 68%

compared with plasma.[69] Although lung tissue penetration is good, daptomycin is inactivated when bound to surfactant,[70] rendering this antibiotic inappropriate for treating *S aureus* pneumonia.

Tigecycline

Tigecycline is a broad-spectrum antibiotic approved by the FDA for cSSSI and complicated abdominal infections in patients aged 18 years and older. Chemically related to minocycline, this modified molecule is less susceptible to bacterial efflux mechanisms through macrolide or tetracycline efflux mechanisms, except in *Pseudomonas* strains. As a result, tigecycline does not provide adequate pseudomonal coverage. Tigecycline achieves C_{max} of 0.87 mcg/mL when infused over 30 minutes, with a loading dose of 100 mg/kg, followed every 12 hours by 50 mg/kg, despite its long (40-hour) half-life and PAE. In contrast to earlier tetracyclines, an oral formulation of tigecycline is not available.[64]

Though not specifically indicated for *S aureus* or MRSA infections, several other antibiotics enjoy widespread use for these infections, largely in community settings.

TMP/SMX

Although not approved by the FDA for use in *S aureus* or MRSA, the fixed combination of TMP/SMX is often included as a treatment consideration for simple infections caused by either *S aureus* or MRSA. In a single comparison with vancomycin for *S aureus* infections in IV drug users, TMP/SMX was inferior to vancomycin.[71]

Clindamycin

FDA-approved for serious *S aureus* infections, although not specifically for MRSA, clindamycin has had reported success in treating CA-MRSA infections.[72,73] If empiric clindamycin therapy has been initiated and inducible resistance is subsequently detected, patient response to therapy should be carefully evaluated since treatment failures have been reported.[6,39] Other options should be considered in case of poor response or inducible resistance in vitro.

Dosing Considerations

Elderly Patients

Dosing changes are not warranted for linezolid, daptomycin, or tigecycline in elderly men or women, or in patients with mild to moderate liver disease. Use in severe liver disease has not been studied.[68,74,75]

Renal Impairment

Because of the dominant renal route of excretion, the vancomycin dose must be adjusted for renal impairment, with calculations based on creatinine clearance, age, and weight. To prevent toxicity, patients with altered physiology, including burn patients and elderly or obese patients might also require dose adjustments.[53]

Daptomycin is also primarily excreted via the kidneys, necessitating a change in dosing frequency for patients with renal compromise.[68] Dosing frequency for those with normal renal function (creatinine clearance [CrCl] ≥30 mL/min) is 4 mg/kg once every 24 hours. For patients with renal impairment (CrCl ≤30 mL/min), the dosing frequency is prolonged to 4 mg/kg once every 48 hours. This includes patients on dialysis, who should receive the antibiotic dose after the completion of the dialysis session.

For linezolid, dose adjustments are not required for patients with renal impairment; however, caution is warranted owing to the lack of data regarding the renal clearance of active metabolites of linezolid.[74] Patients on dialysis should be dosed after the dialysis session because 30% to 40% is cleared by hemodialysis. For tigecycline, it is not necessary to adjust the dose for patients with renal impairment or patients undergoing hemodialysis.[75]

Products in the Pipeline

Several antibiotics in late-stage development hold promise for the management of *S aureus* and MRSA infections.

Dalbavancin is a novel lipoglycopetide that is structurally related to teicoplanin, which exhibits bactericidal activity. Dalbavancin is unique in that its long (180 hr) half-life and linear dose-dependent AUC allow effective once-weekly dosing; 1000 mg on day 1 and 500 mg on day 8.[76] In a large phase 3 trial of persons with cSSSI infections, dalbavancin was as effective as linezolid, with no overall difference in side effects.[77] In a smaller phase 2 trial of gram-positive catheter-related bacteremia, dalbavancin achieved greater clinical response compared with vancomycin.[78]

Televancin is also a novel lipoglycopeptide, structurally related to vancomycin, which demonstrates rapid dose-dependent bactericidal activity. In vitro studies suggest that televancin acts through two mechanisms: inhibition of late-stage peptidoglycan biosynthesis (as with vancomycin) and disruption of membrane permeability to K+ and adenosine 5′-triphosphate.[79] With a half-life of 7 to 9 hours, both the AUC and C_{max} are linearly related to infusion dose.[80] In a phase 2 comparison with vancomycin, nafcillin, and oxacillin for gram-positive skin and skin structure infections, televancin was equally effective to the comparator when administered via IV at 7.5 mg/kg per day for a mean of 7 days.[81]

Ceftobiprole medocaril (BAL5788) is a novel pro-form of ceftobiprole (BAL9141). When converted to the active molecule, ceftobiprole acts as a fourth-generation cephalosporin with extended activity against gram-positive pathogens, including MRSA, VISA, and VRSA, and gram-negative pathogens.[82] Activity against MRSA is attributed to an unusually high binding affinity for the penicillin binding protein BPB2a, and resistance to degradation by beta-lactamase. Ceftobiprole is currently in phase 3 trials for cSSSI [NTC00210899] and hospital-acquired pneumonia [NTC00210964].

Iclaprim is a new, selective inhibitor of dihydrofolate reductase with activity against trimethoprim-sensitive and resistant enterococci and staphylococci,

including MRSA, VISA, and VRSA. Iclaprim exhibits rapid cidal activity and has demonstrated similar cure rates to vancomycin for cSSSI.[83] Iclaprim is currently in phase 3 trials and is being compared with linezolid for cSSSI infections (the ASSIST-2 trial, NCT00303550).

Recommendations for MRSA Infections

For suspected or proven nosocomial MRSA pneumonia, recent American Thoracic Society/Infectious Diseases Society of America guidelines recommend empiric therapy with either vancomycin or linezolid, with adjustments as needed when culture results are available.[5] Linezolid is recommended for patients at risk of renal compromise. For skin and soft tissue infections, recent guidelines emphasize a tiered approach to antibiotic selection, ranging from the use of penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin for cellulitis to vancomycin, linezolid, daptomycin, or tigecycline for severe infections requiring hospitalization.[6]

Linezolid has been shown to be similar in safety and clinical and microbiologic efficacy to oxacillin in the treatment of cSSSIs.[84] Linezolid has shown similar[85] or superior[86-88] efficacy compared with vancomycin against MRSA skin and soft tissue infections. Treating these infections with linezolid has been shown to reduce the duration of IV therapy and hospital length of stay compared with vancomycin[88-90] and is a cost-effective alternative to vancomycin.[88,91] Against *S aureus*, linezolid is indicated for the treatment of:

- cSSSI, including diabetic foot infections without concomitant osteomyelitis, caused by *S aureus* (MSSA and MRSA)
- Uncomplicated skin and skin structure infections caused by *S aureus* (MSSA only)
- Nosocomial pneumonia caused by *S aureus* (MSSA and MRSA)
- Community-acquired pneumonia caused by *S aureus* (MSSA only)

Daptomycin demonstrated similar efficacy and safety compared with vancomycin for skin and skin structure infections caused by MRSA and other gram-positive pathogens[92] and bacteremia.[37] Daptomycin is indicated for:

- cSSSI caused by *S aureus* (MSSA and MRSA)
- Bacteremia and right-side endocarditis (MSSA and MRSA)

Tigecycline has been shown to have comparable efficacy in cSSSI compared with vancomycin plus aztreonam, even in patients with gram-positive infections.[93] Tigecycline is indicated for:

- cSSSI caused by *S aureus* (MSSA and MRSA)
- Complicated intra-abdominal infections (MSSA only)

In a preliminary re-analysis of the pooled phase 3 trial data for the ITT patient population, there was no difference in overall hospital length of stay when compared with vancomycin plus aztreonam.[94]

Summary

Pharmacodynamic principles of antimicrobials play a significant role in the selection, dosing, and ultimately, the success of antistaphylococcal therapy. Skin and soft tissue infections, including surgical site infections, caused by MRSA might be effectively treated with vancomycin, linezolid, daptomycin, or tigecycline; however, linezolid has recently demonstrated clinical and pharmacoeconomic superiority over vancomycin in several studies.

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Notes

Gram-Positive Antibiotic Selection: PK/PD Considerations

Select the single response that best answers the question or completes the sentence.

1) In a recent report from the TSN network, MRSA prevalence trends from 1998 to 2005 are best described as:

a. Increasing faster in community vs hospital settings
b. Increasing for patients in hospital and outpatient settings with a slower rate of increase for patients in the ICU
c. Increasing faster in hospitalized patients compared with the outpatient setting

2) In a recent review of outpatient antibiotic prescriptions for skin infections, what percent of the initial antibiotic prescriptions were ineffective against MRSA?

a. 20%
b. 46%
c. 68%
d. 73%

3) The postantibiotic effect is longest for which of the following anti-MRSA agents?

a. Vancomycin
b. Linezolid
c. Daptomycin
d. Tigecycline

4) Protein binding is lowest for which of the following anti-MRSA agents?

a. Vancomycin
b. Linezolid
c. Daptomycin
d. Tigecycline

5) True or False: Recent studies have shown that the MIC for vancomycin has increased in recent years, but this increase is not associated with changes in clinical outcome.

6) The following agents are administered on a weight-based dosing schedule:

a. Daptomycin, vancomycin, and tigecycline
b. Vancomycin and daptomycin
c. Vancomycin and linezolid
d. Vancomycin and tigecycline

7) True or False: A recent comparative trial of linezolid vs vancomycin for febrile neutropenia and daptomycin vs vancomycin for bacteremia did not show a clear advantage of bactericidal over bacteriostatic agents.

8) For patients with renal impairment, dose adjustments should be considered for:

a. Vancomycin
b. Vancomycin and tigecycline
c. Vancomycin and daptomycin
d. Vancomycin and linezolid

9) True or False: A recent study of patients with MRSA healthcare-associated pneumonia demonstrated that higher vancomycin dosing schedules do not improve clinical outcome.

10) True or False: In two recent studies, high-dose vancomycin therapy for MRSA infections did not alter renal function.

Gram-Positive Antibiotic Selection: PK/PD Considerations

Released: January 23, 2007 **Expires: January 23, 2008**

A passing score of 70% or higher on the posttest awards the participant a maximum of 1.0 *AMA PRA Category 1 Credit™* or 1.0 contact hour (0.1 CEUs) of continuing pharmacy education credit. To claim continuing education credit, individuals must complete the self-study activity, posttest, and evaluation and mail this form to:

Attn: Distance Education
University of Kentucky Colleges of Pharmacy and Medicine
Continuing Education Office
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Signature:_____

Posttest Answers (circle the correct answer)

1.	a	b	c	
2.	a	b	c	d
3.	a	b	c	d
4.	a	b	c	d
5.	True	False		
6.	a	b	c	d
7.	True	False		
8.	a	b	c	d
9.	True	False		
10.	True	False		

Evaluation	**Poor**		**Satisfactory**		**Excellent**
1. Extent to which the objectives were achieved:	1	2	3	4	5
2. Potential impact on your practice:	1	2	3	4	5
3. Detail of information presented:	1	2	3	4	5
4. Extent to which commercial bias appeared:	1	2	3	4	5

5. Suggestions for future CE topics:

_____

_____

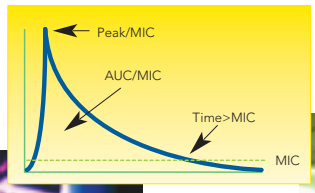
_____

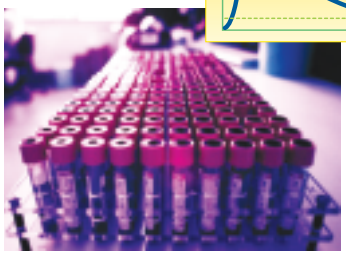
ISMR Update

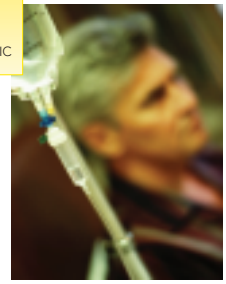
INTERNATIONAL SOCIETY ISMR OF MICROBIAL RESISTANCE

Gram-Positive Antibiotic Selection: PK/PD Considerations

CME Opportunity
From the 2006 MRSA
Education Summit







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