



A CLINICIAN'S ROADMAP TO MRSA MANAGEMENT

Stewardship for Optimal Care

E-NEWSLETTER #2

Confronting the Challenges of MRSA Infections

FROM THE EDITOR'S DESK

The increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has been a major concern in the healthcare community over the past 15 years.

Though this pathogen had historically been limited to healthcare institutions, MRSA has now become a major cause of community-associated infections, particularly skin infections and community-acquired pneumonia.

In response to this emerging health threat, the healthcare community has reinvigorated efforts to develop novel antimicrobials targeting MRSA leading to several new agents in various classes since 2000. Expansion of the anti-MRSA armamentarium has allowed clinicians more choices to treat these serious infections. To provide guidance on the use of these agents, the Infectious Diseases Society of America (IDSA) released in February 2011 their first-ever clinical practice guidelines for the treatment of MRSA infections. These guidelines provide evidence-based recommendations that can be the foundation for making clinical decisions when confronted with these types of infections.

This second E-Newsletter reviews recommendations for the treatment of serious MRSA infections and challenges that may be encountered when managing these infections. I hope you find the information in this issue useful when confronting MRSA infections in your practice.

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E-NEWSLETTER #2 CONFRONTING THE CHALLENGES OF MRSA INFECTIONS

TARGET AUDIENCE

This activity is designed for physicians, pharmacists, and other healthcare professionals on the frontline of managing patients with serious MRSA infections.

LEARNING OBJECTIVE

Healthcare professionals participating in this educational activity will be able at its conclusion to:

- Recognize appropriate antimicrobial therapy for serious MRSA infections

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ACCREDITATION

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- Review the entire CME/CPE information including target audience, learning objective, and disclosures.
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Disclosure: Guest Editor

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Disclosure: Planning Committee

All employees of Center for Independent Healthcare Education and Vemco MedEd have no relevant financial relationships to disclose.

Disclosure of Off-label Use

During this activity, the following off-label use of an antimicrobial agent is discussed: daptomycin (at 8–10 mg/kg/dose for the treatment of bacteremia; and for the treatment of osteomyelitis).

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Skin and Soft Tissue Infections

The increased prevalence of community-associated MRSA (CA-MRSA) has led to a growing number of emergency room visits and hospitalizations due to skin infections.¹ While less serious skin and soft tissue infections (SSTIs) can be treated without systemic antimicrobial therapy (**Table 1**), antimicrobial therapy is recommended for certain abscesses and cellulitis.²

Inpatient management and surgical intervention is recommended for patients with rapidly progressing or worsening infection despite antimicrobial therapy.² For patients with complicated SSTIs (cSSTIs)—deeper soft tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns—in addition to surgical debridement and broad-spectrum antibiotics, empiric therapy for MRSA should be considered pending culture data (**Table 2**).² Treatment for 5–10 days is recommended for most outpatient infections and 7–14 days for hospitalized infections but should be individualized based on the patient's clinical response.²

Table 1. Management of SSTIs Caused by MRSA²

Type of SSTI	Suggested Management Approach
Minor Skin Infection (eg, impetigo)	Mupirocin 2% topical treatment
Secondarily Infected Skin Lesions (ie, eczema, ulcers, or lacerations)	
Simple Cutaneous Abscesses	Incision and drainage
Small Furuncles	Moist heat
Purulent Cellulitis (cellulitis associated with purulent drainage or exudate in the abscess of a drainable abscess)	Empiric antimicrobial therapy with activity against CA-MRSA, until culture data available

SSTIs: Situations when antimicrobial therapy is recommended²

- Severe or extensive disease
- Rapid progression in presence of associated cellulitis
- Signs and symptoms of systemic illness, associated comorbidities, or immunosuppression
- Extremes of age
- Abscess in areas difficult to drain
- Associated septic phlebitis
- Lack of response to incision and drainage alone

Table 2. Antimicrobial Agents for cSSTIs due to MRSA²

Antimicrobial Agents included in the IDSA Guidelines	Recommended Adult Dosing
Vancomycin	15–20 mg/kg/dose q8–12h
Linezolid	600 mg PO/IV BID
Daptomycin	4 mg/kg/dose IV QD
Telavancin	10 mg/kg/dose IV QD
Clindamycin	600 mg PO/IV TID
Antimicrobial Agents not included in the IDSA Guidelines	Recommended Adult Dosing
Tigecycline <i>Note: Recently received an FDA warning—increased risk in all-cause mortality versus comparator drugs in a pooled analysis of clinical trials.*³</i>	100 mg (first dose) followed by 50 mg BID (IV) ³
Ceftaroline <i>Note: FDA-approved in October 2010, after completion of the final draft of the guidelines.</i>	600 mg BID (IV) ⁴

* Because of the recent FDA warning, the drug was not included in the guidelines. However, the greatest increase in risk of death with tigecycline was observed in patients with ventilator-associated pneumonia, an unapproved use, and there was no significant difference in mortality in complicated skin infection trials (1.4 % vs 0.7%; 95% confidence interval, -0.3 to 1.7).⁵

Bacteremia and Infective Endocarditis

MRSA bacteremia and infective endocarditis are associated with high morbidity and mortality rates.^{6,7} In addition to antimicrobial therapy (**Table 3**)—with therapy duration based on infection classification (**Table 4**)—clinical assessment is recommended to identify the source and extent of infection.² Elimination and/or debridement of other sites of infection should be conducted.² To document clearance of bacteremia, it is recommended to perform additional blood cultures 2–4 days after initial positive cultures (and as needed thereafter).²

Table 3. Antimicrobial Agents for Bacteremia and Infective Endocarditis due to MRSA: IDSA Guideline Recommendations²

Antimicrobial Agent	Recommended Adult Dosing
Vancomycin	15–20 mg/kg/dose q8–12h <i>Note: For prosthetic valve endocarditis, add rifampin 300 mg IV/PO q8h for at least 6 weeks + gentamicin 1 mg/kg/dose IV q8h for 2 weeks.</i>
Daptomycin	6 mg/kg/dose IV QD <i>Note: Some experts recommend higher dosages of 8–10 mg/kg/dose IV QD to possibly reduce the risk of resistance development.</i>

Table 4. Recommended Duration of Antimicrobial Therapy by Type of Bacteremia: IDSA Guideline Recommendations²

Type of Bacteremia	Definition	Duration of Therapy
Uncomplicated	Patient with positive blood culture results and <ul style="list-style-type: none"> • exclusion of endocarditis • no implanted prostheses • follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA • defervescence within 72 hours of initiating antimicrobial therapy • no evidence of metastatic sites of infection 	At least 2 weeks
Complicated	Patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia	4 to 6 weeks, depending on the extent of infection

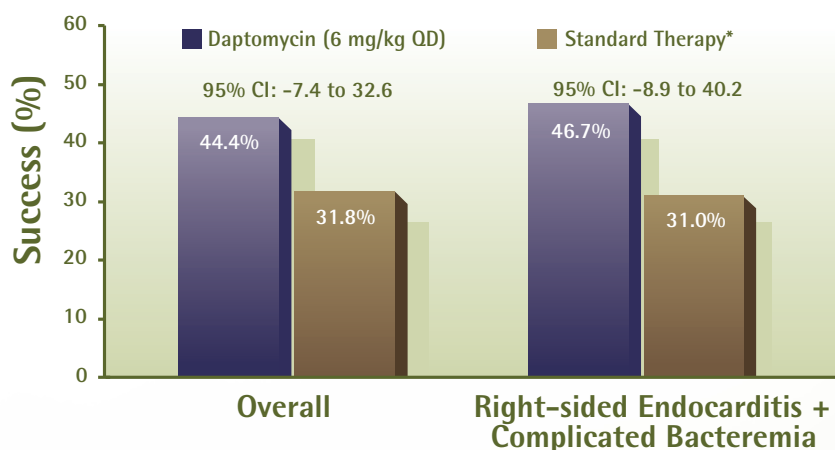
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Persistent bacteremia and relapse are common among patients with infective endocarditis and account for a large proportion of vancomycin treatment failures.^{2,8} When vancomycin treatment failure occurs, change the therapy rather than adding another agent (eg, rifampin or gentamicin) to vancomycin.² Daptomycin, an alternative to vancomycin, is FDA-approved for MRSA bloodstream infections, including those with right-sided infective endocarditis.⁹ It offers rapid bactericidal activity and has been shown to be effective in treating MRSA bacteremia with or without infective endocarditis (**Figure 1**).⁸

Reasons for vancomycin failures in patients with persistent bacteremia²

- Slow vancomycin bactericidal activity against MRSA
- Emergence of strains with reduced susceptibility
- Possible enhanced virulence of CA-MRSA strains
- Inadequate debridement or retained prosthetic device

Figure 1. Success Rate for Daptomycin Versus Standard Therapy in Treating MRSA Bacteremia With or Without Endocarditis⁸



*Low-dose gentamicin plus either antistaphylococcal penicillin or vancomycin.

Pneumonia

MRSA is increasingly being identified as the cause of severe community-acquired pneumonia (CAP), particularly in association with influenza infections.^{10,11} For hospitalized patients with severe CAP (defined by one of the following: a requirement for ICU admission; necrotizing or cavitary infiltrates; or empyema), empiric therapy should include coverage for MRSA pending sputum and/or blood culture results.² MRSA is also a leading cause of healthcare-associated pneumonia including ventilator-associated pneumonia.¹² The recommended duration of antimicrobial treatment for MRSA pneumonia is 7–21 days depending on the extent of infection (Table 5).²

Treatment with vancomycin is associated with high failure rates that may be attributed to poor penetration to pulmonary tissue and epithelial lining fluid.^{14–16} Linezolid, an alternative to vancomycin, is FDA-approved for the treatment of nosocomial pneumonia caused by MRSA.¹⁷ Linezolid would seem to have some theoretical advantages that include better penetration into the lung compartments and the possibility to reduce toxin production for CA-MRSA. Despite this, there remains controversy based on the different results of pooled analyses and meta-analyses of clinical trials.²

Table 5. Antimicrobial Agents for Pneumonia due to MRSA: IDSA Guideline Recommendations²

Antimicrobial Agent	Recommended Adult Dosing
Vancomycin	15–20 mg/kg/dose q8–12h*
Linezolid	600 mg PO/IV BID
Clindamycin	600 mg PO/IV TID

* In order to achieve rapid attainment of an adequate target concentration for seriously ill patients, a loading dose of 25–30 mg/kg can be considered.¹³



Osteomyelitis

Management of bone and joint infections requires surgical debridement of the necrotic bone or the joint space and drainage of the adjacent abscesses, along with antimicrobial therapy (**Table 6**).² Bone and joint infections typically require prolonged antimicrobial therapy, with current recommendations of at least 8 weeks for those caused by MRSA.² Some experts suggest an additional 1–3 months of oral therapy chosen on the basis of susceptibility tests.²

As most of the newer anti-MRSA agents are only available in intravenous formulations, many patients are treated with outpatient parenteral antimicrobial therapy (OPAT) after stabilization in the hospital setting.¹⁸

Table 6. Antimicrobial Agents for Osteomyelitis due to MRSA: IDSA Guideline Recommendations ²

Antimicrobial Agent	Recommended Adult Dosing*
Vancomycin	15–20 mg/kg/dose q8–12h
Daptomycin	6 mg/kg/day IV QD
Linezolid	600 mg PO/IV BID
Clindamycin	600 mg PO/IV TID
Trimethoprim-Sulfamethoxazole and Rifampin	3.5–4.0 mg/kg/dose (Trimethoprim component) PO/IV q12h

*Some experts recommend adding rifampin (600 mg QD or 300–450 mg BID) to the chosen antimicrobial.²



OPAT: A Strategy for MRSA Infections Requiring Prolonged Therapy

Outpatient parenteral antimicrobial therapy (OPAT) can be an important strategy to manage MRSA infections when used appropriately. It has been shown to be effective and safe and can potentially lead to earlier hospital discharge and reduced costs.¹⁹ To maximize the chance for successful outcomes with OPAT it is important to consider certain patient factors as well as antimicrobial characteristics.²⁰

Patient Selection Criteria for OPAT

- IV antimicrobial therapy required
- Infection not life-threatening
- Responding to treatment
- Medically stable otherwise
- Able to return for infusions or emergencies
- Good home situation
- Family support available

Antimicrobial Selection Criteria for OPAT

- Known to be effective against pathogen — culture results important
- Proven to be safe
- Well tolerated with few side effects
- Long half-life for infrequent administration (QD preferred)
- Stable when mixed



Utilizing Susceptibility Testing to Guide Vancomycin Use

As discussed in the first newsletter of this series, evidence for vancomycin MIC creep along with the emergence of hVISA, VISA, and VRSA isolates challenges clinicians when using this agent to treat MRSA infections.²¹⁻²³ Vancomycin effectiveness decreases significantly if the MIC of the infecting isolate is greater than 1 µg/mL.²⁴⁻²⁷ This was among the reasons for the recent lowering of Clinical and Laboratory Standards Institute (CLSI) breakpoints—for susceptible isolates, the breakpoint was reduced from ≤4 µg/mL to ≤2 µg/mL.²⁸

Current recommendations suggest an alternative agent for MRSA infections when the vancomycin MIC is >2 µg/mL.¹³ Therefore, susceptibility testing is critical when selecting an appropriate agent. There are several limitations, however, when interpreting vancomycin susceptibility results:

- 1.** hVISA detection is challenging through traditional susceptibility methods when a small, resistant subpopulation of cells is present.^{29,30} The “gold standard” (population analysis profile [PAP] divided by the AUC) is labor intensive and not practical for the clinical laboratory.³¹
- 2.** Considerable variability in MIC determination is based on the testing method. Acceptable variability for MIC is ± 1 doubling dilution.³² This can make it difficult to distinguish isolates with an MIC of 1 µg/mL versus 2 µg/mL (or isolates with an MIC of 2 µg/mL versus 4 µg/mL).
- 3.** Some methods, such as Etest, MicroScan, and BD-Phoenix, tend to report higher MIC values compared with the reference broth microdilution method leading to over-reporting of intermediate-resistant isolates.³³ Other methods, such as Sensititre and Vitek 2, tend to undercall MIC values.³³

The difficulty in reliably distinguishing isolates with an MIC of 1 µg/mL versus 2 µg/mL has resulted in the IDSA recommending evaluation of the patient's clinical and microbiological response in addition to vancomycin MIC results when making decisions about antimicrobial therapy.²

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POST TEST Please select the most appropriate response.

1. What is the suggested management approach for simple cutaneous abscess?

- Topical mupirocin Vancomycin
 Trimethoprim-sulfamethoxazole Incision and drainage

2. In which situations is antimicrobial therapy for SSTIs recommended?

- Severe or extensive disease Extremes of age
 Signs and symptoms of systemic illness All of these

3. What is the recommended duration of therapy for uncomplicated MRSA bacteremia?

- 7 days 10 days At least 2 weeks 4-6 weeks

4. What is the vancomycin loading dose recommended by the IDSA for seriously ill pneumonia patients?

- 5-10 mg/kg 10-15 mg/kg 15-20 mg/kg 25-30 mg/kg

5. Which antimicrobial agent is FDA-approved for treatment of MRSA bloodstream infections?

- Linezolid Daptomycin Telavancin Cefaroline

COMMITMENT TO CHANGE

As an accredited provider of continuing education, Center for Independent Healthcare Education is increasingly focusing on the outcomes of our offerings, particularly as reflected in changes and improvements in clinical practices. Accordingly, we are now asking our learners to reflect on how they might alter their practices as a result of participating in our CE activities. The following request solicits your commitments to change, based on what you have learned. We hope that you will find this exercise useful and thank you in advance for participating.

Do you wish to make commitments to change in your practice?

- Yes No

As a result of what I learned participating in this activity, I intend to make the following practice changes:

OVERALL EVALUATION

	Yes	Somewhat	No
1. The following learning objective was achieved. • Recognize appropriate antimicrobial therapy for serious MRSA infections	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. The content was relevant to my practice and educational needs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. The activity format enhanced achievement of learning objectives.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. This activity was fair, balanced, and without commercial bias.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If you answered "No" to any of the above, please explain.

5. Quality of Guest Editor. Excellent Good Fair Poor

6. Do you have (1) any suggestions for improving this activity or (2) any additional comments?

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