Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

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Evidence-based guidelines for the management of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections were prepared by an Expert Panel of the Infectious Diseases Society of America (IDSA). The guidelines are intended for use by health care providers who care for adult and pediatric patients with MRSA infections. The guidelines discuss the management of a variety of clinical syndromes associated with MRSA disease, including skin and soft tissue infections (SSTI), bacteremia and endocarditis, pneumonia, bone and joint infections, and central nervous system (CNS) infections. Recommendations are provided regarding vancomycin dosing and monitoring, management of infections due to MRSA strains with reduced susceptibility to vancomycin, and vancomycin treatment failures.

EXECUTIVE SUMMARY

MRSA is a significant cause of both health care–associated and community-associated infections. This document constitutes the first guidelines of the IDSA on the treatment of MRSA infections. The primary objective of these guidelines is to provide recommendations on the management of some of the most common clinical syndromes encountered by adult and pediatric clinicians who care for patients with MRSA infections. The guidelines address issues related to the use of vancomycin therapy in the treatment of MRSA infections, including dosing and monitoring, current limitations of susceptibility testing, and the use of alternate therapies for those patients with vancomycin treatment failure and infection due to strains with reduced susceptibility to vancomycin. The guidelines do not discuss active surveillance testing or other MRSA infection–prevention strategies in health care settings, which are addressed in previously published guidelines [1, 2]. Each section of the guidelines begins

Received 28 October 2010; accepted 17 November 2010.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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Clinical Infectious Diseases 2011;52(3):e18–e55

1058-4838/2011/523-0001$37.00
DOI: 10.1093/cid/ciq146

with a specific clinical question and is followed by numbered recommendations and a summary of the most-relevant evidence in support of the recommendations. Areas of controversy in which data are limited or conflicting and where additional research is needed are indicated throughout the document and are highlighted in the Research Gaps section. The key recommendations are summarized below in the Executive Summary; each topic is discussed in greater detail within the main body of the guidelines.

Please note that specific recommendations on vancomycin dosing and monitoring are not discussed in the sections for each clinical syndrome but are collectively addressed in detail in Section VIII.

I. What is the management of skin and soft-tissue infections (SSTIs) in the era of community-associated MRSA (CA-MRSA)?

SSTIs

1. For a cutaneous abscess, incision and drainage is the primary treatment (**A-II**). For simple abscesses or boils, incision and drainage alone is likely to be adequate, but additional data are needed to further define the role of antibiotics, if any, in this setting.
2. Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (eg, involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (eg, face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone (**A-III**).
3. For outpatients with purulent cellulitis (eg, cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess), empirical therapy for CA-MRSA is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary (**A-II**). Five to 10 days of therapy is recommended but should be individualized on the basis of the patient's clinical response.
4. For outpatients with nonpurulent cellulitis (eg, cellulitis with no purulent drainage or exudate and no associated abscess), empirical therapy for infection due to β-hemolytic streptococci is recommended (**A-II**). The role of CA-MRSA is unknown. Empirical coverage for CA-MRSA is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. Five to 10 days of therapy is recommended but should be individualized on the basis of the patient's clinical response.
5. For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin (**A-II**), trimethoprim-sulfamethoxazole (TMP-SMX) (**A-II**), a tetracycline (doxycycline or minocycline) (**A-II**), and linezolid (**A-II**). If coverage for both β-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone (**A-II**) or TMP-SMX or a tetracycline in combination with a β-lactam (eg, amoxicillin) (**A-II**) or linezolid alone (**A-II**).
6. The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTI is not recommended (**A-III**).
7. For hospitalized patients with complicated SSTI (cSSTI; defined as patients with 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, empirical therapy for MRSA should be considered pending culture data. Options include the following: intravenous (IV) vancomycin (**A-I**), oral (PO) or IV linezolid 600 mg twice daily (**A-I**), daptomycin 4 mg/kg/dose IV once daily (**A-I**), telavancin 10 mg/kg/dose IV once daily (**A-I**), and clindamycin 600 mg IV or PO 3 times a day (**A-III**). A β-lactam antibiotic (eg, cefazolin) may be considered in hospitalized patients with nonpurulent cellulitis with modification to MRSA-active therapy if there is no clinical response (**A-II**). Seven to 14 days of therapy is recommended but should be individualized on the basis of the patient's clinical response.
8. Cultures from abscesses and other purulent SSTIs are recommended in patients treated with antibiotic therapy, patients with severe local infection or signs of systemic illness, patients who have not responded adequately to initial treatment, and if there is concern for a cluster or outbreak (**A-III**).

Pediatric considerations

9. For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used (**A-III**).
10. Tetracyclines should not be used in children <8 years of age (**A-II**).
11. In hospitalized children with cSSTI, vancomycin is recommended (**A-II**). If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) is an option if the clindamycin resistance rate is low (eg, <10%) with transition to oral therapy if the strain is susceptible (**A-II**). Linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose PO/IV every 8 h for children <12 years of age is an alternative (**A-II**).

II. What is the management of recurrent MRSA SSTIs?

Recurrent SSTIs

12. Preventive educational messages on personal hygiene and appropriate wound care are recommended for all patients with SSTI. Instructions should be provided to:

i. Keep draining wounds covered with clean, dry bandages (**A-III**).

ii. Maintain good personal hygiene with regular bathing and cleaning of hands with soap and water or an alcohol-based hand gel, particularly after touching infected skin or an item that has directly contacted a draining wound (**A-III**).

iii. Avoid reusing or sharing personal items (eg, disposable razors, linens, and towels) that have contacted infected skin (**A-III**).

13. Environmental hygiene measures should be considered in patients with recurrent SSTI in the household or community setting:

i. Focus cleaning efforts on high-touch surfaces (ie, surfaces that come into frequent contact with people's bare skin each day, such as counters, door knobs, bath tubs, and toilet seats) that may contact bare skin or uncovered infections (**C-III**).

ii. Commercially available cleaners or detergents appropriate for the surface being cleaned should be used according to label instructions for routine cleaning of surfaces (**C-III**).

14. Decolonization may be considered in selected cases if:

i. A patient develops a recurrent SSTI despite optimizing wound care and hygiene measures (**C-III**).

ii. Ongoing transmission is occurring among household members or other close contacts despite optimizing wound care and hygiene measures (**C-III**).

15. Decolonization strategies should be offered in conjunction with ongoing reinforcement of hygiene measures and may include the following:

i. Nasal decolonization with mupirocin twice daily for 5–10 days (**C-III**).

ii. Nasal decolonization with mupirocin twice daily for 5–10 days and topical body decolonization regimens with a skin antiseptic solution (eg, chlorhexidine) for 5–14 days or dilute bleach baths. (For dilute bleach baths, 1 teaspoon per gallon of water [or ¼ cup per ¼ tub or 13 gallons of water] given for 15 min twice weekly for ~3 months can be considered.) (**C-III**).

16. Oral antimicrobial therapy is recommended for the treatment of active infection only and is not routinely recommended for decolonization (**A-III**). An oral agent in combination with rifampin, if the strain is susceptible, may be considered for decolonization if infections recur despite above measures (**CIII**).

17. In cases where household or interpersonal transmission is suspected:

i. Personal and environmental hygiene measures in the patient and contacts are recommended (**A-III**).

ii. Contacts should be evaluated for evidence of *S. aureus* infection:

a. Symptomatic contacts should be evaluated and treated (**A-III**); nasal and topical body decolonization strategies may be considered following treatment of active infection (**C-III**).

b. Nasal and topical body decolonization of asymptomatic household contacts may be considered (**C-III**).

18. The role of cultures in the management of patients with recurrent SSTI is limited:

i. Screening cultures prior to decolonization are not routinely recommended if at least 1 of the prior infections was documented as due to MRSA (**B-III**).

ii. Surveillance cultures following a decolonization regimen are not routinely recommended in the absence of an active infection (**B-III**).

III. What is the management of MRSA bacteremia and infective endocarditis?

Bacteremia and Infective Endocarditis, Native Valve

19. For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: 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 h of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**AI**) for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

20. For adults with infective endocarditis, IV vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**A-I**) for 6 weeks is recommended. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

21. Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (**A-II**).

22. Addition of rifampin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (**A-I**).

23. A clinical assessment to identify the source and extent of the infection with elimination and/or debridement of other sites of infection should be conducted (**A-II**).

24. Additional blood cultures 2–4 days after initial positive cultures and as needed thereafter are recommended to document clearance of bacteremia (**A-II**).

25. Echocardiography is recommended for all adult patients with bacteremia. Transesophageal echocardiography

(TEE) is preferred over transthoracic echocardiography (TTE) (**A-II**).

26. Evaluation for valve replacement surgery is recommended if large vegetation (>10 mm in diameter), occurrence of ≥1 embolic event during the first 2 weeks of therapy, severe valvular insufficiency, valvular perforation or dehiscence, decompensated heart failure, perivalvular or myocardial abscess, new heart block, or persistent fevers or bacteremia are present (**A-II**).

Infective Endocarditis, Prosthetic Valve

27. IV vancomycin plus rifampin 300 mg PO/IV every 8 h for at least 6 weeks plus gentamicin 1 mg/kg/dose IV every 8 h for 2 weeks (**B-III**).

28. Early evaluation for valve replacement surgery is recommended (**A-II**).

Pediatric considerations

29. In children, vancomycin 15 mg/kg/dose IV every 6 h is recommended for the treatment of bacteremia and infective endocarditis (**A-II**). Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin 6–10 mg/kg/dose IV once daily may be an option (**C-III**). Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus (**B-III**).

30. Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis (**C-III**); the decision to use combination therapy should be individualized.

31. Echocardiogram is recommended in children with congenital heart disease, bacteremia more than 2–3 days in duration, or other clinical findings suggestive of endocarditis (**A-III**).

IV. What is the management of MRSA pneumonia?

Pneumonia

32. For hospitalized patients with severe community-acquired pneumonia defined by any one of the following: (1) a requirement for intensive care unit (ICU) admission, (2) necrotizing or cavitary infiltrates, or (3) empyema, empirical therapy for MRSA is recommended pending sputum and/or blood culture results (**A-III**).

33. For health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia, IV vancomycin (**A-II**) or linezolid 600 mg PO/IV twice daily (**A-II**) or clindamycin 600 mg PO/IV 3 times daily (**B-III**), if the strain is susceptible, is recommended for 7–21 days, depending on the extent of infection.

34. In patients with MRSA pneumonia complicated by empyema, antimicrobial therapy against MRSA should be used in conjunction with drainage procedures (**A-III**).

Pediatric considerations

35. In children, IV vancomycin is recommended (**A-II**). If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) can be used as empirical therapy if the clindamycin resistance rate is low (eg, <10%) with transition to oral therapy if the strain is susceptible (**A-II**). Linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose every 8 h for children <12 years of age is an alternative (**A-II**).

V. What is the management of MRSA bone and joint infections?

Osteomyelitis

36. Surgical debridement and drainage of associated soft-tissue abscesses is the mainstay of therapy and should be performed whenever feasible (**A-II**).

37. The optimal route of administration of antibiotic therapy has not been established. Parenteral, oral, or initial parenteral therapy followed by oral therapy may be used depending on individual patient circumstances (**A-III**).

38. Antibiotics available for parenteral administration include IV vancomycin (**B-II**) and daptomycin 6 mg/kg/dose IV once daily (**B-II**). Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX 4 mg/kg/dose (TMP component) twice daily in combination with rifampin 600 mg once daily (**B-II**), linezolid 600 mg twice daily (**B-II**), and clindamycin 600 mg every 8 h (**B-III**).

39. Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg PO twice daily to the antibiotic chosen above (**B-III**). For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.

40. The optimal duration of therapy for MRSA osteomyelitis is unknown. A minimum 8-week course is recommended (**A-II**). Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities (**C-III**).

41. Magnetic resonance imaging (MRI) with gadolinium is the imaging modality of choice, particularly for detection of early osteomyelitis and associated soft-tissue disease (**A-II**). Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) level may be helpful to guide response to therapy (**B-III**).

Septic Arthritis

42. Drainage or debridement of the joint space should always be performed (**A-II**).

43. For septic arthritis, refer to antibiotic choices for osteomyelitis (recommendation 37 above). A 3–4-week course of therapy is suggested (**A-III**).

Device-related osteoarticular infections

44. For early-onset (<2 months after surgery) or acute hematogenous prosthetic joint infections involving a stable implant with short duration (≤3 weeks) of symptoms and debridement (but device retention), initiate parenteral therapy (refer to antibiotic recommendations for osteomyelitis) plus rifampin 600 mg daily or 300–450 mg PO twice daily for 2 weeks followed by rifampin plus a fluoroquinolone, TMP-SMX, a tetracycline or clindamycin for 3 or 6 months for hips and knees, respectively (**A-II**). Prompt debridement with device removal whenever feasible is recommended for unstable implants, late-onset infections, or in those with long duration (>3 weeks) of symptoms (**A-II**).

45. For early-onset spinal implant infections (≤30 days after surgery) or implants in an actively infected site, initial parenteral therapy plus rifampin followed by prolonged oral therapy is recommended (**B-II**). The optimal duration of parenteral and oral therapy is unclear; the latter should be continued until spine fusion has occurred (**B-II**). For late-onset infections (>30 days after implant placement), device removal whenever feasible is recommended (**B-II**).

46. Long-term oral suppressive antibiotics (eg, TMP-SMX, a tetracycline, a fluoroquinolone [which should be given in conjunction with rifampin due to the potential emergence of fluoroquinolone resistance, particularly if adequate surgical debridement is not possible should be given in conjunction with rifampin], or clindamycin) with or without rifampin may be considered in selected cases, particularly if device removal not possible (**B-III**).

Pediatric considerations

47. For children with acute hematogenous MRSA osteomyelitis and septic arthritis, IV vancomycin is recommended (**A-II**). If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) can be used as empirical therapy if the clindamycin resistance rate is low (eg, <10%) with transition to oral therapy if the strain is susceptible (**A-II**). The exact duration of therapy should be individualized, but typically a minimum 3–4-week course is recommended for septic arthritis and a 4–6-week course is recommended for osteomyelitis.

48. Alternatives to vancomycin and clindamycin include the following: daptomycin 6 mg/kg/day IV once daily (**C-III**) or linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose every 8 h for children <12 years of age (**C-III**).

VI. What is the management of MRSA infections of the CNS?

Meningitis

49. IV vancomycin for 2 weeks is recommended (**B-II**). Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg twice daily (**B-III**).

50. Alternatives include the following: linezolid 600 mg PO/IV twice daily (**B-II**) or TMP-SMX 5 mg/kg/dose IV every 8–12 h (**C-III**).

51. For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative (**A-II**).

Brain abscess, subdural empyema, spinal epidural abscess

52. Neurosurgical evaluation for incision and drainage is recommended (**A-II**).

53. IV vancomycin for 4–6 weeks is recommended (**B-II**). Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg twice daily (**B-III**).

54. Alternatives include the following: linezolid 600 mg PO/IV twice daily (**B-II**) and TMP-SMX 5 mg/kg/dose IV every 8–12 h (**C-III**).

Septic Thrombosis of Cavernous or Dural Venous Sinus

55. Surgical evaluation for incision and drainage of contiguous sites of infection or abscess is recommended whenever possible (**A-II**). The role of anticoagulation is controversial.

56. IV vancomycin for 4–6 weeks is recommended (**B-II**). Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg twice daily (**B-III**).

57. Alternatives include the following: linezolid 600 mg PO/IV twice daily (**B-II**) and TMP-SMX 5 mg/kg/dose IV every 8–12 h (**C-III**).

Pediatric considerations

58. IV vancomycin is recommended (**A-II**).

VII. What is the role of adjunctive therapies for the treatment of MRSA infections?

59. Protein synthesis inhibitors (eg, clindamycin and linezolid) and intravenous immunoglobulin (IVIG) are not routinely recommended as adjunctive therapy for the management of invasive MRSA disease (**A-III**). Some experts may consider these agents in selected scenarios (eg, necrotizing pneumonia or severe sepsis) (**C-III**).

VIII. What are the recommendations for vancomycin dosing and monitoring?

These recommendations are based on a consensus statement of the American Society of Health-System Pharmacists, the IDSA, and The Society of Infectious Diseases Pharmacists on guidelines for vancomycin dosing [3, 4].

Adults

60. IV vancomycin 15–20 mg/kg/dose (actual body weight) every 8–12 h, not to exceed 2 g per dose, is recommended in patients with normal renal function (**B-III**).

61. In seriously ill patients (eg, those with sepsis, meningitis, pneumonia, or infective endocarditis) with suspected MRSA infection, a loading dose of 25–30 mg/kg (actual body weight) may be considered. (Given the risk of red man syndrome and possible anaphylaxis associated with large doses of vancomycin, one should consider prolonging the infusion time to 2 h and use of an antihistamine prior to administration of the loading dose.) (**C-III**).

62. Trough vancomycin concentrations are the most accurate and practical method to guide vancomycin dosing (**B-II**). Serum trough concentrations should be obtained at steady state conditions, prior to the fourth or fifth dose. Monitoring of peak vancomycin concentrations is not recommended (**B-II**).

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (**B-II**).

64. For most patients with SSTI who have normal renal function and are not obese, traditional doses of 1 g every 12 h are adequate, and trough monitoring is not required (**B-II**).

65. Trough vancomycin monitoring is recommended for serious infections and patients who are morbidly obese, have renal dysfunction (including those receiving dialysis), or have fluctuating volumes of distribution (**A-II**).

66. Continuous infusion vancomycin regimens are not recommended (**A-II**).

Pediatrics

67. Data are limited to guide vancomycin dosing in children. IV vancomycin 15 mg/kg/dose every 6 h is recommended in children with serious or invasive disease (**B-III**).

68. The efficacy and safety of targeting trough concentrations of 15–20 μg/mL in children requires additional study but should be considered in those with serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (ie, necrotizing fasciitis) (**B-III**).

IX. How should results of vancomycin susceptibility testing be used to guide therapy?

69. For isolates with a vancomycin minimum inhibitory concentration (MIC) ≤2 μg/mL (eg, susceptible according to Clinical and Laboratory Standards Institute [CLSI] breakpoints), the patient's clinical response should determine the continued use of vancomycin, independent of the MIC (**A-III**).

i. If the patient has had a clinical and microbiologic response to vancomycin, then it may be continued with close follow-up

ii. If the patient has not had a clinical or microbiologic response to vancomycin despite adequate debridement and removal of other foci of infection, an alternative to vancomycin is recommended regardless of MIC.

70. For isolates with a vancomycin MIC >2 μg/mL (eg, vancomycin-intermediate *S. aureus* [VISA] or vancomycin-resistant *S. aureus* [VRSA]), an alternative to vancomycin should be used (**A-III**).

X. What is the management of persistent MRSA bacteremia and vancomycin treatment failures in adult patients?

71. A search for and removal of other foci of infection, drainage or surgical debridement is recommended (**A-III**).

72. High-dose daptomycin (10 mg/kg/day), if the isolate is susceptible, in combination with another agent (e.g. gentamicin 1 mg/kg IV every 8 h, rifampin 600 mg PO/IV daily or 300-450 mg PO/IV twice daily, linezolid 600 mg PO/IV BID, TMP-SMX 5 mg/kg IV twice daily, or a beta-lactam antibiotic) should be considered (**B-III**).

73. If reduced susceptibility to vancomycin and daptomycin are present, options may include the following: quinupristin-dalfopristin 7.5 mg/kg/dose IV every 8 h, TMP-SMX 5 mg/kg/dose IV twice daily, linezolid 600 mg PO/IV twice daily, or telavancin 10 mg/kg/dose IV once daily (**C-III**). These options may be given as a single agent or in combination with other antibiotics.

XI. What is the management of MRSA infections in neonates?

Neonatal pustulosis

74. For mild cases with localized disease, topical treatment with mupirocin may be adequate in full-term neonates and young infants (**A-III**).

75. For localized disease in a premature or very low-birthweight infant or more-extensive disease involving multiple sites in full-term infants, IV vancomycin or clindamycin is recommended, at least initially, until bacteremia is excluded (**A-II**).

Neonatal MRSA sepsis

76. IV vancomycin is recommended, dosing as outlined in the Red Book (**A-II**) [160].

77. Clindamycin and linezolid are alternatives for non-endovascular infections (**B-II**).

The prevalence of MRSA has steadily increased since the first clinical isolate was described in 1961, with an estimated 94,360 cases of invasive MRSA disease in the United States in 2005 [5]. Initially almost exclusively health care–associated, by the mid-1990s, MRSA strains were reported as causing infections among previously healthy individuals in the community who lacked

health care–associated risk factors [6]. Unlike HA-MRSA, these so-called CA-MRSA isolates are susceptible to many non–ß-lactam antibiotics. Furthermore, they are genetically distinct from HA-MRSA isolates and contain a novel cassette element, SCCmec IV and exotoxin, Panton-Valentine leukocidin (PVL). The epidemiology of MRSA has become increasingly complex as CA-MRSA and HA-MRSA strains have co-mingled both in the community and in health care facilities [7, 8]. Not unexpectedly, MRSA disease has had an enormous clinical and economic impact [9, 10].

The wide spectrum of illness caused by MRSA includes SSTIs, bacteremia and endocarditis, pneumonia, bone and joint infections, CNS disease, and toxic shock and sepsis syndromes. CA-MRSA was the most common cause of SSTI in a geographically diverse network of emergency departments in the United States [11]; however, there may be differences in local epidemiology to consider when implementing these guidelines. SSTIs may range in clinical presentation from a simple abscess or cellulitis to deeper soft-tissue infections, such as pyomyositis, necrotizing fasciitis, and mediastinitis as a complication of retropharyngeal abscess [12–15]. Bacteremia accompanies the majority (75%) of cases of invasive MRSA disease [5]. A multitude of disease manifestations have been described, including, but not limited to, infective endocarditis; myocardial, perinephric, hepatic, and splenic abscesses; septic thrombophlebitis with and without pulmonary emboli [16]; necrotizing pneumonia [17–21]; osteomyelitis complicated by subperiosteal abscesses; venous thrombosis and sustained bacteremia [16, 22, 23]; severe ocular infections, including endophthalmitis [24]; sepsis with purpura fulminans [25]; and Waterhouse-Friderichsen syndrome [26].

The Expert Panel addressed the following clinical questions in the 2010 Guidelines:

I. What is the management of SSTIs in the CA-MRSA era?

II. What is the management of recurrent MRSA SSTIs?

III. What is the management of MRSA bacteremia and infective endocarditis?

IV. What is the management of MRSA pneumonia?

V. What is the management of MRSA bone and joint infections?

VI. What is the management of MRSA infections of the CNS?

VII. What is the role of adjunctive therapies for the treatment of MRSA infections?

VIII. What are the recommendations for vancomycin dosing and monitoring?

IX. How should results of vancomycin susceptibility testing be used to guide therapy?

X. What is the management of persistent MRSA bacteremia and vancomycin treatment failures?

XI. What is the management of MRSA in neonates?

PRACTICE GUIDELINES

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [27]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [27].

METHODOLOGY

Panel Composition

The IDSA Standards and Practice Guidelines Committee (SPGC) convened adult and pediatric infectious diseases experts in the management of patients with MRSA.

Literature Review and Analysis

For the 2010 guidelines, the Expert Panel completed the review and analysis of data published since 1961. Computerized literature searches of PUBMED of the English-language literature were performed from 1961 through 2010 using the terms "methicillin-resistant *Staphylococcus aureus*" or "MRSA" and focused on human studies but also included studies from experimental animal models and in vitro data. A few abstracts from national meetings were included. There were few randomized, clinical trials; many recommendations were developed from observational studies or small case series, combined with the opinion of expert panel members.

Process Overview

In evaluating the evidence regarding the management of MRSA, the Panel followed a process used in the development of other IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (Table 1) [28].

Consensus Development Based on Evidence

The Panel met on 7 occasions via teleconference to complete the work of the guideline and at the 2007 Annual Meeting of the IDSA and the 2008 Joint Interscience Conference on Antimicrobial Agents and Chemotherapy/IDSA Meeting. The purpose of these meetings was to discuss the questions to be addressed, to make writing assignments, and to deliberate on the recommendations. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guideline was reviewed and endorsed by the Pediatric Infectious Diseases Society, the American College of Emergency Physicians, and American Academy of Pediatrics. The guideline was reviewed and

Table 1. Strength of Recommendation and Quality of Evidence

Category/grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use.
B	Moderate evidence to support a recommendation for or against use.
C	Poor evidence to support a recommendation.
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial.
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

NOTE. Adapted from [28]. Reproduced with the permission of the Minister of Public Works and Government Services Canada.

approved by the IDSA SPGC and the IDSA Board of Directors prior to dissemination.

Guidelines and Conflict of Interest

All members of the Expert Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts are listed in the Acknowledgements section.

LITERATURE REVIEW

Antimicrobial therapy

Clindamycin. Clindamycin is approved by the US Food and Drug Administration (FDA) for the treatment of serious infections due to *S. aureus*. Although not specifically approved for treatment of MRSA infection, it has become widely used for treatment of SSTI and has been successfully used for treatment of invasive susceptible CA-MRSA infections in children, including osteomyelitis, septic arthritis, pneumonia, and lymphadenitis [22, 29–31]. Because it is bacteriostatic, it is not recommended for endovascular infections, such as infective endocarditis or septic thrombophlebitis. Clindamycin has excellent tissue penetration, particularly in bone and abscesses, although penetration into the CSF is limited [32–34]. In vitro rates of susceptibility to clindamycin are higher among CA-MRSA than they are among HA-MRSA [35], although there is variation by geographic region [29, 36, 37]. The D-zone test is recommended for detection of inducible clindamycin resistance in erythromycin-resistant, clindamycin-susceptible isolates and is now readily available [38]. Diarrhea is the most common adverse effect and occurs in up to 20% of patients, and *Clostridium difficile*–associated disease may occur more frequently, compared with other oral agents. [39]. The oral suspension is often not well tolerated in children, although this may be overcome with addition of flavoring [40]. It is pregnancy category B [41].

Daptomycin. Daptomycin is a lipopeptide class antibiotic that disrupts cell membrane function via calcium-dependent binding, resulting in bactericidal activity in a concentration-dependent fashion. It is FDA-approved for adults with *S. aureus* bacteremia, right-sided infective endocarditis, and cSSTI. It should not be used for the treatment of non-hematogenous MRSA pneumonia, because its activity is inhibited by pulmonary surfactant. It is highly protein bound (91%) and renally excreted. The daptomycin susceptibility breakpoint for *S. aureus* is ⩽1 μg/mL. Nonsusceptible isolates have emerged during therapy in association with treatment failure [42–45]. Although the mechanism of resistance is not clear, single-point mutations in *mprF*, the lysylphosphatidylglycerol synthetase gene, are often present in such strains [46]. Prior exposure to vancomycin and elevated vancomycin MICs have been associated with increases in daptomycin MICs, suggesting possible cross-resistance [45, 47, 48]. Elevations in creatinine phosphokinase (CPK), which are rarely treatment limiting, have occurred in patients receiving 6 mg/kg/day but not in those receiving 4 mg/kg/day of daptomycin [49, 50]. Patients should be observed for development of muscle pain or weakness and have weekly CPK levels determined, with more frequent monitoring in those with renal insufficiency or who are receiving concomitant statin therapy. Several case reports of daptomycin-induced eosinophilic pneumonia have been described [51]. The pharmacokinetics, safety, and efficacy of daptomycin in children have not been established and are under investigation [52]. Daptomycin is pregnancy category B.

Linezolid Linezolid is a synthetic oxazolidinone and inhibits initiation of protein synthesis at the 50S ribosome. It is FDA-approved for adults and children for the treatment of SSTI and nosocomial pneumonia due to MRSA. It has in vitro activity against VISA and VRSA [53–55]. It has 100% oral bioavailability; hence, parenteral therapy should only be given if there are problems with gastrointestinal absorption or if the patient is unable to take oral medications. Linezolid resistance is rare, although an outbreak of linezolid-resistant MRSA infection has been described [56]. Resistance typically occurs during prolonged use via a mutation in the 23S ribosomal RNA (rRNA) binding site for linezolid [57] or *cfr* gene-mediated methylation of adenosine at position 2503 in 23SrRNA [58, 59]. Long-term use is limited by hematologic toxicity, with thrombocytopenia occurring more frequently than anemia and neutropenia, peripheral and optic neuropathy, and lactic acidosis. Although myelosuppression is generally reversible, peripheral and optic neuropathy are not reversible or are only partially reversible [60]. Linezolid is a weak, nonselective, reversible inhibitor of monoamine oxidase and has been associated with serotonin syndrome in patients taking concurrent selective serotonin-receptor inhibitors [61]. Linezolid causes less bone marrow suppression in children than it causes in adults [62]. The most common adverse events in children are diarrhea, vomiting, loose stools, and nausea [63]. The linezolid suspension may not be tolerated because of taste and may not be available in some pharmacies. It is considered pregnancy category C.

Quinupristin-Dalfopristin. Quinupristin-dalfopristin is a combination of 2 streptogramin antibiotics and inhibits protein synthesis. It is FDA-approved for cSSTI in adults and children >16 years of age. It has been used as salvage therapy for invasive MRSA infections in the setting of vancomycin treatment failure in adults and children [64–66]. Toxicity, including arthralgias, myalgias, nausea, and infusion-related reactions, has limited its use. Quinupristin-dalfopristin is considered pregnancy category B.

Rifampin. Rifampin has bactericidal activity against *S. aureus* and achieves high intracellular levels, in addition to penetrating biofilms [67–69]. Because of the rapid development of resistance, it should not be used as monotherapy but may be used in combination with another active antibiotic in selected scenarios. The role of rifampin as adjunctive therapy in MRSA infections has not been definitively established, and there is a lack of adequately powered, controlled clinical studies in the literature [120]. The potential use of rifampin as adjunctive therapy for MRSA infections is discussed in various sections throughout these guidelines. Of note, rifampin dosing is quite variable throughout the literature, ranging from 600 mg daily in a single dose or in 2 divided doses to 900 mg daily in 2 or 3 divided doses [70–74]. The range of rifampin dosing in these guidelines is suggested on the basis of the limited published data and is considered reasonable on the basis of expert opinion. Additional study is needed to define the role and optimal dosing of rifampin in management of MRSA infections.

Telavancin. Telavancin is a parenteral lipoglycopeptide that inhibits cell wall synthesis by binding to peptidoglycan chain precursors, causing cell membrane depolarization [75]. It is bactericidal against MRSA, VISA, and VRSA. It is FDA-approved for cSSTI in adults and is pregnancy category C. Creatinine levels should be monitored, and dosage should be adjusted on the basis of creatinine clearance, because nephrotoxicity was more commonly reported among individuals treated with telavancin than among those treated with vancomycin in 2 clinical trials [75]; monitoring of serum levels is not available.

Tetracyclines. Doxycycline is FDA-approved for the treatment of SSTI due to *S. aureus*, although not specifically for those caused by MRSA. Although tetracyclines have in vitro activity, data on the use of tetracyclines for the treatment of MRSA infections are limited. Tetracyclines appear to be effective in the treatment of SSTI, but data are lacking to support their use in more-invasive infections [76]. Tetracycline resistance in CA-MRSA isolates is primarily associated with *tetK* [77]. Although the *tet*(M) gene confers resistance to all agents in the class, *tet*(K) confers resistance to tetracycline [78] and inducible resistance to doxycycline [79], with no impact on minocycline susceptibility. Therefore, minocycline may be a potential alternative in such cases. Minocycline is available in oral and parenteral formulations. Tigecycline is a glycylcycline, a derivative of the tetracyclines, and is FDA-approved in adults for cSSTIs and intraabdominal infections. It has a large volume of distribution and achieves high concentrations in tissues and low concentrations in serum (<1 μg/mL) [80]. For this reason, and because it exhibits bacteriostatic activity against MRSA, caution should be used in treating patients with bacteremia. The FDA recently issued a warning to consider alternative agents in patients with serious infections because of an increase in all-cause mortality noted across phase III/IV clinical trials. Tetracyclines are pregnancy category D and are not recommended for children <8 years of age because of the potential for tooth enamel discoloration and decreased bone growth.

TMP-SMX. TMP-SMX is not FDA-approved for the treatment of any staphylococcal infections. However, because 95%–100% of CA-MRSA strains are susceptible in vitro [81, 82], it has become an important option for the outpatient treatment of SSTI [83–85]. A few studies, primarily involving methicillin-susceptible *S. aureus* (MSSA), have suggested a role in bone and joint infections [86–88]. A few case reports [89] and 1 randomized trial indicate potential efficacy in treating invasive staphylococcal infections, such as bacteremia and endocarditis [90]. TMP-SMX is effective for the treatment of purulent SSTI in children [91]. It has not been evaluated for the treatment of

invasive CA-MRSA infections in children. Caution is advised when using TMP-SMX to treat elderly patients, particularly those receiving concurrent inhibitors of the renin-angiotensin system and those with chronic renal insufficiency, because of an increased risk of hyperkalemia [92]. TMP-SMX is not recommended in pregnant women in the third trimester, when it is considered pregnancy category C/D, or in infants younger than 2 months of age.

Vancomycin. Vancomycin has been the mainstay of parenteral therapy for MRSA infections. However, its efficacy has come into question, with concerns over its slow bactericidal activity, the emergence of resistant strains, and possible "MIC creep" among susceptible strains [93–95]. Vancomycin kills staphylococci more slowly than do β-lactams in vitro, particularly at higher inocula (10^7–10^9 colony-forming units) [96] and is clearly inferior to β-lactams for MSSA bacteremia and infective endocarditis [97–101]. Tissue penetration is highly variable and depends upon the degree of inflammation. In particular, it has limited penetration into bone [102], lung epithelial lining fluid [103] and CSF [104, 105]. Vancomycin is considered pregnancy category C [41]. Vancomycin dosing, monitoring, and susceptibility testing are discussed in Sections VIII and IX.3

RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH INFECTIONS CAUSED BY MRSA

I. What is the management of SSTIs in the era of CA-MRSA?

SSTI

1. For a cutaneous abscess, incision and drainage is the primary treatment **(A-II).** For simple abscesses or boils, incision and drainage alone is likely adequate but additional data are needed to further define the role of antibiotics, if any, in this setting.

2. Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (eg, involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in area difficult to drain (eg, face, hand, and genitalia), associated septic phlebitis, lack of response to I &D alone **(A-III)**.

3. For outpatients with purulent cellulitis (eg, cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess), empirical therapy for CA-MRSA is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely unnecessary **(A-II)**. Five to 10 days of therapy is recommended but should be individualized on the basis of the patient's clinical response.

4. For outpatients with nonpurulent cellulitis (eg, cellulitis with no purulent drainage or exudate and no associated abscess), empirical therapy for infection due to β-hemolytic streptococci is recommended **(A-II).** The role of CA-MRSA is unknown. Empirical coverage for CA-MRSA is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. Five to 10 days of therapy is recommended but should be individualized on the basis of the patient's clinical response.

5. For empirical coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include the following: clindamycin **(A-II)**, TMP-SMX **(A-II),** a tetracycline (doxycycline or minocycline) **(A-II)**, and linezolid **(A-II)**. If coverage for both β-hemolytic streptococci and CA-MRSA is desired, options include the following: clindamycin alone **(A-II)** or TMP-SMX or a tetracycline in combination with a β-lactam (eg, amoxicillin) **(A-II)** or linezolid alone **(A-II)**.

6. The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTI is not recommended **(A-III).**

7. For hospitalized patients with complicated SSTI (cSSTI: defined as patients with deeper soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns) SSTI, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Options include the following: IV vancomycin **(A-I)**, linezolid 600 mg PO/IV twice daily **(A-I)**, daptomycin 4 mg/kg/dose IV once daily **(A-I)**, telavancin 10 mg/kg/dose IV once daily **(A-I),** clindamycin 600 mg IV/PO three times a day **(A-III)**. A β-lactam antibiotic (eg, cefazolin) may be considered in hospitalized patients with nonpurulent cellulitis with modification to MRSA-active therapy if there is no clinical response **(A-II).** Seven to 14 days of therapy is recommended but should be individualized on the basis of the patient's clinical response.

8. Cultures from abscesses and other purulent SSTI are recommended in patients treated with antibiotic therapy, patients with severe local infection or signs of systemic illness, patients who have not responded adequately to initial treatment, and if there is concern for a cluster or outbreak **(A-III).**

Pediatric considerations

9. For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used **(A-III).**

10. Tetracyclines should not be used in children <8 years of age **(A-II).**

11. In hospitalized children with cSSTI, vancomycin is recommended **(A-II).** If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) is an option if the clindamycin resistance rate is

low (eg, <10%) with transition to oral therapy if the strain is susceptible (**A-II**). Linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose PO/IV every 8 h for children <12 years of age is an alternative (**A-II**).

Evidence Summary

The emergence of CA-MRSA has led to a dramatic increase in emergency department visits and hospital admissions for SSTIs [106, 107]. For minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment may be effective. For cutaneous abscesses, the main treatment is incision and drainage [108]. For small furuncles, moist heat, which helps to promote drainage, may be sufficient [109]. It remains controversial whether antibiotics provide any clinically significant additional benefit, but incision and drainage is likely adequate for most simple abscesses. Multiple, mostly observational studies indicate high cure rates (85%–90%) whether or not an active antibiotic is used [11, 81, 110–112]. Two recently published randomized clinical trials involving adult [113] and pediatric [114] patients showed no significant difference in cure rates when TMP-SMX was compared with placebo; however, there was a suggestion that antibiotics may prevent the short-term development of new lesions. Two retrospective studies suggest improved cure rates if an effective antibiotic is used [85, 115]. We hope that additional prospective, large-scale studies that are currently already underway will provide more-definitive answers to these questions. Antibiotic therapy is recommended for abscesses associated with the conditions listed in Table 2 [83, 116].

Oral antibiotics that may be used as empirical therapy for CA-MRSA include TMP-SMX, doxycycline (or minocycline), clindamycin, and linezolid. Several observational studies [85, 117] and one small randomized trial [84] suggest that TMP-SMX, doxycycline, and minocycline are effective for such infections. Clindamycin is effective in children with CA-MRSA SSTI [91, 118]. Linezolid is FDA-approved for SSTI but is not superior to less expensive alternatives [119]. Because of the likely development of resistance, rifampin should not be used as monotherapy for the treatment of MRSA infections. The adjunctive use of rifampin with another active drug for the treatment of SSTI is not recommended in the absence of data to support benefit [120].

The need to include coverage against β-hemolytic streptococci in addition to CA-MRSA is controversial and may vary depending on local epidemiology and the type of SSTI as discussed below. Although TMP-SMX, doxycycline, and minocycline have good in vitro activity against CA-MRSA, their activity against β- hemolytic streptococci is not well-defined [121–123]. Clindamycin is active against β- hemolytic streptococci, although MRSA susceptibility rates may vary by region [85, 124, 125]. The D-zone test is recommended for erythromycin-resistant, clindamycin-susceptible isolates to detect inducible clindamycin resistance. The clinical significance of inducible clindamycin resistance is unclear because the drug may still be effective for some patients with mild infections; however, its presence should preclude the use of clindamycin for more-serious infections.

Outpatients presenting with purulent cellulitis (cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess) should empirically receive oral antibiotics active against CA-MRSA while awaiting culture data. Among patients presenting with purulent SSTI to 11 emergency departments throughout the United States, CA-MRSA was the dominant organism, isolated from 59% of patients, followed by MSSA (17%); β- hemolytic streptococci accounted for a much small proportion (2.6%) of these infections [11]. In nonpurulent cellulitis (cellulitis with no purulent drainage or exudate and no associated abscess), ultrasound may be considered to exclude occult abscess [126, 127]. For nonpurulent cellulitis, the absence of culturable material presents an inherent challenge to our ability to determine its microbiologic etiology and make decisions regarding empirical antibiotic therapy. In the pre–CA-MRSA era, microbiologic investigations using needle aspiration or punch biopsy cultures of nonpurulent cellulitis identified β-hemolytic streptococci and *S. aureus* as the main pathogens. In the majority of cases, a bacterial etiology was not identified, but MSSA was the most common pathogen among those who were culture positive [128–133]. A retrospective case-control study in children with nonpurulent cellulitis found that, compared with β-lactams, clindamycin provided no additional benefit, whereas TMP-SMX was associated with a slightly higher failure rate [134]. The only prospective study of nonculturable cellulitis among hospitalized inpatients found that β-hemolytic streptococci (diagnosed by acute- and convalescent-phase serological testing for anti-streptolysin-O and anti-DNase-B antibodies or positive blood culture results) accounted for 73% of the cases; despite the lack of an identifiable etiology in 27% of cases, the overall clinical response rate to β-lactam therapy was

Table 2.

Conditions in which Antimicrobial Therapy is Recommended after Incision and Drainage of an Abscess due to Community-Associated Methicillin-Resistant *Staphylococcus aureus*
Severe or extensive disease (eg, involving multiple sites of infection) or rapid progression in presence of associated cellulitis
Signs and symptoms of systemic illness
Associated comorbidities or immunosuppression (diabetes mellitus, human immunodeficiency virus infection/AIDS, neoplasm)
Extremes of age
Abscess in area difficult to drain completely (eg, face, hand, and genitalia)
Associated septic phlebitis
Lack of response to incision and drainage alone

Table 3. Recommendations for the Treatment of Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Manifestation	Treatment	Adult dose	Pediatric dose	Class[a]	Comment
Skin and soft-tissue infection (SSTI)					
Abscess, furuncles, carbuncles	Incision and drainage			AII	For simple abscesses or boils, incision and drainage is likely adequate. Please refer to Table 2 for conditions in which antimicrobial therapy is recommended after incision and drainage of an abscess due to CA-MRSA.
Purulent cellulitis (defined as cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess)	Clindamycin	300–450 mg PO TID	10–13 mg/kg/dose PO every 6–8 h, not to exceed 40 mg/kg/day	AII	*Clostridium difficile*–associated disease may occur more frequently, compared with other oral agents.
	TMP-SMX	1–2 DS tab PO BID	Trimethoprim 4–6 mg/kg/dose, sulfamethoxazole 20–30 mg/kg/dose PO every 12 h	AII	TMP-SMX is pregnancy category C/D and not rec ommended for women in the third trimester of pregnancy and for children <2 months of age.
	Doxycycline	100 mg PO BID	⩽45kg: 2 mg/kg/dose PO every 12 h >45kg: adult dose	AII	Tetracyclines are not recommended for children under 8 years of age and are pregnancy category D.
	Minocycline	200 mg × 1, then 100 mg PO BID	4 mg/kg PO × 1, then 2 mg/kg/dose PO every 12 h	AII	
	Linezolid	600 mg PO BID	10 mg/kg/dose PO every 8 h, not to exceed 600 mg/dose	AII	More expensive compared with other alternatives
Nonpurulent cellulitis (defined as cellulitis with no purulent drainage or exudate and no associated abscess)	β-lactam (eg, cephalexin and dicloxacillin)	500 mg PO QID	Please refer to Red Book	AII	Empirical therapy for β-hemolytic streptococci is recommended (AII). Empirical coverage for CA-MRSA is rec-ommended in patients who do not respond to β-lactam ther-apy and may be considered in those with systemic toxicity.
	Clindamycin	300–450 mg PO TID	10–13 mg/kg/dose PO every 6–8 h, not to exceed 40 mg/kg/day	AII	Provide coverage for both β-hemolytic streptococci and CA-MRSA
	β-lactam (eg, amoxicillin) and/or TMP-SMX or a tetracycline	Amoxicillin: 500 PO mg TID See above for TMP-SMX and tetracycline dosing	Please refer to Red Book See above for TMP-SMX and tetracycline dosing	AII	Provide coverage for both β-hemolytic streptococci and CA-MRSA
	Linezolid	600 mg PO BID	10 mg/kg/dose PO every 8 h, not to exceed 600 mg/dose	AII	

Table 3. (*Continued*)

Manifestation	Treatment	Adult dose	Pediatric dose	Class[a]	Comment
					Provide coverage for both B-hemolytic streptococci and CA-MRSA
Complicated SSTI	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	AI/AII	
	Linezolid	600 mg PO/IV BID	10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose	AI/AII	For children ⩾12 years of age, 600 mg PO/IV BID. Pregnancy category C
	Daptomycin	4 mg/kg/dose IV QD	Ongoing study	AI/ND	The doses under study in children are 5 mg/kg (ages 12–17 years), 7 mg/kg (ages 7–11 years), 9 mg/kg (ages 2–6 years) (Clinicaltrials.gov NCT 00711802). Pregnancy category B.
	Telavancin	10 mg/kg/dose IV QD	ND	AI/ND	Pregnancy category C
	Clindamycin	600 mg PO/IV TID	10–13 mg/kg/dose PO/IV every 6–8 h, not to exceed 40 mg/kg/day	AIII/AII	Pregnancy category B
Bacteremia and infective endocarditis					
Bacteremia	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	AII	The addition of gentamicin (AII) or rifampin (AI) to vancomycin is not routinely recommended.
	Daptomycin	6 mg/kg/dose IV QD	6–10 mg/kg/dose IV QD	AI/CIII	For adult patients, some experts recommend higher dosages of 8–10 mg/kg/dose IV QD (BIII). Pregnancy category B.
Infective endocarditis, native valve	Same as for bacteremia				
Infective endocarditis, prosthetic valve	Vancomycin and gentamicin and rifampin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	BIII	
		1 mg/kg/dose IV every 8 h	1 mg/kg/dose IV every 8 h		
		300 mg PO/IV every 8 h	5 mg/kg/dose PO/IV every 8 h		
Persistent bacteremia	Please see text				
Pneumonia					
	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	AII	
	Linezolid	600 mg PO/IV BID	10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose	AII	For children ⩾12 years, 600 mg PO/IV BID. Pregnancy category C.
	Clindamycin	600 mg PO/IV TID	10–13 mg/kg/dose PO/IV every 6–8 h, not to exceed 40 mg/kg/day	BIII/AII	Pregnancy category B.

Table 3. (*Continued*)

Manifestation	Treatment	Adult dose	Pediatric dose	Class[a]	Comment
Bone and joint infections					
Osteomyelitis	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	BII/AII	Surgical debridement and drainage of associated soft-tissue abscesses is the mainstay of therapy. (AII). Some experts recommend the addition of rifampin 600 mg QD or 300–450 mg BID to the chosen antibiotic (BIII). For children ⩾12 years of age, linezolid 600 mg PO/IV BID should be used. A single-strength and DS tablet of TMP-SMX contains 80 mg and 160 mg of TMP, respectively. For an 80-kg adult, 2 DS tablets achieves a dose of 4 mg/kg.
	Daptomycin	6 mg/kg/day IV QD	6–10 mg/kg/day IV QD	BII/CIII	
	Linezolid	600 mg PO/IV BID	10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose	BII/CIII	
	Clindamycin	600 mg PO/IV TID	10–13 mg/kg/dose PO/IV every 6–8 h, not to exceed 40 mg/kg/day	BIII/AII	
	TMP-SMX and rifampin	3.5–4.0 mg/kg/dose PO/IV every 8–12 h	ND	BII/ND	
		600 mg PO QD			
Septic arthritis	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	BII/AII	Drainage or debridement of the joint space should always be performed (AII).
	Daptomycin	6 mg/kg/day IV QD	6–10 mg/kg/dose IV QD	BII/CIII	
	Linezolid	600 mg PO/IV BID	10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose	BII/CIII	
	Clindamycin	600 mg PO/IV TID	10–13 mg/kg/dose PO/IV every 6–8 h, not to exceed 40 mg/kg/day	BIII/AII	
	TMP-SMX	3.5–4.0 mg/kg/dose PO/IV every 8–12 h	ND	BIII/ND	
Prosthetic joint, spinal implant infections	Please see text				
Central nervous system infections					

Table 3. (*Continued*)

Manifestation	Treatment	Adult dose	Pediatric dose	Class[a]	Comment
Meningitis	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	BII	Some experts recommend the addition of rifampin 600 mg QD or 300–450 mg BID to vancomycin for adult patients (BIII). For children ⩾12 years of age, linezolid 600 mg BID.
	Linezolid	600 mg PO/IV BID	10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose	BII	
	TMP-SMX	5 mg/kg/dose PO/IV every 8-12 h	ND	CIII/ND	
Brain abscess, subdural empyema, spinal epidural abscess	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	BII	Some experts recommend the addition of rifampin 600 mg QD or 300–450 mg BID to vancomycin for adult patients (BIII). For children ⩾12 years of age, linezolid 600 mg BID.
	Linezolid	600 mg PO/IV BID	10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose	BII	
	TMP-SMX	5 mg/kg/dose PO/IV every 8–12 h	ND	CIII/ND	
Septic thrombosis of cavernous or dural venous sinus	Vancomycin	15–20 mg/kg/dose IV every 8–12 h	15 mg/kg/dose IV every 6 h	BII	Some experts recommend the addition of rifampin 600 mg QD or 300–450 mg BID to vancomycin for adult patients (BIII). For children ⩾12 years of age, linezolid 600 mg BID
	Linezolid	600 mg PO/IV BID	10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose	BII	
	TMP-SMX	5 mg/kg/dose PO/IV every 8-12 h	ND	CIII/ND	

NOTE. BID, twice daily; CA-MRSA, community-associated MRSA; DS, double strength; IV, intravenous; ND, no data; PO, oral; QD, every day; TID, 3 times per day; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Classification of the strength of recommendation and quality of evidence applies to adult and pediatric patients unless otherwise specified. A backslash (/) followed by the recommendation strength and evidence grade will denote any differences in pediatric classification.

96% [135]. Although additional research is needed to characterize the microbiology of nonpurulent cellulitis, currently available data suggests that β-hemolytic streptococci may be the primary pathogen. The relative contribution of CA-MRSA, compared with β-hemolytic streptococci and MSSA, remains unknown, but empirical coverage for CA-MRSA is recommended in those who have not responded to β-lactam monotherapy and may be considered in those with systemic toxicity.

For patients with systemic toxicity and/or rapidly progressive or worsening infection despite receipt of appropriate oral antibiotics, inpatient management and surgical intervention is recommended. Several antibiotics with MRSA activity are FDA-approved for the treatment of adult patients with cSSTI, such as deep soft-tissue infections, surgical and/or traumatic wound infections, major abscesses, cellulitis, infected ulcers, and burns: vancomycin, linezolid, daptomycin, tigecycline, and telavancin [50, 136–138]. Because of a recent FDA warning indicating an increased risk in all-cause mortality with tigecycline versus comparator drugs in a pooled analysis of clinical trials, the drug was not included in these guidelines, given the availability of multiple MRSA-active alternatives. Ceftaroline, a novel cephalosporin antibiotic, may become available in the near future for treatment of cSSTI, pending FDA review. When compared with vancomycin, none of these newer agents have demonstrated superiority in the primary outcome of clinical cure. There are limited published data on the use of clindamycin in adults with cSSTI due to MRSA. Options for the treatment of cSSTI in children include clindamycin and linezolid [13, 139]. For hospitalized patients with a nonpurulent cellulitis, a β-lactam antibiotic (eg, cefazolin) can be considered with modification to a MRSA-active agent if there is no clinical response [135].

The duration of therapy for SSTI has not been well-defined, although no differences in outcome were observed among adult patients with uncomplicated cellulitis receiving 5 versus 10 days of therapy in a randomized, controlled trial [140]. In the FDA licensing trials for cSSTI, patients were typically treated for 7–14 days. Duration of therapy should be individualized on the basis of the patient's clinical response.

II. What is the management of recurrent MRSA SSTIs?

Recurrent SSTIs

12. Preventive educational messages on personal hygiene and appropriate wound care are recommended for all patients with SSTI. Instructions should be provided to:

i. Keep draining wounds covered with clean, dry bandages (**A-III**).

ii. Maintain good personal hygiene with regular bathing and cleaning of hands with soap and water or an alcohol-based hand gel, particularly after touching infected skin or an item that has directly contacted a draining wound (**A-III**).

iii. Avoid reusing or sharing personal items (eg, disposable razors, linens, and towels) that have contacted infected skin (**A-III**).

13. Environmental hygiene measures should be considered in patients with recurrent SSTI in the household or community setting:

i. Focus cleaning efforts on high-touch surfaces (ie, surfaces that come into frequent contact with people's bare skin each day, counters, door knobs, bath tubs, and toilet seats) that may contact bare skin or uncovered infections (**C-III**).

ii. Commercially available cleaners or detergents appropriate for the surface being cleaned should be used according to label instructions for routine cleaning of surfaces (**C-III**).

14. Decolonization may be considered in selected cases if:

i. A patient develops a recurrent SSTI despite optimizing wound care and hygiene measures (**C-III**).

ii. Ongoing transmission is occurring among household members or other close contacts despite optimizing wound care and hygiene measures (**C-III**).

15. Decolonization strategies should be offered in conjunction with ongoing reinforcement of hygiene measures and may include the following:

i. Nasal decolonization with mupirocin twice daily for 5–10 days (**C-III**).

ii. Nasal decolonization with mupirocin twice daily for 5–10 days and topical body decolonization regimens with a skin antiseptic solution (eg, chlorhexidine) for 5–14 days or dilute bleach baths. (For dilute bleach baths, 1 teaspoon per gallon of water [or ¼ cup per ¼ tub or 13 gallons of water] given for 15 min twice weekly for ~3 months can be considered.) (**C-III**).

16. Oral antimicrobial therapy is recommended for the treatment of active infection only and is not routinely recommended for decolonization (**A-III**). An oral agent in combination with rifampin, if the strain is susceptible, may be considered for decolonization if infections recur despite above measures (**CIII**).

17. In cases where household or interpersonal transmission is suspected:

i. Personal and environmental hygiene measures in the patient and contacts are recommended (**A-III**).

ii. Contacts should be evaluated for evidence of *S. aureus* infection:

a. Symptomatic contacts should be evaluated and treated (**A-III**); nasal and topical body decolonization strategies may be considered following treatment of active infection (**C-III**).

b. Nasal and topical body decolonization of asymptomatic household contacts may be considered (**C-III**).

18. The role of cultures in the management of patients with recurrent SSTI is limited:

i. Screening cultures prior to decolonization are not routinely recommended if at least 1 of the prior infections was documented as due to MRSA (**B-III**).

ii. Surveillance cultures following a decolonization regimen are not routinely recommended in the absence of an active infection (**B-III**).

Evidence Summary

There are few studies to guide the development of evidence-based recommendations on the management of recurrent CA-MRSA SSTI. Although no standardized definition exists, most experts define recurrent disease as 2 or more discrete SSTI episodes at different sites over a 6-month period. The pathogenesis of recurrent infection is unclear and likely involves a complex interplay between the pathogen, host colonization, patient behavior, and environmental exposures [141]. The Panel suggests a multifaceted approach that actively engages the patient in personal and environmental hygiene measures applicable to the household or community setting [142] while accounting for individual preferences. Infected skin and draining wounds should be covered, and sharing of personal items should be avoided. Commercially available cleaners or detergents should be used for surfaces that come into frequent contact with people's bare skin each day.

Given the potential role of colonization in the pathogenesis of recurrent SSTI, prevention strategies have also focused on decolonization, the use of antimicrobial or antiseptic agents to suppress or eliminate *S. aureus* carriage as a means of preventing auto-infection or transmission. Decolonization measures may be considered for patients with multiple recurrent SSTI despite hygiene measures or when there is ongoing transmission in a well-defined, closely associated cohort [83]. Although decolonization strategies are frequently employed, there are no published data to support its efficacy in patients with recurrent MRSA SSTI. The optimal regimen, frequency of application, and duration of therapy are unclear. Furthermore, it is unknown whether it will select for or result in replacement with more-resistant or more-virulent strains.

Although mupirocin appears to be effective in reducing MRSA colonization, it has not conclusively been shown to prevent infections among nasal carriers [143, 144], although most studies have included patients in the health care setting, where evidence for benefit is limited to certain high-risk populations. A Cochrane Review found that mupirocin was associated with a reduction in nosocomial *S. aureus* (mostly MSSA) infections, primarily among patients undergoing surgical procedures or receiving dialysis [145]. No benefit was seen in the 2 studies that included nonsurgical patients and MRSA carriers [146, 147]. The combination of mupirocin and chlorhexidine soap reduced the rate of surgical site infections among MSSA nasal carriers [148]. Only 1 small clinical trial examined the role of mupirocin in the management of recurrent MSSA SSTI; a 5-day course of mupirocin, followed by repeated application on a monthly basis for 1 year, reduced the prevalence of nasal colonization and the number of cases of recurrent SSTI [149]. A trial conducted in the era of CA-MRSA found that, although mupirocin decreased the prevalence of nasal colonization, it did not reduce the incidence of first-time SSTI, compared with placebo [150]. Although it does not appear to be widespread, a high prevalence of mupirocin resistance has been reported among MRSA isolates in some community settings [151]. Because of the lack of FDA breakpoints for mupirocin, along with limited availability of commercial tests in the United States, we are unable to provide specific recommendations on mupirocin susceptibility testing for individual patients at this time. Clinical laboratories that wish to perform susceptibility testing may consider validating in-house prepared assays, such as polymerase chain reaction or disk diffusion assays [152]. The role of other colonization sites in the development of infection or recurrent disease is unknown, and eliminating nasal colonization alone may be insufficient. Colonization at nonnasal sites, such as the groin, axilla, and rectum, is more common among those with CA-MRSA than it is among those with CA-MSSA or HA-MRSA [153], although it may be difficult to distinguish true colonization from transient contamination at these sites because of active infection.

The potential effectiveness of topical skin antiseptics, such as chlorhexidine and hexachlorophene, is extrapolated from data on community outbreaks whereby, when bundled together with other interventions, it prevents ongoing transmission and infection [154–158]. When used alone, chlorhexidine does not appear to be effective; a recent randomized trial found no impact of chlorhexidine-impregnated wipes on SSTI rates [159], and at best, it appears to have a transient effect on colonization, with recolonization occurring soon after discontinuation [161]. Hexachlorophene should not be used in infants <2 months of age, because it has been linked to adverse neurological outcomes in newborns. The addition of bleach to bath water has previously been used for treatment of recurrent SSTI in children with eczema [162]. In vitro sodium hypochlorite at a concentration equivalent to 1/2 cup of bleach in 1/4 tub (13 gallons) of water kills CA-MRSA after 5 min [163]. Some experts suggest that bleach baths at a concentration of 1 teaspoon per gallon of bath water (1/4 cup per 1/4 tub of water) for 15 min given twice weekly for $\sim$3 months is well-tolerated and may be effective. Given the potential for skin irritation if not adequately diluted, clear instructions should be provided.

No clinical trials have evaluated the role of oral antimicrobials for treatment of recurrent CA-MRSA SSTI. A Cochrane review found no benefit of oral antibiotics for eradication of MRSA colonization among patients in the health care setting when

compared with placebo, no treatment, or topical antibiotics; none of these studies examined their impact on infection rates [164]. A systematic review of comparative controlled trials found that a rifampin-based combination, compared with monotherapy with other oral antibiotics, was more likely to eradicate *S. aureus* carriage, but again, no studies examined infection rates as an outcome [165]. Both reviews noted the emergence of rifampin resistance and adverse events associated with systemic agents.

While awaiting guidance from ongoing clinical trials, the Panel suggests mupirocin alone or a combined strategy of mupirocin and topical antiseptics (eg, chlorhexidine and diluted bleach baths) if decolonization is being considered. The optimal dosage and duration of such regimens is unknown; suggested dosages are based on several ongoing clinical trials [166–168]. Oral antimicrobials are not routinely recommended for decolonization; they should only be considered in patients who continue to have infections in spite of the other measures. If prescribed for decolonization, the optimal regimen and duration is unknown, although a rifampin-based combination (eg, with TMP-SMX or doxycycline) is suggested and administered in short courses (eg, 5–10 days) to decrease the potential for development of resistance. Hygiene measures should be reinforced, and the oral regimen may be offered in conjunction with a topical antiseptic, such as chlorhexidine [169]. Additional studies are needed to guide the prevention of recurrent SSTI.

III. What is the management of MRSA bacteremia and infective endocarditis?

Bacteremia and Infective Endocarditis, Native Valve

19. For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: 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 h of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**AI**) for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

20. For adults with infective endocarditis, IV vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**A-I**) for 6 weeks is recommended. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

21. Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (**A-II**).

22. Addition of rifampin to vancomycin is not recommended for bacteremia or native valve infective endocarditis (**A-I**).

23. A clinical assessment to identify the source and extent of the infection with elimination and/or debridement of other sites of infection should be conducted **(A-II).**

24. Additional blood cultures 2–4 days after initial positive cultures and as needed thereafter are recommended to document clearance of bacteremia **(A-II).**

25. Echocardiography is recommended for all adult patients with bacteremia. TEE is preferred over TTE (**A-II**).

26. Evaluation for valve replacement surgery is recommended if large vegetation (>10 mm in diameter), occurrence of ⩾1 embolic event during the first 2 weeks of therapy, severe valvular insufficiency, valvular perforation or dehiscence, decompensated heart failure, perivalvular or myocardial abscess, new heart block, or persistent fevers or bacteremia are present (**A-II**).

Infective Endocarditis, Prosthetic Valve

27. IV vancomycin plus rifampin 300 mg PO/IV every 8 h for at least 6 weeks plus gentamicin 1 mg/kg/dose IV every 8 h for 2 weeks (**B-III**).

28. Early evaluation for valve replacement surgery is recommended (**A-II**).

Pediatric considerations

29. In children, vancomycin 15 mg/kg/dose IV every 6 h is recommended for the treatment of bacteremia and infective endocarditis **(A-II).** Duration of therapy may range from 2 to 6 weeks depending on source, presence of endovascular infection, and metastatic foci of infection. Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin 6–10 mg/kg/dose IV once daily may be an option **(C-III).** Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus **(B-III).**

30. Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis **(C-III)**; the decision to use combination therapy should be individualized.

31. Echocardiogram is recommended in children with congenital heart disease, bacteremia more than 2–3 days in duration, or other clinical findings suggestive of endocarditis **(A-III).**

Evidence Summary

MRSA bacteremia and infective endocarditis are serious diseases associated with high morbidity, and mortality rates are 30%–37% for MRSA endocarditis [170, 171]. In addition to antimicrobial therapy, the source and extent of infection, including embolic or metastatic foci, should be determined through careful history and physical examination and imaging, with

removal or debridement whenever possible. Vancomycin has been the mainstay of therapy for MRSA bacteremia and endocarditis. However, compared with β-lactam agents, vancomycin is less effective for the treatment of MSSA bacteremia and endocarditis [98, 99]. Although rifampin or gentamicin is occasionally used in combination with vancomycin to improve outcomes, clinical data do not support this practice. In one study, the duration of bacteremia was longer in the rifampin-combination therapy group than in the vancomycin monotherapy group [172]. The use of rifampin combination therapy in a study of native valve *S. aureus* endocarditis did not improve outcomes but was associated with hepatic adverse effects, drug interactions, and the emergence of resistance [173]. Short-course, low-dose gentamicin combined with vancomycin for MRSA bacteremia and native valve endocarditis was associated with an increased risk of nephrotoxicity [49, 174]; the duration of bacteremia was comparable to that observed with vancomycin monotherapy [172]. The recommendation to treat prosthetic valve MRSA endocarditis with vancomycin, gentamicin, and rifampin is based on small retrospective studies of methicillin-resistant coagulase-negative staphylococci [175, 176] and the 2005 American Heart Association (AHA) Infective Endocarditis Guidelines [74].

Daptomycin 6 mg/kg/dose IV once daily is an alternative to vancomycin for adults in the treatment of MRSA bacteremia or endocarditis. In a randomized trial, it was noninferior to initial low-dose gentamicin plus either vancomycin or an antistaphylococcal penicillin [49]. Emergence of reduced susceptibility to daptomycin was observed in several daptomycin-treated patients who experienced failure of therapy, most of whom had deep-seated infections or left-sided endocarditis. Because it exhibits concentration-dependent killing, some experts recommend doses of up to 8–10 mg/kg, which appear to be safe, although additional studies are needed [177, 178]. Whether this higher dosing strategy prevents the emergence of resistance [179–181] or improved outcomes is unknown and is under investigation. Although daptomycin should not be used in patients with pneumonia because of inactivation by pulmonary surfactant [182], it can be used in septic pulmonary emboli [183]. The safety and efficacy of daptomycin in children have not been established, but it may be effective when given in combination with other agents in children with disseminated MRSA infections associated with prolonged bacteremia [184]. Doses of 8–10 mg/kg appear to be safe in children, although additional study is needed [185]. Quinopristin-dalfopristin, linezolid, TMP-SMX, and telavancin are not recommended as first-line therapy for MRSA bacteremia. Their role as salvage agents for persistent MRSA bacteremia is discussed in Section X.

The duration of therapy for MRSA bacteremia is based on several factors. Patients receiving <14 days of therapy, including those with catheter-associated bacteremia, had success rates that were lower than those for patients who received a longer course [186, 187]. For adults, the recommended minimum duration of therapy for uncomplicated bacteremia is 2 weeks, as defined by: (1) exclusion of endocarditis, (2) no implanted prostheses (eg, prosthetic valves, cardiac devices, and arthroplasties), (3) follow-up cultures of blood samples drawn 2–4 days after the initial set that do not grow MRSA, (4) defervescence within 72 h of therapy, and (5) no evidence of metastatic sites of infection [49, 188]. If the above criteria are not met, 4–6 weeks of therapy is recommended for complicated bacteremia depending on the extent of infection; longer durations of therapy may be needed in those who are slow to clear their bacteremia. Whether the entire course must be given parenterally is unknown; there are limited data on the use of oral ciprofloxacin in combination with oral rifampin primarily in patients with MSSA right-sided endocarditis [189, 190]. In the absence of additional studies among patients with MRSA, transition from parenteral to oral therapy should be done cautiously and only in those with uncomplicated bacteremia.

TEE is preferred in adults with MRSA bacteremia because of its superiority, compared with TTE, for the detection of vegetations [191–193] and identification of complications, such as intracardiac abscess and valvular perforation [194]. In young children, TTE is likely adequate, given their thin chest wall. Echocardiogram is not routinely recommended for young children except in those with congenital heart disease, bacteremia of >2–3 days duration, or other clinical findings suggestive of endocarditis [195]. In patients with MRSA bacteremia and infected intravascular or prosthetic devices, a higher relapse and mortality rate has been associated with failure to remove infected materials [196, 197]. The management of cardiac device-related infections was recently reviewed in the 2010 AHA guidelines on cardiovascular implantable electronic device infections [198]. Patients with endocarditis should be evaluated for valve replacement on the basis of clinical and echocardiographic criteria as per AHA guidelines [74, 199]; data suggest that patients with staphylococcal endocarditis may benefit from early surgical intervention [200–204].

IV. What is the management of MRSA pneumonia?

Pneumonia

32. For hospitalized patients with severe community-acquired pneumonia defined by any one of the following: (1) a requirement for ICU admission, (2) necrotizing or cavitary infiltrates, or (3) empyema, empirical therapy for MRSA is recommended pending sputum and/or blood culture results (**A-III**).

33. For HA-MRSA or CA-MRSA pneumonia, IV vancomycin (**A-II**) or linezolid 600 mg PO/IV twice daily (**A-II**) or clindamycin 600 mg PO/IV three times daily (**B-III**) if the strain is susceptible is recommended for 7-21 days, depending on the extent of infection.

34. In patients with MRSA pneumonia complicated by empyema, antimicrobial therapy against MRSA should be used in conjunction with drainage procedures (**A-III**).

Pediatric considerations

35. In children, IV vancomycin is recommended (**A-II**). If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) can be used as empirical therapy if the clindamycin resistance rate is low (eg, <10%) with transition to oral therapy if the strain is susceptible (**A-II**). Linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose every 8 h for children <12 years of age is an alternative (**A-II**).

Evidence Summary

Although it remains an uncommon etiology of community-acquired pneumonia (CAP), MRSA has emerged as a cause of severe CAP [17–21], particularly in the context of a preceding or concurrent influenza-like illness, although not exclusively so [205]. Empirical therapy for MRSA should be considered in patients with severe CAP defined by any one of the following: (1) a requirement for ICU admission, (2) necrotizing or cavitary infiltrates, or (3) empyema. Empirical coverage for MRSA should be discontinued if sputum or blood cultures do not grow the organism.

High failure rates have been observed in the treatment of MRSA pneumonia, particularly ventilator-associated pneumonia (VAP) [206–208], which has been attributed to vancomycin's poor penetration into pulmonary tissue and lung epithelial lining fluid [209]. The addition of rifampin to vancomycin for the treatment of HA-MRSA appears to improve clinical outcomes, compared with treatment with vancomycin alone, in a small, randomized open-label trial, and this deserves additional study [210]. Linezolid is an alternative to vancomycin for the treatment of MRSA pneumonia, achieving greater levels in lung epithelial lining fluid than in plasma [211]. Linezolid and vancomycin were associated with comparable cure rates in 2 prospective studies involving adult patients with nosocomial pneumonia [212, 213]; a retrospective pooled subgroup analysis of MRSA cases in these studies found higher cure rates and improved survival in the linezolid arm [214]. A randomized study of linezolid versus vancomycin for MRSA VAP found no significant difference in early microbiologic response rates [215]. Thus, it is unclear whether 1 drug is definitively superior to the other for treatment of MRSA VAP, and additional studies are ongoing. Linezolid has not been compared with vancomycin for the treatment of VAP in children.

Clindamycin is an alternative to vancomycin for the treatment of MRSA pneumonia in children [29], and there is limited data regarding its use in adults [205]. Data are insufficient to recommend for or against the use of protein synthesis (eg, toxin) inhibitors, such as clindamycin or linezolid, as adjunctive therapy for the treatment of MRSA pneumonia; this topic is discussed further in section VII. Fluoroquinolones may have activity against some CA-MRSA isolates, but they are not routinely recommended, because resistance may emerge with monotherapy. One small randomized study found that TMP-SMX was effective as prophylaxis for MRSA VAP in patients with burns [216], but additional study is needed to determine its role in MRSA pneumonia.

V. What is the management of MRSA bone and joint infections?

Osteomyelitis

36. Surgical debridement and drainage of associated soft-tissue abscesses is the mainstay of therapy and should be performed whenever feasible (**A-II**).

37. The optimal route of administration of antibiotic therapy has not been established. Parenteral, oral, or initial parenteral therapy followed by oral therapy may be used depending on individual patient circumstances (**A-III**).

38. Antibiotics available for parenteral administration include IV vancomycin (**B-II**) and daptomycin 6 mg/kg/dose IV once daily (**B-II**). Some antibiotic options with parenteral and oral routes of administration include the following: TMP-SMX 4 mg/kg/dose (TMP component) twice daily in combination with rifampin 600 mg once daily (**B-II**), linezolid 600 mg twice daily (**B-II**), clindamycin 600 mg every 8 h (**B-III**).

39. Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg PO twice daily to the antibiotic chosen above (**B-III**). For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.

40. The optimal duration of therapy for MRSA osteomyelitis is unknown. A minimum 8-week course is recommended (**A-II**). Some experts suggest an additional 1-3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline/minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities (**C-III**).

41. MRI with gadolinium is the imaging modality of choice, particularly for detection of early osteomyelitis and associated soft-tissue disease (**A-II**). ESR and/or CRP level may be helpful to guide response to therapy (**B-III**).

Septic Arthritis

42. Drainage or debridement of the joint space should always be performed (**A-II**).

43. For septic arthritis, refer to antibiotic choices for osteomyelitis (#37 above). A 3-4-week course of therapy is suggested (**A-III**).

Device-related osteoarticular infections

44. For early-onset (<2 months after surgery) or acute hematogenous prosthetic joint infections involving a stable implant with short duration (≤3 weeks) of symptoms and debridement (but device retention), initiate parenteral therapy (refer to antibiotic recommendations for osteomyelitis) plus rifampin 600 mg daily or 300–450 mg PO twice daily for 2 weeks followed by rifampin plus a fluoroquinolone, TMP-SMX, a tetracycline or clindamycin for 3 or 6 months for hips and knees, respectively (**A-II**). Prompt debridement with device removal whenever feasible is recommended for unstable implants, late-onset infections, or in those with long duration (>3 weeks) of symptoms (**A-II**).

45. For early-onset spinal implant infections (≤30 days after surgery), or implants in an actively infected site, initial parenteral therapy plus rifampin followed by prolonged oral therapy is recommended (**B-II**). The optimal duration of parenteral and oral therapy is unclear; the latter should be continued until spine fusion has occurred (**B-II**). For late-onset infections (>30 days after implant placement), device removal whenever feasible is recommended (**B-II**).

46. Long-term oral suppressive antibiotics (eg, TMP-SMX, a tetracycline, a fluoroquinolone [which should be given in conjunction with rifampin due to the potential emergence of fluoroquinolone resistance, particularly if adequate surgical debridement is not possible], or clindamycin) with or without rifampin may be considered in selected cases, particularly if device removal not possible (**B-III**).

Pediatric considerations

47. For children with acute hematogenous MRSA osteomyelitis and septic arthritis, IV vancomycin is recommended (**A-II**). If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin 10–13 mg/kg/dose IV every 6–8 h (to administer 40 mg/kg/day) can be used as empirical therapy if the clindamycin resistance rate is low (eg, <10%) with transition to oral therapy if the strain is susceptible (**A-II**). The exact duration of therapy should be individualized, but typically a minimum 3–4-week course is recommended for septic arthritis and a 4–6-week course is recommended for osteomyelitis.

48. Alternatives to vancomycin and clindamycin include the following: daptomycin 6 mg/kg/day IV once daily (**C-III**) or linezolid 600 mg PO/IV twice daily for children ≥12 years of age and 10 mg/kg/dose every 8 h for children <12 years of age (**C-III**).

Evidence Summary

MRSA bone and joint infections arise from hematogenous seeding, a contiguous focus of infection, or direct inoculation from trauma or a medical procedure. Definitive therapy requires surgical debridement of necrotic bone or the joint space and drainage of adjacent abscesses, along with antimicrobial therapy [217, 218]. Current treatment strategies are based largely on noncomparative case series, case reports, and animal models and are extrapolated from those for MSSA infection. The optimal route of administration (parenteral vs oral vs initial parenteral therapy followed by oral therapy) has not been clearly established; this decision should be based on individual patient circumstances after weighing the pros and cons of each approach. Compared with oral therapy, parenteral therapy may offer the potential for better compliance, superior serum levels for certain drugs, and greater historical experience, although at increased expense, patient inconvenience, and potential for line-related complications (eg, infections, line malfunction, and thrombophlebitis).

Despite concerns about poor bone penetration and relative inefficacy in animal models, vancomycin remains the primary treatment of MRSA osteomyelitis [218–220]. Failure rates of up to 35%–46% have been reported [221–223], and compared with β-lactam therapy, patients with *S. aureus* osteomyelitis treated with vancomycin had a 2-fold higher recurrence rate [224]. These unsatisfactory responses to vancomycin have led some experts to recommend the addition of rifampin because of its excellent penetration into bone and biofilm [219]. In animal models of *S. aureus* osteomyelitis, therapy with rifampin combined with a second agent is more effective than is therapy with the companion agent given alone [120]. There are no controlled trials of MRSA osteomyelitis, but 2 small trials of MSSA osteomyelitis suggested higher cure rates were associated with receipt of rifampin combination therapy [73, 225]. Retrospective studies of rifampin-based regimens for MRSA osteomyelitis have yielded mixed results, with 1 study indicating cure rates of up to 80% [226]; however, 1 study showed no added benefit of rifampin if debridement occurred [227]. For patients with concurrent bacteremia, rifampin should be added to the treatment regimen after clearance of bacteremia. Daptomycin is a parenteral alternative to vancomycin. In a noncomparative study involving adults with osteomyelitis treated with daptomycin, clinical improvement was noted in ~90%, with better outcomes at 6 mg/kg/day than at lower dosages [228]. Daptomycin may have benefit when added to standard therapy in children with refractory invasive MRSA disease if osteomyelitis is present [184]. Susceptibility testing must be performed, because daptomycin-nonsusceptible isolates have been described in cases of treatment failure [42, 43, 229–231].

Oral therapies, administered as either primary or step-down therapy, appear to be suitable alternatives to prolonged parenteral therapy. In a randomized trial involving adult patients with chronic nonvertebral MSSA osteomyelitis, equivalent cure rates of ~90% were achieved for 8 weeks of oral TMP-SMX (7–8 mg/kg/day of TMP component) plus rifampin 600 mg once daily and a 6-week regimen of IV cloxacillin followed by 2 weeks of

oral therapy [86]; there are no data regarding TMP-SMX plus rifampin involving children with osteomyelitis. In another study of MSSA and MRSA osteomyelitis, similar outcomes were observed in those patients who received prolonged parenteral therapy and those who received oral step-down therapy (>50% of regimens included rifampin in combination with another agent) following initial parenteral therapy for 2 weeks [221]. Oral antibiotics that have been used following initial parenteral therapy for the treatment of osteomyelitis include the following: clindamycin, linezolid, fluoroquinolones, and doxycycline or minocycline with or without rifampin [221, 222, 226]. Clindamycin achieves good bone concentrations and is highly effective for treatment of non–critically ill children with MRSA osteomyelitis [34, 232]; there are limited data regarding its use in adults. Linezolid achieves good concentrations in infected bone; small case series involving adults and children with MRSA osteomyelitis, septic arthritis, or prosthetic joint infections suggest that it is effective [233–237]. Weekly monitoring of complete blood counts is recommended if therapy exceeds 2 weeks; an ophthalmologic examination should be performed at 1 month after therapy initiations, because optic neuritis may occur with prolonged treatment [119, 236, 237]. There are limited data regarding the use of tetracyclines for the treatment of *S. aureus* osteomyelitis [76, 226], and although fluoroquinolones may be effective, they should only be used in combination with rifampin because of the potential for the development of resistance.

The optimal duration of therapy for osteomyelitis is unknown. Antibiotic therapy for 8 weeks, compared with shorter durations, have been associated with improved outcomes in those with *S. aureus* osteomyelitis [226, 238], whereas undrained abscesses and inadequate debridement are associated with relapse rates of 30%–60%, which emphasizes the importance of surgical therapy [227, 239]. Some experts suggest oral consolidative treatment after a course of parenteral therapy for an additional 1–3 months and possibly longer for treatment of chronic infection, if debridement is not performed or if inflammatory markers, such as ESR and CRP level, remain elevated [222]. In a study of vertebral osteomyelitis, this approach yielded an 83% cure rate [226].

In a randomized study of staphylococcal prosthetic hip and knee joint infections (which included no infections due to MRSA) in patients with early-onset (<2 months after surgery) infections, stable implants, and < 3 weeks of symptoms, 3–6 months of rifampin-based combination therapy plus surgical debridement without device removal was found to be effective [72]. Rifampin dosing in studies of staphylococcal prosthetic joint infections is variable, ranging from 600 mg daily to 300–450 mg twice daily [72, 240, 241]. Debridement and device removal using a 2-stage exchange arthroplasty is recommended for late-onset infections, unstable implants, or a prolonged duration (>3 weeks) of symptoms [242]. For early-onset spinal implant infections (≤30 days of implant placement), 6 weeks of parenteral therapy followed by prolonged oral suppressive therapy until spine fusion resulted in improved outcomes [243]. For late-onset infections (>30 days after implant placement), implant removal was critical to success. For ankle fractures, 6 weeks of therapy after hardware removal appears to be effective [244].

Drainage and debridement of the intra-articular cavity is essential for effective treatment of septic arthritis [217]. In children, surgical debridement of the hips is recommended, whereas arthrocentesis may be adequate for other infected joints [245]. Although a randomized trial in children with septic arthritis demonstrated that 10 days of antibiotics was noninferior to 30 days of comparable therapy, only 35 episodes of *S. aureus* arthritis, none of which involved MRSA, were treated for 10 days; in 3 of these cases, therapy was extended to 20 days because of inadequate response [246]. Most experts suggest treating for 3-4 weeks and longer if contiguous osteomyelitis, noted in up to 30% of children, is present [245]. Clinical response should guide the decision to convert from parenteral to oral therapy; in one study, switching to oral therapy at 7 days, compared with switching at 18 days, resulted in similar outcomes [247].

VI. What is the management of MRSA infections of the CNS?

Meningitis

49. IV vancomycin for 2 weeks is recommended (**B-II**). Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg twice daily (**B-III**).

50. Alternatives include the following: linezolid 600 mg PO/IV twice daily (**B-II**) or TMP-SMX 5 mg/kg/dose IV every 8–12 h (**C-III**).

51. For CNS shunt infection, shunt removal is recommended and it should not be replaced until CSF cultures are repeatedly negative (**A-II**).

Brain abscess, subdural empyema, spinal epidural abscess

52. Neurosurgical evaluation for incision and drainage is recommended (**A-II**).

53. IV vancomycin for 4–6 weeks is recommended (**B-II**). Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg twice daily (**B-III**).

54. Alternatives include the following: linezolid 600 mg PO/IV twice daily (**B-II**) and TMP-SMX 5 mg/kg/dose IV every 8–12 h (**C-III**).

Septic Thrombosis of Cavernous or Dural Venous Sinus

55. Surgical evaluation for incision and drainage of contiguous sites of infection or abscess is recommended whenever possible (**A-II**). The role of anticoagulation is controversial.

56. IV vancomycin for 4–6 weeks is recommended (**B-II**). Some experts recommend the addition of rifampin 600 mg daily or 300–450 mg twice daily (**B-III**).

57. Alternatives include the following: linezolid 600 mg PO/IV twice daily (**B-II**) and TMP-SMX 5 mg/kg/dose IV every 8–12 h (**C-III**).

Pediatric considerations

58. IV vancomycin is recommended (**A-II**).

Evidence Summary

CNS infections caused by MRSA occur as a complication of a neurosurgical procedure, in association with a contiguous focus of infection, or hematogenously as a complication of bacteremia or infective endocarditis. Treatment is difficult because of the critical location of these infections and the blood brain barrier, which limits penetration of systemically administered antibiotics to the site of infection. Thus, surgical drainage of focal abscesses and removal of any foreign body, such as an infected shunt, should be performed whenever possible.

Resistance to multiple antibiotics and the inability of many antibiotics to achieve therapeutic concentrations in CSF severely limit the choices for antimicrobial therapy of MRSA CNS infections. CSF penetration of vancomycin is poor, approximately 1% and 5% for uninflamed and inflamed meninges, respectively, with maximum CSF concentrations of 2–6 μg/mL [248–250]. Linezolid has good CSF penetration, as high as 66%, with CSF peak and trough concentrations of 7–10 μg/mL and 2.5–6.0 μg/mL, respectively [251–253]. CSF penetration of TMP-SMX is similar for uninflamed and inflamed meninges, 13%–53% for TMP and 17%–63% for SMX; CSF concentrations are 1.9–5.7 μg/mL for TMP and 20–63 μg/mL for SMX after a 10 mg/kg/day dosage and a 50 mg/kg/day dosage, respectively [254, 255]. CSF penetration of rifampin is 22% and is similar for inflamed and noninflamed meninges, and bactericidal concentrations are achievable in CSF. A 600-mg dose in adults without inflamed meninges produced CSF concentrations of 0.57–1.24 μg/mL [70]. In a rabbit meningitis model, CSF penetration of daptomycin was 5%–6% with concentrations of 3.2–4.0 μg/mL; values were halved for uninflamed meninges [256, 257].

There are no prospective randomized trials on the treatment of MRSA infections of the CNS. Vancomycin has been the drug of choice, but outcomes have been very poor when it has been used as monotherapy [258, 259]. Because of the limited penetration of vancomycin across even inflamed meninges, concentrations in CSF (and presumably other CNS sites as well) may be marginal when the drug is administered intravenously at standard dosages. Because it achieves bactericidal concentrations in CSF, some experts recommend rifampin in combination with vancomycin for meningitis and other CNS infections, despite a paucity of clinical data demonstrating benefit of the combination [120, 260–262]. High-dose, continuous infusion of vancomycin may be considered in patients not responding to standard dosing methods. CSF penetration was increased and concentrations were almost doubled, compared with standard dosing, when vancomycin was administered as a 15 mg/kg loading dose, followed by continuous infusion of 50–60 mg/kg/day for patients with normal renal function [105]. The regimen was well tolerated, although nephrotoxicity has been associated with high doses [263]. Several case reports describe the successful use of linezolid [264–267], TMP-SMX [255, 268], and daptomycin [269] for the treatment of MRSA CNS infections, but additional research is needed to define their role in the management of such infections.

For meningitis in association with a CNS shunt, shunt removal with placement of an external ventricular drain is critical to therapy [270–273]. CSF cultures should be repeatedly negative prior to placement of a new shunt [273]. Retention of infected shunts is associated with a high failure rate despite administration of both intraventricular and systemic antibiotics [274]. Once the shunt has been removed, systemic antimicrobial therapy is usually effective. Although there are very limited data to guide use, intraventricular vancomycin [248, 275] or daptomycin [276] may be considered in patients who have ventricular access or who do not respond to systemic antimicrobial therapy.

Considerable controversy surrounds the use of systemic anticoagulation for septic cavernous or dural sinus thromboses because of the risk of intracranial hemorrhage [277, 278]. If anticoagulation is used, heparin should be used, because it is reversible, and imaging should be performed to exclude lesions predisposing to hemorrhage.

VII. What is the role of adjunctive therapies for the treatment of MRSA infections?

59. Protein synthesis inhibitors (eg, clindamycin and linezolid) and IVIG are not routinely recommended as adjunctive therapy for the management of invasive MRSA disease (**A-III**). Some experts may consider these agents in selected scenarios (eg, necrotizing pneumonia or severe sepsis) (**C-III**).

Evidence Summary

Specific recommendations regarding combination antibiotic therapy for individual disease entities are discussed in the respective sections of the text. This section will focus on the use of protein synthesis inhibitors and IVIG as adjunctive therapy. Data are insufficient to recommend for or against the use of protein synthesis inhibitors as adjunctive therapy of invasive disease caused by MRSA. Limited in vitro data suggest that clindamycin and linezolid inhibit production of staphylococcal toxic shock syndrome toxin type 1 and PVL [279–281] and that linezolid suppresses alpha- and beta-hemolysins, staphylococcal enterotoxin A and B, and protein A [282]. However,

clindamycin or linezolid in combination with vancomycin can be antagonistic in vitro [283–286], and vancomycin alone was more effective than vancomycin plus linezolid in a rabbit endocarditis model [287]. Existing clinical data are limited to case reports for patients with staphylococcal toxic shock syndrome [281] and necrotizing/cavitary pneumonia [205, 288], and additional studies are needed.

The role of IVIG in the management of invasive MRSA disease is even less clear. IVIG neutralizes staphylococcal exotoxins, including PVL [289], although staphylococcal superantigens and exotoxins are less efficiently inhibited by IVIG than by streptococcal superantigens [290]. Children with invasive disease have higher concentrations of antibody to PVL than do those with SSTIs [291]; it is unclear whether antibody to PVL in IVIG offers additional benefit. In fact, one study suggests that antibody to PVL may be detrimental [292]. Meta-analyses on the use of IVIG in sepsis and septic shock have indicated a mortality benefit, but no benefit was observed when only high-quality trials were included in the analyses [293–296]. Given the available data, IVIG is not recommended in the management of MRSA disease, although its use may be considered in children with severe MRSA sepsis [297].

VIII. What are the recommendations for vancomycin dosing and monitoring?

These recommendations are based on a consensus statement of the American Society of Health-System Pharmacists, the IDSA, and the Society of Infectious Diseases Pharmacists on guidelines for vancomycin dosing [3,4].

Adults

60. IV vancomycin 15–20 mg/kg/dose (actual body weight) every 8–12 h, not to exceed 2 g per dose, is recommended in patients with normal renal function (**B-III**).

61. In seriously ill patients (eg, those with sepsis, meningitis, pneumonia, or infective endocarditis) with suspected MRSA infection, a loading dose of 25–30 mg/kg (actual body weight) may be considered. (Given the risk of red man syndrome and possible anaphylaxis associated with large doses of vancomycin, one should consider prolonging the infusion time to 2 h and use of an antihistamine prior to administration of the loading dose.) (**C-III**).

62. Trough vancomycin concentrations are the most accurate and practical method to guide vancomycin dosing (**B-II**). Serum trough concentrations should be obtained at steady state conditions, prior to the fourth or fifth dose. Monitoring of peak vancomycin concentrations is not recommended (**B-II**).

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (**B-II**).

64. For most patients with SSTI who have normal renal function and are not obese, traditional doses of 1 g every 12 h are adequate and trough monitoring is not required (**B-II**).

65. Trough vancomycin monitoring is recommended for serious infections and patients who are morbidly obese, have renal dysfunction (including those receiving dialysis), or have fluctuating volumes of distribution (**A-II**).

66. Continuous infusion vancomycin regimens are not recommended (**A-II**).

Pediatric considerations

67. Data are limited to guide vancomycin dosing in children. IV vancomycin 15 mg/kg/dose every 6 h is recommended in children with serious or invasive disease (**B-III**).

68. The efficacy and safety of targeting trough concentrations of 15–20 μg/mL in children requires additional study but should be considered in those with serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (ie, necrotizing fasciitis) (**B-III**).

Evidence Summary

Vancomycin doses of 15–20 mg/kg/day every 8–12 h are recommended for adult patients on the basis of actual body weight and are adjusted for the patient's estimated creatinine clearance, not to exceed 2 g per dose. Weight-based dosing is particularly important in obese patients, who are likely to be underdosed when conventional dosing strategies of 1 g every 12 h are used. Some experts suggest vancomycin loading doses for serious suspected or documented MRSA infections (sepsis, meningitis, pneumonia, or endocarditis) to enable early achievement of target trough concentrations, although clinical data are lacking [298, 299]. A vancomycin loading dose of 25 mg/kg was found to be safe in a small study [300]. Because of the lack of a clear benefit over intermittent dosing, and because time >MIC is not the primary predictor of efficacy [301–303], continuous infusion vancomycin is not recommended.

The pharmacodynamic parameter that best predicts efficacy of vancomycin is the ratio of the area under the curve (AUC) to the MIC (AUC/MIC) [304–306]. A single study involving patients with *S. aureus* lower respiratory tract infections reported that an AUC/MIC ⩾400, compared with an AUC/MIC <400, was associated with improved clinical response and microbiologic eradication [307]. In a study involving patients with MRSA health care–associated pneumonia, mean trough vancomycin levels of 9.4 μg/mL and 20.4 μg/mL correlated with a mean AUC (± standard deviation) of 318 ± 111 μg·h/mL and 418 ± 152 μg·h/mL, respectively, although no association between trough concentrations and clinical response was observed [308]. Additional studies are needed to verify the target AUC/MIC ⩾400 but, on the basis of currently available data, vancomycin trough concentrations of 15–20 μg/mL are needed to achieve this target

if the MIC of the organism is ≤1 μg/mL. The probability of achieving target AUC/MIC of >400 is 100% for vancomycin MIC of 0.5 μg/mL and 0% for MIC value of 2 μg/mL even if aggressive dosing strategies are used [298]. In patients with normal renal function, up to 3–4 g/day of vancomycin may be required to attain target AUC/MIC.

Measuring trough serum concentrations, which are predictive of AUC/MIC, is the most practical means of monitoring vancomycin. Vancomycin trough concentrations <10 μg/mL have been associated with treatment failures, perhaps attributable to variable penetration into tissue compartments and selection of vancomycin-heteroresistant *S. aureus* (hVISA) [309]. Clinical data to support higher target troughs are limited. A trough ≥15 μg/mL has not clearly been associated with improved outcomes [310] [311], duration of bacteremia, or mortality [308, 312]. However, to optimize vancomycin pharmacodynamics, improve tissue penetration, and minimize selection of resistant strains, the Panel suggests targeting higher trough concentrations for serious infections due to MRSA. For less serious infections, including most SSTIs, traditional dosing in the adult patient with normal renal function and weight is likely to be adequate on the basis of excellent clinical response rates without a more aggressive dosing strategy [50, 136, 138, 313, 314]. Higher vancomycin doses and trough concentrations may be associated with increased nephrotoxicity [263, 311, 315, 316] and high-frequency hearing loss in older patients [317]. Such investigations are limited by small sample sizes, retrospective design, and co-administration of other nephrotoxic agents. Clearly, additional prospective studies are needed, particularly because higher dosing strategies are implemented.

There are limited data to guide vancomycin dosing in children with MRSA. Pharmacodynamic data suggest that higher dosages (60 mg/kg/day) are required to achieve AUC/MIC >400 for isolates with a vancomycin MIC ≤1 μg/mL [318], but additional research is needed. A loading dose of 20–25 mg/kg may be considered in seriously ill children. The efficacy and safety of targeting trough concentrations of 15–20 μg/mL for invasive infections in children have not been studied but should be considered in serious infections, such as bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (ie, necrotizing fasciitis). Vancomycin nephrotoxicity is more common with concomitant aminoglycoside use [319].

IX. How should results of vancomycin susceptibility testing be used to guide therapy?

69. For isolates with a vancomycin MIC ≤2 (eg, susceptible according to CLSI breakpoints), the patient's clinical response should determine the continued use of vancomycin, independent of the MIC **(A-III).**

i. If the patient has had a clinical and microbiologic response to vancomycin, then it may be continued with close follow-up

ii. If the patient has not had a clinical or microbiologic response to vancomycin despite adequate debridement and removal of other foci of infection, an alternative to vancomycin is recommended regardless of MIC.

70. For isolates with a vancomycin MIC >2 μg/mL (eg, VISA or VRSA), an alternative to vancomycin should be used **(A-III).**

Evidence Summary

The emergence of hVISA, VISA and VRSA poses an additional challenge to use of this drug. Although these strains are relatively uncommon, they are associated with vancomycin treatment failures and poor outcomes [235, 309, 320, 321]. As a result, MIC breakpoints were lowered by the CLSI in 2006 from ≤4 μg/mL to ≤2 μg/mL for susceptible strains, with MICs of 4–8 μg/mL and ≥16 μg/mL now indicating intermediate and resistant strains, respectively. Detection of these strains—in particular, hVISA, in which a small, resistant subpopulation of cells is present—remains a limitation of susceptibility testing methods [322–324]. The current "gold standard" for hVISA detection is population analysis profile (PAP) divided by the AUC; however, this method is labor-intensive and impractical for the clinical laboratory [325, 326]. Several less laborious tests, including the macrodilution Etest, Etest glycopeptide resistance detection, and Mueller-Hinton agar with 5 mg/L teicoplanin, are more sensitive and specific for hVISA detection than are other methods [322, 327–329], although the optimal assay most predictive of outcomes is unclear. Given current limitations, testing for hVISA is not routinely recommended. For patients with an isolate with a vancomycin MIC of 2 μg/mL, particularly those patients with limited or no clinical response to vancomycin therapy, an alternate method, such as Etest, should be performed to improve detection of VISA [330].

In recent years, several centers have observed an "MIC creep" among MRSA isolates characterized as susceptible by CLSI criteria [331, 332], with the principle concern being the gradual loss of vancomycin activity, because clinical failures appear to be more common among those with MIC values of 2 μg/mL than among those with MIC values <2 μg/mL [95, 310, 311, 333, 334]. To date, no alternate regimens have been clearly shown to result in better clinical outcomes in those patients with isolates with vancomycin MICs of 2 μg/mL. In addition, data regarding the presence or absence of "MIC creep" is conflicting and has not been confirmed by other groups [335–338]. In a large multicenter study, the frequency of MRSA isolates with an MIC >1 μg/mL as determined by reference broth microdilution ranged from 1.6%–3.7% and was primarily attributable to clonal dissemination of a USA100 strain with reduced susceptibility to vancomycin [338].

Interpretation of these data is further complicated by limitations in currently available susceptibility testing methods and

the considerable variability in MIC results, depending on the method used. One challenge is that acceptable variability for MIC methods is ± 1 doubling dilution [339], which makes it difficult to distinguish between an MIC of 1 versus 2 μg/mL. Etest, MicroScan, and BD-Phoenix report MIC values that are higher than those reported by reference broth microdilution, overcalling susceptible strains as intermediate in some cases, whereas the Sensititre and Vitek 2 systems tend to undercall resistance [330]. In one study, up to 98% of MICs were reported as 1.5 or 2 μg/mL by Etest, but when CLSI broth dilution method was used, only 3% of isolates were found to have a vancomycin MIC of 2 μg/mL [340]. Because Etest and other methods have a tendency to report MIC results that are higher than those reported by reference broth microdilution, it is unknown whether the "MIC creep" represents a true phenomenon, whether it is a technical artifact that depends on the test method used, or whether it applies to a few institutions as a result of clonal spread. The existence or extent of "MIC creep" for pediatric MRSA isolates is not well characterized. In one children's hospital, an increase in the vancomycin MIC for *S. aureus* isolates was observed with Etest but not with broth microdilution testing [341]. Because current susceptibility testing methods are unable to reliably distinguish MICs of 1 μg/mL from MICs of 2 μg/mL, the Panel recommends evaluation of the patient's clinical and microbiologic response along with MIC results when making decisions regarding therapy.

X. What is the management of persistent MRSA bacteremia and vancomycin treatment failures in adult patients?

71. A search for and removal of other foci of infection, drainage or surgical debridement is recommended **(A-III).**

72. High-dose daptomycin (10 mg/kg/ day), if the isolate is susceptible, in combination with another agent (e.g. gentamicin 1 mg/kg IV every 8 h, rifampin 600 mg PO/IV daily or 300-450 mg PO/IV twice daily, linezolid 600 mg PO/IV BID, TMP-SMX 5 mg/kg IV twice daily, or a beta-lactam antibiotic) should be considered (**B-III**).

73. If reduced susceptibility to vancomycin and daptomycin are present, options may include the following: quinupristin-dalfopristin 7.5 mg/kg/dose IV every 8 h, TMP-SMX 5 mg/kg/dose IV twice daily, linezolid 600 mg PO/IV twice daily, or telavancin 10 mg/kg/dose IV once daily **(C-III)**. These options may be given as a single agent or in combination with other antibiotics.

Evidence Summary

Clinical or microbiological failures occur in a substantial proportion of invasive MRSA infections treated with vancomycin. Persistent bacteremia and relapse are common among patients with infective endocarditis [171] and account for 17% of the vancomycin failures in a randomized trial [49]. Persistent bacteremia is associated with worse clinical outcomes [171, 342]. Vancomycin treatment failures have been attributed to the drug's slow bactericidal activity, emergence of strains with reduced susceptibility to vancomycin, possible enhanced virulence of CA-MRSA, and inadequate debridement or retained prosthetic device. Yet, at this time, no alternative agent or regimen has proven to be superior to vancomycin in achieving clinical cure or sterilizing blood cultures, which poses a challenge to the management of such infections.

The point at which the patient should be considered to have experienced treatment failure and alternative therapy sought is a complex issue. Because the median time to clearance of MRSA bacteremia is 7–9 days [49, 172], most experts agree that persistent bacteremia at or around day 7 of therapy should prompt an assessment to determine whether a change in therapy is indicated. Several factors should be considered, including the following: (1) the patient's overall clinical response; (2) vancomycin trough serum concentrations; (3) results of susceptibility testing; and (4) the presence of and ability to remove other foci of infection. The decision to modify therapy and the time frame at which this occurs may vary depending on the clinical scenario. Although modification of therapy should generally be considered if the patient is persistently bacteremic after 1 week of vancomycin therapy, the threshold to change therapy may be earlier if the patient's clinical condition is worsening despite adequate debridement and removal of other foci of infection or if the vancomycin MIC is 2 μg/mL, particularly in septic or critically ill patients. On the other hand, no immediate change in therapy may be indicated if the patient is clinically responding and the vancomycin MIC is <2 μg/mL; in many cases, the bloodstream will clear with continued vancomycin therapy.

In general, when constructing an alternate regimen in the setting of vancomycin treatment failure in adult patients, the Panel recommends a change in therapy rather than the addition of other agents (eg, rifampin and gentamicin) to vancomycin. Among the possible choices, daptomycin has the most rapidly bactericidal activity [343, 344], although the use of daptomycin to treat patients who have not responded to vancomycin requires special consideration. Isolates with vancomycin MICs ≥ 2 μg/mL may have daptomycin MICs in the nonsusceptible range (>1 μg/mL) and in vitro exposure to vancomycin may select for higher daptomycin MICs [47, 48, 179, 345–347]. Persistent bacteremia and clinical failures with daptomycin have been associated with daptomycin MICs >1 μg/mL [49, 348]. The 10-mg/kg dose, which appears to be safe [178], is recommended on the basis of limited in vitro evidence that suggests that higher doses may suppress the emergence of resistance [179–181] and some clinical data that indicates the potential efficacy of daptomycin at 10 mg/kg/day in clearing complicated MRSA bacteremia due to strains with a daptomycin MIC of 2 μg/mL [349].

Although there are no clinical data, and although additional study is needed, some experts suggest the use of daptomycin in combination with another agent, such as gentamicin administered at a dosage of 1 mg/kg every 8 h, rifampin, or both drugs if the strain is susceptible to both [96, 181, 350, 351]. Synergy has been described in vitro and in animal models between daptomycin and gentamicin [96, 181, 350–352], daptomycin and rifampin [351, 353], and among all 3 drugs [351], although one study suggests that the combination of daptomycin and rifampin may be antagonistic [354]. Once-daily gentamicin at 5 mg/kg may be an alternative to traditional dosing and has a lower risk of nephrotoxicity [355].

There are even less data to guide the management of patients with isolates that are nonsusceptible to both vancomycin and daptomycin and who are experiencing failure of therapy [324]. Quinupristin-dalfopristin has been used successfully as salvage therapy in patients with vancomycin treatment failure [65], although response rates were lower for patients with endocarditis and bacteremia of unknown source [64]. TMP-SMX is bactericidal in vitro, it but was inferior to vancomycin for the treatment of *S. aureus* infections, although all treatment failures occurred among those with MSSA infection, whereas all patients with MRSA infection were cured [90]. Thymidine release from damaged host cells and bacteria may limit the efficacy of folate antagonists, so caution should be exercised when using TMP-SMX for the treatment of serious *S. aureus* infections [356]. Some experts suggest the addition of gentamicin or rifampin if TMP-SMX is used in salvage therapy. The combination of daptomycin and trimethoprim-sulfamethoxazole had rapid bactericidal activity compared to daptomycin alone for a daptomycin non-susceptible strain in an in vitro study [371]. Linezolid has been used with some success in several series either alone or in combination with other agents (eg, rifampin, fusidic acid, gentamicin, amikacin, and carbapenem), but outcomes for patients with left-sided endocarditis have been poor [235, 357–360]. Of note, rifampin may decrease linezolid levels when given in combination via an unclear mechanism [361–363]. There is one case report of persistent MRSA bacteremia in a patient with tricuspid valve endocarditis that was successfully treated with telavancin [364]. The combination of vancomycin plus a β-lactam has been shown to be synergistic in vitro and in vivo for VISA and VRSA [365, 366], although additional clinical studies are needed. More recently, similar observations have been seen with daptomycin in combination with a β-lactam for treatment of infection due to daptomycin nonsusceptible strains [367]. Hopefully, newer compounds that are under development for the treatment of MRSA infections will provide more effective alternatives in the future.

Data are insufficient to guide the management of persistent MRSA bacteremia in children, and the decision regarding use of alternate or combination therapy should be individualized.

XI. What is the management of MRSA infections in neonates?

Neonatal pustulosis

74. For mild cases with localized disease, topical treatment with mupirocin may be adequate in full-term neonates and young infants (**A-III**).

75. For localized disease in a premature or very low-birthweight infant or more-extensive disease involving multiple sites in full-term infants, IV vancomycin or clindamycin is recommended, at least initially, until bacteremia is excluded (**A-II**).

Neonatal MRSA sepsis

76. IV vancomycin is recommended, dosing as outlined in the Red Book (**A-II**).

77. Clindamycin and linezolid are alternatives for non-endovascular infections (**B-II**).

Evidence Summary

For neonates with localized pustulosis, clinical experience suggests that topical mupirocin alone may be effective, although parenteral antibiotic therapy is recommended for more-extensive disease. Lumbar puncture is not necessary in a full-term infant <30 days of age with localized pustulosis with no signs or symptoms of sepsis [368]. Vancomycin is the primary treatment for serious MRSA infections in the neonatal period. There are limited data on the potential benefit of combination therapy with rifampin, gentamicin, or daptomycin in neonatal staphylococcal sepsis [184, 369]; the decision to use combination therapy should be individualized. Experience with clindamycin and linezolid for serious neonatal MRSA infections is limited, but these drugs may be considered for treatment of patients with susceptible isolates who have nonendovascular infections [29, 370]. TMP-SMX is not recommended during the immediate neonatal period because of increased risk of kernicterus.

RESEARCH GAPS

The initial step in developing a rational clinical research agenda is the identification of gaps in information. The process of guideline development, as practiced by the IDSA, serves as a natural means by which such gaps are identified. Thus, the guidelines identify important clinical questions and identify the quality of evidence supporting those recommendations. Clinical questions identified by guideline authors and members of the IDSA Research Committee that could inform a MRSA research agenda are included below.

Bacteremia and Endocarditis

What is the role of echocardiography, and does it improve outcome? Should it be performed routinely in all patients with *S. aureus* bacteremia or only in certain subsets? Should the

preferred modality be TEE or is a transthoracic examination sufficient in certain cases?

How extensive should the work-up be to identify occult foci of metastatic infection? Is a symptoms-and-signs based approach sufficient, or is there a minimal panel of studies that should be performed?

What is the optimal initial therapy? Should vancomycin be the first drug of choice for empirical therapy? Should the patient also receive a β-lactam antibiotic to cover for methicillin-susceptible strains pending susceptibility test data?

What is the optimal therapy once susceptibility test results are available? What is the optimal therapy for patients with metastatic foci of infection? Is there any role for combination therapy?

What regimens should be used in treating persistent or relapsing infection? What duration of persisting bacteremia signals a need for a change in antibiotic therapy? What alternative antibiotic regimens should be used? What is the role of combination therapy? What susceptibility test methods and breakpoint best predict treatment failure, particularly for vancomycin? Should strains with a vancomycin MIC of 2 μg/mL be considered to be nonsusceptible, and if so, what test should be used to determine MIC? Does infection by so-called hVISA strains predict treatment failure, and if so, what are the optimal tests for detecting these strains?

What is the optimal duration of therapy? Is rapid clearance of bacteremia an indicator that an abbreviated course of antibiotic therapy is sufficient? Are there subsets of patients for whom shorter courses of therapy (ie, less than the generally accepted minimum of 14 days) would be effective? What is the role of biological markers (eg, C-reactive protein or procalcitonin) in determining duration of therapy? What is the optimal duration of therapy for patients with metastatic foci of infection?

Osteomyelitis

What is the optimal therapy? What is the importance of bactericidal therapy and antimicrobial bone penetration in the management of osteomeylitis? What is the efficacy of oral versus parenteral therapy? Is oral step-down therapy an alternative to prolonged parenteral therapy? Is there any benefit of targeting higher vancomycin troughs in osteomyelitis? What are alternatives to vancomycin for the management of osteomyelitis caused by MRSA strains with elevated vancomycin MICs? What is the role of rifampin combination therapy? Does early surgical intervention improve outcome?

What is the optimal management of hardware-associated infections?

What is the optimal duration of therapy? How best should laboratory markers of inflammation (ESR and CRP level) be used to guide therapy?

SSTI

What is the optimal management of nonpurulent cellulitis? What is the microbiology of nonpurulent cellulitis (eg, cellulitis with no purulent drainage or exudate and no associated abscess) in the era of CA-MRSA? Is initial empirical coverage for MRSA necessary?

What is the optimal management of abscesses? Is there any additional benefit of antibiotics, particularly with regard to impact on recurrent infections and household transmission?

What is optimal management for recurrent SSTIs? What is the pathogenesis of recurrent SSTIs? What is the nature of the interplay between the pathogen, host colonization, and the environment? Is decolonization effective in preventing recurrent SSTI? If so, what are the appropriate regimens? What specific environmental hygiene measures should be taken to prevent recurrent SSTI and household transmission?

PERFORMANCE MEASURES

1. The management of all MRSA infections should include identification, elimination and/or debridement of the primary source and other sites of infection when possible (eg, drainage of abscesses, removal of central venous catheters, and debridement of osteomyelitis).

2. In patients with MRSA bacteremia, follow-up blood cultures 2–4 days after initial positive cultures and as needed thereafter are recommended to document clearance of bacteremia.

3. To optimize serum trough concentrations in adult patients, vancomycin should be dosed according to actual body weight (15–20 mg/kg/dose every 8–12 h), not to exceed 2 g per dose. Trough monitoring is recommended to achieve target concentrations of 15–20 μg/mL in patients with serious MRSA infections and to ensure target concentrations in those who are morbidly obese, have renal dysfunction, or have fluctuating volumes of distribution. The efficacy and safety of targeting higher trough concentrations in children requires additional study but should be considered in those with severe sepsis or persistent bacteremia.

4. When an alternative to vancomycin is being considered for use, in vitro susceptibility should be confirmed and documented in the medical record.

5. For MSSA infections, a β-lactam antibiotic is the drug of choice in the absence of allergy.

Acknowledgments

The Expert Panel wishes to express its gratitude to Drs. Gordon Archer, Frank Lowy, and Brad Spellberg for their thoughtful reviews of earlier drafts of the guideline. The Expert Panel also recognizes the following for their important contributions in identifying critical gaps where funding of research is needed to advance clinical treatment and care: William Burman, David M. Margolis, and Louis B. Rice (IDSA Research Committee), Stanley

C. Deresinski (IDSA SPGC), and Padma Natarajan (IDSA staff). The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. IDSA.

Potential conflicts of interest. H.F.C. has received honoraria and research grants and has served as a consultant to Cubist, Ortho-McNeil, Pfizer, Theravance, and Targanta. S. E. C. has received honoraria from Forest and RibX, has served as a consultant for Merck and has received research support from Astellas, Cubist and AdvanDx. R.D. has received research funding from Pfizer, Clorox, Sanofi Pasteur, Sage, and GeneOhm. S.L.K. has received grant funding from Pfizer, has served as MRSA Leadership Advisor to Pfizer, and is participating in a pediatric daptomycin study. A.W.K. has received honoraria and grants from Cubist Pharmaceuticals, Merck, Wyeth, and Pfizer and has served as a consultant for Cubist Pharmaceuticals, Theravance, Astellas, Pfizer, Merck, and Ortho-McNeil and has owned stock from Cubist Pharmaceutical, Pfizer, and Johnson and Johnson. D.P.L. has received research support from Cubist, Johnson & Johnson, and Theravance and has served as a speaker for Cubist. B.E.M. has served as a consultant and received research support from Johnson & Johnson, Astellas, Pfizer, Cubist, Theravance, Targanta, Sanofi-Aventis, Vicuron Pharmaceuticals, and Wyeth-Ayerst. M.R. has received grants and or has served as a consultant speaker for the Pfizer, Cubist, Theravance/Astellas, Targanta, and Johnson & Johnson. D.A.T. has served on the advisory board to Pfizer, Ortho-McNeil, Astellas, Schering-Plough, and Replidyne. All other authors: no conflicts.

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