

IDSA Guidelines on the Treatment of MRSA Infections in Adults and Children

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The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States continues to increase, with more than 94,000 cases of invasive disease reported in 2005. Illnesses caused by MRSA include skin and soft-tissue infections, bacteremia and endocarditis, pneumonia, bone and joint infections, central nervous system disease, and toxic shock and sepsis syndromes. The Infectious Diseases Society of America (IDSA) has released its first evidence-based guidelines on the treatment of MRSA infections. In addition to common clinical syndromes, the guidelines address treatment with vancomycin, limitations of susceptibility testing, and alternative therapies.

Skin and Soft-Tissue Infections in Community-Associated MRSA

Simple abscesses or boils may be managed with incision and drainage alone; more data are needed on the use of antibiotics in this setting. Antibiotics are recommended for patients who have abscesses associated with severe or extensive disease (e.g., multiple sites of infection) or rapid progression in the presence of associated cellulitis; signs and symptoms of systemic illness; associated comorbidities or immunosuppression; very young or very old age; abscesses in areas difficult to drain (e.g., face, hand, genitalia); associated septic phlebitis; or lack of response to

incision and drainage alone. Empiric therapy for five to 10 days is recommended pending culture results for outpatients with purulent cellulitis. Infection from β -hemolytic streptococci does not usually require empiric therapy. For those with nonpurulent cellulitis, five to 10 days of empiric therapy for β -hemolytic streptococcal infection is recommended, based on the patient's clinical response. Empiric coverage for community-associated MRSA is recommended in patients who do not respond to beta-lactam antibiotics, and also may be considered in those with systemic toxicity.

Oral antibiotic options for treating skin and soft-tissue infections in patients with community-associated MRSA include clindamycin, trimethoprim/sulfamethoxazole (TMP/SMX; Bactrim, Septra), a tetracycline (doxycycline or minocycline [Minocin]), and linezolid (Zyvox). Options for treating both β -hemolytic streptococci and community-associated MRSA include clindamycin alone, TMP/SMX or a tetracycline in combination with a beta-lactam antibiotic (e.g., amoxicillin), or linezolid alone. Rifampin is not recommended for use as a single agent or adjunctive therapy.

For hospitalized patients with complicated skin and soft-tissue infections (i.e., deeper soft-tissue infections, surgical or traumatic wound infection, major abscesses, cellulitis, or infected ulcers and burns), empiric therapy for MRSA should be considered pending culture results, in addition to surgical debridement and broad-spectrum antibiotics. Empiric therapy options include intravenous vancomycin, linezolid (600 mg orally or intravenously twice per day), daptomycin (Cubicin; 4 mg per kg intravenously once per day), telavancin (Vibativ; 10 mg per kg intravenously once per day), or clindamycin (600 mg

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intravenously or orally three times per day). A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with nonpurulent cellulitis. MRSA-active therapy may be modified if there is no clinical response. Treatment for seven to 14 days is recommended, but should be individualized to the patient's clinical response. Cultures from abscesses and other purulent infections are recommended in patients who have received antibiotic therapy, those with severe local infection or signs of systemic illness, and those who have not responded adequately to initial treatment. Cultures are also recommended if there is concern of a cluster or outbreak.

CHILDREN

In children with minor skin infections (e.g., impetigo) or secondarily infected lesions (e.g., eczema, ulcers, lacerations), treatment with mupirocin 2% topical cream (Bactroban) is recommended. Tetracyclines are not recommended for children younger than eight years. Vancomycin is recommended in hospitalized children. If the child is stable without ongoing bacteremia or intravascular infection, empiric therapy with clindamycin (10 to 13 mg per kg intravenously every six to eight hours for a total of 40 mg per kg per day) is an option if the resistance rate is less than 10 percent. If the strain is susceptible, transition to oral therapy is advised. Linezolid may be considered as an alternative (600 mg orally or intravenously twice per day for children 12 years and older; 10 mg per kg orally or intravenously every eight hours for children younger than 12 years).

Recurrent MRSA Skin and Soft-Tissue Infections

Physicians should provide instructions on personal hygiene and wound care for patients with skin and soft-tissue infections. Patients should cover draining wounds with clean, dry bandages. Regular bathing is advised, as well as hand washing with soap and water or an alcohol-based hand gel, especially after touching infected skin or an item that has been in contact with a draining wound. Patients should also avoid reusing or sharing items that have touched infected skin (e.g., disposable razors, linens, towels). Commercially available cleaners or detergents should be used to clean high-touch surfaces (e.g., doorknobs, counters, bathtubs, toilet seats) that may come in contact with bare skin or uncovered infections.

Decolonization may be considered if a patient develops a recurrent infection despite good personal hygiene and wound care, or if other household members develop infections. Strategies for decolonization include nasal decolonization with mupirocin twice per day for five to 10 days, or nasal decolonization with mupirocin twice per day for five to 10 days plus topical body decolonization with a skin antiseptic solution (e.g., chlorhexidine

[Peridex]) for five to 14 days or dilute bleach baths. Dilute bleach baths can be made with 1 teaspoon of bleach per 1 gallon of water (or one-fourth cup per one-fourth bathtub or 13 gallons of water) and are given for 15 minutes twice per week for three months. Oral antimicrobial therapy is recommended only for treating active infection and is not routinely recommended for decolonization. An oral agent in combination with rifampin, if the strain is susceptible, may be considered if infections recur despite these measures.

If household or interpersonal transmission is suspected, patients and contacts should be instructed to practice personal and environmental hygiene measures. In symptomatic contacts, nasal and topical body decolonization strategies may be considered after treating the active infection. Decolonization strategies also may be considered in asymptomatic household contacts. The role of cultures in managing recurrent skin and soft-tissue infections is limited. Screening cultures before decolonization are not routinely recommended if at least one of the previous infections was caused by MRSA. Surveillance cultures after a decolonization regimen are not routinely recommended if there is no active infection.

MRSA Bacteremia and Infective Endocarditis

BACTEREMIA AND INFECTIVE ENDOCARDITIS, NATIVE VALVE

Uncomplicated bacteremia is defined as positive blood culture results and the following: exclusion of endocarditis; no implanted prostheses; follow-up blood cultures performed on specimens obtained two to four days after the initial set that do not grow MRSA; defervescence within 72 hours of initiating effective therapy; and no evidence of metastatic sites of infection. Recommended treatment for adults with uncomplicated bacteremia includes vancomycin or daptomycin at a dosage of 6 mg per kg intravenously once per day for at least two weeks. For adults with complicated bacteremia (positive blood culture results without meeting criteria for uncomplicated bacteremia), four to six weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin (8 to 10 mg per kg intravenously once per day).

For adults with infective endocarditis, intravenous vancomycin or daptomycin (6 mg per kg intravenously once per day for six weeks) is recommended. Some experts recommend higher dosages of daptomycin (8 to 10 mg per kg intravenously once per day). Adding gentamicin or rifampin to vancomycin is not recommended in patients with bacteremia or native valve infective endocarditis. A clinical assessment to identify the source and extent of the infection with elimination and/or debridement of other sites of infection is ►

recommended. Additional blood cultures two to four days after initial positive cultures and as needed thereafter are recommended to document clearance of bacteremia. Echocardiography is recommended for all adults with bacteremia. Transesophageal echocardiography is preferred over transthoracic echocardiography. Evaluation for valve replacement surgery is recommended if any of the following are present: large vegetation (greater than 10 mm in diameter), occurrence of one or more embolic events during the first two 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.

INFECTIVE ENDOCARDITIS, PROSTHETIC VALVE

Patients with infective endocarditis and a prosthetic valve should be treated with intravenous vancomycin and rifampin (300 mg orally or intravenously every eight hours for at least six weeks), plus gentamicin (1 mg per kg intravenously every eight hours for two weeks). Early evaluation for valve replacement surgery is recommended.

CHILDREN

In children, intravenous vancomycin (15 mg per kg every six hours) is recommended for treating bacteremia and infective endocarditis. The duration of therapy may range from two to six weeks depending on the source, the presence of endovascular infection, and metastatic foci of infection. Data regarding the safety and effectiveness of alternative agents in children are limited, although daptomycin (6 to 10 mg per kg intravenously once per day) may be an option. Clindamycin and linezolid should not be used if there is concern of infective endocarditis or an endovascular source of infection, although they may be considered in children with bacteremia that rapidly clears and is not related to an endovascular focus. Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. The decision to use combination therapy should be individualized. Echocardiography is recommended in children with congenital heart disease, bacteremia lasting more than two to three days, or other clinical findings suggestive of endocarditis.

MRSA Pneumonia PNEUMONIA

Empiric therapy for MRSA is recommended, pending sputum and/or blood culture results, for hospitalized patients with severe community-acquired pneumonia defined by one of the following: a requirement for

admission to the intensive care unit, necrotizing or cavitary infiltrates, or empyema. Treatment options for health care-associated MRSA or community-associated MRSA pneumonia include seven to 21 days of intravenous vancomycin or linezolid, or clindamycin (600 mg orally or intravenously three times per day) if the strain is susceptible. In patients with MRSA pneumonia complicated by empyema, antimicrobial therapy should be used with drainage procedures.

CHILDREN

In children, intravenous vancomycin is recommended for treating MRSA pneumonia. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin (10 to 13 mg per kg intravenously every six to eight hours for a total of 40 mg per kg per day) can be used as empiric therapy if the clindamycin resistance rate is low (e.g., less than 10 percent). Patients can be transitioned to oral therapy if the strain is susceptible. Linezolid is an alternative option.

MRSA Bone and Joint Infections OSTEOMYELITIS

The mainstay of therapy for osteomyelitis is surgical debridement with drainage of associated soft-tissue abscesses. 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 patient circumstances. Antibiotic options for parenteral administration include intravenous vancomycin and daptomycin (6 mg per kg intravenously once per day). Antibiotic options with parenteral and oral routes of administration include the following: TMP/SMX (4 mg per kg [TMP component] twice per day) in combination with rifampin (600 mg once per day), linezolid, and clindamycin (600 mg every eight hours). Some experts recommend adding oral rifampin (600 mg per day, or 300 to 450 mg twice per day) to the chosen antibiotic. For patients with concurrent bacteremia, rifampin should be added after bacteremia has cleared.

The optimal duration of therapy for MRSA osteomyelitis is unknown, although a minimum of eight weeks is recommended. Some experts suggest an additional one to three 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 based on susceptibilities. Magnetic resonance imaging with gadolinium is the imaging modality of choice for detecting early osteomyelitis and associated soft-tissue disease. Measuring erythrocyte sedimentation rate, C-reactive protein level, or both may help guide the response to therapy.

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SEPTIC ARTHRITIS

Drainage or debridement of the joint space should be performed. For patients with septic arthritis, the antibiotic choices for osteomyelitis are recommended; a three- to four-week course of therapy is suggested.

DEVICE-RELATED OSTEOARTICULAR INFECTIONS

For patients with early-onset (less than two months after surgery) or acute hematogenous prosthetic joint infections involving a stable implant with short duration of symptoms (three weeks or less) and debridement (but device retention), parenteral therapy should be initiated (see antibiotic recommendations for osteomyelitis) plus rifampin (600 mg per day, or 300 to 450 mg orally twice per day for two weeks), followed by rifampin plus a fluoroquinolone, TMP/SMX, a tetracycline, or clindamycin for three months for hips and six months for knees. Prompt debridement with device removal is recommended for unstable implants or late-onset infections, or in patients with more than three weeks of symptoms.

For early-onset spinal implant infections (30 days or less after surgery) or implants in an actively infected site, initial parenteral therapy plus rifampin followed by prolonged oral therapy is recommended. The optimal duration of parenteral and oral therapy is unclear; oral therapy should be continued until spinal fusion has occurred.

For late-onset infections (more than 30 days after surgery), device removal is recommended. Long-term oral suppressive antibiotics (e.g., TMP/SMX, a tetracycline, a fluoroquinolone in conjunction with rifampin, clindamycin) with or without rifampin may be considered, particularly if device removal is not possible.

CHILDREN

Vancomycin is recommended in children with acute hematogenous MRSA osteomyelitis and septic arthritis. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin (10 to 13 mg per kg intravenously every six to eight hours for a total of 40 mg per kg per day) can be used as empiric therapy if the resistance rate is low (e.g., less than 10 percent), with transition to oral therapy if the strain is susceptible. The duration of therapy should be individualized, but a minimum of three to four weeks is recommended for patients with septic arthritis, and four to six weeks for patients with osteomyelitis. Daptomycin (6 mg per kg intravenously once per day) and linezolid are alternative therapies.

MRSA Infections of the Central Nervous System MENINGITIS

The recommended treatment for patients with meningitis is intravenous vancomycin for two weeks. Some experts recommend adding rifampin (600 mg per day,

or 300 to 450 mg twice per day). Alternatives include linezolid or TMP/SMX (5 mg per kg intravenously every eight to 12 hours). Shunt removal is recommended in cases of central nervous system shunt infection, and the shunt should not be replaced until cerebrospinal fluid cultures are repeatedly negative.

BRAIN ABSCESS, SUBDURAL EMPYEMA, AND SPINAL EPIDURAL ABSCESS

Neurosurgical evaluation for incision and drainage is recommended for patients with brain abscess, subdural empyema, or spinal epidural abscess. Recommended treatment is intravenous vancomycin for four to six weeks. Some experts recommend adding rifampin. Alternatives include linezolid and TMP/SMX.

SEPTIC THROMBOSIS OF CAVERNOUS OR DURAL VENOUS SINUS

Surgical evaluation for incision and drainage of contiguous sites of infection or abscess is recommended. The role of anticoagulation is controversial. Recommended treatment is intravenous vancomycin for four to six weeks. Some experts recommend adding rifampin. Alternatives include linezolid and TMP/SMX.

CHILDREN

Children with MRSA infections of the central nervous system should be treated with intravenous vancomycin.

Adjunctive Therapies for the Treatment of MRSA Infections

Protein synthesis inhibitors (e.g., clindamycin, linezolid) and intravenous immune globulin are not routinely recommended as adjunctive therapy for the management of invasive MRSA disease, although they may be considered in certain scenarios (e.g., necrotizing pneumonia, severe sepsis).

Vancomycin Dosing and Monitoring

Recommendations for vancomycin dosing are based on a consensus statement of the American Society of Health-System Pharmacists, the IDSA, and the Society of Infectious Diseases Pharmacists.

ADULTS

In patients with normal renal function, intravenous vancomycin (15 to 20 mg per kg every eight to 12 hours) is recommended, but should not exceed 2 g per dose. In seriously ill patients (e.g., those with sepsis, meningitis, pneumonia, or infective endocarditis) with suspected MRSA infection, a loading dose of 25 to 30 mg per kg may be considered. Because of the risk of red man syndrome and possible anaphylaxis associated with large doses of

vancomycin, physicians should consider prolonging the infusion time to two hours and giving an antihistamine before administering the loading dose.

Use of trough vancomycin concentrations is the most accurate and practical method to guide vancomycin dosing. Serum trough concentrations should be obtained at steady state conditions, before the fourth or fifth dose. Monitoring peak vancomycin concentrations is not recommended. Vancomycin trough concentrations of 15 to 20 mcg per mL are recommended in patients with serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, or severe skin and soft-tissue infections (e.g., necrotizing fasciitis) caused by MRSA. For most patients with skin and soft-tissue infections who have normal renal function and are not obese, traditional dosages of 1 g every 12 hours are adequate, and trough monitoring is not required. Trough vancomycin monitoring is recommended for patients with serious infections or who are morbidly obese, have renal dysfunction (including those receiving dialysis), or have fluctuating volumes of distribution. A regimen of continuous infusion is not recommended.

CHILDREN

Data on vancomycin dosing in children are limited. The recommended treatment is vancomycin (15 mg per kg intravenously every six hours) in children with serious or invasive disease. The effectiveness and safety of targeting trough concentrations of 15 to 20 mcg per mL in children require additional study, but should be considered in those with serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, or severe skin and soft-tissue infections.

Vancomycin Susceptibility Testing for Guiding Therapy

For isolates with a vancomycin minimal inhibitory concentration of 2 mcg per mL or less (e.g., susceptible according to Clinical and Laboratory Standards Institute breakpoints), the patient's clinical response should dictate the continued use of vancomycin, independent of the minimal inhibitory concentration. If the patient has had a previous clinical and microbiologic response to vancomycin, it may be continued with close follow-up. If the patient has not responded to vancomycin therapy

despite adequate debridement and removal of other foci of infection, an alternative agent is recommended. For isolates with a vancomycin minimal inhibitory concentration greater than 2 mcg per mL (e.g., vancomycin-intermediate *S. aureus*, vancomycin-resistant *S. aureus*), an alternative agent should be prescribed.

Persistent MRSA Bacteremia and Vancomycin Treatment Failures in Adults

A search for and removal of other foci of infection, drainage, or surgical debridement is recommended. High-dose daptomycin (10 mg per kg per day), if the isolate is susceptible, in combination with another agent (e.g., gentamicin, rifampin, linezolid, TMP/SMX, a beta-lactam antibiotic) should be considered. If reduced susceptibility to vancomycin and daptomycin is present, alternative treatment options include dalbapristin/quinupristin (Synercid; 7.5 mg per kg intravenously every eight hours), TMP/SMX, linezolid, or telavancin. These may be given as a single agent or in combination with other antibiotics.

MRSA Infections in Neonates NEONATAL PUSTULOSIS

For mild cases of pustulosis with localized disease, topical treatment with mupirocin may be adequate in full-term neonates and young infants. For localized disease in a premature or very low-birth-weight infant or more extensive disease involving multiple sites in full-term infants, intravenous vancomycin or clindamycin is recommended until bacteremia is excluded.

NEONATAL MRSA SEPSIS

Recommended treatment of neonatal MRSA sepsis is intravenous vancomycin, with dosing as outlined in *Red Book*. Clindamycin and linezolid are alternative treatments for nonendovascular infections. ■

Answers to This Issue's CME Quiz

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|----------|----------------|----------------|
| Q1. D | Q5. A, B, C, D | Q8. A, B, C, D |
| Q2. B | Q6. D | Q9. A |
| Q3. A, B | Q7. B | Q10. D |
| Q4. A | | |