Staphylococcus aureus

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LEARNING OBJECTIVES

1. Evaluate patients for signs of epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.
2. Justify the use of diagnostic tests to detect antibiotic resistance in *S. aureus.*
3. Develop patient-specific diagnostic and antibiotic treatment plans using infection-specific *S. aureus* epidemiology.
4. Develop antibiotic treatment strategies for MRSA infections using patient- and infection-specific information and available scientific evidence.

ABBREVIATIONS IN THIS CHAPTER

BMD	Broth microdilution
BSI	Bloodstream infection
CAP	Community-acquired pneumonia
CLSI	Clinical and Laboratory Standards Institute
DNS	Daptomycin nonsusceptible
GAS	Group A streptococci
HAP	Hospital-acquired pneumonia
hVISA	Heterogeneous vancomycin-intermediate *Staphylococcus aureus*
IE	Infective endocarditis
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NVO	Native vertebral osteomyelitis
PK/PD	Pharmacokinetics/pharmacodynamics
SSTI	Skin and soft tissue infection
VISA	Vancomycin-intermediate *Staphylococcus aureus*

Table of other common abbreviations.

INTRODUCTION

General Epidemiology and Burden of *S. aureus*

Staphylococcus aureus remains a public health threat to patients around the world in all settings. Data from 477 hospitals reported nearly 20,000 deaths among more than 119,000 cases of *S. aureus* bloodstream infections in 2017 (Kourtis 2019). More worrisome is the prevalence of methicillin-resistant *S. aureus* (MRSA) in many regions; it was first reported in the 1960s, when *S. aureus* acquired methicillin (oxacillin) resistance, thereby rendering all β-lactams ineffective (Barber 1961). About 40% of all clinical *S. aureus* isolates obtained from more than 400 centers worldwide from 1997 to 2016 were MRSA (Diekema 2019). More contemporary U.S. data from 2015 to 2017 suggest that MRSA constituted more than 57% of S. aureus bloodstream isolates (Sader 2018). The WHO estimates that MRSA prevalence exceeds 50% in most countries—including the United States—and reaches nearly 80% in African and western Pacific Ocean regions (WHO 2014). Although not designated as at the highest threat level, the CDC estimated that MRSA accounted for 323,700 cases of hospitalized patients, with the higher prevalence levels in the southern states (CDC 2019). Methicillin-resistant *S. aureus* remains the leading cause of death (from antibiotic-resistant infections) and was responsible for more than 10,000 deaths in 2017 (CDC 2019). Collectively, MRSA infections likely exceed $1.7 billion in health care costs (CDC 2019).

DIAGNOSTIC TESTS TO DETECT ANTIBIOTIC RESISTANCE IN *S. AUREUS*

Diagnostic testing to detect antibiotic resistance in *S. aureus* is essential to maximize patient outcomes and antimicrobial stewardship. The two primary functions of such diagnostic tests are to identify the organism and to determine the isolate's antibiotic susceptibility. When receiving patient specimens, clinical microbiology

labs use multiple tests as part of a coordinated workflow to provide clinicians with quick and comprehensive diagnostic information about potential infection.

Gram stains cannot directly detect antibiotic resistance but can greatly aid in antibiotic treatment decisions. Knowledge of intrinsic *S. aureus* antibiotic susceptibilities and local resistance epidemiologies such as antibiograms enables clinicians to alter antibiotic therapy based on Gram stains. Coagulase-positive gram-positive cocci in clusters on Gram stain usually give the first diagnostic information signifying *S. aureus* infection. Gram stain results are available for clinicians 12–36 hours after sample collection. The presence of *S. aureus* is confirmed after Gram stain using an *S. aureus*-selective agar, PCR, or another advanced, rapid-diagnostic test.

Isolate-specific antibiotic susceptibility is determined immediately after identification of *S. aureus* in clinical specimens. The gold standard for measuring antibiotic susceptibility is nonautomated BMD. Minimum inhibitory concentrations of clinically important antibiotics are determined and compared with antibiotic susceptibility breakpoints set by various agencies based on epidemiologic, pharmacodynamic, and clinical outcomes data to determine whether the isolate is susceptible to a particular antibiotic. Broth microdilution requires an additional 24 hours of incubation after Gram stain, and so, results are unavailable for 48–72 hours after culture collection. Broth microdilution is not used in clinical microbiology lab workflows because it is labor-intensive.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Antibiotic spectrum of activity
- Antibiotic mechanism of action
- Antibiotic pharmacokinetics/pharmacodynamics
- Common and serious antibiotic adverse reactions

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Tong SY, Davis JS, Eichenberger E, et al. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603-61.
- Ortwine JK, Bhavan K. Morbidity, mortality, and management of methicillin-resistant *S. aureus* bacteremia in the USA: update on antibacterial choices and understanding. Hosp Pract (1995) 2018;46:64-72.

Several FDA-approved automated susceptibility testing (AST) platforms are available. Because they are less laborious and more cost-efficient than BMD, they represent the most commonly used method for MIC testing in clinical microbiology labs. The automated susceptibility testing of MIC results still requires initial incubation of clinical specimens, and MIC results are usually unavailable for more than 48 hours from culture. Despite frequent essential agreement with BMD (i.e., MIC result within +/- one $\log_2$ dilution), AST variability relative to BMD is sometimes differential (i.e., overestimated or underestimated more often). In contrast, BMD misclassification is usually nondifferential around the true MIC. A study involving AST of *S. aureus* isolates with a BMD vancomycin MIC of 1 mg/L found that MicroScan WalkAway's prompt and turbidity methods overestimated the MIC to be 2 mg/L 74.1% and 29.7% of the time, respectively, but underestimated the MIC less than 1% of the time (Rybak 2013). In *S. aureus* isolates with BMD vancomycin MICs of 2 mg/L, the BD Phoenix system underestimated the MIC to be 1 mg/L 76% of the time and overestimated the MIC only 4% of the time, whereas the VITEK 2 system underestimated the MIC 20% of the time and overestimated the MIC 12% of the time. Although the clinical significance of a vancomycin MIC of 2 mg/L is still inconclusive, vancomycin MIC has implications for dosing and therapeutic drug monitoring. The variability of commonly used AST platforms—coupled with the fact that more than 90% of clinical *S. aureus* isolates in the world have vancomycin MICs equal to or less than 1 mg/L—is why the recommendations in the 2020 vancomycin therapeutic monitoring guidelines for MRSA infections assume an infecting isolate MIC of 1 mg/L.

Agar diffusion is another alternative to BMD that is often used to determine antibiotic MIC in clinical microbiology labs. The Etest is the most commonly used agar diffusion method for measuring antibiotic MIC of *S. aureus* isolates. The Etest strip is an antibiotic-impregnated strip that has an increasing antibiotic concentration gradient from bottom to top. An Etest can provide more-detailed MIC results than BMD can, with each antibiotic concentration threshold increasing by 50% (e.g., an increase from 1 to 1.5 mg/L) rather than doubling (e.g., an increase from 1 to 2 mg/L). However, when reporting, many clinical microbiology labs round the result up to the nearest $\log_2$ dilution (e.g., 1.5 mg/L is reported at 2 mg/L). Etest MIC results are usually one half to one $\log_2$ dilution greater than BMD results. But despite the overestimation, the Etest is regularly used at some institutions as a conservative estimate of vancomycin MIC for serious MRSA infections based on evidence indicating patients with MRSA bloodstream infections caused by isolates with a vancomycin MIC equal to or more than 1.5 mg/L may be at increased risk of vancomycin failure and death (van Hal 2012). It is unclear why that relationship between vancomycin MIC and outcome is not observed when automated susceptibility testing methods are used, but it may be a result of the increased variability of AST results (Kalil 2014). When available, an Etest can also

be useful for newer antibiotics that have not been added to AST platforms (e.g., ceftaroline).

Numerous rapid diagnostic tests have emerged in recent decades that facilitate quicker pathogen identification and/or reveal antimicrobial susceptibility (see feature on rapid diagnostic testing). Many tests can rapidly identify *S. aureus* and/or detect methicillin resistance. Methods of identifying *S. aureus* from a positive subculture of clinical specimens such as peptic nucleic acid fluorescent in situ hybridization have been shown to reduce time to appropriate antibiotic therapy in patients with *S. aureus* bloodstream infections (Schweizer 2010). Methods of detecting methicillin-resistance presence via the *mecA* gene—such as PCR (e.g., Xpert MRSA/*S. aureus* assay) or nanoparticle probes (e.g., Verigene gram-positive blood culture assay)—can also reduce time to appropriate and/or optimal antibiotic therapy for *S. aureus* bloodstream infection by alerting the clinician the isolate is MRSA before susceptibility tests become available. The use of a rapid diagnostic test appears to be most effective when coupled with antimicrobial stewardship programs (Timbrook 2017). Together these interventions can reduce mortality in patients with bloodstream infections, including those caused by *S. aureus* (Timbrook 2017, Wenzler 2017).

There are additional nontraditional diagnostic tests relevant to antibiotic susceptibility in *S. aureus*. The clindamycin D test can test for inducible clindamycin resistance in strains that are erythromycin resistant but clindamycin susceptible (CLSI 2020) . This agar diffusion test places an erythromycin-impregnated disc close to the left of a clindamycin-impregnated disk on agar inoculated with the strain in question. If inducible clindamycin resistance is present, erythromycin will strongly induce the inducible macrolide-lincosamide-streptogramin B (MLSB) phenotype, resulting in clindamycin resistance and bacterial growth in the region where erythromycin and clindamycin diffusion overlaps. Because clindamycin is a weaker inducer of the inducible MLSB phenotype, the clindamycin-only diffusion region will not induce resistance, and bacterial growth is still effectively inhibited. This results in a zone of inhibition shaped like a capital letter *D* and signifies a positive D test (Figure 1), suggesting high likelihood of treatment failure if clindamycin is used to treat the infection (Steward 2005).

Another potentially important antibiotic susceptibility phenotype in *S. aureus* that cannot be measured with traditional antimicrobial susceptibility testing is the hVISA phenotype. Testing for hVISA is not typically done in the clinical setting because of the suspected low prevalence in most clinical settings and laborious testing methodologies (Howden 2010, Leonard 2009, Wootton 2001, Zhang 2015). The gold standard for hVISA testing is the modified population-analysis-profile (PAP) method (Wootton 2001), which involves isolation of increasingly less-susceptible subpopulations of *S. aureus* by plating the strain on multiple vancomycin-impregnated agar

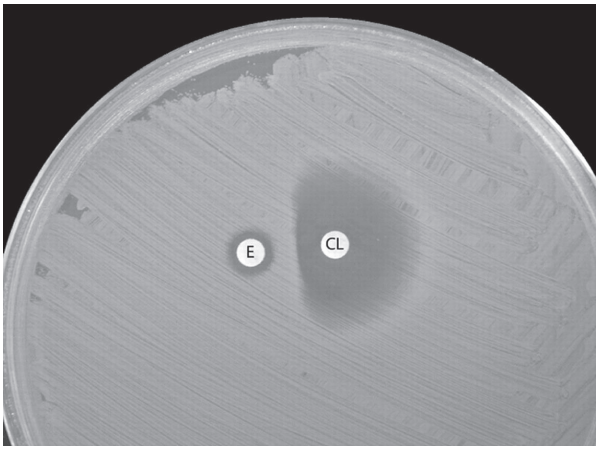

Figure 1. Positive D test; E, erythromycin; CL, clindamycin.

Reprinted with permission from: Levin TP, Suh B, Axelrod P, et al. Potential clindamycin resistance in clindamycin-susceptible, erythromycin-resistant *Staphylococcus aureus*: report of a clinical failure. Antimicrob Agents Chemother 2005;49:1222-4.

plates with increasing vancomycin concentrations. The bacterial growth concentration from each plate is plotted, and the area under the resulting curve (PAP-AUC) is compared with the PAP-AUC of the reference hVISA strain mu 3. A strain of *S. aureus* with a PAP-AUC of more than or equal to 90% of the PAP-AUC of mu 3 is considered to exhibit the hVISA phenotype (Wootton 2001). The glycopeptide resistance detection Etest and the macromethod Etest are less labor-intensive compared with the PAP method but are less sensitive to hVISA detection and still too labor- and resource intensive for routine clinical use (Howden 2010, Leonard 2009). A novel method using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry coupled with machine learning was recently shown to differentiate VISA/hVISA strains from susceptible strains with an overall accuracy of 89% in a small pilot study (Mather 2016).

INFECTIONS ASSOCIATED WITH MRSA – SKIN AND SOFT TISSUE INFECTIONS

Epidemiology

S. aureus is a major skin and soft tissue infection (SSTI) pathogen (Stevens 2014), which is especially true for purulent SSTIs such as cutaneous abscesses, furuncles, and carbuncles. It is estimated that upwards of 75% of cutaneous abscesses are caused by *S. aureus* (Moran 2017). In addition, *S. aureus* is commonly isolated from wound infections—especially surgical-site infections—as well as diabetic foot infections. Evidence suggests *S. aureus* is uncommon among nonpurulent cellulitises,

the vast majority of which are caused by GAS (Stevens 2014). However, patients often present with mixed abscess cellulitis or purulent cellulitis in which an abscess cannot be identified. Such cellulitis cases tend to have bacteriologies similar to those of cutaneous abscesses, including high prevalence of *S. aureus*. Antibiotic-resistant *S. aureus* is also common in SSTIs. The major resistance phenotype that dictates choices of antistaphylococcal antibiotic therapy in SSTIs is MRSA. The prevalence of MRSA in the United States is high and varies from 30% to 70% (CDC 2015). Because of that high but variable MRSA prevalence, both over- and underprescribing of anti-MRSA therapy for SSTIs is common in practice.

Treatment

Treatment recommendations from the Infectious Diseases Society of America (IDSA) reflect the high prevalence of *S. aureus* in purulent SSTIs. Empiric coverage of *S. aureus*, including MRSA, is indicated for all patients with purulent SSTIs (abscess, furuncle, carbuncle) who are deemed candidates for antibiotic therapy (Stevens 2014). Because the addition of antibiotic therapy to abscess incision and drainage does not improve cure or clinical outcome in most patients, current IDSA guidelines recommend only adjunctive systemic antibiotic therapy in patients with moderate or severe SSTIs. The IDSA guidelines define moderate infections as those occurring in patients with systemic signs or symptoms of infection, such as temperature of more than 38°C or less than 36°C, white blood cell count of more than 12,000 or less than 4000 cells/mcL, heart rate of more than 90 beats/minute, or respiratory rate of more than 24 breaths/minute. The guidelines define patients with severe infections as patients with the same systemic signs of infection listed for moderate severity or patients who are immunocompromised or for whom initial incision and drainage plus oral antibiotics have failed. Those guideline criteria do not clearly delineate the difference between moderate and severe infection. The decision to provide intravenous therapy for a severe infection is based on clinical judgment in practice. Antibiotic therapy should also be considered in patients with multiple abscesses, in patients at extremes of age, or when incision and drainage is not possible.

Empiric antibiotic regimens for purulent SSTI should include MRSA coverage (Box 1) (Stevens 2014). Antibiotic choice should, ideally, be informed by antibiogram or local surveillance data. Initial oral therapy is recommended for moderate infections and intravenous therapy for moderate or severe infections. Vancomycin should generally be the preferred intravenous therapy unless the patient is unable to tolerate vancomycin because of allergy or adverse reaction. No currently available antibiotic has been conclusively shown superior to vancomycin for SSTI, including SSTI caused by *S. aureus* or MRSA. Limited data indicate that certain newer antibiotics—such as linezolid, daptomycin, and ceftaroline—may improve cure and/or be more cost-effective relative to vancomycin (Davis 2007, Trinh 2019, Zhang 2019). Dalbavancin and oritavancin are new single-dose intravenous therapies with MRSA activity that may also be promising options that avoid unnecessary hospitalization and reduce cost in selected patients requiring intravenous therapy but not needing intensive inpatient monitoring (Lodise 2016). However, clinical data demonstrating widespread use and benefits of this strategy in SSTI are currently lacking, and identification of patients most likely to benefit from such a strategy can be challenging (Lodise 2019).

Empiric antibiotic therapy should be narrowed to pathogen-directed antibiotic therapy based on microbiologic testing results when available (Stevens 2014). Culture and susceptibility testing is recommended for all moderate and severe purulent SSTIs. Culture and susceptibility testing is not always performed routinely, and empiric treatment often extends for the entire treatment duration. For MRSA infections, continuation of empiric anti-MRSA therapy with the agents listed in Box 1 is warranted. Patients initially treated with intravenous antibiotics may be transitioned to oral antibiotic therapy once clinical stability and SSTI improvement have been achieved. In purulent SSTI cases in which antibiotic therapy is indicated, a 5- to 10-day treatment duration is recommended (Stevens 2014).

Box 1. Antibiotic Treatments for MRSA Skin and Soft Tissue Infections

Intravenous

Ceftaroline 600 mg every 8–12 hours[a]
Clindamycin 600 mg every 8 hours
Dalbavancin 1500 mg 1 dose[a] or 1000 mg x 1 dose, then 500 mg x 1 dose 1 week later[a]
Daptomycin 4–6 mg/kg every 24 hours[a]
Linezolid 600 mg every 12 hours
Oritavancin 1200 mg x 1 dose
Tedizolid 200 mg daily
Telavancin 10 mg/kg every 24 hours[a]
Vancomycin 15 mg/kg every 12 hours[b]

Oral

Clindamycin 300–450 mg four times a day
Doxycycline 100 mg twice daily
Linezolid 600 mg every 12 hours
Minocycline 100 mg twice daily
Tedizolid 200 mg daily
Trimethoprim/sulfamethoxazole 160–320 mg (trimethoprim component) orally twice daily[a]

[a]Requires dose adjustment in patients with renal impairment.

[b]Consider patient-specific dosing with or without therapeutic drug monitoring targeting trough concentration 10–20 mg/L or AUC 400–600 mg*h/L.

Information from: Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:e10-52.

Coverage of *S. aureus* is not routinely recommended in nonpurulent cellulitis because it is not a common pathogen (Stevens 2014). Coverage of MRSA for cellulitis is recommended under circumstances involving presence of abscess or purulence, cellulitis associated with penetrating trauma or injection-drug use, concurrent MRSA infection or colonization, severe infection as defined by the presence of systemic inflammatory-response-syndrome criteria, or severe immunocompromise. The anti-MRSA antibiotics in Box 1 that are reliably active and effective against GAS may be used.

In patients with surgical-site infections who give evidence of systemic response to infection, empiric coverage of *S. aureus* (see Box 1) is routinely recommended in addition to suture removal and evacuation of infected material (Stevens 2014). Coverage of MRSA is recommended in selected patients with high MRSA risk, including MRSA nasal colonization, prior MRSA infection, recent hospitalization, or recent antibiotic therapy (Stevens 2014). Culture and susceptibility testing of infected material is also recommended in surgical-site infection and can be used for guiding antibiotic therapy (Stevens 2014).

Similarly, empiric coverage of *S. aureus* is routinely recommended in patients with diabetic foot infections (DFIs) (see Box 1) (Lipsky 2012). Coverage of MRSA is recommended in patients with severe DFIs or those with high MRSA risk, including those with MRSA colonization, those with prior MRSA infection, and those in regions with high MRSA prevalence, where more than 30%–50% of *S. aureus* are MRSAs. Culture and susceptibility testing is recommended in DFIs and is especially important for guiding antibiotic therapy given the fact that DFIs are often polymicrobial in nature and have high prevalence of gram-negative and antibiotic-resistant organisms.

BONE/JOINT INFECTIONS

Epidemiology

Staphylococcus aureus is the most common pathogen in adults with bone and joint infections. Bone infection occurs by way of hematogenous or contiguous spread, the latter being more common in adults and more likely polymicrobial in nature. Hematogenous spread accounts for 20% of adult osteomyelitis, wherein NVO is one of the most common presentations. Contiguous spread often occurs after a trauma (e.g., open fractures), progressive soft tissue infection (e.g., diabetic foot osteomyelitis), or direct inoculation during a surgical procedure (e.g., prosthetic joint infection after hip and knee arthroplasty).

In a single-center study at a level I trauma site, *S. aureus* constituted 56% of fracture fixation osteomyelitis, and 58% of the *S. aureus* isolates were MRSA (Torbert 2015). Local MRSA prevalence should be considered when determining the most likely pathogens. Timing of infection onset relative to known inciting events (e.g., orthopedic surgery, grade of open fractures) may also provide insight on likelihood of MSSA versus MRSA. The heterogeneity of bone infections (e.g., acute versus chronic) and joint infections makes it difficult to accurately estimate the disease burden. However, higher recurrence likelihood and complications (e.g., decreased bone mineral density and fragile bones) represent substantial comorbid conditions that also reduce patients' quality of life.

Treatment

Complex bone and joint infections often require a combination of surgery and prolonged systemic antibiotics together with local antibiotics in certain cases. The overarching principle is to obtain cultures (e.g., bone biopsy or intraoperative fluid aspirate) *prior to* empiric antibiotic initiation in otherwise hemodynamically stable patients, because false-negative blood or biopsy cultures are common when obtained *after* antibiotic initiation. Parenteral antibiotics or oral antibiotics with high bioavailability and bone tissue penetration are preferred. Treatment is needed for several weeks. It is expected that empiric antibiotics would be revised to target organisms in positive cultures.

Patients should be screened for epidemiological risk factors for MRSA (e.g., MRSA bacteremia in the year preceding persistent back pain that has been unresponsive to conventional treatment; recent trauma; or surgery) prior to empiric therapy selection. Local MRSA prevalence is also an important consideration. Given that most bone and joint infections are caused by *S. aureus* and that upwards of 50% are MRSA, empiric treatment should consist of MRSA-active antibiotics. Results from the Oral versus Intravenous Antibiotics for Bone and Joint Infection Trial observed no difference in treatment failure at one year between those who received intravenous antibiotics versus oral antibiotics (with high bioavailability) during the first 6 weeks (Li 2019).

Native Vertebral Osteomyelitis

The IDSA NVO guidelines currently recommend empiric glycopeptide and β-lactam combination to cover MRSA, and gram-negative bacilli when empiric therapy is warranted (Berbari 2015). Withholding of empiric antibiotic therapy is recommended so as to wait for microbiologic diagnosis in neurologically and hemodynamically stable patients. Nearly 50% of NVO cases also require surgical debridement, and the presence of a large epidural abscess on imaging is one of several indications for surgical intervention. Targeted MRSA treatment options include vancomycin or daptomycin and other alternatives for 6 weeks (Table 1). Some experts say an additional 3 months of oral antibiotics for MRSA NVO can minimize treatment failures in this high-risk group, but only limited evidence supports that recommendation, and the risks and benefits must be weighed. Oral trimethoprim/sulfamethoxazole should not be used for staphylococcal NVO. Oral clindamycin can be considered for susceptible MRSA isolates. Oral doxycycline is more commonly used for NVO

Table 1. Targeted Antibiotic Treatment for NVO Caused by MRSA

Regimen	Dose and route	Duration (weeks)	Comments
Preferred (first-line)			
Vancomycin	IV targeting AUC_{24} 400–600 mg*h/L[a]	6	Consider a loading dose
Alternative			
Daptomycin	6-8 mg/kg IV Q24H[a]	6	Consider 8–10 mg/kg to optimize PK/PD
Linezolid	600 mg IV or PO Q12H	6	Great oral bioavailability
Levofloxacin plus rifampin	Levofloxacin: 500–750 mg PO Q24H[a] Rifampin: 600 mg PO Q24H	6	Check MRSA susceptibility first, and consider whether risks with fluoroquinolones outweigh the benefits

[a]Requires dose adjustment in patients with renal impairment.

AUC_{24} = 24-hour area under the concentration-time curve; IV = intravenous; NVO = native vertebral osteomyelitis; PO = orally; Q12H = every 12 hours; Q24H = every 24 hours.

Information from: Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis 2015;61:e26-46.

Table 2. Targeted Treatment for Methicillin-Resistant *Staphylococcus aureus* Diabetic Foot Osteomyelitis

Infection severity	Duration	Intravenous options	Oral options
No residual infected tissue (e.g., amputation)	2–5 days	Vancomycin, daptomycin, linezolid	TMP/SMX, doxycycline
Residual infected soft tissue but not bone	1–3 weeks		
Residual infected bone but viable[a]	4–6 weeks		
Residual dead bone postoperatively—or no surgery[a]	6 weeks		

[a]For more severe infections, may consider starting with an intravenous course for 1 week and then transition to oral options.

IV = intravenous; PO = oral; TMP/SMX = trimethoprim/sulfamethoxazole

Information from: Lipsky BA, Aragon-Sanchez AJ, Diggle M, et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev 2016;32 Suppl 1:45-74; Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:e132-73.

from other organisms (e.g., brucellosis). Shorter courses of intravenous therapy (e.g., 2 weeks) and then transition to oral antibiotics is a reasonable option.

Diabetic Foot Osteomyelitis

Empiric antibiotics for suspected diabetic foot osteomyelitis must cover *S. aureus* (Lipsky 2012, 2016). It is inferred that MRSA risk factors for diabetic foot infections be assessed as part of empiric coverage (refer to the SSTI section). Recommended anti-MRSA antibiotic treatment options are listed in Table 2. There is no consensus on treatment duration, which depends largely on infection severity (i.e., presence of residual infected or necrotic bone and soft tissue). Inflammatory marker trends (e.g., c-reactive protein, erythrocyte sedimentation rate, white blood cell count), radiologic improvements, and resolution of soft tissue infection should be the indicators of when to stop antibiotics. Careful monitoring for adverse effects associated with prolonged daptomycin, linezolid, and vancomycin is required. There is limited evidence with clindamycin for severe infections, but clindamycin can be considered when the isolate is clindamycin susceptible and lacks inducible clindamycin resistance. International guidelines also recommend fluoroquinolones, but the benefits must be weighed against the many adverse-event and antibiotic-resistance risks associated with fluoroquinolones.

Prosthetic Joint Infections

Empiric treatment with an anti-MRSA antibiotic consists of assessing epidemiological and patient factors. Antibiotic selection and duration depend on the prosthesis, and empiric therapy consists of either vancomycin or daptomycin in combination with rifampin for potential biofilms on the implant. Recommended antibiotic regimens for prosthetic joint infections caused by MRSA are listed in Table 3. Surgical debridement is recommended, and in certain cases, device removal is necessary.

Table 3. Treatment Durations for Methicillin-Resistant *Staphylococcus aureus* Prosthetic Joint Infections

Infection onset	Initial regimen	Long-term regimen	Duration
Early (<2 months after surgery) Stable implant but with ≤3 weeks of symptoms	Vancomycin or daptomycin plus rifampin PO for 2 weeks	Rifampin PO plus a fluoroquinolone, TMP/SMX, a tetracycline, or clindamycin	• Hip: 3 months • Knee: 6 months
Early spinal implant (≤30 days after surgery) or implant is in active infection site	Vancomycin or daptomycin plus rifampin PO	Rifampin PO plus a fluoroquinolone, TMP/SMX, a tetracycline, or clindamycin	Unknown
Late spinal implant (>30 days after surgery)	Device removal is recommended and long-term suppressive therapy PO is recommended in certain cases—especially if device removal is not possible		

PO = orally; TMP/SMX = trimethoprim/sulfamethoxazole.

Information from American Academy of Orthopaedic Surgeons. Diagnosis and Prevention of Periprosthetic Joint Infections Clinical Practice Guideline. 2019.

PNEUMONIA

Epidemiology

S. aureus is a common cause of pneumonia. It is the causative pathogen in approximately 15%–20% of HAP cases and 20%–30% of VAP cases (Kalil 2016). In contrast, *S. aureus* accounts for only 1%–5% of CAP (Metlay 2019). Because of a decreasing incidence of *S. pneumoniae* as a result of vaccination, *S. aureus* is constituting a larger percentage of community-acquired bacterial pneumonia cases compared with historical data. Thus, *S. aureus* makes up an important portion of community-acquired bacterial pneumonia as the third or fourth leading bacterial pathogen. Methicillin-resistant *S. aureus* represents a minority of *S. aureus* CAP and is associated with specific risk factors.

Treatment

Most of the empiric antibiotic treatment regimens for CAP are not constructed with MRSA coverage explicitly in mind. Specific risk factor indications for MRSA coverage are listed in Table 4 (Metlay 2019). For patients with those risk factors, the addition of vancomycin or linezolid to regular CAP antibiotics is recommended in the inpatient setting. Guidelines acknowledge that some outpatients may require MRSA coverage based on those risk factors, but no specific antibiotic agents are recommended. Oral linezolid is the most-evidence-based anti-MRSA option to add to CAP antibiotic regimens for outpatients—given the wealth of evidence supporting linezolid for MRSA pneumonia in the inpatient setting and linezolid's 100% oral bioavailability. Guidelines recommend obtaining sputum and blood cultures in patients with CAP who have MRSA risk factors. Nasal swab PCR tests for MRSA are also recommended to guide antibiotic therapy in such patients. The negative predictive value of a negative MRSA nasal swab is high—especially among patients with CAP when MRSA is uncommon. Thus, MRSA coverage can be de-escalated in patients with CAP in response to a negative nasal swab—especially in patients with nonsevere CAP and those with negative culture results. Empiric antibiotic regimens for HAP and VAP are recommended to routinely cover *S. aureus* but not always MRSA. Indications for empiric MRSA coverage in HAP/VAP are listed in Table 4. Vancomycin or linezolid is recommended for patients meeting these criteria.

Recommended directed treatments for MRSA pneumonia are listed in Table 5. Vancomycin or linezolid is recommend as first-line treatment based on evidence from four randomized trials that compared vancomycin and linezolid and indicated similar survival between the two treatments (Kalil 2016). Patient-specific factors and antimicrobial stewardship principles should be applied in selecting between those agents. Based on low drug acquisition cost and low vancomycin resistance rates despite decades of heavy use, vancomycin should be generally preferred to linezolid for most patients to preserve linezolid susceptibility. Vancomycin should also be preferred in patients with thrombocytopenia, neutropenia, or pancytopenia given the risk of myelosuppression with linezolid. Because of the extremely rare but real risk of serotonin syndrome when linezolid is coadministered with concomitant selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors, vancomycin is also preferable in patients receiving those medications (Hasani 2019, Lodise 2013). It is reasonable to consider linezolid over vancomycin in patients at increased risk of acute kidney injury to minimize the risk of vancomycin-associated nephrotoxicity. Linezolid may also be preferred in patients who have experienced current or previous vancomycin treatment failure and/or when the infecting

Table 4. Indications for MRSA Empiric Coverage Among Inpatients with Pneumonia

Pneumonia type	Risk factor/indication
CAP	Severe CAP + hospitalization and IV antibiotics in the past 90 days
HAP	IV antibiotics in the past 90 days OR Contracted HAP in a hospital or unit with MRSA prevalence greater than 20% or unknown
VAP	IV antibiotics in the past 90 days OR Septic shock OR acute respiratory distress syndrome preceding VAP OR 5 or more days of hospitalization prior to VAP OR acute renal replacement therapy prior to VAP OR Contracted VAP in a hospital or unit with MRSA prevalence greater than 10%–20% or unknown

CAP = community-acquired pneumonia, HAP = hospital-acquired pneumonia, IV = intravenous, MRSA = methicillin-resistant *Staphylococcus aureus*, VAP = ventilator-associated pneumonia.

Information from: Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200:e45-e67; Kalil AC, Van Schooneveld TC, Fey PD, et al. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. JAMA 2014;312:1552-64.

Table 5. Parenteral Directed Antibiotic Therapies for MRSA Pneumonia

Preferred therapy	Alternative therapy
Vancomycin targeting AUC_{24} 400–600 mg*h/L[a]	Ceftaroline 600 mg every 8–12 hours[a]
Linezolid 600 mg every 12 hours	Quinupristin-dalfopristin 7.5 mg/kg every 8 hours
	Telavancin 10 mg/kg every 24 hours[a]
	TMP/SMX 5 mg/kg (TMP) every 8–12 hours[a]
	Clindamycin 600 mg every 8 hours

[a]Requires dose adjustment in patients with renal impairment.

AUC_{24} = 24-hour area under the concentration-time curve, TMP/SMX = trimethoprim/sulfamethoxazole.

MRSA isolate has reduced-vancomycin susceptibility (Claeys 2016a).

Effective, evidence-based options for MRSA pneumonia aside from vancomycin or linezolid are currently lacking. Although telavancin is FDA approved for HAP/VAP caused by *S. aureus*, it should be reserved for alternative therapy of MRSA pneumonia (Kalil 2016). The combined results of two randomized trials comparing telavancin with vancomycin for HAP/VAP with a majority caused by *S. aureus* demonstrated similar clinical cure rates but increased 28-day mortality in the subgroup of patients with CrCl < 50 mL/min (Corey 2014, Rubinstein 2011). There was also a signal that telavancin may cause higher rates of nephrotoxicity compared with vancomycin.

Other potential alternatives for MRSA pneumonia with less supporting clinical evidence include quinupristin/dalfopristin, ceftaroline, sulfamethoxazole/trimethoprim, and clindamycin. Ceftaroline has some clinical data demonstrating efficacy for *S. aureus* pneumonia, including MRSA, but those data are predominantly observational and noncomparative in nature (Kaye 2015). Similarly, TMP/SMX and clindamycin appear effective for MRSA pneumonia based on the limited available clinical data (Eliakim-Raz 2017, Hong 2019, Liu 2011). Tigecycline should not be used for MRSA pneumonia because it resulted in lower clinical cure rates compared with vancomycin in a randomized controlled trial—particularly among the patients infected with *S. aureus* and those with VAP (Freire 2010). Daptomycin also must be avoided for treatment of pneumonia because it is ineffective for pneumonia based on the fact that it gets inactivated by pulmonary surfactant.

The currently recommended duration of therapy for *S. aureus* pneumonia is 7 days (Kalil 2016). Data from patients with HAP or VAP indicate that those receiving short courses of antibiotic (7 or 8 days) did not have worse clinical outcomes compared with those receiving longer antibiotic courses (10 to 15 days) (Pugh 2015). The shorter antibiotic courses were associated with reduced recurrent VAP caused by multidrug-resistant pathogens. The lack of difference in outcome was also observed in the group of patients with MRSA pneumonia, but it is important to note that that represented a minority of patients in the studies. Serum procalcitonin concentrations in concert with patient clinical status may be useful in patients when antibiotic discontinuation at day 7 is in question (Kalil 2016).

Patient Care Scenario

A 57-year-old man (weight 75 kg) with a medical history that includes atrial fibrillation and alcoholism is admitted to the medical ICU with a GI bleed. He subsequently develops VAP. Pertinent labs: SCr 3 mg/dL; BUN 46 mg/dL; platelets 39*10^9/L; WBC 15*10^9 cells/L. Results of the tracheal aspirate sent for culture before antibiotics is listed below. Use this information to develop a treatment regimen.

Source: Tracheal aspirate
Organism: *S. aureus*

Drug	MIC (mg/L)	Interpretation
Clindamycin	≥4	R
Daptomycin	1	S
Erythromycin	≥8	R
Gentamicin	≤4	S
Linezolid	0.5	S
Oxacillin	≥4	R
Rifampin	≥4	R
Tetracycline	2	S
TMP/SMX	≥4/76	R
Vancomycin	4	I

PCR test: *mecA* positive

ANSWER

The patient has MRSA VAP caused by an isolate with intermediate susceptibility to vancomycin on automated susceptibility testing. That result will have to be confirmed via BMD before calling it a true VISA, but it should not be treated with vancomycin at this time. Linezolid is also first line therapy for MRSA pneumonia—including VAP—but the patient is severely thrombocytopenic. Linezolid may not be a safe treatment option at this time because it causes thrombocytopenia and could worsen the platelet count or inhibit recovery. Telavancin is FDA approved for HAP/VAP caused by *S. aureus*, but increased mortality among a subgroup of patients with CrCl < 50 mL/min causes many clinicians to hesitate to use telavancin for serious MRSA infections. This patient has a CrCl < 30 mL/min. Remaining treatment options have limited clinical data, including ceftaroline, TMP/SMX, clindamycin, and quinupristin-dalfopristin. The isolate is resistant to TMP/SMX and clindamycin. Quinupristin-dalfopristin is poorly tolerated with infusion reactions, myalgia, and arthralgias. Ceftaroline 300 mg intravenously every 12 hours is arguably the best treatment option at this time. If available, a ceftaroline Etest should be performed to confirm susceptibility, but resistance to ceftaroline is currently uncommon in the United States. Some clinicians choose to administer ceftaroline every 8 hours for serious MRSA infections, but clinical data indicating that that is necessary are lacking. Data covering PK/PD suggest it may be beneficial when the ceftaroline MIC is 1-2 mg/L. Given the patient's poor renal function, every-12-hours dosing should suffice and would theoretically minimize the possibility of ceftaroline-associated rash or neutropenia.

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BLOODSTREAM INFECTIONS

Epidemiology

Staphylococcus aureus is a leading cause of BSIs in the community and health care settings. Data from 477 hospitals reported nearly 20,000 deaths among more than 119,000 cases of *S. aureus* BSI in 2017 (Kourtis 2019). A major contributor to the associated morbidity and mortality is MRSA BSI. The prevalence of MRSA in *S. aureus* BSIs in the United States is 40% – 60% (CDC 2015). Among patients with *S. aureus* BSI, MRSA is a major cause of delayed appropriate therapy and has been associated with increased mortality and health care cost.

Treatment

Because BSIs result from many different sources of infection and modes of acquisition, empiric antibiotic therapy of *S. aureus* BSI is selected based on the suspected source of infection. Because the majority of *S. aureus* BSIs are health care associated or occur in patients with risk factors for antibiotic-resistant infection, most of the empiric antibiotic regimens contain MRSA coverage with vancomycin. Recommended directed antibiotic therapies for MRSA are displayed in Table 6. Vancomycin and daptomycin are considered equivalent for *S. aureus* BSI based on a randomized trial and several observational studies (Fowler 2006, Liu 2011). Although

daptomycin is FDA approved for *S. aureus* BSI at 6 mg/kg every 24 hours, a wealth of in vitro and clinical data indicate the optimal daptomycin dose for serious MRSA infections is 8–10 mg/kg (Timbrook 2018). Although some observational data suggest daptomycin is associated with reduced failure and/or mortality compared with vancomycin, the observational nature of those data preclude a definitive conclusion that daptomycin is superior to vancomycin.

Evidence to support antibiotic therapies aside from vancomycin or daptomycin for MRSA BSI is currently lacking. Ceftaroline is often used when an alternative to vancomycin and daptomycin is needed. There are currently no published randomized controlled trials comparing ceftaroline with standard of care for MRSA BSI. In comparisons with standard of care in small observational studies, there is no indication that ceftaroline is inferior to standard of care (Paladino 2014). However, because of the small sample sizes and low quality of evidence, the data are insufficient to support the use of ceftaroline as a first-line option for MRSA BSI. Observational studies suggest ceftaroline monotherapy can be an effective salvage therapy for MRSA BSI after vancomycin and/or daptomycin failure (Zasowski 2017). Ceftaroline is a useful option in patients with MRSA BSI of pneumonia source because daptomycin is ineffective for pneumonia. Ceftaroline also displays consistent synergy when combined with daptomycin, and that combination is currently the most-evidence-based salvage option for patients with persistent MRSA BSI as detailed in the interactive case feature on combination antibiotics for *S. aureus*. Choosing between FDA-labeled every 12 hour and off-label every 8 hour dosing frequency is a consideration when using ceftaroline for MRSA BSI. Some clinicians choose to administer ceftaroline every 8 hours for serious MRSA infections. Available clinical data evaluating dosing frequency do not show any signal of improved effectiveness with every 8 hour dosing but further study specifically designed to address this question are needed prior to conclusion. Ceftaroline PK/PD data suggest every 8 hour dosing may be beneficial when the ceftaroline MIC is 1-2 mg/L, at or near the susceptibility breakpoint. These isolates are currently uncommon in the U.S. (Zasowski 2017). Infection severity, renal function, and risk of adverse reactions should be considered when selecting a dosing frequency.

Evidence to support telavancin for MRSA BSI is limited and suggest telavancin should be reserved for patients with few other viable treatment options (Stryjewski 2014). Small observational studies suggest telavancin may be effective as salvage therapy for patients with MRSA BSI (Britt 2018). Evidence evaluating dalbavancin for MRSA BSI is also limited. In a phase II randomized, controlled, open-label trial of 51 patients with catheter-related gram-positive BSI, patients receiving dalbavancin 1000 mg intravenously x 1 followed by 500 mg intravenously x 1 on day 8 were statistically significantly more likely to experience clinical cure compared with vancomycin-treated patients (Raad 2005). However, the majority of patients in the trial were infected with coagulase-negative staphylococci; only 14 patients had MRSA; and no organism-specific outcomes were reported. Small case series suggest dalbavancin may be an effective and well-tolerated consolidation therapy for gram-positive BSI after initially effective intravenous antibiotic therapy and blood culture clearance to facilitate discharge and outpatient therapy given its long half-life (Tobudic 2018). Dosage regimen varied but generally consisted of a loading dose of 1000 mg or 1500 mg followed by weekly doses of 500 mg or 1000 mg, with duration dependent on source of infection. Twice-weekly dosing was used in some cases. It is important to note that cases of dalbavancin failure and emergence of *S. aureus* with reduced glycopeptide and lipoglycopeptide susceptibility have been reported after dalbavancin use for MRSA BSI and IE (Steele 2018, Werth 2018). Oritavancin has been used similar to dalbavancin as consolidation therapy to facilitate discharge or outpatient therapy of gram-positive BSI—usually as a onetime, 1200-mg dose.

Table 6. Parenteral Directed Antibiotic Therapies for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection

Preferred therapy	Vancomycin targeting AUC24 400–600 mg*h/L[a] Daptomycin 8–10 mg/kg every 24 hours[a]
Alternative/ salvage therapy	Ceftaroline 600 mg every 8–12 hours[a] Linezolid 600 mg every 12 hours Quinupristin-dalfopristin 7.5 mg/kg every 8 hours Telavancin 10 mg/kg every 24 hours[a] Daptomycin + ceftaroline[a] Daptomycin + cefazolin[a] Daptomycin + TMP/SMX[a] Vancomycin + ceftaroline[a] Vancomycin + cefazolin[a] Vancomycin + nafcillin[a]

[a]Requires dose adjustment in patients with renal impairment.

AUC_{24} = 24-hour area under the concentration-time curve, TMP/SMX = trimethoprim/sulfamethoxazole.

Monitoring Therapeutic Response and Salvage Therapy

Patients with *S. aureus* BSI should be monitored daily for improvement or worsening of signs and symptoms of infection. Blood clearance is one of the primary objective measures of infection resolution. Two separate sets of blood cultures should be obtained at least every other day until clearance is documented. Clearance can be concluded once two consecutive sets of blood cultures from separate days are negative. Persistently positive blood cultures are common indications

for *S. aureus* BSI salvage therapy. There is no universal definition of persistent *S. aureus* BSI, but 7 or more days despite adequate antibiotic therapy is commonly used (Liu 2011). Evidence suggests that *S. aureus* BSI durations of more than 5–7 days are most strongly associated with mortality. Reassessment of antibiotic therapy should occur no later than day 7 using blood culture results from previous days.

Salvage therapy of MRSA BSI is a heterogeneous practice due primarily to the lack of clear, evidence-based options for MRSA BSI. Daptomycin is the primary salvage therapy option after vancomycin failure (Liu 2011). It is worth noting that as *S. aureus* strains become less susceptible to vancomycin, daptomycin MIC is sometimes also increased (Sakoulas 2006). Reduced vancomycin susceptibility phenotypes are more common among patients with persistent MRSA BSI (Casapao 2013). Nonetheless, observational data demonstrate that daptomycin is still relatively effective in a salvage role compared with vancomycin (Claeys 2016b). After daptomycin failure or after vancomycin failure in patients with pneumonia BSI source who cannot receive daptomycin, there is no clear next-best therapy. Ceftaroline monotherapy has a large observational body of evidence that suggests it can be effective as second- or third-line therapy. Smaller bodies of evidence demonstrate that telavancin, linezolid, and quinupristin-dalfopristin may also be effective salvage therapy, but each agent has limitations (Park 2012).

Synergistic combination therapy is another option that is becoming increasingly used for salvage therapy. The addition of aminoglycosides to vancomycin or antistaphylococcal penicillin fell out of favor because of an increased risk of acute kidney injury. Instead, the addition of various β-lactam antibiotics to either glycopeptide, lipopeptide, or lipoglycopeptide antibiotics has been shown to be synergistic against *S. aureus* in vitro, including VISA and DNS strains. Clinical evidence suggests β-lactam combination therapy reduces BSI duration but does not reduce mortality (Tong 2020). Combining vancomycin with certain β-lactams such as flucloxacillin, cloxacillin, or piperacillin/tazobactam appear to increase vancomycin-associated nephrotoxicity, although cefazolin appears safe. The most-evidence-based combination salvage therapy at this time is daptomycin plus ceftaroline. Numerous observational studies demonstrate rapid clearance of blood cultures in the majority of patients with persistent BSI given daptomycin plus ceftaroline. Two studies, including a small randomized controlled trial of patients administered daptomycin plus ceftaroline earlier in the course of therapy showed faster bloodstream infection clearance and reduced mortality relative to standard of care consisting of vancomycin or daptomycin (Geriak 2019, McCreary 2020). Many β-lactams other than ceftaroline have been shown synergistic with vancomycin or daptomycin, but their clinical evidence as salvage therapy is limited.

Duration of therapy for *S. aureus* BSI depends on the source of infection, the patient's underlying medical conditions, and whether the infection is considered complicated (Liu 2011). Duration of therapy also depends on how quickly the BSI clears, because duration should be counted from date of blood culture clearance. The minimal duration of therapy for *S. aureus* BSI is 14 days for uncomplicated and catheter-associated BSI. Uncomplicated MRSA BSIs are defined by IDSA guidelines as (1) absence of metastatic infection site (e.g., endocarditis, osteomyelitis) or implantable prosthesis, (2) defervescence within 72 hours of starting effective antibiotic therapy, and (3) negative follow-up blood cultures 2–4 days after initial positive blood cultures. Four to six weeks of antibiotic therapy are recommended for most complicated MRSA BSIs. Durations of 6 or more weeks are recommended for patients with IE and osteomyelitis.

INFECTIVE ENDOCARDITIS

Epidemiology

S. aureus represents a major cause of serious infections in community and acute-care settings. It has outpaced streptococci and become the leading cause (>50%) of culture-positive IE in the United States and other developed countries. Despite overall decreases in MRSA infections, MRSA accounts for nearly half of *S. aureus* and about 25% of all culture-positive IE cases (McCarthy 2020). The epidemiology reflects increases of specific *S. aureus* risk factors driven largely by health care exposure (e.g., indwelling catheters and implantable cardiac devices, including prosthetic valves) and intravenous drug use (IDU). Non-IDU patients with *S. aureus* commonly present with left-sided IE, whereas people who inject drugs often experience right-sided IE that affects the tricuspid valve. In-hospital mortality is higher for *S. aureus* IE compared with other organisms and ranges from 18% to 25% (Holland 2016).

Treatment

The treatment goal is to completely sterilize the valvular vegetations, which may involve valvular surgery with pharmacotherapy (Baddour 2015). High bacterial densities within vegetations pose PK/PD challenges to antibiotic selection (e.g., inoculum effect with vancomycin and β-lactam). The overarching principles are to obtain blood cultures prior to antibiotic initiation, then administer parenteral antibiotics initially, use higher doses, and treat for several weeks. Empiric treatment consists of evaluating epidemiological risk factors and promptly initiating antibiotics that treat the most-likely pathogens and that should contain MRSA coverage. Recommended directed treatment regimens for MRSA IE are listed in Table 7. Vancomycin and daptomycin are first-line options for MRSA IE. Clindamycin is not recommended because it has been associated with relapse. There are limited data with ceftaroline, linezolid, TMP/SMX, quinupristin-dalfopristin, and telavancin for salvage of persistent MRSA IE. The addition of gentamicin and rifampin is not recommended in native valve

Table 7. Empiric and Targeted Treatment of IE Caused by MRSA

Regimen	Dose and route	Duration (weeks)
Native valve endocarditis		
Vancomycin	Target AUC_{24} 400–600 mg*h/L[a]	6
Daptomycin	≥8 mg/kg IV Q24H[a]	6
Prosthetic valve endocarditis (combination necessary)		
Vancomycin, plus	Target AUC_{24} 400–600 mg*h/L[a]	≥6
Rifampin, plus	300 mg IV or PO Q8H	≥6
Gentamicin	1 mg/kg IV or IM Q8H[a]	2

[a]Requires dose adjustment in patients with renal impairment.

AUC_{24}, 24-hour area under the concentration-time curve, IV = intravenous, PO = orally.

Information from: Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.

endocarditis because the risks (e.g., nephrotoxicity, hepatotoxicity) outweigh the benefits. Empiric antibiotics should be revised to target organisms identified from positive blood cultures (e.g., cefazolin or antistaphylococcal penicillin for MSSA). Combination antibiotics (e.g., vancomycin, rifampin, and gentamicin) are considered when prosthetic valves are involved because of the high mortality risk. Furthermore, animal studies showed that rifampin effectively sterilized the prosthetic valves and other foreign materials.

Treatment duration begins counting on the first day of a negative blood culture—in patients who were previously bacteremic. In patients who undergo valve surgery and whose tissue cultures are positive, the entire course should be given after surgery. If the tissue culture is negative, then the treatment days prior to surgery may be counted as part of the entire course. There are limited data on managing IE from vancomycin-resistant staphylococci (e.g., hVISA, VISA, or vancomycin-resistant *S. aureus*), and thus the recommendation is to consult with an infectious disease specialist in these cases.

CONCLUSION

Staphylococcus aureus is a common pathogen associated with both community- and hospital-acquired infections. Balancing the need for broad-spectrum empiric therapy covering MRSA with the need for antimicrobial stewardship to limit negative effects of antibiotic therapy and preserve antibiotic activity for the future is a constant challenge. Many disease-state-specific guidelines exist to aid clinicians in selecting empiric therapy. Challenges also exist with therapy directed against MRSA, which can be difficult to eradicate and which can cause persistent infection, morbidity, and mortality. As a result, guideline-recommended therapies often fail, and clinicians must be familiar with primary clinical, pharmacokinetic, and in vitro literature to provide optimal patient care.

Practice Points

- **Empiric therapy of infections commonly caused by *S. aureus* should be based on established risk factors for MRSA and local MRSA epidemiology.**
- **Vancomycin is the intravenous treatment of choice for most invasive MRSA infections.**
- **Daptomycin and linezolid also have strong clinical evidence for various MRSA infection types and are often the best vancomycin alternatives.**
- **Optimal dosing and antibiotic combination therapy can be used to eradicate difficult-to-treat MRSA infections.**

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Self-Assessment Questions

1. A 56-year-old man with a medical history of hypertension, diabetes, obesity, and depression presents to the ED with a swollen lump on his back. On physical examination, an abscess measuring 6 cm in diameter is noted on his right scapula. His temperature is 38.5°C, heart rate 75 beats/min, blood pressure 134/76 mm Hg, respiratory rate 18 breaths/min. His basic metabolic panel is within normal limits and his WBC count is 14,000 cells/mcL. He has no known drug allergies. His home medications include losartan, hydrochlorothiazide, metformin, and sertraline. He is diagnosed with a cutaneous abscess and incision and drainage is performed. The institution's ED *S. aureus* antibiogram 2018-2019 is as follows:

	Percent susceptible				
	Clindamycin	Daptomycin	Linezolid	Oxacillin	Vancomycin
S. aureus (*n* = 200)	70	100	100	42	99

Which one of the following is best to recommend for this patient?

A. IV daptomycin
B. IV linezolid
C. IV clindamycin
D. No antibiotics

2. A 32-year-old woman with a medical history of hypertension and obesity presents to the ED with pain and swelling in her right calf. On physical exam an area of erythema measuring ~ 90 cm^2 is noted on her left calf, which is warm and edematous. No abscess or purulence is noted. Her temperature is 37.1°C, heart rate 75 beats/min, blood pressure 134/76 mm Hg, respiratory rate 18 breaths/min. Her basic metabolic panel is within normal limits and her WBC count is 10,000 cells/mcL. She has no known drug allergies. She is diagnosed with cellulitis. Which one of the following is best to recommend for this patient?

A. Clindamycin
B. TMP/SMX + cephalexin
C. Cephalexin
D. TMP/SMX

3. A 66-year-old man with surgical site infection after pacemaker placement has been receiving IV vancomycin for the past 48 hours and symptoms have improved. The medical team would like to transition the patient to an oral antibiotic to facilitate discharge. The patient has a medical history of hypertension, heart failure, and atrial fibrillation. His home drugs include losartan, metoprolol succinate, furosemide, and warfarin. The results of the culture obtained during debridement of the infected wound are as follows:

Source: Wound
Organism: *S. aureus*

Drug	MIC (mg/L)	Interpretation
Clindamycin	0.5	S
Daptomycin	0.5	S
Erythromycin	≥8	R
Gentamicin	≤4	S
Linezolid	0.5	S
Oxacillin	≥4	R
Rifampin	≤ 1	S
Tetracycline	2	S
TMP/SMX	<0.5/9.5	S
Vancomycin	1	S
D test: Positive		
PCR test: *mecA* positive		

Which one of the following is best to recommend for this patient?

A. TMP/SMX
B. Doxycycline
C. Clindamycin
D. Cephalexin

4. A 62-year-old man is admitted to the hospital with a severe, recurrent diabetic foot infection with osteomyelitis. His last diabetic foot infection at the same infection site 6 months ago was caused by MRSA and was successfully treated with vancomycin followed by oral TMP/SMX. He has a medical history of hypertension, diabetes, obesity, and stage III chronic kidney disease, peripheral vascular disease, and depression. His temperature is 38.5°C, heart rate 95 beats/minute, blood pressure 110/70 mm Hg, respiratory rate 18 breaths/minute. His basic metabolic panel is normal except for a creatinine of 1.9 mg/dL, which is at baseline. His WBC count is 15,000 cells/mcL. His home drugs include glipizide, lisinopril, atorvastatin, fluoxetine, and aspirin. Because the patient has systemic signs of infection and possible sepsis, the medical team has chosen to start empiric antibiotic therapy before culture results. Which one of the following is best to recommend for this patient?

A. Vancomycin + cefepime
B. Linezolid + piperacillin/tazobactam
C. Cefepime
D. Piperacillin/tazobactam

5. A 59-year-old woman presents with a right knee prosthetic joint infection status post debridement and implant retention. Four of six intra-operative cultures are growing the bacterial isolate below. The patient has a medical history of hypertension and atrial fibrillation. Her home medications include lisinopril, hydrochlorothiazide, and warfarin.

Source: intra-operative, R knee
Organism: *S. aureus*

Drug	MIC (mg/L)	Interpretation
Clindamycin	0.5	S
Daptomycin	0.5	S
Erythromycin	≤ 0.5	S
Gentamicin	≤ 4	S
Linezolid	0.5	S
Oxacillin	≥4	R
Rifampin	≤ 1	S
Tetracycline	2	S
TMP/SMX	<0.5/9.5	S
Vancomycin	1	S
PCR test: *mecA* positive		

Which one of the following is best to recommend for this patient?

A. Vancomycin
B. Vancomycin + rifampin
C. Vancomycin + gentamicin
D. Vancomycin + gentamicin + rifampin

6. A 67-year-old man with a medical history of hypertension and dyslipidemia was admitted to the general ward of the hospital for acute coronary syndrome. On hospital day 5, he develops signs and symptoms consistent with pneumonia but remains hemodynamically stable and does not require ventilator support. He has had no recent hospitalizations or antibiotic exposure. The hospital antibiogram with the percentage of isolates susceptible to relevant antimicrobials is as follows:

Organism	Cefepime	Ceftriaxone	Linezolid	Oxacillin	Piperacillin/tazobactam	Vancomycin
E. coli	81	77	–	–	94	–
H. influenzae	100	100	–	–	100	–
K. pneumoniae	77	80	–	–	90	–
S. aureus	85	85	100	85	85	100
S. pneumoniae	95	97	100	100	96	100
P. aeruginosa	86	–	–	–	84	–

Which one of the following is best to recommend for this patient?

A. Cefepime + ciprofloxacin
B. Linezolid + cefepime + tobramycin
C. Telavancin + cefepime + tobramycin
D. Vancomycin + cefepime + tobramycin

7. A 57-year-old woman with a medical history of type 2 diabetes mellitus, hypertension, and dyslipidemia, was admitted to the neurologic intensive care unit following a stroke and requires mechanical ventilation. On hospital day 7, she developed ventilator-associated pneumonia (VAP) with septic shock. A tracheal aspirate is sent for culture and you are consulted for an empiric antibiotic treatment recommendation. The neurologic ICU antibiogram data are shown below. The neurologic ICU has had an outbreak of resistant *S. aureus* harboring the *cfr* gene in recent weeks.

Organism	Cefepime	Ceftriaxone	Linezolid	Oxacillin	Piperacillin/tazobactam	Vancomycin
E. coli	78	70	–	–	84	–
H. influenzae	100	100	–	–	100	–
K. pneumoniae	74	73	–	–	80	–
S. aureus	65	65	99	65	65	99
S. pneumoniae	95	97	100	100	96	100
P. aeruginosa	76	–	–	–	66	–

Which one of the following is best to recommend for this patient?

A. Cefepime
B. Linezolid + cefepime
C. Telavancin + cefepime
D. Vancomycin + cefepime

8. A 67-year-old man is currently being treated for hospital-acquired pneumonia with broad-spectrum antibiotics. Gram stain of the bacteria isolated from the sputum culture obtained before antibiotics were started show coagulase-positive gram-positive cocci in clusters and no gram-negative bacteria present. A rapid diagnostic PCR test performed on the specimen indicates the presence of the *mecA* gene. Which one of the following is best to recommend for this patient?

A. Telavancin
B. Ceftaroline
C. Linezolid
D. Tedizolid

9. You are designing an intervention to improve care of patients with *S. aureus* bloodstream infection (BSI) at your hospital with the goal of reducing mortality. Preliminary data indicate infectious diseases is nearly always consulted and most patients receive optimal antibiotic therapy (in vitro active, evidence based), defined as vancomycin or daptomycin for MRSA and antistaphylococcal penicillin or cefazolin for MSSA. However, the average time to optimal antibiotic therapy is 66 hours. Your current microbiologic workflow for positive blood cultures includes Gram stain with automated susceptibility testing. Which of the following is best to recommend to improve care of patients with SAB and potentially reduce mortality at your hospital?

   A. Perform modified population analysis on all *S. aureus* bloodstream isolates.
   B. Perform modified population analysis on all *S. aureus* bloodstream isolates and provide antimicrobial stewardship support.
   C. Perform the Verigene gram-positive blood culture assay on all *S. aureus* bloodstream isolates.
   D. Perform the Verigene gram-positive blood culture assay on all *S. aureus* bloodstream isolates and provide real-time antimicrobial stewardship support.

Questions 10 and 11 pertain to the following case

D.J. is 48-year-old man with a *S. aureus* BSI secondary to an epidural abscess source who is currently being treated with vancomycin. On treatment day 3, blood cultures have not cleared and the patient experiences acute kidney injury. The medical team is concerned it could be vancomycin-associated nephrotoxicity and they consult you on an alternative antibiotic treatment recommendation. The initial positive blood culture results are as follows:

Source: blood, R arm
Organism: *S. aureus*

Drug	MIC (mg/L)	Interpretation
Clindamycin	0.5	S
Daptomycin	0.5	S
Erythromycin	≤ 0.5	S
Gentamicin	≤ 4	S
Linezolid	0.5	S
Oxacillin	≥4	R
Rifampin	≤ 1	S
Tetracycline	2	S
TMP/SMX	<0.5/9.5	S
Vancomycin	1	S
PCR test: *mecA* positive		

10. Which one of the following is best to recommend for D.J.?

    A. Intravenous daptomycin
    B. Oral linezolid
    C. Intravenous linezolid
    D. Intravenous telavancin

11. D.J.'s blood cultures clear after a total of 5 days of bacteremia, and no osteomyelitis or other metastatic sources of infection develop. Which of the following is best to recommend as the minimum antibiotic treatment durations for D.J.?

    A. 2 weeks
    B. 4 weeks
    C. 8 weeks
    D. 12 weeks

12. A 54-year-old man with a persistent *S. aureus* BSI is currently being treated with daptomycin 6 mg/kg every 24 hours. Vancomycin was switched to daptomycin on day 6 of BSI. No source or foci of infection has been identified; transesophageal ECHO did not show evidence of valvular vegetation and tagged white blood cell scan failed to identify a nidus of infection. Results of blood cultures taken on BSI day 1 and day 9 are as follows:

BSI day 1			**BSI day 9**		
Source: blood, R arm **Organism: *S. aureus***			**Source: blood, R arm** **Organism: *S. aureus***		
Drug	MIC (mg/L)	Interpretation	Drug	MIC (mg/L)	Interpretation
Clindamycin	0.5	S	Clindamycin	0.5	S
Daptomycin	0.5	S	Daptomycin	2	–
Erythromycin	≤ 0.5	S	Erythromycin	≤ 0.5	S
Gentamicin	≤ 4	S	Gentamicin	≤ 4	S
Linezolid	0.5	S	Linezolid	0.5	S
Oxacillin	≥4	R	Oxacillin	≥4	R
Rifampin	≤ 1	S	Rifampin	≤ 1	S
Tetracycline	2	S	Tetracycline	2	S
TMP/SMX	<0.5/9.5	S	TMP/SMX	<0.5/9.5	S
Vancomycin	2	S	Vancomycin	4	I
PCR test: *mecA* positive			**PCR test:** *mecA* positive		

Which one of the following is best to recommend for this patient?

   A. Daptomycin 10 mg/kg every 24 hours
   B. Daptomycin 10 mg/kg + gentamicin 3 mg/kg every 24 hours
   C. Daptomycin 10 mg/kg + cefazolin 2000 mg every 8 hours

D. Daptomycin 10 mg/kg + ceftaroline 600 mg every 8 hours

13. A 32-year-old woman with an MRSA bloodstream infection (BSI) secondary to MRSA pneumonia is currently being treated with vancomycin and is clinically stable. On treatment day 2, initial blood culture results from a MicroScan WalkAway indicate the isolate is vancomycin susceptible with a vancomycin MIC of 2 mg/L. The medical team is concerned about the vancomycin MIC of 2 mg/L and has consulted you for an antibiotic treatment recommendation. Which one of the following is best to recommend for this patient?

    A. Continue vancomycin.
    B. Switch to ceftaroline.
    C. Switch to daptomycin.
    D. Switch to linezolid.

14. A 58-year-old man presents with a *S. aureus* BSI. Transesophageal ECHO identified a 3 cm vegetation on the mitral valve. The patient does not have any symptoms or findings suggestive of septic metastatic complications at this time and does not have any implantable prosthesis or heart valves. The results of the initial positive blood culture are listed below.

Source: blood, R arm
Organism: *S. aureus*

Drug	MIC (mg/L)	Interpretation
Clindamycin	0.5	S
Daptomycin	0.5	S
Erythromycin	≤ 0.5	S
Gentamicin	≤ 4	S
Linezolid	0.5	S
Oxacillin	≥4	R
Rifampin	≤ 1	S
Tetracycline	2	S
TMP/SMX	<0.5/9.5	S
Vancomycin	2	S
PCR test: *mecA* positive		

Which one of the following is best to recommend for B.D.?

    A. Vancomycin for 6 weeks
    B. Daptomycin + gentamicin for 2 weeks, then daptomycin for 4 weeks
    C. Daptomycin for 2 weeks
    D. Vancomycin + gentamicin for 2 weeks, then vancomycin 4 weeks

15. A 38-year-old man with a medical history of tricuspid valve endocarditis presents with a *S. aureus* BSI. Transesophageal ECHO identified a 3-cm vegetation on his mechanical tricuspid valve. The results of the initial positive blood culture are as follows:

Source: blood, R arm
Organism: *S. aureus*

Drug	MIC (mg/L)	Interpretation
Clindamycin	0.5	S
Daptomycin	0.5	S
Erythromycin	≤ 0.5	S
Gentamicin	≤ 4	S
Linezolid	0.5	S
Oxacillin	≥4	R
Rifampin	≤ 1	S
Tetracycline	2	S
TMP/SMX	<0.5/9.5	S
Vancomycin	1	S
PCR test: *mecA* positive		

Which one of the following is best to recommend for this patient?

    A. Vancomycin for 6 weeks
    B. Vancomycin + gentamicin for 2 weeks, then vancomycin for 4 weeks
    C. Vancomycin + gentamicin + rifampin for 2 weeks, then vancomycin + rifampin for 4 weeks
    D. Vancomycin + gentamicin + rifampin for 6 weeks