Methicillin-Resistant *Staphylococcus aureus* Infections

Paul S. Pottinger, MD

KEYWORDS

• MRSA • Methicillin-resistant *Staphylococcus aureus* • Community-acquired MRSA • Vancomycin • Ceftaroline • Daptomycin • Linezolid

KEY POINTS

- Methicillin-resistant *Staphylococcus aureus* (MRSA) evolved when methicillin-sensitive *Staphylococcus aureus* acquired the *mecA* gene, probably from coagulase-negative staphylococci. MRSA is resistant to all β-lactam antibiotics, except for ceftaroline.
- There are 2 main types of MRSA: hospital-acquired (HA) and community-acquired (CA). CA-MRSA is more common than HA-MRSA, more drug-susceptible, and more likely to present as skin and soft tissue infections (SSTI).
- MRSA SSTI should be suspected if patients present with purulent discharge or abscess. Incision and drainage alone is usually sufficient for cure, although patients with warning signs should also receive a short course of antibiotics.
- Recurrent MRSA SSTI should prompt consideration of decolonization maneuvers; these efforts often fail on first attempt, perhaps because of the many anatomic locations that MRSA may inhabit.
- Treatment of MRSA bloodstream infections includes draining any foci of infection, and infected central lines should be removed. Patients should be carefully assessed for complications, including endocarditis.
- Uncomplicated bacteremia should be treated with 2 weeks of therapy. Complicated bacteremia should be treated for 4 to 6 weeks, and endocarditis for at least 6 weeks. The ideal drug choice for bacteremia remains controversial, but vancomycin is often still appropriate. If patients fail to respond to vancomycin, a change to another agent (daptomycin or linezolid) is warranted, regardless of the vancomycin minimum inhibitory concentration.
- MRSA pneumonia is a highly morbid and mortal infection. Linezolid has not shown superiority over vancomycin in terms of mortality, and it is expensive and potentially toxic, although a modest improvement in short-term clinical outcomes was seen in an industry-sponsored trial, and its dosing is simple. Ceftaroline is not approved by the US Food and Drug Administration for this indication, and it also costs more than vancomycin. Daptomycin should never be used in MRSA pneumonia, because it is inactivated by pulmonary surfactant.
- The number of cases of HA-MRSA seems to be decreasing with good infection prevention techniques in hospitals. CA-MRSA incidence seems to have plateaued. Assiduous use of simple infection control techniques remains the most effective prevention strategy.

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1959 Northeast Pacific Street, Box 356130, Courier BB-302, Seattle, WA 98195, USA
E-mail address: abx@uw.edu

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WHAT IS METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*?

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a species of drug-resistant *Staphylococcus aureus* bacteria.[1] Although methicillin is no longer used in clinical practice (less toxic and more stable drugs such as oxacillin and nafcillin replaced it years ago), the moniker persists.

Where did it come from, and how did it become resistant to methicillin?

Alexander Fleming was working on *S. aureus* in 1928 when he observed inhibition of its growth on media contaminated by *Penicillium* mold.[2] He hypothesized that the mold was secreting an antibacterial chemical, which he called penicillin. When Howard Florey and colleagues[3] subsequently isolated penicillin, and when clinical trials were completed in 1941, the world finally had an effective treatment for deep staphylococcal infections; the antibiotic era had begun in earnest. Although initial production was slow, the precious medication was administered with great effect to infected Allied soldiers during World War II, leading to cures of acute and chronic infected battle wounds which might previously have been fatal.

However, staphylococcal resistance to penicillin was documented within a few years. This resistance happened because, under selective antibiotic pressure, certain strains of *S aureus* began to express penicillinases, enzymes that hydrolyze the lynchpin β-lactam ring of the drug. Although some *S. aureus* strains are still susceptible to penicillin, its usefulness has greatly diminished. Chemists developed a semisynthetic penicillin called methicillin to combat this problem. It was relatively unstable, only available for intravenous (IV) use, and caused an alarming number of cases of interstitial nephritis, but it was resistant to hydrolysis by staphylococcal β-lactamases. It was first deployed in 1959.

Resistance to methicillin was reported in Europe just 2 years later, and then in Boston in 1968.[4] This time, resistance was mediated not by β-lactamases, but by a fundamental change in bacterial cell wall chemistry. Penicillins work by attaching to penicillin-binding proteins, especially penicillin binding protein 2 (PBP-2). PBP-2 is a transpeptidase enzyme that serves the vital function of cross-linking bacterial cell wall precursors into strong, functional walls; they are like the mortar that glues precursor bricks together. Without that mortar, walls cannot form properly, and the cell dies. In MRSA, the *mecA* gene encodes for a mutant gene product called PBP-2A, which is resistant to binding by penicillins and all subsequent β-lactam drugs, including the cephalosporins (with one notable exception, as described later) and carbapenems. The *mecA* gene is located on a transmissible genetic element called the staphylococcal chromosomal cassette (SCC), which has facilitated the acquisition of methicillin resistance by multiple strains of *S. aureus*. Seven major SCC*mec* types have been described. Genetic analysis indicates that they are related to each other and suggests that they probably originated from coagulase-negative staphylococci (eg, *S. epidermidis*).[5] How the SCC*mec* elements entered *S. aureus* is unclear, although the presence of multiple types in MRSA colonizing European swine has led to the theory that swine may have served as a kind of mixing vessel between *S. aureus* and coagulase-negative *Staphylococcus* before transmitting the germs to humans.[6]

The increase of MRSA may be in part a result of our own conquest of other microbes. For example, MRSA itself becomes more drug resistant when patients are treated with antibiotics for other reasons (eg, sinopulmonary infections, urinary tract infections)[7] It is reasonable to suspect that the injudicious use of antibiotics may open up ecological niches in humans that are then colonized by MRSA, although there are many cases in which personal antibiotic exposure is not associated with

colonization or infection. In the throat, MRSA may simply be filling the vacuum left by the absence of *S. pneumoniae*. *S. pneumoniae* has been observed to kill MRSA through the elaboration of hydrogen peroxide,[8] and throat MRSA colonization rates have been observed to increase in conjunction with the broad deployment of pneumococcal vaccines.[9,10] This hypothesis remains unproved; if substantiated, it would be a stunning example of an unintended consequence of an otherwise successful public health intervention.

What is the difference between hospital-acquired and community-acquired MRSA?

For the first 20 years after its description, MRSA was something of a clinical oddity: it was found in a small fraction of clinical *S aureus* isolates, and virtually always among patients who had exposure to hospitals. In 1974, only about 2% of *S. aureus* isolates from hospitalized American patients were MRSA; the rest were methicillin-sensitive *S. aureus* (MSSA).[11] Risk factors for hospital-acquired MRSA (HA-MRSA) were understood to include extensive previous antimicrobial exposure, admission to intensive care, presence of an endotracheal tube or central venous catheter, long duration of hospital admission, and poor health care worker compliance with standard hand hygiene practices.[12] MRSA was approached as a rare problem, created in hospitals, spread within hospitals, and seen only in hospitals.

However, in the early 1980s, substantial outbreaks of MRSA infections were reported among patients who had not been recently hospitalized, including injection drug users in Detroit.[13] Spread seemed linked to close contact between patients, and risk factors for infection included incarceration, homelessness, injection drug use, athletics, or living in dormitories or military quarters. In 1999, a report from the Centers for Disease Control (CDC) described 4 previously healthy children with skin infections who were treated empirically with cephalosporins, and later died of culture-proven MRSA, without any identified risk factors for infection.[14]

These cases came to be referred to as community-acquired or community-associated MRSA (CA-MRSA). Genetic analysis of isolates from CA and HA cases reveals molecular differences between the strains beyond their drug susceptibilities. In particular, certain strains of CA-MRSA are notorious for carrying virulence genes on their SCC, including a toxin called Panton-Valentine leukocidin (PVL). This molecule is toxic to host phagocytes, and seems to confer a survival advantage to CA-MRSA even in hosts with normal immune function. Experimental data have raised controversy regarding the role of PVL as a virulence factor,[15] and a recent meta-analysis found that PVL expression was independently associated with skin and soft tissue infections (SSTI) but not necessarily with invasive bloodstream, lung, or musculoskeletal infections.[16] On the other hand, the strain of CA-MRSA that often harbors PVL, called USA300, increased steadily in frequency during the 2000s, and has been shown to cause not only SSTI but also more severe episodes of sepsis when cultured from the bloodstream (**Table 1**).[17]

So, is MRSA worse than MSSA? And is CA-MRSA worse than HA-MRSA?

MRSA and MSSA are more similar than different. Both can present in a variety of ways, ranging from asymptomatic colonization to simple skin abscesses to invasive catastrophes such as necrotizing fasciitis, bacteremia, or pneumonia. Without appropriate treatment, MSSA infections can be as devastating as those caused by MRSA. However, treatment options are more favorable for MSSA. Plus, in some cases, CA-MRSA is not only more drug resistant but also more virulent.[18] Regardless of which

Table 1
Overview of HA-MRSA versus CA-MRSA

	HA-MRSA	CA-MRSA
Risk factors	Health care exposure (current or recent hospitalization, hemodialysis, central venous catheter)	No health care exposure (injection drug use, closely cohorted in jail or dormitories or barracks, athletes, family member infected or colonized)
Common clinical presentations	Bacteremia, Ventilator-associated pneumonia	Asymptomatic colonization, SSTI (especially abscess), orthopedic, bacteremia, pneumonia
Common SCC*mec* type in United States	II	IV
Toxin production	Rare	Common (especially PVL)
Comparative drug resistance	Highly drug resistant	Less drug resistant
Notes	Becoming less common over time, as infection control in hospitals becomes more robust	US incidence stable circa 50% of *S. aureus*. Readily transmitted by contact

gene product(s) are responsible for this virulence, outcomes in deep infections caused by MRSA are often worse than with MSSA. A meta-analysis of 3963 patients with *S. aureus* bacteremia found a pooled mortality odds ratio of 1.93 (95% confidence interval, 1.54–2.42; $P<.001$), meaning roughly 2-fold risk of dying of MRSA bacteremia compared with MSSA.[19]

In terms of comparing implications of CA-MRSA versus HA-MRSA, both are bad. HA strains are comparatively more drug resistant, and CA strains have a propensity for producing more toxins. However, these distinctions may be blurring. In a recent study,[20] outcomes among patients who acquired their infections in the hospital with phenotypic CA-MRSA were similar to those whose infections was caused by phenotypic HA-MRSA: in 384 patients, treatment failure was reported in 23% versus 15%, and 30-day mortality in 16% versus 19%, respectively (no statistically significant differences between groups). Although serious MSSA infections are easier to treat than similar MRSA infections, and although patients with MRSA have increased risk of poor outcomes, all *S. aureus* strains are associated with high morbidity and mortality, and all merit prompt attention and care.

My patients are worried about MRSA. These infections seem bad, but are they actually overblown by the lay media?

Patients should be reassured that there is no need to panic. Whereas approximately 29% of all Americans have asymptomatic nasal colonization with MSSA, the number for MRSA is only 1.5%.[21] The prevalence of MRSA colonization and infection varies substantially by region, and even by patient population within a given city or county. However, the overall numbers of invasive infections are sobering. It is now clear that a dramatic shift has occurred in the epidemiology of MRSA in the United States. Although HA-MRSA infection cases remained essentially steady in the 1990s, CA-MRSA increased astonishingly, from 2% of clinical *S. aureus* isolates in the 1970s

to roughly 50% in 1997.[22] The absolute numbers are substantial. Of an estimated 478,000 hospitalizations with a diagnosis of *S. aureus* infection in US hospitals in 2005, approximately 278,000 were related to either HA-MRSA or CA-MRSA.[23] By a different estimate using the CDC's Active Bacterial Core Surveillance system, in 2005 roughly 94,000 patients developed their first invasive MRSA infection, and approximately 19,000 died.[24] In other nations, MRSA remains extremely rare and limited to HA-MRSA, prompting a "search-and-destroy" approach in response to even a single case. However, as those nations face the development of CA-MRSA, their approach may need to change.[25] In the United States, MRSA is in the community, and seems here to stay, at least for the foreseeable future.

My clinic patient is young, otherwise healthy, and has an abscess on his buttock. This is his first episode. How should I treat skin infections in the age of MRSA?

CA-MRSA has a predilection for the skin, especially the USA300 clone commonly found in the United States. Distinguishing CA-MRSA SSTI from those caused by pyogenic streptococcal species (eg, *Streptococcus pyogenes*) can be challenging without a Gram stain, but there may be helpful clues on presentation. Folliculitis is a common starting point for CA-MRSA infections, and a moist, hot compress may encourage them to drain if applied early enough. However, if drainage is not achieved, lesions may progress to furuncles, carbuncles, and frank abscesses. Significant surrounding cellulitis may complicate these boils, but this is the exception rather than the rule, at least early in the course of illness. Thus, when patients present with uncomplicated, focal, purulent skin infections, suspicion should be high for MRSA, regardless of previous exposure history or classic risk factors.[26] In contrast, simple cellulitis without a focal head may be caused by MRSA, but pyogenic streptococcal species (including *Streptococcus pyogenes*) should move higher on the differential diagnosis (**Table 2**).[27]

Drainage alone is the appropriate treatment of uncomplicated MRSA skin abscesses; antibiotics in addition to drainage are usually unnecessary.[28] This recommendation is based on numerous clinical trials, all of which have yielded essentially the same conclusion. In one example,[29] patients with this syndrome were managed with drainage plus either cephalexin or placebo. However, most were proved to have MRSA, meaning that this was effectively a placebo-versus-placebo study. Even so, 91% of patients in the placebo arm and 84% of those in the cephalexin arm had full resolution of symptoms, presumably because all lesions were drained. Drainage can be performed quickly in the examination room with standard skin preparation, local

Table 2
Features suggestive of SSTI caused by CA-MRSA versus pyogenic streptococci

CA-MRSA	Pyogenic Streptococci

• Furuncle, carbuncle, boil, or abscess
• Unwitnessed "spider bite"
• Recurrent infection
• Common Host Factors:
  ○ No clear risk factors
  ○ Any Age; often adolescents & young adults
  ○ Athletes
  ○ Injection drug users
  ○ Closely cohorted (living in dormitories, barracks, prison)
	• Generalized erythema, sharp borders, no purulence
	• Honey crust of impetigo
	• May also recur if underlying disorder not addressed
	• Common host factors:
	  ○ Any age; impetigo in children, cellulitis in elderly individuals
	  ○ Lymphatic obstruction (eg, postsurgical lymphedema)
	  ○ Tinea pedis, interdigital macerations

anesthesia, and a sterile scalpel or large-gauge needle for smaller lesions. Wounds should be left open and encouraged to drain (with sterile packing material if necessary, changed once or twice daily until drainage has abated). I encourage sending purulent material for Gram stain and culture, but this is optional; because drainage alone is the treatment of choice for uncomplicated infection, confirmation of MRSA and antibiotic resistance testing rarely affects immediate management. However, this information may prove useful in the future, particularly if the infection fails to improve with drainage.

I think my patient has CA-MRSA SSTI, because there is a purulent focus; she is nontoxic, but there is a lot of surrounding erythema and tenderness. I think she needs antibiotics in addition to drainage.

Antibiotics should be considered in addition to drainage for complicated abscesses associated with warning signs (**Box 1**). Many of these patients require at least a brief admission with IV antibiotics to ensure adequate response, and to allow for proper tailoring of step down to oral therapy.

However, initial outpatient management with oral antibiotics can be considered for otherwise healthy patients who have only modest surrounding cellulitis, a nontoxic appearance, and reliable early follow-up plans. In this setting, selection of an oral antibiotic depends on local resistance data, as well as individual patient factors such as allergy history, tolerability, expense, and potential medication interactions. Generally, the most reliable anti-MRSA oral drugs in the United States in 2013 are trimethoprim-sulfamethoxazole (TMP/SMX), doxycycline, minocycline, and linezolid. TMP/SMX and doxycycline often have susceptibility profiles of roughly 90%, versus virtually 100% for linezolid. However, because of its considerable expense, and because it has not been shown to have superior efficacy for this syndrome, linezolid is often a less attractive option than the other two. Clindamycin is less desirable as well, both because of its generally lower susceptibility rates and because of its notorious association with *Clostridium difficile* colitis. However, if the other options are unattractive and local clindamycin resistance patterns are favorable (perhaps >80% susceptible), then it could be considered, provided that an isolate is obtained for testing and that early follow-up is

Box 1
Conditions in which antimicrobial therapy is recommended after incision and drainage of an abscess caused by CA-MRSA (adapted from Infectious Diseases Society of America [IDSA] MRSA guidelines)

- Severe or extensive disease (eg, involving multiple sites of infection) or rapid progression in presence of associated cellulitis
- Signs and symptoms of systemic illness
- Associated comorbidities or immunosuppression (diabetes mellitus, human immunodeficiency virus infection/AIDS, neoplasm)
- Extremes of age
- Abscess in area difficult to drain completely (eg, face, hand, genitalia)
- Associated septic phlebitis
- Lack of response to incision and drainage alone

From Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis 2011;52(3):285–92.

ensured. Laboratories should test specifically for inducible clindamycin resistance by performing a "D-zone test," because this finding has been associated with clinical failures (**Fig. 1**, **Table 3**).[30]

Regardless of which antibiotic is chosen for outpatient use, the suggested duration is 5 to 10 days, and should be tailored based on individual patient response. Patients who still have considerable signs of inflammation at 10 days of therapy may be failing because of inadequate drainage of the primary lesion or antibiotic resistance, and consultation with an ID specialist is advised.

The patient looks good to go home with oral antibiotics after incision and drainage. Should I give her a dose of vancomycin first?

No reliable evidence supports the practice of administering a single dose of IV antibiotics for those patients who are planning to be discharged on oral medications, and this practice should generally be discouraged.

My patient with suspected MRSA skin infection has one or more warning signs for complicated disease, including a toxic appearance, and I want to admit her. I am comfortable with vancomycin. Is there anything new I should know?

IV therapy is advised for patients admitted with suspected serious MRSA infections, regardless of the source. Vancomycin is an appropriate first-line choice. Its

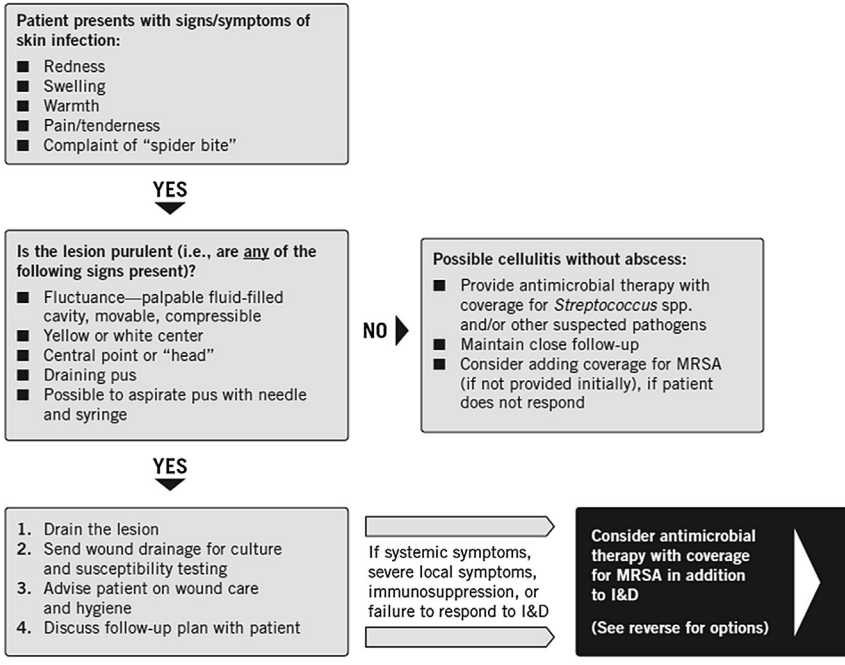

Fig. 1. Outpatient[a] management of CA-MRSA SSTI[b]. [a] For severe infections requiring inpatient management, consider consulting an infectious disease specialist. [b] Visit http://www.cdc.gov/mrsa for more information. I&D, incision and drainage. (*From* Centers for Disease Control. Outpatient Management of MRSA Skin and Soft Tissues Infections. Available at: http://www.cdc.gov/mrsa/treatment/outpatient-management.html.)

Table 3
Options for empirical outpatient antimicrobial treatment of SSTI when MRSA is a consideration[a]

Drug Name	Considerations	Precautions[b]
Clindamycin	FDA-approved to treat serious infections caused by *S aureus* D-zone test should be performed to identify inducible clindamycin resistance in erythromycin-resistant isolates	*Clostridium difficile*-associated disease, although uncommon, may occur more frequently in association with clindamycin compared with other agents
Tetracyclines Doxycycline Minocycline	Doxycycline is FDA-approved to treat *S aureus* skin infections	Not recommended during pregnancy. Not recommended for children younger than 8 y Activity against group A streptococcus, a common cause of cellulitis, unknown
TMP/SMX	Not FDA-approved to treat any staphylococcal infection	May not provide coverage for group A streptococcus, a common cause of cellulitis Not recommended for women in the third trimester of pregnancy Not recommended for infants <2 mo
Rifampin	Use only in combination with other agents	Drug-drug interactions are common
Linezolid	Consultation with an infectious disease specialist is suggested FDA-approved to treat complicated skin infections, including those caused by MRSA	Has been associated with myelosuppression, neuropathy, and lactic acidosis during prolonged therapy
MRSA is resistant to all currently available β-lactam agents (penicillins and cephalosporins) Fluoroquinolones (eg, ciprofloxacin, levofloxacin) and macrolides (erythromycin, clarithromycin, azithromycine) are not optimal for treatment of MRSA SSTIs because resistance is common or may develop rapidly		
Role of decolonization Regimens intended to eliminate MRSA colonization should not be used in patients with active infections. Decolonization regimens may have a role in preventing recurrent infections, but more data are needed to establish their efficacy and to identify optimal regimens for use in community settings. After treating active infections and reinforcing hygiene and appropriate wound care, consider consultation with an infectious disease specialist regarding use of decolonization when there are recurrent infections in an individual patient or members of a household		

[a] Data from controlled clinical trials are needed to establish the comparative efficacy of these agents in treating MRSA SSTIs. Patients with signs and symptoms of severe illness should be treated as inpatients.
[b] Consult product labeling for a complete list of potential adverse effects associated with each agent.

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mechanism of action (binding to cell wall precursors, not PBP-2) allows it to remain active even against MRSA. It has been in clinical use since 1958. It is affordable, generally well tolerated, and remains a cornerstone of treatment of MRSA infections. However, it has weaknesses. Over time, some strains of MRSA have shown increasing

minimum inhibitory concentrations (MICs) to vancomycin. This "MIC creep" usually happens because of increased cell wall thickness: the more cell wall to target, the more drug required to inhibit growth. Pharmacokinetic modeling indicates that achievement of an area under the curve:MIC ratio of at least 400 should provide the best chance of clinical cure.[31] Achieving that ratio is virtually impossible if the MIC is greater than 2 μg/mL, because the doses of vancomycin required would result in unacceptable risks of side effects, particularly renal toxicity and myelosuppression. This issue is more than academic. Overall, clinical outcomes track negatively with MICs: the higher the MIC, the higher the risk for complications or mortality.[32,33] The implication is that if the vancomycin MIC is greater than 1, then vancomycin should not be used. However, the story is more nuanced. First, recent findings[34] suggest that vancomycin MICs greater than 1.5 are associated with poorer outcomes regardless of the drug chosen. This effect was observed even in patients with MSSA treated appropriately with flucloxacillin, suggesting that increased vancomycin MICs may indicate the presence of yet-undefined virulence factors. Furthermore, many patients with deep MRSA infections treated with vancomycin do well, even if the MIC is later found to be 2 μg/mL.

MICs greater than 2 μg/mL are more alarming. By convention, *S. aureus* with a vancomycin MIC of 4 to 8 μg/mL is called vancomycin intermediate *S. aureus* (VISA). VISA remains rarely detected in the United States, although laboratories face challenges in identifying strains of heteroresistant VISA.[35] Even more alarming (although less common) is vancomycin-resistant MRSA, a term reserved for strains with MICs 16 μg/mL or greater. These strains seem to happen when MRSA acquires the genetic resistance element from vancomycin-resistant *Enterococcus* (VRE), rendering them resistant to vancomycin at any concentration. Regardless of the genetic basis of resistance, isolates with vancomycin MICs greater than 2 μg/mL should not be treated with vancomycin. Alternative treatments are available for these infections, including linezolid, daptomycin, and ceftaroline (described further later).[36]

If vancomycin is selected for SSTI and the patient responds, then no change in therapy is necessary, regardless of vancomycin MIC. On the other hand, if the patient fails to respond, then a change should be considered, especially if the vancomycin MIC is 1 to 2. Vancomycin should not be used if the MIC is known to be greater than 2 (**Box 2**).

My patient's MRSA abscesses keep coming back! Could she be colonized? If so, could I try decolonization?

By definition, MRSA colonization is asymptomatic. Most colonized patients never develop infection, and for that reason, screening is not recommended for the general population. However, many patients who develop MRSA infections are found to be colonized with the same organism at sites distant from the infection, especially the nares. Because nasal colonization with MRSA may be transient, decolonization is not recommended after a first MRSA infection. However, some patients (for reasons that remain unclear) progress from colonization to infection, in the skin or elsewhere, time after time. It may be possible to break the cycle of colonization and infection by attacking MRSA on the surfaces where it dwells, both on the patient's body and in the environment.

Nasal carriage of MRSA has been the focus of attention for many years, and this is the rationale for incorporating topical mupirocin (Bactroban) ointment into decolonization regimens. However, it is now clear that MRSA also readily inhabits other body locations, including the throat, rectum, vagina, and fingernails. It has the ability to remain viable in a wide range of environments, from countertops to beaches[37] to bed bugs.[38]

Box 2
Practical advice for the use of vancomycin in treating serious MRSA infections

- Vancomycin must be dosed IV for MRSA infections (oral vancomycin is not absorbed).
- Dosage in adults should be based on body weight:
  - Loading: weight 70 kg or greater: 2 g IV × 1 dose; weight less than 70 kg: 1.5 mg IV × 1 dose
  - Maintenance: 15 mg/kg (rounded to nearest 250 mg, max 2 gm per dose) IV every 12 hours thereafter; for central nervous system (CNS) infection, dose every 8 hours.
- Time to check vancomycin trough: before fourth or fifth dose, then weekly thereafter if stable renal function; check more frequently if dynamic renal function.
- Target trough level: 15 to 20 μg/mL for pneumonia, bacteremia, bone infection, CNS infection; target 10 to 20 μg/mL for SSTI.
  - If trough is lower than desired level: increase by increment of 250 to 500 mg per dose, and recheck 4 doses later.
  - If trough higher than desired level: if poor renal function, hold vancomycin and recheck level 24 hours later, then restart at same dose but now at daily interval; if normal renal function, reduce dose by 250 to 500 mg and recheck trough before fourth dose.
- Peak level: vancomycin peaks should not be checked.

For this reason, multiple attempts at decolonization may be necessary. In one case series, an average of 2 rounds of aggressive decolonization were required to achieve eradication, and some patients needed 10 rounds.[39] Furthermore, that study used oral antibiotics for patients with urinary or rectal carriage. However, the IDSA guidelines do not recommend routine use of oral antibiotics, because of concern that benefits may be outweighed by toxicity and drug resistance. The bottom line: whether decolonization is attempted with a regimen of mupirocin plus chlorhexidine gluconate or chlorinated water, patients should be counseled on diligence, persistence, and attention to detail (**Box 3**).

My hospitalized patient developed a fever unexpectedly 2 days ago. I drew blood cultures, and yesterday the laboratory reported 1 of 2 sets positive for gram-positive cocci in clusters. I anticipated coagulase-negative Stapyhylococcus, but today the report was updated as MRSA. What should I do?

By convention, the discovery of *S. aureus* in a blood culture (either MRSA or MSSA) is taken seriously, even if some bottles are negative. Because MRSA lives on the skin, it can contaminate blood cultures just like coagulase-negative *Staphylococcus*. However, because the consequences of true *S. aureus* bacteremia may be so grave, a workup is recommended. The essential task is to determine whether bacteremia is uncomplicated (and can thus be treated for a minimum of 14 days) or complicated, which requires double, triple, or longer length of therapy (**Box 4**).

Should I add gentamicin for synergy in S. aureus bacteremia?

The practice of adding gentamicin to regimens for *S. aureus* bacteremia stems from that approach in enterococcal endocarditis, in which it is important and well established. However, the benefit of this practice has been insubstantial in uncomplicated *S aureus* bacteremia or native-valve endocarditis. Gentamicin shows synergy *in vitro*

Box 3
Environmental and personal decolonization tips for recurrent MRSA infections

Environmental hygiene: regularly clean high-touch surfaces (eg, counters, door knobs, bath tubs, and toilet seats) with standard household detergents.

Personal hygiene: regular bathing and cleaning of hands with soap and water or an alcohol-based hand gel. Avoid reusing or sharing personal items (disposable razors, linens, and towels) that have contacted infected skin.

Decolonization strategies:

- Nasal decolonization with mupirocin twice daily for 5 to 10 days, plus
- Topical body decolonization regimens with 4% chlorhexidine gluconate for 5 to 14 days (apply to whole body except eyes; allow to dwell for 5 minutes before rinsing off), or
- Dilute bleach baths (1 teaspoon per gallon of water [or 0.75 cup per 0.75 tub or 13 gallons of water]; soak up to the jawline for 15 minutes twice weekly for 3 months).
- Keep fingernails trim, scrub under nails gently with soap and water, avoid picking skin.
- Oral antimicrobial therapy not routinely recommended for decolonization. An oral agent plus rifampin, if the strain is susceptible, may be considered for decolonization if infections recur despite above measures.
- Nasal and topical body decolonization of asymptomatic household contacts may be considered.
- Screening cultures before or after decolonization are not routinely recommended.

Data from Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis 2011;52(3):285–92.

Box 4
Management highlights for patients with MRSA bacteremia

- Prompt initiation of antibiotics, regardless of the number of blood culture bottles positive
- MIC testing to vancomycin and at least 1 alternative agent (daptomycin, linezolid, or ceftaroline)
- Consider switching to alternative agent if vancomycin MIC greater than 1, or if failure to improve within 72 hours, or if patient worsens at any time
- Remove central venous catheters
- 2 weeks of therapy if bacteremia is uncomplicated, as defined by:
  - Negative echocardiogram to rule out infective endocarditis, and
  - No indwelling prosthetic material (eg, valves, joints, shunts), and
  - Negative blood cultures within 4 days of antibiotic initiation, and
  - Defervescence within 72 hours of antibiotic initiation, and
  - No evidence of metastatic foci (eg, pulmonary or CNS emboli)
- 4 to 6 weeks of therapy if the above criteria are not met, starting the clock at the patient's first negative blood culture
- Involvement of ID and cardiology if patient rules in for endocarditis. Outcomes are superior for early surgery among those who require valve replacement

and in animal models when added to β-lactams for MSSA endocarditis.[40] However, the benefit of this practice in clinical trials was to shorten bacteremia by an average of 1 day, and no improvement in terms of mortality was shown.[41] Concern over potential renal toxicity prompted a recent trial that found decreased creatinine clearance in 22% of patients who received initial gentamicin (plus nafcillin or vancomycin) versus 8% of patients who received daptomycin only and no gentamicin ($P = .005$). Gentamicin is not recommended for uncomplicated bacteremia or native-valve endocarditis; for now, in the absence of data regarding gentamicin-free regimens for prosthetic valve infections, and in light of the serious nature of those infections, gentamicin is still endorsed for prosthetic valve endocarditis (plus rifampin and a backbone antibiotic such as vancomycin).

My patient with central-line associated MRSA bacteremia has not cleared his cultures after line removal and a week of IV vancomycin. The vancomycin MIC is 2 μg/mL. What about drugs besides vancomycin for MRSA bacteremia?

Daptomycin (Cubicin) is a lipopeptide antibiotic that attacks the cell membrane (not the outer wall), causing cell death via potassium loss and membrane depolarization. It is approved by the US Food and Drug Administration (FDA) for gram-positive SSTI, *S. aureus* bacteremia, and *S. aureus* right-sided endocarditis. It has also been used off-label for orthopedic infections, with outcomes generally similar to those of patients treated with standard therapy.[42] Because of its chemical structure, daptomycin is inactivated by pulmonary surfactant, and thus is unreliable as a treatment of pneumonia. Therapeutic dose monitoring is neither necessary nor available. Most patients tolerate daptomycin well, although celebrated toxicities include rare instances of rhabdomyolysis in patients also receiving statins,[43] and even more rare cases of pulmonary eosinophilic pneumonia.[44] Daptomycin is officially dosed at 4 mg/kg IV daily for SSTI, and at 6 mg/kg IV daily for bacteremia and endocarditis. However, higher doses may be necessary in cases of bloodstream infection. Perversely, as vancomycin MICs creep up, so too may daptomycin MICs, even although the drugs act on different bacterial targets. In a landmark study of patients with *S aureus* bacteremia (MSSA or MRSA, complicated or uncomplicated), clinical outcomes for patients treated with daptomycin were not inferior to those of patients treated with standard therapy (vancomycin with or without gentamicin for MRSA infections).[45] Of 120 patients in the daptomycin arm, 19 (16%) failed to achieve microbiological cure; 6 of these (32%) developed resistance to daptomycin (MIC $\geq$2 μg/mL) during treatment. It is not clear whether higher doses of daptomycin may overcome this phenomenon, but it seems to be well tolerated at doses of 10 mg/kg daily,[46] and that dose is recommended by the IDSA for bacteremia that has failed treatment with vancomycin.[1] The duration of bacteremia with MRSA is often longer than that with MSSA, and 7 to 9 days of MRSA bacteremia is common, whether vancomycin or daptomycin is used. Daptomycin is a potent, well-tolerated IV medication with potential benefits in MRSA SSTI and bacteremia; it should never be used in pulmonary infections; and (like any drug) it may fail as a result of resistance acquired during therapy.

My patient has MRSA in a urine culture. Can this be a true pathogen in the urine?

MRSA has been cultivated from virtually every location and fluid in and on the human body; urine is no exception. As with any bacteriuria, contamination of introital flora may contaminate a clean-catch specimen, and the presence of 5 or more squamous epithelial cells per high-powered field should trigger consideration of obtaining a

new specimen. However, in the absence of suspicion of contamination, the central question is: does your patient have asymptomatic MRSA bacteriuria or a true ascending urinary tract infection, and if so, is your patient also bacteremic? Concern for the latter possibility has led to the teaching that *S. aureus* in the urine (either MRSA or MSSA) should prompt a workup for bacteremia. But how often are bacteriuric patients also bacteremic?

Satisfactory answers are not readily available. Clearly, bacteremia is often associated with bacteriuria. Among hospitalized patients with *S. aureus* bacteremia (MRSA or MSSA), 24% to 34% also had bacteriuria.[47,48] *S. aureus* in the urine also correlated with a roughly 2-fold increase in complications of bacteremia, including endocarditis, osteomyelitis, septic emboli, or septic shock. In one study, *S. aureus* bacteremic patients who also had bacteriuria were more likely to die of their infection (32% vs 14%; $P = .036$).[47] However, it is less clear how many patients with MRSA in the urine are at risk of developing bacteremia. Given the serious nature of concurrent bacteriuria and bacteremia, it is reasonable to rapidly assess patients with true *S. aureus* bacteriuria (either MSSA or MRSA) and to consider drawing blood cultures, especially in hospitalized patients, those with indwelling urinary catheters or recent urinary surgery, or those at high risk for infective endocarditis.

My patient has culture-proven MRSA pneumonia. What is the best treatment?

MRSA pneumonia is a highly lethal condition, and yet the ideal treatment of MRSA pneumonia remains controversial. Vancomycin has been the treatment of choice for many years, and current recommendations to achieve vancomycin troughs of 15 to 20 μg/mL are based on both experimental data[49] and clinical observations[50] that patients who achieve that level have modestly lower mortality than those whose troughs are higher or lower. However, a meta-analysis of 2 small studies[51] suggested that linezolid (Zyvox) might be superior to vancomycin for MRSA pneumonia. A subsequent larger randomized trial[52] of linezolid versus vancomycin failed to show any significant difference in all-cause mortality at 60 days, although 11% more patients in the linezolid arm achieved clinical improvement.

Linezolid is an oxazolidinone antibiotic which functions by attacking the ribosome, thereby blocking protein synthesis. Its main indications are for nosocomial pneumonia and complicated SSTI. Its spectrum is limited to gram-positive organisms, including MRSA and VRE; like vancomycin, it has no activity against gram-negatives. Linezolid has a reputation for toxicity, including myelosuppression, peripheral neuropathy, optic neuritis, and serotonin syndrome in patients on selective serotonin reuptake inhibiting medications. However, in the pneumonia trial discussed earlier, there was no significant difference in frequency of side effects or toxicities between the linezolid and vancomycin arms. The ease of dosing linezolid, lack of monitoring, and ability to step down to oral dosing are all attractive; cost and potential toxicity are obvious downsides.

What about the new anti-MRSA cephalosporin I have heard about?

Ceftaroline (Teflaro) is a cephalosporin with the unique property of high-level activity against MRSA. It was designed specifically to bind avidly to PBP-2A, and also retains excellent avidity for other PBPs, giving it low MICs for other gram-positives and also a variety of aerobic enteric gram-negatives. It does not possess activity against *Pseudomonas* species, facultative abdominal anaerobes, or atypical respiratory pathogens. It is FDA-approved for the treatment of CA pneumonia and for complicated SSTIs. It is an

exciting class of medication, which seems to possess the best attributes of cephalosporins (predictable pharmacokinetic/pharmacodynamic qualities) and vancomycin (anti-MRSA activity). It is available only for IV administration, and is dosed every 12 hours. In approval trials, it was generally well tolerated, although minor adverse events included nausea, rash, and subclinical positive direct Coombs tests.[53] Ceftaroline was found to be clinically noninferior to ceftriaxone in CA pneumonia[54] or to the unconventional regimen of vancomycin plus aztreonam in cSSTI.[55] It has shown more favorable MICs for *S. pneumoniae* than ceftriaxone and for MRSA than vancomycin. However, the number of patients with MRSA pneumonia in phase 3 trials was insufficient to earn FDA approval for that indication. Similarly, although hopes are high and there is a strong reason to think it will be highly effective, ceftaroline has not yet been approved for MRSA bacteremia. Ceftaroline may be an attractive option for a variety of MRSA infections in the future, but its value in MRSA bacteremia and pneumonia remains unproved. It should generally be used only in consultation with ID specialists.

When should I get help from an ID specialist?

This depends on your individual experience, comfort level, and specific patient situation. ID consultation for patients hospitalized with *S. aureus* bacteremia may provide enhanced guideline-directed care (**Box 5**).[56]

Things sound bleak. Are we making any progress with MRSA?

The overall situation with MRSA in the United States is mixed. On the one hand, HA-MRSA infections seem to be decreasing. During 3 years of intensive national surveillance, from 2005 to 2008, all HA-MRSA infections decreased by 28%.[57] From 1997 to 2007, the National Healthcare Safety Network reported a decrease in nosocomial MRSA bloodstream infections of nearly 50%.[58] This situation is still unacceptable, but the trend toward improvement is clear; so much so, that CDC has labeled the fight against health care-acquired MRSA infection a winnable battle.[59]

The situation with CA-MRSA is less rosy, and no substantial decrease in CA-MRSA infections has been reported. This situation should not come as a surprise. HA-MRSA can be reduced through a series of evidence-based practices related to health care worker hand hygiene, hospital sanitation, sterile technique during procedures, and so forth. CA-MRSA, on the other hand, is transmitted outside the hospital, and thus outside our direct control. Public health interventions (including information for

Box 5
Suggested criteria for infectious diseases consultation for MRSA infection

- Bloodstream infection or endocarditis
- Orthopedic infection
- MRSA isolates with vancomycin MIC greater than 1 μg/mL
- Patients with underlying renal insufficiency
- Patients who develop toxic effects of antibiotics
- Use of IV antibiotics other than vancomycin
- Failure to improve after 3 to 5 days of therapy, or progression of illness after any period of therapy
- Anticipation of outpatient parenteral therapy after discharge

patients and the general public) may drive CA-MRSA rates down over time, but that change will likely happen more slowly.

Why is there no vaccine for MRSA?

There is substantial ongoing effort in development of an MRSA vaccine. Experimental vaccines have yielded intriguing results, including in mouse models.[60,61] However, immunity to *S. aureus* seems to be complex, as shown by the observation that repeat infections are common. The immune response to MRSA involves both humoral and phagocyte responses, and the best antigenic stimuli remain elusive.[62] A recent human trial yielded impressive antistaphylococcal antibody titers but disappointing results in terms of protection against staphylococcal infection in patients undergoing cardiac surgery; and, perversely, the vaccine was associated with an increased risk of multiorgan system failure compared with placebo (0.9 vs 0.5/100 person-years; $P = .042$).[63] Clearly, there is work to be done in this important area.

I would like to know more about MRSA. What is the single best resource for further reading?

The 2011 IDSA Guidelines[1] are a superb resource. They are freely available online, along with guidelines for treating a variety of other pathogens and infectious syndromes: http://www.idsociety.org/IDSA_Practice_Guidelines.

Where can I find high-quality information to share with my patients about MRSA?

The CDC publishes excellent information online regarding MRSA, for both patients and health care workers: http://www.cdc.gov/mrsa.

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