Review and Treatment of Community-Associated Methicillin-Resistant Staphylococcus aureus Infections

by Spencer Durham, PharmD, BCPS (AQ-ID); Chelsea Frantz, PharmD; and Marroyln Simmons, PharmD, MS, BCPS

Upon successful completion of this activity, the pharmacist should be able to:

1. Review microbiological data regarding Staphylococcus aureus.
2. Discuss the differences between hospital-associated methicillin-resistant Staphylococcus aureus (HA-MRSA) infections and community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) infections.
3. Review pharmacotherapy of the management of CA-MRSA in both the outpatient and inpatient settings.
4. Describe methods to decolonize a patient with a history of recurrent MRSA and understand when it is appropriate to consider decolonization.
5. Discuss the special considerations that must be made when treating a pediatric patient with a CA-MRSA infection.

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2. List drugs used to treat CA-MRSA in both the outpatient and inpatient settings.
3. Describe methods to decolonize a patient with a history of recurrent MRSA and understand when it is appropriate to consider decolonization.
4. Discuss the special considerations that must be made when treating a pediatric patient with a CA-MRSA infection.

INTRODUCTION

Staphylococcus aureus is a leading cause of infection in both the community and hospital settings. It is a highly virulent bacterial organism capable of causing a wide variety of infections, ranging from simple disorders such as cellulitis and abscesses to severe disorders such as pneumonia, osteomyelitis, and bacteremia. In the clinical setting, Staphylococcus aureus is generally classified into two major types: methicillin-sensitive Staphylococcus aureus (MSSA) and methicillin-resistant Staphylococcus aureus (MRSA). While MRSA was traditionally thought of as a pathogen encountered primarily in large, tertiary teaching hospitals, MRSA has been increasingly common in the community setting since the 1990s, leading to the introduction of the term community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA). Infections caused by CA-MRSA are becoming increasingly common in patients with no known risk factors for MRSA infections, in some cases with fatal consequences. This has received much media attention in recent years. As the prevalence of CA-MRSA infections increases, pharmacists will play an important role in the management of these infections. Thus, pharmacists must have thorough knowledge of this pathogen and its viable treatment options.

STAPHYLOCOCCUS AUREUS REVIEW

The name “Staphylococcus” is derived from a Greek word meaning “bunch of grapes.” The pathogen was given this name as a reference to the way it appears on agar plates. All species of Staphylococcus are gram-
positive, facultative anaerobes, meaning they can grow with or without the presence of oxygen. *Staphylococcus aureus* is distinguished from all other species of *Staphylococcus* via the coagulase test, which is positive if the pathogen is *Staphylococcus aureus*. All other species of *Staphylococcus* are thus termed coagulase-negative staphylococci (CoNS). Although CoNS are much less prevalent than *Staphylococcus aureus*, several species, such as *Staphylococcus epidermidis*, are pathogenic to humans and are frequently isolated in infections involving indwelling foreign medical devices.

*Staphylococcus aureus* is a remarkably hardy organism, capable of surviving in extreme environmental conditions. Unlike many other bacteria, it can grow in wide pH ranges, extreme temperatures, and high salt concentrations. This helps to explain why *Staphylococcus aureus* can survive on inanimate objects, or fomites. The ability of this pathogen to survive on fomites is thought to be a major reason why outbreaks of CA-MRSA occur, particularly among athletic teams. Additionally, *S. aureus* is notorious for causing colonization in humans. Some reports suggest that up to 40 percent of adults are asymptomatic carriers. The most common place of colonization is the anterior nares, but the vagina, perianal area, and nasopharynx may also harbor the pathogen.

As mentioned previously, *Staphylococcus aureus* can cause an extremely broad range of disorders, and this remarkably high pathogenicity is explained by an array of virulence factors inherent to the pathogen. Of note is that all *staphylococcal* species produce a narrow-spectrum beta-lactamase. This beta-lactamase mediates resistance to penicillin, ampicillin, and amoxicillin, but does not deactivate other beta-lactam antibiotics, such as nafcillin and the cephalosporins. However, amoxicillin and ampicillin will be effective if given in combination with a beta-lactamase inhibitor. In addition to this beta-lactamase, some strains of *S. aureus* acquire a gene known as mecA, which allows for the production of penicillin binding protein 2a (PBP2a). This unique penicillin binding protein has an exceptionally low binding affinity for beta-lactam antibiotics, and its presence is what determines an *S. aureus* strain to be “methicillin-resistant.” Interestingly, MRSA isolates are resistant to not only the anti-staphylococcal penicillins but all beta-lactam antibiotics due to the presence of mecA (with the one notable exception of the new cephalosporin antibiotic ceftaroline, which will be discussed in a subsequent section).

*Staphylococcus aureus* also produces coagulase and clumping factors A and B. These substances interfere with prothrombin and fibrinogen, which causes large clusters of organisms to form, effectively hindering phagocytosis. The clumping factors are also thought to promote adherence to skin and foreign substances, which may help to explain the major role of *S. aureus* in skin and foreign medical device infections. Phagocytosis is also hindered by Protein A, located in the cell wall. Protein A is capable of absorbing serum immunoglobulins, specifically IgG, which hinders opsonization and thus phagocytosis.

One of the most notable properties of *S. aureus* is its propensity to produce a vast array of toxins. Toxin production mediates many of the clinical syndromes caused by *S. aureus*. One of the most serious toxins is toxic shock syndrome toxin-1 (TSST-1), which is implicated in cases of staphylococcal toxic shock syndrome. This toxin causes a massive release of cytokines within the body, known mediators of the sepsis syndrome. Other toxins, such as exfoliative toxins A and B, cleave glycoproteins in the skin and cause skin separation, which can lead to localized skin disorders such as bullous impetigo, or more severe disorders such as the well-known staphylococcal scalded skin syndrome (SSS). One particular toxin that has received much attention in the medical literature is the Panton-Valentine leukocidin (PVL), a toxin implicated in many CA-MRSA infections. PVL causes death of neutrophils and macrophages by producing pores in the plasma membrane and is also associated with severe inflammation. PVL-producing strains of CA-MRSA have been associated with both skin and lung infections, particularly necrotizing pneumonia.

**HEALTH CARE VERSUS COMMUNITY-ASSOCIATED MRSA**

The gene cassette known as staphylococcal chromosomal cassette (SCCmec), which includes the *mecA* gene mentioned previously, is responsible for bacterial resistance to methicillin and methicillin-like drugs by altering penicillin-binding protein (PBP) in the bacterial cell wall. Therefore, a drug whose mechanism involves binding to PBP, such as penicillins, cephalosporins, and carbapenems,
will not be active against MRSA. The type of SCCmec determines the level of susceptibility to other antibiotics such as clindamycin, fluoroquinolones, and aminoglycosides. Historically, health care-associated strains of MRSA contained SCCmec types such as type I, II, and III that conferred more resistance to these other antibiotics. Community-associated strains frequently remained susceptible, because they often contained subtypes IV and V. It is important to remember that the epidemiology of bacterial strains changes over time, and there is now a considerable amount of genetic overlap between nosocomial-derived and community strains of MRSA.

A major difference between health care associated-MRSA (HA-MRSA) and CA-MRSA is the risk factors associated with infection. Risk factors for HA-MRSA generally include prolonged hospitalization, presence of indwelling medical devices such as catheters, hemodialysis, and long-term antibiotic use. In contrast, patients that develop infections from CA-MRSA are often otherwise healthy with no other major risk factors for infection. Some risk factors identified for CA-MRSA include individuals in close physical contact such as prison inmates, military personnel, and athletes, as well as poor communal hygiene practices such as sharing towels. Other populations that are commonly affected by CA-MRSA include injection drug users, homeless, HIV seropositive individuals, and certain ethnic groups such as native Alaskans, Hawaiian Islanders, and American Indians.

CA-MRSA has a strong propensity to cause skin and soft tissue infections characterized by cellulitis and abscess formation. It has also been shown to cause necrotizing pneumonia, diabetic foot infections, and infective endocarditis. Based on a report from the Centers for Disease Control and Prevention, hospitalizations for S. aureus-related cellulitis and abscesses have increased consistently by more than 25 percent per year from 1999 to 2005. In contrast, S. aureus-related osteomyelitis, post-operative infections, and device-related infections did not see a dramatic increase over the study period. This data shows that CA-MRSA has become increasingly more common within the health care setting, and the division between HA-MRSA and CA-MRSA is becoming more and more blurred.

**EPIDEMIOLOGY**

MRSA was a health care associated infection until the 1980s, when it was identified in an outbreak among intravenous drug users in Detroit. Outbreaks of MRSA were later found in community populations such as the Australian aborigines, Native Americans, soldiers, homosexual males, prisoners, and athletes. In 1999, CA-MRSA received national attention when four school children in the United States died from infections with the organism. Worldwide incidence varies, but consistently high prevalence rates are found in the United States, Australia, South America, Japan, and southern Europe.

Within the United States, the incidence of CA-MRSA can vary significantly by region, state, and even city or county. Information from the Center for Disease Dynamics, Econom-
ics, and Policy showed a sharp increase in the incidence of MRSA in the early 2000s that was followed by a plateau period. In 2000, four of the nine United States census divisions reported *S. aureus* resistance rates to methicillin at greater than 30 percent. By 2004, seven of the nine divisions demonstrated resistance levels of at least 40 percent, and all census divisions had a resistance rate greater than 40 percent by 2005. In the East South Central region of the United States, which includes Mississippi, Alabama, Kentucky, and Tennessee, MRSA accounts for nearly 70 percent of all *S. aureus* infections. To further break down the varying incidence of MRSA, the 2009 Florida Annual Morbidity Statistics Report lists the MRSA incidence for the state at about 50 percent. However, within Florida, the North Central Region demonstrated a MRSA incidence of 57.2 percent while the South East Region reported an MRSA incidence of only 45.4 percent. Additionally, population-based surveillance studies have indicated a disease incidence of 18 per 100,000 people in Baltimore, and 24.7 per 100,000 persons in Atlanta. In Chicago, CA-MRSA incidence increased from 24 per 100,000 persons

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Adult Dose</th>
<th>Pediatric Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Cellulitis: 300–450 mg Q8h x 5–10 days</td>
<td>(Max: 40 mg/kg/day)</td>
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<tr>
<td></td>
<td>Cellulitis: 600 mg Q8h x 7–14 days</td>
<td>Cellulitis: 10–13 mg/kg/dose Q6–8h x 5–10 days</td>
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<tr>
<td></td>
<td>OM: x 8 weeks (⁺/- Rifampin)</td>
<td>OM: x 7–14 days</td>
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<tr>
<td></td>
<td>Septic Arthritis: x 3–4 weeks</td>
<td>PNA: x 7–21 days</td>
</tr>
<tr>
<td></td>
<td>PNA: x 7–21 days</td>
<td>Septic Arthritis: x 3–4 weeks</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxazole – Trimethoprim</td>
<td>800/160 mg to 1600/320 mg Q12h x 5–10 days</td>
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<tr>
<td></td>
<td>4–6 mg TMP/kg/dose Q12h x 5–10 days</td>
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</tr>
<tr>
<td>Linezolid</td>
<td>600 mg IV/PO Q12h</td>
<td>40 mg/kg/day</td>
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<tr>
<td></td>
<td>SSTI/PNA: x 10–14 days</td>
<td>Age ≤ 11: 10 mg/kg Q8h</td>
</tr>
<tr>
<td></td>
<td>HA-PNA: x 7–21 days</td>
<td>(Max Dose: 600 mg)</td>
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<tr>
<td></td>
<td>Meningitis: x 2 weeks</td>
<td>Age ≥ 12: Refer to adult dosing</td>
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<tr>
<td></td>
<td>Septic Arthritis: x 3–4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain/Spinal Abscess: x 4–6 weeks</td>
<td></td>
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<td></td>
<td>OM: x 8 weeks (minimum)</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg BID x 5–10 days</td>
<td>Age &lt; 8 years: Use alternate agent (8+ years ≤ 45 kg): 2 mg/kg/dose Q12h</td>
</tr>
<tr>
<td></td>
<td>100 mg BID</td>
<td>(8+ years ≥ 45 kg): Refer to adult dosing</td>
</tr>
<tr>
<td>Minocycline</td>
<td>200 mg x 1, then 100 mg BID</td>
<td>Age &lt; 8 years: Use alternate agent initial: 4 mg/kg (max 200 mg/dose)</td>
</tr>
<tr>
<td></td>
<td>Maintenance: 2 mg/kg/dose Q12h (max: 100 mg/dose)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250–750 mg Q12h x 7–14 days</td>
<td>10–15 mg/kg/dose Q12h x 7–14 days</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>500–750 mg Q24h x 7–14 days</td>
<td>Age 6 months to 5 years: 10 mg/kg/dose Q12h</td>
</tr>
<tr>
<td></td>
<td>Age ≥ 5 years: 10 mg/kg/dose Q24h</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg Q24h x 7 – 21 days</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Rifampin (decolonization)</td>
<td>600 mg/day or 300–450 mg Q12h x 5–10 days</td>
<td>7.5 mg/kg/dose Q12h x 5–10 days</td>
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<td></td>
<td><strong>Must use in combination with another antistaphylococcal antibiotic to prevent rapid resistance</strong></td>
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<td>7.5 mg/kg/dose Q12h x 5–10 days</td>
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| cSSTI: complicated skin and soft tissue infection; OM: osteomyelitis; PNA: pneumonia; TMP: trimethoprim; HA-PNA: healthcare-associated pneumonia; *Pediatric doses should not exceed the recommended adult doses; **Adapted from the IDSA guidelines on the treatment of MRSA infections
to 164.2 per 100,000 persons in a five-year period.

While the incidence of MRSA may vary by the region of the United States, the strain of MRSA causing disease is almost exclusively the USA300 strain. The USA300 strain accounts for 97 percent of the MRSA that causes skin and soft tissue infections. The USA300 strain of MRSA typically exhibits susceptibility to trimethoprim-sulfamethoxazole, clindamycin, and tetracycline. Resistance to erythromycin is almost absolute, with a resistance rate as high as 92.8 percent. The CDC recommends that a D-Test be performed in order to test for inducible resistance to clindamycin in MRSA isolates that are found to be resistant to erythromycin but susceptible to clindamycin.

More resistant strains of USA300 have been found in men who have sex with men (MSM) in San Francisco and Boston. These strains have large, conjugative plasmid carrying genes encoding for resistance to mupirocin, macrolides, and clindamycin. Some of these strains may carry an additional plasmid that can cause resistance to tetracycline in up to 66 percent of cases and resistance to ciprofloxacin in up to 77 percent of cases. However, these strains continue to be susceptible to trimethoprim-sulfamethoxazole.

While most of the MRSA seen throughout the United States is the USA300 strain, the USA400 clone of MRSA is the dominant MRSA species in Alaska. This strain has been found to be resistant to erythromycin and clindamycin but it continues to be susceptible to other agents. Overall, antibiotic resistance patterns vary remarkably by region and clinicians should monitor susceptibility patterns within their practice area.

PHARMACOTHERAPY OPTIONS FOR THE OUTPATIENT MANAGEMENT OF CA-MRSA

The management of MRSA infections in the outpatient setting may be challenging for the clinician as MRSA is resistant to many antibiotics and susceptibility patterns vary greatly by geographic region. Treatment has become so challenging that, in 2011, the Infectious Disease Society of America (IDSA) published new guidelines for the treatment of MRSA infections in adults and children. It is important for pharmacists to review and become familiar with the antibiotics that typically treat CA-MRSA infections, as this may be one of the most frequently encountered infections in the community setting. These agents will be reviewed in detail here. Appropriate dosages and treatment durations may be further reviewed in Table 2.

**Sulfamethoxazole-Trimethoprim**

(Bactrim, Septra, Sulfratrim)

Trimethoprim-sulfamethoxazole (SMZ/TMP) is a broad-spectrum combination antibiotic with a unique action mechanism against bacteria. Sulfamethoxazole inhibits the conversion of para-aminobenzoic acid (PABA) to dihydrofolate (DHF), and trimethoprim blocks the conversion of DHF to tetrahydrofolate (THF) by inhibiting dihydrofolate reductase. These two mechanisms block folate production and thus its incorporation into purines, preventing further bacterial DNA synthesis. Together, they exhibit time-dependent killing against a wide variety of gram positive and gram negative organisms, including CA-MRSA. SMZ/TMP achieves high concentrations in the urine and is commonly prescribed for the treatment of urinary tract infections. It also penetrates secretions such as the sputum and bronchial secretions, vaginal fluid, and middle ear fluid; all common infection sites.

*S. aureus* is able to develop resistance to SMZ/TMP in a number of ways. A unique mechanism is an increased production of PABA. The amount of PABA within the bacteria exceeds SMZ/TMP’s capacity to inhibit folate production within the bacterial cell allowing DNA synthesis to continue. Other mechanisms include plasma mediated resistance such as altering enzyme affinity, and loss of permeability preventing the drug from entering the cell to reach its site of action.

Combination products are available in intravenous solution, oral tablets, and an oral suspension. Oral dosage forms include two strengths of oral tablets—single strength (SS) SMZ/TMP 400-80 mg and double strength (DS) SMZ/TMP 800-160 mg. The cherry-flavored oral suspension is available as SMZ/TMP 200-40 mg/5mL. Intravenous SMZ/TMP is available in 80-16 mg/mL in single and multiple dose vials. In general, it should be dosed based on the trimethoprim component, particularly in pediatric patients who require weight-based dosing.

There are several clinically important adverse reactions related to the use of SMZ/TMP. Gastrointestinal adverse effects such as nausea, vomiting, and diarrhea are common. SMZ/TMP is known to contribute to cholestasis and is as-
associated with cholestatic jaundice, pancreatitis, and hepatotoxicity for which fatal hepatic necrosis has occurred. Patients with a history of serious sulfa allergy are at an increased risk of hypersensitivity reactions with sulfamethoxazole.

Dermatologic reactions are among the most common adverse effects associated with SMZ/TMP and often involve rash, photosensitivity, pruritus, or urticaria. If dermatologic side effects occur, very close observation is needed to prevent serious skin reactions. If a patient experiences extensive rash while taking SMZ/TMP, the prescriber should be contacted and the drug may need to be changed to another active agent and/or discontinued. Steven-Johnson Syndrome (SJS) is a rare but potentially fatal skin reaction that can occur with use of SMZ/TMP. Use of SMZ/TMP is among the most commonly suspected drug-induced causes of Steven-Johnson Syndrome. Patients should be encouraged to maintain adequate hydration during their treatment period to prevent crystalluria and potential renal failure. Aseptic meningitis presents very similar to viral or bacterial meningitis; however, analysis and culture of cerebrospinal fluid (CSF) via lumbar puncture would not show evidence of an infectious origin. Once the drug is stopped, symptoms will resolve.

There is risk for developing aseptic meningitis upon re-challenge, and often patients are served best to not receive the drug in the future. SMZ/TMP can also cause a number of hematologic reactions such as agranulocytosis, aplastic anemia, methemoglobinemia, hemolytic anemia, and megaloblastic anemia. Hemolytic anemia is related to genetic glucose-6-phosphate dehydrogenase (G6PD) deficiency, and patients known to have this mutation should not receive SMZ/TMP. Patients should be encouraged to maintain a healthy diet rich in folic acid or a multivitamin supplement if taking SMZ/TMP for an extended duration of time due to the risk for megaloblastic anemia secondary to folate deficiency.

SMZ/TMP is also associated with several clinically significant drug interactions. The use of SMZ/TMP in combination with cyclosporine increases the risk for renal failure and should be avoided if possible. SMZ/TMP, as well as other sulfonamides, can increase the international normalized ratio (INR) in patients taking warfarin through the inhibition of CYP2C9 enzymes. A warfarin dose reduction of up to 20 percent may be warranted in patients requiring SMZ/TMP.

Phenytoin levels can also be increased by the same mechanism, and patients should be closely observed for signs of toxicity such as sedation, confusion, or loss of motor coordination.

Clindamycin (Cleocin)
Clindamycin is a protein synthesis inhibitor within a class of antibiotics known as lincosamides. Clindamycin inhibits protein synthesis by binding to the 50s subunit of ribosomal RNA. It is bacteriostatic against S. aureus, and therefore should not be used in patients who are immunosuppressed or have severe, complicated infections such as bacteremia. Clindamycin is commonly used to treat skin and soft tissue infections because it is thought to decrease the release of toxins by pathogens such as S. aureus. In MSSA infections, it is an alternative option for patients who are allergic to penicillins or cephalosporins.

Methicillin-resistant S. aureus (MRSA) is often susceptible to clindamycin, but it might be less likely to be effective against MRSA depending on the resistance patterns of the region. The in vitro susceptibility of clindamycin to CA-MRSA is highly dependent on the presence or absence of a resistance mechanism known as “inducible resistance.” While inducible clindamycin resistance is more likely to occur in HA-MRSA isolates, it is important to perform additional testing to determine if clindamycin will develop resistance during treatment. On a susceptibility report, if the isolate shows resistance to erythromycin, it is necessary to assess for the presence of inducible macrolide-lincosamide-streptogramin B resistance with a D-Test. If the D-Test is positive, the isolate will develop resistance during treatment with clindamycin and increase the risk for therapeutic failure.

Clindamycin is available in multiple dosage forms for various indications other than S. aureus infections. It has the advantage of being available in intravenous and oral dosage forms, making the transition from inpatient to outpatient more convenient. The injectable formulations contain clindamycin phosphate as 150 mg/mL, and oral capsules contain clindamycin hydrochloride in
strengths of 75 mg, 150 mg and 300 mg. The cherry-flavored oral solution contains clindamycin palmitate hydrochloride at a concentration of 75 mg/5 mL. Of note, all clindamycin preparations express concentrations using the amount of clindamycin base, and therefore intravenous and oral doses are equivalent. Clindamycin penetrates into skin tissue, bone, and concentrates well in the urine; however, it does not achieve significant levels within the CSF even in the presence of inflamed meninges. Therefore, it should not be used to treat MRSA infections involving the central nervous system such as meningitis and brain or spinal abscesses.

The most common adverse effects associated with the use of oral clindamycin include nausea, vomiting, and diarrhea. It is often implicated in cases of *Clostridium difficile* associated diarrhea (CDAD) and carries a Black Box Warning regarding this adverse effect. It is otherwise well tolerated but does carry the risk of SJS and jaundice. As it is hepatically metabolized, caution is advised in patients with severe hepatic impairment. However, no dose adjustments are recommended.

**Linezolid (Zyvox)**

Approved by the Food and Drug Administration in early 2000, linezolid is the only drug within a new class of antibiotics called oxazolidinones. It works by binding to the 23s ribosomal RNA at the 50s subunit, thereby inhibiting bacterial protein synthesis. While it has bactericidal activity against *Streptococcus*, it is only bacteriostatic against *Staphylococcus*, making it less ideal for immunocompromised patients. It is FDA approved for use in MRSA nosocomial pneumonia, complicated and uncomplicated skin and soft tissue infections (SSTI) including diabetic foot infections, community-acquired pneumonia, and vancomycin-resistant *Enterococcus* (VRE). However, it is not approved for the treatment of osteomyelitis.

Linezolid is a convenient pharmacologic option for clinicians and patients because it is 100 percent bioavailable when given orally. The major drawback to linezolid is cost. Even co-pays, especially in multi-tiered formularies, may not be affordable for all patients. Unlike most antibiotics, it will achieve serum levels equivalent to intravenous dosing making it unnecessary to begin a patient on IV antibiotic therapy. Therefore, there is no reason to use intravenous linezolid unless a patient is unable to tolerate oral medications. It is commercially available as an orange-flavored 100 mg/5mL oral suspension, 400 mg oral tablet, and 600 mg oral tablets. The oral suspension contains phenylalanine 20 mg per 5 mL, which some individuals are unable to metabolize because they lack the enzyme phenylalanine hydroxylase. Patients with the autosomal recessive trait are at risk for phenylketonuria (PKU) if large amounts of phenylalanine are consumed. Most states require neonatal blood testing for PKU shortly after birth, and all sources of phenylalanine should be avoided if an infant is positive for the trait.

The most frequent adverse effects of linezolid therapy include headache, diarrhea, nausea, and vomiting. Linezolid can also cause myelosuppression, resulting in thrombocytopenia, decreased hemoglobin, or leukopenia. Patients treated for extended durations (greater than 28 days) may be at risk for peripheral or optic neuropathy. Optic neuropathy has been reported as blurred vision in patients treated for less than 28 days and progressive loss of vision after extended durations. Patients taking linezolid for three months or more should be monitored for changes in visual function, and patients should be promptly evaluated if vision changes are noted anytime during treatment.

Linezolid is also a weak, reversible, nonselective monoamine oxidase inhibitor (MAO-I) and should not be used within two weeks of other monoamine oxidase inhibitors such as phenylzine and selegiline due to the risk for hypertensive crisis and serotonin syndrome. Hypertensive patients should also avoid sympathomimetics such as phenylephrine and pseudoephedrine, as well as foods high in tyramine due to the risk for increased blood pressure and heart rate. Clinicians should also use caution in patients on drugs that increase serotonin levels such as serotonin receptor uptake inhibitors (SSRI), tricyclic antidepressants (TCA), and serotonin agonists to prevent serotonin syndrome. Symptoms of serotonin syndrome include restlessness, tremors, confusion, diaphoresis, and fever.

The exact mechanism of linezolid metabolism is not completely understood, but it is affected by strong CYP450 modulators such as carbamazepine, phenytoin, and rifampin. Linezolid is primarily excreted unchanged; however, it does undergo some hepatic metabolism to inactive metab-
olite. It is not necessary to adjust linezolid doses in patients with renal or hepatic insufficiency. However, it has not been evaluated in patients with severe hepatic failure, so prescribers should use caution in this patient population.

**Doxycycline (Vibramycin, Doryx) & Minocycline (Minocin, Dynacin)**

Doxycycline and minocycline are members of the tetracycline class of antibacterial agents, and their action mechanism involves inhibiting bacterial protein synthesis at the 30s ribosomal subunit in a bacteriostatic fashion. They both have a broad spectrum of activity with many uses outside of the treatment of CA-MRSA infections. Resistance patterns for CA-MRSA and Group A streptococci can range significantly for both drugs, and there is a considerable amount of geographic variability in resistance patterns; therefore, they may not be ideal for empiric treatment in the absence of cultures and sensitivities when *Staphylococcus* and *Streptococcus* are both suspected.

Doxycycline is commercially available in multiple dosage forms and strengths, but all preparations are expressed in base content and therefore interchangeable. At the time of this writing, some of the oral tablets and capsules are on a national manufacturer backorder. Pharmacists should be cognizant that another agent, such as clindamycin or SMZ/TMP, may be needed if doxycycline is unavailable for use. Doxycycline is additionally available in a lyophilized powder for solution for intravenous preparation, as a 25 mg/5 mL oral raspberry-flavored suspension for reconstitution, and 50 mg/5 mL oral raspberry-apple flavored syrup. Doryx, a delayed release formulation, is available as a tablet of delayed release coated pellets in 75 mg, 100 mg, and 150 mg strengths. These tablets may be broken & sprinkled in applesauce; however, once the pellets are exposed, they should not be chewed or crushed. Minocycline is available in 50 mg, 75 mg, and 100 mg capsules and tablets, multiple strengths of extended-release tablets, and an intravenous dosage form. In contrast to doxycycline’s delayed release preparation, extended release formulations of minocycline should not be broken.

Adverse effects are not uncommon with the use of doxycycline and minocycline, with gastrointestinal upset involving nausea, vomiting, or diarrhea being the most frequent. If gastrointestinal upset occurs, these medications should be administered with food. However, dietary and medicinal sources of calcium, magnesium, aluminum, zinc, and iron should be avoided, along with bismuth subsalicylate, sucralfate, and bile acid sequestrants due to their propensity to decrease oral bioavailability. Oral doxycycline should be taken with an 8 ounce glass of water and patients should avoid lying down for 30 minutes to prevent esophageal ulcerations. The same risk exists for minocycline; however, most of the case reports in the literature related to esophageal ulceration involved doxycycline. Photosensitivity can also occur with tetracyclines manifesting as sunburn, and patients should be encouraged to wear sunscreen, avoid prolonged exposure to ultraviolet light, and avoid concomitant use of retinoic acid derivatives. Therapy should be discontinued if skin erythema occurs, because both are also linked to severe, potentially fatal dermatologic reactions such as SJS, erythema multiforme, and anaphylactoid purpura. All tetracyclines can cause tooth and bone discoloration that can be permanent and should be avoided in children less than 8 years of age and in breastfeeding mothers. Doxycycline has good fluid and tissue penetration and is able to penetrate synovial fluid, seminal fluids, and bronchial secretions. However, CSF penetration is relatively poor compared to minocycline. Doxycycline and minocycline can also be responsible for exacerbating systemic lupus erythematosus (SLE) and are commonly associated with drug-induced lupus.

A systematic review compared case reports and incidence of adverse events reports in clinical trials for minocycline and doxycycline. Both drugs had a high incidence of gastrointestinal adverse effects, and minocycline had more reports of central nervous system effects such as headache, dizziness, lightheadedness, vertigo, and tinnitus compared to doxycycline.

Use in pregnancy is discouraged due to the risk for teratogenesis and permanent tooth discoloration in the fetus. Tooth discoloration can range from yellow, gray, or brown, and has occurred during short- and long-term treatment. Doxycycline and minocycline are categorized as pregnancy
category D for these reasons. As stated previously, children under 8 are also at risk of tooth discoloration. Theoretically, tetracyclines can disrupt gastrointestinal microflora, potentially resulting in decreased bioavailability of oral contraceptives. For this reason, patients taking doxycycline or minocycline and oral contraceptives should use a back-up method of birth control for the duration of antibiotic therapy and the remainder of the cycle after completion.

Ciprofloxacin (Cipro), Levofloxacin (Levaquin) & Moxifloxacin (Avelox)
Fluoroquinolones work by inhibiting topoisomerase II, also known as DNA gyrase, and preventing bacterial DNA replication. This results in bactericidal killing for all fluoroquinolones. Fluoroquinolones may be effective in the treatment of MRSA infections, but susceptibility among MRSA isolates is highly variable. They are not routinely recommended by the IDSA’s MRSA guidelines because there is increased risk for the emergence of resistance when used as monotherapy. Therefore, fluoroquinolones are not ideal agents for empiric therapy unless combined with another active agent. Because susceptibility patterns of MRSA are so variable for the fluoroquinolones, their use in the treatment of MRSA infections is best reserved for cases when susceptibility is known and patients are intolerant to other possible treatments.

Fluoroquinolones are typically well tolerated, with the most common adverse effects being headache, insomnia, nausea, and vomiting. However, fluoroquinolones carry a black box warning due their association with an increased risk for tendon inflammation and/or rupture. They have also been associated with QT prolongation greater than 450–460 msec depending on gender and should also be avoided in patients with myasthenia gravis. Hypersensitivity reactions, photosensitivity, and peripheral neuropathy are uncommon but potential adverse effects.

Ciprofloxacin is commercially available in immediate release tablets of 100 mg, 250 mg, 500 mg, 750 mg, and extended release tablets of 500 mg and 1000 mg. It is also available as microcapsules for oral suspension in the concentrations of 250 mg/5 ml and 500 mg/5 ml. Levofloxacin is available in 250 mg, 500 mg, and 750 mg tablets, and a 250 mg/5 mL solution. Moxifloxacin is available as 400 mg tablets. All of the fluoroquinolones are available in intravenous dosage forms. When administered orally, all fluoroquinolone absorption may be affected by concomitant use of acid-suppressing medications such as antacids, histamine-2 receptor antagonists, proton pump inhibitors, and products containing calcium, zinc, or iron. Metabolism of narrow therapeutic index drugs like warfarin, theophylline, digoxin, and cyclosporine may be affected by fluoroquinolones.

INTRAVENOUS ANTIBIOTICS
As discussed earlier, infections caused by CA-MRSA are an increasing cause of hospital admissions. Hospitalized patients are sometimes treated with the intravenous formulations of the same antibiotics that can be used on an outpatient basis, such as clindamycin or trimethoprim/sulfamethoxazole, but severe infections may require the use of newer antibiotics only available intravenously. Although community pharmacists are much less likely to encounter these antibiotics, it is nevertheless important to be familiar with them since they are important for the treatment of MRSA infections, and will thus be briefly reviewed here.

Vancomycin (Vancocin)
Vancomycin has been the mainstay treatment for hospital-acquired MRSA for several decades. As more hospital admissions are due to CA-MRSA infections, vancomycin has also proven to be a highly effective antibiotic for its treatment as well. A glycopeptide antibiotic, vancomycin is a bacterial cell wall synthesis inhibitor but works at a different site than the beta-lactam antibiotics. It is bactericidal against MRSA and works in a time-dependent fashion, meaning that the time above the minimum inhibitory concentration (MIC) of the pathogen is the best predictor of clinical efficacy, not the peak serum concentration achieved by the drug. Due to its large molecular size and polarity, it is effective only against gram-positive bacteria since it is unable to penetrate the outer membrane of gram-negative bacteria. It is not absorbed systemically if given orally, so the only therapeutic use of oral vancomycin is in the treatment of CDAD infections.

Vancomycin does require therapeutic drug monitoring. Traditionally, both vancomycin peaks and troughs were mea-
sured in the clinical setting. Desirable troughs ranged from 5–15 mg/L and peaks 20–40 mg/L. However, in 2009, new guidelines were released regarding the monitoring of vancomycin in adult patients. While these new guidelines make numerous recommendations, some are particularly important since they change the way vancomycin has traditionally been monitored. Due to vancomycin’s time-dependent killing of bacteria, it is no longer recommended that peak concentrations be monitored. Additionally, trough values should be kept at or above 10 mg/L to prevent bacterial resistance from developing. For certain infections such as endocarditis, bacteremia, meningitis, osteomyelitis, and pneumonia due to MRSA, it is recommended that the trough concentration be kept between 15 and 20 mg/L.

Vancomycin does have several notable adverse effects. Nephrotoxicity and ototoxicity are two well-known reactions associated with vancomycin use, though these adverse effects are highly controversial. When vancomycin was first introduced into the market, there were numerous reports of nephrotoxicity associated with its use. However, the early formulation of vancomycin had numerous impurities, giving rise to the name “Mississippi Mud.” It was these impurities that were thought to cause most of the nephrotoxicity associated with vancomycin. After the formulations became more pure, reports of nephrotoxicity dramatically decreased. Of the reports that persisted, most were in patients also receiving a known nephrotoxic medication, such as an aminoglycoside. Reports of ototoxicity also primarily occurred in patients receiving other ototoxic medications. Vancomycin can also cause a reaction called “red-man syndrome,” which is an anaphylactoid reaction mediated by histamine release and causes flushing of the upper body and face, and may cause itching and a tingling sensation. This reaction can be helped or avoided by slowing the rate of infusion to at least one hour but may be extended to two hours. Pretreatment with diphenhydramine may also be beneficial.

**Daptomycin (Cubicin)**

One of the newer agents to come to the market for the treatment of MRSA is daptomycin, the first lipopeptide antibiotic. Daptomycin has a unique action mechanism, causing disruption of the bacterial cell membrane which causes an efflux of potassium ions, resulting in rapid cell death. While many antibiotics used for CA-MRSA are only bacteriostatic against the organism, daptomycin is bactericidal and manifests concentration-dependent killing, a useful feature as it can be given once a day. Like vancomycin, daptomycin cannot penetrate the outer membrane of gram negative organisms, and is thus only effective against gram-positive bacteria. It is FDA-approved for the treatment of *S. aureus* bacteremia, right-sided endocarditis, and skin and soft tissue infections. Daptomycin is typically well-tolerated, though it can cause elevations in creatinine phosphokinase (CPK). Patients should have weekly CPK levels monitored, and more frequent monitoring may be desired if a patient has renal dysfunction or is receiving concomitant statin therapy. Patients should also be monitored for muscle pain and weakness. There have been case reports of eosinophilic pneumonia associated with daptomycin use, but the full clinical significance of this has not been fully elucidated at this time. Of note, daptomycin should not be used in the treatment of lung infections due to inactivation by pulmonary surfactant.

**Quinupristin-Dalfopristin (Synercid)**

Quinupristin-Dalfopristin is the first streptogramin antibiotic introduced to the market. It is a two drug combination of the semi-synthetic pristinamycin derivatives quinupristin and dalfopristin. The drug targets the 50s subunit of the bacterial ribosome to inhibit protein synthesis. Interestingly, when the agents quinupristin and dalfopristin are used alone, they are bacteriostatic. However, when used in combination, they have synergistic activity, which results in bactericidal killing of staphylococcal species. Quinupristin-dalfopristin is associated with significant adverse effects which has limited its clinical use, among which include venous irritation, myalgias, arthralgias, and severe nausea. It also has numerous drug interactions. Quinupristin-dalfopristin is considered a second line agent in the treatment of MRSA infections, typically reserved as salvage therapy for patients who have failed more conventional therapies.

**Tigecycline (Tygacil)**

Tigecycline is a glycylcycline antimicrobial, the first in its class and a pharmacologic derivative of the
tetracycline family. The drug minocycline composes the primary backbone of tigecycline, but unlike minocycline, tigecycline has an N-alkyl-glycylamido group in the 9 position. This substitution confers a broad spectrum of activity against gram positive bacteria (including MRSA), gram negative bacteria, and obligate anaerobes. Like the tetracyclines, it is an inhibitor of protein synthesis and is bacteriostatic against MRSA. It has a large volume of distribution and obtains high concentrations in tissues, but low serum concentrations. It is thus a viable option for SSTIs and also has an FDA approval for intraabdominal infections. However, it should not be used for bacteremia due its poor serum concentrations and its bacteriostatic nature. Additionally, the FDA has issued a warning asking practitioners to consider alternatives to tigecycline if treating severe infections, because phase III and IV clinical trials noted an increase in all-cause mortality associated with its use. Like the tetracyclines, tigecycline should be avoided in children under 8 years of age due to the potential for tooth discoloration and decreased bone growth.

Ceftaroline (Teflaro)
The newest agent to come to the market for the treatment of MRSA infections is the advanced generation cephalosporin antibiotic ceftaroline, which was approved for use in 2010. Ceftaroline is highly notable in that it is currently the only beta-lactam antimicrobial agent with activity against MRSA. Like other beta-lactams, it exerts its antimicrobial activity through inhibition of bacterial cell wall synthesis. Unlike many of the intravenous antibiotics available for the treatment of MRSA, ceftaroline is also effective against many gram-negative organisms. Adverse effects of ceftaroline are similar to that of other cephalosporins and are generally considered mild. The most common adverse effects reported are rash, diarrhea, and nausea. Ceftaroline is currently FDA approved for the treatment of skin and skin structure infections and community-acquired bacterial pneumonia. The therapeutic niche of ceftaroline will be elucidated in time as experience with the drug increases.

DECOLONIZATION
Because CA-MRSA is often transmitted in areas where individuals are in close physical contact, such as prisons and military living quarters, it would not be unusual to consider decolonizing individuals who develop recurrent infection and those who share their living quarters. This is similar to the concept of providing prophylaxis to household contacts of patients diagnosed with meningococcal menigitis. However, the MRSA guidelines released by the IDSA do not recommend routinely providing decolonization therapies. The guidelines recommend optimizing hygiene measures and wound care before considering decolonization in situations where household transmission is suspected. All household contacts should be evaluated for signs and symptoms of infection and treated if necessary. Personal hygiene and wound care measures should include regular bathing; frequent hand washing or use of alcohol-based hand gels, particularly when in contact with wounds; keeping wounds covered with clean, dry bandages when it is draining; and avoid reusing or sharing items that come in contact with infected skin such as razors, linens, and towels. Environmental hygiene measures should focus on cleaning efforts of high-touch surfaces such as door knobs, surfaces, and toilet seats. Once these measures have been exhausted, decolonization can be considered if the patient or close contacts continue to develop CA-MRSA infections.

The options for decolonization include nasal decolonization with mupirocin ointment, topical body decolonization with bleach or chlorhexidine baths, or systemic oral therapy with a combination of rifampin and another antibiotic with CA-MRSA activity. Often, nasal and topical body decolonization strategies are implemented together, whereas systemic therapy is reserved for refractory cases. Each treatment modality may be instituted as monotherapy or in combination with one another. Hygiene and wound care measures should continue to be encouraged at all times. Each treatment option will be discussed in further detail as follows, and specific dosing and length of therapies may be seen in Table 3.

Mupirocin 2 Percent (Bactroban)
Mupirocin is actively bactericidal against MRSA by binding bacterial isoleucyl transfer RNA synthetase, thereby inhibiting protein synthesis. It also shares activity against Streptococcus, making it particularly useful as an empiric treatment for
minor skin infections such as impetigo when *Staphylococcus* and *Streptococcus* are both suspected pathogens.

Nasal decolonization with mupirocin ointment should be administered twice daily for 5–10 days. Mupirocin is only available in a topical dosage form as a cream or ointment. It is manufactured as an intranasal ointment packaged in single-use tubes. Patients should wash their hands before and after applying half of the contents of a single use tube in each nostril. If the single use intranasal tubes are unavailable, larger ointment tubes may be substituted. Exact dosing would not be possible in this case, but patients could apply the ointment with a cotton swab.

Mupirocin is minimally absorbed through intact skin but contains high concentrations of polyethylene glycol that can be potentially toxic if systemically absorbed. Therefore, it should not be applied to large skin surface areas, open wounds, or burns. The most common adverse effects include dermatitis, redness, and localized burning. It should be discontinued if a patient experiences skin irritation, particularly urticaria, edema, or pain.

**TOPICAL BODY DECOLONIZATION**

Eradication of MRSA from the skin can be accomplished by using dilute bleach baths and/or antiseptic solutions such as chlorhexidine. It should be noted that there is very little evidence to support the efficacy of topical decolonization in preventing skin and soft tissue infections. Overall, it seems to only have a transient impact on skin with recolonization occurring soon after discontinuation.

Diluted bleach baths given twice weekly for three months can be considered in children and adults requiring topical decolonization. It is important for patients to be adequately instructed on the proper dilution of bath water due to the potential for skin irritation if too concentrated. For every one quarter tub of water, a one quarter cup of household bleach can be used and is generally well tolerated. As a reference, a standard tub should hold approximately 13 gallons of water. If this concentration is used, an individual should bath in lukewarm water for 15 minutes per session.

Chlorhexidine gluconate 4 percent w/v is an antiseptic wash that is available over the counter and is commonly used as a surgical scrub, oral mouthwash for the treatment of gingivitis, and the prevention of ventilator-associated pneumonia (VAP). It is a cationic compound that binds to bacterial cell walls and alters cell permeability, resulting in leakage of intracellular components. It has bactericidal activity against CA-MRSA and a post-antibiotic effect lasting approximately six hours. Patients should be instructed to wash the affected area with the solution daily for five to 14 days. Erythema, skin dryness, and skin allergy are the most common adverse effects, and there have also been case reports of serious anaphylactic reactions. Patients should take special care to avoid contact with the eyes and ears. It can also cause staining if it comes into contact with clothing items. There is a significant amount of isopropyl alcohol in most commercially available products that makes them potentially flammable and should be kept away from open flames. Chlorhexidine gluconate is available in several dosage forms depending on the indication, but common over the counter brands include Hibiclens and Hibistat.

**RIFAMPIN COMBINATION TREATMENT**

Oral antibiotics are not generally recommended for the decolonization of MRSA. However, if infections still recur even after the above mentioned methods are utilized, an oral antibiotic that is effective against MRSA may be used in combination with rifampin may be considered. Rifampin is bactericidal against *Staphylococcus* spp. and exhibits concentration-dependent killing by binding to the β-subunit on bacterial RNA polymerase and inhibiting RNA synthesis. More commonly known as rifampicin outside of the United States, it was first approved by the FDA in 1971 for the treatment of mycobacterial tuberculosis. It has many ideal properties to treat *S.aureus* infections such as the ability to penetrate leukocytes and kill bacteria hiding in neutrophils. Also, rifampin is able to reduce bacterial exotoxin release such as PVL, and kill bacteria in its stationary phase. It has excellent penetration into all tissues. Patients taking rifampin can expect a pink to reddish-orange discoloration of any bodily fluids (such as tears, urine, stool, seminal fluid, breast milk) during therapy. Contact lenses may be permanently discolored if they are worn during treatment.

The most frequent adverse effects caus-
ing rifampin therapy to be discontinued include nausea, vomiting, and diarrhea. In patients with inflammatory bowel disease, rifampin has been implicated as a drug that can trigger or exacerbate ulcerative colitis episodes. Maculopapular rash is also common with prolonged therapy, and it is a common cause of drug-induced lupus erythematosus. Serious side effects associated with the use of rifampin include hemolytic anemia, hepatotoxicity, and interstitial nephritis. Particular caution is advised in patients with HIV on antiretroviral therapy, because rifampin is contraindicated in patients taking protease inhibitors, and some non-nucleoside reverse transcriptase inhibitors (NNRTIs) also interact with rifampin.

Rifampin is a very strong inducer of the p-glycoprotein and several cytochrome P450 enzymes, including CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2. This results in the potential for clinically significant drug interactions due to decreased bioavailability and/or reduced serum drug levels. Since more than 75 percent of drugs are metabolized through the cytochrome P450 enzyme system, there are numerous possibilities for drug interactions. Among the most significant that may require dose adjustments are oral anticoagulants such as clopidogrel, warfarin, and rivaroxaban, anticonvulsants such as phenytoin, systemic azole antifungals, pain medications, and other antimicrobials such as doxycycline, moxifloxacin, and linezolid. Female patients taking systemic contraceptives, particularly oral contraceptives, should be counseled to use a secondary form of contraception during the cycle in which they are treated with rifampin to avoid the risk of contraceptive failure. Rifampin can also result in a false positive urine opiate drug screen; however, the use of gas chromatography can eliminate this test interaction.

Despite the advantageous properties rifampin has for S. aureus-killing, it develops resistance very easily through a one-step mutation in rpoB which codes for an RNA polymerase with a decreased binding affinity for rifampin. Resistance rapidly develops in the presence of monotherapy; therefore, it is always important to combine rifampin with a second active agent such as doxycycline or SMZ/TMP when providing decolonization therapy. The second agent should be chosen based on susceptibilities identified from recent previous cultures.

**PEDIATRIC CONSIDERATIONS**

When choosing an appropriate agent for the outpatient treatment of CA-MRSA in children, there are several considerations that must be made that are not present in adult patients. For example, fluoroquinolones have been associated with arthropathy due to their ability to affect cartilage in juvenile animals. However, irreversible arthropathy has not been shown in case reports and retrospective cohort studies of children, most commonly with cystic fibrosis, being treated with a fluoroquinolone. Despite these findings, it is still recommended that these agents be reserved for situations when use of an alternative agent is not feasible.

Age of the patient is another important consideration when choosing an antibacterial agent. As mentioned previ-

<table>
<thead>
<tr>
<th>Method</th>
<th>Adult Dose</th>
<th>Pediatric Dose*</th>
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<tbody>
<tr>
<td>Dilute Bleach Bath</td>
<td>1 teaspoon per gallon of water</td>
<td>Same as adults</td>
</tr>
<tr>
<td>(Household bleach)</td>
<td>[or ¼ cup per ¼ tub or 13 gallons of water]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>given for 15 minutes twice weekly x 3 months</td>
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<tr>
<td>Mupirocin 2% Intranasal Ointment</td>
<td>½ of ointment from single use tube in each nostril BiD x 5–10 days</td>
<td>½ of ointment from single use tube in each nostril BiD x 5–10 days</td>
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<tr>
<td>Chlorhexidine (Hibiclens®)</td>
<td>x 5–14 days</td>
<td>x 5–14 days</td>
</tr>
<tr>
<td>Rifampin + 2nd Active Drug</td>
<td>600 mg/day x 5–10 days</td>
<td>7.5 mg/kg/dose Q12h x 5–10 days</td>
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<tr>
<td></td>
<td><strong>Must use in combination with another systemic antistaphylococcal antibiotic</strong></td>
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*Pediatric doses should not exceed the recommend adult doses
**Adapted from the iDSA guidelines on the treatment of MRSA infections
ously, the tetracycline antibiotics have been shown to accumulate in developing bone and teeth leading to potential decreased bone growth and tooth enamel discoloration. For these reasons, tetracycline antibiotics are not recommended for children less than eight years of age. Trimethoprim-sulfamethoxazole is another antibiotic in which age of the patient must be considered. This antibiotic has the ability to compete with bilirubin for plasma-protein binding sites. This increases the risk for kernicterus, particularly in preterm and already jaundiced neonates. This medication is not indicated for use in infants less than two months of age.

Other considerations for selection of antibiotics in children are available dosage forms due to the utilization of weight based dosing in these patients and palatability of the medication. Clindamycin, linezolid, ciprofloxacin, trimethoprim-sulfamethoxazole, and doxycycline are all commercially available as a suspension. Clindamycin and linezolid are typically poorly tolerated because of their taste.

Ciprofloxacin and trimethoprim-sulfamethoxazole are variably tolerated based on taste.

CA-MRSA is an increasingly prevalent infection throughout the United States and many other countries. It is of utmost importance for pharmacists and other health care professionals to be familiar with current recommended treatments, prevention strategies, decolonization techniques, and modes of antibacterial resistance for this pathogen. Many resources exist for the education of health care professionals and patients about MRSA. (See box for information)

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**MRSA Resources**

The Centers for Disease Control and Prevention website (www.cdc.gov/mrsa) provides a range of educational materials for healthcare professionals and the general public. Handouts and posters on prevention of MRSA infection directed at parents, athletes, school officials, and others may be downloaded and printed directly from the website.

- The National Center for Preparedness, Detection, and Control of Infectious Diseases has created podcasts in English and in Spanish on MRSA. These podcasts can be viewed at www2c.cdc.gov/podcasts.
- The Infectious Disease Society of America website (www.idsociety.org) provides health care professionals access to the practice guidelines for MRSA and other infectious diseases.
- The MedlinePlus website (www.nlm.nih.gov/medlineplus/mrsa.html) is operated by the United States National Library of Medicine and National Institutes of Health. It provides information on MRSA as well as links to patient education handouts and videos.
- The Nemours Foundation operates the www.kidshealth.org website that provides information on prevention, mode of transmission, and treatment of MRSA specifically for children.

Along with these resources, the Department of Health website for each state can provide local prevalence and resistance data. Health care professionals should make every effort to stay well informed about MRSA.

**Editor’s Note:** For the list of references used in this article, please contact America’s Pharmacist Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.
CONTINUING EDUCATION QUIZ
Select the correct answer.

1. Which of the following virulence factors is thought to be associated with the ability of CA-MRSA to cause skin and soft tissue infections and necrotizing pneumonia?
   a. Panton-Valentine leukocidin (PVL) toxin
   b. Toxic shock syndrome toxin-1 (TSST-1)
   c. Production of clumping factors A and B
   d. Production of exfoliative toxins A and B

2. T.J. is a 4-year-old white male presenting to his primary care pediatrician with a complaint of a left buttock abscess. The pediatrician wishes to place the patient on an oral antibiotic and calls you to ask if amoxicillin would be appropriate. What should your response be?
   a. Amoxicillin is appropriate for the treatment of this infection.
   b. Amoxicillin is not an appropriate option since it will be inactivated by the beta-lactamase produced by staphylococcal species.
   c. Amoxicillin is not appropriate because abscesses should only be treated with intravenous antibiotics.
   d. Amoxicillin is not appropriate because it doesn’t penetrate into skin tissue.

3. The strain of MRSA most prevalent throughout the United States is
   a. USA100
   b. USA200
   c. USA300
   d. USA400

4. In the 1980s, CA-MRSA was responsible for an outbreak among:
   a. High school football players
   b. College freshmen
   c. Intravenous drug users
   d. Day care employees

5. The typical antibiotic profile of the USA300 strain of MRSA include susceptibility to
   a. Erythromycin, levofloxacin, and azithromycin
   b. Clindamycin, tetracycline, and trimethoprim-sulfamethaxole
   c. Clarithromycin, trimethoprim-sulfamethaxole, ciprofloxacin
d. Clindamycin, erythromycin, and azithromycin
6. The CDC recommends obtaining a D-test for inducible resistance in which of the following situations?
   a. When MRSA isolates test resistant to tetracycline and susceptible to doxycycline
   b. When MRSA isolates test resistant to doxycycline and susceptible to tetracycline
   c. When MRSA isolates test resistant to erythromycin and susceptible to clindamycin
   d. When MRSA isolates test resistant to clindamycin and susceptible to erythromycin

7. Which of the following best describes why Staphylococcus aureus is capable of surviving in extreme environmental conditions?
   a. Capable of growth in high salt concentrations
   b. Ability to survive extreme environmental temperatures
   c. Able to survive variable changes in pH
   d. All of the above

8. Between 1999 and 2005, hospitalization rates for which type of S. aureus infection increased by greater than 25 percent annually?
   a. Osteomyelitis
   b. Cellulitis & abscesses
   c. Device-related infections
   d. Post-operative wound infections

9. CA-MRSA is most commonly associated with which type of infection?
   a. Bacteremia resulting from a hemodialysis catheter
   b. Catheter-related urinary tract infection
   c. A soft tissue infection such as a groin abscesses
   d. Bacterial meningitis

10. Which of the following individuals are likely at risk for CA-MRSA infection?
    a. A 19-year-old male who plays on his college football team and shares a dorm room with other players.
    b. An otherwise healthy 48-year-old male who recently spent six months in state prison.
    c. A 28-year-old female with no co-morbidities for infection.
    d. All of the above

11. Which of the following are risk factors for CA-MRSA?
    a. Close communal living conditions (such as a prison or military barracks)
    b. Sharing hygiene products with someone colonized with CA-MRSA
    c. Homeless individuals and injection drug users
    d. All of the above

12. A 26-year-old male presents to the urgent care center complaining of painful swelling and redness in his right axilla. Upon examination, it is determined that he has a 5 x 6 cm fluctuant abscess that is noted to have some purulent drainage upon palpation. The physician assistant at the urgent care center incises and drains the abscess and discharges the patient with prescription(s) for oral antibiotics. Which antibiotic regimen is appropriate to treat a CA-MRSA abscess?
    a. Clindamycin 300 mg Q8h for 7 days
    b. Doxycycline 100 mg PO BiD for 21 days
    c. Sulfamethoxazole-Trimethoprim 400/80 mg Q12h x 7 days
    d. Rifampin 300 mg PO Q8h x 5 days

13. T.M. is admitted to the hospital for a CA-MRSA abscess due to symptoms of possible systemic infection (fever or more than 101 degrees, tachycardia, and WBC greater than 15) and is treated with IV antibiotics. Upon questioning the patient and family, the physician discovers that T.M.’s uncle who lives in the same house was treated for a CA-MRSA abscess a few weeks prior. Should T.M.’s household contacts receive decolonization therapy?
    a. Yes, T.M. and all household contacts should receive Rifampin 600 mg PO daily with SMZ/TMP 800/160 mg PO BID for five days.
    b. No, the patient and household contacts should be counseled on proper wound care and hygiene measures at this point.
    c. No, only household contacts who sleep in the same room require decolonization.
    d. Yes, all household contacts should receive decolonization with rifampin only.
14. The action mechanism of which of the following antibiotics involves inhibiting bacterial protein synthesis?
   a. Clindamycin
   b. SMZ/TMP
   c. Moxifloxacin
   d. Vancomycin

15. Which of the following is an appropriate drug regimen to treat an adult with an uncomplicated CA-MRSA skin and soft tissue infection?
   a. Minocycline 200 mg PO BID for five days
   b. Linezolid 600 mg IV daily for 7 days
   c. SMZ/TMP 800/160 mg PO BID for 10 days
   d. Levofloxacin 500 mg PO Q8h for 14 days

16. Which of the following is true regarding sulfamethoxazole/trimethoprim?
   a. It must be given intravenously in the treatment of CA-MRSA infections.
   b. It inhibits protein synthesis similar to clindamycin.
   c. The INR would be expected to increase if SMZ/TMP is taken with warfarin.
   d. All of the above

17. Of the drugs listed below, which of the following is true?
   a. Fluoroquinolones such as levofloxacin and moxifloxacin have variable activity against CA-MRSA.
   b. Linezolid is a weak monoamine oxidase inhibitor (MAO-I) and can increase the risk for serotonin syndrome in patients taking SSRIs.
   c. Doxycycline, minocycline, and rifampin can cause drug-induced lupus.
   d. All of the above

18. Which of the following are options for CA-MRSA decolonization?
   a. Mupirocin intranasal 2 percent ointment for five to 10 days
   b. Dilute bleach baths given for 15 minutes twice a week for three months
   c. Washing the wound with chlorhexidine gluconate 4 percent w/v antiseptic wash
   d. All of the above

19. Which of the following is false regarding rifampin?
   a. If a patient experiences adverse effects to other oral antibiotics, it can be used alone for decolonization.
   b. Women taking contraceptives should use a secondary form of contraception while taking rifampin.
   c. Rifampin is a potent CYP3A4 inducer and can result in many clinically significant drug interactions.
   d. Nausea, vomiting, and maculopapular rash are side effects of rifampin.

Use the following case to answer question 20.
B.P. is a 55-year-old African-American female who presents to her primary care physician with a history of worsening cough, sputum production, and fever up to 102.6 degrees. She is admitted to the hospital for further management. Upon admission to the hospital, a chest x-ray reveals a right lower lobe pneumonia and a sputum culture shows MRSA.

20. Which of the following antibiotics would be inappropriate in the management of this infection?
   a. Quinupristin-Dalfopristin
   b. Linezolid
   c. Daptomycin
   d. Clindamycin