

An Ongoing Infectious Disease Challenge

Community-associated methicillin-resistant *Staphylococcus aureus*

by Warren E. Rose, PharmD



CE FOR PHARMACISTS ONLY.

S *taphylococcus aureus* is a predominant human pathogen that has been associated with a variety of infection types ranging from minor skin and soft tissue infections to pneumonia and endocarditis.¹ This organism has developed mechanisms to continually evade the effects of antibiotics, and resistance is now a universal problem with few treatment options. After the introduction of penicillin in the 1940s, penicillin-resistance in *S. aureus* due to the production of penicillinase was rapidly detected. The development of extended spectrum penicillins such as methicillin provided active agents against these strains until the emergence of

Although the high rates of MRSA were concerning, this pathogen was typically found in the health care setting with only a handful of isolated cases occurring in the community. However beginning in the late 1990s, multiple reports of infections due to MRSA begin occurring in the community in previously healthy patients with no known risk factors for infection.⁵ These new community associated-MRSA (CA-MRSA) infections first appeared as clustered outbreaks and were mostly confined to skin and soft tissue infections.^{6,7} The first reported clustered outbreaks appeared in close contact settings such as sports participants, inmates and day care institutions.⁷ A few select cases of rapidly progressive and fatal necrotizing pneumonia and fasciitis in

young, healthy patients raised concerns over the aggressive nature of this new strain.⁸ The epidemiology of these infections suggested that while these strains contained the methicillin-resistance gene similar to HA-MRSA, the genotypic and phenotypic properties represented a new strain of *S. aureus* rapidly



Goal. This program will provide education to pharmacists on the characteristics and treatment options of community associated methicillin-resistant *Staphylococcus aureus* infections.

Objectives. 1) Identify the differences in the clinical and molecular characteristics and virulence factors between CA-MRSA and HA-MRSA; 2) Discuss the oral and intravenous treatment options for CA-MRSA and identify appropriateness for use of each agent; 3) Identify epidemiological factors and patient populations that are involved in outbreaks of CA-MRSA.

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methicillin-resistance *S. aureus* (MRSA).² The prevalence of MRSA in the hospital setting began to rise in the 1980s and now represents over 50% of *S. aureus* strains in most institutions, with even higher rates (60-80%) in the intensive care units in the United States.³ This strain causes a significant health care burden as these infections are associated with increased morbidity and mortality, length of hospitalization, health care-related costs, and antibiotic failure rates.^{1,4}

spreading across the county. This strain is now endemic throughout the population and outbreaks have occurred in every U.S. state, including Wisconsin.

Epidemiologic studies of CA-MRSA have distinguished this new pathogen from HA-MRSA. The criteria for the diagnosis of CA-MRSA according to the Centers for Disease Control (CDC) is determined in the outpatient setting or culture of MRSA within 48 hours after admission to the hospital. Persons must

also have no history of MRSA infection or colonization, no history of hospitalization in the past year, admission to a nursing home, skilled nursing facility or hospice; dialysis; or surgery. They must also have no permanent indwelling catheters or medical devices that pass through the skin into the body. However recent epidemiology studies indicate that CA-MRSA strains may not be solely identified in the community setting. Isolates with a molecular background unique to CA-MRSA now represent an important percentage of MRSA strains in the hospital setting.^{1,9} Therefore, it is increasingly difficult to identify a community-derived strain based on the clinical definition provided from the CDC. Due to the highly virulent nature of this pathogen, the introduction of CA-MRSA into the hospital setting is challenging in patient populations at an increased risk for infection.

CA-MRSA is now found within any practice setting and patient population, and this review will provide essential knowledge for pharmacists on the epidemiology, molecular characteristics and treatment of CA-MRSA.

MOLECULAR CHARACTERISTICS OF MRSA

The molecular comparisons between CA-MRSA and HA-MRSA have led to an appreciation of the unique aspects of the community-derived strain (Table 1). The *mecA* gene, the key resistance determinant, is responsible for methicillin resistance in *S. aureus*. This gene encodes for alterations in the penicillin-binding protein, PBP-2a, which results in decreased binding affinity of beta-lactam antibiotics to the target protein. Through the use of multilocus sequence typing (MLST) of a worldwide collection of *S. aureus* strains, a common genetic link is shared among all MRSA isolates and can be traced back to a single clone known as ST-250 (Iberian clone).¹⁰ This strain evolved from an MSSA strain and developed methicillin resistance by acquisition of the *mec* gene from an unknown source. The five major clonal complexes found throughout the world, ST-5, ST-8, ST-22, ST-30, and ST-45 are believed to have developed from this original single strain.¹⁰ Current MRSA outbreaks are due to either decedents of these clones or

products of the transfer of the *mec* complex into MSSA. The genotype of MRSA strains found throughout the United States has been determined by pulsed-field gel electrophoresis (PFGE) to fit into eight distinct lineages.¹¹ The majority of clonal outbreaks of CA-MRSA have been due to strains classified as USA 300 and USA 400 PFGE patterns according to the Centers for Disease Control.¹¹ More recent epidemiologic reports of CA-MRSA indicate that USA 300 has become the predominant strain consistent with the clonal nature of this pathogen.¹²⁻¹⁴

The mobile genetic elements known as the staphylococcal cassette chromosome (SCC) *mec* is responsible for carrying the *mecA* gene. As demonstrated in Figure 1, this element also contains regulatory and recombinase genes that are responsible for insertion and excision of SCC*mec*. Currently, five SCC*mec* types (I-V) have been identified from the *S. aureus* strains found throughout the world.^{15,16} Although each type confers β -lactam resistance, differences in size, virulence, and non- β -lactam antibiotic susceptibility exist. SCC*mec* type 1 (size=34 kb) is a hospital-derived strain type and contains the *mecA* gene for resistance. The more common hospital SCC*mec* types II and III are larger in size (53 and 67 kb, respectively) and contain additional resistance determinants that

are consistent with the multi-drug resistant MRSA strains now endemic in the hospital setting. The remaining SCC*mec* types IV and V are typically community-associated strains. These *mec* cassettes are smaller in size from 21-28 kb and are more susceptible to non- β -lactam antibiotics, similar to that found in MSSA strains.^{15,17,18} Although SCC*mec* type V has been clinically described, type IV is much more frequent in outbreaks of CA-MRSA and is considered the dominant strain in the epidemic.

CA-MRSA VIRULENCE

Multiple virulence factors have been identified in CA-MRSA. Some of the more

common factors that have been noted to significantly contribute to disease severity include the Pantone-Valentine leukocidin toxin, toxic shock syndrome toxin 1 and the staphylococcal enterotoxins. CA-MRSA can be recognized from HA-MRSA by the prevalence and diversity of these virulence factors

Although toxins can be transferred between strains, PVL is the most consistently transferable and clinically relevant virulence factor found in clonal outbreaks of CA-MRSA throughout the world.¹⁹ It is classified as a bicomponent synergohymenotropic toxin that exerts toxic effects on host cell membranes via a two-component pore formation resulting in concentration

Figure 1. Representation of the staphylococcal cassette chromosome (SCC) *mec* in *Staphylococcus aureus* (adapted from reference 15). The *mecA* gene responsible for methicillin resistance is carried on the SCC*mec* complex. Other components include chromosome recombinases *ccrA* and *ccrB* that mobilize *mec*, an insertion sequence element *IS1272*, an integrated plasmid *IS431mec* encoding tetracycline resistance, a signal transducer gene *mecR1* that allows the expression of *mecA*, and an open reading frame *orfX*

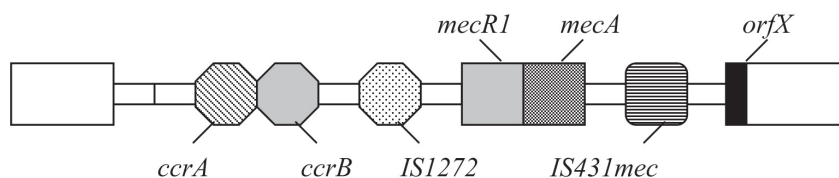


TABLE 1. COMPARISON OF CA-MRSA AND HA-MRSA CHARACTERISTICS

	CA-MRSA	HA-MRSA
Genotype	USA 300 SCC <i>mec</i> IV/V pvl-positive	USA 800 SCC <i>mec</i> II/III pvl-negative
Clinical definition	Diagnosis <48 h after hospitalization No history of MRSA No hospitalization, nursing home, skilled nursing facility or hospice (<1 yr) No dialysis or surgery No indwelling parenteral catheters or devices	Diagnosis >48 h after hospitalization
Infection type (most common)	Skin and soft tissue	Bone and joint Bloodstream Respiratory Skin and soft tissue Other
Antibiotic susceptibility	Susceptible to many non- β -lactams	Multi-drug resistant
Documented in community/hospital setting	Yes/Yes	Yes/Yes

dependent polymorphonuclear cell death by necrosis or apoptosis.²⁰ The two genes encoding this toxin are *lukS-PV* and *lukF-PV*, which have been incorporated into the bacterial genome of most CA-MRSA strains.²¹ Although the prevalence of this toxin in CA-MRSA can vary depending on the clonal strain involved, most epidemiology studies report that 75-95% of these strains are positive for PVL.^{22,23} Therefore it is often used as a descriptive epidemiologic marker of CA-MRSA infection.

The infection types reported with PVL positive strains are highly variable ranging from skin and soft tissue infection to necrotizing pneumonia, sepsis, and death.^{14,24} The impact of the PVL toxin in CA-MRSA was reported in 1999 following the death of four previously healthy children in Minnesota and North Dakota due to necrotizing pneumonia.⁸ The diffuse bilateral necrotic hemorrhagic pneumonia, multilobular alveolar infiltrates, and abscesses found upon autopsy were consistent with the necrotic effects as a result of PVL. However, the clinical significance of a *pvl*-positive strain is controversial, since the majority of CA-MRSA are positive, yet the occurrence of severe disease and production of the toxin remains relatively rare. Animal models of pneumonia and other severe diseases as well as clinical evaluations have tried to address this question. Voyich et al. evaluated *pvl*-positive and negative *S. aureus* strains in mouse sepsis and abscess models and found no difference in disease severity between the two strains.²⁵ However in an acute pneumonia mouse model, Labandeira-Rey et al. reported that the expression of genes encoding for PVL were sufficient to cause pneumonia.²⁶ A recent clinical study evaluated the *in vitro* production of PVL in MRSA strains from various infection types. The production of PVL was highly variable among strains and did not correlate with increased disease severity.²⁷ Further investigation into the role of PVL needs to be performed to understand this toxin's role in CA-MRSA disease.

The toxic shock syndrome toxin 1 (TSST-1) is a staphylococcal superantigen toxin produced by some *S. aureus* and is responsible for a variety of illnesses including toxic shock syndrome, scarlet fever, and superficial disease. Strains that are positive for *tsst*, the gene responsible for

TSST-1 production, appear to be highly virulent and cause these various disease manifestations. This toxin is also been detected in clonal outbreaks of CA-MRSA disease throughout the world.²⁸ Another well-documented group of toxins in CA-MRSA is the staphylococcal enterotoxins. These superantigen toxins are often carried in CA-MRSA that are clonally related and genetically distinct from HA-MRSA.²⁹ They are often responsible for toxic shock effect and food poisoning.²⁸

EPIDEMIOLOGY

Although the appearance of CA-MRSA is relatively new, the epidemiology of this strain is rapidly evolving and is now integrated into new patient populations and health care settings. This rapid development is attributed to the relative increased fitness of CA-MRSA strains. Those with the *SCCmec* IV genotype replicate more quickly than HA-MRSA types possessing *mec* II and III.³⁰ This is hypothesized to confer a competitive advantage for these strains to spread quickly throughout the community and health care setting. Due to the rise of CA-MRSA, a rapid shift in the epidemiology of MRSA infections has occurred throughout the world.

The first appearance of this new strain type has retrospectively been identified from children in Chicago presenting with superficial skin and soft tissue infections between 1988-1995 with no identifiable risk factors for MRSA.⁵ Other subsequent outbreaks of CA-MRSA throughout the country have demonstrated the clonal spread and geographic variability of this strain. In a study of MRSA infections from 3 separate communities in 2001-2002, the prevalence of CA-MRSA infection varied from 8-20% of all MRSA infections. Although the overall prevalence of CA-MRSA was low in this study, hospitalization was common and infection risk was much higher in the black population and in children less than 2 years-of-age.⁶ A more recent study in 2006 evaluated MRSA skin and soft tissue infection presenting to emergency departments throughout the United States. This multi-center study found that the majority (59%) of SSTI were due to MRSA, and 97% of these strains were CA-MRSA isolates (USA 300) based on molecular typing. Antibiotic susceptibility in these iso-

lates demonstrated that >90% were susceptible to non- β -lactam antibiotics including clindamycin, rifampin, trimethoprim/sulfamethoxazole and tetracycline.¹⁴

The identification of risk factors for CA-MRSA infection has been difficult. Due to the clonal nature of the disease, outbreaks have occurred in specific patient populations that share a common factor that often revolves around a close contact setting. These outbreaks have been documented in military recruits, prison inmates, men who have sex with men, intravenous drug users, athletes, and day-care settings, among others.^{7,31} In many of these situations, the sharing of equipment, such as clothing and towels, and lack of hand hygiene were common factors in transmission during clonal outbreaks.³² Other epidemiological findings in outbreaks include patients with previous (<1 month) antibiotic use, history of MRSA infection, and history of insect bites.¹⁴ However, many patients with suspected or documented CA-MRSA infection have no recognizable risk factors for the disease, and therefore it is often difficult to identify patients at risk for infection.

Several reports indicate that the majority of CA-MRSA infections present with skin and soft tissue involvement, however the manifestation of this disease can vary widely.^{1,13,14} Patients presenting to the emergency department or clinic are documented in many studies to complain of an insect, or more specifically a "spider bite," that results in abscess formation even though the culprit cannot be identified.¹⁴ Other common manifestations of CA-MRSA SSTI include cellulitis, folliculitis, impetigo and furunculosis.^{14,21} These infections are relatively superficial in nature and often resolve without significant complications. However in rare instances, these can develop into severe invasive infections, such as necrotizing fasciitis and pneumonia, in otherwise healthy individuals.^{8,33} A study by Miller and colleagues describes 14 patients over a 15-month period in the Los Angeles area presenting from the community with either necrotizing fasciitis and/or myositis. All recovered isolates possessed the PFGE type USA-300 and were *pvl*-positive. Although none of the patients in this study died, they had serious medical complications including the need for reconstructive surgery and

prolonged intensive care unit stay.³⁴ These serious complications attributable to CA-MRSA are concerning.

The line between CA-MRSA and HA-MRSA is now becoming blurred as new evidence suggests that the community pathogen is now being incorporated into the hospital microbial flora and patient population. The increased fitness of this strain may allow for the rapid transmission into the hospital setting. In a study of invasive MRSA infections throughout the country from 2004-2005, a distressing incidence rate of invasive MRSA infection was found in both the hospital and community setting. In health-care associated infections, 22.2% were attributed to isolates with a molecular background consistent with the USA-300 community strain.¹ An epidemiologic study of patient infections meeting the clinical definition for hospital acquisition in the Detroit metropolitan area found that 53% were CA-MRSA by identification of the *SCCmec IV* type. Interestingly, the investigators noted that the susceptibility rates among health care-associated *SCCmec IV* isolates was significantly less for clindamycin, gentamicin and levofloxacin compared to *SCCmec IV* acquired in the community setting. The authors concluded that these strains are rapidly acquiring resistance to non β -lactam antibiotics that is similar to traditional *SCCmec II/III* isolates.⁹

TREATMENT OPTIONS

Due to the increased susceptibility of CA-MRSA to non- β -lactam antibiotics,

multiple treatment options are available as outlined in Table 2. However, the benefit of treatment strategies remains controversial since the majority of CA-MRSA infections are manifested as mild skin and soft tissue infections (SSTI). The furuncles and abscesses that result are often successfully managed by surgical incision and draining alone. In a recent study of patients presenting to emergency departments in the U.S. with SSTIs, approximately 20% were treated with incision and drainage (I&D), 10% with antibiotics, and 66% with both.¹⁴ Outcome studies of non-complicated SSTI have demonstrated no difference in outcome in those treated with incision and drainage alone compared to inactive or no antimicrobial therapy.^{35,36} In infections where definitive loci can be surgically drained, antibiotic therapy may not be necessary. However in complicated SSTI where surrounding tissue inflammation is involved with or without systemic symptoms, incision and drainage as well as active antimicrobial therapy is recommended.³⁷

Unlike hospital associated-MRSA infections, oral antibiotics are available treatment options for CA-MRSA. The two most commonly utilized agents in the United States against this pathogen are trimethoprim/sulfamethoxazole (TMP-SMX) and clindamycin. These two agents are highly utilized because of their low costs, tolerability and high degree of tissue penetration. Although usage can vary by region, TMP-SMX represents the most common agent in treating these infec-

tions. TMP-SMX is an antibiotic with a dual mechanism of action: SMX inhibits dihydropteroate synthase, which blocks folate biosynthesis resulting in bacteriostatic activity, while TMP is a dihydrofolate reductase inhibitor that adds a second step block in folate synthesis, which is necessary to produce thymidine needed for DNA replication. These two antibiotics combine to inhibit folic acid production in *S. aureus* and result in bactericidal activity against the bacteria. The SMX component is a sulfonamide antibiotic and should be avoided or used in caution in patients with documented allergic reactions to this drug class. Evidence of TMP-SMX efficacy in treating staphylococcal infections is based on a 1992 study comparing this drug to vancomycin in a randomized clinical trial of intravenous drug users.³⁸ Vancomycin was superior in reducing duration of bacteremia, fever, treatment failure, and sterilizing the wound. Failure was most attributable to patients with tricuspid valve endocarditis and those with MSSA infections. The authors concluded that vancomycin was superior in treating staphylococcal infections, but TMP-SMX may be considered as an alternative treatment option in select cases of MRSA.³⁸ Although there are no large prospective randomized trials comparing TMP-SMX to other treatment options for CA-MRSA, this agent has demonstrated greater bactericidal activity in vitro.³⁹ In case reports and small randomized trials of SSTI, TMP-SMX treatment correlated with good clinical response, but resistance and treated failure was reported.^{40,41} However resistance and treatment failure appear to not always correlate together. Szumowski and colleagues evaluated MRSA treatment outcomes with oral antibiotics. In the last year of the study when 76% of patients were treated with TMP-SMX, the antibiotic failure rate was 40% despite <3% initial resistance to TMP-SMX. One hypothesis for treatment failure is that thymidine released from damaged host and bacterial cell tissues bypasses the folate synthesis blockade by TMP-SMX and allows for bacterial DNA replication.⁴² Despite this evidence, TMP-SMX is a widely used and relatively successful treatment for CA-MRSA skin infections when accompanied by surgical incision and drainage.

TABLE 2. CURRENT TREATMENT OPTIONS FOR CA-MRSA INFECTIONS

Antibiotic	Route	Dose
Clindamycin	PO/IV	300-600 mg every 6-8 h
TMP-SMX	PO/IV	1-2 DS tablets every 12 h
Linezolid	PO/IV	400-600 mg every 12 h [±]
Doxycycline	PO/IV	100 mg every 12 h
Minocycline	PO/IV	100 mg every 12 h
Vancomycin	IV	1 g every 12 h*
Daptomycin	IV	4-6 mg/kg every 24 h+
Tigecycline	IV	100 mg x 1, then 50 mg every 12 h

[±] 400 mg every 12 h recommended for uncomplicated SSTI
^{*}15 mg/kg every 12 hours for weight-based alternative
⁺4 mg/kg every 24 h recommended for SSTI

Another common antibiotic to treat suspected CA-MRSA SSTI is clindamycin. Susceptibility reports indicate that many MRSA isolates are highly susceptible to this antibiotic, but resistance can occur in the form of inducible resistance through efflux or ribosomal alteration. Testing for inducible resistance to the latter in the clinical microbiology laboratory may not be routinely performed, but it should be requested when selecting clindamycin as a treatment option. This method involves a disc diffusion antibiotic assay or D-test that determines the expression of a resistance phenomenon in *S. aureus* classified as inducible macrolide-lincosamide-streptogramin_b (iMLS_b) resistance. This mechanism of resistance is rendered by a ribosomal methylase of the binding site for erythromycin and clindamycin. The lincosamide antibiotic clindamycin does not induce the production of methylase and results in organisms initially appearing susceptible. A positive D-test, determined by a blunting of the clindamycin zone of inhibition adjacent to the erythromycin disk (resembling the letter D), indicates that the organism of question possesses inducible resistance to clindamycin. The importance of this finding is represented by the reports of clinical treatment failure with the use of clindamycin to treat CA-MRSA with iMLS_b resistance.^{43,44} Although the overall rate of resistance to clindamycin remains low in CA-MRSA isolates, the frequency of inducible resistance to clindamycin is highly variable and not completely known. Most surveillance studies report iMLS_b resistance is present in the minority of CA-MRSA isolates.^{45,46} Regardless, it is recommended to conduct a D-test to determine iMLS_b resistance before clindamycin can be recommended to treat suspected CA-MRSA infections.^{37,47} Some theorized benefits of this antibiotic are its high degree of tissue penetration and potential toxin protective effects including the PVL toxin.^{48,49} Clindamycin continues to be widely used effectively, especially in the pediatric population, despite the lack of randomized controlled trials of efficacy in CA-MRSA.

Vancomycin has long been the gold-standard for the treatment of serious MRSA infections. However, CA-MRSA infections are often limited to the skin

and soft-tissue, and therefore hospitalization and intravenous therapy is often not necessary. In cases where outpatient oral therapy would not be prudent, vancomycin remains a viable treatment options. Recent reports of reduced susceptibility with this antibiotic have raised concerns of its effectiveness in treating MRSA infections. Within the past decade, case reports of vancomycin intermediate susceptibility (VISA), heterogeneous VISA (hVISA), and vancomycin-resistant *S. aureus* (VRSA) potentially underscore the effects of years of vancomycin use. Patients infected with these isolates are linked with poor outcomes and treatment failure with this glycopeptide antibiotic. Additionally these isolates require special procedures for detection and are not noticed on most automated susceptibility panels. Almost all reports of these strains are found in patients from institutional settings with a long duration of vancomycin exposure. Therefore, most CA-MRSA remains highly susceptible, and vancomycin could be considered as an appropriate treatment option for more serious infections.

The oxazolidinone antibiotic linezolid is approved to treat MRSA SSTI as an oral or intravenous formulation. This agent is the first and only member of a new class of synthetic antibiotics that produce bacteriostatic antimicrobial effects in staphylococci by inhibiting protein synthesis. Controlled trials with linezolid have demonstrated effectiveness that is comparable to vancomycin in treating complicated SSTI due to MRSA.⁵⁰ Linezolid has high tissue penetration and is recommended as an alternative treatment option to vancomycin in MRSA pneumonia.⁵¹ CA-MRSA isolates are susceptible to linezolid, with most surveillance studies reporting an MIC in 50% (MIC₅₀) and 90% (MIC₉₀) of isolates of 2 mg/L.⁵² However as utilization of this antibiotic has increased, reports of resistance (MIC ≥8) have begun to emerge.^{53,54} Overall, resistance to linezolid remains relatively rare and may be an option in select patients where CA-MRSA may be suspected.

Daptomycin is a lipopeptide antibiotic that is rapidly bactericidal against staphylococci, including MRSA. It has been approved for the treatment of MSSA and MRSA complicated SSTI at doses of 4 mg/kg daily and bacteremia and endocar-

ditis at 6 mg/kg daily. Although mostly used in the inpatient setting for HA-MRSA infections, daptomycin is highly active against CA-MRSA isolates and is an available intravenous only antibiotic option.⁵⁵ In a study of the clinical and economic impact of daptomycin or vancomycin therapy of complicated SSTI, patients treated with daptomycin had more rapid resolution of symptoms and clinical cure. This corresponded to a decreased duration of inpatient therapy and reduced hospital costs. Although resistance to daptomycin remains clinically rare, studies suggest that strains with reduced susceptibility to vancomycin (hVISA and VISA) concomitantly have reduced susceptibility to daptomycin (MIC >1) even without previous daptomycin exposure.^{56,57} However, the clinical significance of this finding remains unknown since these isolates remain relatively infrequent in the clinical setting.⁵⁸ Daptomycin should not be used to treat MRSA pneumonia because it is inactivated by lung surfactant.⁵⁹

The emergence of CA-MRSA has led to the reassessment of tetracycline antibiotics in treating MRSA. Although relatively limited published data support their use, doxycycline and minocycline are potential treatment options for this pathogen. A response rate between 80-100% has been reported in retrospective studies of tetracycline-susceptible MRSA infections.⁶⁰ The high cure rates in many studies is often accompanied by surgical incision and drainage of skin abscesses, therefore it is difficult to determine the effectiveness of these treatment regimens.⁶¹ Further prospective research is needed to establish tetracycline therapy for CA-MRSA infections.

Although susceptibility panels of CA-MRSA isolates indicate that they are susceptible to many fluoroquinolone antibiotics, the use of these agents in treating this pathogen is not recommended. Upon exposure to fluoroquinolones, MRSA rapidly acquires high-level resistance and renders the antibiotic ineffective.⁶² Recently developed fluoroquinolones may offer advantages in preventing this resistance mutation, but further research is needed to understand the potential role these agents play in CA-MRSA treatment.⁶³

The parenteral antibiotic tigecycline is the first member of the new glycylcycline antibiotic class. It is a derivative of

minocycline and has a similar mechanism of action through inhibition of protein synthesis. However, small chemical modifications increase its potency and protect it from resistance. In clinical trials, tigecycline 100 mg load followed by 50 mg every 12 hours was as effective as vancomycin plus aztreonam in the treatment of complicated SSTI.⁶⁴ Other studies specifically evaluating tigecycline activity against CA-MRSA isolates suggest it is comparable to other highly active agents.⁵² Staphylococcal resistance with tigecycline remains infrequent but is most likely attributable to an efflux pump related mechanism.⁶⁵

New antimicrobials are currently under investigational use as potential agents with activity against MRSA. Although they are not yet approved by the U.S. Food and Drug Administration, four agents have been evaluated in clinical trials of SSTI that include MRSA. Telavancin, oritavancin, and dalbavancin are lipoglycopeptide antibiotics that are bactericidal against MRSA. At doses of 10 mg/kg IV daily, telavancin was noninferior to vancomycin in the treatment of complicated SSTI.⁶⁶ Oritavancin and dalbavancin have demonstrated potent *in vitro* and *in vivo* activity against MRSA, but further study is needed to determine its clinical utility in SSTI due to CA-MRSA. Ceftobiprole is a new broad-spectrum intravenous cephalosporin with MRSA activity. In a study of complicated SSTI that included MRSA, ceftobiprole 500 mg administered every 8 hours was as effective as vancomycin plus ceftazidime.⁶⁷ The development and study of these investigational agents will be necessary as MRSA and especially CA-MRSA continues to evolve to survive against currently available antibiotics.

CONCLUSION

The rapid development of CA-MRSA over the past decade has supplanted this pathogen as a major health care burden. These strains present new therapeutic challenges due to their high pathogenicity, virulence, and ever-increasing antibiotic resistance. Although the majority of disease presents as SSTI, the high number and severity of toxins associated with CA-MRSA increase the potential for acute necrotizing infections in both vulnerable and healthy populations. There is

increasing evidence that this pathogen is now becoming endemic in many hospital institutions as well. Most infections with this strain can be appropriately treated with a combination of surgical and non- β -lactam antibiotic therapy, but potential problems with these options exist. Based on epidemiology reports, it is anticipated that as these CA-MRSA strains become increasingly exposed to antibiotics in both the community and hospital setting, they will develop resistance mechanisms similar to the classic MRSA found currently in many hospital institutions. The development of alternative treatment strategies and investigational antibiotics as well as continued epidemiologic study of CA-MRSA will be necessary in order to provide appropriate therapeutic strategies and positive outcomes against this evolving pathogen. ●

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- 9) a b c d
- 10) a b c d
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Community-associated methicillin-resistant *Staphylococcus aureus*

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Community-associated methicillin-resistant *Staphylococcus aureus*

- Which of the following *SCCmec* types is commonly associated with CA-MRSA clonal outbreaks?
 - SCCmec* I
 - SCCmec* II
 - SCCmec* III
 - SCCmec* IV
- What toxin is the most clinically relevant toxin found in clonal outbreaks of CA-MRSA?
 - Toxic shock syndrome toxin 1
 - Panton Valentine leukocidin toxin
 - Exfoliative D toxin
 - Enterotoxin A
- Isolates with a USA-300 molecular background are confined to the community setting and have not been documented in hospital-acquired infections.
 - True
 - False
- What antibiotic requires a D-test to be performed to test for inducible resistance before it can be considered as a therapeutic option to treat CA-MRSA?
 - Clindamycin
 - Trimethoprim/sulfamethoxazole
 - Erythromycin
 - Vancomycin
- CA-MRSA isolates are generally more susceptible to non- β -lactam antibiotics than those typically found in the hospital setting.
 - True
 - False
- For the treatment of complicated SSTI with abscess formation due to CA-MRSA, surgical incision and drainage along with antibiotic therapy should be recommended.
 - True
 - False
- Although risk factors for CA-MRSA infection have been hard to define, in what patient population has clonal outbreaks of this disease occurred?
 - Day care children
 - Military recruits
 - Sports participants
 - All of the above
- Fluoroquinolones antibiotics can be recommended as first line therapy to treat CA-MRSA because of the low minimum inhibitory concentrations reported by susceptibility testing.
 - True
 - False
- Which of the following is not part of the criteria for the clinical diagnosis of CA-MRSA according to the Centers for Disease Control?
 - No MRSA history
 - No indwelling intravenous catheters
 - Diagnosis made within 72 hours after hospital admission
 - No history of surgery
- Although the manifestations of CA-MRSA infection may vary, the infection type most often associated with this pathogen is
 - Osteomyelitis
 - Skin and soft tissue infection
 - Pneumonia
 - Bacteremia
- The *mecA* gene in *S. aureus* encodes for what type of resistance mechanism?
 - Alterations in the penicillin-binding protein, PBP-2a
 - iMLSb inducible resistance
 - Multi-drug efflux pump NorA
 - Mutations in topoisomerase IV
- Which of the following is true regarding the Panton Valentine leukocidin toxin?
 - The presence of genes encoding the toxin correlate with severe disease
 - Most CA-MRSA strains are negative for the PVL genes
 - It is used as a descriptive epidemiologic marker of CA-MRSA infection
 - It is associated with toxic shock syndrome
- Which of following is an epidemiologic finding in outbreaks of CA-MRSA?
 - History of trauma
 - Previous antibiotic use in preceding month
 - Burn injury
 - Co-infection with another primary pathogen
- TMP-SMX use in CA-MRSA is based on large randomized trials of MRSA infections demonstrating TMP-SMX superiority to vancomycin therapy.
 - True
 - False
- After the discovery of CA-MRSA as a unique strain type, outbreaks with this pathogen have typically been limited to what part of the United States?
 - South
 - Northeast
 - Midwest
 - West
 - None, it has been documented in every region
- How do you rate this lesson?
 - Very Good
 - Good
 - Poor
- Did it meet the learning objectives?
 - Yes
 - No
- How long did it take you to complete this lesson?