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REVIEW ARTICLE

Community-Associated Methicillin-Resistant *Staphylococcus aureus* in the Pediatric Population

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PURPOSE To review the epidemiology and prevalence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), define the differences between community-acquired and hospital-acquired strains, highlight the advantages and disadvantages of antibiotics commonly used to treat infections caused by this pathogen, and identify strategies to limit the spread of this organism and prevent future outbreaks.

DATA Literature was accessed through MEDLINE using the search terms community-acquired methicillin-resistant *Staphylococcus aureus*, community-associated methicillin-resistant *Staphylococcus aureus*, CA-MRSA, pediatrics, and children. Articles evaluated were published in the English language and limited to human studies. References of literature identified by initial search techniques were reviewed for additional relevant articles.

DATA SYNTHESIS Community-associated methicillin-resistant *Staphylococcus aureus* has become a prominent pathogen in pediatric patients in the last ten years. Its increasing prevalence has been reported throughout the United States, and it is the cause of over one half of all skin and soft tissue infections seen in many hospitals and emergency departments. The risk factors for infection with this pathogen differ from those associated with hospital-acquired strains. Mild to moderate infections can generally be treated with oral antibiotics, while more serious infections may require parenteral therapy. Sulfamethoxazole/trimethoprim and clindamycin are the preferred oral agents due to their efficacy, tolerability, well established side effect profiles, and cost. Vancomycin is the standard of care for parenteral therapy, although clindamycin is an acceptable parenteral alternative. More costly agents such as linezolid, daptomycin, and quinupristin/dalfopristin should be reserved for patients with severe infections, multiple allergies, or in strains with unusual resistance patterns. The best way to prevent and control outbreaks is to maintain standard infection control procedures including excellent hand hygiene.

CONCLUSIONS CA-MRSA is a serious and frequently seen pathogen. Proper antibiotic selection that takes into account patient factors, disease severity, ease of administration, and cost is necessary to maximize favorable patient outcomes.

KEYWORDS CA-MRSA, children, community-acquired methicillin-resistant *Staphylococcus aureus,* community-associated methicillin-resistant *Staphylococcus aureus*, pediatrics

J Pediatr Pharmacol Ther 2008;13:212-225

INTRODUCTION

Methicillin resistant *Staphylococcus aureus* (MRSA) was first identified in the 1960s, just 2 years after the discovery of methicillin.[1] Since that time, methicillin resistance has been seen mostly in hospital-associated strains, and is now present in over 60% of all hospital-acquired *Staphylococcus aureus* isolates.[2] More recently, methicillin resistance has been seen

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in *S aureus* strains in the community or those not associated with hospitals or health care facilities. This new strain of MRSA, called community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA) has emerged as a prominent and problematic pathogen particularly in the pediatric population. Clinicians must be aware of the epidemiology and prevalence of this organism, understand how it differs from hospital-acquired strains, be well versed in the advantages and disadvantages of the antibiotics used to treat this pathogen, and identify strategies to prevent and contain outbreaks.

ABBREVIATIONS CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; CA-MSSA, community-acquired methicillin-sensitive *Staphylococcus aureus*; hVISA, heterogeneous VISA; HA-MRSA, hospital-associated MRSA; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus;* PBP, penicillin binding protein; PVL, Panton-Valentine leukocidin; SCC*mec*, staphylococcal cassette chromosome *mec*; SMZ/TMP, sulfamethoxazole/trimethoprim; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SSTI, skin/soft tissue infections; VISA, vancomycin-intermediate *Staphylococcus* aureus; VRSA, vancomycin-resistant *Staphylococcus aureus*

EPIDEMIOLOGY

Reports of CA-MRSA infections have increased throughout the nation. The perceived increase in the number of CA-MRSA infections, particularly in the pediatric population, prompted several hospitals and emergency departments to conduct well designed studies attempting to determine the true incidence of CA-MRSA infection. While these studies have been conducted throughout the country, they all have a unanimous conclusion: rates of CA-MRSA infection are increasing, and have done so within the last 8 to 10 years.[3-7] One study conducted in pediatric patients in Houston, Texas found that CA-MRSA infections accounted for 56% of all *S aureus* infections in hospitalized pediatric patients in 2001, then increased to 78% by 2003.[6] Similarly, from 1990 to 1999, CA-MRSA infections in pediatric patients accounted for about 3.8 cases per 10,000 hospital admissions at Driscoll Children's Hospital in Corpus Christi, Texas. By 2003, CA-MRSA infections accounted for 277.1 cases per 10,000 admissions ($P < .001$).[5]

It is important to point out that these infections are not only increasing, but they now make up a significant proportion of infections seen in the community. Pediatric emergency departments in Alabama and Tennessee reported that CA-MRSA was identified in over one half of all cultured abscesses from skin and soft tissue infections (SSTI) in 2003.[8] Similarly, methicillin resistance was evident in 76.4% of all community-associated *S aureus* infections at Texas Children's Hospital in Houston in 2004.[9] Proper empiric antibiotic selection for skin and soft tissue infections in pediatric patients must take into account the sheer number of infections as well as the increase in infection rates that are being seen with this pathogen.

RISK FACTORS

In order to choose proper empiric therapy for skin and soft tissue infections, the risk factors for CA-MRSA must be well defined. Until recently, risk factors for CA-MRSA were thought to be similar to risk factors for hospital-associated MRSA (HA-MRSA), which included children who had recently been hospitalized; had invasive surgical procedures, indwelling catheters, an endotracheal tube, a chronic illness, or contact with a health care worker; and those that had prolonged or repeated exposure to antibiotics.[4,10,11] However, these traditional risk factors have become obsolete as more and more CA-MRSA infections have been reported in children without these risk factors.[4,10,12] One study in Chicago found that CA-MRSA infections in pediatric patients without traditional risk factors were on the rise.[4] From 1988 to 1990 there were 10 cases of CA-MRSA infection per 100,000 admissions where no typical risk factors for infection were identified. That number increased dramatically, up to 259 cases per 100,000 admissions, from 1993 to 1995.[4] A study at Texas Children's Hospital looked at risk factor differences between CA-MRSA and community-acquired methicillin-sensitive *S aureus* (CA-MSSA) infection.[10] There were no differences in risk factors between children who were infected with CA-MRSA and those infected with CA-MSSA. The presence of antibiotic exposure, underlying illness, health

care worker contact, and hospitalization rates were the same among children with any type of community-associated *S aureus* infection.[10] Similar results were also seen at Driscoll Children's Hospital where, during a 14-year surveillance study, 89% of children with CA-MRSA infections had no identifiable risk factors for infection.[5]

CA-MRSA infections occur in patients without traditional risk factors; therefore, relying on these risk factors alone to determine empiric antibiotic choices would be inappropriate. These traditional risk factors should not be ignored, as they are still predictive of infection, but it is important to keep in mind that the absence of these risk factors does not imply absence of risk. Several other risk factors have been proposed that may indicate an increased risk of CA-MRSA infection. There have been reports that being of younger age; participating in contact sports such as football or wrestling; sharing locker rooms, soap or towels; or living with a person with documented CA-MRSA infection all pose an increased risk for developing a CA-MRSA infection.[13-15] Reports of increased rates of infection have also been seen in incarcerated patients where outbreaks occur and are extremely difficult to control,[16] and in intravenous drug abusers.[17] Increased risk has also been associated with patients who have pulmonary disease, men who have sex with men, and individuals who attend health clubs.[15]

One final risk factor that has been associated with CA-MRSA infection is nasal colonization with CA-MRSA. Several studies have shown that nasal carriage positively correlates with infection rates.[18-20] In one study, 41% of the 51 patients with CA-MRSA infections were also nasal carriers of CA-MRSA. In addition, 20% of their household members were also nasal carriers.[18] The incidence of nasal colonization is increasing along with the incidence of infection, providing further evidence that nasal colonization should be viewed as a serious risk factor for infection. One study compared nasal carriage rates in pediatric patients in 2001 to rates in 2004.[20] In 2001, the average nasal carriage rate of healthy children in the Nashville, Tennessee community was 0.8%. That number rose to 9.2% in 2004, along with an increase in CA-MRSA infection rates.[20] Screening patients and/or household contacts for CA-MRSA nasal carriage who present with skin and soft tissue infections may help identify those patients who are at highest risk for CA-MRSA infection.

DIFFERENCES BETWEEN HA-MRSA AND CA-MRSA

HA-MRSA and CA-MRSA infections are often categorized based on where the infection was acquired, either in a hospital or health care setting or in the community. However, there are several other features that distinguish these two types of infections and they may represent a more accurate way of categorizing these infections. These two strains of MRSA cause different types of infections, have dissimilar genetic profiles, produce different virulence factors, and often have unique antibiotic susceptibility patterns.

Infection Types

The types of infections seen with CA-MRSA are significantly different than the types of infections seen with HA-MRSA. CA-MRSA strains most commonly result in skin and soft tissue infections (SSTI) while HA-MRSA is more likely to cause bloodstream, urinary tract, or respiratory tract infections.[5, 21-23] In one study conducted in several hospitals in Minnesota, skin and soft tissue infections accounted for 75% of all CA-MRSA infections, but only 37% of HA-MRSA infections.[22] In that same study, respiratory and urinary tract infections made up 42% of all HA-MRSA infections and only 7% of CA-MRSA infections.[22]

Even though skin and soft tissue infections make up the majority of CA-MRSA infections, severe invasive disease has also been reported. Pediatric deaths have been described from Minnesota and North Dakota due to CA-MRSA invasive pulmonary disease.[24] Reports of CA-MRSA causing necrotizing pneumonia and necrotizing fasciitis have also been reported throughout the literature and have been associated with significant morbidity and mortality.[25-27] Additionally, a recent epidemiologic study conducted by Klevens et al. concluded that while the majority of invasive disease attributable to MRSA is caused by hospital-acquired strains, over 1200 (14%) cases of invasive MRSA infections reported

in the United States from July 2004 through December 2005 were community-associated and occurred in patients who had no known health care contacts.[28]

Genetics

The genetic profiles of community-associated and hospital-associated strains of MRSA both contain the *mecA* gene. The *mecA* gene encodes resistance to methicillin, and all other β-lactam antibiotics, by encoding for the penicillin binding protein (PBP) 2a, a PBP that is not present in susceptible strains of *S aureus*. PBPs are cell wall bound enzymes that catalyze the cross-linking of peptidoglycan and formation of the bacterial cell wall. PBPs 1, 2, and 3 are essential in maintaining life in strains that do not contain the *mecA* gene (MSSA). PBP 2a has a very low affinity for β-lactam antibiotics, and is essentially unaffected by β-lactams at concentrations seen with therapeutic doses.[11] PBP 2a can perform the essential cross-linking required to prevent cell death even while PBPs 1, 2, and 3 are inactivated by β-lactam antibiotics.[29,30]

In both hospital- and community-associated strains, the *mecA* gene is located on the staphylococcal cassette chromosome *mec* (SCC*mec*), which is a mobile and transferable piece of genetic material. To date, there have been 5 distinct SCC*mec* types identified, and they are labeled SCC*mec* I through V. They vary in size, with I through III being the largest, and IV and V being the smallest.[1] CA-MRSA strains most often contain SCC*mec* type IV or V, while hospital-associated strains are more likely to contain SCC*mec* type II or III.[22,31] SCC*mec* types II and III are large elements that often contain multi-drug resistant genes in addition to the *mecA* gene. SCC*mec* types IV and V are smaller elements, contain only the *mecA* gene, and confer resistance solely to β-lactam antibiotics.[1]

Antibiotic Susceptibilities

The differences in SCC*mec* type between hospital and community-associated strains of *S aureus* help explain the differences seen in their antibiotic susceptibility profiles. Historically, community-associated strains are often resistant to β-lactam antibiotics, but retain their susceptibility to many other classes of antimicrobials such as sulfamethoxazole/trimethoprim (SMZ/TMP), clindamycin, tetracyclines, and gentamicin.[29] Hospital-associated strains, however, are often multi-drug resistant and require the use of vancomycin or newer agents such as daptomycin, linezolid, or quinupristin/dalfopristin.[22,29]

Virulence Factors

Virulence factor production differs between these two strains of MRSA. Community-associated strains frequently produce a virulence factor that HA-MRSA rarely produces, called the Panton-Valentine leukocidin (PVL). The PVL is a pore forming leukotoxin that is able to lyse host leukocytes leading to a more severe disease presentation. It is usually produced by strains associated with outbreaks of skin and soft tissue infections and those that lead to necrotizing pneumonia and other severe invasive infections.[32]

This virulence factor is encoded by two genes, *lukS-PV* and *lukF-PV,* and when transcribed together, they produce the PVL. These two genes are frequently associated with bacteriophages or viruses that infect only bacteria. Bacteriophages carrying the two PVL genes infect strains of CA-MRSA and incorporate the PVL genes into the host genome, thereby becoming part of the CA-MRSA genetic profile. These genes are then transferred to offspring during replication, and horizontal transfer to other isolates may even occur via the same bacteriophages.[32,33] PVL production is more often seen with CA-MRSA strains than HA-MRSA strains, as it is predominately associated with SCC*mec* IV, occasionally associated with SCC*mec* V, and rarely associated with SCC*mec* I, II or III.[32]

TREATMENT OPTIONS

When treating skin and soft tissue infections caused by CA-MRSA, successful treatment is not usually achieved via antibiotics alone. An important therapy that must be considered is surgical incision and drainage of an abscess. One retrospective study conducted in San Francisco found that lack of incision and drainage was associated with lack of cure independent of antibiotic selection.[34] Similar results were seen in a Texas study wherein the

authors concluded that incision and drainage was effective in treating abscesses less than 5 cm in diameter without the use of antibiotics.[35] However, not all studies have shown that incision and drainage alone is curative. A study conducted in Detroit, Michigan found that cure rates were higher among those who received effective antibiotics regardless of whether or not incision and drainage was performed.[15] For these reasons, antibiotics, along with surgical incision and drainage, play a vital role in the management of CA-MRSA infections. Selection of the best antibiotic is essential in order to ensure successful patient outcomes.

Currently, there have been no prospective, randomized, active controlled clinical trials evaluating antibiotics head-to-head in the treatment of CA-MRSA infections. Even fewer studies have been conducted specifically in the pediatric population. Therefore, clinicians are forced to rely on small retrospective studies conducted in adult patients to determine the best antibiotic regimen. What has been shown, at least in adult patients, is that appropriate antibiotic selection improves patient outcomes and prevents disease recurrence.[15,36,37] It is imperative to choose a regimen that has activity against CA-MRSA, does not develop resistance during therapy, reaches the site of infection, and has a tolerable side effect profile. The following is a review of the antibiotics available for the treatment of CA-MRSA infections.

EFFICACY

Sulfamethoxazole/Trimethoprim (SMZ/TMP)

Most CA-MRSA strains are susceptible to SMZ/TMP, with reports of 99% to 100% susceptibility in several studies.[15,29,34,36,37] As stated previously, there are no prospective studies evaluating the outcomes of patients treated with SMZ/TMP for CA-MRSA infections, but there are several retrospective reviews that have reported successful outcomes when skin and soft tissue infections were treated with SMZ/TMP.[15,36,37] These studies showed that successful outcomes were associated with drug therapy that was effective against CA-MRSA. Since extremely low rates of resistance to SMZ/TMP were reported, its use resulted in high numbers of treatment successes.

Clindamycin

While CA-MRSA is often more susceptible to clindamycin compared to HA-MRSA, rates of CA-MRSA resistance to clindamycin may be high in some regions of the country. One study conducted in Boston, Massachusetts found that 48.2% of CA-MRSA isolates from skin and soft tissue infections were resistant to clindamycin.[37] A separate study conducted in Detroit, Michigan discovered similar results; only 54% of CA-MRSA isolates were susceptible to clindamycin.[15] However, these poor rates of clindamycin susceptibility are not consistent among studies. A large epidemiologic study conducted at a separate hospital in Detroit, Michigan found that 96% of CA-MRSA isolates were susceptible to clindamycin.[29] Additionally, another study carried out in Los Angeles, California discovered that 97% of CA-MRSA isolates were susceptible to clindamycin.[34] Due to these conflicting results, it is important to know the local clindamycin susceptibility patterns of CA-MRSA and to refer to local antibiograms.

It is also imperative to realize that *in vitro* susceptibility to clindamycin does not imply that susceptibility will be maintained throughout a treatment course. CA-MRSA strains may contain the *erm* gene, which encodes for a change in the ribosomal binding site of several classes of drugs including macrolides, lincosamides and streptogramins. When the *erm* gene is present, resistance to macrolides is always seen *in vitro* and these drugs should be avoided for treatment. If an additional small mutation occurs, the isolate will also become resistant to clindamycin. These smaller mutations, such as duplications or deletions, can be induced in the presence of macrolides lincosamides, or streptogramins, or they can occur spontaneously.[38] In isolates that contain the *erm* gene, standard broth dilution tests show that the bacteria is clindamycin-susceptible. However, since these isolates contain the *erm* gene, clindamycin resistance can be induced, and treatment failures can occur.[38] A clinician should have a high degree of suspicion for the presence of the *erm* gene if the reported susceptibilities show clindamycin susceptibility but resistance to erythromycin. The standard method used to confirm inducible clindamycin resistance is the D-zone disk diffusion test

(D-test).[39] In this test, an erythromycin susceptibility disc is placed close to a clindamycin susceptibility disc on agar that has been plated with the CA-MRSA isolate. In a positive D-test, the presence of erythromycin will induce resistance to clindamycin and blunt the zone of inhibition around the clindamycin disc creating a "D" shape instead of a well defined ring of inhibition.[38,39,40] Several treatment failures have been reported in pediatric patients who were given clindamycin because initial susceptibility tests showed clindamycin would be effective.[41] Upon disease progression, the bacteria were recultured and were then determined to be resistant to clindamycin.[41] Due to the variable rates of clindamycin resistance, and the possibility of inducible resistance to clindamycin, it is important for clinicians to know the local susceptibility patterns when considering clindamycin for use against CA-MRSA.

Linezolid

While linezolid has never been compared to other agents specifically for the treatment of CA-MRSA infections, it has been compared to vancomycin for the treatment of MRSA infections. In this study, conducted by Stevens et al., the majority of cases were skin and soft tissue infections and there was no difference in efficacy outcomes between linezolid-treated patients and vancomycin-treated patients.[42] The authors concluded that linezolid was an efficacious alternative to traditional vancomycin therapy.[42] Linezolid is generally microbiologically active against CA-MRSA, though a report of a linezolid-resistant isolate has been documented.[43] Furthermore, this report of resistance to linezolid occurred only one year after the drug entered the market. Additional reports of linezolid resistance in other Gram-positive organisms have also been published.[44] Due to this early resistance, linezolid should not be used routinely but instead reserved for patients with multiple allergies or strains with unusual resistance patterns.

Vancomycin

While vancomycin is a standard treatment option for MRSA infections, it is important to realize that it has some limitations. Both β-lactam antibiotics and vancomycin inhibit bacterial cell wall synthesis, however, they have distinct and separate binding sites. Therefore, *S aureus* strains that contain the *mecA* gene confer resistance to β-lactams, but no cross resistance is seen with vancomycin, and thus this drug is still active against MRSA.[45] However, not all strains of MRSA are susceptible to vancomycin. While most reported strains of resistance have been seen in adult patients, the threat that these strains could infiltrate the pediatric population is real. Emergence of vancomycin resistant *S aureus* (VRSA) was first reported in 2002, and several reports have been published since that time.[46] VRSA is still a fairly rare phenomenon, and is easily detectible via standard susceptibility testing. More common are strains that have reduced susceptibility to vancomycin, called vancomycin-intermediate *S aureus* (VISA). These intermediately susceptible strains produce peptidoglycan at an accelerated rate, leading to a thickened cell wall with reduced crosslinking. This causes trapping of vancomycin within the cell wall leading to reduced susceptibility.[46] These VISA isolates have higher MICs than truly susceptible strains, but much lower MICs than VRSA isolates. The most dangerous strains of VISA are those known as heterogeneous VISA (hVISA). These strains appear susceptible to vancomycin but contain subpopulations of cells that have reduced susceptibility. These strains are extremely difficult to detect, as they often appear susceptible via standard susceptibility tests. Clinical failure is often seen when hVISA strains are treated with vancomycin because the subpopulation of resistant organisms is selected for and can continue to grow even in the presence of vancomycin.[46] Traditionally, hVISA, VISA, and VRSA have been most commonly reported among HA-MRSA strains, while community-associated strains have retained their susceptibility.[5,8,36,37] More recently, however, hVISA has been reported in CA-MRSA clones.[47] It is important to be aware that while vancomycin is a standard of care for the treatment of MRSA infections, it does have limitations and clinical failure can still occur.

Other Antibiotics

Daptomycin is a newer antibiotic often used for the treatment of MRSA infections in adults. MRSA strains are frequently susceptible to daptomycin, and it does not share any cross

Table 1. Adverse Effects[45, 49, 56-58, 68] and Drug-Drug Interactions[69-72]

Drug	Most Common Adverse Effects	Serious Adverse Effects	Drug-Drug Interactions
SMZ/TMP	Nausea, vomiting, diarrhea, anorexia, rash, hypersensitivity reactions, kernicterus*	Stevens-Johnson Syndrome, agranulocytosis, hemolytic anemia, nephrotoxicity	Inhibits renal tubular excretion of methotrexate; Inhibits metabolism of phenytoin, rifampin, and warfarin; Displaces sulfonylureas from protein binding sites
Clindamycin	Diarrhea Rash	Pseudomembranous colitis, increased LFTs, neuromuscular blockade	None
Linezolid	Nausea, vomiting, headache, rash	Peripheral neuropathy, optic neuropathy, lactic acidosis, myelosuppression	Pharmacodynamic interaction with SSRI, SNRI, mirtazapine, etc. Increased risk of serotonin syndrome
Vancomycin	Red-man syndrome	Nephrotoxicity, ototoxicity	None
Daptomycin	Headache, injection site reactions, GI disturbances	Rhabdomyolysis	None
Quinupristin/ Dalfopristin	Venous irritation, arthralgia/ myalgia, nausea, vomiting, diarrhea, rash	Angioedema GI hemorrhage	Many due to inhibition of CYP3A4

LFT, liver function tests; SMZ/TMP, sulfamethoxazole/trimethoprim; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors
** In the neonatal period*

resistance with other antibiotics due to its unique mechanism of action.[48,49] Resistance to daptomycin, although rare, has been reported among MRSA isolates.[49] Additionally, and more importantly, the safety, pharmacokinetic parameters, and efficacy have not been established in patients less than 18 years of age. Only one case report of daptomycin use in a pediatric patient has been published in the literature.[50] Since the efficacy of daptomycin has not been established in the pediatric population, its use should be reserved for severe infections caused by isolates that are resistant to other antimicrobials or in those patients unable to tolerate other antibiotics.

Quinupristin/dalfopristin is another agent that also has activity against MRSA, and has been used for the treatment of MRSA infections in the adult population. The use of this drug in the pediatric population is limited, but an analysis of 127 pediatric patients enrolled in the global quinupristin/dalfopristin Emergency-Use Program suggests that it is effective in the pediatric population.[51] However, due to the fairly high number of adverse events seen in the adult population, presence of potentially serious drug interactions, and limited pediatric data, this drug should be reserved for serious infections in patients who cannot tolerate alternative therapies.

Tetracyclines, and the newer glycylcycline, tigecycline, also show activity CA-MRSA. However, both of these products can cause tooth discoloration if administered to pediatric patients under the age of 8 who still have their baby teeth.[52] Due to this relative contraindication, the variable susceptibility of CA-MRSA isolates to tetracyclines,[5,37,53] and the lack of pediatric data with tigecycline, these products will not be discussed further in this review.

SAFETY

Most antimicrobials used in the treatment of CA-MRSA infections are fairly well tolerated, but clinicians must be well versed in the side effect profiles to properly monitor for the most common as well as the most serious adverse events seen with these agents (Table 1). Additionally, clinically important drug-

Table 2. Pharmacokinetics, Comparative Dosing,[45, 49, 56-58, 68] and Cost

Drug	Oral Bioavailability	Elimination Route	Mechanism of Action	Traditional Adult Dose*	Pediatric Dose*	Comparative Cost
SMZ/TMP†	90%-100%	Renal	Inhibits sequential steps in bacterial folic acid synthesis	15-20 mg/kg IV/PO divided q 6-8 hr	15-20 mg/kg IV/PO divided q 6-8 hr	$
Clindamycin‡	90%	Hepatic	Binds to the 50S ribosomal subunit thus inhibiting bacterial protein synthesis	300-450 mg PO q 6-8 hr or 600-900 mg IV q 6-8 hr	30 mg/kg PO divided q 6-8 hr or 40 mg/kg IV divided q 6-8 hr	$
Linezolid‡	100%	Hepatic	Binds to the 50S ribosomal subunit thus inhibiting bacterial protein synthesis	600 mg IV/PO q 12 hr	10 mg/kg IV/PO q 8 hr	$$$$
Vancomycin†	Negligible	Renal	Inhibits the synthesis of the bacterial cell wall	1000 mg IV q 12 hr	15-20 mg/kg IV q 6-8 hr	$$
Daptomycin†	IV only	Renal	Binds to components of the bacterial cell membrane causing depolarization of the cell membrane potential	4-6 mg/kg IV q 24 hr	Unknown	$$$$
Quinupristin/Dalfopristin‡	IV only	Hepatic	Binds to the 50S ribosomal subunit thus inhibiting bacterial protein synthesis	7.5 mg/kg IV q 12 hr	Unknown	$$$

SMZ/TMP, sulfamethoxazole/trimethoprim; $, least expensive agents; $$$$, most expensive agents
** Dosing assumes normal renal and hepatic function*
† May require dosage adjustment in renal impairment
‡ May require dosage adjustment in hepatic impairment

drug interactions can be seen with SMZ/TMP, quinupristin/dalfopristin, and linezolid, also summarized in Table 1.

PHARMACOKINETICS

The oral bioavailabilities of SMZ/TMP and clindamycin have been reported to be 90% to 100%,[54,55] and the oral bioavailability of linezolid has been shown to be 100%.[56] Due to their excellent bioavailability, these three agents are suitable for oral therapy. It is important to emphasize that oral antibiotic therapy is often appropriate for the treatment of skin and soft tissue infections caused by CA-MRSA, while realizing that severe disseminated and invasive disease can also be caused by this organism and parenteral antibiotic therapy may be required.

SMZ/TMP, clindamycin, linezolid, and vancomycin have volumes of distribution that range from 0.3 to 2.0 L/kg and all 4 agents distribute well to skin and soft tissues making them ideal for the treatment of SSTIs, the most common infection type caused by CA-MRSA.[45,54-56]

The elimination half-lives of these drugs are shorter in pediatric patients than in the adult population. For these reasons, pediatric patients often require larger doses of drug on a mg/kg basis, as well as more frequent administration. Table 2 summarizes the pharmacokinetic properties of these agents and compares

Table 3. Developmental Agents with Activity Against MRSA[60-62]

Drug	Mechanism of Action	Half-life	Likely Dosing Regimen
Glycopeptides[60]			
Telavancin	Inhibits cell wall biosynthesis and disrupts the barrier function of the bacterial cell membrane making it rapidly bactericidal	7-9 hr	Once daily
Dalbavancin	Inhibits cell wall biosynthesis	6-10 days	Once weekly
Oritavancin	Disrupts membrane potential of bacterial cell wall	~100 hr	Once daily or every other day
Cephalosporins[61,62]			
Ceftabiprole	Binds to PBP 2a and prevents the cross-linking of peptidoglycan and formation of the bacterial cell wall	3-4 hr	Every 8-12 hr
Ceftaroline	Binds to PBP 2a and prevents the cross-linking of peptidoglycan and formation of the bacterial cell wall	2-4 hr	Every 12 hr

appropriate pediatric dosing to traditional adult dosing.

ADMINISTRATION AND COST

Ease of administration always plays a role in the drug selection process for a pediatric patient. SMZ/TMP is available as an oral tablet as well as an oral suspension.[57] While the oral suspension is designed for the pediatric patient, it can be difficult to administer. It is not a highly concentrated suspension and is only available as 40 mg/ 5 mL of the trimethoprim component. A 30-kg child who receives a 5-mg/kg dose would be given 19 mL of suspension, a volume that is not always tolerated. Clindamycin is also available as an oral suspension, and while it is a much more concentrated suspension, it is not very palatable.[58,59] It is extremely bitter, and some children simply cannot tolerate it. Vancomycin and the newer antibiotics such as daptomycin and quinupristin/dalfopristin must be administered intravenously and are therefore not as desirable for outpatient treatment.

Finally, when selecting an antibiotic regimen, cost of therapy must be a factor in the decision-making process. Oral clindamycin and SMZ/TMP are the least expensive agents used in the treatment of CA-MRSA infections. Linezolid, while also available for oral administration, is much more costly and its price often limits its use. Vancomycin is the least costly parenteral therapy, while daptomycin and quinupristin/dalfopristin are more expensive. Table 2 summarizes the relative costs of these agents.

FUTURE THERAPIES

Due to the relatively small number of agents active against MRSA, and the increasing incidence of resistance to current antimicrobials, several new agents are being developed for the treatment of MRSA. Three new glycopeptide antibiotics and 2 new cephalosporin antibiotics are currently in development.[60-62] Table 3 summarizes the mechanisms of action and likely dosing regimens (in adult patients) of these developmental agents. These new antibiotics in the pipeline have not yet been tested in the pediatric population, but do show promise against MRSA in the adult population. As more trials involving these agents emerge, and testing occurs in children, the role of these agents in the treatment of CA-MRSA will be further elucidated.

RECOMMENDATIONS FOR TREATMENT

Oral antibiotic therapy is appropriate for the treatment of mild to moderate CA-MRSA infections. SMZ/TMP and clindamycin are reasonable choices, and they are two of the most cost effective therapies for these infec-

tions. SMZ/TMP is also a reasonable choice for empiric therapy as long as suspicion of group A streptococcus is low. If suspicion of group A streptococcus is higher, clindamycin may be a better empiric selection as long as local rates of constitutive and inducible resistance are low. Linezolid, while also available for oral administration, should not be used routinely due to its high cost, serious side effect profile, and the emergence of resistant isolates. Its use should be reserved for patients with multiple allergies or strains with unusual resistance patterns. Vancomycin is still the standard of care for more serious CA-MRSA infections that require parenteral therapy. Newer agents such as daptomycin or quinupristin/dalfopristin cannot be recommended as routine therapy due to the lack of safety and efficacy data in pediatric patients. These drugs should be reserved for emergency situations in patients with no other options.

PREVENTION AND CONTAINMENT OF OUTBREAKS

It has been hypothesized that MRSA infections could be prevented and outbreaks could be contained if nasal colonization with *S aureus* was eradicated. Several studies have tested this hypothesis and the results have been mixed.[63-65] Decolonization regimens usually involve treatment with topical mupirocin, and they are often unsuccessful due to mupirocin resistance and a high incidence of recolonization especially in hospitalized patients where MRSA is endemic.[63,64] More aggressive decolonization strategies using oral as well as topical antibiotics have shown greater success rates, but have not been shown to decrease infection rates.[65]

Currently, decolonization strategies are not recommended for widespread use in all colonized patients since their efficacy has not been established. Additionally, resistance to mupirocin has been reported and has been associated with decolonization failure.[63,65,66] Decolonization may, however, be beneficial in patients with recurrent MRSA infections or when MRSA transmission and infection is occurring in a closely linked group, such as a household.[66] The strongest recommendations for prevention of infection are merely standard infection control procedures such as isolation and contact precautions within health care facilities and good hand hygiene practices.[66,67] These recommendations also apply to outpatient settings. Patients must be educated to keep wounds covered with clean bandages, maintain adequate hand and body hygiene, and to avoid sharing towels and other laundry.[66]

CONCLUSIONS

CA-MRSA has emerged as a pathogen distinct from the older and more familiar HA-MRSA. It has a unique genetic makeup, separate antibiotic susceptibility patterns, and different virulence factors. CA-MRSA infections are on the rise in the United States; they have increased dramatically in the last ten years. Clinicians that see patients who present with SSTIs must now have a high suspicion that CA-MRSA is the responsible pathogen. Proper antibiotic selection for the pediatric patient must take into account local susceptibility patterns, the severity of infection, patient specific factors, ease of administration, and cost.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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