Community-acquired Methicillin-resistant Staphylococcus aureus Infection in the Pediatric Population

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Introduction and History of Staphylococcus aureus Infection

Introduction

Community-acquired methicillin-resistant Staphylococcus aureus, commonly known as CA-MRSA, is a prevalent and potentially life-threatening infection that can occur in both the adult and pediatric population. During the past 2 decades, clinicians have performed research to try to better understand the biology of this pathogen and to develop pharmacologic treatments that can combat this infection effectively. The objectives of this review are to discuss the history of CA-MRSA infection, along with its epidemiology, risk factors, and resistance profiles, and to identify the various medications available to treat this infection.

History of Staphylococcus aureus Infection

Staphylococcus aureus is a gram-positive cocci pathogen. In the early 1940s, the major treatment available to combat this organism was penicillin, and all isolates were sensitive to penicillin during that period. With this antibiotic, the mortality rate of bacteremia caused by S. aureus decreased from a striking 80% to 25% (Ladhani & Garbash, 2005). In 1944, the first penicillin-resistant strain of S. aureus was discovered. As clinicians used more and more penicillins as the primary treatment for S. aureus infection, the prevalence of penicillin-resistant strains increased in the 1960s. It was during this time that a new class of antibiotics was developed to target this pathogen specifically. This class of antibiotics is known as the penicillinase-resistant penicillins, which includes nafcillin, dicloxacillin, and oxacillin. One year after this class of antibiotic was developed, a resistant strain known as methicillin-resistant S. aureus (MRSA) was discovered in both the United States and the United Kingdom (Zaoutis et al., 2006). MRSA became increasingly prevalent, especially in larger hospitals, in the 1970s. From the late 1970s to the early 1990s, MRSA was usually a hospital-acquired pathogen. It was not until 1998 that the first case of CA-MRSA in children was identified (Ladhani & Garbash; Zaoutis et al.). Since then, CA-MRSA has become more prevalent in children throughout the United States (Table 1).

Definition of CA-MRSA

Methicillin-resistant S. aureus infection can be separated into two major categories: community-acquired or hospital-acquired. According to the Centers for Disease Control and Prevention (2005), patients need to fulfill several criteria (Box) before the clinician can identify the infection as CA-MRSA. First, patients cannot have any medical devices or indwelling catheters that are permanently placed through their skin, and they cannot have any medical history of MRSA infection. Also, patients cannot have any history of a recent stay in a nursing home, a hospital, or other long-term care facilities. Last but not least, the MRSA infection must be diagnosed in the outpatient environment, or the positive culture for MRSA must be identified within 48 hours of hospital admission.

Epidemiology

The prevalence of CA-MRSA is not really known, but it is certain that the prevalence has increased tremendously during the past few decades. For example, the incidence of CA-MRSA at a children's hospital in Texas increased from 3.8 per 10,000 admissions in the 1990s to 315 per 10,000 admissions in the early 2000s (Le & Lieberman, 2006). CA-MRSA does not only occur in the United States. Numerous cases of CA-MRSA have been reported around the world, including...
Risk Factors

It is important that pediatric nurse practitioners (PNPs) educate their patients or the patients' parents on risk factors for CA-MRSA infections. These risk factors include towel sharing among participants in team sports and attendance at day care or outdoor camps (Paintsil, 2007). Also, children may be more susceptible to CA-MRSA colonization if they have a medical history of antibiotic use. Children who have chronic diseases such as diabetes mellitus and cystic fibrosis or who are immunocompromised (e.g., patients with HIV) also are at an increased risk of becoming infected with CA-MRSA (Ladhani and Garbash, 2005, Le and Lieberman, 2006). Lastly, children are at a higher risk for such infection if they have close contact with people who have been infected with CA-MRSA or if they reside in any kind of correctional facility (Le & Lieberman).

The relationship between ethnicity and CA-MRSA colonization is still quite controversial. Some studies have shown that non-Whites are more susceptible to CA-MRSA infections, while other studies have concluded that African Americans and Mexicans are less likely to be infected with such organisms (Paintsil, 2007). Similarly the relationship between age and CA-MRSA colonization is still not strongly defined, but it is thought that younger children may be at higher risk of CA-MRSA colonization than older children (Paintsil). This trend probably occurs because older children generally have a stronger immune system than do younger children.

Resistance

The two most common clones of CA-MRSA infections are USA 300 and USA 400. They are known as "USA" because these clones were described by researchers in both the United States and Australia. The USA 300 clone is considered to be the primary cause of skin and soft-tissue infections in patients colonized with CA-MRSA (King et al., 2006). As reported in a retrospective study by Ochoa, Mohr, Wanger, Murphy, and Heresi (2005), CA-MRSA isolates usually are resistant to erythromycin and fluoroquinolones. CA-MRSA infections typically are susceptible to clindamycin and sulfamethoxazole-trimethoprim, but hospital-acquired MRSA infections usually are resistant to these antibiotics (King et al.). In one prospective study (David et al., 2006), children were found to have less resistance to non-β-lactam antibiotics (e.g., clindamycin) than do adults, but increasing resistance to these antibiotics, especially clindamycin, can be observed (Braun, Craft, Williams, Tuamokumo, & Ottolini, 2005).

Types of CA-MRSA Infection

Few common types of CA-MRSA infection exist. The most prominent are skin and soft-tissue infections, such as cellulitis and abscesses, which usually comprise 69% to 96% of all CA-MRSA infections. Pneumonia and urinary tract infection comprise less than 14% and 3% to 13% of all CA-MRSA infections, respectively. Other potential CA-MRSA infections include bacteremia and osteomyelitis (d3% and d2%, respectively) (Le & Lieberman, 2006).

Treatment Options

Before prescribing antimicrobial agents to a patient infected with S. aureus, PNPs need to implement a few strategies for treatment. First, they need to know the prevalence of CA-MRSA in and around their region of residence. If the prevalence is high, they need to cover for MRSA empirically; if the prevalence is low, they should reserve antibiotics that are used for MRSA for serious infections like osteomyelitis and bacteremia. In addition, PNPs also should know the severity of the infection (Le & Lieberman, 2006). For example, under most circumstances, PNPs can perform incision and drainage and withhold antibiotics for patients who present with small pustules or abscesses. However, if the infection is severe, it should be managed with aggressive, empiric antibiotics for MRSA. Besides knowing the prevalence of CA-MRSA and the severity of the infection, PNPs also should identify the susceptibility patterns of the strain of CA-MRSA in their community (Le & Lieberman). Based on susceptibility patterns, one can choose an appropriate agent to combat MRSA much more effectively. The susceptibility pattern, however, may vary among different states. For example, clindamycin resistance was observed in only 8% of all the CA-MRSA cases in Texas, compared with 94% in Illinois (Paintsil, 2007). Without knowing the susceptibility pattern, PNPs may not be able to treat patients effectively. The local county or state health department or local hospital laboratory should be able to provide local resistance patterns.

Treatment options for CA-MRSA include vancomycin, linezolid, clindamycin, sulfamethoxazole-trimethoprim, and rifampin for synergy (Table 2). The following information will be a review on the previously mentioned agents and other available pharmacologic options (Ladhani and Garbash, 2005, Le and Lieberman, 2006, Marcinak and Frank, 2003).

Vancomycin (Vancocin®)
community-acquired methicillin-resistant staphylococcus aureus infection

vancomycin is reserved for patients hospitalized with CA-MRSA. It inhibits cell wall synthesis of gram-positive pathogens by binding to D-alanyl-D-alanine moiety of the cell wall precursor. It is bactericidal but is not as effective as other agents for serious S. aureus infection like endocarditis (Le & Lieberman, 2006). Under such circumstances, additional antibiotics (e.g., rifampin or gentamicin) should be administered along with vancomycin for synergistic purposes.

The common intravenous dosage of vancomycin is 15 to 20 mg/kg/dose every 8 hours. Of note, oral vancomycin is not used for systemic infection because it is not absorbed systemically. It is vital to monitor serum trough concentration at steady state while patients are taking vancomycin; the serum trough concentration usually is obtained before the third or fourth dose. The targeted serum trough concentration varies depending on the type and severity of the infections. Most importantly, the serum trough concentration must be five to 10 times above the minimum inhibitory concentration of the organism. In most cases, clinicians usually target for a trough concentration of 5 to 10 μg/mL for mild infections, while a trough concentration of 15 to 20 μg/mL is indicated for serious infections like osteomyelitis and bacteremia. Trough concentration of 15 to 20 μg/mL in adults with community-acquired pneumonia showed improved outcomes over trough concentration of <15 μg/mL (Hidayat, Hsu, Quist, Shriner, & Wong-Beringer, 2006). The best method for obtaining a blood sample for the trough concentration is via a peripheral stick. If the use of this method is not feasible, a nurse can draw the sample through the line that the vancomycin is running through, but the line should be flushed well with saline solution before such a method can be used.

Vancomycin is usually well tolerated. The most commonly seen adverse effect of this antibiotic is "Red Man Syndrome." Patients with this syndrome can present with flushing, pruritus, red neck, and rash involving the majority of the body (Lexi-Comp, 2008). "Red Man Syndrome" is caused by an infusion-related release of histamine. This problem can be resolved by lengthening the infusion rate of the medication from the usual 1 hour to 2 hours; however, administering pre-medications such as acetaminophen and diphenhydramine usually is not necessary to resolve this problem.

Additional possible adverse effects associated with vancomycin include nephrotoxicity and ototoxicity. Nephrotoxicity is not that common unless vancomycin is co-administered with other nephrotoxic agents such as gentamicin. Ototoxicity may occur only when the serum concentration of the antibiotic is extremely high (e.g., >80 μg/mL).

Even though vancomycin is a potent antibiotic against CA-MRSA, more and more resistance has surfaced. In 1996, the first case of vancomycin-intermediate resistant S. aureus (VISA) was reported; subsequently, in early 2000s, a strain of vancomycin-resistant S. aureus (VRSA) was discovered (Le & Lieberman, 2006). This growing number of resistant strains is a huge concern in the medical field. To prevent further incidences of such resistance, clinicians need to prescribe this antibiotic judiciously.

linezolid (zyvox®)

linezolid is a bacteriostatic antibiotic that is ideal for MRSA, penicillin-resistant Streptococcus pneumoniae (PRSP), and vancomycin-resistant enterococcus (VRE) (Ladhani & Garbash, 2005). It inhibits protein synthesis by binding to the 23S ribosomal subunit of gram-positive bacteria.

Common adverse effects of linezolid include headache, nausea/vomiting, and diarrhea. In one clinical study, linezolid, when used in the neonatal period, was found to produce fewer adverse effects compared with vancomycin (Marcinak & Frank, 2003). A potentially more serious problem associated with linezolid is myelosuppression. If this antibiotic is used for more than 2 weeks, it is recommended that a baseline complete blood cell count (CBC) be obtained and that the CBC be monitored at least weekly (Le & Lieberman, 2006). One important counseling point regarding this antibiotic is that it should not be co-administered with monoamine oxidase inhibitors (e.g., phenelzine) and food that contains tyramine because that can increase the risk of the development of a potentially fatal condition known as serotonin syndrome.

The common dosage of linezolid is dependent on the patient's age. If patients are younger than 12 years, the usual dosage is 10 mg/kg/dose intravenous/by mouth every 8 hours (maximum: 600 mg/dose); whereas for patients 12 years and older, the usual dosage is 600 mg intravenous/by mouth every 12 hours. To prevent linezolid-resistant S. aureus, linezolid should be reserved for instances when the pathogen is resistant to vancomycin.

Clindamycin (cleocin®)

Clindamycin exhibits its antimicrobial action by inhibiting protein synthesis (50S ribosomal subunits) in both aerobic gram-positive and anaerobic bacteria. It is mostly bacteriostatic but can become bactericidal at higher concentration. If the S. aureus isolate is susceptible to clindamycin and resistant to erythromycin, a disk-diffusion induction test, better known as the D test, should be done, because development of inducible resistance to clindamycin can occur. The appearance of a "D" shape on an agar plate with erythromycin and clindamycin on it indicates inducible resistance to clindamycin, and alternative therapy should be prescribed (Le & Lieberman, 2006).

The dosing of clindamycin for CA-MRSA in children is dependent on the severity of the infection. For mild infections like
cellulitis, the dosing is 30 mg/kg/day by mouth, divided every 6 to 8 hours. For severe infections such as osteomyelitis, the dosing is 40 mg/kg/day, administered intravenously, divided every 6 to 8 hours (Le & Lieberman, 2006).

Common adverse effects of clindamycin include nausea/vomiting and abdominal pain. Another problem associated with clindamycin is that the oral suspension has a poor taste, so children may not tolerate it as well as other available oral agents that will be discussed later. The most concerning possible adverse event caused by clindamycin is diarrhea, because this antibiotic increases the patients' risk of having pseudomembranous colitis. Patients who have persistent diarrhea while taking this antibiotic should seek medical attention immediately.

Sulfamethoxazole-Trimethoprim (Bactrim® or Septra®)

Sulfamethoxazole-trimethoprim (SMZ-TMP) is an antimicrobial agent that suppresses bacterial DNA synthesis by inhibiting the production of folinic acid. It is bactericidal but does not have any activity against Group A Streptococcus infection that may also cause skin and soft-tissue cellulitis. SMZ-TMP is used mainly for mild cases of CA-MRSA infection with low bacterial burden (Le & Lieberman, 2006).

The usual dosage is 6 to 12 mg/kg/day of the TMP component intravenous/by mouth, divided every 12 hours (Lexi-Comp, 2008). The dose needs to be adjusted in patients with renal dysfunction (i.e., with a creatinine clearance of 15-30 mL/min) (Lexi-Comp, 2008). SMZ-TMP is a sulfonamide derivative, so if a patient is allergic to sulfa drugs, it is possible that he or she is allergic to this antibiotic.

SMZ-TMP can cause rash, pruritus, and anorexia. PNPs should avoid using this antibiotic in the neonatal period because it is highly protein-bound and has the ability to displace bilirubin from albumin. If elevated amounts of bilirubin cross the blood-brain barrier, kernicterus can occur. Stevens-Johnson syndrome is a possible but rare major adverse event that can occur when patients are taking this antimicrobial agent. Other potential serious adverse effects that can become manifest, especially in children, are anemia and thrombocytopenia.

Rifampin (Rifadin®)

Rifampin is a bactericidal antimicrobial agent that inhibits bacterial transcription by binding to RNA polymerase. It has good distribution to both the bones and the lungs (Le & Lieberman, 2006). However, this antibiotic is rarely used as a single agent to treat CA-MRSA because resistance can occur rapidly. It is used for synergy with other antibiotics like vancomycin.

The common dosage of rifampin is 15 to 20 mg/kg/day intravenous/by mouth, divided every 12 hours with a maximum of 600 mg/dose (Le & Lieberman, 2006). The oral formulation of this medication should be given on an empty stomach to increase absorption. If gastrointestinal irritation occurs, patients can take it with food. Rifampin is a potent drug inducer. Thus, it is important to look for any potential drug-drug interactions while the patients are taking this antibiotic. For example, if female patients are using oral contraceptives, they should be advised to use additional forms of protection (e.g., condoms).

Common adverse effects of this antibiotic include nausea/vomiting, anorexia, and abnormal pain. Rifampin can cause discoloration of body fluids, such as sweat, urine, saliva, and tears. Patients should be advised not to wear contacts while taking this antibiotic. In addition, if patients' urine, for example, does not turn orange in color, they need to notify their health care provider because they may have problems with absorption. A rare but possible serious adverse effect associated with rifampin is hepatotoxicity. If jaundice develops while a patient is taking this antibiotic, liver function laboratory tests should be checked.

Other Possible Options

Other possible options to combat CA-MRSA include quinupristin-dalfopristin (Synercid®), daptomycin (Cubicin®), and tigecycline (Tygacil®) (Le & Lieberman, 2006). However, there are insufficient data on the use of these antimicrobial agents in children, so they usually are not prescribed. Doxycycline and fluoroquinolones (e.g., ciprofloxacin) actually can be used for CA-MRSA in an outpatient setting if sensitivities show that the CA-MRSA is susceptible to these agents. Because of the emergence of resistance, however, PNPs are unable to use these agents in the majority of cases (Le & Lieberman; Ochoa et al., 2005).

Prevention

Even though CA-MRSA is so prevalent, it can be prevented by implementing various strategies. Patients and their parents should be educated about CA-MRSA (Table 3). All of us should have good hand hygiene. We should not share towels and should avoid contact with people who are infected with CA-MRSA. If CA-MRSA colonization is discovered, an
eradication protocol should be implemented. Colonized individuals should be cleansed with body disinfectant (e.g., chlorhexidine gluconate) and treated with nasal mupirocin (Paintsil, 2007). Nasal mupirocin can be used to prevent nasal carriage of CA-MRSA. It can be applied to the nares two or three times daily for 3 weeks. Its efficacy, however, is controversial (Le & Lieberman, 2006; Paintsil).

**Conclusion**

With the increasing resistance to antimicrobial agents used for CA-MRSA, health care providers need to develop protocols or guidelines that can enable them to identify the infections in a timely manner and to implement adequate and appropriate pharmacotherapy judiciously. Children or their parents also need to be educated on the importance of preventive strategies to minimize their risk of colonizing with this potential deadly infection. Finally, in the future, researchers will need to come up with alternative agents that may be used for cases when the CA-MRSA isolates are resistant to all currently available antimicrobial medications.

**Table 1. History of Staphylococcus aureus Infection**

<table>
<thead>
<tr>
<th>Date</th>
<th>Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1940s</td>
<td>All isolates were sensitive to penicillin</td>
</tr>
<tr>
<td>1944</td>
<td>First penicillin-resistant <em>S. aureus</em> discovered</td>
</tr>
<tr>
<td>1960</td>
<td>Penicillin-resistant <em>S. aureus</em> became prevalent; dicloxacillin, nafcillin, and oxacillin were developed</td>
</tr>
<tr>
<td>1961</td>
<td>First MRSA discovered in both the United States and United Kingdom</td>
</tr>
<tr>
<td>1970s–early 1990s</td>
<td>MRSA prevalent in hospitals</td>
</tr>
<tr>
<td>1998</td>
<td>First case of CA-MRSA in children was identified</td>
</tr>
<tr>
<td>Today</td>
<td>CA-MRSA in children is prevalent throughout the United States</td>
</tr>
</tbody>
</table>

CA-MRSA, Community-acquired methicillin-resistant *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*.


**Table 2. Major Treatment Options for CA-MRSA in the Pediatric Population**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>MOA</th>
<th>Dose</th>
<th>Availability</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Inhibits cell wall synthesis of gram-positive pathogens</td>
<td>15-20 mg/kg/dose IV every 8 hours</td>
<td>Reconstituted powder for infusion: 500 mg, 1 g, 5 g, and 10 g</td>
<td>Rash, red man syndrome (infusion-related)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Inhibits protein synthesis (23S ribosomal subunit) of gram-positive pathogens</td>
<td>&lt;12 years: 10 mg/kg/dose IV/PO every 8 hours (maximum: 600 mg/dose); ≥12 years: 600 mg</td>
<td>Tablet: 600 mg; suspension: 20 mg/mL; infusion: 200 mg/100 mL, 400 mg/200 mL, and 600 mg/300 mL</td>
<td>Headache, nausea/vomiting, diarrhea; myelosuppression (rare)</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>Mechanism of Action</td>
<td>Dosage</td>
<td>Route of Administration</td>
<td>Side Effects</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>Clindamycin</td>
<td>Inhibits protein synthesis in aerobic gram-positive and anaerobic bacteria</td>
<td>Mild infection: 30 mg/kg/day PO divided every 6 to 8 hours; severe infection: 40 mg/kg/day IV divided every 6 to 8 hours</td>
<td>Capsules: 75 mg, 150 mg, and 300 mg; solution: 75 mg/5 mL; injection: 150 mg/mL</td>
<td>Poor taste (oral), diarrhea (clostridium difficile), abdominal pain, nausea/vomiting</td>
</tr>
<tr>
<td>Sulfamethoxazole–Trimethoprim</td>
<td>Inhibits folinic acid production → suppresses DNA synthesis</td>
<td>6-12 mg/kg/day TMP IV/PO divided every 12 hours</td>
<td>Tablet: SS, 400 mg/80 mg (TMP) and DS, 800 mg/160 mg (TMP); Suspension: 200 mg/40 mg (TMP)/5 mL; Injection: 80 mg/16 mg (TMP)/mL</td>
<td>Rash, pruritus, anorexia; anemia, thrombocytopenia, Steven-Johnson syndrome (rare)</td>
</tr>
<tr>
<td>Rifampin (use for synergy with other agents)</td>
<td>Inhibits bacterial transcription by binding to RNA polymerase</td>
<td>15-20 mg/kg/day IV/PO divided every 12 hours (maximum: 600 mg/dose)</td>
<td>Capsule: 150 mg and 300 mg; reconstituted powder for infusion: 600 mg</td>
<td>Nausea/vomiting, anorexia, discoloration of body fluids, abdominal pain; hepatotoxicity (rare)</td>
</tr>
</tbody>
</table>

CA-MRSA, Community-acquired methicillin-resistant Staphylococcus aureus; DNA, deoxyribonucleic acid; DS, double strength; IV, intravenous; MOA, mechanism of action; PO, by mouth; RNA, ribonucleic acid; SS, single strength; TMP, trimethoprim.


Table 3. Educational Points on CA-MRSA for Patients and Their Parents
**Box 1. Definition of CA-MRSA**

- Diagnosed as an outpatient
- Culture positive for MRSA within 48 hours after hospitalization
- No medical devices or indwelling catheters that are permanently placed through the skin
- Medical history negative for MRSA infection
- No history of recent stay in nursing home/hospital/long-term care facility

CA-MRSA, Community-acquired methicillin-resistant Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus.

Data from Centers for Disease Control and Prevention, 2005.

**References**


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