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Treatment Strategies for Methicillin-Resistant *Staphylococcus aureus* Infections in Pediatrics

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Abstract

Staphylococcus aureus is an important pathogen that frequently causes clinical disease in children. A wide array of illnesses can be caused by this common pathogen ranging from non-invasive skin infections to severe, life-threatening sepsis. Additionally, as antibacterials have been used to eradicate *S. aureus*, it has developed resistance to these important therapeutic agents. Methicillin-resistant *S. aureus* (MRSA) has become an increasing problem in pediatric patients over the past decade. In this review, we discuss the epidemiology, pathogenesis, and treatment options available in treating MRSA infections in children. Specifically, we address the importance of abscess drainage in the treatment of skin and soft tissue infections, the most common clinical manifestation of MRSA infections, and highlight the various agents that are available for treating this common infection. In severe, life-threatening invasive MRSA infections the primary therapeutic option is vancomycin. In cases of MRSA toxic shock syndrome the addition of clindamycin is necessary. In other invasive MRSA infections, such as pneumonia and musculoskeletal infections, the empiric treatment of choice is clindamycin. Finally, newer agents and additional treatment options are discussed.

Staphylococcus aureus is a ubiquitous bacterium that has been a notorious pathogen throughout history. Within a year from the initial clinical use of penicillin to treat an invasive *S. aureus* infection, resistance to penicillin was observed.[1] History repeated itself in the 1960s when methicillin-resistant *S. aureus* (MRSA) was discovered within hospitals only a year following the introduction of this semi-synthetic penicillin designed to treat this common pathogen.[2] Not surprisingly, MRSA is now being observed frequently in the community.

1. Epidemiology

In the past, MRSA was the prototypical pathogen implicated in hospital-acquired (HA) or nosocomial infections. MRSA is considered to be HA when it is isolated 48 hours after a patient is admitted. Risk factors for such infections are well known and include prolonged hospitalization, admission to a burn or intensive care unit, surgery, invasive procedures, implanted medical devices, and exposure to patients colonized or infected with MRSA.[3] In adult studies, patients who become colonized with MRSA are noted to be at increased risk for developing invasive infection.[4-6] In children's hospitals, similar risk factors have been outlined and notable common infection sites involved in HA-MRSA infections include the lower respiratory tract, skin and soft tissue, and blood.[7,8]

In the US, a unique change regarding this pathogen occurred over the past decade. In 1998, Herold et al.[9] reported an increase in MRSA infection cases, primarily of the skin and soft tissue, among children from the community who had no predisposing risk factors. MRSA is considered to be community-acquired (CA) when the isolate is grown at presentation or within 48 hours of admission. Numerous reports have subsequently followed that identify CA-MRSA as a common and emerging pathogen in children. Additionally, outbreaks have been observed among jail inmates,[10] homosexual men,[10] athletes on sports teams,[10] children in child care centers,[11] military recruits,[12] and neonates cared for in newborn nurseries.[13] Fridkin et al.[14] found that children aged <2 years were 1.5-fold more likely to experience CA-MRSA infections compared with those aged ≥2 years. Rates of CA-MRSA in children's hospitals have been reported to account for up 40–75% of all *S. aureus* isolates.[8,15,16]

An increase in the percentage of MRSA isolates has also been observed in parts of Europe, though it has not been as widespread as seen in the US. As of 2006, the European countries with the highest percentage of MRSA include Romania (54%), Portugal (48%), the UK (42%), and Greece (42%). Norway, Sweden, and the Netherlands have continued to have MRSA rates of ≤1%.[17]

Although most MRSA infections involve skin and soft tissue, the incidence of invasive MRSA disease in the US has been recently described. In one multicenter study the overall, standardized incidence of invasive MRSA in 2005 was 31.8 per 100 000 persons. The incidence of invasive CA-MRSA infections among the nine sites ranged from 1.6 to 29.7 per 100 000 persons.[18] In pediatrics, children aged <1 year had the highest incidence of all pediatric age groups. African American children aged <1 year had the highest incidence at 65.9 per 100 000 persons. In all age groups, African Americans had a higher incidence of invasive disease. In this study the standardized mortality rate was found to be 6.3 per 100 000 persons.[18]

The molecular epidemiology of CA-MRSA is quite different from HA-MRSA strains. The resistance mechanism for MRSA infection is an abnormal penicillin binding protein, PBP2A, that is encoded by the *mecA* gene.[19] This gene is located within the staphylococcal cassette chromosome (SCC*mec*). Five SCC*mec* types (I–V) have been identified. Type II and III are the largest in size, contain genes that encode resistance against non-β-lactam drugs, and are found in HA-MRSA isolates. The type IV SCC*mec* cassette is found most frequently in CA-MRSA. This cassette is small and lacks genes that encode resistance against non-β-lactam antibacterials.[20]

Distinct differences in susceptibility patterns are noted between HA-MRSA and CA-MRSA. Traditionally, the HA-MRSA strains are resistant to all β-lactams and other non-β-lactam antibacterials because of their type II and III SCC*mec* cassette. Reported resistance rates in pediatric HA-MRSA are: clindamycin (27–44%), erythromycin (91%), and cotrimoxazole (0–11%).[7,21]

In contrast, CA-MRSA infections are often susceptible to the non-β-lactams, such as cotrimoxazole and clindamycin. Strains of CA-MRSA can demonstrate a constitutive or an inducible resistance to clindamycin in the presence of erythromycin that can be assessed in the laboratory by D-testing. Studies of CA-MRSA have shown a resistance rate to clindamycin of 3–33%,[7,8,16,22] while those for cotrimoxazole ranged from 0.6% to 3%.[7,8,16] Reported resistance rates of other non-β-lactams are: levofloxacin or ciprofloxacin (18–53%), tetracyclines (22–83%), erythromycin (78–97%), and gentamicin (3%).[7,8,15,16,22]

As CA-MRSA infections have become more common, isolates are being identified from children associated with the healthcare environment. Hulten et al.[15] noted that among their patients with frequent hospital exposure, 90% of the MRSA strains were similar to the common CA-MRSA strain. At the Children's Hospital of Philadelphia, PA, USA all MRSA isolates from patients with risk factors for hospital-associated infections were similar to isolates from healthy children. Additionally, this study noted that children with risk factors for hospital-associated infections were more likely to experience an invasive MRSA infection than healthy children.[16]

2. Pathogenesis

S. aureus is a commensal bacteria found in the nares and on the skin of humans. Clinical disease often follows breaks in the

integument. Once the bacteria invade the skin, infection may be limited to abscess formation. Hematogenous seeding may occur either through the skin or mucosal surfaces with the potential for dissemination to distant sites such as the heart, joints, muscle and bones. In most instances, *S. aureus* bacteremia is associated with other sites of infection.[23]

Sepsis-like syndromes and toxic shock syndrome (TSS) consequent to toxin production may result from infection with *S. aureus* as the organism can produce virulence factors that are important in the pathogenesis of clinical disease. These virulence factors include genes for superantigens (TSS toxin-1 [TSST-1]), exotoxins, and leukotoxins. The most notable toxin produced by MRSA is Panton-Valentine leukocidin (PVL), which has been associated with pulmonary involvement of CA-MRSA.[24,25] Controversy does exist on whether PVL is the major virulence determinant of MRSA.[26,27] Although many virulence factors of MRSA play a role in clinical disease, it is not clear which ones are primarily responsible.

3. Clinical Manifestations

The clinical manifestations of MRSA are similar to those observed in methicillin-susceptible *S. aureus* (MSSA). Although reports have suggested MRSA infections are more severe than MSSA infections,[28,29] data are not consistent. Sattler et al.[30] noted that more deep-seated infections were associated with MSSA infections. Therefore, it is important for the clinician to realize that both MRSA and MSSA can cause similar clinical manifestations with similar severity. Therapeutic intervention of suspected and/or proven infection with *S. aureus* is guided by clinical presentation/scenario, the most common of which are described in sections 4.1 to 4.9.

3.1 Skin and Soft Tissue Infections (SSTIs)

Nothing defines the impact of the emergence of MRSA infection more for the clinician in practice than the epidemic occurrence of skin and soft tissue infections (SSTIs). CA-MRSA SSTIs are the most common clinical manifestation and account for 66–95% of all isolates.[16,31,32] The most common types of SSTIs observed with MRSA are folliculitis (infected hair follicle), furuncles (also referred to as boils and deeper infections than folliculitis), carbuncles (group of furuncles), and localized skin abscesses. Other types of skin infections that can occur include impetigo (bullous or nonbullous) and surgical incision cellulitis, which is a typical presentation for nosocomial MRSA infection.

The most common presentation consists of the sudden onset of erythematous papules that develop into pustules; these may initially be mistaken for spider bites. The most common locations are the buttock and thigh. Fever has been observed in 40–50% of the cases,[21,33] but the majority of children appear to be well and have no systemic signs or symptoms. Although rare, invasive infections have been observed following and concurrently with SSTIs.[34]

3.2 Lymphadenitis

The second most common clinical presentation that practitioners are likely to encounter is acute lymphadenitis caused by *S. aureus*. Lymphadenitis caused by CA-MRSA has been observed in 3–22% of isolates.[31,35] Infants and children are most likely to be affected, and anterior cervical lymph nodes are most likely to be infected. Presentation consists of fever along with erythema, warmth, swelling, and pain overlying the lymph node.

3.3 Sepsis

A severe sepsis syndrome has been reported in pediatric patients infected with CA-MRSA. A recent study observed an increase from one case of CA-MRSA sepsis between 1999 and 2001 to 12 cases between 2002 and 2004.[34] Pulmonary and musculoskeletal findings are the most common clinical manifestations in patients with MRSA sepsis, with multifocal disease being common.[34,36] In children with sepsis, pulmonary findings have consisted of embolic disease, pneumatoceles, and complicated parapneumonic effusions. In up to 70% of patients, mechanical ventilation will be necessary.[36]

Musculoskeletal infections in patients with MRSA sepsis often involve infection in two or more sites. Gonzalez et al.[34] observed septic arthritis of two or more joints in 71% of patients, with concomitant pyomyositis present in 80% of those patients. Additional findings of MRSA sepsis include hypotension, coagulopathy, an erythroderma rash, and desquamation. Although the clinical picture in these patients resembled TSS, not all of the established diagnostic criteria were fulfilled.

Mortality and morbidity are not uncommon in children with MRSA sepsis. In one report, four children died of this syndrome between 1997 and 1999.[37,38] Gonzalez et al.[34] observed a case fatality rate of 17%. Additionally a case fatality rate of 27% was observed in patients with severe MRSA pneumonia, sepsis, and acute influenza infection.[39]

3.4 Toxic Shock Syndrome (TSS)

Similar in clinical presentation to the sepsis-like syndrome, TSS caused by MRSA, although rare, has been reported.[40-42] TSS syndrome caused by MSSA was first described in 1978, and an epidemic occurred in 1979–80 that was related to the use of high absorbency tampons.[43,44] Subsequently, surgical associated cases have been described as well as cases without an identifiable infectious focus. All age groups are at potential risk as illustrated by an MRSA TSS-like syndrome that was observed in a neonatal outbreak.[45]

TSS is by definition a toxin-mediated illness related to *S. aureus* strains that produce TSST-1. The common denominators among patients appear to be lack of antibodies to the TSST-1 toxin produced by the bacteria, coupled with compromise in mucosal or skin integrity, and presence of a foreign body (tampon, surgical implants). Although TSS can occur in the setting of invasive staphylococcal disease, including pneumonia and skeletal infection, it is important to note that blood cultures are positive in <5% of such patients. The clinical case definition for staphylococcal TSS is well described.[46] The clinical manifestations and clinical criteria for the diagnosis of TSS can be found in an in-depth review by Chuang et al.[47]

3.5 Pneumonia

Pneumonia is a common facet of staphylococcal infection and is associated with approximately 10–20% of MRSA infections.[7,22,31] Antecedent viral infection has been observed as a potential predisposing factor with influenza virus representing the most common viral pathogen isolated.[48] There have also been reports of MRSA pneumonia in association with parainfluenza virus infection.[24] Although up to 67% of MRSA primary pneumonias are associated with empyema[24] cases of MRSA-associated necrotizing pneumonia without empyema are reported.[24,37,39] Pulmonary involvement may be clinically apparent in older children with septic arthritis and/or osteomyelitis and is often related to septic emboli that seed the lungs causing a nodular pneumonia.[24,49]

As is typical for MSSA pneumonia, children with primary MRSA pneumonia tend to be younger with 45% being aged <1 year.[24] A relatively benign clinical presentation followed by rapid deterioration is notable. Severe cases of MRSA pneumonia in otherwise healthy children have been reported and similarly may be associated with the rapid development of hypotension and respiratory failure.[38]

Clinically, children present with an acute onset of fever often associated with tachypnea. Auscultory examination may reveal crackles in 50% of cases of pneumonia. Chest radiographs commonly reveal consolidations with or without pleural effusions. Spontaneous pneumothorax is common and presentation with pyopneumothorax is a hallmark of such infections.[30,50]

3.6 Musculoskeletal Infections (Osteomyelitis, Septic Arthritis, Pyomyositis)

S. aureus is the major cause of childhood musculoskeletal infections. While the pathogenesis is most commonly the result of hematogenous seeding of bones and/or joints, direct inoculation (following trauma) or postsurgical cases (especially in the setting of indwelling orthopedic hardware) have been reported.[51]

In the past 5 years, standard empiric therapy has changed for these infections because of the emergence of MRSA. In one institution, MRSA osteoarticular (osteomyelitis and septic arthritis) infections increased from 2.6 to 6 per 1000 admissions while MSSA infections remained unchanged. In this study, it was noted that subperiosteal abscesses occurred in 71% of the children with MRSA osteomyelitis versus only 38% of the children with MSSA osteomyelitis.[52] A recent study from Martinez-Aguilar et al.[28] observed more severe bone and joint infections in PVL-positive strains of *S. aureus*. In this study, 11 of the 13 isolates were MSSA. Osteomyelitis is the most common musculoskeletal infection observed; however, pyomyositis and/or septic arthritis may be present in a single patient. Martinez-Aguilar et al.[28] found osteomyelitis to comprise 84% of the musculoskeletal MRSA infections, while septic arthritis and pyomyositis occurred in 10% and 6%, respectively.

Most children with a musculoskeletal infection present with fever. In patients with osteomyelitis, a focal area of bone pain can be elicited by palpation.[53] In cases of septic arthritis, a joint may be swollen, warm, and painful. In septic arthritis of the hip, a decrease in range of motion is observed.[54] Most often, weight-bearing bones and joints are involved, which makes fever with an antalgic gait a prominent clinical presentation. Patients with pyomyositis, similar to osteomyelitis, present with pain and often have a focal area of tenderness and swelling.[23]

The most common site of infection is the lower extremity and pelvis.[55] Martinez-Aguilar et al.[28] noted that fever (5 days vs 1.5 days) and length of hospital stay (14.5 days vs 12.7 days) were longer in MRSA-associated musculoskeletal infections than in those produced by MSSA. Furthermore, Arnold et al.[52] observed that children with MRSA osteomyelitis were more likely to have subperiosteal abscesses and require surgical intervention than children with MSSA infections.

3.7 Endocarditis

Although the majority of cases of bacterial endocarditis primarily involve heart valves, septum and/or endocardium can also be the sites of infection. Although rare, endocarditis should be suspected in patients with bacteremia that is refractory to appropriate therapy. Intravascular devices have been associated in up to 50% of cases of *S. aureus* endocarditis.[56]

Clinically, the presentation may vary based on the extent of the infection. The most common clinical symptoms are fever, malaise, and weight loss. On physical examination, splenomegaly, petechiae, signs of embolic phenomenon, and a new heart murmur are often noted. In some cases, the presentation is one of septic shock with multiorgan system failure. Blood cultures may be positive for days consequent to tissue involvement and the difficulty with penetration of antibacterial (i.e. poor vascularity to infected structure/biomass) required for rapid eradication of infection. Other

abnormal laboratory findings that can aid in the diagnosis include an elevated erythrocyte sedimentation rate, presence of anemia, hematuria, and a positive rheumatoid factor.[57,58]

Since prompt diagnosis and initiation of treatment is essential for the successful outcome of endocarditis and in some cases the classic clinical manifestations (e.g. bacteremia, evidence of active valvulitis, peripheral emboli, and immunologic vascular phenomena) are absent, diagnostic strategies have been developed to aid the diagnosis. In 1994, Durack et al.[59] from Duke University, Durham, NC, USA established criteria for the diagnosis of endocarditis. These criteria combine the findings of persistent bacteremia, new regurgitant murmur and vascular complications with standardized echocardiographic findings.

3.8 Bacteremia

Bacteremia is virtually always associated with specific clinical disease, although the site of involvement may be occult. As mentioned previously, indwelling vascular devices can serve as a nidus for infection. Presentation with erythema, warmth, pain, and/or exudative discharge at the insertion site of the catheter can be seen. However, in most cases fever is the presenting symptom.[23]

3.9 Other Clinical Syndromes

CA-MRSA has been isolated in association with other infections, including otitis media and sinusitis.[60,61] Postviral bacterial tracheitis is commonly caused by *S. aureus*. Children with bacterial tracheitis generally present with a history of croup followed by high fever, toxicity and upper airway obstruction several days into the course of illness. Purulent secretions can obstruct the airway and intubation may be necessary, especially in younger children.[23,62,63]

Like MSSA, MRSA can cause renal and liver abscesses.[23] In addition, CNS system involvement can relate to complications of bacteremia, extension from sinus disease (usually frontal sinus), complication of an underlying disease (brain abscess in the setting of congenital heart disease), or infection of a ventriculo-peritoneal shunt.[64,65]

4. Treatment

Conceptually, the approach to treating MRSA infections is similar to that utilized for other infections. Empiric therapy is predicated upon the clinical syndrome with an educated guess as to the pathogen, and assumption of antimicrobial penetration to the presumed site(s) of infection. Definitive therapy assumes that the pathogen has been identified and susceptibility data are defined. The duration and route of antimicrobial administration is decided upon based on the clinical syndrome and the site(s) of infection. Additionally, the need for prophylactic therapy is contemplated based upon considerations that involve both microbial and host factors.

The treatment of MRSA infections has changed in the last decade as a result of the introduction of CA-MRSA. Isolation of the pathogen is imperative and knowledge of local epidemiology and susceptibility patterns is essential. Choice of antimicrobial agent, route of administration and duration of therapy should be individualized and relate to the host setting, clinical presentation, and condition of the patient.

The important characteristics of antimicrobials utilized in patients with suspected MRSA SSTIs are presented in table I. Microbiology refers to the ability of the antibacterial to treat common skin pathogens. Doxycycline, ciprofloxacin, and cotrimoxazole are able to treat MRSA but lack activity against group A streptococcus. Rifampicin must be used in combination with another antimicrobial agent or resistance may develop. The ability of the agent to penetrate abscesses, its bioavailability, and its tissue penetrance is represented by its pharmacokinetics. For example, the oral form of vancomycin has no bioavailability and therefore should not be used in the treatment of SSTIs. Finally, formulation refers to the availability of both oral and intravenous forms of the antibacterial agent.

The empiric antibacterial selections for treating suspected invasive MRSA infections are provided in figure 1. Further details regarding each clinical syndrome are discussed in sections 5.1 to 5.7.

4.1 SSTIs and Lymphadenitis

Simple skin abscess caused by CA-MRSA can often be treated with incision and drainage. The addition of a systemic agent may not be essential in such cases as studies have shown that patients whose abscesses were drained but received ineffective antimicrobials did as well as patients who received effective antibacterial therapy either initially or after culture results were known.

Table I. Characteristics of antibacterials to treat suspected methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections

Drug	Microbiology	Pharmacokinetics	Formulation
Clindamycin	++	+++	+++
Linezolid	+++	++	+++
Cotrimoxazole	+	++	+++
Doxycycline	+	++	+++
Ciprofloxacin	+	+++	+++
Vancomycin	+++	+	++
Daptomycin	+++	+++	+
Tigecycline	+++	++	+
Quinupristin/dalfopristin	+++	++	+
Rifampicin	++	+++	+++

+ indicates fair; **++** indicates good; **+++** indicates excellent.

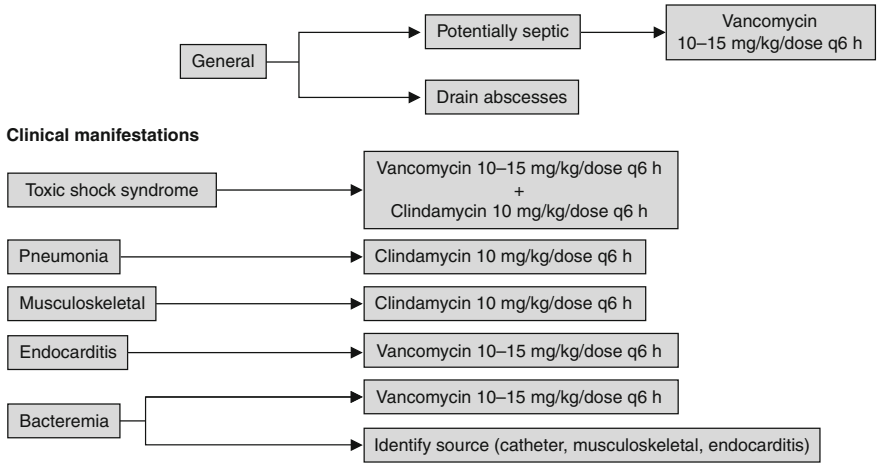

Fig. 1. Empiric treatment options for invasive methicillin-resistant *Staphylococcus aureus* infections. **q*x*h** = every *x* hour.

Importantly, no patients developed an invasive MRSA infection.[33]

Recurrent skin abscesses caused by MRSA are a common problem. MRSA can be difficult to eradicate as it can also be found contaminating the environment. Strategies have focused on eliminating colonization with MRSA in hopes of decreasing the risk for recurrence. Unfortunately, data are scarce on the best methods to achieve this. In the hospital setting, intranasal mupirocin was effective, but recolonization occurred frequently.[66] A recent study was performed in hospitalized adults colonized with MRSA. Among the patients who received 7 days of intranasal 2% mupirocin, 2% chlorhexidine washes, rifampicin, and doxycycline, 74% and 54% were culture negative at 3 and 8 months, respectively. This was significantly greater than for the patients who did not receive the decolonization regimen; 32% were culture negative at 3 months ($p = 0.0001$).[67] Some clinicians utilize bleach baths in place of chlorhexidine; however, data does not exist to support this practice.

In many instances, clindamycin is chosen for the empiric treatment of suspected MRSA lymphadenitis and most cases of SSTIs in children. Drainage is imperative if a large abscess exists. Treatment with cotrimoxazole should be avoided until culture and susceptibilities are obtained as it does not provide adequate coverage for *Streptococcus pyogenes*. The length of therapy is commonly 10 days or 5 days after the initial resolution of clinical signs and symptoms.[68] Longer courses of therapy may be necessary for more complicated infections.

Children who appear septic or clinically deteriorating should receive intravenous vancomycin. It is important to note that oral vancomycin should not be used as it is not systemically absorbed. To date, no pediatric reports exist of vancomycin-resistant *S. aureus* (VRSA). Nevertheless, VRSA was first observed in Japan in 1996 and in the US in 2002.[69,70] Cases of infection with vancomycin-intermediate *S. aureus* (VISA) [minimum inhibitory concentration, MIC, 4–8 μg/mL] in adults have been published;[71] none have been reported in pediatric patients. Some *S. aureus* strains have been reported to exhibit a heteroresistance (hVISA) to vancomycin. This term refers to a subpopulation of VISA organisms within a susceptible population (MIC ≤4 μg/mL). Generally, the overall MIC of these organisms is 1–4 μg/mL.[72,73] It is important for physicians to be aware of this potential change in susceptibilities as it could change future treatment strategies, including vancomycin dosing strategies when guided by target systemic exposure levels.

An oral or intravenous agent that can be utilized in SSTIs is linezolid, the first US FDA-approved oxazolidinone. Linezolid provides an oral option for MRSA SSTIs that are resistant to clindamycin and cotrimoxazole. In more severe skin infections, linezolid was as effective as intravenous vancomycin with clinical cure rates of 93.2% and 90%, respectively. Furthermore, fewer adverse events occurred in the linezolid group.[74] Linezolid has also been demonstrated to be more cost effective than vancomycin in the treatment of MRSA-complicated SSTIs.[75,76] To date, three pediatric cases of linezolid-resistant MRSA have been published. In all cases, the patients had an underlying condition and were receiving prolonged low-dosage (5–9 mg/kg/day) linezolid therapy at the time their isolates were identified.[77,78] Both *in vitro* and *in vivo* data have demonstrated that the susceptibility profile of linezolid-resistant MRSA can revert upon discontinuation of the drug.[78,79]

Other antibacterials that have been utilized for the treatment of SSTIs are the long-acting tetracyclines and ciprofloxacin. In an adult study, the long-acting tetracyclines doxycylcine and minocycline were successful in treating 100% of SSTIs.[80] Their use should be avoided in children aged <8 years because of the potential of discoloration of permanent teeth. Ciprofloxacin has also been shown to be successful in adults. When it was used in combination with rifampicin, MRSA recolonization occurred less

frequently.[81] Ciprofloxacin is not recommended as first-line therapy in children consequent to early findings of drug-associated arthropathy in preclinical studies performed in juvenile dogs.[82]

4.2 Sepsis and TSS

The initial treatment of sepsis and associated TSS is stabilization of the patient and institution of empiric antibacterial therapy containing vancomycin. In addition, identification and drainage (or removal) of any identifiable focus of infection is imperative. When TSS is evident, clindamycin should be added to vancomycin to halt the production of the bacterial toxin.[47] Adjunctive use of intravenous immunoglobulin should be considered,[47] as should gentamicin and/or rifampicin when a high inoculum of bacteria is suspected or if blood cultures remain persistently positive. Rifampicin should not be used alone as resistance develops rapidly in these situations.[83] Many clinicians elect to add this agent to vancomycin treatment in complicated invasive disease. In a study of patients with MRSA septicemia, the addition of rifampicin to vancomycin improved survival.[84] In a small case series of five neonates with MRSA bacteremia, the addition of rifampicin led to eradication of the organism within 1 day in four of the patients.[85]

Because of the severity of these clinical manifestations, clindamycin and cotrimoxazole should not be utilized as initial treatment. Once the patient has been stabilized, the source of the MRSA is determined, the MRSA is isolated and antibacterial susceptibilities are known, it is possible to utilize clindamycin for certain clinical conditions (osteomyelitis, pyomyositis, pneumonia). More data are needed to determine if the use of cotrimoxazole in invasive disease is appropriate. Finally, although linezolid is comparable to vancomycin for treatment of infections produced by MRSA,[86,87] it is not generally recommended for the treatment of life-threatening infections because of limited data documenting its efficacy in these conditions.

4.3 Pneumonia

Pneumonia is a common clinical manifestation caused by MRSA. Frequently, pleural effusions or empyemas are observed. In patients with empyema, video-assisted thorascopic surgery (VATS) has been shown to be superior to conventional thoracostomy drainage. Within the first 48 hours of admission VATS has been shown to decrease the length of hospitalizations by as many as 5 days and decrease the total duration of fever by 2 days.[88,89] Sonnappa et al.[90] demonstrated in a randomized prospective trial that chest tube drainage with the instillation of urokinase was as effective as VATS in regards to length of hospital stay, treatment cost, and treatment failure rate. In cases where embolic phenomena are suspected, identification of the primary site of infection is important.

Clindamycin has been utilized successfully in the treatment of MRSA pneumonia.[28] Its penetration into the pleura, pleural fluid and lung parenchyma is good and may exceed serum concentrations.[91] The bioavailability of oral clindamycin is approximately 90%, which enables intravenous to oral conversion of therapy without concern for reduced efficacy.[92]

Vancomycin should be utilized empirically in critically ill patients with pneumonia and in HA-pneumonias until culture and susceptibility data are available. In children, vancomycin has been used successfully to treat MRSA pneumonia.[86] A major concern regarding its use for pneumonia is its relative inability to concentrate well in lung tissue, as reflected by tissue concentrations ranging from 20% to 30% of corresponding serum concentrations.[93,94] Consequently, recommendations have been made that vancomycin trough plasma concentrations be maintained at 15–20 μg/mL to assure therapeutic concentrations within the lungs can be achieved.[93,94]

Linezolid has become an important therapeutic option in the treatment of MRSA pneumonia. Unlike vancomycin, an oral form exists with a bioavailability approaching 100%. In addition, linezolid distributes extensively into both extracellular and intracellular fluid, thereby producing tissue concentration profiles that are similar to those in plasma.[95] Children with CA-MRSA-complicated pneumonias or HA-MRSA ventilator-associated pneumonias have been successfully treated with linezolid.[96] In both children and adults, linezolid has been shown to be as effective as vancomycin in treating patients with nosocomial MRSA pneumonia.[86,97]

Most strains of MRSA are susceptible to cotrimoxazole. No data exist in children on the use of cotrimoxazole in treating invasive MRSA infections as well as pneumonia. Based on its pharmacokinetics, trimethoprim concentration within lung tissue is 3.5-fold greater than in blood, and the sulfamethoxazole component is approximately 30% of the corresponding serum concentration.[98] Although these concentrations may translate into effective therapy, more clinical data in pediatrics are needed before cotrimoxazole can be routinely used in treating MRSA pneumonia. Caution is warranted while escalating the cotrimoxazole dose in order to enhance intrapulmonary concentrations given the potential for sulfamethoxazole to produce serious hypersensitivity reactions (e.g. Stevens Johnson syndrome, toxic epidermal necrolysis).

Absence of objective evidence to support a specific duration of treatment for complicated pneumonia results in a length of therapy that is determined based on the clinical situation and extent of disease. Patients with pulmonary abscesses may require a longer length of therapy so as to ensure sufficient bacterial eradication from diseased tissue repositories of infection. Some experts recommend treatment approximately 1 week after the patient becomes afebrile, which in many instances equates to approximately 3 weeks of antibacterial therapy. The decision as to wheth-

er to maintain intravenous antibacterial therapy or switch to an oral agent is predicated upon having evidence of a clinical response to initial treatment, those pharmacokinetic properties of a drug that determine its pharmacodynamics (e.g. tissue distribution/penetration, bioavailability) and considerations pertaining to adherence with the prescribed treatment regimen.

4.4 Musculoskeletal Infections (Osteomyelitis, Septic Arthritis, Pyomyositis)

As the percentage of MRSA isolates has increased, so has the number of MRSA bone, muscle, and joint infections. Frequently, musculoskeletal infections caused by MRSA are associated with abscess formation. Surgical drainage of the abscess is imperative as reflected by use of this treatment modality in up to 91% of MRSA musculoskeletal infections.[28,52,55]

The emergence of MRSA has produced a shift in antibacterial selection for empiric treatment of musculoskeletal infections from an antistaphylococcal β-lactam to clindamycin. Since clindamycin achieves concentrations within the bone that are 60–80% of those in the blood and penetrates into abscesses where it maintains its antimicrobial activity, it has become the drug of choice. Clinically, most clindamycin-susceptible MRSA musculoskeletal infections are successfully treated with clindamycin.[28,52,55] In critically ill patients with musculoskeletal infections produced by MRSA, empiric therapy with vancomycin has produced success.[28,55] This is an outcome associated with the ability of the drug to attain therapeutic concentrations in bone.[99]

Although most isolates of MRSA are cotrimoxazole susceptible, its use in treating musculoskeletal infections in children is limited. Despite case series demonstrating the effectiveness of cotrimoxazole in treating 5 of 6 adults with osteomyelitis,[100] pediatric data sufficient to support its use for this indication currently do not exist. The same can be said for linezolid, which in adults has been successfully used in the treatment of MRSA-associated musculoskeletal infections[101] but data clearly demonstrating its efficacy are lacking in pediatric patients with this condition. Finally, it is important to note that in a rat model of MSSA osteomyelitis, animals treated with linezolid had outcomes that were not different from those in untreated controls.[102]

4.5 Endocarditis

Guidelines from the American Heart Association recommend vancomycin as the standard therapy for native valve MRSA endocarditis.[57] The pharmacokinetic and pharmacodynamic properties of vancomycin are not ideal for the treatment of endocarditis. Specifically, glycopeptide penetration into a fibrinous vegetation (a reservoir for persistent infection) has only been observed at the periphery of the lesion.[103] Vancomycin is less effective when the bacterial inoculum is high and therefore a slower clinical response has been observed in the setting of endocarditis.[104-106]

No clinical data are published on the use of clindamycin monotherapy in treating MRSA endocarditis. One adult case report described successful treatment of MRSA endocarditis with vancomycin plus clindamycin and surgical replacement of the infected valve.[107] Clindamycin has been successfully used to treat cases of *S. aureus* endocarditis. However, it is not a recommended therapeutic option because of a high relapse rate.[57,108]

Limited data exist on the use of cotrimoxazole in treating MRSA endocarditis. In an experimental rabbit model of endocarditis, treatment with cotrimoxazole did not sterilize any MRSA vegetation.[109] However, in a randomized, double-blind trial of cotrimoxazole versus vancomycin in intravenous drug users with *S. aureus* infections, no treatment failures were observed in patients with an MRSA infection.[110] More studies are needed to evaluate whether cotrimoxazole is a viable option in treating MRSA endocarditis in pediatrics.

The use of linezolid in the treatment of MRSA endocarditis has been infrequent. Experimental rabbit models of MRSA endocarditis have shown linezolid to be as effective as vancomycin.[111] However, studies using another MRSA endocarditis rabbit model observed that therapy with vancomycin alone was more effective than linezolid alone or linezolid plus vancomycin.[112] In children, linezolid has been shown to be equivalent to vancomycin in treating invasive infections produced by MRSA that did not include endocarditis.[86,113]

Evidence exists for the roles of aminoglycosides in treating MRSA-associated endocarditis in pediatric patients. Combination therapy of vancomycin plus gentamicin is an optional recommendation by the American Heart Association.[57] Gentamicin can be considered for the first 3–5 days of treatment for endocarditis produced by gentamicin-susceptible MRSA strains. Although clinical data are lacking in regard to the addition of gentamicin, a study performed using an *in vitro* endocarditis model observed an increase in vancomycin bactericidal activity and a faster rate of killing with the addition of gentamicin.[114] In contrast, in a more recent *in vitro* study, no benefit was seen when gentamicin was added to vancomycin.[115]

Finally, a putative role exists for rifampicin treatment of MRSA-associated endocarditis. Specifically, rifampicin is recommended in the treatment of endocarditis associated with prosthetic valves.[57]

4.6 Bacteremia and Catheter-Related Bloodstream Infection

In patients with MRSA bacteremi as a source (bone, joint, lungs, heart) of infection should be determined. Investigating for the potential source should be structured based on the clinical presentation of the patient. Cases of isolated bacteremia do occur

in patients with severe skin disease (e.g. eczema) and in the presence of a central venous catheter (CVC). In addition to appropriate doses of parenteral vancomycin, the removal of the CVC is essential. Appropriate intravenous antibacterials for 10–14 days is the ideal treatment strategy.[116] In situations where removal of the CVC is not possible because of vascular access issues, treatment should be provided for 14 days from the first negative culture through the infected CVC.[116]

4.7 New Agents

Overall, data are limited on the use of daptomycin, dalbavancin, tigecycline, ceftobiprole, and quinupristin/dalfopristin in children. Daptomycin (a lipopeptide), dalbavancin (a lipoglycopeptide), and tigecyline (a glycylcycline) have been successfully utilized in the treatment of MRSA SSTIs in adults.[117-119] Ceftobiprole, an extended spectrum cephalosporin, is currently in phase III trials of adults with complicated skin infections or nosocomial pneumonia.[120]

Among these newer agents, quinupristin/dalfopristin, an intravenous streptogramin antibacterial, has the most information available on its use in children, although it is not approved for children aged <16 years. In adults, quinupristin/dalfopristin has been successfully used in the treatment of SSTIs.[121] Loeffler et al.[122] reported on quinupristin/dalfopristin use in five children with an SSTI, four of whom were treated successfully. Additionally, treatment success was observed in cases of endocarditis, bone and joint infections, respiratory tract infections, and bacteremia.[122] Although it was unclear which cases were due to MRSA, approximately 50% of those where MRSA was isolated had a good clinical response to treatment. Also, it should be noted that in 47% of the cases, vancomycin and quinupristin/dalfopristin were used concomitantly.

A large clinical trial in adults with MRSA bacteremia with or without endocarditis observed daptomycin to be noninferior to vancomycin therapy in invasive infections.[123] However, in cases of MRSA pneumonia, daptomycin and quinupristin/dalfopristin have been clinically inferior to standard therapy.[124] Daptomycin is inhibited by surfactant, which mitigates against its use for pulmonary infection.[125] Also, recent pharmacokinetic data from a population of pediatric patients receiving a single dose of daptomycin suggest that consequent to higher plasma clearance of the drug in young children, age-adjusted dosing may be necessary.[126] Finally, clinical data are currently lacking for the use of tigecycline in the treatment of MRSA pneumonia.

5. Conclusions

MRSA is an emerging pathogen in infants, children and adolescents. Although skin and soft tissue infections are the most common clinical manifestation, MRSA can cause invasive disease such as lymphadenitis, osteomyelitis, pneumonia, endocarditis, and sepsis. The treatment of skin and soft tissue infection can often be successful with drainage of the abscesses without antimicrobial therapy. Clindamycin can be utilized in more invasive infections such as lymphadenitis, pneumonia, and osteomyelitis. Children experiencing sepsis or endocarditis should initially be treated with vancomycin as no reports exist in pediatric patients of vancomycin-resistant *S. aureus*. Although the general principles for selection of antimicrobial treatment in adults do generally apply to pediatric patients, developmental differences in drug disposition[127] and accumulated clinical experience – often limited to case series as opposed to definitive treatment trials – drive the selection of drug and dose. The overall goal of safe and effective therapy of MRSA infections in pediatric patients requires that the clinician consider all of the pertinent treatment variables unique to this age group if rapid eradication of the pathogen and good clinical outcomes are to be attained.

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