

Implications of Methicillin-Resistant *Staphylococcus aureus* as a Community-Acquired Pathogen in Pediatric Patients

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is now an established community pathogen in many areas of the United States and the world [1–5]. Community-acquired MRSA (CA-MRSA) infections have changed several aspects of staphylococcal infections in children, including the epidemiology, clinical manifestations, laboratory diagnosis, treatment, and prevention.

Epidemiology

The incidence of *S aureus* infections in children is unknown because this determination depends on specific culture data, and until more recently, most skin and soft tissue infections were treated empirically without cultures being obtained. Nevertheless, in a Centers for Disease Control and Prevention study examining CA-MRSA infections in 2001–2002, the incidence for white children and black children younger than 2 years old was approximately 16/100,000 and 70/100,000 in Atlanta and 18/100,000 and 40/100,000 in Baltimore [6]. The incidence for white children and black children 2 to 18 years old was approximately 9/100,000 and 24/100,000 in Atlanta and 12/100,000 and 15/100,000 in Baltimore. Other investigators also have noted the differences in frequency of CA-MRSA infections among

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different racial groups. In other regions, CA-MRSA infections are particularly common among Native Americans [2].

In several areas, the number of CA-MRSA infections is increasing in children, although how much is a real increase compared with physicians being more aggressive about obtaining cultures is unclear. At Texas Children's Hospital, the percentage of community-acquired *S aureus* isolates that are MRSA and the overall number of community-acquired *S aureus* isolates have increased significantly in the 3 years from August 1, 2001, to July 31, 2004 [7]. The percentage of community-acquired *S aureus* isolates resistant to methicillin increased from 72% to 76%, and the total number of isolates virtually doubled over 3 years (771 to 1562). Determining what factors are related to this increase in *S aureus* infections is under investigation, but may relate in part to specific virulence characteristics of the more common CA-MRSA clones in circulation. The clone designated USA300 by the Centers for Disease Control and Prevention is particularly capable of spreading rapidly when in the community [8].

CA-MRSA infections also seem to be more common among family members than has been seen in the past with community-acquired methicillin-susceptible *S aureus* (CA-MSSA) isolates. Spread among daycare attendees and athletes has been documented [9,10]. *S aureus* isolates with the characteristics associated with CA-MRSA isolates (SCC*mec* IV, presence of *pvl* genes, limited antimicrobial resistance) have been isolated from patients with nosocomial infections, including neonates in the neonatal intensive care unit [11,12].

Clinical manifestations

Skin and soft tissue infections constitute greater than 90% of the infections caused by CA-MRSA in children [1,2,6,7]. Cellulitis, abscesses, and folliculitis are the predominant skin infections. Head and neck CA-MRSA infections, such as cervical lymphadenitis, otitis externa, otitis media with otorrhea, and acute mastoiditis, also are being encountered with increasing frequency [13]. Recurrent skin infections are seen frequently in children with CA-MRSA infections. Most CA-MRSA isolates carry the genes encoding the cytotoxin Pantone-Valentine leukocidin (PVL), which has been implicated as a factor in the possible enhanced ability of CA-MRSA isolates to cause skin infections [13–15]. PVL also may contribute to the ability of CA-MRSA isolates to cause more complicated infections at other sites.

Among the invasive infections caused by CA-MRSA isolates, musculoskeletal infections are the most common. At Texas Children's Hospital, acute hematogenous osteomyelitis now is caused most commonly by CA-MRSA isolates. Over the 3-year study previously mentioned, there were 54 and 28 children with CA-MRSA and CA-MSSA osteomyelitis [7]. The clinical manifestations of osteomyelitis caused by CA-MRSA versus

CA-MSSA isolates are different in that multiple sites of infection are more common in patients with CA-MRSA infection at Texas Children's Hospital. In the author's series, children with CA-MRSA osteomyelitis had a longer duration of fever and hospital stay than children with osteomyelitis caused by CA-MSSA isolates [16].

The presence of the *pvl* genes in community-acquired *S aureus* isolates was associated with laboratory and clinical differences among the author's patients with acute osteomyelitis. Children with *pvl*-positive isolates had greater measures of inflammation at admission and during hospitalization (white blood cell count, erythrocyte sedimentation rate, C-reactive protein), greater frequency of positive blood cultures, and greater frequency of subperiosteal or intraosseous abscesses than children whose isolates did not carry the *pvl* genes [17]. More complications of osteomyelitis, such as the development of chronic osteomyelitis or an associated deep venous thrombosis, were seen in the children with *pvl*-positive isolates [16]. Venous thrombophlebitis leading to septic pulmonary emboli and other sites of dissemination occurs more commonly with the CA-MRSA USA300 clone for reasons that are not yet determined. In these circumstances, anti-coagulation may be warranted.

CA-MRSA isolates are isolated less commonly from children with septic arthritis than from children with acute osteomyelitis. Over the aforementioned 3-year study, CA-MRSA and CA-MSSA isolates were recovered from 9 and 10 children with septic arthritis. The clinical manifestations were no different for these two groups [7].

Myositis and pyomyositis are being recognized with increasing frequency in children with CA-MRSA infections, and as with osteomyelitis, multiple sites of muscle involvement are not unusual [17]. A concomitant osteomyelitis also is common [16]. In studies at Texas Children's Hospital, myositis or pyomyositis was seen in association with osteomyelitis in 28 of 45 children with *pvl*-positive isolates compared with 6 of 19 children with *pvl*-negative isolates ($P = .05$) [17]. These children typically complain of pain in the region with tenderness to palpation of the involved muscles. In large muscles of the extremities, swelling and warmth may be appreciated. Of imaging techniques, MRI generally shows the muscle involvement most readily (Fig. 1), and its increased use may explain in part the increasing recognition of this infection [18]. Because multiple sites of myositis/pyomyositis or osteomyelitis can occur, physicians must examine the patient carefully daily to detect areas of infection that may not have been appreciated even the previous day. Repeat imaging, weekly in some cases, may be necessary to show these areas of inflammation and abscess formation as they develop.

Necrotizing fasciitis caused by CA-MRSA has been described in adults, many of whom have chronic underlying illnesses [19]. It is likely that this manifestation of CA-MRSA infection also will be described in children.

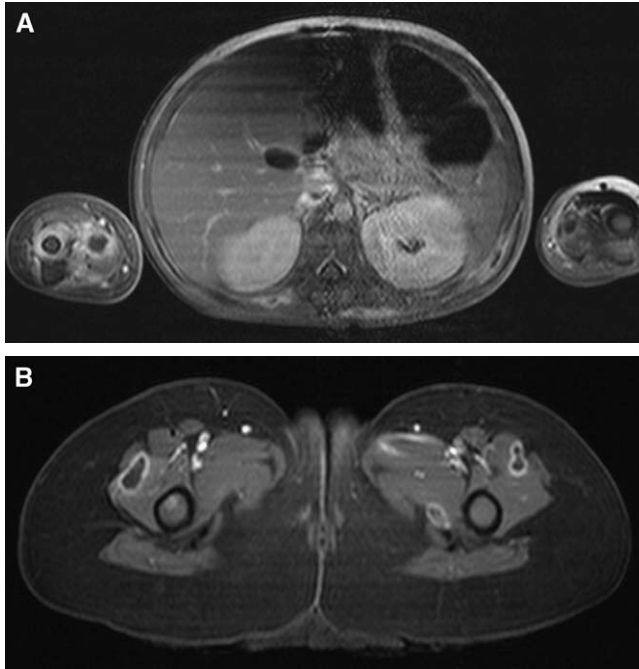


Fig. 1. (A and B) MRI of a child with multiple sites of pyomyositis caused by CA-MRSA.

Complicated pneumonias with empyema also have been encountered more frequently in children since CA-MRSA isolates have become so common. At Texas Children's Hospital, CA-MRSA is now the most common cause of pleural empyema in children [20]. Clinical findings for pneumonia with empyema are similar for CA-MRSA infections compared with other organisms, such as *Streptococcus pneumoniae*. The length of stay for children with CA-MRSA empyema was longer (mean 18.8 days), however, than seen in children with CA-MSSA empyema (mean 14 days). Children with primary CA-MRSA pneumonia are younger than children with CA-MRSA pulmonary manifestations associated with infections at other sites, typically bones or joints. Among children with invasive infections, community-acquired *S aureus* isolates carrying the genes encoding PVL are more likely to be associated with abnormal chest imaging than isolates negative for the *pvl* genes [21]. CA-MRSA isolates have been associated with a necrotizing pneumonia, especially in children coinfecting with a respiratory virus [22]. The mortality rates for necrotizing pneumonia are quite high.

As CA-MRSA infections continue to increase, the number of children with severe invasive CA-MRSA infections also has increased in many areas [23,24]. At Texas Children's Hospital, from September 2002 through January 2004, about 10% (16 of 150) of the children with invasive

community-acquired *S aureus* infections were admitted to the intensive care unit [25]. Fourteen of the 16 patients were older than age 10 years, with an average age of 12.9 years and mean weight of 63 kg. Focusing on the 14 older children, most had skeletal infections, bacteremia, and pulmonary involvement; 11 required mechanical ventilation. Four had vascular thromboses. The mean duration of bacteremia was 4 days (range 1–11 days), and the mean duration of fever was 13 days. Three of these 14 patients died. One of the two younger patients also died.

Despite the impressive increase in CA-MRSA infections overall and the invasive infections in particular, the author has not noted a remarkable increase in the number of children with infective endocarditis owing to this organism. Transthoracic echocardiograms are performed in virtually all patients with persistent bacteremia (>4 days), and in only a few children have vegetations been identified [25].

CA-MRSA isolates have been associated with a purpura fulminans presentation in adults and children similar to severe meningococcemia [26]. Rapid onset of purpura with the need for amputation of extremities with high mortality can occur [27]. The relationship of this clinical presentation to specific superantigens, such as TSST-1, SEB, or SEC, or the CA-MRSA clone (USA400 versus USA300) is unclear. Large spinal epidural abscesses spanning from the cervical to the lumbar regions caused by CA-MRSA isolates have been noted in several children at Texas Children's Hospital.

Laboratory studies

Microbiology laboratories have to be capable of rapidly identifying and providing antimicrobial susceptibility data for antibiotics appropriate for pediatric use. Using newer molecular techniques, the presence of the *mecA* gene now can be detected rapidly in isolates and possibly in patient specimens directly in the future [28]. Up-to-date information regarding the current antimicrobial susceptibility patterns of community-acquired *S aureus* isolates in a community is crucial to being able to treat patients with suspected staphylococcal infections most optimally. It is quite difficult, however, for laboratories to separate out community-acquired from health care-associated *S aureus* infections. Physicians are encouraged to obtain purulent specimens for culture for the benefit of the patient and for determining the proportion of MRSA among community-acquired *S aureus* isolates or at least to know the proportion in a specific office or clinic.

Vancomycin, trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, doxycycline, and linezolid should be included in the routine panel of agents tested. Detecting inducible macrolide-lincosamide-streptogramin B is recommended when clindamycin is an important option for treatment because treatment failures with clindamycin have been documented in patients treated for an invasive infection caused by *S aureus* isolates with inducible macrolide-lincosamide-streptogramin B resistance [29].

Clindamycin resistance among CA-MRSA isolates varies from 4% to 6% to 20% or greater in some regions.

Treatment

Skin and soft tissue infections

When CA-MRSA is an initial consideration as the cause of an infection or is isolated, β -lactam antibiotics, such as dicloxacillin or cephalexin for outpatients or nafcillin, oxacillin, or cefazolin for inpatients, are no longer appropriate for empirical treatment or for completing treatment. The optimal management of skin and soft tissue infections is unclear. Although incision and drainage of abscesses alone without antimicrobial therapy may be effective in many patients, particularly for abscesses less than 5 cm in diameter, antimicrobial therapy usually is still provided [30].

Empirical antistaphylococcal β -lactam antibiotic treatment for skin and soft tissue infections is not recommended in areas where CA-MRSA isolates are known to account for 10% to 15% or more of community isolates. In this setting, TMP-SMX or clindamycin can be employed [31]. Whether adding rifampin to TMP-SMX is beneficial is unknown. Clinical studies of TMP-SMX treatment of CA-MRSA infections are limited, although early clinical studies showed that TMP-SMX was effective in treating MSSA infections [32–34]. TMP-SMX is not active against group A streptococcus, another common cause of skin and soft tissue infections. TMP-SMX may result in hypersensitivity reactions or bone marrow suppression. There are no data on TMP-SMX treatment of invasive CA-MRSA infections in children. Doxycycline or minocycline has been efficacious in treating adults with skin and soft tissue infections secondary to MRSA and is a consideration for children older than age 8 years [35].

Invasive infections

Vancomycin is recommended for inclusion in initial empirical antibiotic regimens for seriously ill patients with infections that may be due to CA-MRSA. Gentamicin with or without rifampin frequently is added to vancomycin for suspected life-threatening MRSA infections. Nafcillin/oxacillin is more rapidly bactericidal than vancomycin for MSSA isolates, and clinical data in adults suggest that nafcillin/oxacillin is superior to vancomycin for the treatment of bacteremic pneumonia secondary to MSSA [36]. Nafcillin/oxacillin also is recommended in addition to vancomycin in the initial empirical regimen to cover for MSSA isolates optimally.

CA-MRSA isolates generally are susceptible to clindamycin and TMP-SMX, but regional differences occur. Clindamycin is efficacious in treating serious infections caused by clindamycin-susceptible CA-MRSA isolates, including osteomyelitis, septic arthritis, and pleural empyema [16,20,31,37,38]. Clindamycin is administered intravenously at a dose of 30 to

40 mg/kg/day in three divided doses. Clindamycin is well absorbed by the oral route, so treatment can be completed with oral clindamycin at the same dose. The most concerning adverse effect of clindamycin is *Clostridium difficile* enteritis, which is a relatively rare complication. Perhaps the most common effect is loose stools or diarrhea. Clindamycin also may be associated with a rash; the oral suspension of clindamycin is not very palatable.

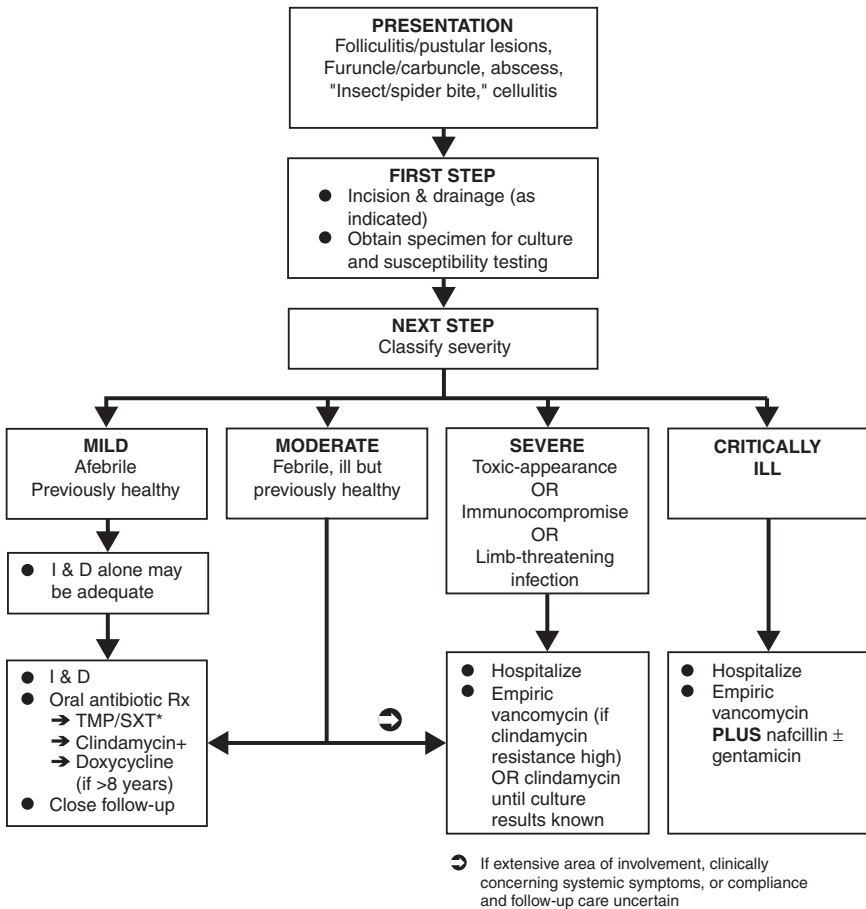
In some regions of the United States, a high proportion of CA-MRSA strains are clindamycin resistant. If the proportion of CA-MRSA isolates resistant to clindamycin exceeds 10% to 15%, clindamycin should not be used for empirical treatment of suspected staphylococcal infections.

Linezolid is an oxazolidinone antibiotic that is equivalent to vancomycin for the treatment of serious MRSA infections, including bacteremia and pneumonia in children [39]. Linezolid has not been studied in the treatment of osteomyelitis, but case reports or series and a compassionate use summary suggest linezolid is effective in treating osteomyelitis caused by MRSA [40,41]. The main side effect of linezolid is diarrhea; thrombocytopenia, optic neuritis, and neuropathy may occur with prolonged administration. Linezolid is well absorbed after oral administration, and therapy can be completed with an oral formulation at the same dose as given intravenously. Daptomycin is approved for the treatment of serious staphylococcal infections in adults, but may not be efficacious in treating pulmonary infection [42]. The dosage and safety profile of daptomycin are unknown in children. The American Academy of Pediatrics has outlined an approach to managing suspected CA-MRSA skin and soft tissue infections and more invasive infections (Fig. 2) [43].

Aggressive drainage of abscesses or other purulent collections is crucial to the successful management of these patients. Surgical incision and drainage of large abscesses in soft tissue or intraosseous/subperiosteal collections is ideal. Drainage by an interventional radiologist may suffice or may be the only way to approach safely some abscesses in deep locations, especially in critically ill children. In these situations, infectious disease and critical care medicine physicians have to remain in close communication with general surgery or orthopedic surgery colleagues to facilitate the optimal timing for these drainage procedures. MRI is invaluable for locating and showing these collections so that the surgeons can plan the approach to drainage most optimally. The value of adjunctive therapies, such as intravenous immunoglobulin preparations enriched for antibodies against specific toxins or surface proteins of *S aureus*, is under investigation [44].

Prevention

Prompt attention to cuts, abrasions, or other injuries to the skin, such as keeping the area clean and dry and applying a topical antibiotic at the first sign of inflammation, may help prevent superficial infections. Recurrent



* TMP/SXT = trimethoprim/sulfamethoxazole

+ Assume ≥90% prevalence of "D" test negative, erythromycin-resistant CA-MRSA strains

Fig. 2. Algorithm for managing children with suspected CA-MRSA infections suggested by the American Academy of Pediatrics. Initial outpatient management of suspected CA-MRSA skin and soft tissue infections is schematically illustrated and assumes CA-MRSA strains are prevalent in a community. (Data from Baker CJ, Frenck RW Jr. Change in management of skin/soft tissue infections needed. AAP News 2004;25:10.)

CA-MRSA infections in a child and CA-MRSA infections among multiple family members are quite common. Keeping fingernails clean and cut short and changing towels, washcloths, underwear, and sleepwear daily are reasonable measures to recommend. Applying mupirocin to the anterior nares may be useful to diminish nasal colonization by CA-MRSA, although a Cochrane review did not find topical antibiotics to be useful for eradicating nasal MRSA [45]. Resistance to mupirocin is increasing worldwide [46]. Finally, taking a bath twice a week for 15 minutes in water to which regular-strength Clorox bleach (1 teaspoon per 1 gallon of water)

has been added seems to be helpful in preventing recurrent infections in the author's experience.

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