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Why has MRSA Become Such a Successful Pathogen? A Pediatric Perspective

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Target Audience

Infectious disease physicians, hospital epidemiologists, clinical microbiologists, pharmacists, public health authorities, practicing physicians, and other healthcare professionals interested in the treatment of serious infections due to MRSA.

Learning Objectives

Describe the epidemiology, pathogenesis, and clinical characteristics of MRSA infections in the pediatric population

Participation in the Learning Process

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Introduction

Methicillin resistant *Staphylococcus aureus* (MRSA) infection traditionally has been associated with health-care settings, colonizing patients with underlying health conditions until its emergence in the community among healthy adults and children in the late 1990s. Since then, physicians and the public have become increasingly aware of issues related to MRSA infections in the pediatric population. Community-acquired MRSA (CA-MRSA) has become a successful pathogen. The emergence of new clones of CA-MRSA – USA-300, and to a lesser extent, USA-400 – is evident in adults and children. USA-300 is the predominant CA-MRSA clone. These MRSA clones are now appearing in new hosts – previously healthy children. The emergence of clinical syndromes with MRSA infections (e.g., skin and soft tissue infections and hematogenous osteomyelitis with multiple bone involvement) requires a more vigilant approach to diagnosis and treatment, including routine cultures, emergent surgical drainage, and new empirical antimicrobial therapies.

Risk Factors

The majority of children do not have risk factors for acquiring CA-MRSA. The most common risk factors are listed in Table 1. Children with chronic skin conditions, particularly eczema, are most vulnerable. Children of Native American, Pacific Islander, or African-American heritage are more likely to have CA-MRSA infections. Children in day care centers and their childcare providers are also at higher risk for CA-MRSA infections. Also,

children with obesity are at increased risk for CA-MRSA skin and soft tissue infections.

Children participating in contact sports such as wrestling and football are at risk for acquiring CA-MRSA because abrasion of the skin or penetration of the skin barrier is usually the access point for CA-MRSA. A history of previous infections in family members is a risk factor that is often overlooked by pediatricians. The majority (80-85%) of CA-MRSA infections originate in skin and soft tissue. In the current CA-MRSA landscape, patients may have had multiple episodes of skin and soft tissue infections.

Table 1.

CA MRSA Infections: Risk Factors

- None
- Chronic skin conditions (e.g., eczema)
- Native Americans, Pacific Islanders, African-Americans
- Obesity
- Daycare attendees
- Sports teams (contact such as wrestling, football, etc.)
- History of infections in family members

Reports of CA-MRSA Outbreaks in the Pediatric (and Related) Population

In 2003, Saiman and colleagues reported on an outbreak of CA-MRSA infections that occurred in eight postpartum women in a New York hospital.¹ Mastitis occurred in four patients; three cases progressed to breast abscess. Other infections attributed to CA-MRSA included: a postoperative C-section wound infection (one patient), cellulitis (one patient), pustulosis (one patient), and a urinary tract infection (one patient). The median onset occurred at 23 days post-delivery (range 4-73 days). Five patients were re-admitted for infection. Surveillance cultures of hospital employees and newborns were negative and the route of transmission was never discovered. The CA-MRSA strain was identified as a USA-300 clone that contained the staphylococcal chromosomal cassette *mec* (SCC*mec*) type IV gene and expressed the Panton-Valentine Leukocidin (PVL) and staphylococcal enterotoxins C and H.

The first report of CA-MRSA in a neonatal intensive care unit came from Texas Children's Hospital NICU in 2003 in infants who had not been outside the hospital.² Five infants had a median birth weight below 1500 g. The median age of onset was 24 days (range: 11-394 days). Of eight infants with MRSA bacteremia, six infants carried the SCC*mec* gene characteristic of CA-MRSA (all USA-300 clone). Other manifestations included pneumonia, soft tissue infection, and endocarditis with vegetations. Three infants died and three required prolonged antimicrobial therapy. There was no evidence of an outbreak or a point source as the deaths were spread out by date, caregivers, and nursery. Transmission likely occurred through horizontal contact with an adult or through vertical transmission from the mother at the time of delivery.

An outbreak of CA-MRSA was reported in 22 full-term and otherwise healthy infants in a Chicago hospital and in a Los Angeles hospital in 2004.³ The median age of the infants was seven days (range four to 23 days). Ninety one percent (n=20) of infants were male. A higher incidence of MRSA infections in males has also been noted in older children, though the reason for the gender differences in MRSA infections is unknown. The majority of infants were delivered by cesarean section, suggesting the possibility of vertical transmission. The mean age of onset of infection after discharge was 21 days (range one to eighteen days) for 95% of the infants. All infants had superficial skin lesions and 43% of infants were admitted, presumably because of physicians' concern of immunologic immaturity. Eight infants (73%) received intravenous therapy, thirteen (59%) received topical treatment, and three (14%) received oral treatment. No community sources were identified. All isolates were identified as the USA-300 clone.

In a retrospective study conducted at Texas Children's Hospital between August 2001 and March 2005, 61 previously healthy neonates aged ≤ 30 days acquired CA-MRSA after nursery discharge.⁴ Infants had no hospitalizations other than at birth and no surgery other than circumcision. The peak age of onset of infection was seven to twelve days. One infant died. The number of CA-MRSA infections increased each year. Maternal skin infection history was present in 20% of infants. The predominant community clone was USA-300 with the PVL toxin gene.

In a follow-up study between August 2001 and July 2006 at Texas Children's Hospital, 126 CA- *S. aureus* infections of previously healthy neonates aged ≤ 30 days (greater than 36 weeks gestation at birth) were evaluated.⁵ Eighty-four isolates (67%) were MRSA isolates. The peak age of onset of infection was 11 to 17 days. *Staphylococcus aureus* infections included pustulosis (n=43), cellulitis/abscess (n=68), and invasive (n=15). One patient died with systemic *S. aureus* and herpes simplex virus infection. The predominant clone was USA-300. Diagnostic procedures and treatment strategies varied; therefore, optimal management strategies were not identified by the authors.

Children with serious CA-MRSA septic infections and complications may need to be admitted to the pediatric intensive care unit (Table 2).⁶ These complications can include: multiple large abscesses requiring surgery; extensive cellulitis involving multiple areas; suspected septic arthritis, pyomyositis, and/or multifocal osteomyelitis; necrotizing pneumonia; and septicemic syndromes such as deep venous thrombosis (DVT), septic pulmonary emboli and purpura fulminans.

Table 2.

CA MRSA Infections in the Pediatric ICU: Sepsis plus

- Multiple abscesses requiring surgery
- Cellulitis (extensive; multiple areas)
- Suspected septic arthritis, pyomyositis, or osteomyelitis (multi-focal)
- Necrotizing pneumonia
- Septicemia (purpura fulminans, DVT, septic pulmonary emboli)

In a prospective surveillance study of 3,578 *S. aureus* isolates at Texas Children's Hospital between August 2001 and July 2004, the percentage of CA-MRSA isolates increased from 71.5% in year one to 76.4% in year three. Sixty-two percent of children with MRSA isolates were admitted to the hospital. Among CA-MRSA isolates, 4.4% were obtained from children with invasive infections. The most common invasive infections caused by CA-MRSA isolates were musculoskeletal and pulmonary infections. Clinical syndromes of CA-MRSA infections included osteomyelitis (54 cases), pulmonary involvement (either necrotizing pneumonia or septic pulmonary emboli) (23 cases), and septic arthritis (nine cases).

Diagnosis, Treatment, and Follow-Up

An important message to pediatricians is that diagnosis requires culture and susceptibility testing. First, patients with soft tissue infection, bone, or joint foci optimally should have more than one blood culture *before* therapy. Pediatricians should not depend on a single (and sometimes poor quality) blood culture to determine whether or not a patient has bacteremia. Second, physicians need to identify the foci of infection, usually by MRI, to assess the need for drainage by a surgeon or by interventional radiology. Third, if there are septic pulmonary emboli, Doppler and cardiac ECHO should be used to identify deep vein thrombosis and, if detected, anticoagulation should be considered. Finally, daily reassessment by blood culture and careful physical examination is essential to detect new foci of infection.

Empirical antibiotic therapy of hospitalized pediatric patients begins with vancomycin (a loading dose of 20 mg/kg followed by 15 mg/kg/dose every eight hours), plus nafcillin or oxacillin, because of the difficulty in differentiating methicillin susceptible *S. aureus* (MSSA) from MRSA clinically and the superiority of a semisynthetic penicillin if MSSA is the pathogen (Table 3). Gentamicin is often added for synergy but

clinical data documenting enhanced efficacy is absent. Fluoroquinolones, trimethoprim/sulfamethoxazole (TMP/SXT), or linezolid should not be used for invasive disease in children because of the lack of efficacy and safety data (drug metabolism pharmacokinetic (PK) studies) in children. Similarly, the lack of efficacy and safety in children for the new antimicrobial agents, such as daptomycin or tigecycline, precludes their use in the pediatric population.

Table 3.

Empirical Antimicrobial Therapy in Hospitalized Pediatric Patients

- Vancomycin (15 mg/kg/dose q8h) plus nafcillin or oxacillin ± gentamicin
- For invasive disease, do not routinely use TMP/SXT, fluoroquinolones or linezolid
- New agents? Little data for PK safety; none for efficacy

Summary

CA-MRSA has become a successful pathogen in the pediatric population. The increasing incidence of CA-MRSA over recent years suggests that pediatricians take a more vigilant approach to diagnosis and treatment of CA-MRSA to prevent serious complications and recurrence of infections. This approach may include routine cultures, emergent surgical drainage, new empirical antimicrobial therapies, and careful follow-up physical examination.⁷



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References

1. Saiman L, O'Keefe M, Graham PL III, et al. Hospital transmission of community-acquired methicillin-resistant *Staphylococcus aureus* among postpartum women. *Clin Infect Dis*. 2003;37(10):1313-1319.
2. Healy CM, Hulten KG, Palazzi DL, Campbell JR, Baker CJ. Emergence of new strains of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Clin Infect Dis*. 2004;39(10):1460-1466.
3. Center for Disease Control and Prevention (CDC). Community-associated methicillin resistant *Staphylococcus aureus* infection among healthy newborns—Chicago and Los Angeles County, 2004. *MMWR Morb Mortal Wkly Rep*. 2006;55(12):329-332.
4. Fortunov RM, Hulten KG, Hammerman WA, Mason EO Jr., Kaplan SL. Community-acquired *Staphylococcus aureus* infections in term and near-term previously healthy neonates. *Pediatrics*. 2006;118(3):874-881.
5. Fortunov RM, Hulten KG, Hammerman WA, Mason EO Jr., Kaplan SL. Evaluation and treatment of community-acquired *Staphylococcus aureus* infections in term and late-preterm previously healthy neonates. *Pediatrics*. 2007;120(5):937-945.
6. Kaplan SL, Hulten KG, Gonzalez BE, et al. Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. *Clin Infect Dis*. 2005;40(12):1785-1791.
7. American Academy of Pediatrics. Staphylococcal Infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: pages 601-615.

A minimum assessment score of 80% is required.

1. Which of the following is not a risk factor for acquiring a CA-MRSA infection in children?

- A. Native American, Pacific Islander, African American heritage
- B. Asthma
- C. Chronic skin conditions
- D. Participants of sports teams
- E. History of infections in family members

2. Complications of CA-MRSA infections in children can include which of the following?

- A. Septic arthritis
- B. Necrotizing pneumonia
- C. Septic pulmonary emboli
- D. All of the above
- E. None of the above

3. Considerations for evaluation of CA-MRSA infection include:

- A. Blood cultures to determine bacteremia
- B. Identify foci of infection to determine need for drainage
- C. Doppler studies and cardiac echocardiogram
- D. B and C only
- E. All of the above

4. Empirical antibiotic therapy for treating serious CA-MRSA in children should include:

- A. Fluoroquinolones
- B. Trimethoprim/sulfamethoxazole
- C. Linezolid
- D. Vancomycin
- E. None of the above

5. The predominant community CA-MRSA strain responsible for outbreaks reported in recent years has been identified by Pulsed-Field Gel Electrophoresis (PFGE) as:

- A. USA-100
- B. USA-200
- C. USA-300
- D. USA-400
- E. None of the above

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