Rate of Invasive CA-MRSA Increasing in Children

BY MIRIAM E. TUCKER

BETHESDA, MD. — Invasive infections in children caused by community-acquired methicillin-resistant *Staphylococcus aureus* are on the rise.

Though still far less common than simple skin and soft tissue CA-MRSA infections, increasing reports of serious infections such as osteomyelitis, bacteremia, and pneumonia have been raising concern in recent years. The increase appears to be related at least in part to the emergence of the "USA300" *S. aureus* clone containing the Panton-Valentine leukocidin (PVL) genes, Dr. Sheldon L. Kaplan said at the annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

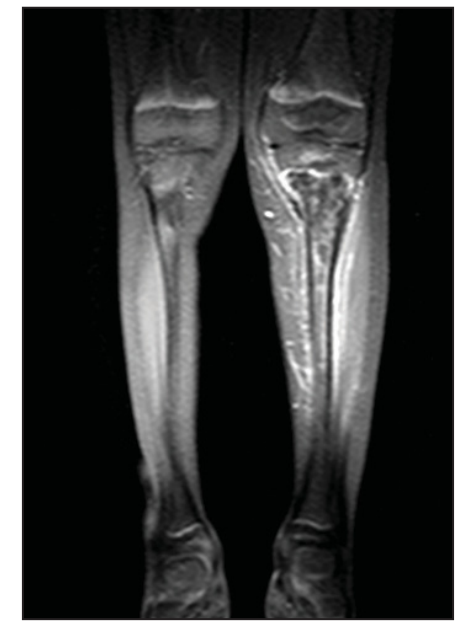
Rates of severe infection have been rising as MRSA has become more common in the community. Recommendations from the American Academy of Pediatrics state that in areas where MRSA accounts for 10% or more of CA-MRSA isolates, initial empiric therapy of severe infections that could be due to *S. aureus* should include vancomycin. Naficillin should also be included because it's superior to vancomycin for treating methicillin-sensitive *S. aureus* (MSSA).

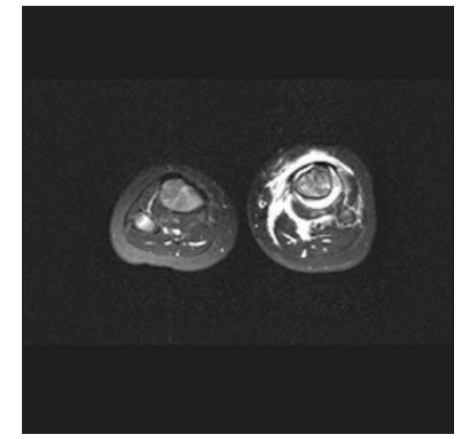
Use of clindamycin should be based on local susceptibility. "You need to know the clindamycin susceptibility of CA-MRSA isolates in your area," said Dr. Kaplan, head of the pediatric infectious disease section at Baylor College of Medicine and chief of the infectious disease service at Texas Children's Hospital, both in Houston.

At Le Bonheur Children's Medical Center in Memphis, the rate of acute osteoarticular infections increased from 2.6 to 6.0 per 1,000 admissions between 2000 and 2004. The proportion of those infections caused by MSSA remained constant at 10%-13%, but those caused by MRSA rose from 4% to 40%. Moreover, 71% of the patients with MRSA had subperiosteal abscesses, compared with 38% of those with MSSA, and surgical procedures were required in 91% with MRSA versus 62% with MSSA (J. Pediatr. Orthop. 2006; 26:701-2). Similar findings have been reported elsewhere, Dr. Kaplan noted.

Recent studies have shown that osteomyelitis caused by PVL-positive *S. aureus* strains was associated with more severe local disease and a greater systemic inflammatory response, compared with osteomyelitis caused by *S. aureus* not containing that gene (Pediatrics 2006;117:433-40), and that PVL-positive isolates were associated with an increased likelihood of complications in children with osteomyelitis (Pediatr. Infect. Dis. J. 2005;24:284-5).

Continued on following page





IMAGES COURTESY SHELDON L. KAPLAN

Severe CA-MRSA infections such as osteomyelitis (above, with subperiosteal abscess and soft tissue inflammation) have a high risk of complications.

Continued from previous page

MRI appears to be the optimal method for detection of osteomyelitis resulting from community-acquired *S. aureus*.

In a retrospective study by Dr. Kaplan and his associates of 199 such children seen between August 2001 and December 2006, MRI had a sensitivity of 98% for diagnosing the infection, compared with a 53% sensitivity with bone scintigraphy. Of 36 patients who had both imaging studies done, results were discordant in 17 cases. In all of those, the MRI diagnosis proved to be the correct one (Pediatr. Radiol. 2008;38:841-7).

The study also showed that MRI—but not bone scan—allowed for visualization of extraosseous complications, including subperiosteal abscesses in 77 patients, pyomyositis in 43, septic arthritis in 31, and deep vein thrombosis in 12. "Clearly, MRI was superior to bone scan in detecting bone infection. In our institution, MRI is the first thing we use. It can help pick up other areas of concern," Dr. Kaplan noted.

Some of these extraosseous complications also appear to be on the rise. At least two recent reports have documented cases of venous thrombophlebitis among children with invasive *S. aureus* infections. At Children's Medical Center in Dallas, 10 of 35 children with confirmed osteomyelitis developed deep vein thrombosis during the acute infection, with evidence of dissemination in six (J. Pediatr. 2006;149:537-41).

And at Texas Children's, Dr. Kaplan and his associates reported on 9 children seen between 1999 and 2004 who had venous thrombosis adjacent to the site of staphylococcal osteomyelitis. Seven patients had community-acquired infections caused by MRSA belonging to the same USA300 clonal group, and all 7 carried PVL genes. The USA300 clone may "have a unique propensity to cause [venous thrombosis] in association with osteomyelitis," they concluded (Pediatrics 2006;117:1673-9).

Though still far less common than simple skin and soft tissue CA-MRSA infections, serious infections such as osteomyelitis, bacteremia, and pneumonia have been increasing.

Since then, they've seen about 40-50 children with osteomyelitis who developed thrombosis, despite not having genetic prothrombotic conditions. "We don't understand what's going on. There's clearly something different about these community isolates, especially the USA300 strain," Dr. Kaplan commented.

The USA300 MRSA genotype has also been implicated in septic arthritis. Among 44 isolates taken from 45 patients at Texas Children's with septic arthritis caused by *S. aureus*, 16 were MRSA; of these, 13 were USA300 and 14 were PVL-positive. Infections caused by USA300 were more likely to be associated with a longer duration of fever, bacteremia, and a C-reactive protein level of 10 mg/dL or greater (Pediatr. Infect. Dis. J. 2009;28:1076-80).

Rates of pyomyositis and myositis also have been on the rise at Texas Children's, and can be correlated to the emergence of CA-MRSA. Among 45 previously healthy children with bacterial pyomyositis or myositis, the cause was *S. aureus* in 58%. Of 24 community-acquired *S. aureus* isolates that were available, 15 were MRSA and 9 were MSSA. A total of 16 (including all the MRSA) isolates were found to be USA300, and 17 carried the PVL genes. The presence of MRSA, USA300, and/or the PVL genes was associated with a greater requirement for drainage procedures (Clin. Infect. Dis. 2006;43:953-60).

"Infection of muscles is something we just never saw in the past," Dr. Kaplan commented.

Pulmonary manifestations are another increasingly common complication of CA-MRSA. An investigation of 70 children with invasive staphylococcal infections at Texas Children's between 2001 and 2004 showed that 47 had MRSA. Compared with 10 who had MSSA, those with MRSA were more likely to have pneumonia, empyema, lung abscess, and atelectasis. The presence of PVL was associated with abnormal chest image findings in patients with secondary pneumonia (Clin. Infect. Dis. 2005;41:583-90).

Influenza complicated by staph infections also is becoming more common, with most of these cases attributable to MRSA. In a study by the Centers for Disease Control and Prevention comparing pediatric deaths during three influenza seasons, bacterial coinfection rose substantially, from 6% in 2004-2005 to 15% in 2005-2006 to 34% in 2006-2007. Isolation of *S. aureus* from a sterile site rose from just 1 case in 2004-2005 to 22 in 2006-2007, of which two-thirds were MRSA. Children with staph coinfection were significantly older and more likely to have pneumonia and acute respiratory distress syndrome than those not coinfected (Pediatrics 2008;122:805-11).

Severe staphylococcal infections also are emerging along with CA-MRSA. In a descriptive report of 14 previously healthy adolescents with severe community-acquired *S. aureus* infections admitted to intensive care at Texas Children's with coagulopathy and sepsis, 12 were found to have MRSA and 2 had MSSA. Thirteen also had pulmonary involvement and/or bone and joint infection, four developed vascular complications, and three died. All isolates were identical or closely related to the USA300 clone (Pediatrics 2005;115:642-8).

The typical patient is an adolescent, usually with some trauma to an extremity, who may have underlying osteomyelitis and may develop pulmonary manifestations, and then becomes very ill. "We've now had seven deaths due to *S. aureus* sepsis in otherwise completely healthy children," Dr. Kaplan said. ■

Disclosures: *Dr. Kaplan has received research grants from Pfizer and Cubist Pharmaceuticals.*

Keep Tabs on CA-MRSA Infection by Obtaining Cultures

BY MIRIAM E. TUCKER

BETHESDA, MD. — Draining abscesses and obtaining cultures are now more important to the management of pediatric skin and soft tissue infections in the era of community-acquired methicillin-resistant *Staphylococcus aureus* infections.

Skin and soft tissue infections remain the most common manifestations of community-acquired MRSA (CA-MRSA) infection, which has increased dramatically in the past decade.

Draining abscesses and obtaining cultures from purulent skin infections helps physicians keep tabs on local and regional antibiotic susceptibility patterns, Dr. Sheldon L. Kaplan said at the annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

"It's important to send cultures, which wasn't the case years ago. It helps to know what we're dealing with on a local level," said Dr. Kaplan, head of the pediatric infectious disease section at Baylor College of Medicine and chief of the infectious disease service at Texas Children's Hospital, both in Houston.

Although invasive CA-MRSA infections are increasingly a concern, skin and soft tissue infections continue to make up the majority of CA-MRSA infections. Among the 12,876 children with community-acquired *S. aureus* infections who were seen at Texas Children's between Aug. 1, 2001, and June 30, 2009, 73% had a MRSA infection. Of those, 97% were skin and soft tissue infections, compared with 93% of the methicillin-susceptible *S. aureus* (MSSA) infections.

Over the 8 years, children with CA-MRSA skin and soft tissue infections were more likely to be admitted to the hospital than were those with CA-MSSA isolates (58% vs. 51%).

Virtually all CA-MRSA isolates remain susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), and about 90% remain susceptible to doxycycline-minocycline, although few pediatric data are available for those agents and they can be used only in children over 8 years of age, Dr. Kaplan noted.

'It's important to send cultures, which wasn't the case years ago. It helps to know what we're dealing with.'

DR. KAPLAN

Clindamycin susceptibility varies widely around the country. Data from 2000-2005 suggest that resistance rates in children with CA-MRSA ranged from 3% in Baltimore (Pediatr. Infect. Dis. J. 2007;26:852-4) to 22% in Chicago (Emerg. Infect. Dis. 2006; 12:631-7).

In Houston, rates of clindamycin resistance have slowly increased from about 2%-3% in 2001 to approximately 10% for the last few years, Dr. Kaplan noted.

The good news is that for many abscesses, incision and drainage alone may clear the infection.

A study published a few years ago showed that this was the case for both CA-MRSA and non-MRSA staph infections. Of 69 children with skin and soft tissue abscesses caused by CA-MRSA, 62 had their abscesses drained and 45 had wound packing. All of the children were treated with empiric antibiotics, which were ineffective in 58.

After the culture results were known, an antibiotic active against CA-MRSA was given to 21 of those 58.

However, no significant differences in response were observed between those who never received an effective antibiotic and those who did.

Having an initial lesion larger than 5 cm was a significant predictor of hospitalization, whereas initial ineffective antibiotic therapy was not, the authors concluded (Pediatr. Infect. Dis. J. 2004;23:123-7).

And in a study presented at an infectious disease conference last year, there were no differences in response between clindamycin and cephalexin at 48-72 hours or at 7 days after surgical or spontaneous drainage among 200 children with uncomplicated skin and soft tissue infections, including the 69% of infections caused by CA-MRSA.

The researchers concluded that "antibiotic therapy may be of limited value in the management of children with uncomplicated, drained skin and soft tissue infections."

A definitive answer to the question of how to treat uncomplicated skin and soft tissue infections may come from a current study funded by the National Institute of Allergy and Infectious Diseases, comparing TMP-SMX, clindamycin, or placebo in 1,310 nonhospitalized immunocompetent adults and children. The study, which began in April 2009, is scheduled to be completed in July 2011, Dr. Kaplan said.

"So here we are in 2010, still trying to figure out the best way to treat an abscess," he commented.

"Hopefully, 4-5 years from now, we'll have some information as to whether it helps to add a systemic antibiotic. We'll have to wait and see," Dr. Kaplan added. ■

Disclosures: *Dr. Kaplan has received clinical research grants from Pfizer and Cubist Pharmaceuticals.*