Rate of Invasive CA-MRSA Infections Increasing

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.

'Infection of muscles is something we just never saw in the past.'

DR. KAPLAN

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. While the proportion of those infections caused by MSSA remained constant at 10%-13%, 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).

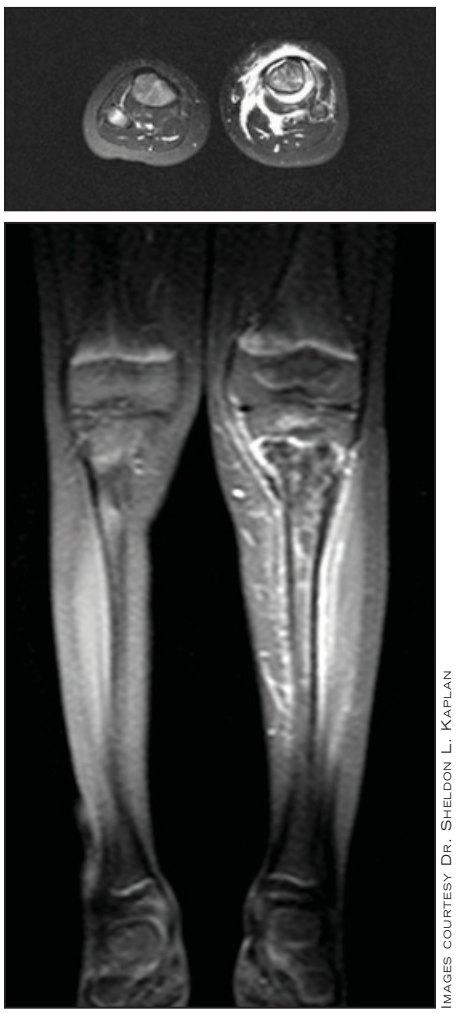
MRI appears to be the optimal method for detection of osteomyelitis resulting from community-acquired *S. aureus*.

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 6 (J. Pediatr. 2006;149:537-41).

And at Texas Children's, Dr. Kaplan and his associates reported on nine 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 seven carried PVL genes. The USA300 clone may "have a unique propensity to cause [venous thrombosis] in association with osteomyelitis," they wrote (Pediatrics 2006;117:1673-9).



IMAGES COURTESY DR. SHELDON L. KAPLAN

An axial view of proximal left tibial osteomyelitis with subperiosteal abscess and extraosseous soft tissue inflammation is shown (top). A sagittal view is also shown (bottom).

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 is also becoming more common, with most of these cases attributable to MRSA. A study by the Centers for Disease Control and Prevention comparing pediatric deaths during three influenza seasons revealed that bacterial coinfection increased 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. ■

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

FDA Approves Orphan Drug to Treat Cystic Fibrosis

BY LAUREN SMITH

"The Pink Sheet"

The Food and Drug Administration has approved Cayston to improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*, a therapeutic area with few meaningful therapies.

The approval comes as no surprise, as the orphan drug was seen as an urgently needed therapeutic to treat the respiratory and pulmonary symptoms of CF, and led the FDA's Anti-Infective Drugs Advisory Committee to overwhelmingly support approval of Cayston (aztreonam for inhalation solution). The drug is manufactured by Gilead Sciences.

Members of the committee said the bar for approval should be set "quite low" due to the lack of meaningful alternatives, despite both the FDA's and the panelists' misgivings about missing data and negative regimen effects in the two pivotal trials.

The approval was lauded by the Cystic Fibrosis Foundation, whose president and CEO Robert Beall said in Gilead's press release, "As the first new inhaled antibiotic approved for use in cystic fibrosis in more than a decade, Cayston therefore represents an important therapeutic option in the care of patients with cystic fibrosis."

The foundation is also working with Gilead's marketing team to establish the Cayston Access Program, a call center developed with the Cystic Fibrosis Foundation Pharmacy (a wholly owned subsidiary of the Cystic Fibrosis Foundation), which will assist people with cystic fibrosis and members of their care team with insurance verification, referral to participating specialty pharmacies, claims support, and copay assistance. ■

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