MRSA Warrants Culturing All Skin Infections

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 help 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.

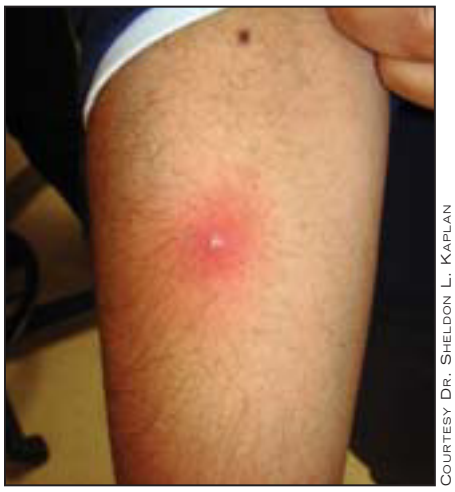
Over the 8 years, children with CA-MRSA skin and soft tissue infections were more likely to be admitted to the hospital than were those with CA-MSSA isolates (58% vs. 51%).

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, he noted.

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, he 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 were treated with empiric antibiotics, which were ineffective in 58. After 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.



COURTESY DR. SHELDON L. KAPLAN

This pustule with surrounding cellulitis is a prime candidate for culturing.

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 began in April 2009 and is scheduled to be completed in July 2011. ■

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

To watch a video of Dr. Kaplan, go to www.familypracticenews.com.

Next-Generation Imiquimod Deemed More Convenient

BY BRUCE JANCIN

WAIKOLOA, HAWAII — The next generation of imiquimod therapy for actinic keratoses will offer a simpler, more convenient regimen that is easier to tolerate than the available 5% cream, according to Dr. Brian Berman, professor of dermatology at the University of Miami.

A 3.75% topical formulation of imiquimod has been designed for once-daily treatment. The new formulation received marketing approval in Canada earlier this year but is investigational in the United States. Called Zyclara (Graceway Pharmaceuticals), it is used in cyclic fashion over a 6-week period: 2 weeks on, 2 weeks off, and 2 weeks on.

The 5% imiquimod formulation (Aldara, Graceway Pharmaceuticals) isn't supposed to be applied to an area greater than 25 cm^2. The 3.75% formulation, however, can be used to treat the full face or balding scalp, he said at the annual Hawaii Dermatology Seminar sponsored by Skin Disease Education Foundation.

As part of four clinical trials, a 2.5% and a 3.75% formulation of imiquimod cream were evaluated in two regimens. Reponses were measured in a total of 969 patients, each having 5-29 facial and scalp actinic keratoses (AKs) with up to 1 mm of hyperkeratosis.

Trial participants were randomized to receive either 2.5% or 3.75% imiquimod cream or placebo. Patients were further randomized to either a schedule of 3-weeks-on/3-weeks-off/3-weeks-on therapy or to the 2-2-2 regimen. Outcomes were best with 3.75% imiquimod on the 2-2-2 cycle.

After the first 2 weeks of treatment with the 3.75% cream given on the 2-2-2 regimen, subclinical AK lesions became apparent in 85% of patients. At 8 weeks post treatment, their AK lesion count was reduced by nearly 82%. The placebo group had a 25% decrease in lesion count at 8 weeks.

An earlier study of 5% imiquimod cream, applied twice weekly for 16 weeks, resulted in an 83% median decrease in AKs.

The complete clearance rate was nearly 36% with 3.75% imiquimod on a 2-2-2 schedule, compared to 6.3% with placebo. The partial clearance rate, defined as at least 75% clearance of AKs, was slightly over 59% with 3.75% imiquimod and nearly 23% with placebo.

VITALS

Major Finding: The number of actinic keratoses was reduced by nearly 82% at 8 weeks after treatment with 3.75% imiquimod cream, given on a 2-weeks-on, 2-weeks- off, 2-weeks-on regimen.

Data Source: Four placebo-controlled, randomized clinical trials comparing 2.5% and 3.75% formulations of imiquimod cream given in two regimens to a total of 969 patients.

Disclosures: The studies were funded by the drug's manufacturer, Graceway Pharmaceuticals. Dr. Berman, an investigator in the trials, is on the company's speakers bureau and advisory board.

The efficacy of 3.75% imiquimod on the 3-3-3 cycle was comparable, but the rate of treatment-related adverse events was nearly twice as great, and the number of unscheduled rest periods was more than doubled.

Favorable outcomes also were impressively durable. Among patients who were completely cleared at 8 weeks post treatment, the median number of AKs was zero at 6 months and one at 1 year.

Following cryotherapy, the 1-year sustained clearance rate is typically in the low single digits, he observed.

Audience members asked Dr. Berman's preferences for treating AKs in his own practice. He replied that his favorable clinical trial experience would make 3.75% imiquimod, if it is made available in the United States, his first-line treatment for AKs on the balding scalp, face, and ears. He has relied upon topical 5-FU for AKs on the arms, since these lesions tend to be quite hyperkeratotic.

Given the good responses to 3.75% imiquimod in the numerous trial patients with mildly hyperkeratotic AKs, Dr. Berman said he would be equally likely to turn to topical 5-FU or imiquimod 2-2-2 cycle therapy for lesions on the arms.

He also discussed important new developments in the pathogenesis of AKs and squamous cell carcinomas—and how imiquimod counters this process.

Among its multiple immunomodulatory effects, topical imiquimod activates toll-like receptor-7, NFkappaB, and Th1 lymphocytes that have antiviral and antitumor activities.

Investigators at Dongguk University in Kyongju, Korea, recently identified a new major player in the development of AKs and squamous cell carcinoma: the Forkhead box p3 (Foxp3)–positive cell. These cells infiltrate and surround AKs and squamous cell carcinomas, where they induce immune suppression and ultimately immune tolerance to the tumor. Foxp3-positive T regulatory cells do so through direct cell-to-cell contact and by elaborating the immunosuppressive cytokines interleukin-10 and transforming growth factor-beta (Yonsei Med.J. Dec. 31, 2008;49:942-8).

"The good news is in vivo application of imiquimod to squamous cell carcinomas of the skin blocks these two immunosuppressive agents—IL-10 and TGF-beta—reversing the immune suppression. This obviously has a sanguine effect on removing AKs as well," Dr. Berman explained.

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