

More Deep Infections Seen in Community MRSA

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SAN FRANCISCO — Invasive methicillin-resistant *Staphylococcus aureus* was more likely to cause skin and soft tissue disease or joint infections if acquired in the community rather than in a hospital, according to preliminary data from a large surveillance study.

Skin or soft tissue infection occurred in 34% of community-associated methicillin-

resistant *S. aureus* (MRSA), compared with 10% of hospital-associated MRSA in the study of 6,413 cases of invasive MRSA in nine U.S. sites with a population of about 16 million people.

Endocarditis was more common with community-associated MRSA than with hospital-associated MRSA (12% vs. 4%), as were internal or deep-seated abscesses (9% vs. 4%) and septic arthritis, Susan M. Ray, M.D., said at the annual meeting of the Infectious Diseases Society of America.

"These differences may be explained by virulence factors in the staph strain, and/or by delay in presentation for care," said Dr. Ray of Emory University, Atlanta. "The clinical evaluation of community-associated MRSA should include the investigation of deep-seated foci of infections."

Patients with hospital-associated invasive MRSA were more likely to have uncomplicated bacteremia.

A previous analysis of 2001-2002 data from the Centers for Disease Control and Prevention reported that about 17% of MRSA cases in three sites were community associated, and about 7% of these were invasive disease (with a culture from a normally sterile site).

The current study analyzed federal data from 2004 and 2005 in nine geographic areas for culture-positive invasive MRSA infections. Surveillance officers reviewed patient records to classify 86% of cases as hospital-associated based on risk-factor criteria; all others were deemed community-associated infections (14%) or uncertain (less than 0.5%).

The rate of community-associated MRSA varied widely by geography, comprising

24% of invasive MRSA cases in Maryland but only 3% of cases in New York.

Compared with hospital-associated invasive MRSA, higher rates of community-associated MRSA were seen in children, smokers, and men with a history of intravenous drug use, HIV, or AIDS. Community-associated MRSA was less likely to be resistant to antimicrobials besides methicillin or to be resistant to multiple classes of antibiotics compared with hospital-associated MRSA.

Community-associated MRSA accounted for 35% of invasive MRSA in children aged 3 years or younger, 50% of cases in 4- to 19-year-olds, 25% of patients aged 20-49 years,

and 7% of those aged 50 years or older.

Cases were defined as hospital-associated MRSA if records showed at least one of the following: previous MRSA colonization or infection; a culture obtained more than 48 hours after hospitalization; the presence of an invasive device at the time of evaluation; or a history within the past year of hospitalization, surgery, dialysis, or residence in a long-term care facility.

Investigators in the study began collecting isolates from a sample of cases in 2005. "In the future, this will allow us to compare the epidemiologic classification of community-associated MRSA with its microbiologic characteristics," Dr. Ray said. ■

VYTORIN® (ezetimibe/simvastatin)

VYTORIN: There are insufficient data for the safe and effective use of VYTORIN in pediatric patients. (See *Ezetimibe and Simvastatin* below.)

Ezetimibe: The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin: Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses >40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use

Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

ADVERSE REACTIONS

VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated.

Table 1 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 3 similarly designed, placebo-controlled trials.

Table 1*

Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/ Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1236
<i>Body as a whole - general disorders</i>				
Headache	6.4	6.0	5.9	6.8
<i>Infection and infestations</i>				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
<i>Musculoskeletal and connective tissue disorders</i>				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.

** All doses.

Post-marketing Experience: The adverse reactions reported for VYTORIN are consistent with those previously reported with ezetimibe and/or simvastatin.

Ezetimibe: Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Body as a whole - general disorders*: fatigue; *Gastrointestinal system disorders*: abdominal pain, diarrhea; *Infection and infestations*: infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders*: arthralgia, back pain; *Respiratory system disorders*: coughing.

Post-marketing Experience: The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment: Hypersensitivity reactions, including angioedema and rash; elevated creatine phosphokinase; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely, myopathy/rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

Simvastatin: Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Body as a whole - general disorders*: asthenia; *Eye disorders*: cataract; *Gastrointestinal system disorders*: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; *Skin and subcutaneous tissue disorders*: eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy. *Musculoskeletal system disorders*: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgia.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances. *Ear and labyrinth disorders*: vertigo.

Psychiatric disorders: anxiety, insomnia, depression, loss of libido.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomiting. *Hepatobiliary disorders*: hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma. *Metabolism and nutrition disorders*: anorexia.

Skin and subcutaneous tissue disorders: alopecia, pruritus. A variety of skin changes (eg, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive system and breast disorders: gynecomastia, erectile dysfunction.

Eye disorders: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ -glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

Adolescent Patients (ages 10-17 years)

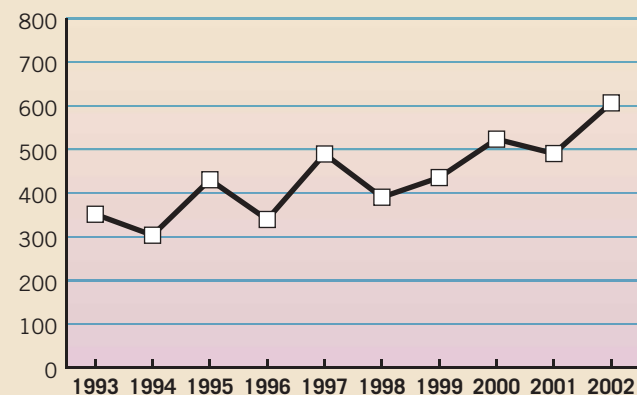
In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).

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DATA WATCH

In-Hospital Deaths From Postoperative and Posttraumatic Infections Are on the Rise



Note: Based on weighted estimates from the Healthcare Cost and Utilization Project nationwide inpatient sample.

Source: Agency for Healthcare Research and Quality

Severe MRSA Infections Rising in the Young

BY NANCY WALSH
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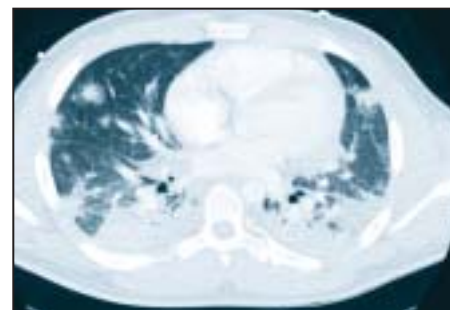
WARSAW — Community-acquired methicillin-resistant *Staphylococcus aureus* infections in children are on the increase around the world, and while most cases involve the skin and soft tissue and are susceptible to clindamycin, severe invasive infections requiring treatment with vancomycin also are being reported, Sheldon L. Kaplan, M.D., said.

Infections are being seen in children who have no traditional risk factors, such as recent hospitalization, underlying illness, or frequent antibiotic exposure.

It appears that a number of different clones of *S. aureus* have acquired resistance genes, and most isolates contain a gene that codes for a toxin called Panton-Valentine leukocidin (PVL). This cytotoxin causes leukocyte destruction and tissue necrosis, and has been associated with particularly severe forms of infection including hemorrhagic pneumonia, Dr. Kaplan said at an international congress of the World Society for Pediatric Infectious Diseases.

"In our hospital at the moment, *S. aureus* is the most common cause of pneumonia with empyema, which used to be predominantly caused by pneumococcus," he said.

It is not clear whether PVL is truly the causative factor in these highly virulent infections or is in some way participating in the ability of this organism to spread from person to person. What is clear is that mortality is high with *S. aureus* strains carrying the PVL gene: In one survey in France, the



CT scan of the lungs shows septic pulmonary emboli in a 14-year-old with severe staph sepsis and a DVT in the leg.

survival rate 48 hours after hospital admission was 63% among patients with PVL-positive infections, compared with 94% among those with PVL-negative infections (Lancet 2002;359:753-9).

Among other severe infections that have been seen are pyomyositis and myositis in association with osteomyelitis. "It's true that we're doing more MRI and that allows us to see these muscle infections, but

I don't think we missed these infections prior to MRI. The organism just has more ability to invade muscle tissue," said Dr. Kaplan, professor of pediatrics and infectious disease at Baylor College of Medicine, Houston.

Other infections that have been seen include extensive epidural abscesses, septic shock, and necrotizing fasciitis.

Almost all of the methicillin-resistant *S. aureus* (MRSA) isolates are susceptible to vancomycin, gentamicin, and trimethoprim-sulfamethoxazole. Rates of susceptibility to clindamycin vary somewhat, but in general are in the 92%-95% range. "In our area, clindamycin has been used quite a bit for community-acquired MRSA, and we are starting to see an increase in resistance, from 2% to 7%, so this is a warning," Dr. Kaplan said. Once resistance rates reach 10%-15%, clindamycin would not be an appropriate drug to use for initial empiric treatment, he added.

When asked about possible reasons why some children develop fulminant, overwhelming infections with MRSA, Dr. Kaplan said it may be host related. "Is it related to polymorphisms in toll-like receptor 2, or some other immune factor? We can't explain it. Many have not had an obvious site of skin infection that preceded their invasive infection." ■