

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 con-

cern 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. Nafcillin 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

HUMALOG® INSULIN LISPRO INJECTION (rDNA ORIGIN) BRIEF SUMMARY: Consult package insert for complete prescribing information.

INDICATIONS AND USAGE: Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than regular human insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Humalog may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump. Humalog administration in insulin pumps has not been studied in patients with type 2 diabetes.

CONTRAINDICATIONS: Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or any of its excipients.

WARNINGS: This human insulin analog differs from regular human insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump).

External Insulin Pumps: When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin. Patients should carefully read and follow the external insulin pump manufacturer’s instructions and the “PATIENT INFORMATION” leaflet before using Humalog.

Physicians should carefully evaluate information on external insulin pump use in the Humalog physician package insert and in the external insulin pump manufacturer’s instructions. If unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt identification and correction of the cause is necessary. The patient may require interim therapy with subcutaneous insulin injections (see PRECAUTIONS, For Patients Using External Insulin Pumps, and DOSAGE AND ADMINISTRATION).

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (eg, regular, NPH, analog), species, or method of manufacture may result in the need for a change in dosage.

PRECAUTIONS: *General*—Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (eg, patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Humalog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia—As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment—The requirements for insulin may be reduced in patients with renal impairment.

Hepatic Impairment—Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog, may be necessary.

Allergy—Local Allergy—As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient. In Humalog-controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving Humulin R® (N=2969) and 30 patients receiving Humalog (N=2944) (P=.053).

Antibody Production—In large clinical trials, antibodies that cross-react with human insulin and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As expected, the largest increase in the antibody levels during the 12-month clinical trials was observed with patients new to insulin therapy.

Usage of Humalog in External Insulin Pumps—The infusion set (reservoir syringe, tubing, and catheter), Disetronic® D-TRON^{®2,3} or D-TRONplus^{®2,3} cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced and a new infusion site selected every 48 hours or less. Humalog in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F).

In the D-TRON^{®2,3} or D-TRONplus^{®2,3} pump, Humalog 3 mL cartridges may be used for up to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.

When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin (see INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, For Patients Using External Insulin Pumps, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and Storage).

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic hemoglobin A1C testing, recognition and management of hypoglycemia and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant. Refer patients to the “PATIENT INFORMATION” leaflet for timing of Humalog dosing (≤15 minutes before or immediately after a meal), storing insulin, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the “PATIENT INFORMATION” leaflet that accompanies the drug product and the User Manual that accompanies the delivery device. They should also reread these materials each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen to a stream of insulin, and properly dispose of needles. Patients should be advised not to share their Pens with others.

For Patients Using External Insulin Pumps: Patients using an external infusion pump should be trained in intensive insulin therapy and in the function of their external insulin pump and pump accessories. Humalog was tested in the MiniMed^{®1} Models 506, 507, and 508 insulin pumps using MiniMed^{®1} Polyfin^{®1} infusion sets. Humalog was also tested in the Disetronic^{®2} H-TRONplus^{®2} V100 insulin pump (with plastic 3.15 mL insulin reservoir), and the Disetronic D-TRON^{®2,3} and D-TRONplus^{®2,3} insulin pumps (with Humalog 3 mL cartridges) using Disetronic Rapid^{®2} infusion sets.

The infusion set (reservoir syringe, tubing, catheter), D-TRON^{®2,3} or D-TRONplus^{®2,3} cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced, and a new infusion site selected every 48 hours or less. Humalog in the external pump should not be exposed to temperatures above 37°C (98.6°F).

A Humalog 3 mL cartridge used in the D-TRON^{®2,3} or D-TRONplus^{®2,3} pump should be discarded after 7 days, even if it still contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected.

Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump. **Laboratory Tests**—As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of hemoglobin A1C is recommended for the monitoring of long-term glycemic control.

Drug Interactions—Insulin requirements may be increased by medications with hyperglycemic activity, such as corticosteroids, isoniazid, certain lipid-lowering drugs (eg, niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy (see CLINICAL PHARMACOLOGY).

Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (eg, octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur. The American Diabetes Association warns in its Position Statement on Insulin Administration, “On mixing, physicochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately.” Mixing Humalog with Humulin[®] N or Humulin[®] U does not decrease the absorption rate or the total bioavailability of Humalog.

Given alone or mixed with Humulin N, Humalog results in a more rapid absorption and glucose-lowering effect compared with regular human insulin.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies with insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and well-controlled studies with Humalog in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there are limited clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers—It is unknown whether Humalog is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when Humalog is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog dose, meal plan, or both.

Pediatric Use—In a 9-month, crossover study of prepubescent children (n=60), aged 3 to 11 years, comparable glycemic control as measured by A1C was achieved regardless of treatment group: regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%, and Humalog immediately after meals 8.5%. In an 8-month, crossover study of adolescents (n=463), aged 9 to 19 years, comparable glycemic control as measured by A1C was achieved regardless of treatment group: regular human insulin 30 to 45 minutes before meals 8.7% and Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all 3 treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the Humalog vial, the shelf life may be reduced (see DOSAGE AND ADMINISTRATION).

Geriatric Use—Of the total number of subjects (n=2834) in 8 clinical studies of Humalog, 12% (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes. A1C values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of Humalog action have not been performed.

ADVERSE REACTIONS: Clinical studies comparing Humalog with regular human insulin did not demonstrate a difference in frequency of adverse events between the 2 treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole—allergic reactions (see PRECAUTIONS).

Skin and Appendages—injection site reaction, lipodystrophy, pruritus, rash.

Other—hypoglycemia (see WARNINGS and PRECAUTIONS).

OVERDOSAGE: Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION: Humalog is intended for subcutaneous administration, including use in select external insulin pumps (see DOSAGE AND ADMINISTRATION, External Insulin Pumps). Dosage regimens of Humalog will vary among patients and should be determined by the healthcare provider familiar with the patient’s metabolic needs, eating habits, and other lifestyle variables. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to regular human insulin (ie, one unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin), but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to Humalog, particularly to prevent premeal hyperglycemia.

When used as a mealtime insulin, Humalog should be given within 15 minutes before or immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal. To achieve optimal glucose control, the amount of longer-acting insulin being given may need to be adjusted when using Humalog.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 U/kg regular human insulin or Humalog at abdominal, deltoid, or femoral sites, the 3 sites often used by patients with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its rapid onset of action and has less variability in its onset of action among injection sites compared with regular human insulin (see PRECAUTIONS). After abdominal administration, Humalog concentrations are higher than those following deltoid or thigh injections. Also, the duration of action of Humalog is slightly shorter following abdominal injection, compared with deltoid and femoral injections. As with all insulin preparations, the time course of action of Humalog may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog in a vial may be diluted with STERILE DILUENT for Humalog, Humulin N, Humulin R, Humulin 70/30, and Humulin® R U-500 to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog contained in a cartridge or Humalog used in an external insulin pump.

Parenteral drug products should be inspected visually before use whenever the solution and the container permit. If the solution is cloudy, contains particulate matter, is thickened, or is discolored, the contents must not be injected. Humalog should not be used after its expiration date. The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be refilled with insulin.

External Insulin Pumps—Humalog was tested in MiniMed^{®1} Models 506, 507, and 508 insulin pumps using MiniMed^{®1} Polyfin^{®1} infusion sets. Humalog was also tested in the Disetronic^{®2} H-TRONplus^{®2} V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the Disetronic D-TRON^{®2,3} and D-TRONplus^{®2,3} pumps (with Humalog 3 mL cartridges) using Disetronic Rapid^{®2} infusion sets. Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

HOW SUPPLIED:

Humalog (insulin lispro injection, USP [rDNA origin]) is available in the following package sizes (with each presentation containing 100 units insulin lispro per mL [U-100]):

10 mL vials	NDC 0002-7510-01	(VL-7510)
3 mL vials	NDC 0002-7510-17	(VL-7533)
5 x 3 mL cartridges ³	NDC 0002-7516-59	(VL-7516)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8725-59	(HP-8725)
5 x 3 mL prefilled insulin delivery devices (Humalog® KwikPen™)	NDC 0002-8799-59	(HP-8799)

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²Disetronic®, H-TRONplus®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.

³3 mL cartridge is for use in Eli Lilly and Company’s HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD insulin delivery devices, Owen Mumford, Ltd.’s Autopen® 3 mL insulin delivery device, and Disetronic D-TRON® and D-TRONplus® pumps. Autopen® is a registered trademark of Owen Mumford, Ltd. HumaPen®, HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD are trademarks of Eli Lilly and Company.

Other product and company names may be the trademarks of their respective owners.

Storage—Unopened Humalog should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated (below 30°C [86°F]) 12 vials, cartridges, Pens, and KwikPens must be used within 28 days or be discarded, even if they still contain Humalog. Protect from direct light.

Use in an External Insulin Pump—A Humalog 3 mL cartridge used in the D-TRON^{®2,3} or D-TRONplus^{®2,3} should be discarded after 7 days, even if it still contains Humalog. Infusion sets, D-TRON^{®2,3} and D-TRONplus^{®2,3} cartridge adapters, and Humalog in the external insulin pump reservoir should be discarded every 48 hours or less.

Literature revised December 7, 2009

KwikPens manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA.

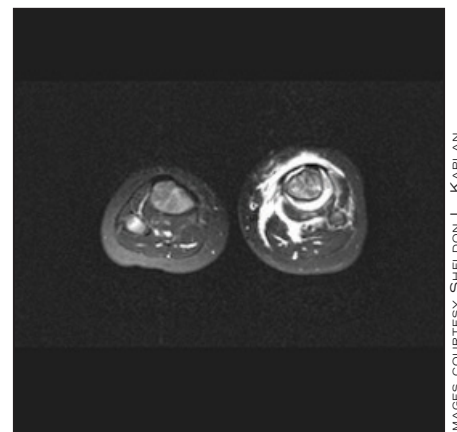
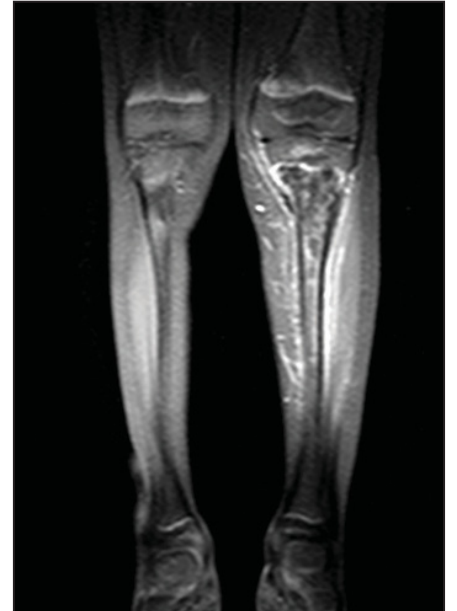
Pens manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA or Lilly France, F-67640 Fegersheim, France.

Vials manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA or Hospira, Inc., Lake Forest, IL 60045, USA or Lilly France, F-67640 Fegersheim, France.

Cartridges manufactured by Lilly France, F-67640 Fegersheim, France for Eli Lilly and Company, Indianapolis, IN 46285, USA.

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

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).

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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).

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 coinfecting (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.

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.



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DR. KAPLAN