AN ENEMY IN OUR MIDST
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by Judy Bolyard Purdy
The phone rang just as Robert Daum was preparing to attend a bar mitzvah, where 13-year-old Sam Schwartz had decided to contribute all the money he received to Daum’s University of Chicago research on an emerging, potentially deadly strain of bacteria.

But the phone diverted Daum. The call that October Saturday came from the pediatric intensive care unit.

“They had just admitted a child and they thought he had severe sepsis,” said Daum, MD, professor and section chief of pediatric infectious diseases at Chicago.

When a child arrives at Comer Children’s Hospital at the University of Chicago with severe sepsis, the staff begins aggressive treatment on the assumption the patient is infected with the strain of bacteria Daum studies. Depending on the nature of the infection, a young patient can die in a matter of hours.

“I just couldn’t believe [the coincidence],” Daum said. “I came into the hospital to get the care for this kid started with the ICU team, and then I went to Sam’s bar mitzvah. His family was pretty amazed that I’d just been to the hospital and seen ‘the enemy.’”

Daum’s “enemy” is community-associated methicillin-resistant Staphylococcus aureus (MRSA, pronounced “mersa”), a frightening bug that is resistant to standard treatments such as penicillin, oxacillin and all related antibiotics.

Virulent strains produce the nasty toxin PVL (for Panton-Valentine leukocidin) that attacks white-blood cells and causes flesh to appear to dissolve. Deep-tissue infections of virulent strains can turn deadly for healthy children and adults, as well as the usual targets—the elderly and people with compromised immune systems.

And unlike the health care-associated (HA-MRSA) strains that first appeared in the 1960s—and which, as their name implies, tend to strike certain patients who need frequent health care visits—the community-associated (CA-MRSA) infections can suddenly strike otherwise healthy, robust people, swiftly making them seriously ill.
Just a little scrape

Daum’s patient on this October weekend was 8-year-old Jewaun Smith. Seven days before arriving at the ER, Jewaun had been enjoying a Sunday afternoon bike ride around his South Side Chicago neighborhood. His mother, Kansonia Love, was sitting on the porch when he came home and announced that he had fallen off his bike. “It was just a little scrape on his upper thigh,” she said, “so I cleaned it with hydrogen peroxide and put a bandage over it.”

Jewaun went back to playing.

Later that night and again the next morning he reported that his injury still hurt, so Jewaun’s grandmother took him to a neighborhood emergency clinic. The doctor on call gave him antibiotics and pain medication for a sprained muscle and sent him home.

But as the week wore on, Jewaun’s injury still troubled him. His temperature remained normal, but his mom noticed a waning appetite. By midweek, she took him to a nearby community hospital where she got the same diagnosis and another prescription for pain. The next day, he wasn’t eating and was getting weaker, Love said, “but I thought the medicine needed time to work.”

By Friday morning it was obvious the prescriptions weren’t working. Jewaun had developed “15 or 20 puff-like things in the middle of his forehead and the whites of his eyes had turned yellow,” his mom said. The doctor at the clinic took one look at him and recommended she take him immediately to a full-service hospital for a battery of tests.

The tests provided no insight. “That doctor told me, ‘We still don’t know what is wrong, but this child is very ill. His lungs are damaged and his upper respiratory system, kidneys and liver are failing,’” Love said.

An ambulance sped Jewaun to another hospital. By this time his breathing had become labored, he had a high fever and “you could see his heart beating at a fast pace through his shirt,” his mom said. “I was very scared. [In the ambulance] I’m praying, praying, praying, and we made it to the hospital.”

He spent Friday night in the hospital and Saturday morning began vomiting his medication along with blood. Frightened, Love pleaded with the doctors to help her child. Jewaun was then transferred to the University of Chicago.

At Comer, Love learned her son had a severe CA-MRSA infection. And the doctors, she said, told her they didn’t know whether Jewaun would survive.

Aggressive treatment

It’s very hard to know how to treat these patients, said Daum, who was the first to identify and document CA-MRSA strains. “It is not just a question of giving them the right antibiotics,” he said. “The infection is very progressive and the patient’s condition runs downhill rapidly, despite the heroic efforts and care of our ICU.”

For nearly a decade, Daum and his pediatric infectious disease colleagues at Chicago have studied and treated CA-MRSA. The emerging strains have evolved from other strains of the old, familiar staph bacteria that can cause run-of-the-mill infections such as acne, boils and sinusitis. When staph infections require antibiotics, physicians frequently prescribe beta-lactams, such as penicillins and cephalosporins.

But these are usually ineffective in treating CA-MRSA infections.

Like other strains of staph, CA-MRSA may cause mild infections of the skin and soft tissue, including red, pus-filled abscesses or painful, swollen infections just under the skin. With a little over-the-counter care, mild CA-MRSA infections often heal quickly. Moderate ones may require medical treatment to drain an infection. Occasionally,
infections are serious enough to warrant an antibiotic. However, when a toxin-producing CA-MRSA infection sets up in deep tissue, it can cause severe infections of the bloodstream (bacteremia), skin (necrotizing fasciitis) and lungs (necrotizing pneumonia, which destroys lung tissue).

In the past year, Comer medical staff have treated 14 children with severe sepsis caused by staph infections; half have not survived, Daum said. Similarly dire statistics confront epidemiologists and clinicians elsewhere in America, Europe and Asia where CA-MRSA infections have erupted. The three pediatric cases of community-associated staph infections that immediately preceded Jewaun’s ended in death, all within a couple of days of arriving at the ER. “We were on a losing streak to a nasty opponent,” Daum said. Coincidentally, the paper describing some of those fatal cases was published in the New England Journal of Medicine on Sept. 22, 2005—a month before Jewaun arrived at Comer.

Jewaun’s symptoms—fever and malaise followed by severe sepsis, labored breathing, fast pulse and organ failure—are typical of children with severe CA-MRSA infections, said Madelyn Kahana, MD, a pediatric anesthesiologist and the medical director of the pediatric intensive care unit. By the time most kids with a deep-tissue CA-MRSA infection arrive at an emergency room, it may be too late to reverse the cellular damage the toxin has produced.

“My nightmare is MRSA,” Kahana said. “It’s such a potent microbe and it causes pneumonia that is unbelievable. These are otherwise healthy kids who come down with a cold or the flu, and in a day they are dead. There’s nothing we can do because it moves so fast.”

Comer’s medical team pumps these young patients full of vancomycin, often called the “drug of last resort” because it’s one of the few antibiotics powerful enough to overcome CA-MRSA at this late stage. Other antibiotics in the arsenal include one that’s very pricey and not effective in some severe cases (linezolid) and a recently licensed compound that isn’t effective against pneumonia and hasn’t been tested in children (daptomycin).

In addition to employing antibiotics, the medical team oxygenates the patient’s bloodstream with aggressive ventilation procedures. Patients also may require surgery to drain pus that accumulates in lungs and other soft tissue, as well as intravenous antibody to combat the effects of staphylococcal toxins.

Despite a hospital’s swift, concerted efforts, a child still might die from the potent toxins. “MRSA literally kills the lung tissue,” Kahana said. “The child’s lungs look like Swiss cheese because they have so many holes in them.”

Jewaun’s lungs had more than 500 holes.
A monster movie

The threat posed by these infections has changed the way Comer medical staff practice emergency pediatric medicine, said Kahana, who estimates that four out of five staph isolates now brought in from the community to Comer are resistant to antibiotics.

“MRSA is becoming more potent and more virulent, producing more toxins that dissolve the soft tissues such as lungs. The toxins literally melt the tissue, producing quarts of pus,” she said.

“It’s frightening. It’s like a monster movie. And the more the infection has penetrated to deep tissue, the more likely it is to be resistant to a wide spectrum of antibiotics that until five years ago worked effectively on such infections.”

Jewaun’s medical team at Comer numbered close to 100 people: the entire ICU team, the entire pediatrics infectious diseases team, plus orthopedics, respiratory therapy and other specialists.

“They did everything they could for him,” Daum said. “This severe end of the clinical spectrum is where it gets frightening: Previously healthy children come into the ER in shock. We can do everything right once they get here—we can give them the right antibiotics and great care—yet the mortality rate is still 50 percent.”

First recognized in 1998, CA-MRSA strains now have been reported on nearly every continent. Kahana and Daum agree that in recent years it has become an epidemic. Roughly two kids come into the University of Chicago Hospitals each day with an illness that looks like CA-MRSA, while five to 10 adults come in for drainage of skin abscesses, Daum said.

Young children may be more susceptible to infection because “the younger you are, the less likely your body is familiar with various microbes,” Kahana said. “It takes longer for their bodies to mount a defense than for an older person who has been exposed to more pathogens.”

Approximately one of every three people has microscopic colonies of *Staphylococcus aureus* living on the skin or in the nose. The colonies are relatively harmless, causing no symptoms or ill effects. Even CA-MRSA strains—which represent about 50 percent of these colonies—are not harmful to healthy people, Daum said. It’s only when a virulent MRSA strain gets under the skin and deep into tissue that big trouble begins.

Bigger than Chicago

In 1996, Daum and former University of Chicago colleague Betsy Herold, MD, now at Mount Sinai School of Medicine in New York, were among the first to observe something “new and unusual” happening in the hospital. “Children who had been perfectly healthy were coming into the hospital with serious, invasive MRSA infections,” Daum said. “If you would flash back five years before, you never saw a patient who was healthy come in like that.”

When health care-associated MRSA burst onto the scene in the 1960s, it was largely confined to people with specific risk factors associated with hospital treatment—recent surgery, lengthy hospital stays or chronic illness. Daum and Herold suspected that a new strain of MRSA was originating outside the hospital. “So we decided we needed to do a study to see if our idea was right,” he said.

They reviewed pediatric medical records from 1988 to 1990 and from 1993 to 1995, and discovered that the number of MRSA cases rose from eight to 35 and that hospitalization rates had increased 25 fold for children with no identified risks. This was the first study to show antibiotic-resistant staph infections arising outside of hospital settings. It also showed that CA-MRSA infections are less similar to health care-associated strains and more like strains that are methicillin-susceptible. They submitted their findings to the *Journal of the American Medical Association*.

The paper initially was rejected.

“They said that the idea was preposterous, that we were wrong,” Daum said. “The paper came back with the criticism that we obviously did not know how to tell MRSA strains from other kinds of staph bacteria.”
Daum called *JAMA*'s editor, offering to provide physical DNA evidence that it was a MRSA strain and eventually convincing his skeptic. But even after *JAMA* published the paper on Feb. 25, 1998, many in the medical field failed to understand that CA-MRSA was more than an isolated Midwestern phenomenon, Daum said.

“People would come up to me and tell me ‘We thought this was a Chicago curiosity,’” he said.

About 65 of every 100 MRSA infections are community-associated, and about half of those will need hospital treatment, according to Daum. But how do the community-associated MRSA strains spread and who’s at risk? Daum’s team seeks to answer those questions.

CA-MRSA spreads through skin-to-skin contact, skin injuries and abrasions, and exposure to sores and contaminated bandages. Because the bacteria survive for up to 24 hours on inanimate surfaces, infection can spread through contaminated personal items (shared towels or razors). The bacteria can proliferate in situations where people interact in close contact—athletic fields, locker rooms, homes and military barracks—or practice poor personal hygiene.

Daum and other scientists, as well as recent CDC surveys, have documented CA-MRSA outbreaks in jails. Inmates, guards, attorneys and other members of the larger jail community are at greater risk for CA-MRSA infections, which at first glance are often mistaken for spider bites.

Daum’s team is now collaborating with Illinois’ Cook County jail, one of the nation’s largest correctional facilities, to learn more about how CA-MRSA spreads through the penal system. “Ten thousand people live there; 300 new people come in each day and 300 leave every day,” he said. “Our study aims to get a better understanding of the risk factors and how the jail could be acting as an amplifier.”

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—Robert Daum, MD, Pediatric Infectious Diseases Specialist

These days though, his North Side colleagues are reporting more community-associated cases as well. “Every locale that has experienced the epidemic has continued to, and new locales are unfortunately coming online with this every day,” Daum said. “The epidemic is spreading.”

Germs as microscopic terrorists
Determining the origins of CA-MRSA may be as challenging as halting its spread.

To understand how quickly microorganisms adapt and evolve in changing circumstances, such as exposure to new antibiotics, just look at the World War II era. By the early 1940s—less than two decades after the discovery of penicillin—pharmaceutical companies began commercially manufacturing the “wonder drug.” But the

> Evolution of CA-MRSA

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has a sleek cassette that can move in and out of bacteria easily, spreading the resistance gene. Another cassette also may enter the bacteria carrying with it the genes for making PVL toxin, which can cause necrosis.

1. Phages carrying sleek cassettes (red)—one with the resistance gene (yellow) and the other with the PVL toxin genome (black)—infect a staph cell.

2. The cassettes integrate with the bacterium’s genetic material.

3. The result is a strain of toxic CA-MRSA.
microscopic, one-celled staph bacteria that penicillin targeted can reproduce in less than 30 minutes; in 24 hours, a single bacterium produces millions of descendents. Before the war was over, bacteria already were outwitting the new miracle antibiotics, with *Staphylococcus aureus* leading the pack.

Resistant strains can develop and flourish in short order through spontaneous mutations and gene swapping. Natural selection favors bacterial strains that survive an antibiotic onslaught. In the span of a single human lifetime, the medicine chest—which once could eliminate virtually any staph infection—has lost its punch. A whopping 90 percent of staph strains now are penicillin-resistant.

Bacteria haven’t made such phenomenal strides all by themselves. We humans foster antibiotic resistance every time we insist on antibiotics to treat our viral conditions, such as the common cold, where antibiotics are unnecessary. And when we do fight bacteria but don’t finish the entire antibiotic prescription, we’ve given bacteria another chance to multiply and develop stronger resistance. We also add antibiotics to animal feed, which creates resistant bacteria in and on the animals we eat.

“We’re in a precarious position,” said Kahana, who advocates more MRSA research funding. “If MRSA stops responding to vancomycin, we have very few antibiotics to use against it. Time is running out. While the nation prepares for bird flu and SARS, MRSA is here, and it’s a devastating, aggressive microorganism. MRSA may be the biggest pathogenic threat yet.”

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—Madelyn Kahana, MD, Pediatric Anesthesiologist

Research to understand antibiotic resistance is expensive and CA-MRSA research funding from the federal government has been limited, said Daum, who relies on external sponsors to support his research. “I spend one-third to one-half of my time just looking for funding,” he said. “It’s kind of like the JAMA paper: I have to convince people that what we’re doing is important.”

The CDC called for proposals to conduct MRSA research to the tune of $2 million, which is less than one percent of their total infectious disease spending; the previous pot of $3 million was divvied up among five institutions, said Daum, whose CA-MRSA research has received support from the CDC, the National Institute of Allergy and Infectious Diseases, and the Grant HealthCare Foundation. “It’s important for people to let public health officials and Congress know that you want this kind of research funded,” he said.

The threat of ever-increasing bacterial resistance to antibiotics is why doctors zealously guard powerful treatments like vancomycin. Even so, a vancomycin-resistant staph was discovered in 1997, and many more have emerged since. “These drugs are precious. They must not be abused,” said molecular geneticist Susan Boyle-Vavra, PhD, research associate (associate professor) in pediatric infectious diseases and a member of Daum’s team. A growing chorus of scientists now warns that overuse of antibiotics—from common-cold prescriptions to additives in livestock feed—may be setting the stage for bleak days reminiscent of the pre-penicillin era.

**Gene swapping**

Meanwhile Boyle-Vavra, who is married to Daum, and others in his lab are sorting out the genetics and evolutionary histories of susceptible and resistant staph strains that have sprung from hospital and community settings. Their studies are contributing to a better understanding of how pathogens adapt to a world filled with antibiotics.

Boyle-Vavra led the team that identified genetic differences among CA-MRSA strains and verified that both resistance and virulence
A staph vaccine would put an end to flesh-eating infections like the one that kept Jewaun in a medically induced coma for two months.

Jewaun was still struggling for his life as Thanksgiving came and went. Just days before Christmas the doctors gave Love the sobering news that her son's condition was grave and that they had done all they could for him. "I ran to the chapel, fell on my knees and prayed and prayed," Love said. "When I came back, the doctors said things were looking a little better," she said. "It seemed God answered my prayer. On Christmas, Jewaun woke up and fully opened his eyes for the first time."

Within days, Jewaun was able to swap the feeding tubes that had nourished him since October for his mom's fried chicken. By the time his ninth birthday rolled around, he was breathing on his own and he was progressing well enough to transfer to a residential rehabilitation facility. There he began practicing how to walk and talk. He also began playing video games and catching up on his schoolwork. At his birthday celebration on Jan. 31, 2006, he saw his 6-year-old sister, Kayla, for the first time since October.

Five months after falling off his bike and scraping his leg, Jewaun moved back home in March to resume the life of a normal 9-year-old. "He was on the severe end of things," Daum said, "and we never, never thought he was going to pull through it. He's a miracle boy."

A staph vaccine?

While antibiotics are an important defense against staph infections, Daum is beginning to think they're no longer enough. "We have the right antibiotics and kids get sick and die anyway," he said. "We’ve never thought a vaccine against staph is something that everybody should have. But I’m changing my mind. This epidemic suggests that we ought to have something to protect everybody."

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