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I am delighted to have this opportunity to communicate information regarding epidemic community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) disease that we are experiencing in Chicago and most locales in the United States.

My presentation today includes two recent articles that I hope will be helpful. The first is called "Community-Associated Methicillin-Resistant *Staphylococcus aureus*," by Susan E Crawford, Susan Boyle-Vavra and myself. The second is entitled "Skin and Soft Tissue Infections Caused by Methicillin-Resistant *Staphylococcus aureus*." My hope is that these two recent review articles will provide helpful background material. In this document, I would like to highlight a few points representing my views and concerns regarding the current CA-MRSA.

The term methicillin-resistant *Staphylococcus aureus* refers to bacterial isolates that are resistant to all penicillin-type antibiotics and cephalosporin antibiotics that are currently available. The term methicillin resistant *Staphylococcus aureus* isolates, or MRSA, has persisted despite the fact that methicillin is no longer used clinically. When methicillin was introduced into clinical practice in the early 1960s, some MRSA isolates were noted almost immediately. Over the next several decades, their prevalence slowly increased. It

wasn't until the mid 1970s that these MRSA infections were recognized in the United States. Previous reports had emanated from Western Europe and Australia.

Even after their recognition in the United States, MRSA isolates remained confined to the health care environment – almost exclusively. Thus, if you were a patient who frequented such environments because, for example, you had a chronic illness or the need for recurrent medical attention, you were at risk for acquiring MRSA. Healthy persons in the community who did not frequent such environments generally did not encounter MRSA.

The situation changed in the mid-1990s with the detection of MRSA infections in the community. People who had not had contact with the health care system began presenting with MRSA infections, often sick enough to require hospitalization. What was apparent, almost immediately, was that the MRSA bacteria isolated from these "health care risk free" patients in the community appeared to be different from the MRSA bacteria found in the health care environment. That is to say, the *Staphylococcus aureus* bacterial strains were different. The differences included susceptibility to most antibiotics besides penicillin and cephalosporins. In contrast to the hospital-associated strains, the community strains were usually susceptible to non-penicillin, non-cephalosporin antibiotics, whereas the hospital strains were commonly resistant to them. Moreover, molecular typing of these so-called community isolates revealed that the community-associated strains of MRSA affecting healthy people in the community were not the hospital strains simply migrating into the community (although that has also occurred to some extent), but rather the development of novel strains that have arisen *de novo*. This is

a crucial point that many people trying to understand the CA-MRSA epidemic have not yet grasped.

Thus, so-called health care-associated MRSA strains and community-associated strains are only distant cousins to each other and exhibit susceptibility to different antibiotics. For example, CA-MRSA strains are more susceptible to clindamycin and less resistant to multiple non-penicillin, non-cephalosporin antibiotics than healthcare-associated MRSA. Another distinguishing feature of these community MRSA isolates is a high prevalence of genes encoding a toxin called the Panton Valentine leukocidin or PVL. This toxin is present in nearly all community-associated MRSA strains and very few (less than 5 percent) of hospital-associated MRSA strains. The role of PVL in causing the community MRSA disease is controversial and is the subject of ongoing research. Additionally, the community strains contain novel DNA cassettes, or pieces of DNA that insert themselves into the bacterial chromosome, that express the methcillin resistant phenotype. These DNA cassettes are small and presumably promiscuous. That is to say, they spread from strain to strain relatively easily and have been identified for the first time in community strains. Hospital MRSA strains contained similar cassettes but they are much larger in size and presumably less able to move from strain to strain.

Reports have suggested that these new community MRSA strains are easily transmissible in settings where people are in close contact. For example, multiple members in the household are frequently plagued by skin and soft tissue infections. Other examples of close contact situations include daycare centers, military institutions, correctional

facilities, and athletic facilities. Before the community MRSA epidemic began, such evidence of contagion among close contacts was infrequent. Other groups that have been reported to be at increased frequency for community MRSA infections include Native Americans, Pacific Islanders and men who have sex with men. Careful epidemiology needs to be done to demonstrate whether reporting of outbreaks or clusters of cases in these groups truly represents high risk or reporting artifacts.

Individual institutions have similarly reported large increases in the occurrence community-associated MRSA infections. In particular, at Driscoll Children's Hospital in Corpus Christi, the number of MRSA infections increased from 9 per year in 1999 to 459 per year in 2003. Similar increases have been documented at Texas Children's Hospital in Houston. In most US cities, community-associated MRSA is the most common pathogen isolated from skin and soft tissue infections presenting to Emergency Rooms, although, curiously, the epidemic has not still yet spread to all regions of the United States. It is noteworthy that CA-MRSA not only stays in the locales it invades, but spreads to new locales daily.

The most common manifestation of community-associated MRSA infections is asymptomatic colonization, usually of the nose, throat and, occasionally, of the skin. Several studies have suggested that the incidence of such asymptomatic colonization is increasing both in children and adults. Rates approaching 10 percent have been documented among healthy children in Nashville and among adolescents and adults in Atlanta.

Among patients with clinical disease, skin and soft tissue infections (SSTIs) represent the most frequent disease syndrome. SSTIs probably account for 75 – 80 percent of individuals who become ill with community MRSA. Interestingly, SSTIs often resemble the bite of a spider although these lesions are found persons that live in areas where the species of spiders do not produce bite like this. The reason these lesions look like spider bites is not clear, although some have attributed it to the PVL toxin, which is locally dermonecrotic (kills the skin), described above.

A number of new, or at least more severe, community MRSA infections have also accompanied the advent of invasive CA-MRSA disease. In particular, an aggressive form of pneumonia called necrotizing pneumonia has been documented and is a cause of morbidity, the need for intensive care, and severe lung infections. The term necrotizing refers to an infection that actually destroys part of the lung that it is infecting. In addition, necrotizing fasciitis, a disease that requires immediate surgical removal of dead tissue as well as antibiotic therapy, has been described with community-associated MRSA infections. A novel clinical syndrome called septic phlebitis (infection of the vein) with pulmonary embolization has occurred particularly in large veins in the pelvis and particularly among adolescents. This severe infection often presents with fever and a limp. It is frequently misdiagnosed. It requires admission to the hospital and often to intensive care units. Patients with this “pelvic syndrome” often have the need for frequent visits to the operating room to evacuate pus from the pelvic region. They often have infections of the pelvic bones and joints such as the hip joint. The most severe of the

CA-MRSA syndromes is called severe sepsis, sometimes with purpura fulminans, an aggressive hemorrhagic skin rash and the Waterhouse Friderichsen Syndrome or hemorrhage into the adrenal glands, often a fatal event.

The advent of epidemic CA-MRSA has posed a number of emergent issues. First, it has changed the paradigm of medical practice. No more can clinicians pull a ß-lactam (penicillin or cephalosporin) off the shelf with confidence that it will reliably treat a patient seeking urgent care for a skin and soft tissue infection. Practitioners have been forced to resort to old drugs with minimal track records in the therapy of any *S. aureus* infection such as clindamycin or trimethoprim/sulfamethoxazole (TMP/SMX, Bactrim or Septra). It is not known how well these compounds actually work in the therapy of CA-MRSA disease. The National Institutes of Health has come to the rescue, funding two large trials to evaluate these agents, scheduled to begin in mid-2008. Linezolid has emerged as a new alternative but is very expensive. Resistance has already become a clinical issue, especially for clindamycin and linezolid.

For patients ill enough to require hospitalization, there are also new problems and ominous black clouds on the horizon. Vancomycin, long the antibiotic of last resort reserved for hospitalized patients with MRSA infections, has begun to undergo serious erosion. Frank resistance has emerged and is a growing concern. Moreover, a phenomenon called MIC creep has emerged whereby *S. aureus* isolates have become steadily and globally less susceptible to this crucial antibiotic. There are, to be sure, several so-called beyond vancomycin compounds. They are few in number and all have

problems. For example, the newly licensed daptomycin has not been evaluated in children. Higher doses have been associated with increased toxicity in adults. The drug is ineffective in pneumonia, a common *S. aureus* syndrome. Worse, resistance occurs frequently during therapy. Tigecycline has a very broad antibacterial spectrum, too broad for treating solely CA-MRSA infections. It is also not suitable for therapy of children because it is a cousin to tetracycline and can stain bones and teeth. **We need new antibiotics.**

In some instances, technology and the drive to "do something" has outstripped our ability to construct paradigms to deal with new tests. For example, it is now possible to detect MRSA on a swab placed into the nostril to identify carriers. The problem here is simple. We have no data on the meaning of such detection. Is the person at risk for disease? Is the person at risk to spread MRSA to others? How should we deal with the anxiety that identification of such carriers creates? I receive emails from people identified as carriers who ask me what it means that they carry MRSA and if they should take action. We do not have an effective strategy to eliminate carriage. Nor do we know if it is even necessary. The State of Illinois has responded to the presence of this test by enacting legislation requiring screening and isolation of all patients admitted to ICUs. While at first glance, this may sound like a helpful strategy, it is an expensive program that is likely, at best, to effect a modest reduction in ICU transmission of MRSA. It offers multiple downsides; it is expensive, it provides false reassurance that it will diminish the overall burden of MRSA disease, and it creates a new cohort of anxious individuals who may (or may not) be carriers with no real strategy to change their carrier status.

**Expanding screening programs with our present state of knowledge is not the way to proceed!**

A recent paper from the public health sector published in the JAMA calls attention to rates of invasive MRSA disease in the ABC surveillance network much higher than had been believed. Most of these infections had their onset in the community. There are several crucial inferences from the ABC network data. First, invasive infections and the mortality caused by them is only the tip of the iceberg. If these rates reflect the burden of invasive MRSA disease, one has to suppose that the incidence of MRSA disease prompting medical attention is an order of magnitude higher. **Invasive MRSA infections in general, and CA-MRSA in particular, constitute an enormous and pressing public health problem.**

The ABC data have been widely interpreted as a wake-up call for better prevention and reporting of MRSA infections in hospitals. One can hardly counter this. There are too many nosocomial infections and we tolerate them far too much. However, the epidemiology of MRSA has changed. The hospital is no longer the epicenter. The focus has moved to the community. The ABC network data tell us this: **about 2/3 of the invasive disease detected by this network had an onset in the community.**

What are the lessons we have learned from the aggregate and growing literature on our ongoing epidemic of CA-MRSA disease in the United States? First, CA-MRSA is the epidemic now. The CDC authors and JAMA editorialist Dr. Elizabeth Bancroft conclude

that this is an enormous public health burden. We must act. We need to create resources to fill in the multiple information gaps created largely by the continuing focus on MRSA in hospitals instead of MRSA in the community. We need to immediately institute a multi-pronged program to provide the missing information. We must answer the following questions regarding the epidemiology of CA-MRSA: Who is at risk? How do the novel organisms responsible for much of the community disease spread? Which interventions work and which do not work? Is there an important role for inanimate objects (fomite transmission) such as athletic equipment, towels, linens, etc, that helps to account for high rates of transmission on athletic teams, in households, and in jails? **We need an enhanced CDC effort to answer these questions and to help us define MRSA in the community, study its new epidemiology and find methods to control it.**

The NIH is the public institute that clearly sets our research agenda. We require their support in helping us build targeted research programs that address the following lengthy list of questions: What do the novel CA-MRSA isolates have that make them such effective pathogens? Which of their genes is the "new" virulence determinant (s)? What is the role of the ubiquitous PVL genes? Are they virulence determinants or are they markers for something else that is? What is the best method for treating MRSA infections? Which antibiotic is best for managing skin and soft tissue infections in outpatients? Which parenteral drugs are best for in-patients? What is the best way to foster the development, identification and deployment of new antibiotics? How do the antibiotics we have now actually work? How do bacteria strategize to become resistant to antibiotics and what can we learn about watching how they do this? Our current system is

not serving us optimally; the identification of new targets for antimicrobials has drastically slowed. What is the best formula to re-energize this process? There are no easy answers for this area. I suggest a blue ribbon panel consisting of industry, academic experts, and public health experts to survey the state of the art of antibiotic development and devise strategies to assist the ailing process.

There are more questions to be answered. How do human beings become immune to *S. aureus* infections? Some have suggested that immunity is sufficiently poor and that the recurrence rates of MRSA disease are unacceptably high. Why is this? How can it be overcome? These basic questions will also require an NIH initiative. We need new programs targeted at understanding how a common commensal pathogen, *S. aureus,* is able to fly under the radar and elude our immune system all too often.

Finally, as a pediatrician, I recognize MRSA as a disease that is more and more difficult to treat with increasing rates of invasive disease; my thoughts turn to the development of a vaccine. The idea that a universal vaccine directed against *S. aureus* would be a useful strategy to prevent invasive disease has been belied by the belief that the general population is not at high risk for invasive infections. The ABC surveillance data change that. The rates of disease described by the public health sector authors in the JAMA article are among the highest for any invasive bacterial infection for which the general population is at risk. Vaccine development must therefore be considered a priority, and a directed program should be initiated by the NIH to foster vaccine development investigative groups in both industry and academic institutions.

I hope these perspectives are helpful. MRSA is only one of many antimicrobial resistant infections plaguing our population. Multiply resistant Acinetobacter and extended spectrum ß-lactamases also require our attention. At this time they largely remain confined to the hospital, but cause too many complications in patients, particularly those requiring intensive care. The Infectious Diseases Society of America (IDSA) has an Antibiotic Resistance Working Group (of which I am a member) that is working with several congressional groups, including the sponsors of the STARR legislation, and a new initiative from Senator Durbin's office to foster the needed global attack on these problems. More needs to be done. The CA-MRSA epidemic truly requires an intense new effort to achieve control and elimination. We owe our children and adults nothing less. Thank you.