Methicillin-Resistant Staphylococcus aureus (MRSA)
Guidance to Patients with Primary Immune Deficiencies

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Lay Language Discussion

Background

Methicillin-resistant Staphylococcus aureus bacteria, often referred to as MRSA, has become a significant infection problem both in hospitals and in the general community. It is a type of staph that is resistant to methicillin and other commonly used antibiotics in the same class, including penicillin, amoxicillin, and oxacillin. While MRSA is of concern to everyone, patients with a variety of primary immune deficiencies (PID) may be at increased risk for at least three important reasons. First, depending on the kind of PID, some patients may be less capable of defending against infection with either regular Staphylococcus aureus (S. aureus) or with MRSA. Second, patients with PID in frequent contact with hospitals and other general health care institutions may have a somewhat increased risk of coming in contact with other individuals who are carriers of, or infected with, S. aureus including the MRSA variety. Third, patients with some forms of PID may have eczema or other skin conditions which enhance the tendency to become colonized with S. aureus including the MRSA variety

Understanding MRSA

To understand the significance of MRSA, it is necessary to know some general information about all S. aureus. Regular everyday S. aureus has been a cause of severe infections in humans for thousands of years. It is a very ancient and durable human pathogen. Even in the antibiotic era of 1950’s to the present, S. aureus has remained a problem and a concern despite the increasing availability of many types of antibiotics that can effectively kill this bacterium. It is important to know that it is very common; in fact, it is the rare person who has not had a S. aureus boil or other infection. It is not unusual for perfectly healthy people to be colonized in their nose with S. aureus. These people comprise the most common source of the bacteria (including the MRSA varieties) in the community. S. aureus, including MRSA varieties, can survive and infect through inanimate damp objects such as dirty towels and shared sports equipment. However, it is most effectively and commonly spread though direct hand and other skin contact with these carriers, as well as by individuals who have actual infections.
The first isolated examples of MRSA were found in hospitals where they caused infections only in very debilitated surgical or hemodialysis patients. It was initially thought that these early hospital-associated MRSA strains were both antibiotic resistant and particularly infectious. However, studies in the past few years indicate that it is actually the community-associated MRSA strains, capable of easily infecting healthy individuals that are more infectious. These community-associated (CA) MRSA strains are very infectious and tissue destructive. They cause outbreaks in the general community of healthy individuals in schools, sports teams, gymnasiums and other settings where there is close physical contact. These CA-MRSA strains actually are genetically distinct from the strains causing infections in debilitated hospitalized patients, and appear to have unique genetic factors that allow them to more effectively infect, spread and cause injury in people with perfectly normal immune systems. This ability to easily infect, spread in the body and cause tissue damage is what is meant by saying an organism is more virulent. It is this greater virulence of these CA- MRSA strains that is the major problem causing the current epidemics and severe infections among otherwise healthy individuals. The antibiotic resistance makes it harder to treat and adds to a high level of anxiety, However, it is not the only concern and is not the main reason that CA-MRSA infections has caused epidemics in the schools, among sports teams, and in long term care institutions.

Guidance for Patients with Primary Immune Deficiencies (PID)

The concern about CA-MRSA in schools, day care centers, sports teams, and health care institutions affects everyone and not just patients with PID. In addition, health care institutions are experiencing problems not just with MRSA but with resistant and virulent strains of a number of other types of bacteria. This has led to increased diligence of hospital epidemiologists in isolating patients with suspect infections and increased training of physicians to be thinking about and recognizing potential problem bacterial infections. Recognition and treatment of health-care workers who may themselves be carriers of resistant bacteria has been improved, and training of physicians to liberally use germicidal hand washes and vigorous hand washing with soap and water has been amplified.

Even for the general populace, early attention to boils and other skin infections, use of germicidal lotions, and frequent hand washing can do much to reduce the spread of S. aureus including MRSA strains. At schools and day care centers, and with sports teams, the sharing of personal items of clothing or equipment should be discouraged. Germicidal hand lotions should be available and encouraged, as should hand washing. Very hot water cycles and bleach should be used in the laundering of any shared towels or similar items.

In busy, active institutions such as schools, it is neither practical, nor cost effective to have janitors disinfect doorknobs or multiple user desks though out the day. However, showers and sports changing areas are special places where frequent attention to cleanup and use of diluted bleach or other disinfectant may help reduce spread of MRSA. Institutions should make antiseptic cleanser gels more available in a variety of locations so that students use them routinely. Sinks should have pump soaps and not bar soaps available for hand washing. In general S. aureus is spread by contact-- it does not come from the floor or on dust to infect someone, but rather is spread through direct contact. It is usually contracted by hand contact, such as touching an infected individual or coming in contact with their personal items that they have recently used.

Patients with PID (depending upon the specific type of PID) may be less capable of defending against infection with S. aureus including the MRSA strains. They may also have frequent contact with hospitals and other general health care institutions where they may be at increased
risk of coming in contact with other individuals who are carriers of, or infected with, \textit{S. aureus} including the MRSA varieties. Patients with PID who have eczema or other skin conditions causing breaks allow for enhanced colonization and infection with \textit{S. aureus} including the MRSA varieties. Nasal or skin carriage with \textit{S. aureus} including MRSA varieties is so common in the general populations that generally it is impractical to do routine testing and treatment for carriers. However, in the case of patients with PID, particularly patients who are thought by their physicians to have a type of PID or associated skin condition that makes them more at risk from \textit{S. aureus}, it may be cost effective to periodically test the patient for carriage. For young children with PID, it may even be reasonable to periodically test their primary care givers to see if they are carriers of \textit{S. aureus} because of the frequent intimate contact between caregiver and child with PID. There are no studies that provide clear guidance with respect to this, but with some types of PID relationships have been observed between carriage and later infection with the same organism. Thus, treatment of or prevention of nasal carriage by use of nasal application of mupirocin ointment may be reasonable in some cases. On a case by case basis that must be determined by the patient’s physician, it may be reasonable to consider treatment to try to eradicate \textit{S. aureus} carriage in a PID patient or young child PID patient’s primary caregiver.

The parents of some children with PID have become concerned about even sending their children to school at all because of the new anxiety raised by the CA-MRSA epidemic. This is a complex decision that does not lend itself to a simple answer that will cover every situation. It should be emphasized that most children with a primary immunodeficiency disease are able to attend school safely. The exposure risk for all pathogens, not just CA-MRSA, is somewhat greater for children attending school than those who are home schooled and who also avoid all other contacts with groups of children. In some unusual special instances, home schooling, homebound and even dual enrollment options may be viable alternatives. However the social, psychological and learning benefits to the child enrolled in a general school environment must remain an important part of the equation when considering one’s options. The child’s physician can help in making this decision, but as a general rule, if children have no restrictions on being in public places, such as movies, malls, and airplanes, they should be able to safely attend school. If it has been determined that school is ordinarily a safe environment for a specific patient, it is usually not advisable to stop schooling because of the current CA-MRSA epidemic, but rather to take the additional precautions outlined above and continue to attend school. The option of requesting that the child be excused from participating in physical education (PE) classes might be considered depending on the type of activities scheduled for those classes.

\textbf{Scientific Language with References about MRSA}

\textit{S. aureus} is the most frequent etiologic agent causing bloodstream, skin / soft tissue, and lower respiratory tract infections in the U.S., Canada, Latin America, Western Pacific, and Europe in a reviewed two year period from 1997-1999 (Diekema et al., \textit{Clin Infect Dis}, 2001, 32:S114). Remember that this data precedes the current epidemic of community-associated MRSA, emphasizing that it is \textit{S. aureus} in general that is a problem, with the MRSA variety raising the additional issues that include the problem of antibiotic resistance. Otherwise healthy people who are colonized (mostly in the nose) with \textit{S. aureus} are a source of the bacteria (including the MRSA varieties) in the community. In fact, a recent study demonstrated that approximately 20\% of individuals in the general population are persistent \textit{S. aureus} nasal carriers, 30\% are intermittent carriers, and 50\% non-carriers (Wertheim et al., \textit{Lancet Infect Dis}, 2005, 5:751).
It is important to appreciate the distinction between virulence and antibiotic resistance. Much of the confusion in the general community and even by some physicians regarding understanding of MRSA arises from failure to appreciate that the virulence and antibiotic resistance characteristics of the bacteria are entirely separate traits that may differ significantly in different strains of *S. aureus*, including the MRSA varieties. Virulence refers to the ability of the bacteria to infect, to spread in the patient and to cause tissue damage. Antibiotic resistance with respect to MRSA refers to resistance to methicillin, oxacillin and some other related antibiotics that previously were very effective against regular *S. aureus*. Many healthcare-associated MRSA strains are multi-drug resistant, i.e., resistant to methicillin and a wide range of antibiotics unrelated to methicillin, including aminoglycosides, tetracycline, bleomycin, erythromycin and spectinomycin (Kuroda et al., *Lancet*. 2001, 357:1225 and Holden et al., *Proc Natl Acad Sci USA*. 2004, 101:9786). Although this is a problem for treatment, there still are several types of intravenous and oral antibiotics available that effectively can treat MRSA strains (vancomycin and linezolid, for example), but the bacteria’s MRSA characteristic must be identified so a physician may choose the appropriate antibiotic. The best way to describe the situation is that among regular *S. aureus* bacteria and among the MRSA strains there are varieties that are modestly infectious, and epidemic strains that are highly virulent tending to be easily spread to others and causing severe infections even in otherwise healthy individuals.

To summarize this important background and provide published references, these are the key points relating to healthcare-associated MRSA and community-associated MRSA:

**Features of healthcare-associated *S. aureus* infections (these are now primarily MRSA)**

Healthcare-associated *S. aureus* infections occur typically in individuals with risk factors for disease (e.g., surgery, hemodialysis).

Methicillin resistance *per se* is not associated with virulence—it is a problem for treatment. Clinically, MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA) are indistinguishable (Miller et al., *Clin Infect Dis*, 2007, 44:471; Zahar et al., *Clin Infect Dis*, 2005, 41:1224). However, earlier reports did appear to link MRSA in hospitals with higher death rates (Melzer et al., *Clin Infect Dis*, 2003, 37:1453-60).

The proportion of *S. aureus* isolates that were MRSA in intensive care units (ICUs) increased from 35.9% in 1992 to 64.4% in 2003 (Klevens et al., *Clin Infect Dis*, 2006, 42:389).

Hospital-associated infections are predominantly caused by strains designated by the genetic types known as USA100 & USA200 (MRSA252) (McDougal et al., *J Clin Microbiol*, 2003, 41: 5113). More recently another genetic strain known as USA300 has moved into hospitals from the community, and it has blurred the line of distinction between “healthcare-associated” and community-associated because as will be noted below it is actually a strain that has the high virulence characteristic of community-associated MRSA (see below).

U.S. economic burden in hospitals in 2003 was $14.5 billion (Noskin et al., *Clin Infect Dis*, 2007, 45:1132)

Incidence rate of all invasive MRSA infections is 31.3 per 100,000 persons. Approximately 20% (estimated 18,650 deaths out of 94,360 invasive infections) caused death (Klevens et al., *JAMA*, 2007, 298:1763)
Features of the recent community-associated (CA) methicillin resistant *S. aureus* infections (CA-MRSA)

The first notable recognition of CA-MRSA in the U.S. was four pediatric deaths in the Midwest (CDC, JAMA, 1999, 282:1123) caused by a strain known as MW2 (pulsed-field gel electrophoresis type [PFGE] USA400).

CA-MRSA is partly defined by the fact that it causes disease in otherwise healthy individuals in the community, and includes areas in which individuals are in close physical proximity (schools, daycare, athletic teams, prisons, etc).

Infections with CA-MRSA are predominantly skin and soft tissue infections (~75%), but invasive disease when it occurs is severe and can lead to death. For example, CA-MRSA can cause necrotizing fasciitis (a type of “flesh eating” destruction of tissues) (Miller et al., *NEJM*, 2005, 352:14) or Waterhouse-Friderichsen Syndrome (a type of widespread shock and bleeding) (Adem et al., *NEJM*, 2005, 353:12).

The most prevalent CA-MRSA genotypes are PFGE USA400 and USA300 (McDougal et al., *J Clin Microbiol*, 2003, 41: 5113). USA300 isolates now account for most of the community infections, up to 98% of all CA-MRSA infections (King et al., *Ann Intern Med*, 2006, 144:309 and Moran et al., *NEJM*, 2006, 355:7), and is the leading current cause of infections among patients coming in to emergency departments (Moran et al., *NEJM*, 2006, 355:7). As previously noted above this USA300 strain now has also appeared in hospitals, blurring the distinction between CA-MRSA and hospital-associated MRSA. It is more accurate and informative to refer to the specific strain/isolate causing the infection.

Epidemic CA-MRSA strains USA300 and USA400 are highly virulent and typically have enhanced virulence (ability to infect and cause tissue destruction) compared with the prominent original hospital strains of MRSA (Voyich et al., *J Immunol*, 2005, 175:3907).

The enhanced ability of CA-MRSA strains to circumvent killing by human blood neutrophils (by causing destruction of the blood neutrophils) is linked to the enhanced virulence of CA-MRSA (Voyich et al., *J Immunol*, 2005, 175:3907). It previously was thought that a protein produced by CA-MRSA called Panton-Valentine leukocidin (PVL) was the cause of their high virulence, but it now appears not to be the cause of their high virulence (Voyich et al., *J Infect Dis*, 2006, 194:1761). Instead it appears that CA-MRSA produce small peptides that cause human blood neutrophils to burst open (a process call cell lysis), thereby explaining why CA-MRSA are so good at evading normal immune defenses and causing such severe infections and epidemics (Wang et al., *Nat. Med.*, Nov 11, 2007, electronic publication ahead of print).