CHAPTER 11

Methicillin Resistant Staphylococcus Aureus

Prior to this third edition of the Handbook, methicillin resistant *Staphylococcus aureus*, or MRSA, was covered in the chapter on bacterial microorganisms. When the first edition was published in 1990, MRSA was still a primarily nosocomial organism which rarely was found in lower extremity infections. By the time the second edition was published in 2003 (written during 2002), the current "epidemic" of MRSA including the differentiation of then titled "community acquired" or CA, and "hospital acquired" or HA strains, was becoming better appreciated. MRSA was being found in patients with none of the traditional risk factors, but it was still a bit of a novelty. Now, the epidemic is in full swing. Some hospital's antibiograms show over 70 percent of their *Staph* isolates MRSA. Nomenclature has evolved. Numerous new drugs have been released with even more in the pipeline. The most remarkable evidence of how pervasive MRSA has become is the saturation of the topic in the popular media. No matter where in the United States you live, the local evening news station has had a story of some local high school athlete being diagnosed with MRSA, replete with video of the school's custodians disinfecting all of the surfaces before the school could re-open. Inevitably there would be a local physician or health department "talking head" explaining why MRSA is so dangerous, and what to look for in you or your child. Much of the information, although technically accurate, is presented to have the greatest broadcast impact. In fact, when one of the oldest, highest rated Sunday evening new programs presented a lead story on MRSA, at one point the reporter looked directly into the camera, and in a very

serious tone, related that "This MRSA is *even resistant to penicillin*!" Not since the "flesh eating bacteria" media blitz of earlier in this decade has a "superbug" received so much popular press notoriety.

None of this introduction is meant to impugn the importance of MRSA. It is a fact of life, and must be dealt with appropriately, and aggressively. It has the potential to devastate the patient with a lower extremity infection as a result of various toxins, and virulence factors that it can express. Furthermore, the organism is evolving, spreading rapidly, and becoming more challenging to treat.

HISTORY OF STAPH

To appreciate how staphylococcal disease has evolved since the beginning of time, it is important to understand a bit about the natural history of the organism. There has been an endless back and forth battle between *Staph*, and the doctors trying to fight it. To understand this, it is necessary to go way back in time…

1. In the beginning there was *Staphylococcus*, and it had it good. Before the beginning of the antibiotic era in the late 1930s to early 1940s, infectious diseases were the greatest cause of mortality. Patients who developed *Staph* skin and skin structure infections frequently died from them. This was especially true during war time. Many readers will remember watching old war movies where the medic sprinkled "sulfa powder" or poured alcohol on the soldiers' gunshot wounds in an attempt to ward off infection. There wasn't much else that could be done. If one were to keep score it would be…*Staph* = 1, Docs = 0
2. Alexander Fleming probably did not realize that he was about to begin the modern antibiotic era in 1928 when he made the serendipitous discovery that if the mold *Penicillium* grew on a culture plate of *Staph*, it had the ability to kill the organism. He concluded that some factor in the mold, "penicillin," had antibacterial activity, but he was unable to develop the drug. Although Fleming is given much of the credit for the discovery of penicillin, the actual development and testing of the drug in human subjects is credited to Howard Florey and Ernst Chain at Oxford 10 years later. The three eventually shared the Nobel Prize. Large scale production ramped up in time for the later stages of World War II. Even then, there was rarely enough to meet demand. Patients would be given penicillin, and their urine collected and dried to retrieve crystals of the drug so it could be re-injected. *Staph* had met its match…*Staph* = 1, Docs = 1.

3. Throughout this book the ID truism that the organisms are always going to be smarter has been repeated, and demonstrated. This point is no better illustrated than in this history of *Staph*. It was not long after penicillin came into common usage that the *Staph* found a way to protect themselves by inactivating the drug. This was accomplished through the production of a "penicillinase," an enzyme that was released by the organism which had the ability to cleave the four member β-lactam ring of penicillin, thus rendering it inactive. *Staph* = 2, Docs = 1.
4. The scientific community realized that the organism had developed a defensive strategy to inactivate their penicillin. In order to prevent this from happening, and to once again save patients' lives, new antibiotics had to be developed which were not inactivated by the penicillinase. The first and prototypical drug of this class of "penicillinase resistant penicillins" (aka "PRPs," "semi-synthetic penicillins," or "anti-staphylococcal penicillins") was methicillin, which was released in 1959. Not currently in use because of a number of pharmacokinetic and toxicity issues, it has been replaced by other superior drugs of the class including nafcillin, oxacillin, dicloxacillin, etc. Despite its lack of clinical acceptance, the name of the drug still remains representative of the entire class. *Staph* = 2, Docs = 2.
5. When the *Staph* realized that the ingenious plan to use penicillinase to inactivate penicillin was failing thanks to the development of PRPs, a new strategy was needed. The organisms then made a genetic change in their makeup that would change the structure of the "penicillin binding protein (PBP)" on their cell wall. The PBP is a site on which the circulating antibiotic binds to the microbial cell to allow access into the cell so that the drug can express its activity. The organism actually changed the structure of what is known as PBP2, a high affinity binding site for β-lactam drugs, to a low affinity site to which the antibiotic is unable to attach. This altered site is known as PBP2a (or PBP2'). This organism, which has been chromosomally altered to have these low affinity binding sites, is what is now known as MRSA. This all occurred within one to two years of the release of methicillin! *Staph* = 3, Docs = 2.
6. From the early 1960s when MRSA was first recognized until the mid-1990s, MRSA was mostly thought of as a nosocomial organism found primarily in hospitals and nursing homes. Patients had specific risk factors to the point that infection with MRSA could almost be predicted. Some of these risk factors for MRSA included:

a. Previous antibiotic therapy within the past year
b. Recent hospitalization
c. Recent nursing home stay
d. Chronic illness
e. IV drug use

When a patient cultured MRSA, effective therapy could be started with an older antibiotic, vancomycin, first released in 1958 but little used in the early days because of fears of toxicity. As MRSA became more commonly isolated in patients not previously considered at risk, many new antibiotics were developed with efficacy against this organism. As of this writing, there are four FDA approved drugs for the treatment of complicated skin and skin structure infections caused by MRSA, with at least two close to approval, multiple unapproved but effective older agents, and new compounds in the pipeline. *Staph*= 3 Docs = 3

7. And so it goes…this one-upmanship will probably continue forever. As this is written there are *Staph* that are frankly resistant to vancomycin, and others that have increased MICs against the drug. There are, thankfully still rare, strains resistant to some of the newer antibiotics. As new drugs are developed, the bugs will find a way to resist them pushing the pharmaceutical industry to even more effective agents.

CLASSIFICATION OF MRSA

The MRSA that is being cultured today from most lower extremity infections is "not your father's MRSA." It has evolved significantly to become the pathogen it is today. Eady and Cove postulated in 2003 that MRSA probably arose from coagulase negative staph (CNS), explaining that:

1. True infecting strains are usually fairly susceptible, and easily killed by antibiotics.
2. Commensal, or community-resident strains (such as CNS), are exposed anytime a patient takes an antibiotic, eventually leading to resistance in those commensals.
3. β-lactam drugs can be delivered to the skin via sweat, thus continually bathing these resident strains in low levels of antibiotic also leading to resistance.
4. Of particular interest in the lower extremity is that fungal toe web infections may produce low levels of β-lactam antibiotics that may select out resistant organisms…leading to another reason to aggressively treat fungal infections of the foot!

By definition, all MRSA contain what is known as the "mecA gene" conferring the methicillin resistance. This gene sits on what is known as the Staphylococcal Chromosomal Cassette (SCCmec). Currently there are thought to be about seven different varieties of this SCCmec numbered I through VII. These can be roughly divided into two broad classifications by which MRSA is currently divided:

1. Healthcare Associated MRSA (HA-MRSA)
   a. Usually contains SCCmec I, II, III gene.
   b. Previously known as "hospital acquired" or "healthcare acquired."
   c. Associated with the traditional risk factors listed above, and is pretty much the organism thought about as MRSA before the mid-1990s.

2. Community Associated MRSA (CA-MRSA).
   a. Contains the SCCmec IV (most common) or V gene.
   b. Previously known as "Community Acquired."
   c. Most common synonym is the "USA300" strain.

This nomenclature is constantly changing. At the time of this writing, the above terms are the most widely accepted, but that too is bound to change as the distinction, other than genetic, blurs, and CA-MRSA takes over in clinical importance from HA-MRSA, and is found in both community and hospital settings regardless of the presence, or lack thereof, of classic risk factors.

Community Associated-MRSA

Given the prevalence, and clinical importance of this particular strain, it is necessary to examine it in more detail. How is it possible to differentiate CA from HA-MRSA? Is it clinically relevant to make the differentiation?

1. To answer the second question first…YES, it is important to differentiate these two types of MRSA. They each have unique antibiotic sensitivity patterns along with varying levels of virulence with CA-MRSA being, by far, the more dangerous organism.
2. On the surface, given the names of each, it would seem easy enough to determine which organism infects a given patient. After all, if the patient is in the healthcare setting, the infecting strain must obviously be HA-MRSA…isn't that what the name implies? Unfortunately, as discussed above, that distinction is fading, and many, if not most of the patients with lower extremity infections in the healthcare setting are infected with CA-MRSA.

3. The traditional risk factors listed above for HA-MRSA do not seem to apply to CA-MRSA transmission. Rather, some authors talk about the "Five Cs" of CA-MRSA risk:
   a. Close **C**ontact
   b. **C**rowding
   c. Lack of **C**leanliness
   d. Exposure to **C**ontaminated items
   e. **C**ompromised skin integrity
4. These are genetically distinct organisms. Diagnostic tests such as PCR and pulse gel field electrophoresis (PGFE) do exist to look specifically for genes unique to each type of MRSA. Unfortunately, most hospitals are not currently using these techniques so, until it becomes a more widely available and utilized modality of differentiating CA from HA-MRSA, it will not help the average clinician.
5. Probably the easiest and most clinically relevant way to determine one from the other is to examine the antibiotic sensitivities on the C&S report.
   a. CA-MRSA tends to be relatively susceptible to a wide range of antibiotics other than β-lactam drugs (this may change in the near future with the development of anti-MRSA cephalosporins). The SCCmec IV gene is known as a "short segment" cassette so there is little room on it for resistance genes. This is why drugs such as trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline can be effective against this organism.
   b. HA-MRSA tends to be relatively resistant to most all antibiotics other than those designed specifically to work against resistant gram-positive organisms (i.e. linezolid, vancomycin, daptomycin).

Virulence

Within Staph there appears to be a hierarchy of virulence:

1. MRSA may be more virulent than MSSA.
2. CA-MRSA is more virulent than HA-MRSA.
3. CA-MRSA is encoded to produce various toxins that cause destruction of tissue, kill white blood cells, and allow more rapid spread of the organism.
   a. **Panton Valentine Leukocidin (PVL***)* – Almost exclusively associated with CA-MRSA, and, in fact, frequently used as a genetic marker for this strain, PVL is probably the best known and studied of the virulence factors expressed by the organism. It was originally felt to be the single most important factor when

it came to causing disease, and tissue destruction. This has more recently been shown to be the case in necrotizing pneumonia but its role in skin, and skin structure infection is less certain, and probably not as critical.

b. **Cytolytic Peptides** – Wang, in late 2007, published a report of discovering a novel peptide that had the "ability to recruit, activate, and subsequently lyse human neutrophils, thus eliminating the main cellular defense against *S. aureus* infection." These may actually play a more important role in soft tissue infections than PVL.

CLINICAL PRESENTATION

Because of the virulence factors formed by CA-MRSA, this organism tends to present in skin and skin structure infections as an aggressively spreading abscess. In fact, there is a practically pathognomonic phrase patients use to describe the lesion, known particularly to emergency physicians and family medicine: "Doc…I have a *spider bite*!"

When a patient makes this statement, the important first question from the treating doctor should be "Did you see the spider?" Invariably, the patient will say that, no, it happened at night, and they woke up with it, or some such variation on this theme. As a rule of thumb:

Always assume a "spider bite" or an "insect bite" reported to you by a patient is a CA-MRSA abscess until proven otherwise!

Although an abscess is the most common presentation of a CA-MRSA infection, any clone of MRSA can cause infection in the lower extremity regardless of the presence or absence of risk factors.

1. Localized abscess (furuncles and carbuncles) – Just restating the obvious to make a point. This is the most common presentation particularly for CA strains.
2. Surgical site infection.
3. Diabetic foot infection.
4. Osteomyelitis.
5. Infected decubitus ulcerations – particularly in patients residing in long term care facilities.
6. Cellulitis – MRSA may play a role in pure cellulitis but it is more commonly caused by *streptococcus*.
7. Impetigo – Again, most commonly caused by *streptococcus* but MRSA has been implicated also.
8. Anything else – basically, any type of infection anywhere in the lower extremity could be caused by one strain or another or MRSA.