

Danica Novacic, MD
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Community Acquired MRSA Evolving Before Your Eyes

There has been a recent outbreak of Community Acquired Methicillin Resistant Staphylococcus Aureus (CA MRSA) in a variety of schools. There has been an increase in mostly skin and soft tissue infections reported but there have also been a few deaths. The media is now following this outbreak and reporting things like “MRSA kills 1/20 hospital patients that get it.” This discussion is meant to clarify some of the questions that patients will be asking with regard to themselves as well as their children.

The first death was in October this year after a noted increase in skin and soft tissue infections. He was a high school senior in Virginia. Area schools closed and were disinfected. After that, at least 7 students were reported to have MRSA in Long Island, and then 10 members of an athletic team at Iona College in New Rochelle, NY. 4 high schools in Anne Arundel County, MD also reported at least 50 cases of MRSA skin and soft tissue infection (SSTI).

Another death attributed to Community Acquired MRSA occurred in Brooklyn, New York 10/26/07. The middle school child had been treated at an area hospital for “allergy” and given Benadryl. Several days later he was noted to have lesions on his back and legs while in school and sent to the school nurse. He never made it back to class. In Kentucky, students staged a sit in demanding that their school be decontaminated after an increase in skin and soft tissue MRSA. The entire school district closed for cleaning.

The CDC follows MRSA and has formed ABCS; the Active Bacterial Core Surveillance program, a part of Emerging Infectious Diseases Network. They have been collecting data since 2001 and providing it for studies. They have also been distributing information to the public such as posters about prevention now being displayed in schools.

Basic good hygiene and cleaning frequently touched surfaces with products effective against MRSA remain the prevention recommendations.

While standard treatments with Clindamycin or Bactrim are still the well known standard, this discussion sets out to answer some clinically relevant questions that aren't already common knowledge. Patients that are positive on surveillance cultures who come into the hospital for other reasons, want to know what it means to have MRSA. Are they going to

become infected? If it's such a bad bug and it's there in their nose, why is it NOT already causing disease? And of course, will we be giving them something to eradicate it? Unfortunately, the answers to these questions are a moving target and they vary according to many variables such as the patient's risk group, local strains, and hospital factors. This discussion points out some of the issues surrounding this infection and how it's evolving. With this knowledge we may make better clinical judgments and be more informative for our patients. Also we will be better equipped to anticipate future developments as they are sure to happen.

FACTORS INFLUENCING VIRULENCE

First we need to understand the very dynamic nature of staph infection in general. It's known to cause a wide spectrum of disease. It causes everything from an abscess to food poisoning, to toxic shock syndrome. This suggests a genome rich in variable factors that can cause a wide variety of clinical appearances.

The Staphylococcus genus has an armamentarium of genes which have promoted its survival. There are proteins to promote surface adhesion, factors that inhibit phagocytosis, invasins that promote spread in tissues, biochemical properties that enhance survival in phagocytes, exotoxins, and properties that provide inherent resistance as well as acquired resistance to antimicrobials. A particular strain of staph may have any combination of these factors. This affords its great variability clinically. To have such genetic diversity the organism must be able to transfer and receive genetic material from its own genera as well as others. The transfer of genetic material in this organism is thought to occur by the methods of transformation and transduction. In transformation, a donor leaks DNA as a result of lysis, then the recipient takes up the DNA by specific receptor binding and incorporates it into its own DNA. The receiving cell must be "competent," in other words equipped with a DNA receptor and other cellular machinery to incorporate the new DNA into its own genome. In transduction, DNA is transferred from a donor to recipient via a viral carrier. A phage infecting one cell incorporates its DNA along with some of the host cells DNA, then goes on to infect other bacteria transferring the first host DNA along with it. Community acquired MRSA has been noted to contain a small plasmid which is evidence of such transfers. Being small, they are known to be more readily transferable to others. An example of this is the now familiar staphylococcal cassette chromosome MEC 4, which confers resistance to methicillin in the community strain. It's counterpart in hospital acquired strains, MEC 2 is a larger more stable genetic element and not as

readily transferable.

Other examples of survival factors are surface proteins that promote attachment to host laminin, collagen, and fibronectin, as well as binding to fibrinogen (clumping factor) which promotes attachment to blood clots in traumatized tissue. Lukocidin, like the famed Panton-Valentine Leukocidin has two component subunits which polymerize into an octomer forming a pore which inserts into host cells causing lysis. This is thought to be involved in necrosis promoting its invasion in skin and lung mucosa. PVL is found in most CA MRSA and is found in strains that cause necrotic pneumonia and skin disease. Alpha toxin is a similar substance which is secreted by some staph. It also has a subunit which oligomerizes into a pore in host cells causing their contents to leak. Protein A is a surface protein that binds IgG by their Fc region. Once bound, the IgG is in the wrong orientation and opsonization cannot take place. Exotoxins such as alpha toxin cause septic shock. While enterotoxins related to food poisoning and TSST-1 related to toxic shock are superantigens. When an antigen-presenting cell with its MHC2 and antigen in place binds a T-cell, a superantigen binds the side of the complex and its union is held tight while the T-cell is hyperstimulated releasing massive amounts of cytokines which then manifest as overwhelming shock. All these are possible in any given CA MRSA. For example a staph that causes boils and pimples might have some adhesin, some collagenase and a little coagulase. Whereas a strain that causes food poisoning might have enterotoxin genes as well.²

In addition to what genes they possess, they also have operons which regulate those genes. For example, a certain genetic element called “accessory gene regulator” agr. Agr induction results in increased expression of a regulatory RNA which modulates the production of staph virulence factors at the transcriptional and posttranscriptional level. A mutation in agr results in increased production of surface proteins and decreased production of exoproteins and thus reduced virulence.¹² Certainly there are operons that relate to modulation of PVL. This may be why some CA MRSA strains have the PVL gene but live peacefully in the nares. Perhaps then some manipulation of the operon occurs, either stimulation or a mutation causing deregulation and allowing PVL to be transcribed uncontrollably wreaking havoc in the host.

COLONIZATION AND HOW IT RELATES TO DISEASE

With regards to determining the prevalence of staph aureus in the community, most assessments are based on health care-based samples. However population-based estimates were compiled from 2001-2002

NHANES data, the National Health and Nutrition Examination Survey by Marinous and published in 2006. They determined risk factors for carriage, as well as population-based estimates of nasal carriage of MRSA for the non-institutionalized US population including children and adults. They found that an estimated 86.9 million persons (32.40% of the population) were colonized with *S aureus*. The prevalence of MRSA among *S aureus* isolates was 2.58%, for an estimated population carriage of MRSA of 0.84% or 2.2 million persons. Among individuals with *S aureus* isolates, individuals aged 65 years or older had the highest MRSA prevalence (8.28%). This was the first nationally representative assessment of carriage of *S aureus* and MRSA. Although the prevalence of MRSA was low, more than 2.2 million people carry this resistant organism. Another paper by Pan from the University of California studied troubled youth at a youth center for runaways and drug abusers. They identified them as a subgroup with higher rates of CA MRSA than the general public. They found similar numbers for carriers of staph, 27.6%. Whereas MRSA colonization was 6.2%. So it seems that in general almost one third of the population carries staph aureus in their nares. Nasal carriage in the general population is about 1% MRSA and up to 8% in high risk populations.⁵ Clearly the incidence of disease is not this high therefore it follows that in a greater portion of cases nasal carriage does not always lead to disease.

The next relevant question is how much illness is seen as a result of this increased colonization? Unfortunately, to date there has not been a prospective study to show what percentage of CA MRSA carriers in the general population eventually develop disease. Admittedly this would be a difficult study to do. We know from hospital studies that those that are colonized appear to be at the greatest risk for contracting disease. Multiple studies have shown that the relative risk of developing MRSA disease is 4-20 times in a colonized hospitalized patient. News media today is quoting that about 94,000 individuals in the US get sick from invasive MRSA (CA and HA) per year. We know that the nasal carriage rate is about 2.2 million. We could theorize that this would translate to a rate of 4% infection in colonized individuals for both HA and CA MRSA. The real figure depends on host factors such as comorbidity and immune status. Certain populations like IV drug users, the institutionalized and the elderly are more frequent carriers of CA MRSA thus their risk may be higher. It is also in this high-risk population, that the most disease seems to occur. Another consideration is that colonization is not always static with persistent colonization in only 20%, intermittent colonization in 60% and no colonization in 20%.

However, definitively nasal carriage has increased, as has skin and

soft tissue infection attributable to CA MRSA. Moran et al identified the causes of purulent skin and soft tissue infections in 11 different emergency departments in the US. The sample consisted of 422 patients presenting to the ER during August 2004. Overall 76% had staph, 59% had MRSA. This is a significant change over a decade or two ago when most of the purulent skin and soft tissue infection was MSSA. Interestingly, of the MRSA, 97% was strain USA300 (the remaining strains found were USA 1000 and 400, 2 isolates each, which also commonly cause SSTI). Also of the MRSA isolates, PVL and mec type 4 were in 98% suggesting that the strain arose in the community and quickly took control of the nasal colonization market. They also looked for genes for enterotoxins and TSST-1 which were identified in five or fewer MRSA isolates. Why didn't those few cause severe disease? Perhaps a key operon was modulating transcription of toxin genes thus not allowing it to take advantage of its toxin producing faculties. Since MRSA is now the most common identifiable cause of SSTI in the ER use of empiric Abx that cover it is indicated.⁴

This obvious increase in CA MRSA skin and soft tissue disease also correlates to an increase in invasive disease. Next we will explore this relationship. Fridkin, one of the Active Bacterial Core Surveillance program investigators (ABCs) looked into this question. They sampled 3 communities; Baltimore, Atlanta and Minnesota during 2001-2002. They got data from labs servicing the area hospitals (outpatient and inpatient) which were positive for MRSA from any body site (but not surveillance cultures). They then searched their charts for risk factors to classify them as CA or HA. They contacted and interviewed the subjects that were identified as CA to insure they didn't have any HA risk factors. Of those definitively classified as community acquired 77% caused abscesses and 6% caused invasive disease. This study included over 12,000 subjects. Most were still hospital associated, with only 17% definitively labeled as community acquired.³

Another Active Bacterial Core surveillance system study by Klevens, Fridkin et al in 2007 described the incidence of invasive MRSA in 9 US communities including Baltimore. They found 8,987 invasive MRSA cases. Most continue to be health care associated (85%), although 58.4% were hospital associated but had onset in the community. They typed the bacteria by strain and gave a break down of the kind of invasive disease. Overall showing that hospital based strains still have the lead with regards to overall clinical virulence and invasive disease. The incidence per 100,000 of US population is 31.8 for invasive MRSA disease. Of that only 4.6 per 100,000 is community acquired. The incidence of death due to invasive MRSA was

6.3 per 100,000 with only 0.5 per 100,000 due to community acquired MRSA. Baltimore city had the greatest incidence of MRSA overall with 116.7 per 100,000. The greatest rates of invasive disease were found among the elderly, and another high-risk group; African American babies were identified. The spectrum of invasive disease is broader with community acquired strains over hospital acquired strains. Bacteremia is by far the most common, followed by pneumonia and cellulitis. Whereas, health care associated MRSA is more specialized at causing bacteremia. This suggests that CA MRSA is more actively evolving than HA MRSA. This speaks to the overall increase in incidence of CA MRSA and provides more evidence that CA MRSA will be more of a problem in the future. Another explanation is that much of the hospital associated disease is in dialysis patients who are at increased risk of bacteremia due to their invasive lines. Perhaps this is caught quicker clinically and treatment initiated before the bacteria have a chance to seed and establish another site of infection. With regards to specific strains, most health care associated disease is due to the strain USA100 which causes invasive disease in a majority of cases. But there is considerable CA-MRSA that causes invasive disease as well. This study elucidates the blurring of the lines between CA and HA MRSA. USA100 traditionally hospital associated and epidemiologically arose from hospitals but it is also found in people with no known factors for HA MRSA. Likewise, USA 300 originated in the community but now can be localized to health care associated disease. It usually causes SSTI but can also cause invasive disease. The Hospital Acquired or Community Acquired designation applies more to epidemiologic discussion in that it describes where something originated. It may be more clinically relevant to distinguish the strain to predict the resistance pattern or type of disease.¹

Can we be sure that it is the same strains causing asymptomatic colonization that are causing the invasive disease? Von Eiff et al from Germany conducted a study to determine if the organisms in the bloodstream originated from the patient's own flora. Two studies were done. The first one simply identified patients with MRSA bacteremia and swabbed their nares. They found that 82% of the time the isolates were identical by pulse field gel electrophoresis. In the second study they identified patients with staph in their nares and prospectively followed them for 5 years. Of 1278 patients, 74 had MRSA (5.8%). They found that 14 patients developed bacteremia but only one of them was a MRSA isolate. The pulse field gel electrophoresis identified the same strains 85.7% of the time. Von Eiff's paper is published in the NEJM in 2001.⁶ They did not address skin and soft tissue infection but rather only bacteremia. This study raises two important

points. All staph, not just MRSA is capable of causing bacteremia, once again illustrating the point that virulence factors and antibiotic resistance are independent in the staph genome. Second, the nares are the source of infection. Yes, the same strain can exist as a benign colonizer and suddenly change into a virulent pathogen. The morphism may be due to a change in the immune status of the host, a mutation in an operon or even transfer of genetic material from unrelated bacteria. Can we extrapolate that one out of 74 patients with MRSA developed bacteremia, a rate of 1.35%? Perhaps, but as stated before this varies by host factors.

Pan et al tied colonization to disease in another study. In the Pan paper mentioned earlier, the data was from a youth center servicing homeless runaways and IV drug abusers. They tested 308 asymptomatic youths in this high risk group. 27.6% had staph in their nares and 6.2% overall had MRSA. They typed them and found USA1000 and USA300 responsible for 84% of the asymptomatic nasal colonization. Of note, these are known to be strains of community origin but many of these patients had health care exposure. At the same time they collected samples from patients at local health care facilities, typed them and compared the two groups to see whether what is seen in clinical disease relates to asymptomatic colonization. They found the same genotypes, USA 300 and 1000 to be responsible for a large percentage, 47.9%, of the CA MRSA disease in the hospital. Interestingly there was a fourth clone ST30:Z (USA1100), which accounted for 28.6% of the CA MRSA disease but this was not found in nares at all. Overall they came up with a general modus operandi for the major strains found. 1. An endemic clone which is a proficient colonizer and causes disease at a relatively stable rate over years. 2. An epidemic clone which has excellent transmissibility, rapid dissemination in the population and thus produces widespread infection. 3. An outbreak clone which is highly infectious but with poor asymptomatic transmission. USA 300 and 1000 also called ST8:C and ST59P were known to be endemic clones in San Francisco since at least 1996. They cause a stable level of disease in the community over years especially in susceptible groups. ST8:S related to USA300 is the epidemic clone. This was first identified in 2000 but already has quickly become 42% of all cases. This appears to be the evolutionarily improved progeny of the first USA300. This clone mostly causes SSTI but has also been responsible for necrotizing fasciitis and other invasive infections. It's improved transmission characteristics allowed it to take hold quickly and cause a surge of disease. The third carriage pattern is the outbreak clone ST30Z or USA1100. It has caused major outbreaks of disease but is rarely found in nares. It has poor transmissibility but is

virulent when it occurs. Even though the asymptomatic nasal carriage group and the disease groups in this study were not the same patients, they represent the same population and the correlation can be drawn between them.

Recent evidence of evolving virulence such as that of the new and improved USA300 was seen in 8/05 when an 18 year old woman presented with malaise, diarrhea, vomiting then collapse. She was treated with broad spectrum antibiotics and recovered. Cultures grew MRSA. She had no risk factors for hospital acquisition. The isolate carried enterotoxin genes G and I.¹⁰ Also in 5/05 Miller et al published in NEJM necrotizing fasciitis caused by CA MRSA in 14 patients.¹¹

There were many papers from around the world studying this epidemic. The big picture is that CA MRSA continues to evolve, continually improving its ability to colonize and cause disease. In turn, disease is increasing everywhere as well but overall remains more prevalent a problem in high-risk populations.

Where does our institution stand? The VA and UMMS have followed the above worldwide trend. In fact the prevalence in Baltimore is continually the highest quoted in terms of hospital and community acquired MRSA. Surveillance activities UMMS are stratified by whether the culture was obtained after 48 hours as an inpatient (hospital acquired) or whether they were obtained as an outpatient (community acquired) or during the first 48 hours of an inpatient admission. Hospital acquired MRSA seems to be stable if not decreased whereas community acquired disease continues to rise. Outpatient cultures for MRSA have been on the rise from the ER since 2004. Per our ER data, most of these patients, did not have the usual risk factors for HA MRSA. Overall they are seeing more purulent skin infections. This correlates with the rise of the USA300 clone in our community as well.

ERADICATION

Given the above discussion, should we be making a greater effort to eradicate CA MRSA? What are the issues surrounding this intervention? As you might guess; resistance and recurrence. The primary therapy for decolonization has been mupirocin used nasally twice a day +/- chlorhexidine wash as a skin cleanser. Jones et al studied Mupirocin resistance in patients with MRSA which had previously been reported in the context of widespread mupirocin use. They found a high rate of resistance in their SICU where there had been low levels of use. The subjects tested

were those admitted to a surgical intensive care unit. Molecular analysis of the mupirocin-resistant isolates revealed that 72.5% of isolates contained staphylococcal cassette chromosome mec II associated with HA MRSA. Of the 302 MRSA isolates available for testing, 13.2% were resistant to mupirocin. The rate of mupirocin use hospital-wide during the study period was considered low at 6.08 treatment-days per 1000 patient-days.⁹

Simor et al from Toronto studied the efficacy of colonization therapy. Treatment with topical mupirocin, chlorhexidine gluconate washes or oral rifampin and doxycycline for 7 days. Both were found to be safe and effective in eradicating MRSA colonization in hospitalized patients for at least 3 months. They used 2% chlorhexidine gluconate washes and 2% mupirocin ointment intranasally, or oral rifampin and doxycycline for 7 days, or no treatment. At 3 months of follow-up, 64 (74%) of those treated had culture results negative for MRSA, compared with 8 (32%) of those not treated. This difference remained significant at 8 months of follow-up, at which time, 54% of those treated had culture results negative. Decolonization therapy was protective with a relative risk, 0.1 Mupirocin resistance did emerge but only in 5% of follow-up isolates.⁸ The populations in these two studies were quite different and this might explain some of the difference in mupirocin resistance. They do address resistance over all but not the specific question of eradicating colonization in otherwise healthy people. However, resistance is a growing concern with mupirocin. Also as shown above the eradication may not last. Still, clearance of the bacterium during the hospital stay should decrease transmission of MRSA in the hospital as well as lower complication rates such as wound infections. Hospitals have taken different approaches based on these issues. UMMS does not routinely administer eradication whereas BWMC eradicates in surgical patients.

SUMMARY

To put the above discussion in perspective consider a MRSA timeline;

- Before the 1940s staph infections were often fatal. In the 1940s penicillin greatly reduced death rate but staph quickly became resistant.
- 1959 Methicillin was introduced and was initially effective.
- 1960s The first reports of methicillin resistance emerge but only in hospitals.
- 1981 The first reports of MRSA in injection drug users in Detroit are reported.

- 1997 4 children die of CA MRSA (no HA risk factors) in Minnesota and North Dakota.

Now...

- A new outbreak of CA MRSA is threatening schools, transmission is mostly thru sports teams. Invasive disease has occurred but mostly STTI.
- CA MRSA accounts for most purulent STTI in the ER.
- Invasive MRSA is still mostly hospital associated but is increasingly found in those with no risk factors.
- CA MRSA causes a wider spectrum of invasive disease than HA MRSA.
- USA300 is prevalent CA MRSA for now. It is found in hospitals as well, causes mostly SSTI but has also caused invasive disease.
- Baltimore is a leader in MRSA infection of both HA as well as CA.
- Eradication is still debatable, recurrence is common and resistance is developing.

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