CHAPTER **20**

COMMUNITY-ACQUIRED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

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INTRODUCTION

Community acquired Methicillin-resistant Staphylococcus aureus (CA-MRSA) has become an all too familiar infection causing pathogen in the world today. However, despite the name familiarity, it is quite different from hospital acquired *MRSA*, the organism synonymous with the name *MRSA*, genetically and in susceptibility to antimicrobial agents. The patient profile is totally different then that of the profile for hospital-acquired *MRSA* infected patients and, with that, clinical suspicion must be high in order to make the diagnosis of and deliver the proper treatment for this organism. It is the purpose of this article to familiarize the reader with the recent literature on this topic and treatment options for this very new and virulent pathogen.

DEFINITION AND PATIENT PROFILE

Probably one of the largest differences between community- and hospital-acquired *MRSA* is the type of person that is affected. This makes the need for a high index of suspicion paramount in order to readily diagnose this pathogen. In order to fully understand the clinical situation in which these organisms arise, first we must establish a working definition of community-acquired Methicillin-resistant *Staphylococcus aureus*. Herold et al described the criteria for the diagnosis as being isolates obtained within 72 hours of hospitalization.[1] However, he was looking at the infection rates within children and did not have to be concerned with other predisposing factors. Some of the predisposing factors that have been mentioned within the literature are no previous hospitalization, antimicrobial therapy within 6 months of *MRSA* infection, no history of endotracheal intubation, no underlying chronic disorder, absence of indwelling venous catheter, absence of indwelling urinary catheter, no history of injectable drug use, a patient with diabetes mellitus type I, no previous history of surgical intervention, being a man who has sex with other men, no previous diagnosis or positive culture revealing MRSA infection and presence of a known carrier or someone with a previous history of MRSA infection/colonization.[1-11]

The clinical picture is often cloudy when seeing patients with CA-MRSA for the first time. Naimi et al noted the average age of the patients with community-acquired *MRSA* as being 23 years old, although the range was 0-95 years.[9] Also within the same study he noted a predilection patients of anglo-saxon descent to be affected approximately 40 percent of the time. This was of no surprise because throughout the literature patients of anglo-saxon descent seem to be the population most afflicted by this organism.[1] Naimi et al also calculated a 53 percent rate of hospital-acquired *MRSA* cases within patients of anglo-saxon descent.[9] Interestingly he also found that the American Indian population having a high number of people affected with a rate of 17 percent with CA-*MRSA*. This was also noted and researched by Groom et al when he examined the prevalence of CA-*MRSA* in a rural American Indian community.[5] He found over the six-year study 55 percent of all *S. aureus* infection to be *MRSA* and of that 74 percent were classified as community-acquired.

Currently at Northlake Medical Center a patient must fit 3 requirements in order to be classified as having a community-acquired Methicillin-resistant *Staphylococcus aureus* infection. First, the culture revealing *MRSA* must be taken within 48 hours after hospitalization; second, the patient must have no history of *MRSA* infection and, finally, their can be no history of hospitalization, dialysis, surgery or residence in long term care facility in the past year. These are not only the criteria used at our institution but it is also the criteria that are recommended by the Centers for Disease Control and Prevention (CDC).

GENETIC COMPOSITION

The gene that is responsible for the resistance to Methicillin is encoded on the *mecA* sequence that is found on the genetic makeup of the chromosomes of the *Staphylococcus* genome. The segment of the genome in particular where one finds this gene is *(SCC)mec,* which is held on the *orfX* chromosome of the pathogen. The *mecA* gene encodes a novel penicillin binding protein, (PBP)-2a, that has a reduced affinity for ß-lactam antibiotics.[12] What normally happens is penicillin binding proteins catalyze the cross-linking between the bacterial cell wall. With this low affinity protein now in place the ß-lactam antimicrobials can not block the cell wall synthesis, which is their mechanism of action.[5,13]

There are two theories for the explanation of the origin of the first incidence of *MRSA*. The first, and least supported by literature, is one in which all of the *MRSA* strains are descendants from a common prototypic strain. The reason that this is not believed to be the case is due to the fact that genomic sequence analysis of the different *MRSA* strains shows large differences between the gene locus compositions. This is a result that does not support the theory of a common "ancestor" *MRSA* strain. This is because of the fact that one would expect the *MRSA* lineages, if they descended from a common clone, to have very similar gene loci. These genetic results favor the second theory as to the development of *MRSA* organisms that is currently believed to be the accepted theory of development of these pathogens. This theory is that independent acquisitions of the *SCCmec* gene occurred along the developmental pathway of the *S. aureus* genome.[12]

The *SCC mec* gene encodes for two recombinase genes, ccrA and ccrB, and mecA with its regulatory genes, *mecR1* and *mec1*. The *mecR1* and the *mec1* genes collectively are referred to as the type A *mec* complex. Also the genes can be expressed where the *mec1* gene is not transcribed leaving a *mecR1* gene. The *mecR1* and the *mecA* gene when put together comprise the type B *mec* complex. This allows four possible combinations for the genome of the *Staphylococci,* type I through IV. It is the type IV of the combination that is referred to as community acquired MRSA. The genetic makeup of this particular breed of pathogen has a *SCCmec* containing *mec* complex type B and *ccr* complex type 2. It is the shortest of the types of sequences consisting of only 21 kb length. This short length makes the genome very compact and easily replicable.

However, the short length works as a double edge sword for the organism. It is this length that allows for quick replications time and hence the ability to survive and compete with other pathogens outside the walls of hospitals. The reason why hospital-acquired organisms are so prevalent within long-term care facilities and hospitals is due to the decreased levels of organisms. This means that there are less organisms to compete with, thus there is a greater chance for the slower, longer replicating genomes of hospital-acquired *MRSA* to proliferate. On the other hand it limits the resistance that these organisms have against multiple antibiotics, thus changing the sensitivity/susceptibility profile of the organisms.

TREATMENT OPTIONS

The treatment for CA-*MRSA* is still the topic of much debate. The advantage to the practioner for CA-*MRSA* versus hospital-acquired MRSA is that CA-*MRSA* has susceptibility to almost all of the antimicrobials with the exception of the ß-lactam and cephalosporin classes. This is why it is of such importance to have a high index of suspicion with these patients because even the slightest delay in appropriate antimicrobial treatment can be fatal. A morbidity and mortality weekly report within the *Journal of the American Medical Association* highlighted the need for expedient diagnosis.[7] It presented four cases of pediatric death that resulted from CA-*MRSA*. The two common threads that the cases had were elevated temperature (average of 104.5, range 103-105.2) and delay in appropriate treatment. Three of the four patients were treated with a cephalosporin medication before changes in their antibiotic. The average length of time before death was 3 weeks, with a range of 1 to 5 weeks.

Although many medications can be used in the treatment of *MRSA* infection, the medications discussed here will be the ones that are focused on the most within the literature.

Vancomycin

Vancomycin has been used clinically since 1956.[11] It has been the drug of choice for hospital-acquired *MRSA* infections and yields the best results when used against gram-positive bacteria. Vancomycin is

bactericidal with its mechanism of action being inhibition of cell wall synthesis by binding to the D-alanyl-D-alanine terminus of cell wall components. Vancomycin binds to this site by the use of five hydrogen bonds thus occupying the site and not allowing the bacteria's transpeptidase to have access to the site for cross-linking. Once this occurs the integrity of the cell wall is compromised and the cell lyses. As one can see this binding to cell wall precursors shares some similarity to the ß-lactams mechanism of action and this is of concern to all who treat infectious processes.

There have been reports of Vancomycin-resistant Staphylococcus aureus strains in the literature.[2,3,12,14,15] At this time the genetic basis of the resistance is unclear but what is known is that the resistance was transferred to *S. aureus* from *enterococci*.[16] There have been studies performed on Vancomycin-intermediate resistant Staphylococcus aureus (VISA) revealing that these pathogens have thickened cell walls with decreased peptidoglycan cross-linking.[17] This allows the cell wall to still bind to the Vancomycin and, due to the increased size and strength of the cell wall, the medication can be sequestered and processed by the organism. With these VISA strains it takes more of the medications to effectively eliminate the organism. Studies have shown the minimum inhibitory concentration (MIC) of Vancomycin to be 4-8 µg/ml in VISA strains opposed to MIC of <1.5 µg/ml for Vancomycin sensitive *Staphylococcus aureus*.[11]

The incidence of Vancomycin-resistance *Staphylococcus aureus* (VRSA) is a very real problem that has been encountered clinically, although infrequently. However, it is the fear of such an organism that has spun research of new antibiotic medications and classes. Also, this has also led to some more rigid guidelines to the use of Vancomycin which are reviewed in Table 1. These guidelines should be followed for obvious reasons, i.e. organism resistance development; with one in particular being the fact that many studies have shown that ß-lactam antibiotics are more effective in the treatment of methicillin-sensitive strains of *Staphylococcus aureus* (MSSA).[12] In the treatment of endocarditis, ß-lactams antibiotics were shown to have a 90-100 percent success rate with vancomycin only being successful 73 to 93 percent of the time.[14] This data supports the fact that vancomycin should be reserved for infections that are resistant to the ß-lactam antibiotics.[11]

Clindamycin

Clindamycin is a lincosamide class medication and is grouped into a group of antibiotics called MLSB antibiotics based upon the mechanism of action of the antimicrobial. Other antibiotics that are grouped with clindamycin in this group include the macrolides and the streptogramin-B medications, i.e. Synercid. These antibiotics function by inhibiting bacterial RNA from producing protein used in the synthesis of the pathogens and their toxins. Specifically, these medications bind to the 23S ribosomal component of the RNA of bacteria. Resistance develops to these medications when organisms begin to methylate the adenosine residue located on the binding site of the 23S ribosome. This decreases the affinity of the medications for this site.

As one can see from the recent literature, CA-*MRSA* does have susceptibility to clindamycin a large portion of the time. However, susceptibility to the macrolides varies at best, with resistance being present a majority of the time. The explanation for this is the fact that most macrolides are comprised of a 14 to 15-membered rings but the larger macrolides and the lincosamides are made up of 16-member rings.[6] This causes the macrolides, like erythromycin, to be inducers of resistance within *Staphylococcus aureus*. This in turn makes the expression of MLS_B-resistance in inducible one and thus these organisms have the phenotype of "erythromycin-resistant, clindamycin-sensitive." It was this phenotype that was seen in 6 out of the 7 patients that were studied by Johnigan et al[6] with head and neck CA-*MRSA* infections. The 7th patient was of the "erythromycin-sensitive, clindamycin-sensitive" phenotype. Naimi et al[9] also alluded to the changing phenotype within CA-*MRSA* when he noted that 93 percent of CA-*MRSA* cases were clindamycin sensitive and only 64 percent of cases were sensitive to erythromycin.

The literature does support the use of oral clindamycin for the treatment of CA-*MRSA*.[4,18,19] Also when comparing vancomycin to clindamycin, one advantage that clindamycin has is the delivery to the site of infection. Vancomycin is a large molecule and does not penetrate into areas of poor blood supply as well as clindamycin has been known to. Clindamycin is concentrated in phagocytes helping its delivery to sites of infection. However, this treatment option is one that must be exercised very judicially due to the difficulty with recognizing and distinguishing CA-*MRSA* from hospital-acquired *MRSA*. Even when oral clindamycin has been used it

was only prescribed after culture and sensitivity data had been had and processed. Johnigan et al made the recommendation that even if oral clindamycin was an option of treatment he still recommended parental vancomycin in the critically ill patient due to the fact that it is the "gold standard".[6]

Fluoroquinolones

The fluoroquinolones have been discussed in the treatment of CA-*MRSA* with much of the discussion being centered on the developing resistance to the medication. The fluoroquinolones mechanism of action is the inhibition of DNA gyrase. This enzyme is responsible for the uncoiling of DNA during the replication of the genome of organisms. One of the advantages of this medication is the oral availability/bioavailability (80-95 percent).[13] This allows patients to be treated on an out-patient basis if necessary. Also moxifloxacin and trovafloxacin are processed in the liver and thus can be given to the patient with renal disease. One of the largest drawbacks is the fact that the fluoroquinolones have been shown to damage cartilage and can cause arthropathy in children.[13] Thus this medication is contraindicated in patients under the age of 18.

Resistance to this medication develops in much of the same way that resistance develops to the ß-lactam medications. One or more point mutations occur within the enzyme that is being targeted. In the case of *staphylococci,* the enzyme that is primarily targeted is topoisomerase IV with DNA gyrase being a secondary target.[13] Usually due to the mechanism in which resistance develops, the *staphylococci* must be treated previously to the medication before resistance can begin to develop. As resistance develops to one of the members of this class usually the organism is resistant to all within the class. In a recent study conducted by Isaacs et al[20] there was shown an increase in the resistance of *MRSA* to ciprofloxacin. Within a 7 month time span, it was shown that in increase from 15 (3/20) to 48 (13/27) percent of *MRSA* were resistant to ciprofloxacin.

Linezolid

This is a medication of a newer class of synthetic antimicrobials also known as the oxazlidinones. The other member of the class is Eperezolid, which is a medication used primarily in Europe. This class has a mechanism of action of inhibiting translation in protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit. Although this mechanism is similar to medications like the macrolides and clindamycin, the binding site is unique and gives this class of medication little cross-resistance with other antimicrobial agents. This is an excellent medication that works well for MRSA, as well as being effective against Vancomycin-resistant *enterococcus* and Vancomycin-intermediately-resistant *Staphylococcus aureus.* One of the benefits that this mediation has is it oral availability, 600mg po q12 hours. However, this medication is only indicated for soft tissue infections not in bone infections with *MRSA.*[21]

Antifolate agents/Rifampin

Trimethoprim and sulfamethoxazole (Bactrim) have a synergistic effect when given together and have been proven to be very effective in the battle against CA-*MRSA*. Trimethoprim inhibits dihydrofolic acid reducatse, an enzyme that catalyzes the dihydrofolic acid to tetrahydrofolic acid reaction that occurs in bacterial purine synthesis. Sulfamethoxazole is an analog of PABA and binds to dihydropterate synthase in the bacterial purine production chain. When both of these medications are given they work synergistically to halt the production of purines in the bacterial genome. This is an excellent medication that CA-*MRSA* is susceptible to almost all of the time. However, there has been trouble with the development of rapid resistance with this medication.

Rifampin is a medication that is derived from Streptomyces mediterranei and works by inhibiting RNA synthesis. More specifically it binds to the ß subunit of bacterial DNA-dependent RNA-polymerase. Resistance develops when administering this medication by itself, due to mutations that prevent the binding of Rifampin to RNA polymerase. Some of the benefits to using rifampin include the fact that there is no cross-resistance deferred to other medications and that rifampin is available orally, 300 mg po BID. One of the most noticed, but benign, adverse effects of Rifampin are the orange discoloration of body fluids.

Despite this problem their have been studies that have shown that, when used in conjunction with other antimicrobials, trimethoprim/sulfamethoxazole to be very effective oral treatment for patient with CA-*MRSA*. In a study by Frank et a,[14] it was noted that almost all of the

isolates that were cultured had susceptibility to clindamycin were also susceptible to erythromycin and trimethoprim/sulfamethoxazole. Johnigan et al[16] used Bactrim in combination with rifampin (PO) for the treatment of four of his seven patients that had CA-*MRSA* infection. Isaacs et al noted the development of resistance to ciprofloxacin in his study but also noted that susceptibilities to rifampin to be unchanged over the same period (97% susceptibility).[20]

DISCUSSION

There are many treatment options available for the patient with an infection due to community-acquired Methicillin-resistant *Staphylococcus aureus*. Proper antimicrobial coverage is paramount. This is partly based on the patient, but also the severity of infectious process that is being treated. With more severe infections, the use of Vancomycin, 1 gram every 12 hours, should be used due to it history of proven success and relatively few contraindications to use. These groups of patients are the patients that must be admitted to the hospital due to signs of systemic infection (i.e., nausea, vomiting, chills, fever, etc.) or the extent of infection.

The real challenge comes with those patients that are seen early on with this pathogen, due to the rapid progression of disease with this organism, that require treatment but do not require hospitalization or parental antibiotics. Clinical suspicion must be high and treatment must be swift in order to halt this organism's progression. In order for treatment to be effective it must not only stop the progression of the organism but also be specific to the organism that is being treated. This is where the choice of medication is so critical. Throughout the literature the combinations of Bactrim, 1 double strength tablet twice a day, and Rifampin, 300 mg twice a day, has been seen to be very effective against the CA-MRSA organism. The medications are relatively cheap, well tolerated by patients and available orally. It seems as though this combination would be the most effective for empiric therapy.

The literature also supports oral antibiotic therapy with clindamycin, 300-900 mg po every 8 hours. There is one very important fact and that is the organism must be sensitive to erythromycin as well. In the case when this is true, then oral clindamycin is a good selection of medication. If this is not true, then that means that the organism has inducible resistance and might develop resistance to clindamycin once administered. This is detrimental not only for the patient but it also breeds resistance to clindmaycin. It is for this reason that clindamycin is not recommended until after culture and sensitivies have been acquired and reviewed.

Another option for therapy is linezolid (Zyvox). This medication is excellent for resistant gram-positive organisms but is somewhat excessive for a true CA-*MRSA* infection, where other antibiotics are available. This medication is offered orally as well as intravenously at a dose of 600mg every 12 hours. The two major drawbacks are the thrombocytopenia and the price of the medication.

Community acquired Methicllin-resistant *Staphylococcus aureus* is on the rise and has become recognized due to its virulence. The organism spreads quickly and can have disastrous outcomes, if not noticed early-on in its progression. Clinical suspicion must be high and treatment quick and effective in order to contain this pathogen.

Table 1

INDICATIONS FOR VANCOMYCIN

The treatment for serious infections due to ß-lactam resistant gram-positive organisms

Treatment of infections due to gram-positive microorganisms in patient with a serious allergy to ß-lactam antimicrobial agents

Prophylaxis for major surgical procedures that involve implantation of prosthetic materials and devices

CDC recommendations[16,17]

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