

# Treatment Options for Skin and Soft Tissue Infections Caused by Methicillin-Resistant Staphylococcus Aureus

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## Abstract

Staphylococcus aureus is a pathogen responsible for common skin infections, such as impetigo, cellulitis, folliculitis, and abscess and it is the most common cause for skin and soft tissue infections (SSTI). Humans are carriers of this microorganism and are responsible for facilitating its spread around the world. Over time it has developed resistance to multiple antibiotics, such as penicillin and methicillin, which has made *S. aureus* a persistent problem in the healthcare world today. Its methicillin resistance has given it the more commonly known name methicillin-resistant *S. aureus* (MRSA). MRSA was initially discovered solely in the healthcare environment and thus became known as healthcare-associated MRSA (HA-MRSA). With time, MRSA began to affect people with no previous exposure to a healthcare facility and was therefore called community-associated MRSA (CA-MRSA). Incision and drainage are often the first and best treatment option used against SSTI caused by MRSA. Antimicrobial therapy is also employed. Vancomycin is currently the leading drug, however other antibiotics such as linezolid, daptomycin, clindamycin, and trimethoprim-sulfamethoxazole are sometimes used due to a growing number of reports of vancomycin resistance. This paper examines the different options for the treatment of SSTI caused by MRSA by comparing different antibiotics, their mechanisms of action and resistance, dosages and administration, as well as adverse effects. No definite conclusion can be made as to the best or most effective treatment option for MRSA. Rather, each reporting of SSTI caused by MRSA needs to be evaluated on a case by case basis to determine the most appropriate choice of therapy. The various aspects of MRSA and therapy choices employed to combat it have been researched by the author using the Touro database, Google Scholar, and PubMed for various links to journals and articles that these databases provide.

## Introduction

Staphylococcus aureus is a gram positive pathogen and the most common cause of skin and soft-tissue infection (SSTI) in the world. A study done in 2008-2009, spanning more than nineteen European countries and more than 3000 cases of complicated skin and soft tissue infections (cSSTI), found that about one third of these cases were due to *S. aureus* (Russo, et al., 2016). *S. aureus* is responsible for common skin infections such as impetigo, cellulitis, folliculitis, carbuncles, abscess, pyomyositis, and necrotizing fasciitis, as well as more deep-rooted infections that lead to blood stream infections, nosocomial pneumonia, and infection of wounds and surgical sites (Popovich, et al., 2008). *S. aureus* is so prevalent that about 25% of humans are consistent carriers of this microorganism, while 50% are observably intermittent carriers. Colonies of *S. aureus* can be found in the anterior nares and other areas of skin throughout the body.

Penicillin was the first antibiotic used to treat *S. aureus* infections; however, within a few years *S. aureus* developed resistance to this "miracle drug". A specific strain of *S. aureus* started to produce an enzyme capable of destroying penicillin, called penicillinase. The plasmid that produced the penicillinase quickly spread among the different strains of *S. aureus*. To combat this new development, methicillin, which is a semisynthetic  $\beta$ -lactamase-resistant penicillin, was created in 1959. After only two short years, the first case of methicillin-resistant staphylococcus aureus (MRSA) was reported. This case of bacterial resistance was the result of a more complex mechanism than found in the penicillin resistant strain of *S. aureus*. Methicillin works by blocking the protein penicillin binding protein (PBP), found in *S.*

*aureus* that is associated with the construction and maintenance of the cell wall. Instead of using these PBP proteins, resistant strains of *S. aureus* acquired a new protein, PBP2a, which has the same function as PBP but is not susceptible to methicillin. PBP2a is encoded by the gene *mecA*, located on the chromosome, unlike the penicillinase gene which is found on the plasmid. This *mecA* gene is a distinguishing characteristic of MRSA and the presence of PBP2a means that *S. aureus* is resistant not only to methicillin, but to all  $\beta$ -lactam antibiotics, including synthetic penicillin, cephalosporin and carbapenem (Mastofsky, et al, 2011; Pantosti, Veniti, 2009; Popovich, Hota, 2008).

## HA-MRSA

MRSA has become a worldwide problem and is common throughout hospitals as well as smaller healthcare facilities. Since its origins in the 1960s, the spread of healthcare-associated MRSA has become a public health concern (Mastofsky et al, 2011; Pantosti, Veniti, 2009). The common strains of MRSA found today originated from a few clones that developed independently of each other (Gardam, 2000). MRSA is spread by direct contact and most often in a healthcare setting where contamination can spread through the hands of healthcare providers (Okado et al, 2016). This spread of infection has led to the definition of HA-MRSA which is an annotation for healthcare-associated MRSA or for hospital-acquired MRSA. Patients with compromised immune system or those that have had extended hospital stays are more susceptible to the contraction of MRSA. In addition, use of antibiotics and undergoing surgery are factors that can contribute to MRSA infection. Once a patient has acquired HA-MRSA it is extremely difficult to eradicate and

the person can be a carrier for an extended period of time (Gardam 2000). A patient can be a carrier for HA-MRSA for longer than six months, long after his discharge from the hospital (Pantosti, Veniti, 2009).

In order to reduce the prevalence of HA-MRSA and to stop the spread of this nosocomial pathogen, hospitals take on two different approaches. The first recommendation is prevention based and includes barrier precautions, hand washing and environmental cleaning for MRSA patients. The second approach is an implementation of an antibiotic stewardship program. The purpose of the program is to control antibiotic prescribing in order to reduce the adverse effects of antibiotics, such as drug resistance and more specifically decreasing the spread of infection caused by multi-drug resistant bacteria. A 10-year program implemented in Saint-Joseph Hospital in Paris, France focused on applying a combination of these two aspects to decrease the prevalence of HA-MRSA found in their hospital. The program, implemented from 2000-2009, showed an 84% decrease in HA-MRSA colonization throughout the hospital. Researchers found that there was an increase in the use of alcohol based hand rubs (ABHR) from 6.8 L to 27.5 L per 1000 patient-days. Additionally, antibiotic use, measured with the Defined Daily Dose (DDD) per 1000 patient-days decreased by 31%. The implementation of this program and its results were significant in that it was conducted in a region known to be endemic for MRSA. From 2000-2009, France had MRSA rates greater than 25%, an alarmingly high rate (Chalfine et al, 2012).

### CA-MRSA

In the 1990s a new strain of MRSA emerged. Known as community-associated methicillin resistant staphylococcus aureus (CA-MRSA) This new epidemiology has the capability of causing infections in otherwise healthy individuals who have had no previous exposure to a healthcare setting. These reported cases of CA-MRSA have statistically worse clinical outcomes than those of HA-MRSA (Mostofsky et al, 2011; Pantosti, Veniti, 2009). CA-MRSA is a more infectious form of *S. aureus* than HA-MRSA and can carry the genes that encode Pantone-Valentine leucocidin (PVL) which is "associated with tissue necrosis and a greater severity of disease" (Russo et al, 2016). However, in most cases CA-MRSA causes skin and soft tissue infections (SSTI) such as furuncles, abscesses, impetigo, and cellulitis (Pantosti, Veniti, 2009). CA-MRSA is the most common cause for patients presenting with SSTI in emergency departments around the United States (Albrecht et al., 2015),

CA-MRSA has a number of distinguishing characteristics that differentiate it from HA-MRSA. Firstly, CA-MRSA, unlike HA-MRSA, is vulnerable to most non- $\beta$ -lactam antibiotics and contains what is known as SCCmec element of type IV and type

V. SCCmec stands for staphylococcal cassette chromosome mec and is the mobile genetic element for *S. aureus* that is responsible for its resistance to methicillin and other  $\beta$ -lactam antibiotics. This SCCmec element is encoded by the gene *mecA* and is divided into subtypes I-VIII (The Working Group etc., 2009). Conversely, HA-MRSA is multidrug-resistant to non- $\beta$ -lactam antibiotics and contains SCCmec type I, II, III. A second difference, as mentioned above, is that CA-MRSA contains PVL, which is a strong virulence factor (Mostofsky et al, 2011; Pantosti, Veniti, 2009).

With the growing number of MRSA cases reported each year, the clearly defined lines between HA-MRSA and CA-MRSA are being blurred. Asymptomatic colonization of MRSA can persist for years and a HA-MRSA can be easily misconstrued for CA-MRSA. Cases have been reported of community-onset HA-MRSA, as well as nosocomial CA-MRSA infections (Mostofsky et al, 2011). The definitions abound as to how to clearly classify and differentiate between HA-MRSA and CA-MRSA. There are many uncertainties as to how to define prior hospitalization and length of time since hospitalization. This question is crucial as it determines if one is still a carrier of MRSA or not. The common definition of prior hospitalization is "hospitalization within six months to one year of current admission". Sometimes, MRSA acquired from long term care facilities and nursing homes is not considered healthcare associated, but rather CA-MRSA, skewing the statistics (Gardam, 2009). One way to differentiate between the two strains is to test the isolate's susceptibility to non- $\beta$ -lactam antibiotics, as this is one key difference between HA-MRSA and CA-MRSA (Popovich et al, 2008).

There are many different treatment options available to treat MRSA infections, including incision and drainage, oral antibiotics, parenteral antibiotics, and topical therapies. More than one mode of therapy can be used. Treatment options can be administered on both an inpatient and outpatient basis (Popovich et al, 2008).

The purpose of this paper is to review some of the current and leading parenteral and oral treatment options used to best treat SSTIs caused by both HA-MRSA and CA-MRSA. It will explore and compare different antibiotics, their uses, benefits and side effects in an effort to understand the most effective way to treat MRSA.

### Methods

This study was performed through the analysis of various original and peer reviewed articles which were accessed using databases such as the Touro Database, PubMed, and Google Scholar. The research collected in this study was used to understand MRSA, its effects and the best way to treat it when found as the cause of SSTIs.

## **Discussion**

There are many different treatment options for MRSA that are currently in use or in development. Some are administered orally or parenterally, while others are administered topically.

### *Incision and Drainage*

The most important part in the treatment of complicated SSTI (cSSTI) is the incision and drainage of the infection site. This procedure is common in the case of furuncle, soft tissue abscesses and other purulent SSTI. An estimated 80% of patients presenting in the emergency departments with acute, purulent SSTI require drainage. Most patients with infections caused by CA-MRSA are cured via incision and drainage alone and do not require any antibiotics. Thus, incision and drainage, where appropriate, is the first step to treating cSSTI caused by MRSA (Ruhe et al., 2007; Stryjewski et al., 2008).

However, there is still much to learn regarding the effectiveness of incision and drainage of infection sites. A study done on children with SSTI, with an infected site of greater than 5 cm, showed that pediatric patients are more likely to experience failure of incision and drainage alone and antibiotic therapy is usually necessary. Additionally, patients with other risk factors such as systemic illness, comorbidities, as well as multiple areas of SSTI are more likely to need antibiotic therapy in addition to or in place of incision and drainage (Popovich et al., 2008).

### *Vancomycin*

Vancomycin is the standard drug used today to treat SSTI caused by MRSA (Stryjewski et al., 2008). Since its introduction in 1958, it has been used to combat gram positive bacteria with great success. Vancomycin is administered parenterally on an inpatient basis. Vancomycin, a glycopeptide, works against MRSA by inhibiting the bacteria's cell wall synthesis. It interacts with a peptide precursor of the peptidoglycan at an important site of attachment and thereby inhibits peptidoglycan polymerase and transpeptidation mechanisms. Penicillin is also bactericidal by hindering biosynthesis of cell wall; however, vancomycin inhibits an earlier stage of the peptidoglycan synthesis thereby eliminating cross-resistance (Wilhelm et al., 1999).

The clinical practice guidelines set by the Infectious Diseases Society of America states that the recommended dose for the average adult with normal renal function for intravenous vancomycin is 15-20mg/kg/dose every 8-12 hours. Dosage amount should not exceed 2000 mg regardless of a patient's weight. For more serious cases, in which a patient is systemically ill and has a suspected MRSA infection, the dosage level may be elevated to 25-30 mg/kg/dose. However, in such a case, one must be cautious for red man syndrome, a reaction associated with a high dosage of vancomycin that can cause anaphylaxis. As a

precaution, infusion time can be lengthened to two hours and an antihistamine can be administered prior to the loading dose. Antibiotics can be administered on an empirical basis until culture results are obtained (Liu et al., 2011). For patients who have problems with renal function, careful monitoring should be ensured while administering vancomycin, as vancomycin can sometimes be associated with nephrotoxicity (Wilhelm et al., 1999).

As with the development of resistance to  $\beta$ -lactam antibiotics which led to the new subset of *S. aureus*, specifically MRSA, new reports have come out of vancomycin resistance. The levels of resistance range from intermediate susceptibility to full resistance of vancomycin (Pantosti et al., 2009). These new strains of *S. aureus* resistant to vancomycin are known as vancomycin-intermediate *S. aureus* (VISA) and as vancomycin-resistant *S. aureus* (VRSA) (Popovich et al., 2008). There is even a third category of vancomycin resistant bacteria known as hetero-VISA, that seems to be vancomycin susceptible when routinely tested, but contain a minority of cells that have intermediate vancomycin susceptibility. Upon exposure to vancomycin, these hetero-VISA bacteria can multiply in number and spread (Pantosti et al., 2009).

VRSA developed from a prolonged use of vancomycin in response to chronic MRSA infection. Over time, the bacteria changed from MRSA to VRSA by the plasmid exchange of *vanA*, the gene for vancomycin resistance, possibly from a co-infecting vancomycin-resistant enterococcus (Pantosti et al., 2009). A minimum inhibitory concentration (MIC) to vancomycin has been observed nationwide in MRSA isolates. This phenomenon, known as the MIC creep, has led to the lowering of the MIC breakpoint for vancomycin in 2006 to  $\leq 2$   $\mu\text{g/ml}$  for susceptible, 4-8  $\mu\text{g/ml}$  for intermediate, and  $\geq 16$   $\mu\text{g/ml}$  for resistant. As a result, higher dosage amounts are being recommended for therapy, yet there is no substantial data to prove its efficacy and a higher dosage may cause greater toxicity, especially nephrotoxicity (Popovich et al., 2008).

*S. aureus* that displays a decrease in vancomycin susceptibility generally has phenotypic features that are different than the strains of both original *S. aureus* and MRSA. The main phenotypic change of vancomycin-susceptible *S. aureus* (VSSA) to cause resistance is a general thickening of the cell wall. Involved in this alteration of cell wall structure is an overexpression of PBP2 and PBP2a, increased level of abnormal muropeptide protein, increased amount of D-alanyl-D-alanine residue, and reduction of peptidoglycan cross-linkage (Sirichoat et al., 2016).

### *Linezolid*

Many test results have shown Linezolid to be a comparable drug, in terms of results, to vancomycin. Linezolid is an oxazolidinone antibiotic that was first discovered in the 1990s and approved

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for use in standard medicine in 2000 (Dumitrescu, Lina., 2014). Linezolid is the first antibiotic of this class to be brought to market. Oxazolidinone represents a new systemic antimicrobial class. Linezolid works by blocking protein function in the cell. It binds to the 50s subunit of the pathogenic cell which prevents it from complexing with the 30s subunit, mRNA, initiation factors, and formylmethionyl-tRNA. This inhibition prevents the formation of the protein initiation complex, preventing the translation step of protein synthesis. Other drugs that are classified as protein synthesis inhibitors, such as macrolides and tetracyclines, have different mechanisms, as each allows the process of mRNA translation to begin, while stopping peptide elongation. This mode of action of linezolid seems to work particularly well against staphylococcal infections. Additionally, its target site is unique and does not interfere with the mechanism for other protein synthesis inhibitors. Linezolid is bacteriostatic (Livermore, 2003).

Reported cases of linezolid resistance have been rare and a number of reasons for the low level of resistance have been proposed. First, linezolid is an entirely synthetic compound, so it is unlikely that naturally occurring mechanisms of resistance, such as those found in antibiotic producing organisms will be employed. Second, oxazolidinones inhibit ribosomal protein synthesis while other antibiotics of similar ribosomal protein synthesis mechanisms do not propose cross-resistance to linezolid. Additionally, linezolid acts by binding to the 23s rRNA of the 50s ribosomal subunit. There are multiple copies of the gene that code for 23s rRNA in each cell. For resistance to occur, mutations would be necessary in each of the copies of the gene. Because of the fear of resistance, caution should be employed when there is a long and repeated use of antibiotics (Meka, Gold, 2004).

Linezolid is administered either intravenously or orally. It has 100% oral bioavailability and therefore allows for rapid transition from parenteral form to an oral one, possibly resulting in early discharge from the hospital. This can result in decreased length of stay and a decrease in overall cost of treatment. MRSA can be treated with oral linezolid exclusively. Outcomes were the same for patients treated only with oral linezolid compared to intravenous vancomycin despite the difference in routes of administration and antibiotic (Dumitrescu, Lima, 2014; Weigelt et al., 2005). Standard dosage of linezolid is 600 mg every 12 hours. For uncomplicated SSTI the recommended dose is 400 mg every 12 hours. Because of its 100% bioavailability, dosage amount is not dependent on the route it is administered (Moellering 2003).

Linezolid can cause some minor side effects, including gastrointestinal discomfort such as nausea, vomiting and diarrhea,

and dermatological effects, like rash and itchiness. Most reported adverse effects ceased with the cessation of therapy. When therapy exceeded 14 days, 12.6% of patients studied, experienced hematologic effects such as decreases in platelet count, hemoglobin level, hematocrit and white blood cell count (Birmingham et al., 2003). Linezolid can also cause reversible myelosuppression when administration of antibiotics exceeds 14 days (Weigelt et al., 2005).

In clinical studies linezolid has performed comparably to vancomycin in treating cSSTI caused by MRSA, with possible advantage. A study showed that "linezolid [was] superior ... to vancomycin in the MRSA subset. The difference between linezolid and vancomycin results was most dramatic in patients with abscesses and surgical-site infections caused by MRSA". Linezolid is more effective in treating SSTI caused by MRSA due to the enhanced penetration of linezolid into the skin and tissue (Weigelt et al. 2005). Linezolid has also shown to be less nephrotoxic than vancomycin (Dumitrescu et al., 2014). In a study comparing the treatment of cSSTI caused by MRSA with linezolid and vancomycin in diabetic and non-diabetic patients, similar results indicated no significant difference in therapy of diabetic patients. However, for non-diabetic patients, results showed a greater success rate for patients treated with linezolid (Lipsky et al., 2011). Other studies have shown no significant benefit of using linezolid over vancomycin. Szczypinska et al. claims that by examining length of stay (LOS) as the determining factor of efficacy of an antibiotic, no significant difference was found between vancomycin and linezolid. As of now, linezolid is used as a secondary choice to vancomycin in cases of vancomycin resistance, despite the proven success and efficacy of linezolid in treating MRSA, in order to prevent the rise of linezolid resistance (2013).

### *Daptomycin*

Daptomycin is another viable antibiotic for the treatment of SSTI caused by MRSA that was brought to market in 2003 (Popovich et al., 2008). Cell death is caused by rapidly depolarizing the bacterial membrane. The lipophilic tail of daptomycin, a cyclic lipopeptide compound, inserts itself into the bacterial cytoplasmic membrane, in this case MRSA, and causes a rapid depolarization of the membrane. This ultimately leads to a loss of DNA, RNA, and protein synthesis. Daptomycin is bactericidal at all of the bacterial growth stages, including the stationary phase (Aikawa et al., 2013; Gonzalez-Ruiz et al., 2016; Seaton, 2008).

Daptomycin resistance is rare but is a growing concern in the healthcare field (Hayden et al., 2005). The mechanism of resistance is unknown but it has been suggested that the mechanism of resistance may be due to irregular *dltA* transcription factor which "may result in a change of the bacterial cell membrane

fluidity and therefore lead to a reduced affinity of daptomycin to its target site” (Gonzalez-Ruiz et al., 2016). It has been hypothesized that the mechanism for daptomycin resistance is similar to that of vancomycin by VISA. Daptomycin is similar in size and weight to vancomycin and may not be able to penetrate the cell wall to reach the cell membrane, which daptomycin interacts with, if the cell wall thickens as it does in VISA. Daptomycin would never have the opportunity to reach the bacterial cytoplasmic membrane in the face of such an obstacle, resulting in daptomycin resistance (Cui et al. 2006). Resistance to daptomycin without previous exposure has so far proved to be extremely rare, with an observation of only 0.04% of 10,000 cultures tested shown to have an MIC of 2 µg (Gonzalez-Ruiz et al., 2016).

The recommended dose of daptomycin to treat cSSTI is 4 mg/kg/day to be administered parenterally with a 30-minute IV infusion. Course of treatment for daptomycin is 7-14 days. Daptomycin use has not been approved for pediatric patients (Gonzalez-Ruiz et al., 2016; Seaton, 2008). Daptomycin is administered only once daily to reduce the risk of elevated creatine phosphokinase (CPK) levels and skeletal muscle toxicity. Elevated CPK levels were resolved upon discontinuation of daptomycin treatment. The most common adverse effects reported are constipation, nausea, and headache (Gonzalez-Ruiz et al., 2016).

In some cases, such as difficult-to-treat infections like recurrent MRSA due to vancomycin resistance, a higher dosage of daptomycin (≥6 mg/kg/day) may be recommended. A higher dosage of daptomycin would allow for rapid clearing of bacteria and would lower the risk for emerging resistance. Daptomycin has also been used in combination with other antimicrobial therapies to prevent the rise of resistance. Such combination therapies should be considered for patients who are at high risk of developing resistance to daptomycin alone. Daptomycin and linezolid combination therapy was synergistic in its effect and was bactericidal for MRSA. Daptomycin has also been used with rifampin, trimethoprim-sulfamethoxazole, fosfomicin, and tigecycline (Gonzalez-Ruiz et al., 2016).

Many studies have been performed measuring the efficacy of daptomycin compared with that of vancomycin. Most show daptomycin and vancomycin to be comparable and a selection should be made based upon physician and patient preference, resistance factors and economic cost/benefit analysis (Gonzalez-Ruiz et al., 2016; Kauf et al. 2015). Patients treated with daptomycin showed a greater probability of clinical success by day 2 than those receiving vancomycin therapy, however length of stay for patients from both antibiotic groups averaged to be the same- four days. Vancomycin is also significantly cheaper than daptomycin (Kauf et al. 2015).

### *Clindamycin*

Clindamycin is especially useful in treating MRSA in an outpatient setting (Frei et al., 2010). Clindamycin is a lincosamide drug and belongs to the class of antibiotics known as macrolides, lincosamides and streptogramin B (MLS). Although similar in function to macrolides, lincosamides and streptogramin B are structurally different. Clindamycin works by binding to the large ribosomal subunit, which is the center responsible for catalyzing the formation of peptide bonds during protein elongation. Clindamycin blocks this ribosomal tunnel, allowing peptide elongation to continue until it reaches a point of steric hindrance caused by the clindamycin. This inhibition will lead to eventual dissociation of the peptidyl-tRNA from the ribosome. Once a peptide has reached a certain length on the ribosome, clindamycin loses its ability to inhibit protein synthesis (Tenson et al., 2003).

Resistance to clindamycin therapy is a cause for concern. The resistance mechanism involves modification of the drug binding site on the ribosome. The mechanism is the same for all MSL antibiotics, and is known as MSLB resistance. MSL drugs bind to the 23s rRNA-binding site. The erm gene is responsible for the methylation of the 23s rRNA-binding site. In the presence of the erm gene, resistance can be expressed constitutively as well as when induced into production. Because of the presence of the erm gene, resistance can occur during the course of clindamycin therapy (Lewis II et al., 2005; Popovich et al., 2008). In testing for clindamycin resistance, MRSA strains may appear susceptible, but can later develop resistance. To test for inducible resistance, a D-zone test is used. This is a double-disk diffusion test in which two disks, a clindamycin disk and an erythromycin disk are placed on a plate growing *S. aureus*. The strain is inducible resistant if the zone of inhibition around the clindamycin disk facing the erythromycin disk is blunted, forming a D shape. Rates of inducible clindamycin resistance varies by region in the United States. Use of clindamycin should be determined by local rates (Popovich et al., 2008).

Clindamycin can be administered parenterally or orally for SSTI. When administered intravenously, the appropriate dosage is 600 mg every 8 hours. For oral administration, patients should be given 300-450 mg four times daily. Courses of treatment range from 10-14 days (Popovich et al., 2008). Clindamycin has a 90% oral bioavailability and can penetrate well into skin and skin structure. It is also less costly than some newer drugs used to treat SSTI caused by MRSA (Lewis II et al., 2005). Clindamycin may also inhibit the PVL gene that is common in CA-MRSA (Forcade et al. 2011).

Clindamycin is commonly associated with gastrointestinal side effects. Most common were reports of diarrhea and pseudomembranous colitis (PMC). In a study comparing gastrointestinal

effects caused by clindamycin and ampicillin, another medication known to have gastrointestinal side effects, it was found that 29.8% of patients developed diarrhea following clindamycin therapy. Patients were evaluated for side effects for six weeks following discontinuance of clindamycin therapy (Lusk et al. 1977).

The findings of a study involving a retrospective chart review to compare the efficacy of vancomycin to the efficacy of clindamycin indicated that vancomycin and clindamycin had similar treatment results (Frei et al. 2010). In some cases, clindamycin is used in conjunction with vancomycin as a combination antimicrobial therapy. However, it has been reported that clindamycin often “antagonizes the antistaphylococcal activity of vancomycin” (Deresinski, 2009).

### *Trimethoprim-Sulfamethoxazole*

Trimethoprim-Sulfamethoxazole (TMP-SMX) is another antibiotic that is used for the treatment of MRSA. TMP-SMX is the most commonly prescribed oral antibiotic for outpatient treatment of CA-MRSA infections, in addition to clindamycin (Forcade et al., 2011; Johnson, Decker, 2008). TMP-SMX is a two part drug consisting of one part trimethoprim to five parts sulfamethoxazole. The interaction of these two drugs inhibits the bacterial synthesis of tetrahydrofolic acid, which is used in the production of bacterial nucleic acid. TMP-SMX inhibits two consecutive steps in the formation of folic acid. Sulfonamides inhibit dihydropteroate synthetase (DHPS), which is responsible for para-aminobenzoic acid to be catalyzed into dihydrofolate. TMP inhibits dihydrofolate reductase (DHFR) which causes dihydrofolate to be catalyzed into tetrahydrofolate (Huovinen, 2001; Michalek et al., 2015). TMP-SMX has also been shown to have anti-inflammatory and immunomodulatory effects, enhancing its antimicrobial capabilities (Michalek et al., 2015).

Resistance to TMP-SMX can be found against both drugs, trimethoprim and sulfonamides, with different mechanisms against each. Resistance of *S. aureus* to TMP is suspected of being caused by a single amino acid change in the *dhfr* gene, altering DHFR. A single amino acid mutation in the *dhps* gene is responsible for sulfonamide resistance of *S. aureus* (Huovinen, 2001). However, a study performed in three cities in the United States in 2005, showed that 97% of CA-MRSA isolates were susceptible to TMP-SMX (Johnson et al., 2008; Popovich et al, 2008).

TMP-SMX is most commonly administered orally with the standard dose of 160/800 mg twice daily for 7-15 days. TMP-SMX can also be administered intravenously with a dosage of trimethoprim (80 mg)/sulfamethoxazole (400 mg) per 5 ml to be given as 5 mg/kg every 6-12 hours (Michalek et al., 2015;

Popovich et al., 2008). TMP-SMX has a high bioavailability, at around 85% for both complexes (Stein et al., 2016). Some recommend a higher dosage, 320/1600 mg twice daily for 7-15 days, of oral TMP-SMX to treat SSTI caused by MRSA. Yet Cadena et al. found that patients treated with the two different doses had similar clinical results. For the treatment of SSTI caused by MRSA, a higher dose may not be necessary (2011). A lower dose may also minimize gastrointestinal adverse effects (Michalek et al., 2015). In studies testing TMP-SMX patients were found to have side effects of diarrhea, nausea, vomiting, pruritus, and rash (Miller et al., 2015).

Studies comparing TMP-SMX to clindamycin, show TMP-SMX to be a comparable treatment option (Frei et al., 2010; Miller et al., 2015). TMP-SMX can be used in combination with clindamycin to treat pediatric patients (Stein et al., 2016). TMP-SMX bactericidal activity against MRSA was greater than that of linezolid, rifampicin, and clindamycin, other popular oral antibiotics used to treat MRSA. The use of TMP-SMX is economically beneficial as well. When compared to linezolid, at \$1352 for a 10-day course of treatment, TMP-SMX is significantly cheaper, costing only \$18 for a 10 day course. These numbers are average wholesale numbers in the United States (Kaka et al. 2006). According to Johnson et al. studies comparing the effectiveness of TMP-SMX to vancomycin, the leading drug, are lacking (2008). However, all VISA strains in the United States are susceptible to TMP-SMX, and TMP-SMX has been used, in combination with other drugs, in its treatment (Cosgrove et al., 2004).

### **Conclusion**

*Staphylococcus aureus* is the leading cause for SSTI in the world. In an effort to combat this growing concern, many antimicrobial agents have been used. The method of defense was penicillin and then methicillin which lead to what is commonly known as MRSA. Initially found only in hospitals and other healthcare facilities, MRSA soon spread to the community at large. Patients with no previous healthcare exposure were now susceptible to MRSA. These infections are typically manifested as SSTI in the form of impetigo, cellulitis, folliculitis, and abscess.

With the rise of methicillin resistance, and subsequently resistance to all  $\beta$ -lactam antibiotics, new treatment options were needed. Vancomycin became the treatment option of choice. However, vancomycin resistance was soon reported as well, though not to the extent of methicillin resistance. Other antibiotics are also used to combat SSTI caused by MRSA. Daptomycin, a newer drug that is administered intravenously, shows great promise. Linezolid, can be administered both parenterally and orally, and therefore has potential to shorten hospital stay. Clindamycin and TMP-SMX are both popular oral drugs used in outpatient treatment of MRSA.

Regardless of the effectiveness and benefits of these non- $\beta$ -lactam antibiotics, vancomycin remains the “gold standard” of treatment therapy for MRSA. Fear of developing resistance to alternative drugs limits the extent of their use and keeps vancomycin as the leading choice. Healthcare professionals and researchers need to remain alert to any signs of resistance of antimicrobial agents to prevent its spread and to help stop the increased presence of MRSA in hospitals and the community.

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