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COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS (MRSA):* WHAT YOU SHOULD KNOW

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In the early 1940s, the discovery of penicillin was seen as the beginning of a new era in the treatment of infectious diseases. One year after its introduction, the first isolates of penicillin resistant *Staphylococcus aureus* were reported by Rammelkamp.[1] In 1944, the first description of penicillinase-producing strains of *S. aureus* was published. Penicillin-resistance was a rapidly growing problem and by the 1950s, penicillinase-resistant strains were common in hospitals throughout the world. Community strains were still largely susceptible to penicillin.[2] By the 1960s, penicillinase-resistant *S. aureus* was as equally prevalent in the community as it was in hospitals.[3]

In 1961, a new penicillinase-resistant semi-synthetic penicillin, methicillin, was introduced. Not surprisingly, less than a year later, methicillin-resistant *S. aureus* (MRSA) was reported.[3] MRSA was a hospital-based problem, especially in intensive care units (ICU) until the early 1980s. Like penicillin resistant strains of *S. aureus*, MRSA eventually emerged in the community. In 1982, the first case of MRSA was reported outside of the hospital among intravenous drug abusers.[3] Over the past decade, the emergence of community-associated MRSA (CA-MRSA) has become a topic of much concern. The initial belief that CA-MRSA originated from MRSA that left the hospital has been challenged by the discovery of novel strains of MRSA, genetically different from hospital-acquired strains.[1,9]

Currently, more than 50% of *S. aureus* isolates in hospitals (even higher in intensive care units) are methicillin-resistant and prevalence in the community is rising.[2,9,10] Failure to appreciate CA-MRSA as an evolving problem can lead to suboptimal patient care and contribute to the rapidly growing antimicrobial resistance problem. Fluoroquinolone use has been attributed to the increase in MRSA isolates. The growing problem of resistance is compounded by the fact that there are very few new antibiotics in the approval process. Spellberg et al noted that new antibacterial agents constitute 6 of 506 drugs in the developmental process.[21] With few new drugs and growing resistance problems, physicians are running out of options. Some old and nearly obsolete antibiotics are re-emerging and proving beneficial when used synergistically in the treatment of certain infections like CA-MRSA. In this article, pertinent litera-

INSIDE THIS ISSUE:

Table 1: Clinical Trial Summaries.

Author	Design	Infection	(n)	Treatment	Outcome
Markowitz et al.[12]	Ra/DB/C	*S. aureus* bacteremia	101	TMP 320mg/SMX 1600mg IV q12h or Vancomycin 1g q12h	Overall cure rate= 86% with TMP/SMX and 98% with vancomycin ($p<0.02$)
Jemni L.[13]	P/O	Skin/soft tissue, arthritis, meningitis, prosthetic valve endocarditis, spondylodiskitis with abscess.	27	TMP 320-480mg/SMX 1600-2400mg/day (divided) +/- Rifampin (8) or PenG or Metronidazole (5)	Overall cure rate= 96%
Iyer et al.[22]	R/CR	Skin and soft tissue	39	TMP/SMX, Rifampin, Clindamycin, Vancomycin, Linezolid, Moxifloxacin	Complete response with TMP/SMX + Rifampin (6/6), Clindamycin (1/1), Vancomycin (5/5), Linezolid (11/11), Mupirocin (3/3), Moxifloxacin (9/16), TMP/SMX (6/12).
Martinez-Aguilar et al.[26]	R/CR	Bacteremia, osteomyelitis, septic arthritis, pneumonia, lymphadenitis, and others	46	Clindamycin 30-40mg/kg/day divided q8h (46) [Clindamycin only (20), Vancomycin initially (18), beta-lactam initially (8)] Vancomycin only (6)	Cure or clinical improvement in 45 of 46 patients treated with clindamycin.
Ruhe et al.[15]	CS	Skin and soft tissue infections	24	Doxycycline or Minocycline 100mg PO bid	Overall clinical success rate= 83%
	LR	Pneumonia, osteomyelitis, skin and soft tissue, and endocarditis.	85	Long acting tetracyclines +/- Rifampin	Overall cure rate= 85%
Clumeck et al.[20]	P/O	Severe *S. aureus* infections	25	Rifampicin 600mg/day + minocycline 200 or 400mg/day administered IV or PO bid.	Mean duration tx = 22 days. Overall cure rate= 76%, clinical improvement= 4%, failure= 20%

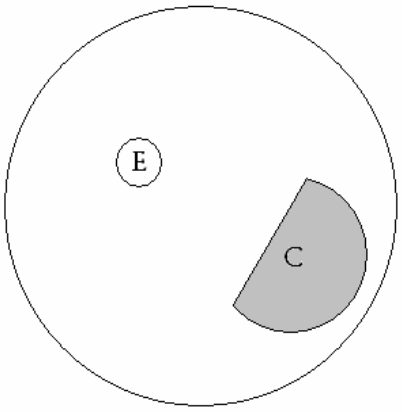
Ra=randomized; R=retrospective; P=prospective; LR=literature review; CS=case series; O=observational; CR=chart review; C=comparative; DB=double blind

ture is reviewed with respect to the prevalence, identification, and proper treatment of CA-MRSA as it differs from hospital-acquired strains.

The New Isolate and Resistance

MRSA was once believed to only be a hospital-acquired pathogen and cases in the community were generally linked to hospital contact.[3] Recently, researchers have identified novel strains of CA-MRSA that are genetically unique and exhibit characteristic traits. These new strains differ in their epidemiology, resistance phenotype, and clinical virulence.

Figure 1. Example of Positive D-Test.



C= clindamycin-impregnated disk. E= erythromycin-impregnated disk. Blunting of the zone of inhibition (shaded area in figure) denotes presence of inducible *erm* gene. Though isolate may be reported as susceptible, induction of *erm* can result in MLSBi phenotype and in vivo clindamycin resistance.

Methicillin-resistance is carried chromosomally by the mecA gene. The mecA gene enters a cassette called the staphylococcal chromosomal cassette (SCC) that is incorporated into chromosomes. To date there are five SCCmec types.[8] Types I-III are common in hospital-acquired strains. Type IV and the more recently discovered type V strains have a community-based origin. Unlike multi-drug resistant hospital-acquired methicillin-resistant staphylococcus aureus (HA-MRSA) strains, CA-MRSA resistance is usually limited to β-lactam antimicrobials.[3] Another distinguishing feature of CA-MRSA is the presence of numerous exotoxin virulence factors, most notably the Panton-Valentine leukocidin (PVL) toxin. The PVL toxin is lethal to neutrophils and is associated with skin necrosis.[3,6] These virulence factors are believed to be the cause of the increasing number of CA-MRSA skin and soft tissue infections, and less commonly necrotizing pneumonia. Also, the presence of toxins appears to increase the likelihood that colonized patients will progress to infection (compared with HA-MRSA). Fluoroquinolone use has been identified as a reason for the increase in MRSA infections. A case control study of 121 patients with MRSA found that levofloxacin use was independently associated with MRSA infections (OR 8.01).[14] Fluoroquinolones are more active against MSSA than MRSA, thus fluoroquinolone exposure exerts a selective pressure for MRSA. As methicillin-susceptible *S. aureus* (MSSA) isolates are suppressed, MRSA persists and may colonize or infect the 'space' once occupied by MSSA.[4,14]

Clinical Presentation

CA-MRSA cases generally lack traditional risk factors associated with MRSA infections. However, increased outbreaks and persistent transmission have been documented in various groups including Alaskan natives, Native Americans, Pacific Islanders, correctional facility inmates, competitive sports participants, children in day care centers, homeless persons, IV drug users, men who have sex with men, and military personnel.[3,7] Community-associated strains are less frequently associated with endocarditis, bacteremia, sinusitis, and brain abscesses when compared to hospital-acquired strains. CA-MRSA primarily causes skin and soft tissue infections (abscesses, cellulitis, furunculosis, impetigo, infected wounds), but has been associated with severe necrotizing pneumonia, fascitis, myositis, osteomyelitis, and prosthetic joint infections.[3,5] Insect and spider bites can also be mistaken for CA-MRSA infections due to the presence of a central necrotic region associated with skin lesions.

Treatment Considerations

The selection of initial antibiotic regimens should be guided by the prevalence of CA-MRSA in the community, presence or absence of health-care associated risk factors, severity and type of clinical presentation, and patient specific factors. When considering probable pathogens, it is important to consider if the patient has an abscess, diabetes mellitus, recent use of antibiotics, a recent hospital stay, close contact with hospitalized patient or day care, or is immunocompromised. Patient allergies and renal/ hepatic function should be evaluated as well.

When CA-MRSA is suspected, it is important to obtain culture and sensitivity reports. The sensitivity of community and hospital strains differ greatly. Unlike multi-drug resistant hospital-acquired strains, CA-MRSA is generally susceptible to non-β-lactam antibiotics. There are several treatment options available; however, many have not been clinically tested and efficacy data is often not available.[8] TMP/SMX (Bactrim®, Septra®), clindamycin (Cleocin®), doxycycline (Adoxa®, Doryx®), minocycline (Dinacin®, Minocin®), and rifampin (Rifadin®) have in vitro activity.[3,5,8]

Incision and drainage should be performed and

Table 2. Summary of Treatment Options for CA—MRSA.

	TMP/SMX	Clindamycin	Doxycycline	Minocycline	Rifampin
MOA	Inhibits bacterial folic acid synthesis	Inhibits bacterial protein synthesis	Inhibit bacterial protein synthesis	Inhibit bacterial protein synthesis	Inhibits bacterial RNA synthesis
Recommended Dose	PO: TMP 320mg SMX 1600mg q12h IV:10mg/kg/day* (divided q12h)	PO: 150-450mg q6h IV/IM: 300mg q6, q8, or q12h	PO: 100mg q12h	PO: 100mg q12h	PO: 300-600mg q12h (never as mono-therapy)
Adverse Drug Reactions	GI distress, photo-sensitivity, hyperkalemia (avoid if sulfa-allergic)	GI distress, pseudo-membranous colitis,	GI distress, photo-sensitivity	GI distress, photo-sensitivity	Reddish orange/ brown urine, saliva, sweat, tear (bodily fluid), flu-like syndrome

*dosing based on Trimethoprim component.

cultures analyzed when appropriate.[3] There has been controversy about whether incision and drainage of cutaneous abscesses without antibiotic therapy is sufficient. A recent review noted small (<5cm) cutaneous abscesses without cellulitis or systemic symptoms can be treated with incision and drainage alone with close follow up.[3] However, this strategy has been challenged.

A handful of small, nonrandomized studies have reported results of CA-MRSA treatment strategies. (Table 1) Lee et al conducted a prospective observational study to determine if incision and drainage of abscesses, without antibiotic use, is adequate therapy in CA-MRSA skin and soft tissue infections.[24] Sixty-nine children were identified with positive MRSA cultures. All abscesses were drained and initial antibiotics were started before culture results were known. Fifty-two patients received cephalexin, 7 received amoxicillin/clavulanate, 5 received clindamycin, and 1 patient received TMP/SMX with rifampin. Two patients never filled their prescriptions. Thirty-seven patients were on an ineffective antibiotic based on culture results and never had their antibiotic changed. Of these 37 patients, 31 improved, 1 deteriorated, and 5 had no follow-up. The study concluded that incision and drainage without adjunctive antibiotic therapy was effective management of CA-MRSA skin and soft tissue abscesses with a diameter of <5 cm in immunocompetent children. Abscesses with a diameter of >5 cm were identified as a significant predictor of hospitalization (p=0.004). It is not clear from these results whether incision and drainage alone was sufficient or if the antibiotics were effective despite in vitro susceptibility results suggesting resistance.

Severe or life threatening infections should be treated with empiric vancomycin (Vancocin®), linezolid (Zyvox®), quinipristin-dalfopristin (Synercid®), or daptomycin (Cubicin®) when C/S reports are pending.[8,9] Daptomycin should be limited to resistant skin and soft tissue infections because it is inactivated by surfactant and has no indication in the treatment of pneumonia. In areas with a low prevalence of CA-MRSA or if suspicion for CA-MRSA is low, patients with less severe infections can be initially treated with a penicillinase-resistant penicillin like oxacillin, nafcillin (Nallpen®, Unipen®), dicloxacillin (Dycill®, Pathocil®) or a first generation cephalosporin like cefazolin (Ancef®) or cephalexin (Keflex®).[9]

The Infectious Diseases Society of Washington and the Washington State Health Department published interim guidelines for evaluation and management of CA-MRSA skin and soft tissue infections in the outpatient setting.[23] They recommend empiric therapy be guided by local S. aureus susceptibility and be modified based on culture and sensitivity results. For susceptible CA-MRSA infections, recommended treatment includes TMP/SMX 160 mg/800

mg by mouth twice daily, minocycline or doxycycline 100 mg by mouth twice daily, or clindamycin 300-450 mg by mouth four times daily. Duration of treatment for most infections is 7-10 days, but varies depending on severity of infection and clinical response. The use of fluoroquinolones is not recommended for treatment of MRSA in most areas due to high resistance rates and their role in MRSA selection.

TMP/SMX has become a viable option for the treatment of CA-MRSA. The combination drug inhibits two steps in the biosynthesis of folic acid, which render it bactericidal against most pathogens. TMP/SMX has excellent oral bioavailability, is inexpensive, has been used for decades, and carries an abundance of safety data.[5] Many physicians are familiar with TMP/SMX in the treatment of urinary tract infections and often under-dose the medication when treating CA-MRSA. Although strong double-blinded, randomized controlled trials are lacking, there are many published articles supporting its use in this setting.[10,12]

Markowitz et al performed a randomized, double-blind comparative trial evaluating 101 intravenous drug abusers hospitalized for *S. aureus* infections.[12] Forty-three patients received TMP 320 mg/ SMX 1600 mg IV every 12 hours (10 mg/kg/day based on trimethoprim component) and 58 patients received vancomycin 1g IV every 12 hours. The overall cure rate was 86% in the TMP/SMX group and 98% in vancomycin group ($P < 0.02$). Treatment failure occurred in 4 patients with tricuspid valve endocarditis and in 2 patients with infections caused by MSSA (1 developed septic arthritis, 1 had a pseudoaneurysm relapse). This study concluded that TMP-SMX may be considered as an alternative to vancomycin in non-life threatening MRSA infections.

Iyer and Jones conducted a retrospective chart review of 39 patients who were evaluated and treated for a positive MRSA skin infection.[22] Twenty patients were HIV positive and 19 were previously healthy with no comorbidities. All patients were treated with antimicrobial therapy and patients who presented with abscesses were also treated with incision and drainage. Twelve of the 39 patients were treated with TMP/SMX and 6 achieved prompt resolution. Rifampin was added to TMP/SMX in the other 6 patients and produced successful eradication of the MRSA infection. Patients treated with vancomycin, linezolid, mupirocin, and clindamycin all achieved complete responses. Only 9 of 16 patients treated with moxifloxacin (Avelox®) received complete responses. The author concluded that treatment with TMP/SMX in combination with rifampin led to a lower recurrence and better response rates when compared to TMP/SMX alone.

In another study, 27 patients with MRSA infections were treated with TMP/SMX.[13] The infections consisted of 15 soft tissue infections, 4 bacteremias, 2 arthritis, 1 meningitis, 1 prosthetic valve endocarditis, and 1 spondylodiskitis with abscess. The daily doses of TMP/SMX ranged from TMP 320-480mg and SMX 1600-2400mg. TMP/SMX plus rifampin was used in 8 patients and TMP/SMX plus penicillin G and/or metronidazole was used in 5 patients with polymicrobial soft tissue infections. Overall cure rate was 96%. The study concluded that TMP/SMX constitutes an effective alternative for treatment of MRSA infections.

Clindamycin is an option for CA-MRSA infections. It is a bacteriostatic agent that inhibits protein synthesis by binding to the bacterial ribosomal 50S subunit. It has good penetration into skin and soft tissue. It has activity against gram-positive bacteria as well as anaerobes. Clindamycin is a reasonable option for treatment of diabetic patients as well as patients with abscesses due to the increased likelihood of anaerobic organisms. It is a good option for patients with a sulfa-allergy who are unable to take TMP/SMX. Clindamycin is relatively inexpensive, available in intravenous and oral formulations, and may be able to inhibit production of toxins and virulence factors associated with CA-MRSA.[11] One potential disadvantage of clindamycin use is its association with *Clostridium difficile* colitis, though this complication can occur with any antibiotic.

There are reported treatment failures with clindamycin from an inducible resistance mechanism. Clindamycin resistance is attributed to modification of the drug-binding site (the ribosome) caused by methylation. This mode of inducible resistance is termed MLSBi. Its presence renders macrolides, lincosamides, and group B streptogrammins ineffective. MLSBi genes encode methylation of the 23S ribosomal subunit, which is a binding site for the three drug classes previously mentioned. MLSBi resistance is not often detected by standard laboratory testing methods. When culture and sensitivity reports show erythromycin resistance, but clindamycin sus-

ceptibility, further analysis is warranted. A double-disk diffusion test (D-test) can be used to differentiate between clindamycin susceptibility and inducible resistance via the MLSBi mechanism. A positive D-test is indicated when MLSBi gene is present and the clindamycin zone of inhibition is blunted on the side nearest the erythromycin disk.[11] The zone of inhibition of clindamycin will be shaped like a D. (See Figure 1) The presence MLSBi indicates a significant risk for clinical failure and clindamycin should not be used.

Martinez-Aguilar et al conducted a retrospective chart review to compare clindamycin efficacy in MRSA and MSSA isolates in children.[26] Thirty-nine of 46 patients with MRSA received clindamycin plus incision and drainage. Twenty patients received clindamycin only, 18 received vancomycin initially, and 8 received a beta-lactam initially. Cure or clinical improvement was seen in 45 of 46 patients with MRSA, which was not a statistically significant difference when compared to MSSA isolates. The study concluded that clindamycin was effective in treating infections caused by susceptible CA-MRSA isolates in children.

Long-acting tetracyclines, minocycline and doxycycline, have been used in the management of MRSA infections. Minocycline and doxycycline bind to the 30S and possibly the 50S ribosomal subunits and inhibit bacterial protein synthesis. They may also cause alterations in the cytoplasmic membranes. These drugs are bacteriostatic, have good absorption, and excellent tissue penetration. They have superior anti-staphylococcal activity when compared to tetracycline.[15]

The SENTRY Antimicrobial Surveillance Program evaluated the frequency of occurrence and antimicrobial susceptibility of isolates collected in the US, Canada, Latin America, Europe, and the Western Pacific Region.[16] In the US, the following MRSA resistance rates were reported for nosocomial isolates: 89% to ciprofloxacin, 93% to erythromycin, 79% to clindamycin, and 26% to TMP/SMX. Resistance to tetracycline was only 16%. Double-blinded randomized controlled trials are lacking, but a recent case series and review reported that long-acting tetracyclines may be a reasonable treatment alternative for patients with certain types of MRSA infections.[15] The case series reviewed medical records of adult patients treated with doxycycline or minocycline for tetracycline susceptible MRSA infections. Medical records were reviewed over a 5.5-year period and 3739 MRSA specimens were isolated. A total of 45 patients were treated with doxycycline or minocycline 100 mg BID, but only 24 patients were included in the study. The overall clinical success rate was 83%. In a literature review, a total of 85 patients from 9 studies were identified as being treated for MRSA infections with long-acting tetracyclines with or without rifampin.[15] The infections included pneumonia, osteomyelitis, skin and soft tissue infections, and endocarditis. The overall cure rate was 85% (72 of 85 patients). The majority of clinical failures occurred in more severe infections including endocarditis and osteomyelitis.

Rifampin has been used synergistically in the treatment of MRSA infections. Rifampin should never be used as a single agent due to the rapid development of resistance.[17] Rifampin inhibits bacterial RNA synthesis by binding to the DNA-dependent RNA polymerase and blocking RNA transcription. Rifampin is dosed 300-600mg PO q12h when used as synergy with other antibiotics.[25] The SENTRY Antimicrobial Surveillance Program showed an 8% resistance rate to MRSA.[16] Rifampin has activity against staphylococci in the stationary-phase and the ability to eliminate intracellular staphylococcus.[5] There is very little data supporting the use of rifampin in the treatment of CA-MRSA. This treatment option was adapted from the use of rifampin with ciprofloxacin in staphylococcal orthopedic device infections and prosthetic valve endocarditis.[5] In a randomized controlled trial by Zimmereli et al, ciprofloxacin plus rifampin was compared to ciprofloxacin alone.[18] Of the 24 patients that completed the trial, 100% of patient in the ciprofloxacin plus rifampin group and 58% of patients in ciprofloxacin monotherapy group achieved clinical cure.

Iyer and Jones, in a retrospective chart review, concluded that TMP/SMX in combination with rifampin was a viable first-line agent in the treatment of MRSA infections.[22] The regimen was given to patients who did not respond to TMP/SMX monotherapy and it resulted in complete responses in all 6 patients. Treatment options for CA-MRSA are summarized in Table 2.

Prevention and Decolonization

Data regarding prevention of CA-MRSA is limited, but basic infection-control principles should always be used. Personal hygiene should be stressed,

including daily showers, use of antibacterial soap, hand sanitizer, and coverage of any open or draining lesions.[3] Limiting inappropriate antimicrobial use may be beneficial in preventing MRSA outbreaks.

MRSA decolonization has been attempted to eradicate and prevent outbreaks. Universal decolonization of CA-MRSA is not recommended due to lack of compelling outcomes data; however, it may be beneficial in patients with recurrent disease, within families, or among discrete patient populations. Various methods of decolonization have been attempted using combinations of systemic and topical antibiotics including TMP/SMX, tetracyclines, or clindamycin each with or without rifampin, mupirocin, and chlorhexidine body washes.[3] Currently, no one regimen is preferred.

The Infectious Diseases Society of Washington and the Washington State Health Department state the efficacy of decolonization in the outpatient setting is not routinely recommended.[23] They recommend consultation with an infectious disease specialist before attempting. The interim guidelines state it is reasonable to consider decolonization for patients with recurrent MRSA infections despite appropriate therapy and MRSA infections with ongoing transmission in a well-defined cohort with close contact. Decolonization regimens listed include rifampin 300mg bid for 5 days in combination with TMP/SMX, doxycycline, or minocycline. Another regimen includes topical intranasal mupirocin used bid for 5 days with or without systemic antimicrobial therapy. Skin antisepsis with chlorhexidine or other agents may also be used in addition to one or both of the above regimens.

Parras et al evaluated MRSA decolonization from the nasal and extranasal carriage using mupirocin vs. oral co-trimoxazole plus fusidic acid.[19] These regimens were administered during a 5-day period and were combined with daily or twice daily chlorhexidine soap baths. The efficacy and safety of both regimens were similar and at the end of treatment, 100% of patients had complete eradication of nasal MRSA. Mupirocin proved to be very effective in this study. Resistance to mupirocin has been demonstrated in MRSA, but its effect on CA-MRSA is unknown.[3]

Conclusion

The emergence of CA-MRSA in the community leaves practitioners with fewer viable treatment options in the community. Luckily, CA-MRSA strains are currently not multi-drug resistant and can be effectively treated with several oral antibiotic regimens, including TMP/SMX +/- rifampin, clindamycin, minocycline, or doxycycline. Vancomycin, linezolid, and other similar drugs should be reserved for severe or life threatening infections. Abscesses should be routinely drained and cultured. Decolonization should not be routinely performed, but may be valuable in select instances. The incidence of CA-MRSA is increasing and it is imperative for practitioners to identify these infections and treat them appropriately.

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