CHAPTER **9**

RISK FACTORS FOR METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) IN SKIN, SOFT TISSUE, AND BONE INFECTIONS IN THE FOOT AND LEG IN A CALIFORNIA COMMUNITY HOSPITAL

Justin Colarco, DPM
Patricia Forg, DPM
Gonzalo Ballon-Landa, MD

INTRODUCTION

Methicillin Resistant Staphylococcus aureus (MRSA) is a category of bacteria that has become resistant to conventional therapies against gram-positive organisms, in particular beta-Lactam antibiotics and penicillins. These strains of bacteria were first identified and described in the 1960s and were closely associated with the advent of penicillinase resistant antibiotics such as methicillin and oxacillin.[1] Resistance in these strains has been specifically defined as acquiring an MIC (minimum inhibitory concentration) of greater than or equal to 4 mcg/ml on susceptibility screening. Although there may be a few mechanisms, the primary method of MRSA resistance is through production of a low affinity penicillinase binding protein PBP2a encoded by a transmissible mecA gene located on a staphylococcal cassette chromosome (SCCmec).[2-5] There have been 5 distinct strains of the SCCmec gene that all vary in size, virulence, and transmissibility depending upon the origin of the bacteria that had been isolated.[2-5] Types 1-3 have been associated with a greater resistance profile and are more common in what have been termed HA-MRSA or Hospital Acquired MRSA.

The majority of early strains had been associated with hospital transmission only.[2,4,5] In the 1990s, however, MRSA was detected in the community and in people who did not have prior health care exposure. These were given the label of Community Acquired CA-MRSA.[2-6] The fourth and fifth strains of SCCmec have been more closely associated with the community acquired bacteria and have a smaller resistance profile.[3,4,6] Both groups have developed a 2-component exotoxin that is referred to as Panton-Valentine leukocidin that is frequently associated with skin necrosis and abscess formation in community strains.[2-6]

Currently, treatment for MRSA documented infections in hospital and healthcare associated strains consists of Vancomycin, Daptomycin, Synercid, Tigecycline, and Linezolid intravenous antibiotics. With a broadened sensitivity spectrum, community acquired strains are treated outpatient or inpatient with Clindamycin, Tetracyclines, Trimethoprim/Sulfamethoxazole, Linezolid, and Vancomycin in either pill or IV routes respectively.[7,8]

With this background being established, it is important to recognize the increasing numbers of MRSA infections in the world population.[8-27] It is estimated from multiple studies that approximately 32% (89.4 million persons) in the US alone are colonized with Staph aureus and 0.8% (2.3 million persons) are colonized by MRSA.[9] While these appear to be small percentages, these numbers are constantly increasing. The proportion of healthcare-associated staphylococcal infections that are due to MRSA has been increasing; 2% S. aureus infections in the ICU were MRSA in 1974, 22% in 1995, and numbers ranging from 55-64% in 2005.[9,12,24] Non ICU patients were as high as 59.2% of Staph aureus infections by 2005 in some studies.[9,12,24] There are an estimated 292,000 hospitalizations with a diagnosis of S. aureus infection annually in US hospitals. Of these, approximately 126,000 are directly related to MRSA.[24] Invasive MRSA infections occur in approximately 94,000 persons each year and are associated with 19,000 deaths.[12] According to a 2007 JAMA article, of these, 86% are healthcare associated and 14% are community associated.[12] Each year from 2001 through 2003 there were an estimated 12 million outpatient healthcare visits for suspected Staph aureus skin and soft tissue infections (SSTIs) in the US.[28] In 2004, approximately 76% of purulent skin and soft tissue infections in adults seen in 11 US emergency departments were caused by Staph. Overall, MRSA caused 59% of all SSTIs.[23,29]

Treatment of all infections typically involves prescription of some antibiotic. Antibiotics are drugs that can be taken by a variety of routes, are not innocuous, and

often have visible side effects. Some of the most dangerous side effects, however, may not be immediately visible.[30] Various studies have established risk factors for generalized MRSA blood infections, pneumonia, major skin and soft tissue infections, including contact with people that had MRSA, recent hospitalization, recent antibiotic use, IV drug use, and various other shared attributes.[9-29] Even with these risk factors established, many physicians still "shotgun" their antibiotic coverage. The number of doctors that practice this method of treatment is decreasing by self report studies,[30-32] but this approach has led to the development of other resistant strains of bacteria, in particular Vancomycin resistant enterococcus (VRE), Vancomycin Intermediate Resistance Staph Aureus (VISA), and Vancomycin Resistant Staph Aureus (VRSA).[31-39] Although a majority of reports of VISA and VRSA are just case studies at the present time, the number of these resistant strains may increase rapidly and eliminate a very useful drug from our treatment of a potentially dangerous disease. The overuse may also leave a more dangerous bacterium behind to colonize or infect in MRSA's place (VREs or ESBLs).[30-39] It has been established that this "shotgun" approach in treatment leads to increasing amounts of resistance development.[30,31] This is one of the "invisible" side effects of over-prescription of unnecessary antibiotics. It has also been studied that reducing the amount of prescribed antibiotics for improper indications, reduces the amount of resistant bacteria in the hospital and the community.[32] This is a physician-controlled factor in the bacterial development of resistance.

Although there are a myriad of general medicine and infectious disease journals that have covered this topic over the past recent decades, there are not many studies in the orthopedic literature that address MRSA.[40-42] With the well documented increasing amounts of MRSA in the community and with the thoroughly researched risk of over-prescribing antibiotics, the establishment of risk factors for foot and leg MRSA infection and institution of guidelines warrants our attention as healthcare workers who frequently prescribe antibiotics. This study is an attempt to focus the foot and ankle clinician on key factors that may be present in a patient's medical history that are more likely associated with MRSA infection. This will hopefully aid in a reduction of "shotgun" therapy and thereby limit the prescription of powerful antibiotics for those patients that are determined to be "high risk" for MRSA of the lower extremity in a triage setting. It will attempt to answer the question, does this patient need MRSA coverage?

MATERIALS AND METHODS

Retrospective Review

The first portion of the study consisted of a detailed chart review of various factors involving MRSA infections in the hospital. This is limited to an objective retrospective review of the charts for the hospital of all of the patients that were diagnosed with an infection that was confirmed by positive culture results in the laboratory from January 2007 to January 2008. All results were confirmed positive cultures from Scripps Mercy Hospital Microbiology Lab from various sources of the foot and leg including wound fluid, swabs, and tissue cultures. The first value that was obtained was the infections from foot and leg wounds (skin and soft tissue samples) and the specific breakdown from infective pathogenic Staph aureus (MRSA versus MSSA) bacteria. This last category was briefly analyzed for resistance patterns and MIC changes. The categories were established for inpatient (admitted patients, inpatient operating room cultures, rehabilitation facility cultures, etc.) and outpatient (emergency room non-admitted, ambulatory surgery, and clinical cultures, etc.) groups to examine the difference in risk factors for these patients. All concomitant medical conditions as well as a few related social conditions were analyzed for association with the different infective organisms establishing possible risk factors that could be associated with MRSA specifically. Utilizing a chi-square analysis for contingency tables, significance was examined for each medical co-morbidity when combined with either a MRSA or MSSA infection. P values less than 0.01 were considered to be significant, and a great positive trend was P less than 0.05.

Prospective Study

Questionnaires were distributed to patients that had a confirmed positive MRSA infection of the foot or leg while they were still admitted in one hospital (SMH) (Figure 1). These were to be filled out confidentially and sealed in envelopes that were non-labeled to secure patient anonymity. This would also encourage patients to be most truthful of their responses concerning various scenarios covered in the questionnaire for a more accurate representation of their background history. The questionnaire contained 3 subdivisions including a medical history section, a social history section, and a living situation section to cover most previously identified risk factors with MRSA carriage and infection in any body system obtained through earlier studies. The questionnaire was approved and analyzed by our infectious disease representative and deemed to be complete enough to cover most major "risk factors" of MRSA infection. This

A. Medical

1. Do you have any of the following diagnoses? (check all that apply)
   __Diabetes __Coronary artery disease __Heart Failure __HTN __Stroke __high cholesterol
   __Peripheral Vascular Disease __Peripheral Neuropathy
   __Cancer Autoimmune Disease (rheumatoid,lupus,etc.) __HIV/AIDS __Hepatitis __Kidney Disease
   __On Dialysis __COPD __Prosthetic/Implantable device (hip/screws/pacer/tubes etc.)
   __Chronic ulcers of skin For How Long? (<3mo, 3-6mo, >6mo.) __Chronic Bronchitis/asthma
   __Tuberculosis __Skin disorder (eczema/psoriasis/scleroderma/etc.)
   Other?_____
2. Have you been in the hospital recently for treatment? Y/N
   If yes, for what?_____
3. Have you had a recent Surgical Procedure? Y/N
   How long ago? <3months/3-6 months/>6months (circle one)
   On the foot? Y/N
   If yes what was done?_____
   Did you receive an implant? Y/N
4. Previous MRSA Infection? Y/N
   On foot/skin other than foot/elsewhere (circle one)
5. Have you been on antibiotics recently? Y/N
   If so, what was name?_____
   How long ago did you receive antibiotics? <3months/3-6 months/>6months (circle one)

B. Living Situation

1. What best describes your living situation?
   Single Family Home/Extended Family Home/Apartment/Hotel/Shelter/No Home (circle those that apply)
2. Do you live alone? Y/N If not how many people live with you?_____
3. Are there children at your home? Few/many/none
   Do they attend daycare or school? Y/N
3. Has anyone in the Family had a MRSA infection?
   On foot/skin other than foot/elsewhere (circle one)
4. Has anyone in the family been on antibiotics recently? Y/N
   If so, what was name?_____
   How long ago did they receive antibiotics? <3months/3-6 months/>6months (circle one)

C. Activity

1. Age?_____ Height?_____ Weight?____
2. Do you smoke? Y/N How much (if yes)_____
3. Do you drink alcohol? Y/N If so, how much per week?_____
4. Have you ever taken any illicit drugs? Y/N
   What type?_____
   Have you ever injected any drugs? Y/N
5. Have you ever spent any time in prison? Y/N How Recently?_____
6. In the military? Y/N How Recently?_____
7. Has anyone you are living with done either of the above? Y/N
   How recently?_____
8. Do you consider yourself active or fairly sedentary?_____
9. Do you belong to a gym?
   How often do you attend per week?_____
   Do you use any of the shared facilities? (shower/bathroom/pool/weight training area/cardio area)
10. Are you a professional athelete or a member of an organized sports team? Y/N
11. Are you/Were you involved in the Health Care professions? Y/N

Figure 1. MRSA Questionaire.

was further analyzed for any significant values and/or trends when all questionnaires were evaluated in a group to identify anything that may be helpful for developing prescreening questions that may be of importance for MRSA foot/leg infection (Figure 1).

RESULTS

Infection Analysis and Medical Review

For the year in question at this facility there were 205 positive cultures for Staphylococcus organisms in the foot and leg. Methicillin Resistant Organisms accounted for 99 of these or approximately 48% of all positive SA cultures. This was further dissected into outpatient and inpatient groupings. The inpatient grouping consisted of 104 patients that were cultured in the hospital setting (admitted patients, inpatient operating room cultures, rehabilitation facility cultures, etc.), whereas the outpatient grouping consisted of 101 total patients cultured in more outpatient settings (emergency room non-admitted, ambulatory surgery, and clinical cultures, etc.). Inpatient group MRSA positive cultures numbered 64 or 104 or 62% of all inpatient Staphylococcal cultures, while outpatient consisted of only 35 of 101 or 34% of the positive cultures in this grouping. Methicillin Sensitive Organisms accounted for 106 of all positive SA cultures or 52%. When divided into outpatient and inpatient groups, MSSA only accounted for 40 of 104 or 38% of all positive inpatient SA cultures, while it increased to 66 of 101 or 66% of outpatient Staph. cultures. These were calculated by means of chi-square testing to be considered significantly separate and independent groupings with a P value < 0.001 (Table 1).

In-Patient MRSA

Of the 64 positive inpatient MRSA cultures, 34 of 64 or 53% had been recently hospitalized within the previous 6 months for one reason or another, 28 of 64 (43%) within the previous 3 months, and 19 of 64 (29%) within the past 1 month time frame. The remainder had not been hospitalized for longer than 6 months or more. Of note 8 of 64 (13%) of the patients had no previous hospital record or hospitalization. Forty-two of the patients or 66% had multiple hospitalizations (>1) for more than 1 week duration in their recent medical history (within the past year). Fifteen (23%) of the patients had recently spent time in a rehabilitation facility. Of the most common listed concomitant medical co-morbidities, history of chronic ulceration with previous infection was first at 36 of 64 or 56%. Diabetes was listed as 27 of 64 or 42% and specifically Insulin Dependant Diabetes was 23 of 27 or 85% of those. Peripheral vascular disease was mentioned in 22 of 64 or 34%, heart disease was a similar 21 of 64 or 33%. Neuropathy was included in 18 of 64 patient's history or 28%. Chronic kidney disease was 17 of 64 or 27% of patients and of these 59% 10 of 17 were dialysis dependant (ESRD). Other risk factors examined were history of previous MRSA infection, which in this population was 20 of 64 or 31%, recent surgery 24 of 64 or 38%, and recent antibiotic use 36 of 64 or 56% of patients, specifically cephalosporins which accounted for 55% of all antibiotics listed (Table 2).

In-Patient MSSA

Out of the 40 positive inpatient MSSA cultures, 7 of 40 or 17% had been recently hospitalized within the previous 6 months for one reason or another, 5 of 40 (13%) within the previous 3 months, and no change 5 of 40 (13%) within the past 1 month time frame. The remainder had not been hospitalized for greater than 6 months or more. Of note 20 of 40 (50%) of the patients had no previous hospital record or hospitalization. Three of the patients or 8% had multiple hospitalizations (>1) for more than 1 week duration in their recent medical history (within the past year). Three (8%) of the patients had recently spent time in a rehabilitation facility. Of the most common listed concomitant medical comorbidities, history of hypertension was first in this group with 17 of 40 or 43%. Diabetes was listed as 16 of 40 or 40% and specifically Non-Insulin Dependant Diabetes was 12 of 16 or 75% of those. Peripheral vascular disease was mentioned in 6 of 40 or 15%, heart disease was a similar 8 of 40 or 20%. Chronic kidney disease was 8 of 40 or 20% of patients and of these 62% 5 of 8 were not dialysis dependant. Chronic wounds were identified in 11 of 40 (28%) of patients.

Table 1

GENERAL RESULTS FOR MRSA AND MSSA CULTURES IN IN-PATIENT AND OUT-PATIENT SETTINGS

	MRSA	MSSA	TOTAL	*P*
Inpt (BEDS/ ICU/CRH)	64/104 (62%)	40/104 (38%)	104	<0.001
Outpt (ED,ASC, Clin)	35/101 (34%)	66/101 (66%)	101	<0.001
Total	99/205 (48%)	106/205 (52%)	205	

Neuropathy was included in 4 of 40 patient's history or 10%. Other risk factors examined were history of previous MRSA infection, which in this population was 1 of 40 or 3%, recent surgery 4 of 40 or 10%, and recent antibiotic use 8 of 40 or 20% of patients. Out of the antibiotic group, penicillin was a number one group with 3 of 9 of the listed antibiotics used, or 33% (Table 2).

Out-Patient MRSA

Out of the 35 positive outpatient MRSA cultures 16 of 5 or 46% had been recently hospitalized within the previous 6 months for various reasons, 12 of 35 (34%) within the previous 3 months, and no change 12 of 35 (34%) within the past 1 month time frame. The remainder had not been hospitalized for greater than 6 months or more. Of note

Table 2

INPATIENT MRSA AND MSSA COMORBIDITIES AND RISKS

	INPATIENT MRSA	MSSA	REL. MULT.	CHI-SQ.	*P*
Risk Factors					
Recent Hospitalization					
<6mo	34 (53%)	7 (17%)	3	13.0815331	<0.001
<3mo	28 (44%)	5 (13%)	3	11.0968843	<0.001
<1mo	19 (30%)	5 (13%)	2	4.09635417	<0.05
Multiple Hospitalization	42 (66%)	3 (8%)	8	33.879322	<0.001
No Hospitalization	8 (13%)	20 (50%)	-2.5	17.593985	<0.001
Rehab Facil	15 (23%)	3 (8%)	2.8	4.36860465	<0.05
Medical comorbidities					
DM	27 (42%)	16 (40%)	1	0.04857034	>0.5
IDDM	23 (36%)	4 (10%)	3	8.61539202	<0.001
NIDDM	4 (6%)	12 (30%)	-5	10.6659091	<0.001
HTN	19 (30%)	17 (43%)	1	1.78537582	<0.5
PVD	22 (34%)	6 (15%)	2	4.69661654	<0.05
CKD	17 (27%)	8 (20%)	1	0.58055696	<0.5
with dialysis	10 (16%)	3 (8%)	1.5	1.48571429	<0.5
without dialysis	7 (11%)	5 (13%)	-1.5	0.05887681	>0.5
Heart Dx	21 (33%)	8 (20%)	2.5	2.00947126	<0.5
Lung Dx	4 (6%)	1 (3%)	2	0.75636364	<0.5
Liver Dx	13 (20%)	2 (5%)	4	4.67610487	<0.05
Thyroid	7 (11%)	2 (5%)	2	1.2480023	<0.5
Obesity	8 (13%)	4 (10%)	1	0.15072464	>0.5
HIV	4 (6%)	0 (0%)	0	2.6	<0.5
Neuropathy	18 (28%)	4 (10%)	2.5	4.84833703	<0.05
Chronic Wound	26 (41%)	11 (28%)	2	1.85010085	<0.5
Prev. Infection	36 (56%)	6 (15%)	4	17.397235	<0.001
Prev. MRSA	20 (31%)	1 (3%)	10	12.6255881	<0.001
Recent Surgery	24 (38%)	4 (10%)	4	9.46165414	<0.01
Recent Abx	36 (56%)	8 (20%)	2.5	13.2521212	<0.001
1st gen ceph.	24 (38%)	1 (3%)	10	16.5136203	<0.001
levaquin	3 (5%)	0 (0%)	0	1.93069307	<0.5
clindamycin	1 (2%)	0 (0%)	0	0.63106796	<0.5
bactrim	7 (11%)	2 (5%)	2	1.09777778	<0.5
vancomycin	6 (9%)	2 (5%)	2	0.66354167	<0.5
penicillin	3 (5%)	3 (8%)	-1.5	0.35816327	>0.5
doxycycline	0 (0%)	0 (0%)	0	undefined	none
ertapenam	0 (0%)	1 (3%)	0	1.61553398	<0.5

9 of 35 (26%) of the patients had no previous hospital record or hospitalization. A total of 20 of 35 of the patients or 57% had multiple hospitalizations (>1) for more than 1 week duration in their recent medical history (within the past year). Five (14%) of the patients had recently spent time in a rehabilitation facility. Of the most common listed concomitant medical co-morbidities, history of chronic ulceration with previous infection was first at 20 of 35 or 60%. Recent antibiotic use was a close second risk factor with 18 of 35 or 57% positive results. Out of these, first generation cephalosporins were the most common accounting for 63% or 10 of 18 followed by Bactrim use at 4 of 18 or 25%. Diabetes was listed as 12 of 35 or 34% and specifically Insulin Dependant Diabetes was 11 of 12 or 92% of those. Previous MRSA infection and history of recent surgery were both recorded at 37% of cases or 13 of 35. Peripheral vascular disease was mentioned in 3 of 35 or 9%, heart disease was a similar 5 of 35 or 14%. Neuropathy was included in 8 of 35 patient's history or 23%. Chronic kidney disease was 1 of 35 or 3% of patients and of these 100% 1 of 1 were non-dialysis dependant (Table 3).

Out Patient MSSA

Out of the 66 positive outpatient MSSA cultures 9 of 66 or 14% had been recently hospitalized within the previous 6 months for various reasons, 6 of 66 (9%) within the previous 3 months, and no change 3 of 66 (5%) within the past 1 month time frame. The remainder had not been hospitalized for greater than 6 months or more. Of note 37 of 66 (57%) of the patients had no previous hospital record or hospitalization. A total of 6 of 66 of the patients or 9% had multiple hospitalizations (>1) for more than 1 week duration in their recent medical history (within the past year). Two (3%) of the patients had recently spent time in a rehabilitation facility. Of the most common listed concomitant medical comorbidities, Diabetes was first accounting for 21 of 66 or 32% most of which were non-insulin dependant 15 of 21 or 70%. This was followed by hypertension which was seen in 17 of 66 or 27% of patients. Recent surgery history was common consisting of 19 of 66 or 29%. History of chronic ulceration with previous infection was 9 of 66 or 14%. Recent antibiotic use was noted in 7 of 66 (11%). Of these, first generation cephalosporins were the most common accounting for 33% or 4 of 12 antibiotics listed. Previous MRSA infection was recorded at 1 of 66 or 2% of cases in this setting. Peripheral vascular disease was mentioned in 5 of 66 or 8%, heart disease was a similar 2 of 66 or 3%. Neuropathy was included in 8 of 66 patient's history or 12%. Chronic kidney disease was 1 of 66 or 2% of patients and of these 100% 1 of 1 were non-dialysis dependant (Table 3).

Results of Prospective Questionnaire

There were a total of 26 prospective patients that were given the questionnaire over the course of 8 months at the institution once they were determined by means of deep culture to have a foot and or ankle infection that involved MRSA on the podiatry service. Of the 26 patients 13 or 50% were recently in the hospital for treatment (<6 months) prior to the admission in question. A total of 17 of 26 had been hospitalized a multiple amount of times in the last year for various reasons, 6 of 26 had only one hospitalization prior, and 3 of 26 had none. None of these patients were involved with a rehabilitation facility in the previous year. A total of 22 of 26 or 85% of these patients were Diabetic, and 82% of these were specifically IDDM (18 of 22); 16 of 26 patients had peripheral vascular disease, and a similar number had neuropathy, both accounting for 62% of respondants. Chronic ulcerations were seen in 69% (18 of 26) patients, and 13 of 26 (50%) had previous infection in the past year. Previous MRSA infection specifically accounted for 7 of 26 or 27%. Half of respondants had a recent dose of antibiotics, most commonly first generation cephalosporins, accounting for 62% of those.

Socially, of the people that responded 5 of 26 (19%) were homeless, 7 of 26 (27%) shared common utilities/facilities, and 4 of 26 or 15% were former or current IV drug users. Out of the 3 people that had no previous hospitalization, one had family members in their household that were active participants in the medical field, and two had gym memberships, where they believed that they contracted their infection from having no other risk factors (Table 4).

DISCUSSION

Methicillin Resistant Staphylococcus Aureus (MRSA), once primarily a healthcare associated infection has now increased in prevalence over the last decades as a community acquired pathogen. The SCOPE database prospective survey demonstrated an increase from 1995 at 22% to 57% in 2001.[43] NNIS through June of 2004 had estimated 53% of ICU patients had MRSA contamination or infection, 46% of non-ICU patients and 31% of outpatients.[44] In March of 2005 these numbers were updated to 59% non-ICU patients and 47.9% outpatients harboring MRSA out of all staph cultures.[45] This bacterium has been studied as a complicating factor in many medical fields, but has only briefly been examined in orthopedic research. Risk factors have been established for invasive infection,[12,18,24,27,43] SSTIs,[28,29] and overall emergency department nasal colonization[9-11,14,16,23] through research in the general medical and infectious

disease literature. Due to the rapidly increasing amount of resistant bacteria that we encounter in foot and ankle infections, we are obligated as practitioners to examine the risk factors involved for patients to be carriers.

Most isolates from the early 1960s, when MRSA was first identified, were from a single clone of MRSA.[1] Since this time 5 major clones have been identified. Most in the scientific community believe that this spread was mediated by cross transference of genetic material between bacteria, increased antibiotic use, and greater demand for health care needs coupled with an increase in exposure to healthcare related facilities.[2-6] Most HA-MRSA are labeled strains I-III and are multi-drug resistant with a separate molecular structure whereas most CA-MRSA are strain IV and demonstrate less resistance to antibiotic categories.[2-6] Many studies earlier in MRSA outbreaks had separated

Table 3

OUTPATIENT MRSA AND MSSA COMORBIDITIES AND RISKS

	OUTPATIENT MRSA	MSSA	REL. MULT.	CHI-SQ.	*P*
Risk Factors					
Recent Hospitalization					
<6mo	16 (46%)	9 (14%)	3	12.635494	<0.001
<3mo	12 (34%)	6 (9%)	4	9.9129922	<0.01
<1mo	12 (34%)	3 (5%)	7	15.996802	<0.001
Multiple Hospitalization	20 (57%)	6 (9%)	8	27.626174	<0.001
No Hospitalization	9 (26%)	37 (56%)	-2	8.4922918	<0.01
Rehab Facil	5 (14%)	2 (3%)	5	4.4919012	<0.05
Medical comorbidities					
DM	12 (34%)	21 (32%)	1	0.0633047	>0.5
IDDM	11 (31%)	6 (9%)	3	8.1523082	<0.01
NIDDM	1 (3%)	15 (23%)	-8	6.7732305	<0.01
HTN	8 (23%)	17 (26%)	1	0.1033012	>0.5
PVD	3 (9%)	5 (8%)	1	0.031088	>0.5
CKD	1 (3%)	1 (2%)	1	0.2122109	>0.5
with dialysis	0 (0%)	0 (0%)	1	undefined	none
without dialysis	1 (3%)	1 (2%)	1	0.2122109	>0.5
Heart Dx	5 (14%)	2 (3%)	5	4.4919012	<0.05
Lung Dx	1 (3%)	0 (0%)		1.9045714	<0.5
Liver Dx	1 (3%)	4 (6%)	-2	0.4988059	<0.5
Thyroid	4 (11%)	4 (6%)	2	0.9036075	<0.5
Obesity	1 (3%)	4 (6%)	-2	0.4988059	<0.5
HIV	4 (11%)	0 (0%)		7.8539028	<0.01
Neuropathy	8 (23%)	8 (12%)	2	1.9773058	<0.5
Chronic Wound	11 (31%)	13 (20%)	1.5	1.7375848	<0.5
Prev. Infection	21 (60%)	9 (14%)	4	23.545544	<0.001
Prev. MRSA	13 (37%)	1 (2%)	18	24.3143	<0.001
Recent Surgery	13 (37%)	19 (29%)	1	0.7376069	<0.5
Recent Abx	18 (51%)	7 (11%)	4.5	20.463465	<0.001
1st gen ceph.	10 (29%)	4 (6%)		9.7066371	<0.001
levaquin	1 (3%)	0 (0%)		1.9045714	<0.5
clindamycin	0 (0%)	1 (2%)		0.5275602	<0.5
bactrim	4 (11%)	2 (3%)		2.8869416	<0.1
vancomycin	2 (6%)	1 (2%)		1.3992829	<0.5
penicillin	0 (0%)	2 (3%)		1.0820325	<0.5
doxycycline	1 (3%)	2 (3%)		0.0023795	>0.5
ertapenam	0 (0%)	0 (0%)		undefined	none

Table 4

PROSPECTIVE QUESTIONNAIRE MRSA RISKS AND COMORBIDITIES

QUESTIONAIRE			
MRSA Foot Total	26		
Risk Factors			
Recent Hospitalization			
<6mo	13 (50%)		
Multiple Hospitalization	17 (65%)		
One Hospitalization	6 (23%)		
No Hospitalization	3 (12%)		
Rehab Facil	0 (0%)		
Medical comorbidities		***Other***	
DM	22 (85%)	Family in health field not in hosp prior	1 (4%)
IDDM	18 (69%)	gym members not in hosp prior	2 (8%)
NIDDM	4 (15%)		
HTN	7 (27%)	homeless	5 (19%)
PVD	16 (62%)	shared facilities	7 (27%)
CKD	5 (19%)	ivda	4 (15%)
with dialysis	2 (8%)		
without dialysis	3 (12%)		
Heart Dx	12 (46%)		
Lung Dx	0 (0%)		
Liver Dx	0 (0%)		
Thyroid	1 (4%)		
Obesity	4 (15%)		
HIV	0 (0%)		
Neuropathy	16 (62%)		
Chronic Wound	18 (69%)		
Prev. Infection	13 (50%)		
Prev. MRSA	7 (27%)		
Recent Surgery	4 (18%)		
Recent Abx	13 (50%)		
ancef	8 (31%)		

these categories, but recently it is suspected that there was an original underestimation of health care exposure from these patients that were given CA-MRSA status. It is believed that many nosocomial strains have spread to these households and community contacts in addition mutating along the way.[12]

Our study results mirror previous studies in the medical literature,[9-29] and while molecular typing was not performed, most strains remained susceptible to the usual anti-MRSA medications in our location. When examined in general, approximately half of all Staph aureus cultures were MRSA,which is alarmingly high but consistent with medical literature. However, this includes subdivisions of inpatient and outpatient grouped together. When separated, inpatient numbers were considerably higher and MRSA accounted for two-thirds of all Staph cultures. This is also consistent with some of the newer studies on MRSA prevalence in hospitals around the country.[23,44,45]

Outpatient numbers were expectantly lower and only accounted for one-third of all Staph cultures. These are all statistically significant groupings with a P value < 0.001. When examined critically, it can be assumed that this difference is most likely due to less chronic and debilitating co-morbid conditions in the outpatient population. There were less severe kidney, heart, liver, and lung diseases in the outpatient population when compared

with the inpatients that had MRSA. Diabetics were still majority insulin dependant, but other co-morbidities were less severe, leading one to believe that these patients spend less time in healthcare arenas than the inpatient group thereby inducing less exposure to potential MRSA sources. These numbers would lead us to believe that increased healthcare exposure may predispose a patient to an increased risk of MRSA foot and leg infection. An overall value of 8.2% of MRSA patients that were seen for Staph aureus infections had no previous hospital record, which does fall within the range of recent studies as well, whose values ranged from 1-15%.[12]

MRSA positive patients when compared with MSSA in foot and leg infections for inpatients had a significantly larger amount of recent hospitalizations within the previous year as well as a greater chance of having had multiple hospitalizations in their recent medical history. These values were almost 4 and 8 times more common among the MRSA positive patients respectively and were all significant with P values < 0.001. The MRSA patients did have a larger amount of liver disease patients that showed a trend toward becoming significant but was not at a P value of < 0.05. The group had similar amounts of diabetes and chronic kidney disease as MSSA patients. However, when further examined in detail, MRSA patients had a significantly larger population that was insulin dependant diabetics ($P < 0.001$) as well as a trend of greater chronic kidney disease in need of dialysis ($P < 0.5$).

While chronic wounds were common findings in both groups, previous infection did significantly differentiate the two categories, MRSA patients being 4 times more likely to have been previously recently infected ($P < 0.001$). Previous MRSA infection in particular was 10 times more common in the MRSA grouping, which is completely expected as a large risk factor ($P < 0.001$). Recent surgery seemed to be a risk factor that was 3 times as likely in the inpatient category for MRSA infection ($P < 0.01$). It was a significant factor in this subgroup with a P value of 0.001. This could be explained by the probable need for more invasive surgery and longer hospital stay in these patients due to their coexisting medical conditions and inpatient status.

Finally, recent antibiotic use was twice as likely in the MRSA patients as their MSSA counterparts with cephalosporins being larger culprits of MRSA promotion ($P < 0.001$). Bactrim and levaquin showed some trend toward favoring MRSA but was not significant ($P < 0.5$). MSSA group had a statistical significant risk in patients with no previous hospitalizations ($P < 0.001$) compared with MRSA. NIDDM was also significant as a risk factor for wounds containing MSSA over MRSA. The risk factors identified for MRSA all correspond with previous studies that were conducted in the medical literature for other categories of infection.[9-12,14,16,18,23,24,27-29] It appears that the greatest risk factors for harboring MRSA in the foot and ankle for inpatients were previous MRSA infection, multiple hospitalizations, recent infection in chronic wounds, recent hospitalization (within 3 months or greater), recent surgery, recent antibiotic use, particularly cephalosporins, IDDM, and trends towards more chronic debilitating states of co-morbid conditions. There may be other factors that are social such as homelessness and shared facilities in addition to IVDA but these were not noted consistently in charting to lend significance to their connection to MRSA in this retrospective portion of the study.

For outpatient groupings of MRSA in the foot and ankle versus MSSA, again larger amounts of recent and multiple hospitalizations were appreciated. These categories were also 4 and 8 times greater in the MRSA patients respectively, ($P < 0.001$). No other co-morbid condition medically was significant, with the exception of the subgroup of insulin dependant diabetics being larger in the MRSA group similar to the inpatient categories but to a lesser degree ($P < 0.01$). HIV was also noted as significant to the same caliber as the insulin-dependant diabetics ($P < 0.01$). Previous infection in a wound was 5 times more likely in the MRSA group, and specifically previous MRSA infection was almost 20 times more common in this patient constituent ($P < 0.001$). Recent surgery was not a significant risk versus the MSSA group as both were similar in occurrence ($P < 0.5$). This could be explained by the probable outpatient nature of these patients' surgical procedures due to their general lack of dangerous co-morbidities. Recent antibiotic use once again greatly favored the MRSA group by nearly a factor of 5 ($P < 0.001$). Cephalosporins ($P < 0.001$) were significant risks, whereas Bactrim ($P < 0.1$), and levaquin ($P < 0.5$) were once again noted to be trends for the MRSA patients. MSSA had a significant value for no hospitalization again ($P < 0.001$). These risks are similar to other medical and infectious disease studies and mirror, to an extent, the inpatient numbers.[9-12,14,16,18,23,24,27-29] The greatest risk was once again previous MRSA infection, followed by multiple hospitalizations, previous antibiotic use, previous infection in a chronic wound, and recent hospitalization respectively.

This was a fairly limited portion of the study since it only examined 26 patients who were diagnosed with a MRSA foot and leg infection. These patients were confirmed positive by means of deep culture perhaps making them a more accurate representation, excluding

some superficial swabs that may have been included in the retrospective study portion. These patients were not compared with a control group, as the retrospective portion was, but were given true values and percentages that had a certain risk or characteristic. This being said, the numbers were very similar percentages for risks in this group. Two-thirds of these patients had multiple hospitalizations, and half had a hospitalization within the previous 6 months. These are considerably large portions of the population that was questioned. Larger percentages of individuals admitted to having co-morbid conditions than in the retrospective analysis. Diabetes in general was a larger percentage of patients, but the insulin dependence percentage was similar to the other portion of the study. Hypertension percentages were similar, but peripheral vascular disease was a much larger proportion that originally determined through chart review. Heart disease and neuropathy were also much larger percentages than originally appreciated in the retrospective analysis. These may be larger due to chart oversights or even omissions on the part of clinicians from the retrospective review. Patients had previous MRSA in one-third of the cases which was consistent with the review values, and had previous infection in chronic wounds half of the time which also corresponded to earlier percentages.

There were a larger portion of chronic wounds, 60%, that were reported in this portion of the study, which may also be attributable to clinician history oversight in the retrospective charts. Recent antibiotic was administered in half of these patients which also correlates with the earlier portion of the study. Two thirds of these were cephalosporin. Out of all of the patients, 3 (12%) had no previous hospital record, which corresponds to our retrospective numbers as well as documented previous studies.[9-12,14,16,18,23,24,27-29] Two of these patients with no hospital exposure had been gym members and shared equipment that led to blistering, and one of these had members in her household that were in the medical field. Other responses involved homelessness, intravenous drug use, and shared facilities as risk factors but these only seemed to be trends around 15-25% of responses. With a larger study cohort these may become significant factors to be aware of as well.

It has been discovered that MRSA has been most commonly transferred from one patient to another by healthcare workers who are transiently contaminated or through droplet or direct contact from a chronic nasal carrier.[46] It has also been estimated that 30-60% of hospitalized patients will acquire MRSA and develop a subsequent MRSA infection.[47] While it does not exclude the more rare healthy patient that is a child or athlete, this study demonstrates the greater risk patients in both inpatient and outpatient settings for MRSA foot and ankle infection continues to currently be patients with previous MRSA infection, those with greater health care exposure, recent antibiotic use, chronic debilitating co-morbidities typically requiring hospitalizations, and history of previous infection in a chronic wound.

Recent studies document the effects of over-prescribing antibiotics.[30-33] Other studies have shown that treating a localized MRSA infection with inappropriate antibiotics and surgical debridement was as effective as treating with appropriate antibiotics.[48,49] With all of this recent literature in mind, a treatment triangle has been proposed to help control the spread of MRSA in addition to properly treating the patients who do have infections from this bacterium.[7] We all as practitioners must be diligent about hand hygiene, isolate patients who are documented carriers or those infected with MRSA, treat with appropriate antibiotics when necessary, and surgically debride wounds when needed. If used properly, this will aid in the decrease in formation of costly resistant bacterial strains such as VISA/GISA, VRSA, and VRE. It will also help prevent the over-prescription of antibiotics which may be unnecessary. Anti-MRSA drugs should be spared unless a patient has known established risk factors and/or a limb threatening infection. This study, while not all inclusive, should help to guide the foot and ankle practitioner to identify the patient that is most at risk for MRSA infection.

This study does have limitations in that it was partially a retrospective study and chart review. This does not always include all diagnoses, and often can miss critical procedures or hospitalizations at other facilities who do not share medical records with our facility. This is a common limitation to many of the MRSA medical studies that are now published. The study also used culture positive results from the lab which were positive for infection, but may have been contaminating organisms if a superficial swab was performed to obtain the culture. Our study also only focused on a majority of patients who were seen at a hospital setting. Further studies should be done to analyze office visits and outpatient areas to determine more obscure risks that are associated with the CA-MRSA strains. The prospective study was conducted on only 26 patients and may need to be distributed to greater numbers for stronger significance in addition to MSSA patients to function as a control for risks of carrying or becoming infected with non-resistant Staph bacteria.

REFERENCES

1. Benner, EJ, Kayser FH. Growing Clinical significance of methicillin-resistant Staphylococcus aureus. *Lancet* 1968;2:741.
2. Ito T, Katayama Y, Asada K, et al. Structural comparison of three types of staphylococcal cassette chromosome mec integrated in the chromosome in methicillin resistant Staphylococcus aureus. *Antimicrob Agents Chemother* 2001;45:1323.
3. Daum RS, Ito T, Hiramatsu K, et al. A novel methicillin resistance cassette in community acquired MRSA isolates of diverse genetic backgrounds. *J Infectious Disease* 2002;186:1344.
4. Baba T, Takeuchi F, Kuroda M, et al. Genome and virulence determinants of high virulence community acquired MRSA. *Lancet* 2002;359:1819.
5. Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community and health care associated MRSA infection. *J Am Med Assoc* 2003;290:2976.
6. Ma XX, Ito T, Tiensasitorn C, et al. Novel type of staphylococcal cassette chromosome mec identified in community acquired MRSA strains. *Antimicrob Agents Chemother.* 2002;46:1147.
7. Grayson ML. The treatment triangle for Staphylococcal infections. *New Engl J Med* 2006;355:724.
8. Fraser TG, Hansen C, Long JK. Newer antibiotics for serious gram positive infections. *Clev Clinic J Med* 2006;73:847.
9. Kuehnert MJ, Kruszon-Moran D, Hill HA, et al. Prevalence of Staph aureus nasal colonization in the United States, 2001-2002. *J Infect Dis* 2006;193:172.
10. Kluytmans J, van Belkum A, verbrugh H. Nasal carriage of staphylococcus aureus: epidemiology, underlying mechanisms and associated risks. *Clin Micro Rev* 1997;10:505.
11. Viallon A, Marjollet O, Berthelot P, et al. Risk factors associated with MRSA infection in patients admitted to the ED. *Am J Emerg Med* 2007;25:880.
12. Klevens RM, Morrisson MA, Nadle J, et al. Invasive MRSA infections in the United States. *J Am Med Assoc* 2007;298:1763.
13. Ellis MW, Hospenthal DR, Dooley DP, et al. Natural history of CA-MRSA colonization and infection in soldiers. *C Infect Dis* 2004;39:971.
14. Hidron AI, Kourbatova EV, Halvosa JS, et al. Risk factors for colonization with MRSA in patients admitted to an urban hospital: emergence of CA-MRSA nasal carriage. *C Infect Dis* 2005;41:159.
15. Salgado CD, Farr BM, Calfee DP. CA-MRSA: A meta-analysis of prevalence and risk factors. *C Infect Dis* 2003;36:131.
16. Davis KA, Stewart JJ, Crouch HK, et al. MRSA nares colonization at hospital admission and its effect on subsequent MRSA infection. *C Infect Dis* 2004;39:776.
17. Begier, EM, Frenette, K, Barrett, NL, et al. A high morbidity outbreak of MRSA among players on a college football team, facilitated by cosmetic body shaving and turf burns. *C Infect Dis* 2004;39:1446.
18. Graffunder EM, Venezia RA. Risk factors associated with nosocomial MRSA infection including previous use of antimicrobials. *J Antimicrob Chemo* 2002;49:999.
19. Weber SG, Gold HS, Hooper DC, et al. Flouroquinolones and the risk for MRSA in hospitalized patients. *Emerg Inf Dis* 2003;9:1415.
20. Furuno JP, Harris AD, Wright MO, et al. Prediction rules to identify patients with MRSA and VRE upon hospital admission. *AJIC* 2004;32:436.
21. Lu PL, Chin LC, Peng CF, et al. Risk factors and molecular analysis of community MRSA carriage. *J Clin Microbio* 2005;43:132.
22. Graham PL, Lin SX, Larson EL. A US population based survey of SA colonization. *Ann Intern Med* 2006;144:318.
23. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. MRSA infections among patients in the Emergency Department. *N Engl J Med* 2006;355:666.
24. Kuehnert MJ, Hill HA, Kupronis BA, et al. MRSA hospitalizations, US. *Emer Inf Dis* 2005;11:868.
25. Gilbert M, MacDonald J, Gregson D, et al. Outbreak in Alberta of community acquired (USA 300) MRSA in people with a history of drug use, homelessness or incarceration. *CMAJ* 2006;175:149.
26. Campbell KM, Vaughn AF, Russell KL, et al. Risk factors for CA-MRSA infections in an outbreak of disease among military trainees in San Diego, CA in 2002. *J Clin Mircro* 2004;42:4050.
27. Huang SS, Platt R. Risk of MRSA infection after previous infection or colonization. *CID* 2003;36:281.
28. McCaig LF, McDonald LC, Mandal S, et al. Staphylococcus aureus associated skin and soft tissue infections in ambulatory care. *Emerg Inf Dis* 2006;12:1715.
29. Daum RS. Skin and soft tissue infections caused by MRSA. *N Engl J Med* 2007;357:380.
30. Bell EA. How can we decrease antibiotic resistance. *IDN Communication* 2007.
31. Belongia EA. A community intervention trial to promote judicious antibiotic use and reduce penicillin resistant streptococcus pneumoniae carriage in children. *Pediatrics* 2001;108:575.
32. Heppala H. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A Streptococci in Finland. *N Engl J Med* 1997;337:441.
33. Fridkin SK, Hageman J, McDougal LK, et al. Epidemiological and microbiological characterization of infections caused by Staph aureus with reduced susceptibility to vancomycin US 1997-2001.
34. MMWR Weekly. Staphylococcus aureus resistant to vancomycin US 2002. 2002;51:565.
35. Smith TL, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in Staphylococcus aureus. *N Engl J Med* 1999;340:493.
36. Fridkin SK. Vancomycin intermediate and resistant Staph aureus: what the infectious disease specialist needs to know. *C Inf Dis* 2001;32:108.
37. Chang S, Sievert DM, Hageman JS, et al. Infection with vancomycin resistant staphylococcus aureus containing vana resistance gene. *N Engl J Med* 2003;348:1342.
38. Wenzel RP. The antibiotic pipeline – challenges cost and values. *N Engl J Med* 2004;351:523.
39. Chambers HF. CA-MRSA – resistance and virulence converge. *N Engl J Med* 2005;352:1485.
40. Citron DM, Goldstein EJC, Merriam CV, et al. Bacteriology of moderate to severe diabetic foot infections and in vitro activity of antimicrobial agents. *J Clin Microbio* 2007;45:2819.
41. Kourbatova EV, Halvosa JS, King MD, et al. Emergence of CA-MRSA USA 300 clone as a cause of health care associated infections among patients with prosthetic joint infections. *AJIC* 2005;33:385.
42. Lecornet, E, Robert, J, Jacqueminet, S, et al. Preemptive Isolation to prevent MRSA cross transmission in diabetic foot. *Diabetes Care* 2007;30:2341.
43. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;5:180.
44. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32:470.
45. Styers D, Sheehan DJ, Hogan P, Sahm DF. Laboratory-based surveillance of current antimicrobial patterns and trends among Staphylococcus Aureus: 2005 status in the United States. *Ann Clin Microbiol Antimicrob* 2006;5:2.
46. Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin-resistant staphylococcus aureus. *Ann Intern Med* 1982;97:309.
47. Boyce JM. Methicillin Resistant Staphylococcus Aureus: detection, epidemiology, and control measures. *Infec Dis Clin N Am* 1989;3:901.
48. Dang CN, Prasad YD, Boulton AJ, Jude EB. Methicillin-Resistant Staphylococcus aureus in the diabetic foot clinic: a worsening problem. *Diab Med* 2003;20:159.
49. Lipsky BA, Armstrong DG, Citron DM, Tice AD, et al. Ertapenem versus pipercillin/tazobactam for diabetic foot infections (SIDESTEP): prospective randomized controlled, double blinded, multi-center trial. *Lancet* 2005;366:1695.