Comparative Mid-Term Outcomes of Pediatric Hematogenous Methicillin-Resistant *Staphylococcus aureus* and Methicillin-Susceptible *Staphylococcus aureus* Osteomyelitis

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ABSTRACT

Background:

Staphylococcus aureus (S. aureus) is the most common etiology of acute hematogenous osteomyelitis (AHO). Methicillin resistant *S aureus* (MRSA) AHO patients have a longer and more complicated hospital course than methicillin sensitive *S aureus*; however, there is a lack of information on mid-term outcomes after these types of bone infections. This study investigates differences in mid-term outcomes, including recurrence, readmission, complications and functional outcomes of pediatric patients with AHO caused by *S aureus*, at a minimum of 2 years post index infection.

Methods:

This is a two-phase study that includes a retrospective review of patients at Phoenix Children's Hospital from 2005-2014 with the diagnosis of *S aureus* AHO. Outcomes compared included complications, re-hospitalization, recurrence of infection, and will include pediatric outcomes documentation instrument (PODCI) scores and activity scale for kids (ASK) scores. Mid-term outcomes were assessed between MRSA and MSSA, and between localized and disseminated infection.

Results:

58 patients, 23 with MRSA (69.6% disseminated) 35 MSSA (51.4% disseminated) were included. Patients with disseminated disease were more likely to be younger, have a longer length of stay (LOS), more PICU days, more febrile and bacteremic days, and have more complications. Disseminated MRSA cases had the most complications and readmissions. MRSA infections had a longer LOS and duration of IV antibiotics. Patients with disseminated MSSA were least likely to require surgical intervention.

Conclusion:

Disseminated AHO has worse outcomes than localized AHO and MRSA AHO is more virulent than MSSA. Disseminated MRSA patients fared the worst of all groups would benefit from more intensive follow up.

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INTRODUCTION/SIGNIFICANCE

There has been a progressive rise of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) seen over the last two decades in the United States, which has in turn resulted in an increase in invasive pediatric infections.[1,2,4,6-9,13,17,20] Acute hematogenous osteoarticular infections, including osteomyelitis and septic arthritis, are relatively common in pediatric patients, occurring at a rate of approximately 1/10,000 children per year.[8,17,18] *Staphylococcus aureus (S. Aureus)* remains the most common pathogenic organism of musculoskeletal infections in children, and accounts for up to 70-90% of acute hematogenous osteomyelitis (AHO) in otherwise healthy pediatric patients.[1,3-8,15] *S. aureus* has the ability to adhere to bone and survive in the osteoblast, which may explain persistence of bone infection with this pathogen.[19]

Numerous studies have compared in-hospital progression of AHO derived from community acquired methicillin-susceptible *S. aureus* (CA-MSSA) infection vs. CA-MRSA. It is well documented that on average, CA-MRSA derived osteomyelitis vs. CA-MSSA, results in longer hospital admissions, more febrile days, a longer regimen of antibiotic therapy, an increase in overall complications, higher erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values, indicative of a more severe inflammatory process.[5-8,13,15,17]

S. aureus has several associated virulence factors that make it a more resistant and aggressive pathogen. The first, associated only with MRSA, is the *mecA* gene, which encodes for the low-affinity penicillin-binding protein PBP 2A on the bacterial cell wall that accounts for the organism's ability to resist methicillin and other Beta lactam antibiotics.[7,17,21] The second and arguably more important virulence factor is the Panton-Valentine leukocidin (*pvl*), which is encoded by genes lukS-PV and lukF-PV.[12] *Pvl* is a cytotoxin that lyses white blood cells (WBCs) via pore formation and promotes tissue necrosis.[11,12] *Pvl*+ *S. aureus* AHO is associated with a much more severe disease course than *pvl*- *S. aureus*.[1, 2, 5, 7, 11] The *pvl* genes are found with much greater frequency in CA-MRSA isolates than CA-MSSA, which is one likely reason why CA-MRSA osteomyelitis tends to have a more severe disease process with more febrile days, greater complications and sequelae.[1,2] A study done by Bocchini et al. noted that more than 90% of the CA-MRSA isolates at Texas Children's Hospital contained the *pvl* gene. In the pediatric population

with *S. aureus* osteomyelitis they reviewed, the 26 patients that were *pvl*- were all MSSA isolates, and of the 59 *pvl+,* 56 were MRSA and only 3 were MSSA. [1]

The *pvl* gene has not only been associated with a worse initial infection, but also a greater number of sequelae after hospital discharge. For example, a study done by Dohin et al. reported that 12 of the 14 *pvl*+ *S. aureus* patients with musculoskeletal infections had some form of complication at a median follow up of 16 months, whereas the *pvl*- infections recovered without any noted complications at follow up.[10]

The available literature does suggest that infection with CA-MRSA is associated with a greater likelihood of sequelae within the first two years after the index infection compared to other organisms.[14,15,22,23] Some of the post discharge complications discussed in such studies include chronic osteomyelitis, recurrence of infection, pathologic fracture, leg length discrepancy, growth plate arrest, avascular necrosis of the femoral head and gait abnormality.[3,7,14]

A study done by Roine et al. found that children with sequelae during their 2 month follow up, had higher CRP levels during days 1-6 of initial treatment, and higher ESRs during days 4-7 of treatment, than children without sequelae at follow up.[23] As previously stated, CA-MRSA osteomyelitis patients tend to have higher CRP levels and ESRs during hospitalization.

In another study, Belthur et al. identified 17 patients who were treated for a long-bone fracture secondary to *S. aureus* osteomyelitis. Of these 17 patients, 15 had MRSA isolates, and only two patients had MSSA isolates, with the mean time from disease onset to fracture being 72.1 days post index infection.[14]

Vander Have et al. in a retrospective study of 27 pediatric patients with MRSA derived musculoskeletal infections noted that 9 (33%) of the patients had "significant long-term sequelae." Four of the patients developed chronic osteomyelitis within the first 12 months from initial presentation. Other sequelae noted in this study includes fixed elbow contracture, heterotopic ossification around the hip, and distal tibial physeal arrest, however no timeframe for these complications was noted.[15]

Karwowska et al. reported in their study from 1998 that only 9 (6.6%) out of the 137 patients with osteomyelitis who were available for follow up had post discharge complications. For this study, the median duration of recorded follow-up was 1.2 months (range, 0.1 to 22.2 months). However, this study includes osteomyelitis caused from any pathogen and does not specify which pathogens resulted in later complications.[3]

Acute hematogenous osteomyelitis with community acquired methicillin-resistant *Staphylococcus aureus* as an etiology is still a relatively new phenomenon, having arisen around the turn of the 20th century. There are numerous studies that evaluate in-hospital and short-term outcomes of the disease course, however with its relatively brief history, there is a gap in the literature related to mid-term and long-term functional outcomes of these pediatric patients. This is the gap that our study aims to begin filling. This study will investigate if and how these infections might affect the child's function, development, activities of daily living, the likelihood of further complication and extended prognosis of pediatric patients with these types of infections at a minimum follow up of 2 years from the index infection.

The main goal of the study is to compare the treatment and outcomes between patients with MRSA and MSSA infections, but also localized and disseminated infections. This study has the potential to help re-think the surgical or non-surgical treatment of these two infections, as well as post hospital follow up and intervention. The original hypothesis is that treatment and outcomes between MRSA and MSSA, and localized and disseminated, will be different, specifically that MRSA and disseminated infection will have worse mid-term outcomes, and therefore clinical management decisions should be made with the type of organism and severity in mind.

MATERIALS AND METHODS

This retrospective study was performed at Phoenix Children's Hospital, Phoenix. To capture all acute, hematogenous, osteoarticular infections, the records of patients with discharge International Classification of Diseases, Ninth Revision codes for any acute or chronic osteoarticular infection (730.00, 730.19, 730.20, 730.39, 730.80, 730.99, 711.00, 711.09, 711.40, 711.49, and 711.80, 711.99) were reviewed. Patients with discharge dates between January 1, 2005 and December 31, 2014 were considered for inclusion.

Patients were included in the study if they had acute osteomyelitis with or without septic arthritis with a duration of symptoms of 14 days or less before clinical presentation. In addition, they had to have documented evidence of infection by at least one of the following 4 criteria adapted from Wald et al: (1) positive culture or Gram stain of bone or joint aspirate or joint fluid cell count of 50,000/mm3 or greater; (2) positive blood culture and an abnormal imaging study (radiograph, ultrasound, technetium bone scan, computed tomographic scan, or magnetic resonance imaging) consistent with osteomyelitis or septic arthritis as interpreted by a staff pediatric radiologist; (3) positive blood culture and abnormal physical examination characteristic (fever, point tenderness, swelling, pseudoparalysis, refusal to bear weight, or joint irritability) and consistent with osteomyelitis or septic arthritis; and (4) abnormal radiograph and physical examination characteristic and consistent with osteomyelitis or septic arthritis (as in criteria 2 and 3). Patients were classified as having osteomyelitis or both osteomyelitis and septic arthritis (osteomyelitis/ septic arthritis) based upon available clinical, radiographic, and operative data.

Patients were excluded if they had penetrating trauma (including a puncture wound of the foot), postoperative osteomyelitis, and foreign body in or adjacent to the affected bone or joint, or were hospitalized at the time of onset of symptoms. Patients with signs of infection in other systems (eg, meningitis, endocarditis, and pneumonia) will be eligible for inclusion. In addition, patients with underlying conditions such as sickle cell disease, immunodeficiency, cystic fibrosis, chronic skin disorder, chronic renal failure or history of malignancy were excluded.

From the medical records, demographic and clinical information was obtained: dates of admission, discharge, number of symptomatic days prior to presentation, last visit, clinical

course, antibiotic regimen, hospital days, days of ICU admission, readmissions, febrile days (=/>100.8°F), days of positive blood cultures in patients with bacteremia, indications for surgery, details of surgical treatment, if the patient required repeat surgeries, underlying medical conditions, complications and outcome at the time of the discharge and during the follow-up. Infections were categorized as localized or disseminated. Disseminated infections were defined as multiple sites of infection or one site of infection with bacteremia. Chronic osteomyelitis, pyomyositis, septic arthritis, deep venous thrombosis, myositis, pyomyositis, bursitis, septic arthritis, cardiac valve disease, endocarditis, pulmonary septic emboli, deep venous thrombosis, pleural effusion, coagulopathy, growth plate arrest, avascular necrosis, and septic shock and fracture at the site of infection were considered complications of osteomyelitis. The most up to date contact information for the patient's family was obtained from the medical record.

In the second phase of the study, the families of patients who were previously evaluated under the care of the Orthopedics Department at Phoenix Children's Hospital, are to be contacted via telephone and invited to participate in this study, which would include completion of two functional outcome questionnaires, the Pediatric Outcomes Documentation Instrument (PODCI) and the Activity Scale for Kids (ASK). The PODCI originated from The American Academy of Orthopaedic Surgeons and Pediatric Orthopaedic Society of North America commissioned work group in 1994, to establish a criteria to evaluate functional health outcomes for children and adolescents, focusing on musculoskeletal health.[24] The ASK Is a child self-report, validated measure of physical disability. It is designed for children 5 – 15 years old who are experiencing limitations in physical activity due to musculoskeletal disorders.[25]

The initial phone call will be completed by the Primary Investigator, an Orthopedic Surgeon at Phoenix Children's Hospital, accompanied by the co-investigator. If the family declines participation, no further contact will be made. If the family agrees to participate, updated contact information will be obtained including phone number, address and best time to contact. A packet of materials will be mailed to each family interested in participating. Each packet will include two copies of the consent and HIPAA forms (one copy to be signed and returned, one copy to remain with the family), two copies of an assent form (for patients aged 8+, one to be signed and returned and one to remain with the family), and both the PODCI and ASK questionnaires with

appropriate stamped return mailing envelopes. After the questionnaires have been sent out and received, the families will be contacted via telephone a second time to obtain informed consent. Consent will be obtained by the Primary Investigator. Once consent is obtained, the co-investigator can assist in completion of questionnaires over the phone, or families can choose to complete the questionnaires individually and return via mail. For Spanish speaking families, Spanish translational assistance will be provided by the Phoenix Children's Translation and Interpretation services department. The signed consent form, assent form, HIPAA form and completed surveys will be returned via the provided stamped and addressed return envelope.

Outcomes measured will be complications, re-hospitalizations, recurrence of infection, PODCI (Pediatric outcomes documentation Instrument) scores and ASK (Activity Scale for Kids) scores in these children.

Data analysis was performed using STATA version 14 (College Station, TX). Continuous variables will be reported as medians, with interquartile ranges and categorical variables with frequencies and proportions. Comparisons between groups for continuous variables will be made using the Wilcoxon Rank Sum test (MSSA vs MRSA and localized vs disseminated status). Comparisons of dichotomous outcomes between groups of patients with different etiologic agents will be performed using Fisher exact test, where appropriate. Logistic regression will be used to report odds ratios and 95% confidence intervals after adjusting for confounding bias. All p-values will be 2-sided and $p< 0.05$ will be considered statistically significant.

The primary outcome for this power and sample size calculation is the proportional difference in complications between MSSA patients vs MRSA patients. If we deem a 30% difference in the proportion of patients with complications as clinically significant, 84 (42 in each group) patients are needed to achieve a statistical power of 80%. If the proportional difference increases to 40%, 48 (24 in each group) patients are needed to achieve a statistical power of 80%.

RESULTS

Overview

Over 400 patients with the appropriate diagnostic codes were reviewed for inclusion, and a total of 58 patients were identified as meeting inclusion criteria as outlined in the methodology. Of the 58 patients, 23 had an index infection with MRSA (localized =7, disseminated = 16), and 35 had MSSA (localized = 17, disseminated = 18). The groups compared included MRSA and MSSA, all localized and all disseminated, MRSA localized and MRSA disseminated, MSSA localized and MSSA disseminated. Amongst all groups compared, there was no statistically significant difference between predilection of gender, ethnicity or whether or not the patient had any pre-existing conditions. However, disseminated infections did tend to occur at a younger age (average of 6 y/o) than localized infections (average of 10 y/o).

Some examples of complications include: myositis, pyomyositis, bursitis, septic arthritis, cardiac valve disease, endocarditis, pulmonary emboli, deep venous thrombosis, pleural effusion, coagulopathy, growth plate arrest, avascular necrosis, pathologic fracture, and chronic osteomyelitis (Figure 1). Localized MRSA infections notably did not have any documented complications from chart review. MRSA disseminated infections accounted for 57.4% of the total complications recorded, as compared with 31.5% of complications being associated with MSSA disseminated and only 11.1% of the complications associated with localized MSSA infections (Figure 1).

The most common site of infection was the lower extremity, with the lower leg (ie: tibia and fibula) accounting for 24.7% of all infectious loci, and the upper leg accounting for another 17.6% (Figure 2).

Figure 1. Complications identified through retrospective chart review. [54 total complications]

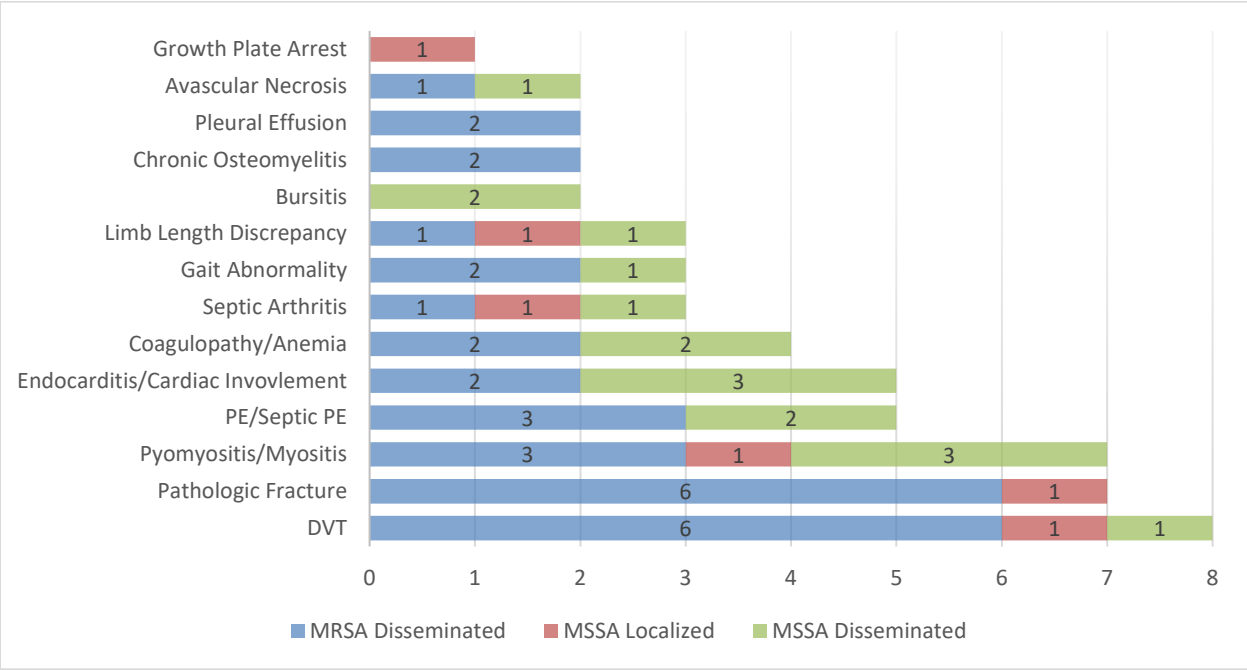
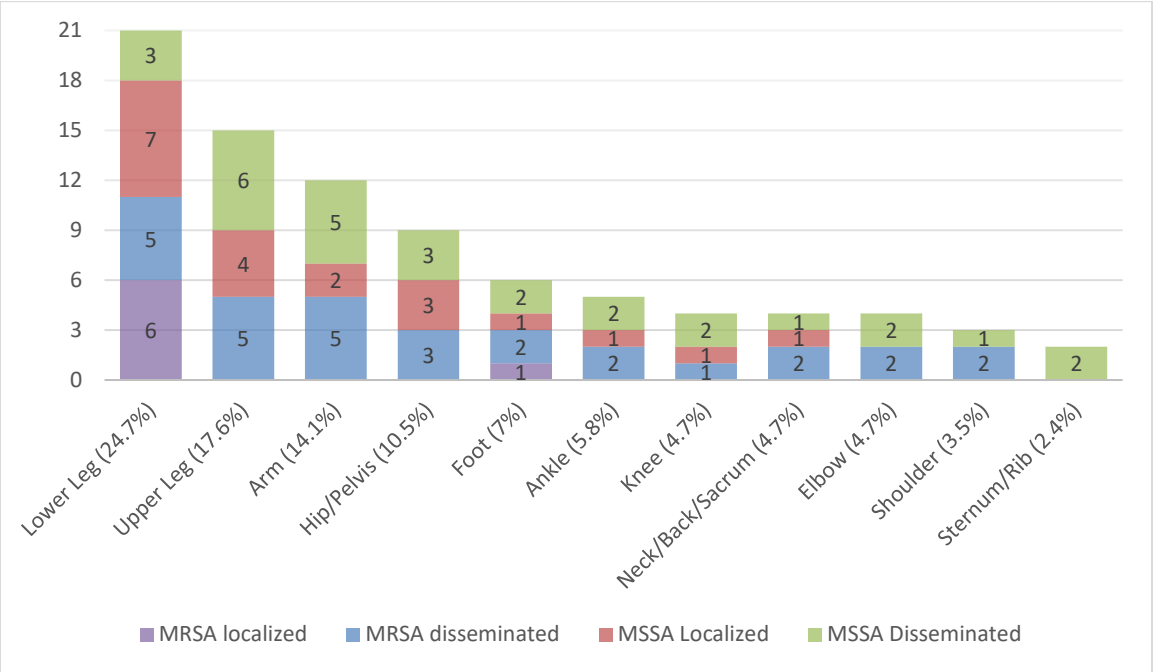


Figure 2. Infection Location. For disseminated infections, all identified infectious loci were included.



MRSA vs. MSSA AHO Infections

The MRSA group had longer hospital stay (p = 0.02) and were followed after discharge for a longer duration, with a median follow up of 5 months (range from no follow up to a maximum of 5 years) as compared to a median of 2 months (range from no follow up to a max of 42 months) in the MSSA group (p = 0.02) (Table 1). Otherwise there was no statistical significance between variable such as age at index infection, days of ICU admission, days symptomatic prior to presentation, or febrile days during admission. There was not a significant difference between complication rates, or rate of recurrence and readmission between the MRSA and MSSA groups (Table 1).

Table 2 depicts odds ratios (95% CI) to report the likelihoods of complication and recurrence/readmission between MRSA versus MSSA and localized versus disseminated infection respectively. Patients with MSSA vs. MRSA are 70% less likely to have recurrence or readmission (p = 0.20); this is clinically significant even though it is not statistically significant, likely representing a type II error secondary to an insufficient sample size.

There was a lower percentage of surgical intervention in the MSSA cohort (77.1% vs. 95.6%). Even though the median duration of antibiotic treatment was the same among MRSA and MSSA, MRSA did tend to have longer treatment (p = 0.04), and received longer intravenous duration of antibiotic therapy (p = 0.04) (Table 3).

Table 1. Demographic and clinical characteristics in overall patient population

Variables	MRSA N=23	MSSA N=35	P-value[1]	Localized N=24	Disseminated N=34	P-value[1]
Age of index infection, years (median, IQR)	8 (3, 12)	9 (3, 12)	0.78	10 (7.5, 13)	6 (2, 10)	0.04*
Current Age, years (median, IQR)	13 (10, 19)	14 (10, 18)	0.78	17.5 (13, 19)	12 (9, 16)	0.02*
Years since index Infection (median, IQR)	5 (3, 7)	4.5 (3, 6)	0.46	5 (3, 6)	5 (3, 6)	0.51
Number of Days of Hospitalization (median, IQR)	12 (8, 22)	7 (5, 15)	0.02*	7 (5, 10)	13.5 (7, 22)	0.001*
Number of Days of PICU Admission (median, IQR)	0 (0, 5)	0 (0, 0)	0.08	0 (0, 0)	0 (0, 7)	0.002*
Number of symptomatic days prior to presentation (median, IQR)	3.5 (2, 7)	5 (3, 8)	0.21	6 (4, 10)	3.5 (3, 7)	0.09
Number of Febrile days during Admission (median, IQR)	5 (3, 9)	4 (2, 6)	0.24	2 (1, 4)	6 (5, 9)	0.001*
Number of days of positive blood culture in Bacteremia Patients (median, IQR)	1 (0, 3)	0 (0, 1)	0.11	0 (0, 0)	1.5 (1, 3.5)	<0.001*
Follow Up Duration, months (median, IQR)	5 (3, 11)	2 (1, 10)	0.02*	2 (1, 10)	3 (2, 11)	0.30
Gender (male, %)	14 (60.9)	22 (62.9)	0.87	14 (58.3)	22 (64.7)	0.62
Ethnicity (Caucasian/White, %)	7 (30.4)	13 (37.1)	0.59	8 (33.3)	12 (35.3)	0.87
Pre-existing Condition (yes, %)	5 (21.7)	9 (25.7)	0.65	6 (25.0)	8 (23.5)	0.98
Complications (yes, %)	14 (60.8)	17 (48.6)	0.34	9 (37.5)	22 (64.7)	0.01*
Recurrence or Readmission (yes, %)	7 (30.4)	6 (17.1)	0.18	4 (16.7)	9 (26.5)	0.29

[1]Wilcoxon Rank Sum to compare continuous variables. Chi-Squared or Fisher's Exact to compare categorical variables.

Table 2. Odds Ratios (95% CI) to report the likelihoods of complication and recurrence/readmission between MRSA vs MSSA, Localized vs Disseminated infection respectively.

Predictors	Complications		Recurrence or Readmission	
	OR (95% CI)	P-value[1]	OR (95% CI)	P-value[1]
MRSA	REF	0.59	REF	0.20
MSSA	0.65 (0.13, 3.1)		0.29 (0.04, 1.89)	
Localized	REF	0.31	REF	0.17
Disseminated	3.79 (0.28, 51.0)		5.5 (0.47, 65.2)	
Antibiotic Duration				
≤ 6 weeks	REF		REF	
>6 weeks	3.13 (0.19, 52.0)	0.42	5.44 (0.19, 154.0)	0.32
IV Antibiotics Duration				
≤ 4 weeks	REF		REF	
>4 weeks	2.99 (0.36, 24.4)	0.30	6.01 (0.60, 60.0)	0.12
PO Antibiotics Duration				
≤ 3 weeks	REF		REF	
>3 weeks	0.72 (0.16, 3.28)	0.67	0.39 (0.05, 3.23)	0.39
Surgical intervention				
No	REF		REF	
Yes	0.53 (0.04, 7.50)	0.64	19.7 (0.03, 13025.6)	N/A

[1]Odds Ratios (95% CI) calculated using multiple logistic regression adjusting for current Age, Gender, Ethnicity, Number of Days of Hospitalization, Follow Up Duration

Table 3.

Variables	MRSA N=23	MSSA N=35	P-value[1]	Localized N=24	Disseminated N=34	P-value[1]
Antibiotic Duration, weeks (median, IQR)	6 (6, 6)	6 (6, 6)	0.04*	6 (6, 6)	6 (6, 6)	0.04*
IV Antibiotics Duration, weeks (median, IQR)	5 (2, 6)	3 (2, 4)	0.04*	2.5 (2, 4)	4.5 (2, 6)	0.01*
PO Antibiotics Duration, weeks (median, IQR)	2 (0, 4)	3 (2, 4)	0.46	3 (2 (4)	2 (0, 4)	0.07
Surgical intervention (yes, %)	22 (95.6)	27 (77.1)	0.07	24 (100.0)	25 (73.5)	0.007*

[1]Wilcoxon Rank sum to compare continuous variables. Fisher's Exact to compare categorical variables.

Disseminated vs. Localized AHO Infections

The disseminated group had statistically significant longer hospital (13.5 vs. 7 days, p = 0.001) and ICU admissions (p = 0.002), had more febrile days during admission (p = 0.001), a greater number of complications (22% vs. 9%, p = 0.01), and affected a younger demographic at an average age of 6 y/o vs. 10 y/o (p = 0.04)(Table 1). There was no difference between number of symptomatic days prior to presentation, follow up duration or recurrence and readmission rates between the disseminated and localized groups (Table 1).

There is nearly a 400% increased likelihood that the disseminated infections would have complications, as well as 5.5 times more likely to have recurrence/readmission if infection was disseminated than if it was localized (p = 0.17) (Table 2). While this is not statistically significant, this is clinically significant, likely representing a type II error secondary to an insufficient sample size.

There was a higher percentage of surgical intervention in the localized cohort (100% vs. 73.5%, p = 0.007) (Table 3). Disseminated infections received longer intravenous (p = 0.01) and total duration of antibiotic therapy (p = 0.04) (Table 3).

MRSA Localized vs. MRSA Disseminated AHO Infections

There were more frequent occurrence of complications (87% vs. 0%, p = 0.003) as well as recurrence or readmission (43% vs. 0%, p = 0.02) in the MRSA disseminated group (Table 4). The disseminated MRSA cohort had longer hospital (median 18.5 days vs. 8 days, p = 0.02) and ICU length of stays (p = 0.04), and required longer outpatient follow up duration (p = 0.03). MRSA localized infections were symptomatic for more days prior to presentation than the disseminated group (median of 8 days vs. 3 days, p = 0.02). The median age of patients with disseminated MRSA was 6 y/o where as localized infections occurred at an older median age of 12 y/o, which is consistent with disseminated vs. localized infections as a whole, however the age difference was not recognized as significant, likely secondary to sample size (p = 0.16) (Table 4). There was no difference between duration of antibiotic therapy or rates of surgical intervention (Table 5).

Table 4. Demographic and clinical characteristics MRSA and MSSA populations, separately.

	MRSA Only			MSSA Only		
Variables	Localized N=7	Disseminated N=16	P-value[1]	Localized N=24	Disseminated N=34	P-value[1]
Age of index infection, years (median, IQR)	12 (4, 14)	6 (3, 10)	0.16	10 (8, 13)	6.5 (2, 12)	0.19
Current Age, years (median, IQR)	18 (12, 20)	12.5 (9.5, 17)	0.13	17 (14, 18)	11 (8, 16)	0.05
Years since index Infection (median, IQR)	5 (3, 7)	5.5 (3, 7)	0.70	5 (3, 6)	4 (3, 6)	0.42
Number of Days of Hospitalization (median, IQR)	8 (6, 10)	18.5 (10, 22.5)	0.02*	7 (5, 10)	8.5 (7, 20)	0.04*
Number of Days of PICU Admission (median, IQR)	0 (0, 0)	1.5 (0, 7.5)	0.04*	0 (0, 0)	0 (0, 7)	0.04*
Number of symptomatic days prior to presentation (median, IQR)	8 (5, 10)	3 (2, 5.5)	0.02*	5 (3, 8)	5.5 (3, 7)	0.96
Number of Febrile days during Admission (median, IQR)	3 (0, 3)	7.5 (5, 14)	0.02*	2 (1, 4)	5 (4, 7)	0.04*
Number of days of positive blood culture in Bacteremia Patients (median, IQR)	0 (0, 0)	2 (1, 4)	0.01*	0 (0, 0)	1 (1, 3)	<0.001*
Follow Up Duration, months (median, IQR)	1.5 (1, 5.5)	9 (3, 24)	0.03*	2 (1, 15)	2 (1, 2)	0.45
Gender (male, %)	5 (71.4)	9 (56.3)	0.65	9 (52.9)	13 (72.2)	0.28
Ethnicity (Caucasian/White, %)	2 (28.6)	5 (31.3)	1.0	6 (35.3)	7 (38.9)	0.82
Pre-existing Condition (yes, %)	2 (28.6)	3 (18.8)	1.0	4 (23.5)	5 (27.8)	1.0
Complications (yes, %)	0 (0.0)	14 (87.5)	0.003*	9 (52.9)	8 (44.4)	0.63
Recurrence or Readmission (yes, %)	0 (0.0)	7 (43.8)	0.02*	4 (23.5)	1 (11.1)	0.38

[1]Wilcoxon Rank sum to compare continuous variables. Fisher's Exact to compare categorical variables.

Table 5

Variables	MRSA Only			MSSA Only		
	Localized N=7	Disseminated N=16	P-value[1]	Localized N=24	Disseminated N=34	P-value[1]
Antibiotic Duration, weeks (median, IQR)	6 (6, 6)	6 (6, 7.5)	0.22	6 (6, 6)	6 (6, 6)	0.16
IV Antibiotics Duration, weeks (median, IQR)	3 (2, 6)	5.5 (2.5, 6)	0.25	2 (2, 4)	3 (2, 6)	0.06
PO Antibiotics Duration, weeks (median, IQR)	3 (0, 4)	1 (0, 3.5)	0.41	4 (2, 4)	2.5 (0, 4)	0.16
Surgical intervention (yes, %)	7 (100.0)	15 (93.7)	1.0	17 (100.0)	10 (55.6)	0.003*

[1]Wilcoxon Rank sum to compare continuous variables. Fisher's Exact to compare categorical variables.

MSSA Localized vs. MSSA Disseminated AHO Infections

The MSSA disseminated group had statistically significant longer hospital ($p = 0.04$) and ICU stays ($p = 0.04$), and number of febrile days during admission ($p = 0.04$) (Table 4). The median age of MSSA localized was 10 y/o, and the median age of the MSSA disseminated group was 6.5 y/o ($p = 0.19$)(Table 4). There was no statistical significance between these groups for number of complications, rate of recurrence and readmission, duration of symptoms prior to emergency department presentation, or duration of antibiotic therapy between the MSSA localized vs. MSSA disseminated groups (Table 4 and Table 5). 100% of MSSA localized infections had surgical intervention whereas only 55.6% of MSSA disseminated infections required surgical intervention ($p = 0.003$) (Table 5).

DISCUSSION

This data suggests that the group most likely to have both complications and recurrence or readmission is the disseminated MRSA infection. There was not a significant difference between these outcomes when solely comparing the MRSA and MSSA groups. This is likely due to the fact that there were no complications or recurrence/readmission identified for the MRSA localized group, and there was no identified difference between MSSA localized vs. MSSA disseminated. The statistical increase in complications between all disseminated infection vs. all localized infection appears to be due to the increased rate of complications in the MRSA disseminated group alone.

The difference in outcomes between MRSA localized vs. MRSA disseminated could be due to several different factors. One possibility could be that the localized infections were seeded by a less virulent strain of MRSA and disseminated infections by more virulent strains, such as *pvl(+)* strains. Unfortunately, genetic testing of the organisms was not completed at time of index infection so the virulence factors are unknown. This data is also suggestive that age may be a factor in likelihood of an infection becoming disseminated, as disseminated infections were more likely to occur at a younger age. The duration of symptoms prior to presentation was longer in the localized MRSA infections, suggesting that disease presentation may have had a more indolent onset.

This study is limited by data obtained in a retrospective manner at a single institution. This study validates prior studies that showed that MRSA has worse outcomes than MSSA; however, this is the first study, to our knowledge to report on mid-term outcomes.

Other potential limitations of the study include the fact that the ASK questionnaire has only been validated in ages 5-15, and the PODCI questionnaire is validated for pediatric patients aged 2-18. The questionnaires will be administered to some patients outside of this age range. Another consideration is location of infection relating to level of impact a patient's daily function, for example, an infection in a long bone may cause more disability than an infection in a single digit.

FUTURE DIRECTIONS

Further work will be to obtain patient data from patients after 2014, which will provide power to many of the comparisons that showed clinical significance, but were not statistically significant. Further research will also include obtaining functional outcomes data from patients and determining if there is a significant difference between any of these infection groups. Another consideration would be to conduct a prospective study, which would allow for a more comprehensive and standardized follow up evaluation.

CONCLUSIONS

Patients with disseminated AHO were younger and had a more complicated course: increased length of stay, more PICU days, more inpatient febrile and bacteremic days, longer duration of intravenous antibiotics and more complications. MRSA AHO had increased LOS and intravenous antibiotic duration. Disseminated MRSA had more complications and recurrence/readmission than any other group.

It is hypothesized that the PODCI and ASK questionnaire scores will also reflect worse patient functionality two to ten years post index infection as well in the MRSA disseminated population.

With a better understanding of mid to long-term disease impact, care can be directed at improving care of, or even prevention of complications, recurrence and readmission, and in turn improve the patient's experience and quality of life. A more comprehensive understanding of outcomes may guide appropriate duration of antibiotic therapy and surgical intervention.

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