Comparative mid-term outcomes of pediatric hematogenous methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *Staphylococcus aureus* osteomyelitis

Tiana Blank, MS4, University of Arizona College of Medicine, Phoenix
Mohan V. Belthur, MD, Pediatric Orthopedic Surgeon, Phoenix Children's Hospital

Introduction

- The bacteria *staphylococcus aureus* is the most common etiology of acute hematogenous osteomyelitis (AHO) in healthy pediatric patients, accounting for 70-90% of cases.
- AHO occurs at a rate of 1/10,000 pediatric patients/year.
- Increasing prevalence of community-acquired methicillin resistant staph aureus (MRSA) is leading to a concurrent rise of such invasive pediatric infections in the US.
- MRSA AHO on average have longer hospital stays, more febrile days, longer antibiotic therapy, and increase in overall complications vs. methicillin sensitive staph aureus (MSSA).
- There is a lack of data on the functional outcome of these patients beyond 2 years post index infection.
- Goal of study: compare treatment and midterm (2 years post index infection) functional outcomes between patients with MRSA vs. MSSA infections, and localized vs. disseminated infections.
- Hypothesis: treatment and outcomes between MRSA and MSSA, and localized and disseminated, will be different, specifically that MRSA and disseminated will have worse mid-term functional outcomes.

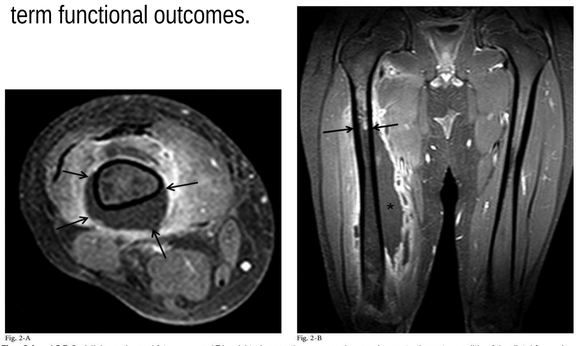

Fig. 2-A Fig. 2-B

Figs. 2-A and 2-B Gadolinium-enhanced fat-suppressed T1-weighted magnetic resonance images demonstrating osteomyelitis of the distal femoral metadiaphysis in an eight-year-old boy (Patient 8) who later developed a pathologic femoral facture. **Fig. 2-A** Axial image demonstrating a subperiosteal abscess encirclng >50% of the bone circumference (arrows). **Fig. 2-B** Coronal image demonstrating a sharp demarcation (arrows) between poorly enhancing abnormal marrow distally and relatively normally enhancing marrow proximally. Note the subperiosteal and muscle abscess (asterisk).

Materials and Methods

Phase 1:

- Retrospective chart review, performed at Phoenix Children's Hospital (admission dates between 01/01/2005 - 12/31/2014).
- Patients with diagnosis of AHO with a duration of symptoms ≤14 days before clinical presentation.
- Complications included: chronic osteomyelitis, myositis, pyomyositis, septic arthritis, deep venous thrombosis, bursitis, cardiac valve disease, endocarditis, pulmonary emboli, pleural effusion, coagulopathy, growth plate arrest, avascular necrosis, gait abnormality, limb length discrepancy and pathologic fracture.

Phase 2:

- Two functional outcomes questionnaires: the Pediatric Outcomes Documentation Instrument (PODCI) and the Activity Scale for Kids (ASK).
- Validated scales to assess pediatric function, quality of life and level of disability.
- Outcomes measured and compared: complications, re-hospitalizations, recurrence of infection, PODCI and ASK scores.

Phase 1 retrospective chart review is complete. Phase 2, functional outcomes questionnaires, is currently being pursued.

Results: Phase 1 Data

- 58 patients : 23 with MRSA (localized = 7, disseminated = 16), and 35 with MSSA (localized = 17, disseminated = 18).
- Localized infections: 1 site of infection without bacteremia
- Disseminated infections: multiple sites of infection ± bacteremia, or one site of infection + bacteremia.
- Amongst all groups, there was no difference between predilection of gender, ethnicity or whether or not the patient had pre-existing conditions.

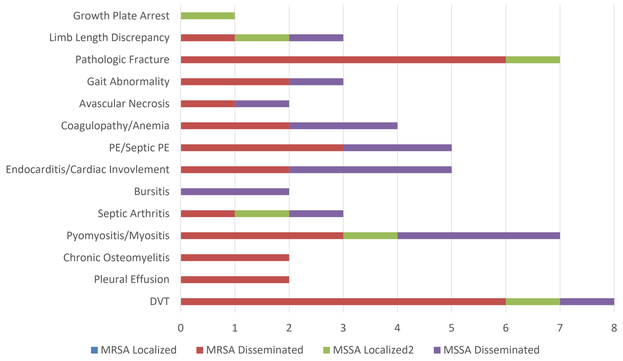

Figure 1: Graph of complications identified through retrospective chart review.

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 1: Compares Phase 1 data between the MRSA vs. MSSA groups and the localized vs. disseminated groups

MRSA vs. MSSA

- MRSA had longer hospital stay and longer follow up (Table 1).
- No difference between: age in years at index infection, days of ICU admission, number of symptomatic days prior to presentation, number of febrile days, complication rates, or rate of recurrence and readmission between (Table 1).
- Patients with MSSA vs. MRSA are 70% less likely to have recurrence or readmission (Table 5).

Disseminated vs. Localized

- Disseminated had longer hospital and ICU admissions, more febrile days, more complications, and affected a younger demographic at an average age of 6 y/o vs. 10 y/o (Table 1).
- No difference between recurrence/readmission rates between disseminated and localized groups (Table 1).
- Disseminated infection with almost 400% increased likelihood to have complications, and 5.5x more likely to have recurrence/readmission (Table 5).

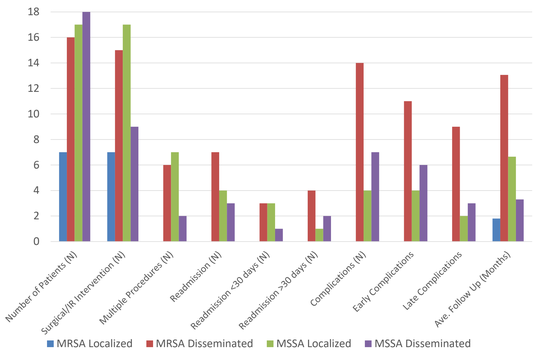

Figure 3: Graph of phase 1 data. Readmissions refer to readmissions related to recurrence of infection or late complications related to the index infection. Early complications occurred during index hospital admission, late complications were after index hospital admission.

Table 2. Demographic and clinical characteristics MRSA and MSSA populations, separately.

Variables	MRSA Only Localized N=7	MRSA Only Disseminated N=16	P-value[1]	MSSA Only Localized N=24	MSSA Only 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 2: Compares phase 1 data between MRSA localized vs. MRSA disseminated, and MSSA localized vs. MSSA disseminated.

MRSA Localized vs. MRSA Disseminated

- Disseminated MRSA: more complications, recurrence or readmission longer hospital and ICU length of stays, longer pre-hospital symptomatic period, and longer follow up (Table 2).
- No difference between age in years of the patient at index infection (Table 2).

MSSA Localized vs. MSSA Disseminated

- MSSA disseminated: longer hospital and ICU stays, and number of febrile days (table 2).
- No difference in number of complications, rate of recurrence and readmission, or duration of symptoms prior to emergency department presentation between the MSSA localized vs. MSSA disseminated groups (table 5).

Table 5. Odds Ratios (95% CI) to report the likelihoods of complication and recurrence/readmission between MRSA vs MSSA, Localized vs Disseminated infection respectively.

Predictors	Complications OR (95% CI)	P-value[1]	Recurrence or Readmission 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 5: Depicts odds ratios (95% CI) to report the likelihoods of complication and recurrence/readmission between MRSA versus MSSA and localized versus disseminated infection respectively.

Discussion and Conclusions

- Disseminated MRSA infections had significantly more complications, recurrence and re-hospitalizations as compared to MRSA localized, MSSA disseminated or MSSA localized infections.
- It is hypothesized that the PODCI and ASK questionnaire scores will also reflect worse patient functionality 2-10 years post index infection in the MRSA disseminated population.
- There is nearly a 400% increased likelihood that disseminated would have complications (p-value = 0.31), and 5.5x more likely to have recurrence/readmission if than localized (Table 5, p-value = 0.17). Patients with the MSSA are 70% less likely to have recurrence or readmission (Table 5, p-value of 0.20). While these outcomes are not statistically significant, they are clinically significant, likely representing a type II error secondary to an insufficient sample size.
- The worse outcomes (complications, readmission, recurrence) in MRSA disseminated vs. MRSA localized could be due to several different factors: longer duration of symptoms prior to ED presentation, or possibly different virulence factors possessed by certain strains of MRSA, that resulted in the likelihood for it to become a disseminated infection and result in worse outcomes.

Clinical Significance: MRSA disseminated group would benefit from prolonged follow up beyond duration of antibiotics and may need more services.

Future Direction:

- Phase 2 methodology has received IRB approval from Phoenix Children's Hospital IRB as of 2/8/2018, and is currently being pursued.
- Other future directions could include:
  - A prospective study would allow for a more comprehensive and standardized follow up evaluation.
  - Gene typing MRSA / MSSA infection may help us identify children who might have the disseminated infections.

Acknowledgements

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*Figure 2 pictures courtesy of Belthur MV, Birchansky SB, Verdugo AA, et al. Pathologic fractures in children with acute *Staphylococcus aureus* osteomyelitis. *The Journal of Bone and Joint Surgery*. 2012;94(1):34-42.