

Bacteremic *Staphylococcus aureus* Osteoarticular Infections: Observations on Treatment and Outcome in a Population with a High Prevalence of MRSA

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ABSTRACT

Background: Bacteremia is often one factor used in deciding the need for prolonged intravenous antimicrobial therapy in osteoarticular infections (OAI). Studies in populations with a low incidence of MRSA have shown little difference in outcome between osteomyelitis patients with and without bacteremia. We examined treatment practices and outcomes of bacteremic *S. aureus* osteoarticular infections (BOAI) evaluated at Texas Children's Hospital (TCH).

Methods: Cases of acute hematogenous osteomyelitis or septic arthritis in children with positive blood cultures for *S. aureus* at TCH from 2011-2014 were reviewed. Orthopedic complications included chronic osteomyelitis, growth arrest, pathologic fracture, avascular necrosis and chronic dislocation. Acute kidney injury (AKI) was defined as a doubling of the baseline creatinine.

Results: 192 *S. aureus* OAI were identified of which 102 had positive blood cultures (35 MRSA). Among patients with BOAI, MRSA infections had a longer duration of fever, bacteremia and length of stay, more frequent abscesses and repeat surgical procedures. 25 patients were discharged home on oral antibiotics. Patients discharged on oral antibiotics had a shorter duration of fever (3 vs. 6 days, p=0.03), a more rapid decline in C-reactive protein (p=0.02) and were less likely to have MRSA (16% vs. 40.3%, p=0.03). The frequency of orthopedic complications did not increase in patients who received early transition to oral antibiotics. For patients with MRSA bacteremia the median duration of vancomycin was 7 days (IQR: 4-23); the rates of complications between those who received ≥ 7 days vs. < 7 days of vancomycin did not differ. Vancomycin serum troughs $> 15 \mu\text{g/ml}$ were not associated with a decreased duration of fever, bacteremia or hospitalization, need for repeat operation or orthopedic complications but were associated with AKI (p=0.001).

Conclusion: Bacteremic *S. aureus* OAI are associated with substantial morbidity. Early transition to oral therapy may be a safe option for select patients with *S. aureus* BOAI, including those due to MRSA. Prolonged courses of vancomycin and elevated vancomycin troughs were not associated with improved outcomes for MRSA OAI.

AIMS

1. Define the impact of positive blood culture on long and short term outcomes of *S. aureus* osteoarticular infection (OAI).
2. To evaluate impact of discharge on oral vs. OPAT or complete hospital IV therapy (CHIT) on orthopedic complications in *S. aureus* bacteremic osteoarticular infection (BOAI).
3. To assess the impact of length of vancomycin therapy and vancomycin serum trough concentration on MRSA BOAI.

INTRODUCTION

- S. aureus* is the most common cause of acute osteoarticular infection (OAI) in children accounting for up to 76% of culture positive cases (Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th Edition 2013).
- Historically, many experts recommended treating *S. aureus* OAI with prolonged courses of IV therapy, however, more recent data support early transition to oral therapy (Pediatrics. 2009; 123: 636-42; JAMA Pediatr. 2015; 169: 120-8).
- Questions arise as to what impact a positive blood culture for *S. aureus* has on the need for or duration of IV therapy for *S. aureus* OAI, especially MRSA.
- Previous studies in populations without MRSA have shown little difference in OAIs with and without bacteremia (J Pediatr Infect Dis Soc. 2015; 4: 174-7).
- MRSA OAI may be associated with more severe complications including venous thrombosis, septic pulmonary emboli and pathologic fracture (Pediatrics 2006; 117: 1673-79; J Bone Joint Surg Am. 2012; 94: 34-43).
- IDSa MRSA guidelines recommend 2-6 weeks of vancomycin for MRSA bacteremia (Clin Infect Dis 2011;52:285-92). The need for this in children with bacteremic osteoarticular infection (BOAI) is unknown

PATIENTS AND METHODS

Patients and Clinical Isolates. Cases were identified from the consult database of the inpatient infectious diseases service at Texas Children's Hospital (TCH). Patients with acute hematogenous osteomyelitis or septic arthritis confirmed to be secondary to *S. aureus* from Jan 2010-Dec 2014 were eligible for inclusion. Patients were followed for complications of OAI up through June 2016. Any and all clinical interventions were at the discretion of the clinicians of record.

Clinical Definitions: Long term orthopedic complications included chronic osteomyelitis, growth arrest, angular deformity, chronic dislocation, pathologic fracture or avascular necrosis. The vancomycin trough used in calculations was the highest one obtained in the first 96 hours of therapy. Acute kidney injury (AKI) was defined as a doubling of the baseline serum creatinine.

Statistical Analysis. Continuous variables were examined with Kruskal-Wallis and Mann-Whitney U tests, dichotomous variables with χ^2 and Fisher's exact tests with the use of STATA ver 12.

RESULTS

- 192 patients with *S. aureus* OAI were identified (Table 1), 53% had BOAI.
- Patients with positive blood cultures more often had osteomyelitis, multiple surgeries, a longer duration of fever, CRP elevation and length of hospital stay than patients without bacteremia (Table 2).

Table 1. General Characteristics of Patients

	N=192 (%)
Median Age, years (IQR)*	7.3 (4.1-12)
Methicillin-Resistant	58 (30.2)
Clindamycin-Resistant	28 (14.6)
Osteomyelitis Alone	95 (49.5)
Septic Arthritis Alone	11 (5.2)
Osteomyelitis + Septic Arthritis	86 (44.8)
Subperiosteal/ Intraosseous Abscess	84 (43.8)
Multiple Foci of Infection	15 (7.8)
Positive Blood Culture	102 (53.1)
Any Surgical Drainage	141 (73.4)

*Continuous variables expressed as medians, interquartile ranges (IQR); categorical variables expressed as n (%)

Table 2. Comparison of *S. aureus* OAI With and Without Bacteremia

	Positive Blood Culture (n=102)	Negative Blood Culture (n=90)	P value
Age, years	7.3 (3.3-12.4)	7.6 (3.5-11.7)	0.5
Methicillin-Resistant	35 (34.3)	23 (25.6)	0.2
Osteomyelitis +/- Septic Arthritis	99 (97.1)	82 (85.6)	0.007
Multifocal Infection	12 (11.7)	3 (3.3)	0.03
≥ 2 Surgical Procedures	31 (30.4)	9 (10)	0.001
Fever At Admission	73 (71.6)	44 (48.9)	0.002
Duration of Fever after Admission, days	6 (3-9)	3 (1.5-4)	<0.001
Initial CRP, mg/dl	13 (4.7-25.4)	6.9 (3.5-15)	0.01
Time to 50% decline in CRP, days	7 (6-10)	6 (5-8)	0.01
Length of Stay, days	11 (8-17)	7 (5-11)	<0.001
Oral Antibiotics at Discharge	26 (25.5)	37 (41.1)	0.03
Orthopedic Complications	18 (17.6)	15 (16.7)	0.9

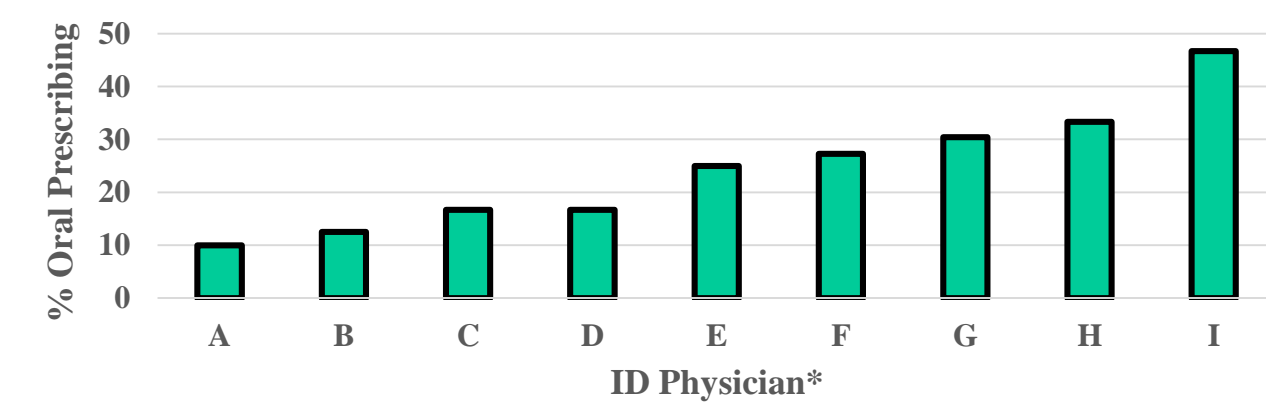
RESULTS

- Patients with MRSA BOAI had a longer duration of fever, bacteremia and stay as well as more surgical procedures vs. MSSA BOAI (Table 3).
- 26 patients were discharged on po antibiotics. Rates of po prescribing varied by ID physician (Figure 1).
- Patients discharged on oral antibiotics had no increase in long term complications (Table 4).

Table 3. Comparison of MRSA and MSSA BOAI

	MRSA (n=35)	MSSA (n=67)	P value
Age, years	7.3 (5.7-12.45)	7.7 (2.3-12.7)	0.9
Length of Stay, days	13 (10-20)	10 (7-13)	0.01
Fever At Admission	32 (91.4)	43 (62.7)	0.002
Duration of Fever after Admit, days	7.5 (5.5-11.5)	4 (2-7)	<0.001
Duration of Bacteremia, days	2 (1-3)	1 (1-1)	0.001
Time to 50% Decline in CRP, days	8.5 (7-11)	7 (6-9)	0.04
Any Surgical Drainage	34 (97.1)	37 (55.2)	<0.001
≥ 2 Surgical Procedures	22 (62.9)	11 (16.4)	<0.001
Subperiosteal/ Intraosseous Abscess	24 (68.6)	23 (34.3)	0.002
Max Diameter of Abscess, cm	4.75 (3.35-8.4)	2.9 (2-5)	0.08
Oral Antibiotics at Discharge	4 (11.4)	22 (32.8)	0.03
Orthopedic Complications	8 (22.9)	10 (14.9)	0.4

Figure 1. Oral Antibiotic Prescribing Rates for BOAI by Physicians



*Only includes physicians seeing >25%-tile of patient volume

Table 4. Comparison of BOAI with Discharge on PO vs. IV Antibiotics

	PO Antibiotics at Discharge (n=26)	OPAT or CHIT (n=76)	P value
Age, years	7.2 (3.3-12.4)	8 (3.1-12.3)	0.6
Methicillin-Resistant	4 (15.4)	31 (40.7)	0.03
Length of Stay, days*	8.5 (6-11)	11.5 (8.5-19)	0.001
Duration of Fever after Admit, days	3 (2-6)	6 (3-10)	0.03
Duration of Bacteremia, days	1 (1-1)	1 (1-2)	0.3
Time to 50% Decline in CRP, days	6 (5.5-8)	8 (7-11)	0.01
Time to First Surgical Procedure, days	2 (2-2)	2 (1-3)	0.8
≥ 2 Surgical Procedures	5 (19.2)	28 (36.8)	0.14
Subperiosteal/Intraosseous Abscess	12 (46.2)	35 (46.1)	1
Maximum Diameter of Abscess, cm	2.7 (1.5-3.2)	4.8 (2.2-7.8)	0.06
Venous Thrombosis	0	4 (5.3)	0.57
Orthopedic Complications	3 (11.5)	15 (19.7)	0.55
High PO Provider†	16 (61.5)	28 (36.8)	0.04

*CHIT patients excluded from length of stay analyses; †Defined as $\geq 75\%$ -tile of oral antibiotic prescribing

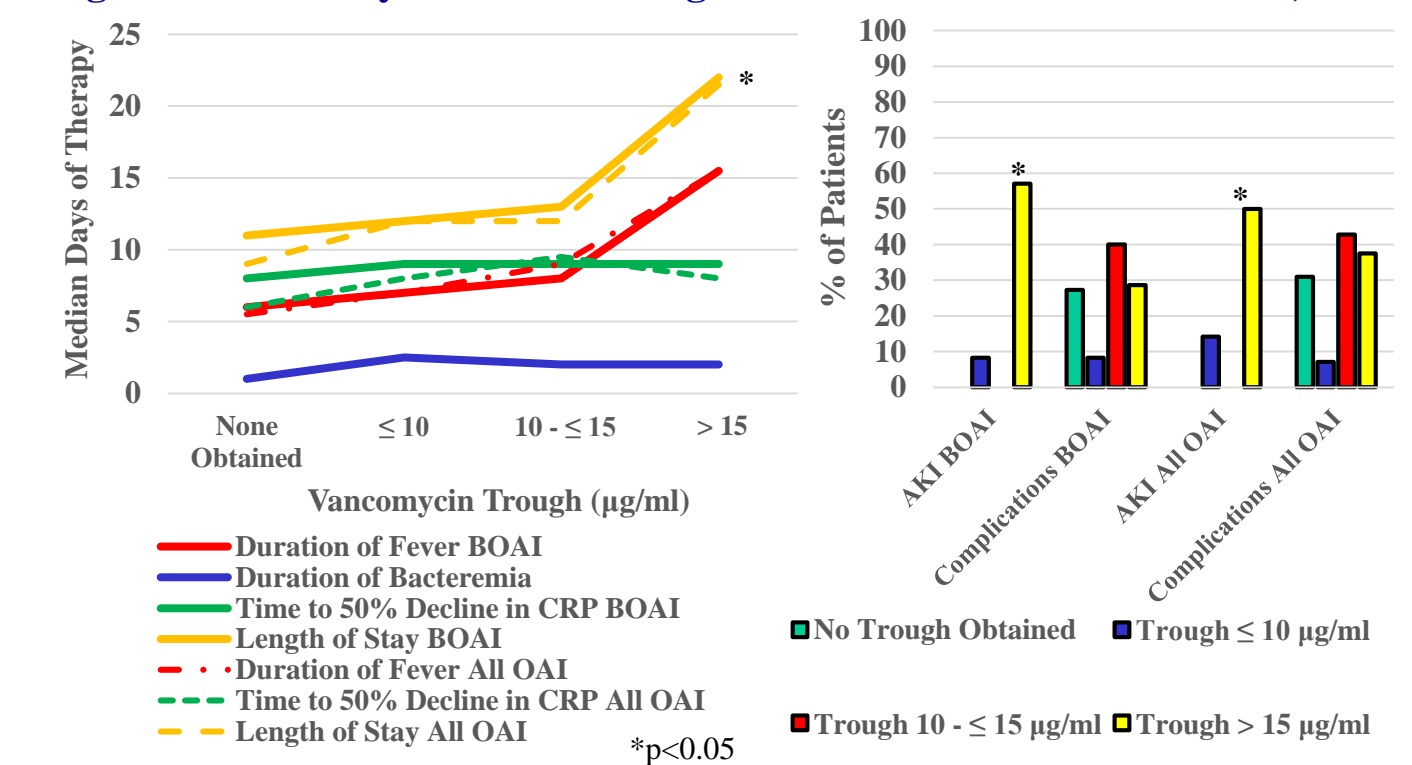
RESULTS

- Among patients with MRSA BOAI, 51.4% received < 7 days of vancomycin (Table 5).
- 38.2% of patients with MRSA OAI had vancomycin troughs performed. There was no improvement in duration of fever, bacteremia or CRP elevation or complications in patients with higher vancomycin troughs.
- Vancomycin troughs $> 15 \mu\text{g/ml}$ were strongly associated with AKI (Figure 2).

Table 5. Length of Vancomycin and Outcomes of MRSA BOAI

	≥ 7 Days of Vancomycin (n=17)	< 7 Days of Vancomycin (n=18)	P value
Age, years	7.3 (5.7-9.7)	7.8 (5.8-12.5)	0.3
Clindamycin-Resistant	4 (23.5)	0	0.045
Length of Stay, days	17 (12-27)	11 (8-13)	0.002
Duration of Bacteremia, days	2 (1-3)	1 (1-2)	0.14
Duration of Fever after Admit, days	10 (7-16)	6 (3-9)	0.005
Multifocal Infection	5/17 (29.4)	1/18 (5.6)	0.08
≥ 2 Surgical Procedures	9/17 (52.9)	13/18 (72.2)	0.3
Time to First Surgical Procedure, days	2 (1-3)	1 (1-2)	0.03
Time to 50% decline in CRP, days	9 (8-11)	7 (6-9)	0.03
Vancomycin Trough $> 15 \mu\text{g/ml}$	5/14 (35.7)	2/10 (20)	0.6
AKI	4 (23.5)	1 (5.6)	0.1
Discharge on Oral Antibiotics	1 (5.9)	3 (16.7)	0.6
Orthopedic Complications	5/17 (29.4)	3/18 (16.7)	0.4

Figure 2. Vancomycin Serum Trough Concentrations & MRSA OAI, BOAI



CONCLUSIONS

- In children with *S. aureus* OAI, positive blood culture is associated with more short term morbidity but no increase in long term complications.
- While the data are limited and subject to bias, in select cases of MRSA BOAI, oral antibiotics can be used safely and effectively.
- In the case of MRSA BOAI, prolonged use of vancomycin and elevated vancomycin trough concentrations are not associated with improved clinical outcomes.
- Vancomycin serum trough concentrations $> 15 \mu\text{g/ml}$ are associated with an increase in AKI, raising concerns about the safety and necessity of this practice in MRSA OAI.