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The influence of the route of antibiotic administration, methicillin-susceptibility, vancomycin duration and serum trough concentration on outcomes of pediatric *Staphylococcus aureus* bacteremic osteoarticular infection

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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). 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 OAI 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 cases of *S. aureus* OAI were identified with 102 cases of BOAI included (35 MRSA). 25 patients were discharged home on oral antibiotics. Patients discharged on oral antibiotics had a shorter duration of fever, a more rapid decline in C-reactive protein and were less likely to have MRSA. The frequency of orthopedic complications did not increase in patients who received early transition to oral antibiotics. For patients with MRSA bacteremia the rates of complications between those who received ≥ 7 days vs. < 7 days of vancomycin did not differ. Vancomycin serum troughs > 15 μg/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.

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 vancomycin troughs > 15 μg/ml were not associated with improved outcomes for MRSA OAI.

Keywords

osteomyelitis; septic joint; bacteremia; vancomycin; *S. aureus*

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Introduction

Osteomyelitis and septic arthritis are two of the most common serious infections in children and are among the most common indications for infectious disease specialist consultation. *S. aureus* is overwhelmingly the most commonly identified etiology of these infections, accounting for >80% of culture positive cases[1, 2]; a recent study at Texas Children's Hospital (TCH) revealed that 31.7% of *S. aureus* causing osteomyelitis were methicillin-resistant.[3] *S. aureus* osteoarticular infections (OAI), particularly those caused by the USA300 pulsotype, are associated with a number of complications including venous thrombosis, septic pulmonary emboli, severe sepsis and pathologic fracture.[4, 5] Given the risks of complications in OAI, aggressive surgical and medical therapy is of importance.

Children with acute OAI are typically treated with 3–4 weeks of antimicrobials for isolated septic arthritis and 4–6 weeks if osteomyelitis is present.[6, 7] In the past, many experts have recommended that children with *S. aureus* OAI receive a prolonged course of intravenous (IV) therapy; several relatively recent studies, however, do not support this as a routine practice.[8–10] Retrospective analysis of the Pediatric Health Information System (PHIS) database revealed no difference in treatment failure in children with osteomyelitis treated with oral versus intravenous antimicrobial agents.[11] Questions arise, however, as to what impact the presence of a positive blood culture has on the need for or duration of IV therapy for *S. aureus* OAI, particularly for methicillin-resistant *S. aureus* (MRSA). Previous studies have suggested that MRSA OAI may be more severe than infection secondary to methicillin-susceptible *S. aureus* (MSSA).[2, 12] The Infectious Diseases Society of America (IDSA) MRSA Treatment Guidelines suggest that vancomycin be utilized as the drug of choice for MRSA bacteremia with durations of therapy ranging from two to six weeks, depending on source and clinical response.[13]

We conducted a retrospective study of *S. aureus* bacteremic osteoarticular infection (BOAI) at a large tertiary care children's hospital. The primary goals of this study were to 1) determine the impact of positive blood culture on short and long term clinical outcomes, 2) determine the impact of discharge on oral antibiotics versus outpatient parenteral antibiotic therapy (OPAT) or complete hospital IV therapy (CHIT) on the development of orthopedic complications, 3) to assess the impact of length of vancomycin therapy and vancomycin serum troughs on the clinical outcomes of MRSA BOAI.

Methods

Case Identification

Cases were identified from a subset of two previously published studies of all cause OAI at TCH, the methods of which are described elsewhere.[3, 14] Briefly, the consult database of the inpatient infectious diseases service at TCH Main Campus was reviewed from January 1, 2011- December 31, 2014 for patients with acute hematogenous osteomyelitis and/or septic arthritis. The inpatient infectious diseases service at TCH was staffed by 15 board certified pediatric infectious diseases physicians during the study period and was routinely consulted in cases of OAI. The route, duration and choice of antibiotic were at the discretion of the infectious diseases physician of record. For purposes of this study, only patients with culture

confirmed *S. aureus* OAI were included. Patients with *S. aureus* OAI with and without bacteremia were included in initial comparisons, however, the primary focus of this study was to describe the outcomes and treatment of patients with *S. aureus* BOAI. Patients were considered eligible for inclusion if disease was acute in nature (< 28 days of symptoms). Patients with open or penetrating trauma, orthopedic hardware in place, osteomyelitis/septic arthritis secondary to a contiguous focus or a surgical procedure (such as sternal osteomyelitis following cardiac surgery) were excluded. The diagnoses of osteomyelitis and/or septic arthritis were defined by the constellation of classic physical examination findings, radiology reports and microbiologic studies (including blood, bone and synovial fluid culture and gram stain). TCH and the affiliated Texas Children's Pediatric Associates clinics (a network of 52 primary care clinics in the greater Houston area) have an integrated electronic medical record system. All clinical records were reviewed for orthopedic complications of septic arthritis and osteomyelitis from the time of admission up through June 30, 2016. This study was approved by the institutional review board of Baylor College of Medicine.

Definitions

The duration of fever was defined as the number of calendar days in hospital with a recorded body temperature ≥ 100.4 °F. The duration of bacteremia was regarded as the number of calendar days with a positive blood culture. Protocols exist at our institution to collect standardized volumes of blood for culture based on patient weight; for patients with bacteremia, it is common practice at our institution to obtain at least one blood culture daily until sterility is documented. The time to 50% decline in CRP was defined as the number of calendar days until a documented ≥50% decrease in CRP compared to the level obtained at the time of hospital admission. The presence of a subperiosteal or intraosseous abscess was based on documentation in radiology reports; critical re-review of radiologic studies was not undertaken, however, all studies were initially evaluated by an attending pediatric radiologist in the routine course of care. OPAT was considered discharge from hospital to receive intravenous antibiotics in the home setting; CHIT was considered complete treatment of IV therapy at TCH or a long term care facility without discharge to home. Long term orthopedic complications included chronic osteomyelitis, limb length discrepancy/ growth arrest, angular deformity, chronic dislocation, avascular necrosis or pathologic fracture. The presence of chronic osteomyelitis was based on diagnosis given by the infectious diseases physician of record at follow-up. Duration of follow-up was considered the time in calendar days from hospital admission until last outpatient follow-up with infectious diseases or orthopedics or their primary care provider if in the TCH system. The need for and frequency of outpatient follow-up appointments was at the discretion of the individual infectious diseases physician and surgeon. Vancomycin serum trough concentrations included in analyses were the highest trough value recorded in the first 96 hours of therapy.[15] The decision to obtain vancomycin troughs and their frequency was at the discretion of the physician of record. Acute kidney injury (AKI) was defined as a documented doubling of the baseline serum creatinine.[16]

Statistical Analysis

Categorical variables were assessed with Fisher's Exact test and continuous variables with Mann-Whitney U-test and Kruskal Wallis tests. In comparisons of clinical outcomes by route of therapy, patients discharged on oral antibiotics were compared with a combined group of patients receiving OPAT and CHIT. Analyses of clinical findings with regards to vancomycin trough levels were performed by categorizing troughs as ≤ 10 μg/ml, >10-≤15 μg/ml, > 15 μg/ml or no trough obtained; analyses were repeated with exclusion of patients without trough data available. Analyses of clinical outcomes by vancomycin trough were performed including all patients, only those with BOAI and then only those with MRSA BOAI. Based on previous estimates of orthopedic complications in *S. aureus* septic arthritis and osteomyelitis (~5–7%),[5, 14] and assuming equal allocation between patients with and without bacteremia, a total sample size of 1498 would be necessary to achieve 80% power in demonstrating a 50% difference in rates of orthopedic complications between these groups with α=0.05. If one were to assume a higher baseline rate of orthopedic complications of approximately 20%, a total sample size of 398 would be necessary to demonstrate a 50% reduction in complication rates with 80% power and α=0.05. Analyses were performed with the assistance of STATA ver. 13.

Results

During the study period 192 patients were identified with *S. aureus* OAI. The median duration of symptoms for patients at time of presentation was 5 days (Interquartile range [IQR]: 3–7); five patients (2.6%) had symptom duration of 14–28 days. Positive blood cultures occurred in 102 (53.1%) patients. Among patients with negative blood cultures, the isolation of staphylococci occurred in bone alone in 62 cases (68.9%), synovial fluid alone in 19 cases (21.1%) and in both in nine cases (10%). Patients with positive blood culture more often had multiple foci of infection (11.7 %vs 3.3%, p=0.03), multiple surgical procedures (30.4% vs. 10%, p=0.001), a longer duration of fever after admission (6 vs. 3 days, p<0.001), a longer time to a 50% decline in C-reactive protein (CRP, 7 vs. 6 days, p=0.01), a longer length of hospital stay (11 vs. 7 days, p<0.001) and were less often discharged on oral antibiotics (25.5% vs 41.1%, p=0.03, [Table 1]). Notably, the rates of long term orthopedic complications between those with and without positive blood cultures were no different.

BOAI and Methicillin-Susceptibility

Among 102 patients with positive blood cultures, 35 cases were secondary to MRSA (34.3%). Substantial differences existed between cases of BOAI caused by MRSA vs. MSSA (Supplemental Table 1). Patients with MRSA had a longer duration of fever, bacteremia and hospital admission, were more likely to have surgical intervention and re-intervention and were less likely to be discharged on oral antibiotics. Four children with *S. aureus* BOAI received both vancomycin and nafcillin empirically; ultimately MSSA was isolated in all four cases.

BOAI and Route of Therapy

Twenty-six patients with BOAI were discharged home from hospital on oral antibiotics (25.4%), 68 were discharged on OPAT (66.6%) and eight received CHIT (7.8%). Patients discharged on oral antibiotics were hospitalized for a median of 8.5 days (Interquartile range [IQR]: 6–11 days) prior to discharge home and received a median of 7 days (IQR: 5–10 days) of intravenous antibiotics before transition to oral agents. The most commonly utilized oral agent was cephalexin (n=20) followed by clindamycin (n=5) and linezolid (n=1). The details of oral antibiotic dosing are described in Supplemental Table 2. Patients with *S. aureus* BOAI were treated by 12 different infectious diseases specialists and the median number of patients seen per physician was 7 (IQR: 5–12). Among physicians seeing ≥ 5 patients, the rate of oral prescribing ranged from 12.5–46.7% for BOAI. Patients with *S. aureus* BOAI who were transitioned to oral agents at time of discharge were compared with those patients who were discharged home with OPAT or received CHIT (Table 2). Patients who were discharged on oral therapy had a shorter duration of fever after hospital admission (3 vs. 6 days, p=0.03), a more rapid decline in CRP (6 vs. 8 days, p=0.01) and were less likely to have MRSA (15.4% vs. 40.7%, p=0.03). Notably, there was no difference in the proportion of cases that developed long term orthopedic complications between patients discharged on oral antibiotics compared to those that received all treatment intravenously. One patient receiving OPAT was readmitted with a central line associated bloodstream infection.

MRSA BOAI

Thirty-five patients were identified with MRSA BOAI. Among these, only one was not treated at least initially with vancomycin (one patient received clindamycin for their entire treatment course). The median duration of vancomycin therapy was 7 days (IQR: 4–23 days). Patients who received < 7 days of vancomycin were compared with those who received ≥ 7 days of vancomycin (Table 3). Patients treated with a longer course of vancomycin had a longer median duration of fever (10 vs. 6 days, p=0.005), a longer time from hospital admission to first surgical procedure (2 vs. 1 day, p=0.03) and a slower decline in CRP (9 vs. 7 days to 50% decline in CRP, p=0.03). There was a trend for patients receiving a prolonged course of vancomycin to more often have multifocal infection (29.4% vs. 5.6%, p=0.08). There was no difference in the proportion of cases with long term orthopedic complications among those receiving long or short courses of vancomycin; furthermore, there was no increase in orthopedic complications among those patients in the bottom quartile of vancomycin duration (<4 days). All patients treated with < 7 days of vancomycin were ultimately prescribed clindamycin for definitive therapy. Sixteen patients (94.1%) had at least one day of negative blood cultures prior to transitioning from vancomycin to clindamycin and the median duration of negative blood cultures prior to antibiotic change was 2 days (IQR: 1–3).

Among 34 patients treated with vancomycin, five did not receive weight based dosing. Among the remaining patients, the median vancomycin dose in the first 96-hours of therapy was 60 mg/kg/day. Five patients received >60 mg/kg/day of vancomycin. There was no statistically significant difference in the outcomes between patients receiving ≥ 60 mg/kg/day or < 60 mg/kg/day of vancomycin.

Vancomycin troughs and outcomes of *S. aureus* OAI

Among all patients with *S. aureus* OAI (with and without bacteremia), 44 (22.9%) had vancomycin troughs obtained (Table 4). Patients without vancomycin troughs obtained were less likely to have MRSA, multifocal infection, multiple surgeries and bacteremia and had a shorter duration of fever and hospitalization. Among patients with vancomycin troughs obtained, vancomycin serum trough concentrations > 15 μg/ml were associated with multifocal infection, a longer duration of hospital stay and a greater proportion of cases of AKI. There was no statistically significant decrease in duration of bacteremia, fever or time to 50% decline in CRP, need for multiple drainage/debridement procedures or long term orthopedic complications with higher vancomycin troughs. Among patients with BOAI, 39 (38.2%) had vancomycin serum troughs obtained. Similar results were seen with regards to clinical outcomes and vancomycin trough concentrations when all cases of BOAI or only MRSA BOAI were considered (Supplemental Table 3). All patients who developed AKI returned to baseline renal function by the time of last follow-up.

Discussion

S. aureus is the most common cause of OAI in children and can be associated with substantial morbidity. The frequency of positive blood culture in *S. aureus* OAI has varied in the literature and may be as high as 60%;[3] MRSA in particular may be associated with persistent bacteremia[2] as well as thrombotic complications.[4, 17] Concerns exist as to whether or not the presence of a positive blood culture for *S. aureus* should modify therapy in *S. aureus* OAI. Previous well designed prospective studies in Finland showed no difference in outcome between pediatric osteoarticular infections with and without bacteremia.[18] These studies, however, did not include patients with infection secondary to MRSA. Our data reveal that bacteremic *S. aureus* OAIs are associated with a longer duration of fever and of hospitalization as well as multiple surgical procedures. Similar findings were observed in comparisons of BOAI caused by MRSA and MSSA. There was no difference, however, in the proportion of cases with long term orthopedic complications between those with and without positive blood culture or between MRSA and MSSA. There was a statistically significant difference in time to 50% decline in CRP between patients with and without bacteremia; although, given that this represents only a one day absolute difference this finding is of unclear clinical significance. In general, however, the time required for CRP normalization may be of clinical import in that many investigators consider this among the criteria for transition to oral antibiotics.[19, 20] Overall, our data would suggest that the presence of bacteremia, in and of itself, is not a risk factor for long term orthopedic sequelae although it may be associated with worse short term outcomes. However, given the sample size constraints, this study was underpowered to detect differences in the proportion of cases developing long term orthopedic complications.

Previous work among children with OAI has shown that outpatient oral antimicrobial therapy is a safe and effective mode of treatment in most children.[11] Among patients with BOAI, 25.5% were discharged home with oral antibiotics and these patients did not experience an increase in proportion of long term orthopedic sequelae compared to children receiving OPAT/CHIT. Notably, however, patients discharged on oral antibiotics had a more

rapid response to therapy with a shorter duration of fever and time to 50% decline in CRP; as such, there is an element of bias in these data as patients discharged on oral antibiotics may have been considered less ill than their counterparts treated with IV antibiotics. Nevertheless, these findings suggest that in select patients with *S. aureus* BOAI, early transition to oral therapy is a generally safe and effective method of treatment.

In the presence of MRSA bacteremia, expert guidelines recommend treatment with a bactericidal antibiotic such as vancomcyin or daptomycin.[13] Among patients with MRSA BOAI in the present study, 34/35 (97.1%) received at least one dose of vancomycin and 51.4% of patients received < 7 days of vancomycin. Importantly, 94.1% of patients receiving < 7 days of vancomycin had documented clearance of bacteremia prior to changing to clindamycin. No patients received other bactericidal drugs such as daptomycin or ceftaroline. Patients treated with a shorter duration of vancomycin had no statistically significant increase in the proportion of cases developing orthopedic complications. Notably patients transitioned from vancomycin to alternative therapy had a shorter duration of fever and more rapid decline in CRP again indicating that these patients may have had a more rapid improvement, likely reflecting a degree of selection bias. Interestingly, patients who received shorter courses of vancomycin also tended to have surgical intervention at an early time after hospital admission perhaps contributing to a more rapid resolution in symptoms, which in turn may have promoted an earlier modification in therapy. Patients with MRSA BOAI transitioned from vancomycin to alternative therapy early were also more likely to be discharged on oral antibiotics than their counterparts (16.7% vs. 5.9%), although this did not achieve statistical significance. In addition, there was a trend for a greater proportion of cases receiving a longer course of vancomycin developing acute kidney injury than among those treated with < 7 days of vancomycin (23.5% vs. 5.6%). While these data are taken from a relatively small number of patients and are observational in a nature, they nevertheless call into question the necessity of prolonged courses of vancomycin for the treatment of MRSA BOAI when alternative agents are available.

Research among adults with MRSA pneumonia has shown improved clinical and microbiologic cure with vancomycin area under the curve (AUC)/minimum inhibitory concentration (MIC) ratio ≥ 400.[21] Furthermore, among adults, a vancomycin serum trough concentration 15–20 μg/ml achieves this goal AUC/MIC ratio in most patients.[22] This serves as the basis for the IDSA recommendation for goal vancomycin troughs in severe MRSA infections for adults;[13] there is very limited literature to support such a recommendation in children. Studies based on pharmacokinetic modeling suggest that ideal vancomycin AUC/MIC ratio may be achievable with much lower vancomycin serum trough concentrations in most children.[23] Previous studies of children with healthcare associated bacteremia at our institution failed to reveal a clinical benefit to vancomycin trough concentrations > 15 μg/ml.[15] Our study found no demonstrable benefit to vancomycin trough > 15 μg/ml in children with *S. aureus* OAI with or without the presence of bacteremia. There was, however, a statistically significant increase in nephrotoxicity with increasing vancomycin troughs which raises concerns about the need and safety of such aggressive vancomycin dosing in children. There are a number of limitations to this finding which should be acknowledged. The number of patients with vancomycin troughs performed was relatively small and thus limits conclusions that can be drawn regarding possible

benefits of elevated vancomycin trough concentrations. In addition, physicians caring for children who were more ill may have prescribed vancomycin in such a way as to push the troughs higher and thus influenced the results. Furthermore, the inclusion of only the highest trough achieved may not paint an accurate picture of continuous vancomycin exposure in these children. Given inconsistencies in the frequency of trough measurement, however, a numerical average of trough values would have provided a false estimate of vancomycin exposure. Other researchers have also used 96 hours as the cutoff time point for the examination of clinical outcomes by vancomycin exposure.[24] In addition, given that we only assessed the highest value, if anything these data may overestimate the potential benefits of vancomycin trough > 15 μg/ml in children with *S. aureus* OAI.

There are limitations of this study in addition to those discussed above. First, this is a single center retrospective study which limits the generalizability of findings. In addition, a small but important number of patients had infection caused by clindamycin-resistant MRSA which, given the limited number of treatment options, likely had an influence on physician treatment practices. Overall, however, these patients represented only 4/35 MRSA BOAI (11.4%) and likely had a small impact on the overall data set. As discussed above, the decision for OPAT/CHIT vs. oral antimicrobial therapy was likely influenced by the severity of the patients illness and the time required for response to medical therapy in hospital. In addition, other factors such as patient discomfort levels, economic considerations, psychosocial factors and parental and/or physician preferences likely influenced prescribing decisions; however, these could not be well accounted for given inconsistent documentation in the medical record. Finally, these data must be interpreted with the knowledge that situations may arise for which prolonged intravenous therapy or high vancomycin troughs may be reasonable such as endovascular infection, prolonged bacteremia, metastatic infection or resistance or intolerance to alternative agents. It is important to acknowledge, however, that no specific data exists to support the goal of vancomycin troughs > 15 μg/ml in children, even in these extreme situations.

In conclusion, *S. aureus* BOAI are associated with substantial short-term morbidity. While the study size is small, the data support early transition to oral therapy in select patients with clinical defervescence with *S. aureus* BOAI, even in the case of MRSA. Furthermore, in the setting of MRSA BOAI, treatment with vancomycin for ≥ 7 days when blood cultures have sterilized and/or vancomycin troughs > 15 μg/ml are not associated with improved clinical outcomes and are likely unnecessary in most patients. Moreover, elevated vancomcyin serum trough concentrations are associated with a higher risk of AKI. Large prospective studies are needed to better understand the optimal management of these infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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sponsored by Forest Laboratories that started after the time period of this study and thus is not directly related to the presented work; Drs McNeil and Vallejo are co-investigators on this trial.

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Table 1

Characteristic of *S. aureus* Osteoarticular Infections With and Without Bacteremia.

	Positive Blood Culture (n=102)	Negative Blood Culture (n=90)	P value
Age, years (IQR) *	7.3 (3.3–12.4)	7.6 (3.5–11.7)	0.5
MRI Performed	96 (94.1)	87 (96.7)	0.5
Methicillin-Resistance	35 (34.3)	23 (25.6)	0.2
Osteomyelitis#	99 (97.1)	77 (85.6)	0.007
Septic Arthritis#	56 (54.9)	40 (44.4)	0.2
Other Sources of Positive Culture			
Bone	97 (95.1)	71 (78.9)	0.002
Synovial Fluid	74 (72.5)	28 (31.1)	<0.001
Adjacent Pyomyositis	4 (3.9)	3 (3.3)	1
Multiple Foci of Infection	12 (11.7)	3 (3.3)	0.03
Subperiosteal Abscess	47 (46.1)	37 (41.1)	0.6
Maximum Diameter of Abscess, cm	3.4 (2–6.1)	2.9 (2.1–5.9)	0.8
Surgical Drainage/Debridement Procedure	71 (69.6)	70 (77.8)	0.2
≥2 Surgical Procedures	31 (30.4)	9 (10)	0.001
Duration of Symptoms on Presentation, days†	6 (3–7)	5 (3–7)	0.34
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
Length of Follow-up, patient days	166.5 (56–461)	123 (45–332)	0.09
Lost to Follow-Up	2 (2)	7 (7.8)	0.09
Long Term Orthopedic Complications‡	17 (16.7)	18 (20)	0.6

*Continuous variables expressed as medians with interquartile ranges (IQR) in all tables.

#Osteomyelitis and septic arthritis in this study are not mutually exclusive.

†104 patients with duration of symptoms documented in medical record.

‡Long term complications in patients with positive blood culture included chronic osteomyelitis (n=15), pathologic fracture (n=2) and limb length discrepancy (n=1); complications among patients without positive blood culture included chronic osteomyelitis (n=14), pathologic fracture (n=1), limb length discrepancy/physeal growth arrest (n=4).

Table 2

Comparison of Cases of BOAI Discharged with Oral Antibiotics Compared to Those Receiving OPAT/CHIT

	Transition to 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
Duration of Follow-Up, patient days	122 (35–572)	180 (77–427)	0.4
Length of Hospital Stay, days	8.5 (6–11)	11 (8–16) *	0.006
Duration of Symptoms on Presentation, days	6 (3–7)	5 (3–7)	0.8
Fever On Admission to Hospital	17 (65.4)	57 (75)	0.4
Duration of Fever after Admission, days	3 (2–6)	6 (3–10)	0.03
Duration of Bacteremia, days	1 (1–1)	1 (1–2)	0.3
Initial CRP, mg/dl	8.8 (5.9–22.7)	13 (4.5–26)	0.7
Time to 50% Decline in CRP, days	6 (5.5–8)	8 (7–11)	0.01
MRSA	4 (15.4)	31 (40.7)	0.03
Clindamycin-Resistant MRSA	0	4 (5.3)	0.6
Surgical Intervention	15 (56.7)	56 (73.7)	0.1
Time from Admission to First Surgical Procedure, days	2 (2–2)	2 (1–3)	0.8
≥2 Surgical Procedures	5 (19.2)	28 (36.8)	0.14
Multifocal Infection	3 (11.5)	9 (11.8)	1
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
Septic Arthritis	11 (42.3)	45 (59.2)	0.17
Venous Thrombosis	0	4 (5.3)	0.57
Total Duration of Antibiotic Therapy, days	35 (28–55)	44 (30–120)	0.14
Long Term Orthopedic Complications	3 (11.5)	14 (18.4)	0.55

* CHIT patients (n=8) excluded from comparisons of length of hospital stay

Table 3

Clinical Features of MRSA BOAI by Duration of Vancomycin Treatment

	≥ 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
Duration of Follow-Up, patient days	405.5 (264–819.5)	263 (135–412)	0.08
Clindamycin Resistance	4 (23.5)	0	0.045
Length of Hospital Stay, days	17 (12–27)	11 (8–13)	0.002
Duration of Symptoms on Presentation, days (IQR)	7 (5–12)	6 (5–8)	0.9
Duration of Bacteremia, days	2 (1–3)	1 (1–2)	0.14
Duration of Fever, days	10 (7–16)	6 (3–9)	0.005
Multifocal Infection	5 (29.4)	1 (5.6)	0.08
Septic Arthritis	13 (76.5)	10 (55.6)	0.3
Surgical Drainage/Debridement Procedure	17 (100)	17 (94.4)	0.5
≥ 2 Surgical Procedures	9 (52.9)	13 (72.2)	0.3
Time from Admission 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
AKI	4 (23.5)	1 (5.6)	0.1
Vancomycin serum Trough > 15 μg/ml	5/14 (35.7)	2/10 (20)	0.6
Total Duration of Antibiotic Therapy, days	44.5 (31–141)	54.5 (39.5–258.5)	0.38
Discharge on Oral Antibiotics	1 (5.9)	3 (16.7)	0.6
Long Term Orthopedic Complications	5 (29.4)	3 (16.7)	0.4

* The patient who received only clindamycin was included in this category.

Table 4

Clinical Features of *S. aureus* Osteoarticular Infection by Vancomycin Trough

	No Trough Obtained (n=148)	Trough ≤ 10 μg/ml (n=20)	Trough 10-≤15 μg/ml (n=9)	Trough > 15 μg/ml (n=15)	P Value, All Categories	P Value, Excluding Cases without Trough
Age, years	7.3 (2.4–11.6)	7.5 (4.5–12.9)	7.3 (6.8–11.9)	8.6 (1.1–13.9)	0.5	0.2
MRSA	29 (19.6)	14 (70)	7 (77.8)	8 (53.3)	<0.001	0.5
Multifocal Infection	8 (5.5)	1 (5)	0	7 (46.7)	<0.001	0.001
≥ 2 Surgical Procedures	21 (14.2)	9 (45)	5 (55.6)	7 (46.7)	<0.001	0.9
Admission CRP, mg/dl	7.5 (3.8–18.6)	7.7 (5.5–24.5)	5.6 (3.8–33.1)	20.6 (15.4–27.8)	0.06	0.3
Time to 50% Decline in CRP, days	7 (5–8)	8 (7–10.5)	7.5 (5.5–10.5)	7.5 (7–10)	0.1	0.7
Duration of Fever, days	3 (2–6)	7 (5.5–9)	9.5 (7–15)	14.5 (6–18)	<0.001	0.5
Positive Blood Culture	63 (42.6)	18 (90)	7 (77.8)	14 (93.3)	<0.001	0.6
Duration of Bacteremia, days	1 (1–2)	1.5 (1–3)	1 (1–2)	1 (1–2)	0.09	0.3
Length of Hospital Stay, days	8 (6–11.5)	11 (7.5–15.5)	13 (12–18)	22 (11–42)	<0.001	0.01
Acute Kidney Injury	5 (3.4)	2 (10)	0	7 (46.7)	<0.001	0.01
Long Term Orthopedic Complications	26 (17.6)	2 (10)	3 (33.3)	4 (26.7)	0.3	0.4