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Clinical Epidemiology and Outcomes of Pediatric Musculoskeletal Infections

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Abstract

Objectives: To understand the epidemiology of acute hematogenous osteomyelitis and septic arthritis, including clinical and demographic features, microbiology, treatment approaches, treatment-associated complications, and outcomes.

Study Design: Retrospective cohort study of 453 children with AHO and/or SA from 2009 – 2015.

Results: Among the 453 patients, 218 (48%) had AHO, 132 (29%) had SA, and 103 (23%) had concurrent AHO/SA. Treatment failure/recurrent infection occurred in 41 (9%). Patients with concurrent AHO/SA had longer hospital stays, longer duration of antibiotic therapy, and were more likely to have prolonged bacteremia and require intensive care. *Staphylococcus aureus* was

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identified in 228 (51%) of patients, of which 114 (50%) were methicillin-resistant *S. aureus* (MRSA). Compared with SA, AHO and concurrent AHO/SA were associated with higher odds of treatment failure (OR 8.19, 95% CI 2.02, 33.21; p=.003; and OR 14.43, 95% CI 3.39, 61.37; p<.001, respectively). Need for more than one surgical procedure was also associated with higher odds of treatment failure (OR 2.98, 95% CI 1.18, 7.52; $P = .021$). Early change to oral antibiotic therapy was not associated with treatment failure (OR 0.64, 95% CI 0.24, 1.74; p=.386). Most (73%) medically-attended treatment complications occurred while on parenteral therapy.

Conclusions: Musculoskeletal infections are challenging pediatric infections. *S. aureus* remains the most common pathogen, with MRSA accounting for 25% of all cases. Concurrent AHO/SA is associated with more severe disease and worse outcomes. Fewer treatment-related complications occurred while on oral therapy. Early transition to oral therapy was not associated with treatment failure.

Pediatric musculoskeletal infections), including acute hematogenous osteomyelitis and septic arthritis, are common invasive infections, occurring in up to 80 per 100,000 children in the US [1]. These infections require prolonged antibiotics and are often complicated by bacteremia, septic thrombophlebitis, and myositis [2]. Despite the frequency and severity of pediatric MSKI, there is a paucity of contemporary US data regarding clinical characteristics, management strategies, and outcomes.

Though *Staphylococcus aureus* has remained the most common causative pathogen of MSKI for decades [3], recent data suggest decreasing rates of once ubiquitous community-associated methicillin-resistant *S. aureus* (CA-MRSA), and resistance to other commonly used antimicrobials, such as clindamycin, has increased [4–6]. The addition of pneumococcal conjugate (PCV7 and PCV13) and *Haemophilus influenzae* type B (Hib) vaccines to the childhood immunization schedule also resulted in substantial declines in invasive disease due to these pathogens [7–11]. Epidemiologic data for other important pathogens in MSKI, including *Streptococcus pyogenes* and *Kingella kingae,* are limited [1, 12].

Changing epidemiologic trends, along with limited evidence for the optimal therapeutic approaches have led to considerable variability in the management of MSKI in children [13]. Several studies suggest that early transition to oral antibiotics may not be associated with increased risk of treatment failure [14–18] and obviates the risk of frequently observed catheter-related complications [14, 19]. A contemporary evaluation of pediatric MSKI in the US is needed.

We sought to define and compare the epidemiology of AHO and SA at two large US children's hospitals, focusing on clinical and demographic features, microbiology, treatment, medically-attended complications, and outcomes.

Methods

We performed a retrospective review of children with MSKI who were treated at Egleston Hospital at Children's Healthcare of Atlanta (Georgia) and the Monroe Carell Jr. Children's Hospital at Vanderbilt University Medical Center (Nashville, Tennessee). This study was

approved by each site's Institutional Review Board. Patients were identified through a query of ICD-9 codes (Table I; available at www.jpeds.com) used for the diagnosis of AHO and SA, and the diagnosis was confirmed by chart review. Inclusion criteria were age 6 months – 18 years (inclusive) and a discharge diagnosis of AHO or SA between 1 January 2009 – 30 September 2015. Exclusion criteria were evidence of subacute or chronic osteomyelitis (symptoms >14 days), history of deep penetrating trauma in or adjacent to the site, presence of a foreign body or hardware in or adjacent to the site, infection that occurred within 12 months of a surgical procedure involving the affected bone or joint, osteomyelitis of skull or jaw, and osteomyelitis of the clavicle (unless a pathogen associated with AHO was recovered as these sites are commonly implicated in chronic recurrent multifocal osteomyelitis). Patients with a primary bone abnormality syndrome (such as osteogenesis imperfecta) and those with compromised immune systems (primary diagnosis or secondary to systemic immunomodulators) were excluded; however, children with sickle cell anemia-associated functional asplenia and selective IgA deficiency were included.

Data abstraction and definitions

Data were abstracted through review of the electronic medical record by trained study personnel and recorded in a standardized electronic case report form into a central database (Research Electronic Data Capture, REDCap). Final review and adjudication of discrepancies was performed by a pediatric infectious disease physician at each site.

Subjective data were recorded directly from clinical documentation during electronic medical record review. If no information was provided, the data were considered missing and the denominator was noted.

Definitions were specified *a priori*. Concurrent AHO/SA was defined as disease of both the bone and contiguous joint identified by examination, imaging and/or surgical procedure and documented in the chart; disseminated infection was defined as presence of visceral abscess, pulmonary nodules, endocarditis, and/or thrombophlebitis; and persistent bacteremia was defined as a positive blood culture >72 hours after initiation of antibiotics. Delayed surgical procedure was defined as the first surgical procedure occurring >3 days after admission. Adherence to a prescribed antibiotic course was determined by the clinician's observation as documented in the chart. Treatment failure was defined as documentation of the following events: worsening AHO or SA while on antibiotic therapy prompting an antibiotic change (not including change to narrow antibiotic activity, adjustment for patient convenience, or changes related to toxicity or reaction); new onset swelling, erythema, or pain in the original site of AHO/SA within 1 month of completing the initial antibiotic course that required an additional course of antimicrobials; or diagnosis of chronic osteomyelitis (identified by notation in the medical record of chronic osteomyelitis/infection or radiographic evidence of chronic infection, such as a sequestrum or Brodie's abscess) in the same extremity after completion of initial antibiotic course.

To investigate differences during the study period, we analyzed the cohort over two time periods: January 2009 – June 2012 and July 2012 – September 2015, as they had a comparable number of patients identified, 229 vs. 224 respectively.

Both institutions follow Infectious Diseases Society of America outpatient parenteral antimicrobial therapy guidelines for laboratory monitoring while receiving intravenous antibiotics [20].

Statistical Analyses

Descriptive statistics were used to describe the epidemiology of AHO and SA. The Fisher exact and Wilcoxon rank-sum tests were used to compare categorical and continuous variables, respectively. For pairwise comparisons between the three infection types (AHO, SA, AHO/SA) or between causative organisms, a Bonferroni correction was applied to penalize for multiple comparisons.

Multiple logistic regression was used to evaluate the independent association of duration of parenteral therapy with treatment failure. Model covariates included patient age, sex, race, ethnicity, clinic site, clinical (parenteral antibiotic duration, surgical procedure, myositis, multifocal infection, infection type) and microbiological variables (positive pathogen culture, bacteremia) significantly associated at the 0.05 level in bivariate analyses with either short course parenteral (≤7 days) or treatment failure. Odds ratios for clinically relevant variables were reported in addition to Wald 95% confidence intervals (CI) and p values.

Results

Patient Demographics and Characteristics

Patients, 268 from Vanderbilt and 185 from Emory, met criteria for inclusion. Demographic and clinical data are shown in Table 2. The majority of patients were non-Hispanic white (55%), male (63%), and had no pre-existing medical conditions (71%). The median age was 6.0 years (IQR 2.2 – 10.5). Children with SA were younger (2.9 years; IQR 1.3–7.7) than children with AHO (8.1 years; IQR 3.3–11.2, p≤.001) (Table 3). AHO was the most common infection type (48%), followed by SA (29%), and concurrent AHO/SA (23%). The pelvis and lower extremities were the most commonly affected sites in children with AHO (92%) with the femur most commonly affected (Table 2). Similarly, the lower extremities and sacroiliac joints were the most commonly affected sites in children with SA (89%) with the knee being the most commonly affected joint. Half of all patients had MSKI-associated myositis, most commonly in children with concurrent AHO/SA (64%). Disseminated infection was present in 7%, most commonly in children with concurrent AHO/SA, occurring in 15% of those children.

Characteristics During Hospitalization

The duration of hospitalization was similar between children with SA and AHO, and children with concurrent AHO/SA had a significantly longer hospitalization (AHO/SA median 8.0 days [IQR 5.0–14.0] versus SA 4.0 days [IQR 3.0–6.0], p<.001; AHO 5.0 days [IQR 4.0–7.0], p<.001) (Table 3). Eleven percent of patients required care in the intensive care unit (ICU), and 4% required mechanical ventilation. A higher proportion of children with concurrent AHO/SA required ICU care (25%) compared with children with AHO (8%, p<.001) or SA (3%, p<.001). Surgery was performed in 76% of patients, and a higher

proportion of children with SA underwent at least one surgical procedure compared with AHO (95% vs 59%, p<.001).

Markers of inflammation (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] and white blood cell [WBC] count) were elevated. Children with concurrent AHO/SA had significantly higher CRP at admission (137.5 mg/L; IQR 74.0–235.0) than those with AHO (65.0 mg/L; IQR 23.0–148.0, p<.001) or SA (51.5 mg/L; IQR 18.0–88.0, p<.001). Peak CRP was higher in those with concurrent AHO/SA (180.0 mg/L; IQR 92.0–270.0) than in those with AHO (85.0 mg/L; IQR 36.0–172.0, p=.007) and SA (66.5 mg/L; IQR 33.0–117.0, p<.001).

Nearly all (98%) initial antibiotic therapy was administered intravenously. Clindamycin was the most common initial and final antibiotic used (Table 4; available at www.jpeds.com). When comparing trends over the study period (Jan 2009 – June 2012 vs. July 2012 – September 2015), empiric vancomycin use decreased from 54% to 35% (p<.001) and use of a PICC decreased from 56% to 26% (p<.001). The majority of patients (67%) were transitioned to oral antibiotics at discharge, a trend that increased over the study period from 58% to 77% (p<.001). Overall, 8% of patients received exclusively parenteral therapy for the duration of treatment. The median duration of total antibiotic therapy for all patients was 34.0 days (IQR 28.0, 46.0); for patients with SA 25.0 days (IQR 21.0–31.0), AHO 37.0 days (IQR 30.0–48.0) and AHO/SA 43.0 days (IQR 33.0–57.0).

Microbiology

A pathogen was identified by sterile site sampling (e.g., blood or surgical site culture or polymerase-chain reaction [PCR]) in 62% of all patients (Table 5). A pathogen was identified more commonly in children with concurrent AHO/SA (81%) compared with AHO (68%, p=.050) or SA (38%, p<.001). Of patients with a pathogen identified (n=277), blood culture alone identified the pathogen in 22%, surgical site sampling in 27%, and blood culture plus surgical site sampling in 50%. Overall, 29% of patients received antibiotic pretreatment prior to admission. Of those, a pathogen was identified in 64%, similar to those that did not receive antibiotic pre-treatment (61%, p=.593).

Bacteremia was identified in 41% of patients that had at least one blood culture (n=419). Bacteremia was most common among patients with concurrent AHO/SA (64%). The median duration of bacteremia was 2.0 days (IQR 1.0 – 4.0). Persistent bacteremia of at least three days was observed in 13%, most commonly in patients with concurrent AHO/SA (24%).

S. aureus was the most commonly identified organism, isolated in 51% of all patients, a proportion that remained similar over time (55% vs. 47%, p=.130). *S. aureus* accounted for 81% of all identified pathogens. *S. aureus* was recovered more frequently in concurrent SA +AHO (74%) than either SA (19%) or AHO (60%) alone (p<.001). Of those with *S. aureus,* 54% were identified by both blood and surgical site cultures, 23% only from surgical specimens, and 23% by blood culture alone. *S. aureus* was the causative pathogen in the majority of patients with bacteremia (91%). Methicillin resistance was observed in 50% of all *S. aureus* isolates and remained similar over time (52% vs. 48%, p=.595), across infection types (p=.278), and within treatment centers (47% vs. 51% [p=0.714] and 58% vs.

44% [p=0.181]). Clindamycin resistance was observed in 8% of all *S. aureus* isolates and was stable over time (8% vs. 9%, p>.999). Trimethoprim-sulfamethoxazole (TMP-SMX) resistance was observed in 1% of *S. aureus* isolates.

S. pyogenes, S. pneumoniae, and *K. kingae* accounted for 5%, 1%, and 1% of infections, respectively. Demographics, and clinical characteristics of patients with *S. pyogenes* compared with *S. aureus* are shown in Table 6 (available at www.jpeds.com). For non-*S. aureus* pathogens, 45% were identified only in surgical site specimens, 35% in both blood and surgical site cultures, and 18% only by blood culture.

Outcomes

The majority of children (87%) had full range of motion at the end of therapy, though this differed by causative organism: 94% of children without *S. aureus* infection had full range of motion at the end of therapy, compared with 87% with MSSA and 76% with MRSA (p<.001 for MRSA vs no *S. aureus).* Nearly all (98%) had mild or no pain at the end of therapy. The overall rate of treatment failure or recurrent infection was 9%, and there was no difference in the frequency over time (7% vs. 11%, p=.140). Of those with treatment failure, 39% required a surgical procedure after their original hospital admission.

Compared with SA, AHO (OR 8.19, 95% CI 2.02, 33.21 p=.003) and concurrent AHO/SA (OR 14.43, 95% CI 3.39, 61.37; p<.001) were associated with higher odds of treatment failure (Figure). Additionally, requiring >1 surgical procedure was associated with higher odds of treatment failure (OR 2.98, 95% CI 1.18, 7.52; p=.02), Hospital location was also associated with higher odds of treatment failure (OR 2.84, 95% CI 1.00, 8.00; p= .049). In contrast, short course parenteral antibiotic therapy (≤7 days), organism, including MRSA, and delayed surgical procedure were not associated with treatment failure.

Non-adherence with outpatient antibiotic therapy was suspected in 8% of patients. Of these, 43% had recurrent infection or treatment failure, compared with 8% in those with no suspicion of non-adherence (p<.001).

Overall, 103 medically-attended events associated with antibiotic complications occurred in 84 (19%) patients (Table 7; available at www.jpeds.com). Seventy-four percent of the complications occurred while on parenteral therapy, with PICC-associated complications being most common. Gastrointestinal intolerance was the most common complication while on oral therapy.

Discussion

In this contemporary epidemiologic study of children with MSKI, we found that empiric vancomycin use and PICC placement decreased over time, and oral antimicrobial therapy at discharge increased over time; importantly, these trends were not associated with increased odds of treatment failure. *S. aureus* remains the most commonly isolated organism, with MRSA causing half of these infections. Our data suggest that children with concurrent AHO/SA had more severe disease than those with either AHO or SA alone.

For decades, the clinical features and epidemiology of MSKI in children changed very little [21]. *S. aureus* has long been reported as the most common cause of MSKI in children. With the emergence of CA-MRSA in the early 2000s, however, these characteristics, as well as management approaches and outcomes, substantially changed [22]. Recent studies of *S. aureus* isolates recovered from children (primarily skin and soft tissue infections) suggest a decreasing proportion of infections due to MRSA, with increasing numbers of MSSA and resistance to clindamycin [4, 23, 24]. In our study, we found that the frequency of MRSA and clindamycin resistance was stable over these 7 years. Our study provides updated epidemiologic and clinical care trends at two large US children's hospitals in the SE US, which is essential to optimize management decisions and resource utilization. In addition, these findings underscore the importance of understanding local epidemiology and consulting antibiograms to inform empiric antibiotic selection.

Additionally, literature regarding the severity of MRSA compared with MSSA infections is conflicting [25]. Although several studies have found infection due to MRSA to be associated with higher inflammatory markers, complications, and longer durations of hospitalization in children with MSKI [26–29], other studies have shown no differences [25, 30]. We found infections due to MRSA were not associated with higher odds of treatment failure than MSSA infection, when controlling for other variables. Numerous variables affect the severity of MSKI. Further investigation into the mechanisms, including host and pathogen factors, is needed.

The frequency of confirmed non-*S. aureus* infection in our study was low. Despite high rates of *K. kingae* infections in children <5 years of age reported in prior studies [27, 28], *K. kingae* accounted for only 1% of infections in our cohort. Notably, patients with SA, in which *K.kingae* is an important pathogen, were less likely to have an identified pathogen. This finding may be attributed to low rates of molecular testing at both study sites during this time period. Previous studies have shown significantly higher yield of *K. kingae* detection with the use of PCR-based techniques [27, 28], and this may represent a portion of the 38% of cases in this series in which no pathogen was identified. In the post-PCV13 and Hib vaccine era, rates of invasive infections caused by *S. pneumoniae* and *H. influenzae* remain low. Interestingly, we found that surgical site sampling was required for pathogen identification in 27% of all patients, increasing to 45% for non-staphylococcal infections. This observation highlights the importance of surgical sampling for diagnostic purposes, as pathogen identification has significant treatment and antimicrobial stewardship implications. Of note, antibiotic pretreatment was not associated with reduced rates of pathogen identification, consistent with prior studies [31].

Our study supports a growing body of literature suggesting that early transition to oral antibiotics is not associated with adverse outcomes in children with MSKI [14–18]. In 2009, Zaoutis et al published a multicenter, retrospective study of children with culture-positive osteomyelitis in the US and found that early transition to oral therapy was not associated with an increased risk of treatment failure [15]. Keren et al published a study finding that the rates of treatment failure were the same in the oral therapy (5.0%) and parenteral therapy (6.0%) groups [14]. In our study, the frequency of treatment failure was 9%. In multivariable regression analysis, early transition to oral antibiotics was not associated with increased risk

of treatment failure. Additionally, consistent with prior studies [14, 32], we found most antibiotic-associated complications occur while on parenteral therapy, with PICC complications being most common. The proportion of treatment failure in patients with documented suspicion for medication nonadherence was 43%, a finding that may be useful for counseling families about the importance of adherence with oral therapy. Overall, our study confirms that early transition to oral antibiotic therapy for children with MSKI is safe and effective with proper adherence, avoiding the potential complications of parenteral therapy.

When investigating other factors associated with severe infection and treatment failure, we found infection type to be a significant factor. Concurrent AHO/SA was associated with increased markers of inflammation, bacteremia, prolonged bacteremia, duration of hospitalization, need for ICU-level care, and a 14-fold increased risk in treatment failure compared with SA alone. These findings are similar to recent reports of patients with concurrent AHO/SA [2, 33, 34]. Alhinai et al described factors that predicted an acute complicated course of osteomyelitis, which included associated suppurative arthritis [33]. Carillo et al found that a CRP of ≥100mg/L along with fever that persisted >2 days after starting treatment and bacteremia correlated with an increased likelihood for concurrent AHO/SA [2]. Branson et al found patients with concurrent infection had longer duration of symptoms on presentation, had *S. aureus* or MRSA as a causative pathogen, had positive blood cultures, a longer duration of fever after admission, higher peak temperature at the time of presentation, higher peak and admission inflammatory markers and positive synovial fluid Gram stain and culture [34]. Further studies on this subset of patients are needed to validate these findings and improve outcomes in these children.

Hospital site was also associated with increased odds of treatment failure in this study though rates of MRSA, antibiotic selection, hospitalization duration was similar between sites. Variables associated with increased severity of disease such as concurrent AHO/SA and need for ICU level care occurred less in the center with higher treatment failures. Thus, reasons for site specific differences are unclear. Although we controlled for a variety of covariates, it is possible that unmeasured patient- or hospital-level confounding factors underly this finding.

We recognize several limitations of our study. First, as a retrospective review, all data, including clinical symptoms, are reliant upon provider documentation. Additionally, by using ICD-9 codes to identify those with SA and AHO, it is possible that some patients with AHO or SA were missed due to incorrect coding. Also, as examination, imaging, and surgical procedure were used to identify patients with concurrent AHO/SA, patients that did not have obvious signs of concomitant infection on examination, or those that did not have imaging or surgery could have been misclassified. Medically-attended events that occurred outside of the study centers were not captured which could underestimate rates of treatment failure and complications. However, for these two comprehensive pediatric healthcare centers with few patients lost to follow up, this limitation is likely minimal. Relying on provider documentation to assess medication nonadherence has the potential to introduce bias as providers are more likely to document nonadherence in patients who fail therapy.

Finally, both centers serve metropolitan areas in the southeastern US, and generalizability to other centers and geographic regions may be limited.

In summary, we found that *S. aureus* remains the major cause of MSKI. Rates of MRSA remained stable over time. Additionally, we found the frequency of non-*S. aureus* pathogens was low, but recovery of these pathogens often necessitates surgical source sampling. We also found that early transition to oral antibiotics was not associated with treatment failure, and carries less risk of treatment complications compared with outpatient parenteral antimicrobial therapy. Finally, we found that concurrent AHO/SA and need for >1 surgery were associated with a high-risk of treatment failure. These findings are consistent with data in smaller studies [5, 6, 33]. This study is unique in that the large sample size across multiple institutions allows for more generalizability.

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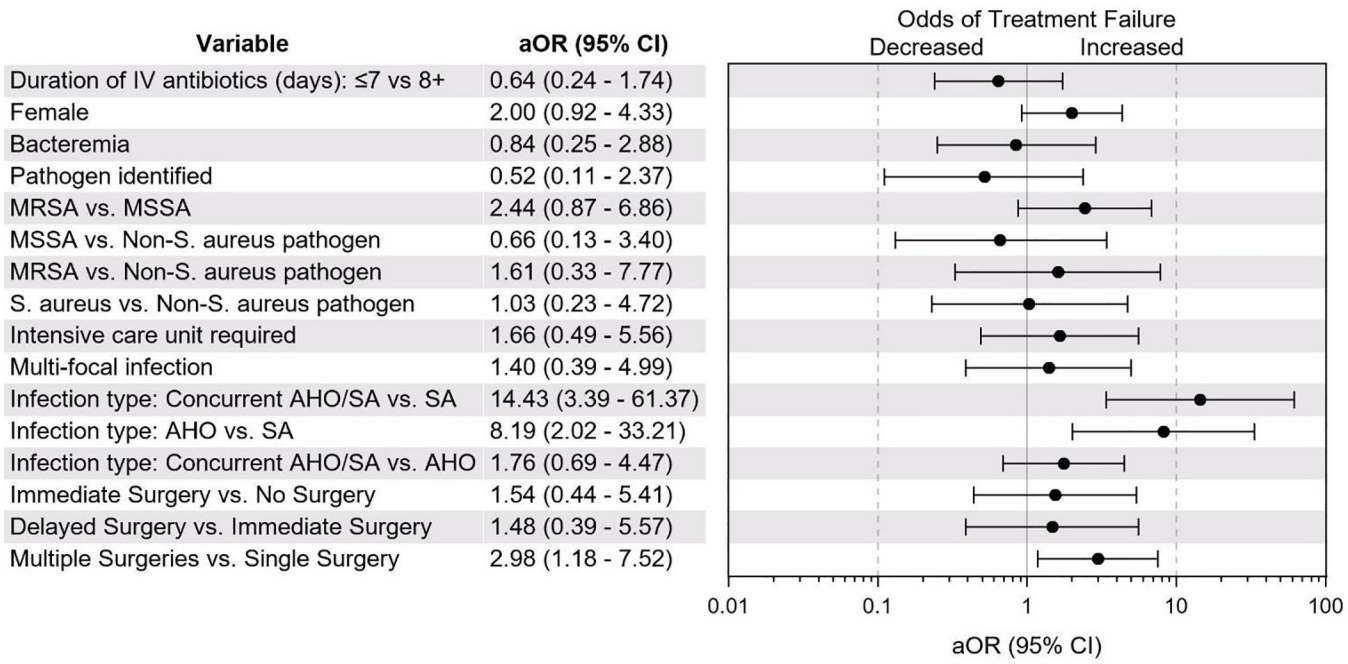

Figure.

Odds of treatment failure by clinical characteristic. Infection type (concurrent AHO/SA vs. SA and AHO vs. SA) and need for multiple surgical procedures was associated with treatment failure. Duration of parenteral antibiotics, causative organism and delayed surgical procedure were not associated with treatment failure.

Table 1.

ICD-9 codes to identify AHO and septic arthritis

ICD-9 Code	Diagnosis
Osteomyelitis codes	
730	Acute osteomyelitis
730.0	Acute osteomyelitis
730.2	Unspecified osteomyelitis
730.8	Other infections involving the bone in diseases classified elsewhere
730.9	Unspecified infection of bone
Septic arthritis codes	
711.0	Pyogenic arthritis
711.4	Arthropathy associated with other bacterial diseases
711.8	Arthropathy associated with infection and other parasitic disease
711.9	Unspecified infective arthritis
713.7	Other general diseases with articular involvement
713.8	Arthropathy associated with other conditions classified elsewhere

Table 2.

Population Characteristics

Characteristic	N[a]	
Age at admission (years, median [IQR])	453	6.00 (2.20, 10.50)
Female, No. (%)	453	168 (37)
Race/Ethnicity, No. (%)	392	
Non-Hispanic White		215 (55)
Non-Hispanic Black		127 (32)
Hispanic		26 (7)
Other		24 (6)
Pre-existing medical condition[b], No. (%)	437	
None		311 (71)
Respiratory		32 (7)
Neurologic		17 (4)
Blood		11 (3)
Ortho		12 (3)
GI		7 (2)
Prematurity		10 (2)
Kidney		3 (1)
Cardiac		5 (1)
Liver		1 (0)
Other		76 (17)
Infection type and location[c], No. (%)		
Acute Hematogenous Osteomyelitis	218	
Femur		53 (24)
Fibula		16 (7)
Foot		39 (18)
Hand		9 (4)
Humerus		9 (4)
Pelvis		39 (18)
Radius		1 (<1)
Tibia		43 (20)
Ulna		3 (1)
Vertebral		8 (4)
Other[d]		6 (3)
Septic Arthritis	132	
Ankle		11 (8)
Elbow		9 (7)
Foot		4 (3)
Hand		2 (2)

Characteristic		
Hip		51 (39)
Knee		54 (41)
Sacro-iliac		1 (1)
Shoulder		3 (2)
Wrist		3 (2)
Pubic symphysis		1 (1)
Concurrent AHO/SA[e]	103	
Lower Extremity		88 (85)
Upper Extremity		20 (19)
Associated Findings, No. (%)	453	
Myositis/pyomyositis		229 (51)
Septic Arthritis	132	41 (31)
Acute Hematogenous Osteomyelitis	218	122 (56)
Concurrent AHO/SA	103	66 (64)
Disseminated infection[f]		30 (7)
Septic Arthritis	132	3 (2)
Acute Hematogenous Osteomyelitis	218	12 (6)
Concurrent AHO/SA	103	15 (15)
Fasciitis		22 (5)
Septic Arthritis	132	3 (2)
Acute Hematogenous Osteomyelitis	218	11 (5)
Concurrent AHO/SA	103	8 (8)

[a] Some subjects had missing data

[b] Subjects may have multiple pre-existing conditions

[c] Subjects may be infected at multiple sites

[d] Other AHO sites- rib, clavicle, scapula, sternum

[e] Five subjects with both upper and lower extremity infections

[f] Defined as visceral abscess, pulmonary nodules, or endocarditis)

Table 3.

Clinical Characteristics and Outcomes

Characteristic[a]	All		Septic Arthritis		Osteomyelitis		Both	
Clinical Presentation	**N**		**N**		**N**		**N**	
Age at admission (years)	453	6.00 (2.20, 10.50)	132	2.90 (1.30, 7.70)	218	8.05 (3.30, 11.20) °	103	8.00 (2.90, 11.50) °
Symptoms prior to presentation, days	452	4.0 (2.0, 7.0)	132	3.0 (2.0, 5.0)	217	5.0 (3.0, 7.0)	103	4.0 (2.0, 7.0)
Fever prior to presentation, days	346	3.0 (1.0, 5.0)	91	2.0 (1.0, 4.0)	174	3.0 (2.0, 5.0)	81	3.0 (2.0, 5.0)
Antibiotic pretreatment, No. (%)	453	133 (29%)	132	24 (18%)	218	71 (33%)	103	38 (37%)
Antibiotic pretreatment, days	123	3.0 (1.0, 5.0)	22	2.5 (1.0, 5.0)	67	3.0 (1.0, 6.0)	34	3.0 (1.0, 5.0)
Fever at admission, No. (%)	453	112 (25%)	132	23 (17%)	218	46 (21%)	103	43 (42%) °*
Symptoms at presentation, No. (%)								
Erythema	438	146 (33%)	129	31 (24%)	210	73 (35%)	99	42 (42%)
Swelling	438	248 (57%)	127	68 (54%)	212	114 (54%)	99	66 (67%)
Tenderness	451	361 (80%)	132	97 (73%)	217	176 (81%)	102	88 (86%)
Functional status at presentation, No. (%)								
Full range of motion	451	143 (32%)	132	30 (23%)	217	91 (42%)	102	22 (22%)
Normal ambulation	377	12 (3%)	112	2 (2%)	181	7 (4%)	84	3 (4%)
Limp	377	221 (59%)	112	71 (63%)	181	106 (59%)	84	44 (52%)
Not ambulating[b]	377	144 (38%)	112	39 (35%)	181	68 (38%)	84	37 (44%)
Ambulatory with assistance[c]	333	71 (21%)	104	12 (12%)	157	40 (25%)	72	19 (26%)
Characteristics During Hospitalization								
Hospitalization duration, days	453	5.0 (4.0, 8.0)	132	4.0 (3.0, 6.0)	218	5.0 (4.0, 7.0) °	103	8.0 (5.0, 14.0) °*
ICU[d] required, No. (%)	453	48 (11%)	132	4 (3%)	218	18 (8%)	103	26 (25%) °*
Mechanical ventilation required	450	16 (4%)	132	3 (2%)	215	6 (3%)	103	7 (7%)
Surgery performed, No. (%)	453	345 (76%)	132	126 (95%)	218	129 (59%) °	103	90 (87%) *
Laboratory Characteristics								
CRP[e] at admission (mg/L)	449	71.0 (29.0, 152.0)	130	51.5 (18.0, 88.0)	217	65.0 (23.0, 148.0) °	102	137.5 (74.0, 235.0) °*
Peak CRP (mg/L)	450	92.0 (42.0, 184.0)	130	66.5 (33.0, 117.0)	217	85.0 (36.0, 172.0)	103	180.0 (92.0, 270.0) °*
WBC[f] at admission (K/mm^3)	444	12.0 (9.0, 15.0)	130	13.0 (10.0, 15.0)	214	11.0 (8.0, 14.0)	100	12.5 (9.5, 16.0)
Peak WBC count (K/mm^3)	444	13.0 (10.0, 16.0)	130	13.0 (11.0, 16.0)	214	12.0 (9.0, 16.0)	100	14.0 (11.0, 21.0)
ESR[g] at admission (mm/hr)	412	47.0 (27.0, 67.0)	124	44.0 (24.5, 64.5)	195	42.0 (25.0, 66.0)	93	52.0 (33.0, 78.0)
Peak ESR (mm/hr)	408	59.0 (36.0, 80.0)	122	53.5 (33.0, 71.0)	196	52.0 (32.0, 79.0)	90	70.0 (53.0, 96.0)
Antibiotic Therapy, No. (%)								
Initial parenteral antibiotics	452	445 (98%)	132	130 (98%)	217	214 (99%)	103	101 (98%)

Characteristic[a]		All		Septic Arthritis		Osteomyelitis		Both
Oral therapy at discharge	451	304 (67%)	131	94 (72%)	217	149 (69%)	103	61 (59%)
Parenteral therapy exclusively	444	37 (8%)	130	15 (12%)	213	14 (7%)	101	8 (8%)
PICC line placed	450	184 (41%)	130	37 (28%)	218	81 (37%)	102	66 (65%)
Total duration of antibiotic treatment (days)	445	34 (28, 46)	131	25 (21,31)	213	37 (30, 48)	101	43 (33, 57)
Outcomes, No. (%)								
Function at end of therapy								
Cast	362	4 (1%)	109	0 (0%)	175	2 (1 %)	78	2 (3%)
Full range of motion	359	314 (87%)	108	103 (95%)	172	160 (93%)	79	51 (65%)
Pain at end of therapy								
None	361	286 (79%)	109	93 (85%)	174	140 (80%)	78	53 (68%)
Mild	361	66 (18%)	109	15 (14%)	174	30 (17%)	78	21 (27%)
Moderate	361	9 (2%)	109	1 (1%)	174	4 (2%)	78	4 (5%)
Pathologic fracture	442	12 (3%)	130	0 (0%)	212	4 (2%)	100	8 (8%)
Treatment failure/Recurrent infection	444	41 (9%)	130	4 (3%)	212	17 (8%)	102	20 (20%)
Nonadherence with outpatient antibiotics[h]	378	31 (8%)	113	7 (6%)	183	15 (8%)	82	9 (11 %)

[a] Data are presented as median (interquartile range) unless otherwise stated

[b] Ambulation status only collected on patients with lower extremity infection

[c] Among subjects not ambulating normally

[d] Intensive care unit

[e] C-reactive protein

[f] White blood cell count

[g] Erythrocyte sedimentation rate

[h] Suspected or confirmed by documentation in medical record

Tests for significance among all three groups were conducted for *a priori* selected categorical or continuous variables using Fisher's exact test or Wilcoxon rank sum test, respectively. If the group differences were significant at $p<0.05$, pairwise comparisons were computed and Bonferroni-adjusted. Significant pairwise differences between groups are marked based on the comparator

[o] = vs. SA

[*] = vs. AHO

Table 4.

Antibiotic use by Infection Type

Characteristic	All (N=453)		Septic Arthritis (N=132)		Osteomyelitis (N=217)		Both (N=104)	
Initial antibiotics								
Vancomycin	452	203 (45%)	132	54 (41%)	216	81 (38%)	104	68 (65%)
Clindamycin	452	321 (71%)	132	91 (69%)	216	164 (76%)	104	66 (63%)
1st generation cephalosporin	452	14 (3%)	132	5 (4%)	216	7 (3%)	104	2 (2%)
2+ generation cephalosporin	452	184 (41%)	132	85 (64%)	216	62 (29%)	104	37 (36%)
Anti-staphylococcal penicillin	452	11 (2%)	132	1 (1%)	216	5 (2%)	104	5 (5%)
Other penicillin	452	9 (2%)	132	2 (2%)	216	3 (1%)	104	4 (4%)
Fluroquinolone	452	5 (1%)	132	0 (0%)	216	5 (2%)	104	0 (0%)
Linezolid	452	1 (0%)	132	0 (0%)	216	1 (0%)	104	0 (0%)
Other	452	29 (6%)	132	2 (2%)	216	11 (5%)	104	16 (15%)
Final antibiotics								
Vancomycin	452	32 (7%)	131	3 (2%)	217	22 (10%)	104	7 (7%)
Clindamycin	452	242 (54%)	131	78 (60%)	217	110 (51%)	104	54 (52%)
1st generation cephalosporin	452	97 (21%)	131	23 (18%)	217	49 (23%)	104	25 (24%)
2+ generation cephalosporin	452	82 (18%)	131	48 (37%)	217	27 (12%)	104	7 (7%)
Anti-staphylococcal penicillin	452	30 (7%)	131	5 (4%)	217	17 (8%)	104	8 (8%)
Other penicillin	452	29 (6%)	131	13 (10%)	217	9 (4%)	104	7 (7%)
Fluroquinolone	452	20 (4%)	131	6 (5%)	217	12 (6%)	104	2 (2%)
Linezolid	452	15 (3%)	131	2 (2%)	217	9 (4%)	104	4 (4%)
Other	452	11 (2%)	131	5 (4%)	217	4 (2%)	104	2 (2%)

Table 5.

Microbiologic Characteristics

Characteristic	All		Septic Arthritis		Osteomyelitis		Both	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Duration of bacteremia (days)	171	2.0 (1.0, 4.0)	16	1.5 (1.0, 2.0)	92	2.0 (1.0, 4.0)	63	3.0 (2.0, 4.0)
Bacteremia	419	171 (41%)	118	16 (14%)	203	92 (45%)	98	63 (64%)
Persistent bacteremia (>72 h)	419	53 (13%)	118	3 (3%)	203	26 (13%)	98	24 (24%)
Organism identified by blood or infection site culture[a]	448	277 (62%)	132	50 (38%)	213	144 (68%)	103	83 (81%)
None		171 (38%)		82 (62%)		69 (32%)		20 (19%)
S. aureus		228 (51%)		25 (19%)		127 (60%)		76 (74%)
S. pyogenes		21 (5%)		9 (7%)		7 (3%)		5 (5%)
K. kingae		5 (1%)		3 (2%)		2 (1%)		0 (0%)
S. pneumoniae		6 (1%)		4 (3%)		2 (1%)		0 (0%)
H. influenzae		2 (0%)		2 (2%)		0 (0%)		0 (0%)
Salmonella spp.		4 (1%)		0 (0%)		3 (1%)		1 (1%)
Other organism[b]		14 (3%)		8 (6%)		4 (2%)		2 (2%)
S. aureus antibiotic resistance	228		25		127		76	
Methicillin		114 (50%)		10 (40%)		61 (48%)		43 (57%)
Clindamycin		19 (8%)		3 (12%)		11 (9%)		5 (7%)
TMP/SMX		3 (1%)		1 (4%)		1 (1%)		1 (1%)
Erythromycin		126 (55%)		11 (44%)		70 (55%)		45 (59%)
MRSA resistance	114		10		61		43	
Clindamycin		8 (7%)		2 (20%)		4 (7%)		2 (5%)
TMP/SMX		1 (1%)		0 (0%)		0 (0%)		1 (2%)
Doxycycline		0 (0%)		0 (0%)		0 (0%)		0 (0%)
Erythromycin		90 (79%)		9 (90%)		49 (80%)		32 (74%)
MSSA resistance	114		15		66		33	
Clindamycin		11 (10%)		1 (7%)		7 (11%)		3 (9%)
TMP/SMX		2 (2%)		1 (7%)		1 (2%)		0 (0%)
Erythromycin		36 (32%)		2 (13%)		21 (32%)		13 (39%)

[a] Three subjects had polymicrobial infections

[b] Other organisms include coagulase negative *Staphylococcus*, Group C *Streptococcus*, Group G *Streptococcus*, viridans group *Streptococcus, Leclercia adecarboxylata, Enterobacter asbunae, Enterobacter cloacae, Pseudomonas fluorescens, Bacillus* spp.

Table 6:

Staphylococcus aureus (SA) vs Streptococcus pyogenes (GAS)

Characteristic	SA (N=228)		GAS(N=21)	
	N	Median (IQR)	N	Median (IQR)
Age at admission (yrs)	228	8.80 (3.60, 11.60)	21	6.10 (2.90, 7.80)
Female, n (%)	228	76 (33%)	21	10 (48%)
Duration of hospitalization (days)	228	7.00 (5.00, 10.50)	21	4.00 (3.00, 8.00)
Total (IV + PO) duration of antibiotic treatment (days)	227	42.00 (31.00, 52.00)	21	36.00 (29.00, 47.00)
Peak CRP (mg/L) during hospitalization	228	158.00 (76.00, 245.00)	21	129.00 (62.00, 184.00)
Peak WBC count (*10^3) during hospitalization	222	13.00 (10.00, 17.00)	21	14.00 (12.00, 22.00)
Peak ESR (mm/hr) during hospitalization	202	65.50 (38.00, 88.00)	19	57.00 (44.00, 80.00)
Infection Type, n (%)				
Both	228	76 (33%)	21	5 (24%)
Osteomyelitis	228	127 (56%)	21	7 (33%)
Septic Arthritis	228	25 (11%)	21	9 (43%)
Bacteremia, n (%)	214	156 (73%)	18	7 (39%)
Persistent bacteremia (>72 h), n (%)	214	52 (24%)	18	0 (0%)
Surgery performed, n (%)	228	187 (82%)	21	18 (86%)
ICU required, n (%)	228	41 (18%)	21	4 (19%)
PO therapy at discharge, n (%)	228	135 (59%)	21	15 (71%)
Function at end of therapy, n (%)				
Cast	185	4 (2%)	19	0 (0%)
Full ROM	185	151 (82%)	18	16 (89%)
Pain at end of therapy, n (%)				
None	185	135 (73%)	19	17 (89%)
Mild	185	43 (23%)	19	2 (11%)
Moderate	185	7 (4%)	19	0 (0%)
Pathologic fracture, n (%)	225	12 (5%)	21	0 (0%)
Concern for recurrence of infection/treatment failure, n (%)	225	26 (12%)	21	1 (5%)

Table 7.

Treatment-associated complications at follow up

	Number of complications		
Complication Type[a]	**Total**	**IV**	**PO**
Any medically attended events due to complications	103	76	27
Medication intolerance	58	31	27
Hypersensitivity reaction/rash	22	13	9
GI intolerance/vomiting/diarrhea	16	6	10
Drug fever	8	8	0
Hematologic abnormality	6	2	4
Kidney injury	4	4	0
Transaminase elevation	2	2	0
C. diff colitis	1	0	1
Anaphylaxis	1	1	0
Other	6	2	4
PICC/catheter problem	46	46	
Catheter malfunction		16	
Catheter pulled out		11	
Line-associated infection		7	
Thrombus		5	
Catheter leak		3	
Dermatitis		3	
Catheter fracture		2	
Other		2	

[a]Some patients had multiple complications during a medically attended event