

The Contemporary Microbiology and Rates of Concomitant Osteomyelitis in Acute Septic Arthritis

Jessica Branson, PA-C, Jesus G. Vallejo, MD, Anthony R. Flores, MD, MPH, PhD, Kristina G. Hulten, PhD, Edward O. Mason, PhD, Sheldon L. Kaplan, MD, and J. Chase McNeil, MD

Background: Septic arthritis (SA) and acute osteomyelitis (AO) are among the most common serious bacterial infections of childhood. Knowledge of the microbiology of SA is critical to treatment. Awareness of the presence of attendant AO is also important to guide clinical management. We sought to describe the current microbiology of SA in children and clinical features associated with coexisting AO.

Materials and Methods: Patients with SA were identified from the infectious diseases consult service records from 2010 to 2014. Patients with penetrating/open trauma and orthopedic hardware in situ were excluded.

Results: A total of 168 patients with SA were included. The most common causative organism was *Staphylococcus aureus* accounting for 47.7% of cases (29.1% were methicillin-susceptible *S. aureus* and 18.5% were methicillin-resistant *S. aureus*), followed by group A streptococcus (GAS, 8.9%). The proportion of cases due to GAS increased from 2011 to 2014 (3.3%–16.7%; $P = 0.1$). One hundred eight (64.3%) patients had concurrent AO. The presence of osteomyelitis was associated with older median age (5.9 vs. 2.4 years; $P = 0.04$), a longer duration of symptoms (5 vs. 2.5 days; $P < 0.001$), *S. aureus* (62.1% vs. 21.7%; $P < 0.001$), bacteremia (46.2% vs. 20.3%; $P = 0.001$), a longer duration of fever after admission (5 vs. 2 days; $P < 0.001$) and a longer length of stay (10 vs. 6 days; $P < 0.001$).

Conclusions: Methicillin-resistant *S. aureus* continues to be an important cause of SA though GAS may be increasing in frequency. The presence of concomitant osteomyelitis is higher than previously reported and associated with older age, a longer duration of symptoms and fever, bacteremia and *S. aureus*.

Key Words: septic arthritis, osteomyelitis, children, complications, methicillin-resistant *Staphylococcus aureus*, group A streptococcus

(*Pediatr Infect Dis J* 2017;36:267–273)

Musculoskeletal infections, including acute hematogenous osteomyelitis and septic arthritis, are among the most common serious bacterial infections of childhood. Septic arthritis, particularly when combined with osteomyelitis, carries a significant risk of complications including dislocation, avascular necrosis, growth disturbance, chronic osteomyelitis and pathologic fracture of the adjacent bones.^{1–5} Prompt medical and surgical interventions are necessary for optimal outcomes.⁶ Furthermore, knowledge of the causative organism and the presence of associated osteomyelitis early in the course of treatment is important for guiding therapy.

Staphylococcus aureus is the most common cause of septic arthritis overall, accounting for 26%–50% of culture-positive cases.^{2,7–10} Among patients with *S. aureus* septic arthritis at Texas Children's Hospital (TCH) between 2001 and 2008, 36% of isolates were methicillin-resistant *S. aureus* (MRSA).¹¹ Other important etiologies of septic arthritis include group A streptococcus (GAS), *Streptococcus pneumoniae*, *Salmonella* spp. and *Kingella kingae*. Based on studies of diagnostic code utilization from 1997 to 2012, the incidence of MRSA as a cause of childhood osteoarticular infection appears to be increasing in the United States,¹² underscoring the importance of obtaining a microbiologic diagnosis.

Septic arthritis and osteomyelitis can occur in isolation or simultaneously in a given patient. Rates of contiguous osteomyelitis in the setting of septic arthritis have varied tremendously in the literature from 20.8% to 68%.^{2,13,14} Among children with osteomyelitis, 21%–42% will have infection of the adjacent joint.^{7,15} Knowledge of the presence of concomitant osteomyelitis is of clinical importance as it alters the recommended treatment duration of children with septic arthritis.¹⁶ Furthermore, children with concomitant septic arthritis and osteomyelitis have a less favorable clinical course including bacteremia, ICU admission and need for more surgical procedures^{11,17} as well as increased risk for growth arrest, dislocation and pathologic fracture compared to those with septic arthritis alone.¹⁸ Few studies have sought to identify clinical features of septic arthritis that predict associated osteomyelitis or other complications. Many previous studies focused only on surgically managed patients or a single pathogen or were performed before the era of community-acquired MRSA.^{11,18,19}

The primary goal of this study was to identify the clinical and microbiologic characteristics of patients with septic arthritis and osteomyelitis compared to those children with septic arthritis alone. A secondary goal of this study was to describe the contemporary microbiology of septic arthritis at a tertiary care children's hospital.

MATERIALS AND METHODS

Patient Identification and Data Collection

Patients were identified from consultation records of the inpatient infectious diseases service of TCH Main Campus. Infectious diseases are routinely consulted for known or suspected septic arthritis or osteomyelitis at TCH. Infectious diseases consultations between January 1, 2010, and December 31, 2014, were reviewed to identify patients with a diagnosis of septic arthritis. Patients were excluded after review of clinical records if they were given a diagnosis other than septic arthritis by the physician of record (such as toxic synovitis or isolated osteomyelitis). Patients with septic arthritis that developed following penetrating or open trauma or surgery were also excluded. To assess completeness of the consult database, a search for the number of discharges with the International Classification of Diseases, 9th revision (ICD-9) code 711.0X, pyogenic arthritis, during the study period was obtained from TCH administrative data.

TCH and the affiliated Texas Children's Pediatric Associates clinics (a network of >50 primary care clinics with >200 pediatricians in the greater Houston area) have had a fully integrated

Accepted for publication July 27, 2016.

Departments of Pediatrics and Allied Health Science and Section of Infectious Diseases, Department of Pediatrics, Baylor College of Medicine, Houston, Texas.

J.C.M. receives funding through NIAID K23AI099159. The authors have no conflicts of interest to disclose.

Address for correspondence: J. Chase McNeil, MD, Departments of Pediatrics and Allied Health Science and Section of Infectious Diseases, Department of Pediatrics, Baylor College of Medicine, 1102 Bates Street, Suite 1150, Houston, TX 77030. E-mail: Jm140109@bcm.tmc.edu.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.
ISSN: 0891-3668/17/3603-0267

DOI: 10.1097/INF.0000000000001417

electronic medical record since 2010 including inpatient and outpatient encounters. All clinical records were reviewed for complications of septic arthritis including avascular necrosis and dislocation as well as complications related to a contiguous osteomyelitis such as pathologic fracture, growth arrest and chronic osteomyelitis when available up through June 20, 2016. When available, reports of follow-up imaging studies after hospital discharge were also reviewed; there was no rereview of the actual images by a radiologist. The Institutional Review Board of Baylor College of Medicine approved this study.

Definitions

The diagnosis of septic arthritis was defined using a combination of classic clinical findings (joint swelling, erythema, tenderness, limited range of motion, etc.), radiologic findings and results of synovial fluid Gram stain and culture. Associated osteomyelitis was based on a combination of radiographic evidence of bone infection [by plain radiographs, computerized tomography or magnetic resonance imaging (MRI)], clinical examination findings (such as point tenderness along with fever, erythema and swelling) and/or bone culture or histology. The isolation of coagulase-negative staphylococci, α -streptococci (other than *S. pneumoniae* or *Streptococcus milleri* group), diphtheroids and *Bacillus* spp. were regarded as culture contaminants.²⁰ Fever was defined as a body temperature $\geq 100.4^{\circ}\text{F}$; duration of fever was defined as the number of calendar days with fever. Antibiotic pretreatment was considered ≥ 1 hour of intravenous antimicrobials before obtaining synovial fluid for culture.

Microbiology

Organism identification and antimicrobial sensitivity were performed by the clinical microbiology laboratory during the routine course of care. All synovial fluid samples submitted for culture are routinely inoculated into blood culture bottles at our institution. TCH employs the VersaTREK blood culture system (Thermo Fisher Scientific, Waltham, MA) using blood culture vials without resin. Polymerase chain reaction for *K. kingae* is not routinely performed at TCH. A prospective surveillance study for *S. aureus* infections has been ongoing at TCH since 2001 (principal investigator: S.L.K.); bacterial isolates were collected and stored in the Infectious Diseases Research Laboratory. This surveillance study database was searched to correlate bacterial strain types with corresponding infections in this study. When available, *S. aureus* isolates were characterized by pulsed field gel electrophoresis.²¹

Statistical Analysis

Continuous variables were examined with the Mann-Whitney *U* and Kruskal-Wallis tests. Dichotomous variables were analyzed by χ^2 and Fisher exact tests. When available, the relationship between serum white blood cell (WBC) and synovial fluid WBC counts was examined with the Spearman correlation test. Two-tailed *P* values < 0.05 were considered statistically significant. A multivariate logistic regression model was used to examine clinical findings and laboratory values associated with underlying osteomyelitis using stepwise forward and backward selection of variables; dichotomous variables with *P* value < 0.1 were eligible for inclusion in this model. A priori, it was decided to not include synovial fluid WBC count or positive synovial fluid culture in this model as these factors are often used in the definition of septic arthritis by other studies. Inpatient pharmacy data were included in the electronic medical record beginning in 2011; for examination of specific antibiotic choices, duration of therapy and the impact of antibiotic pretreatment on culture yield, only cases from 2011 to 2014 were considered. All analyses were conducted using STATA version 13 (STATA Corp, College Station, TX).

RESULTS

Two-hundred ninety discharges with the diagnosis of pyogenic arthritis based on ICD-9 coding occurred from January 1, 2010, to December 31, 2014; during the study period, 249 infectious diseases consultations for septic arthritis occurred representing 85.9% of the coding database. After review of all medical records, 168 cases of acute hematogenous septic arthritis were identified meeting inclusion criteria. The median age of patients was 4.2 years [interquartile range (IQR): 1.8–9.7 years; Table 1]. The most commonly involved joints were the hip (29.1%), knee (29.1%), ankle (21.4%) and shoulder (11.9%); 5.4% of patients had involvement of ≥ 2 joints. One hundred forty-six (86.9%) patients underwent a surgical drainage procedure (arthrocentesis, arthrotomy or corticotomy of bone) by the orthopedic surgery service; an additional 7 (4.2%) patients had aspiration of joints performed by interventional radiology. Among patients with synovial fluid sent for cytology, there was a lower median synovial fluid WBC count among those with positive synovial cultures [36,000 cells/mm³ (IQR: 12,225–86,844)] compared with negative cultures [55,962 cells/mm³ (IQR: 25,375–125,500); *P* = 0.1], although this was not statistically significant. There was no correlation between peripheral WBC and synovial WBC counts (Spearman *r* = 0.08).

Microbiology

A microbiologic etiology was determined in 113 (67.3%) patients. The most commonly identified infectious agent was methicillin-susceptible *S. aureus* (49, 29.2%; Fig. 1) followed by MRSA

TABLE 1. Overall Study Population

| Clinical Characteristics | N = 168 |
|---|---------------------------|
| Age, yr (IQR) | 4.2 (1.8–9.7) |
| Male gender, n (%) | 104 (61.9) |
| Underlying chronic medical conditions, n (%) | 28 (16.7)* |
| Duration of symptoms on presentation, d (IQR) | 4.5 (2–7) |
| Fever on presentation, n (%) | 118 (70.2) |
| Duration of fever after admission, d (IQR) | 3 (2–7) |
| Duration of hospitalization, d (IQR) | 8 (6–12) |
| MRI performed, n (%) | 162 (96.4) |
| Positive blood culture, n/N (%) | 61/165 (37) |
| Positive synovial fluid culture, n/N (%) | 77/138 (55.8) |
| Synovial fluid WBC count, cells/mm ³ (IQR)† | 50,800 (19,425–86,844) |
| Synovial fluid neutrophil count, cells/mm ³ (IQR)† | 34,382 (17,483–76,326) |
| Concomitant osteomyelitis, n (%) | 108 (64.2) |
| Presence of subperiosteal/intraosseous abscess, n (%) | 32 (19.1) |
| Concomitant pyomyositis, n (%) | 37 (22) |
| Most common anatomic sites, n (%) | |
| Hip | 49 (29.1) |
| Knee | 49 (29.2) |
| Ankle | 36 (21.4) |
| Shoulder | 20 (11.9) |
| Elbow | 11 (6.5) |
| Wrist | 4 (2.4) |
| Multiple sites | 9 (5.4) |
| Surgical procedures performed, n (%) | |
| Arthrocentesis alone | 7 (4.2) |
| Arthrotomy alone | 50 (29.4) |
| Arthrocentesis and arthrotomy | 85 (50.6) |
| Corticotomy/drainage of subperiosteal abscess | 42 (24.7) |

Continuous variables reported as medians along with IQRs.

*Chronic medical conditions included eczema (n = 6), prematurity (n = 5), hemoglobinopathy (n = 4), malignancy (n = 2), juvenile idiopathic arthritis (n = 2), epilepsy (n = 2), asthma (n = 2) and 1 patient each with cystic fibrosis, chronic lung disease, uropathy with nephrostomy tube placement, renal transplant recipient, trisomy 21, short gut and single kidney.

†Among 49 patients with fluid sent for cytology.

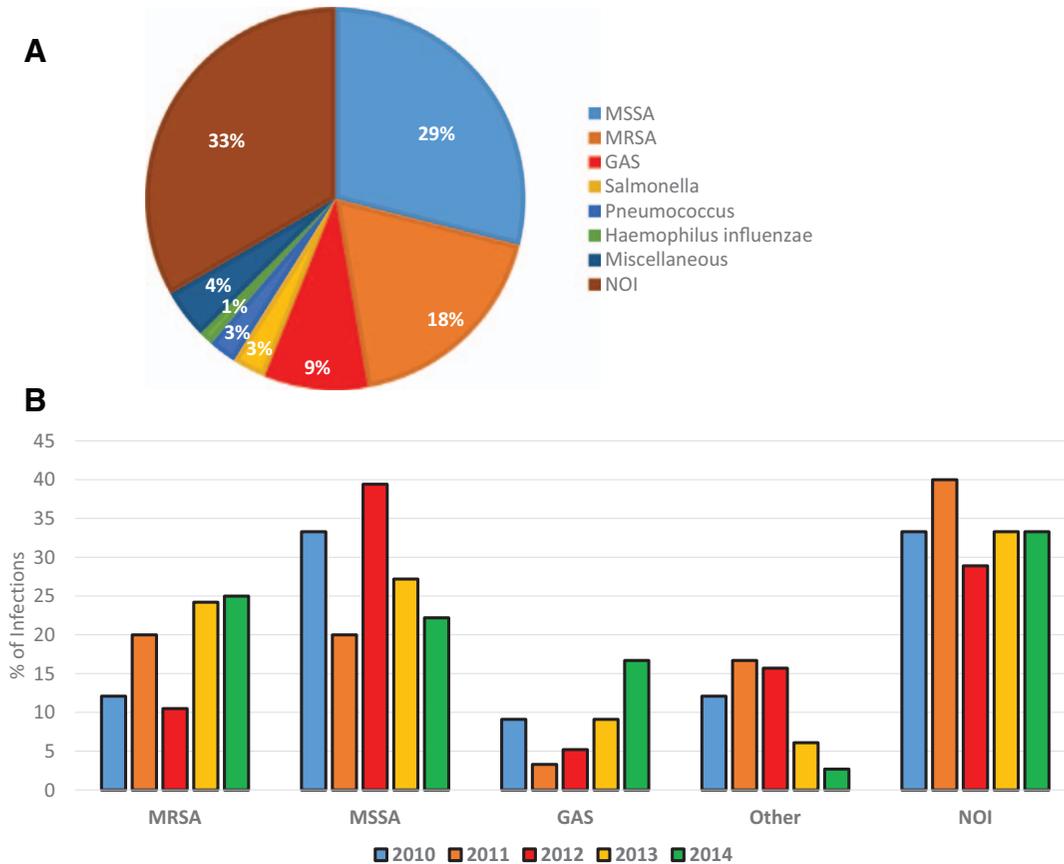


FIGURE 1. Causative agents of septic arthritis. A: Relative proportion of various causative agents. “Miscellaneous” refers to n = 1 each of *Candida albicans*, *Enterobacter cloacae*, group B streptococcus, *K. kingae*, *Pasteurella canis*, *Pseudomonas aeruginosa* and *Streptococcus intermedius*. B: Temporal trends in causative agents of septic arthritis. NOI indicates no organism isolated.

(31, 18.5%), GAS (15, 8.9%), *Salmonella* spp. (5, 2.9%) and *S. pneumoniae* (4, 2.4%). A single case of *K. kingae* septic arthritis was identified. The relative number of cases caused by GAS increased from 2011 to 2014 (from 3.3% to 16.7%; $P = 0.1$). Infections caused by MRSA were more often associated with bacteremia, concomitant osteomyelitis, a longer duration of fever after admission and a higher rate of positive synovial fluid Gram stains (Table 2). Specific treatment data are provided in Table (Supplemental Digital Content 1, <http://links.lww.com/INF/C600>). Among children with *Salmonella* septic arthritis, 2 had hemoglobinopathy and another had eczema; the other 2 patients were previously healthy and none of the patients were <6 months old. Two additional patients with hemoglobinopathy had MRSA and no organism isolated, respectively. Pulsed field gel electrophoresis types were available for 32/80 *S. aureus* isolates; 20 of 32 belonged to pulsotype USA300 (62.5%). Seven USA300 isolates were methicillin-susceptible.

Bacteremia

The vast majority of patients had blood cultures performed [165/168 (98.2%)] of which 37% were positive for a pathogen. The median time to blood culture positivity was 15.7 hours (IQR: 12.5–19.5 hours). Patients with bacteremia were more likely to have disease caused by *S. aureus* [45/61 (73.8%) vs. 35/104 (33.7%); $P < 0.001$], concomitant osteomyelitis [49/61 (80.3%) vs. 57/104 (54.8%); $P = 0.001$], a higher median admission C-reactive protein (CRP, 12.9 vs. 5.4 mg/dL; $P < 0.001$), a longer duration of fever

after admission (6 vs. 2 days; $P < 0.001$) and a longer duration of hospitalization (11 vs. 7 days; $P < 0.001$). Patients with bacteremia also had lower median synovial fluid WBC counts [14,438 (IQR: 11,150–60,750) vs. 62,989 (IQR: 28,313–139,375) cells/mm³, $P = 0.003$] and lower median synovial fluid neutrophil counts [13,188 (IQR: 10,051–36,003) vs. 48,288 (IQR: 25,764–93,575) cells/mm³; $P = 0.007$]. Notably, among patients with blood and synovial fluid cultures taken, patients with bacteremia more often had positive synovial cultures [42/51 (82.4%)] than those without bacteremia [32/77 (41.6%); $P < 0.001$]. There was no difference in duration of symptoms on presentation or peripheral WBC counts between patients with and without bacteremia.

Septic Arthritis and Osteomyelitis

One hundred eight (64.2%) patients were found to have concurrent osteomyelitis along with septic arthritis (Table 3). The age of the patients with osteomyelitis was older (5.9 years) compared to those without osteomyelitis (2.4 years). The proportion of cases with osteomyelitis in the <2 year old group was similar to that in the 2–5 year old groups (54.1% vs. 60.1%); a greater proportion of children >5 years old had underlying osteomyelitis (72.1%).

Patients with associated osteomyelitis more often had a longer duration of symptoms on presentation (5 vs. 2.5 days; $P < 0.001$), had *S. aureus* (62.1% vs. 21.7%; $P < 0.001$) or MRSA (25% vs. 6.7%; $P = 0.003$) as a causative pathogen, had positive blood cultures (46.2% vs. 20.3%; $P = 0.001$), a longer

TABLE 2. Clinical Features by Infecting Organism

| Clinical Characteristics | MRSA (n = 31) | MSSA (n = 49) | GAS (n = 15) | Other Organism* (n = 18) | No Organism Identified (n = 55) | P |
|--|---------------------------|---------------------------|----------------------------|--------------------------------|---------------------------------------|--------|
| Age, yr (IQR) | 7 (3.5–12.5) | 4.1 (1.9–10.8) | 5.2 (2.1–8.1) | 1.8 (0.7–9.4) | 2.7 (1.8–8.4) | 0.1 |
| Male gender, n (%) | 19 (61.3) | 31 (63.2) | 12 (80) | 12 (66.7) | 30 (54.5) | 0.5 |
| Duration of symptoms on presentation, d (IQR) | 5 (3–7) | 3 (2–6) | 4 (2–5) | 3 (1.5–7) | 5 (1–7) | 0.6 |
| Fever on presentation, n (%) | 24 (77.4) | 39 (79.6) | 12 (73.3) | 14 (77.8) | 31 (56.4) | 0.09 |
| Duration of fever after admission, d (IQR) | 7 (5–11) | 4 (2–8) | 4 (2–5) | 4 (2–5) | 2 (1–3) | <0.001 |
| Length of hospital stay, d (IQR) | 12 (9–21) | 10 (6–15) | 9 (6–12) | 9.5 (7–16) | 6 (5–8) | <0.001 |
| Positive blood culture, n (%) | 21 (67.8) | 24 (48.9) | 4/14 (28.6) | 11 (61.1) | n/a | 0.07 |
| Concomitant osteomyelitis, n (%) | 27 (87.1) | 38 (77.6) | 9 (60) | 10 (55.6) | 21 (38.2) | <0.001 |
| Admission WBC count, × 10 ³ cells/mm ³ | 13.7 (10.9–20.8) | 12.9 (9.6–15.2) | 17.1 (13.8–22.8) | 12.4 (9.8–17.9) | 12.4 (8.6–16.4) | 0.02 |
| Admission ESR, mm/h (IQR) | 75 (57–90) | 54 (28.5–84.5) | 57 (38–104) | 39.5 (25–61) | 51.5 (35.5–74) | 0.007 |
| Peak ESR, mm/h (IQR) | 98 (79–113) | 84.5 (41.5–103.5) | 108 (74–116) | 59 (35–77) | 63 (42–86) | <0.001 |
| Admission CRP, mg/dL (IQR) | 14.7 (5.1–26) | 8.8 (4.6–19.3) | 16.9 (6.8–24.9) | 6.8 (3.3–15) | 4.5 (2.7–7.2) | <0.001 |
| Peak CRP, mg/dL (IQR) | 17.5 (6.2–26) | 12.8 (5.1–23.1) | 20.6 (14.7–26.5) | 7.8 (3.7–15) | 4.8 (3.2–8) | 0.001 |
| Synovial fluid Gram stain positive, n/N (%) | 17/27 (63) | 23/43 (53.5) | 7/12 (58.3) | 6/16 (37.5) | 6/40 (15) | <0.001 |
| Synovial fluid culture positive, n/N (%) | 22/27 (81.5) | 34/43 (79.1) | 11/12 (91.6) | 12/16 (91.6) | n/a | 0.2 |
| Synovial fluid WBC count, cells/mm ³ (IQR) | 14,438 (10,600–60,750) | 71,813 (19,425–86,844) | 52,625 (32,200–223,000) | 50,625 (36,000–157,750) | 61,128 (25,560–125,500) | |
| Duration of intravenous antibiotics, d (IQR)† | 35.5 (28–42) | 30.5 (15.5–42) | 8 (6–18) | 21 (7–28) | 5 (3–21) | <0.001 |
| Total duration of antibiotics, d (IQR) | 35.5 (28–42) | 42 (28–42) | 29 (21–40) | 28 (21–42) | 21 (21–28) | <0.001 |
| Discharge from hospital on oral antibiotics, n/N (%) | 2/21 (9.5) | 7/22 (31.8) | 9/11 (81.8) | 5/13 (38.5) | 25/34 (73.5) | <0.001 |
| Combination therapy at discharge, n/N (%) | 0 | 0 | 0 | 1/13 (7.7) | 6/34 (17.6) | 0.04 |

Continuous variables reported as medians along with IQRs.

*Other refers to *Salmonella* spp. (n = 5), *pneumococcus* (n = 4), *Haemophilus influenzae* (n = 2) and n = 1 each of *Candida albicans*, *Enterobacter cloacae*, group B streptococcus, *Kingella kingae*, *Pasteurella canis*, *Pseudomonas aeruginosa* and *Streptococcus intermedius*.

†Among patients with full treatment information available.

ESR indicates erythrocyte sedimentation rate; MSSA, methicillin-susceptible *Staphylococcus aureus*.

duration of fever after admission (5 vs. 2 days; $P < 0.001$), higher peak temperature at the time of presentation (103.2 vs. 102.3°F; $P = 0.01$), higher peak and admission inflammatory markers and positive synovial fluid Gram stain (54.7% vs. 27.8%; $P = 0.004$) and culture (72% vs. 37%; $P < 0.001$). The following variables were included in a stepwise logistic regression analyses to examine features associated with underlying osteomyelitis: age >5 years, symptom duration >3 days at presentation, fever >3 days after admission, *S. aureus* or MRSA as causative pathogen, positive blood culture, platelet count >300,000 cells/mm³, initial or peak erythrocyte sedimentation rate >60 mm/h, initial CRP >7.5 mg/dL, peak CRP >10 mg/dL, positive synovial fluid Gram stain and site of infection. Of these many variables, only symptom duration >3 days on presentation ($P = 0.005$) and *S. aureus* as the causative pathogen ($P < 0.001$) remained statistically significant in multivariate analysis.

Among patients with positive joint cultures who were given the diagnosis of septic arthritis with osteomyelitis, 42 of 54 had follow-up radiographs after hospital discharge. In 33 cases (78.6%), the follow-up radiographs revealed evidence of healing or progressive osteomyelitis. Among patients with positive joint cultures who were not diagnosed with osteomyelitis, 9 of 20 had follow-up radiographs performed (45%), of which 1 revealed features consistent with osteomyelitis (11.1%).

Antibiotic Pretreatment and Synovial Culture Yield

Ninety-patients with synovial fluid obtained for culture also had full pretreatment information available. There was no difference in culture positivity rate among those who were pretreated and those who were not [26/42 (61.9%) vs. 25/48 (52.1%); $P = 0.3$]. In addition, among those who were pretreated, there was no difference in duration of pretreatment among those with positive and negative synovial fluid cultures [26.3 hours (IQR: 13–43 hours) vs. 16.5 hours (14.8–23.3 hours); $P = 0.2$].

Complications

Eight (4.7%) patients were found to have orthopedic complications on subsequent follow-up encounters. Three patients developed progressive/chronic osteomyelitis, 2 patients developed pathologic fractures and 1 patient each developed avascular necrosis, physal growth arrest and chronic dislocation. Seven of these patients were diagnosed with concomitant osteomyelitis at the time of initial presentation (87.5%) and 3 (37.5%) had subperiosteal or intraosseous abscesses (compared with 17.9% of those without complications; $P = 0.1$). Among patients who developed orthopedic complications, *S. aureus* was more often the causative agent compared with those that did not develop complications [6/8 (75%) vs. 74/163 (45.3%); $P = 0.1$]; among those with isolates available for testing, USA300 *S. aureus* specifically was more common among those with orthopedic complications (83.3% vs. 59.3%; $P = 0.3$). All 8 patients had MRI and surgical procedures performed with their initial encounter; 5 patients underwent corticotomy and 3 patients underwent multiple procedures. Patients who developed complications received a longer course of total antibiotic therapy (42 days; IQR: 30–42) than those who did not develop complications although this was not statistically significant (28 days; IQR: 21–42; $P = 0.2$).

DISCUSSION

S. aureus continues to be the most common causative organism of septic arthritis in children, responsible for 70.8% of culture-positive cases in our study; 18.5% of infections were caused by MRSA, which is notably a lower proportion than those found in previous studies.^{11,22,23} Bocchini et al²² reported that MRSA accounted for 62.9% of *S. aureus* osteomyelitis from 2001 to 2004. The relative decline in MRSA as a cause of septic arthritis is consistent with recent studies from our own institution on the microbiology of acute hematogenous osteomyelitis.²⁰ This is of clinical import in that empiric therapy for musculoskeletal infections in many

TABLE 3. Comparisons of Patients With Septic Arthritis With and Without Concomitant Osteomyelitis

| Clinical Characteristics | With Osteomyelitis (n = 108) | Without Osteomyelitis (n = 60) | P |
|---|------------------------------|--------------------------------|--------|
| Age, yr (IQR) | 5.9 (2.1–10) | 2.4 (1.5–7.4) | 0.04 |
| Age >5 yr, n (%) | 57 (52.7) | 22 (36.7) | 0.05 |
| Male gender, n (%) | 71 (65.7) | 33 (55) | 0.2 |
| Duration of symptoms on presentation, d (IQR) | 5 (2.5–7) | 2.5 (1–5) | <0.001 |
| Duration of symptoms on presentation >3 d, n (%) | 51/84 (60.7) | 18/50 (36) | 0.007 |
| MRI performed, n (%) | 106 (98.1) | 56 (93.3) | 0.2 |
| <i>Staphylococcus aureus</i> as causative agent, n (%) | 67 (62.1) | 13 (21.7) | <0.001 |
| MRSA, n (%) | 27 (25) | 4 (6.7) | 0.003 |
| No organism identified, n (%) | 21 (19.4) | 34 (56.7) | <0.001 |
| Length of hospital stay, d (IQR) | 10 (7–15) | 6 (5–8.5) | <0.001 |
| Positive blood culture, n (%) | 49/106 (46.2) | 12/59 (20.3) | 0.001 |
| Fever on presentation, n (%) | 76/104 (73.1) | 42/60 (70) | 0.7 |
| Highest temperature at time of presentation, °F (IQR) | 103.2 (102.1–103.9) | 102.3 (101.2–103.2) | 0.01 |
| Duration of fever after admission, d (IQR) | 5 (2–8.5) | 2 (1–4) | <0.001 |
| Duration of fever >3 d after admission, n (%) | 46/76 (60.5) | 12/42 (28.6) | 0.001 |
| WBC count on admission, × 10 ³ cells/mm ³ (IQR) | 12.9 (9.4–16.4) | 13.5 (10.9–17.8) | 0.1 |
| ANC on admission, cells/mm ³ (IQR) | 7670 (5070–12,000) | 7660 (5,230–11,890) | 0.7 |
| Platelets on admission, × 10 ³ /mm ³ (IQR) | 298 (228–370) | 351 (282–415) | 0.05 |
| Admission platelet >300 × 10 ³ /mm ³ , n (%) | 36/75 (48) | 31/48 (64.6) | 0.09 |
| ESR on admission, mm/h (IQR) | 66 (38–87) | 45 (29–73) | 0.01 |
| Admission ESR >60 mm/h, n (%) | 57/107 (53.3) | 22/59 (37.3) | 0.05 |
| Peak ESR, mm/h (IQR) | 90 (59–112) | 62 (35–85) | <0.001 |
| Peak ESR >60 mm/h, n (%) | 80/107 (74.8) | 33/59 (55.9) | 0.01 |
| CRP on admission, mg/dL (IQR) | 7.7 (4–22.7) | 5.2 (3.4–14.7) | 0.02 |
| CRP on admission >7.5 mg/dL, n (%) | 55/107 (51.4) | 20/60 (33.3) | 0.04 |
| Peak CRP, mg/dL | 13 (4.7–23.5) | 5.4 (3.7–15) | 0.005 |
| Peak CRP >10 mg/dL, n (%) | 55/107 (51.4) | 20 (33.3) | 0.03 |
| Positive synovial fluid Gram stain, n/N (%) | 41/75 (54.7) | 15/54 (27.8) | 0.004 |
| Positive synovial fluid culture, n/N (%) | 54/75 (72) | 20/54 (37) | <0.001 |
| Synovial fluid WBC count, cell/mm ³ (IQR) | 27,200 (12,687.5–75,062.5) | 71,813 (33,875–139,375) | 0.02 |
| Synovial fluid neutrophil count, cell/mm ³ (IQR)* | 29,754 (11,835–62,069) | 48,288 (19,792–115,681) | 0.05 |
| Duration of intravenous antibiotics, d (IQR) | 28 (8–42) | 6 (4–21) | <0.001 |
| Median duration of total antibiotics, d (IQR) | 39 (28–42) | 21 (21–28) | <0.002 |
| Oral antibiotics at discharge, n/N (%) | 20/51 (39.2) | 31/43 (72.1) | 0.002 |
| Joint infected, n (%) | | | |
| Hip | 28 (25.9) | 21 (35) | 0.2 |
| Shoulder | 16 (14.8) | 4 (6.7) | 0.1 |
| Knee | 24 (22.2) | 23 (38.3) | 0.03 |
| Elbow | 8 (7.4) | 3 (5) | 0.7 |
| Ankle | 29 (26.9) | 7 (11.7) | 0.03 |
| Multiple joint | 7 (6.5) | 2 (3.3) | 0.5 |

Continuous variables reported as medians along with IQRs.

*Among 38 patients with synovial fluid sent for cytology and differential performed.

ANC indicates absolute neutrophil count; ESR, erythrocyte sedimentation rate

institutions includes coverage for MRSA with antibiotics such as vancomycin or clindamycin. While it is perhaps on the decline, MRSA continues to be an important cause of septic arthritis and should be considered when choosing empiric antibiotics. This is particularly important in light of MRSA causing a significantly longer length of stay and duration of fever in our study as well as being associated with concurrent osteomyelitis. Similarly, patients with *S. aureus* infections received a longer course of antibiotics and were less likely to be discharged on oral antibiotics. Notably, GAS demonstrated a rise in the relative frequency of occurrence from 2011 to 2014. Although it is one of the most common causes of septic arthritis in Europe, *K. kingae* was only detected in 1 patient in our study. However, polymerase chain reaction for *K. kingae* was not routinely performed in our center as is performed in other institutions,²⁴ and a portion of the culture-negative cases could have been attributable to *K. kingae* that was not isolated. Given the shifts in microbiology, the etiologies of septic arthritis should continue to be monitored to determine the best choices for empiric therapy.

Unexpectedly, our study found a lower median synovial WBC count in children with concomitant osteomyelitis, bacteremia

and positive joint cultures. The reasons for this finding are unclear and not related to peripheral WBC counts. It is possible that this represents selection bias in that only 49 patients (29.2%) had synovial fluid sent for cytologic analysis; an additional 6 patient specimens clotted before analysis (3.6%). It is possible that in patients for whom frank pus was aspirated from the joint, the index of suspicion for bacterial arthritis was so high that cytology was not considered necessary by the provider.

Previous research described concomitant osteomyelitis in 31.1% of children with *S. aureus* septic arthritis.¹¹ Investigators in Little Rock, AR, report underlying osteomyelitis in 21.5% of children with septic arthritis.¹⁷ Our study group had a high rate of coexisting osteomyelitis (62.9%), consistent with another recent report.¹³ One could argue that our findings were a consequence of the large number of patients undergoing MRI studies, which have a very high degree of sensitivity for bone and joint infection and the theoretical risk of false positive results.²⁵ This may particularly be the situation in cases in which MRI detects abnormalities in the bone without evidence of abscess. Previous studies, however, support a high rate of coexistence of these infectious entities. A study

of acute osteomyelitis at our institution revealed that septic arthritis was codiagnosed in 35.2% of cases.²⁰ A recent study of children with metaphyseal osteomyelitis who underwent MRI revealed that 53% of them had coexisting synovial effusions by imaging and that 75% of these were ultimately determined to be septic.²⁶ It is notable that among those patients in our study with positive synovial cultures (and thus unquestionably septic arthritis), the vast majority of those diagnosed with osteomyelitis by MRI had evidence of healing/progressive osteomyelitis on follow-up radiographs (78.6%). Taken together, the presence of either joint effusion in the presence of osteomyelitis or adjacent bone abnormalities by MRI in the presence of septic arthritis should be assumed to be contiguous sites of infection until proven otherwise. An MRI should be considered for any child with known or suspected septic arthritis to evaluate for neighboring sites of osteomyelitis given the high rates of concurrence. This desire for thorough diagnostics, however, must be balanced with the need for timely drainage of the involved joint in children with septic arthritis.

It has been previously reported that the presence of concurrent osteomyelitis with septic arthritis was more commonly seen in neonates, adolescents, children with infection of the shoulder joint, duration of symptoms >6 days and those with infection secondary to *S. aureus*.¹⁷ Carrillo-Marquez et al¹¹ found that attendant osteomyelitis was more common in cases of *S. aureus* septic arthritis with bacteremia, fever >2 days duration and an initial CRP >10 mg/dL. Other investigators have reported that higher CRP values, specifically those >13.8 mg/dL, along with thrombocytopenia are predictive of contiguous sites of infection in the setting of septic arthritis.¹⁹ In contrast, our study did not reveal an association with osteomyelitis and young age or infection of the shoulder or hip joints. Numerous other clinical features including older age, duration of fever, positive blood culture and height of inflammatory markers were significantly associated with underlying osteomyelitis by univariate analysis but lost statistical significance in multivariate analyses. Some of these discrepancies from previous studies may have been related to inclusion of patients with a diagnosis of septic arthritis who only received medical management, a group that had been excluded from some previous studies.^{17,19} However, our data do confirm the association of a longer duration of symptoms and *S. aureus* with septic arthritis and concomitant osteomyelitis in our multivariate model. Thus, while it is often difficult to predict accurately which patients with septic arthritis have underlying osteomyelitis, the presence of a long duration of symptoms on presentation (>3 days) and the isolation of *S. aureus* should alert the clinician to the possibility of concomitant osteomyelitis. These findings could potentially be utilized to guide care for patients with septic arthritis in the future in settings in which MRI for all cases is not feasible.

Long-term orthopedic complications of septic arthritis developed in 4.7% of patients in our study and were associated with substantial morbidity. Reports from the 1980s illustrated that long-term complications of septic arthritis can occur in up to 25% of patients;²⁷ while contemporary reports have suggested lower rates of complications, they are in general more common in neonates, infection of the hip or shoulder joints and when intervention is delayed.⁴ Our study was unfortunately underpowered to fully recognize predictors of orthopedic complications of septic arthritis in children given the sample size. Because information regarding care for complications at facilities outside of the TCH system was unavailable to investigators, it is possible that not all of the cases with complications were captured. Given the scope of the TCH electronic medical record system, which includes numerous primary care offices, this is likely minimized. Further research is needed regarding predictors of complications of this disease in order to establish guidelines

for follow-up in children with septic arthritis. There are limitations of this study, which should be acknowledged in addition to those above. Given the retrospective nature of this study, it is difficult to fully account for all relevant clinical variables on presentation that were not consistently described in the medical record. Another limitation is that this was a single center study and thus results may not be applicable to all settings, particularly as regards microbiology and the contribution of MRSA or GAS to septic arthritis. The reliance on an infectious disease consult database may have preselected for patients with more severe disease (more concomitant osteomyelitis or bacteremia); given that the consult list accounted for >85% of the number of unique pyogenic arthritis ICD-9 codes any such bias is likely minimal. Furthermore, review of radiology reports only was undertaken rather than a systematic review of all imaging studies by a radiologist in a research capacity. In addition, the inclusion of patients without culture confirmed disease and those without synovial WBC counts performed raises the possibility that some of the patients may have had nonbacterial arthritis. In conclusion, *S. aureus* continues to be the most common causative organism of septic arthritis in children. MRSA remains an important pathogen and should be considered when choosing empiric antibiotics, though its occurrence in septic arthritis in the study period is lower than in previous reports. GAS may be increasing in relative frequency as an arthritis pathogen. Concurrent osteomyelitis should be considered in all children with septic arthritis particularly those with >3 days of symptoms on presentation, bacteremia, persistent fever or rising inflammatory markers. Further studies are needed to better predict both concurrent osteomyelitis as well as long-term complications in the setting of pediatric septic arthritis.

REFERENCES

- Gonzalez BE, Teruya J, Mahoney DH Jr, et al. Venous thrombosis associated with staphylococcal osteomyelitis in children. *Pediatrics*. 2006;117:1673–1679.
- Gafur OA, Copley LA, Hollmig ST, et al. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. *J Pediatr Orthop*. 2008;28:777–785.
- Belthur MV, Birchansky SB, Verdugo AA, et al. Pathologic fractures in children with acute *Staphylococcus aureus* osteomyelitis. *J Bone Joint Surg Am*. 2012;94:34–42.
- Belthur MV, Palazzi DL, Miller JA, et al. A clinical analysis of shoulder and hip joint infections in children. *J Pediatr Orthop*. 2009;29:828–833.
- Choi IH, Pizzutillo PD, Bowen JR, et al. Sequelae and reconstruction after septic arthritis of the hip in infants. *J Bone Joint Surg Am*. 1990;72:1150–1165.
- Saisu T, Kawashima A, Kamegaya M, et al. Humeral shortening and inferior subluxation as sequelae of septic arthritis of the shoulder in neonates and infants. *J Bone Joint Surg Am*. 2007;89:1784–1793.
- Perlman MH, Patzakis MJ, Kumar PJ, et al. The incidence of joint involvement with adjacent osteomyelitis in pediatric patients. *J Pediatr Orthop*. 2000;20:40–43.
- Luhmann JD, Luhmann SJ. Etiology of septic arthritis in children: an update for the 1990s. *Pediatr Emerg Care*. 1999;15:40–42.
- Moumille K, Merckx J, Glorion C, et al. Bacterial aetiology of acute osteoarticular infections in children. *Acta Paediatr*. 2005;94:419–422.
- Young TP, Maas L, Thorp AW, et al. Etiology of septic arthritis in children: an update for the new millennium. *Am J Emerg Med*. 2011;29:899–902.
- Carrillo-Marquez MA, Hulten KG, Hammerman W, et al. USA300 is the predominant genotype causing *Staphylococcus aureus* septic arthritis in children. *Pediatr Infect Dis J*. 2009;28:1076–1080.
- Stockmann C, Ampofo K, Pavia AT, et al. National trends in the incidence, outcomes and charges of pediatric osteoarticular infections, 1997–2012. *Pediatr Infect Dis J*. 2015;34:672–674.
- Monsalve J, Kan JH, Schallert EK, et al. Septic arthritis in children: frequency of coexisting unsuspected osteomyelitis and implications on imaging work-up and management. *AJR Am J Roentgenol*. 2015;204:1289–1295.
- Pavlik DF, Johnston JJ, Eldredge JD, et al. Non-type b *Haemophilus influenzae* septic arthritis in children. *J Pediatr Infect Dis Soc*. [published online ahead of print May 5, 2016]. DOI: 10.1093/pids/piw024.

15. Unkila-Kallio L, Kallio MJ, Eskola J, et al. Serum C-reactive protein, erythrocyte sedimentation rate, and white blood cell count in acute hematogenous osteomyelitis of children. *Pediatrics*. 1994;93:59–62.
16. Dich VQ, Nelson JD, Haltalin KC. Osteomyelitis in infants and children. A review of 163 cases. *Am J Dis Child*. 1975;129:1273–1278.
17. Montgomery CO, Siegel E, Blasier RD, et al. Concurrent septic arthritis and osteomyelitis in children. *J Pediatr Orthop*. 2013;33:464–467.
18. Jackson MA, Burry VF, Olson LC. Pyogenic arthritis associated with adjacent osteomyelitis: identification of the sequela-prone child. *Pediatr Infect Dis J*. 1992;11:9–13.
19. Rosenfeld S, Bernstein DT, Daram S, et al. Predicting the presence of adjacent infections in septic arthritis in children. *J Pediatr Orthop*. 2016;36:70–74.
20. McNeil JC, Forbes AR, Vallejo JG, et al. Role of operative or interventional radiology-guided cultures for osteomyelitis. *Pediatrics*. 2016;137:e20154616.
21. Hultén KG, Kaplan SL, Gonzalez BE, et al. Three-year surveillance of community onset health care-associated *Staphylococcus aureus* infections in children. *Pediatr Infect Dis J*. 2006;25:349–353.
22. Bocchini CE, Hultén KG, Mason EO Jr, et al. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous *Staphylococcus aureus* osteomyelitis in children. *Pediatrics*. 2006;117:433–440.
23. Lim SY, Pannikath D, Nugent K. A retrospective study of septic arthritis in a tertiary hospital in West Texas with high rates of methicillin-resistant *Staphylococcus aureus* infection. *Rheumatol Int*. 2015;35:1251–1256.
24. Aupiais C, Ilharreborde B, Doit C, et al. Aetiology of arthritis in hospitalised children: an observational study. *Arch Dis Child*. 2015;100:742–747.
25. Mazur JM, Ross G, Cummings J, et al. Usefulness of magnetic resonance imaging for the diagnosis of acute musculoskeletal infections in children. *J Pediatr Orthop*. 1995;15:144–147.
26. Schallert EK, Kan JH, Monsalve J, et al. Metaphyseal osteomyelitis in children: how often does MRI-documented joint effusion or epiphyseal extension of edema indicate coexisting septic arthritis? *Pediatr Radiol*. 2015;45:1174–1181.
27. Wilson NI, Di Paola M. Acute septic arthritis in infancy and childhood. 10 years' experience. *J Bone Joint Surg Br*. 1986;68:584–587.