

# Effect of Antibiotic Administration Before Joint Aspiration on Synovial Fluid White Blood Cell Count in Native Joint Septic Arthritis

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**Background.** This study was performed to assess the impact of preaspiration antibiotics on synovial fluid analysis and timing of operative treatment in native-joint septic arthritis.

**Methods.** We performed a retrospective record review of adult patients from an urban level 1 trauma center with native joint septic arthritis in 2015–2019, identified by means of codes from the *International Classification of Diseases (Ninth Revision and Tenth Revision)*. Univariate and multivariate analyses were performed to determine whether antibiotics were associated with lower synovial fluid white blood cell counts (WBCs), the percentage of polymorphonuclear neutrophil (PMNs), and rate of culture positivity. Secondary analysis included time elapsed from aspiration to surgery.

**Results.** Of the 126 patients with septic joints included, nearly two-thirds (n = 80 [63.5%]) received antibiotics before joint aspiration. The synovial fluid WBC count, percentage of PMNs, and rate of culture positivity were significantly lower in patients who received preaspiration antibiotics than in those who did not (mean WBC count, 51 379.1/μL [standard deviation, 52 576.3/μL] vs 92 162.7/μL [59 330.6/μL], respectively [ $P < .001$ ]; PMN percentage, 83.6% [20.5%] vs 91.9% [6.0%;  $P = .01$ ]; and culture positivity, 32.5% vs 59.1% [ $P = .008$ ]). Multivariable analyses revealed that these associations remained after controlling for potential confounders (change in PMNs,  $-42\,784.60/\mu\text{L}$  [95% confidence interval,  $-65\,355/\mu\text{L}$  to  $-20\,213.90/\mu\text{L}$  [ $P < .001$ ]; change in PMNs,  $-7.8\%$  [ $-13.7\%$  to  $-1.8\%$ ] [ $P = .01$ ]; odds ratio, 0.39 [.18–.87;  $P = .02$ ). Patients with a synovial fluid WBC count  $\leq 50\,000/\mu\text{L}$  experienced significant delay in time from joint aspiration to operative intervention (mean [standard deviation], 10.5 [11.3] vs 17.9 [17.2] hours;  $P = .02$ ).

**Conclusions.** The administration of antibiotics before joint aspiration for suspected septic arthritis appears to decrease the synovial fluid WBC count, the percentage of PMNs, and the rate of culture positivity. Efforts to limit antibiotic administration before joint aspiration are important to minimize diagnostic dilemmas and circumvent treatment delays.

**Keywords.** preaspiration antibiotics; septic arthritis; synovial fluid analysis; white blood cell count; polymorphonuclear neutrophils; culture positivity.

Septic arthritis is a condition associated with high morbidity and mortality rates [1, 2]. In the United States, septic arthritis was responsible for >16 000 emergency department visits in 2012 [3]. Its diagnosis can be challenging and requires thorough evaluation of clinical presentation, imaging, and laboratory data. Prompt diagnosis and operative decision making are crucial for

preserving joint function because permanent damage to the intra-articular cartilage and subchondral bone can occur in as short a time as 3 days [4, 5].

The reference standard laboratory diagnostic criteria for septic arthritis is identification of a pathogen in synovial fluid [5, 6]. Although this may be a highly specific finding, failure to identify a causative organism occurs in up to 50% of septic arthritis cases, and culture times may ultimately delay diagnosis and treatment [2, 5]. To avoid treatment delays associated with waiting for cultures to finalize, the synovial fluid white blood cell (WBC) count and percentage of polymorphonuclear neutrophils (PMNs) are typically used as a proxy for the presence of a bacterial infection [7, 8]. A presumptive diagnosis can be made in patients with a synovial WBC count  $>50\,000/\mu\text{L}$  and a consistent clinical history [2, 7, 9]. Although ideally the synovial fluid should be aspirated before initiation of antibiotic treatment [10–12], approximately 40%–50% of patients receive antibiotics before aspiration [8, 9, 13].

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Previous investigations have demonstrated that antibiotics reach bactericidal concentrations promptly after administration [6], resulting in up to a 3-fold increase in culture-negative results when a single-dose of antibiotics is administered before obtaining cultures for suspected cases of musculoskeletal infections [8, 13]. Data are limited, however, concerning the impact of preaspiration antibiotics on synovial fluid WBC count and the percentage of PMNs [7]. Two prior investigations found that antibiotics administered before joint aspiration decreased the synovial fluid WBC count in cases of septic arthritis; however, one of the studies included prosthetic joint infections (PJIs), and the other involved a limited sample with ill-defined diagnostic criteria for septic arthritis and did not use multivariable analysis to adjust for confounding factors [7, 11]. Given the importance of synovial fluid analysis in diagnosing native joint septic arthritis, we sought to determine whether or not preaspiration antibiotic administration affects (1) synovial fluid laboratory analysis and (2) the time to operative management.

## METHODS

After receiving approval from the institutional review board, we conducted a retrospective analysis of all patients seen at our institution for evaluation and treatment of native joint septic arthritis between January 2015 and December 2019. We queried the hospitals administrative records for all admissions with *International Classification of Diseases, Ninth Revision* or *International Classification of Diseases, Tenth Revision* billing codes for septic arthritis (codes 711.01, 711.05, 711.06, M00.9, M00.011, M00.012, M00.019, M00.211, M00.212, M00.219, M00.111, M00.112, M00.119, M00.811, M00.812, M00.819, M00.9, M00.051, M00.052, M00.059, M00.251, M00.252, M00.259, M00.151, M00.152, M00.159, M00.851, M00.852, M00.859, M00.061, M00.062, M00.069, M00.261, M00.262, M00.269, M00.161, M00.162, M00.169, M00.861, M00.862, and M00.869).

Patients were included in our cohort using the previously described criteria for native joint septic arthritis: “(1) a pathogen was isolated from the synovial fluid; (2) a pathogen was isolated from a source other than synovial fluid, and the clinical presentation was typical of septic arthritis; or (3) the synovial fluid was turbid, the clinical presentation was typical of septic arthritis, and crystals were absent” [14–16]. A clinical presentation considered typical for septic arthritis included joint swelling, tenderness, severe pain with short arcs in the range of motion, and inability to bear weight in affected lower extremities [1, 2]. The presence of subjective and objective fevers, sweats, and rigors were also suggestive of septic arthritis in cases where a bacterial pathogen was not isolated, but they were not a requirement for diagnosis. We used the stated criteria rather than limit the study to only those with positive culture results, for 2 reasons. First, it has previously been demonstrated that as

few as 57% of patients with suspected septic arthritis have positive synovial fluid culture results [14]; second, administration of antibiotics before joint aspiration has been associated with an increased incidence of culture-negative results in diagnosed cases of septic arthritis [8, 13].

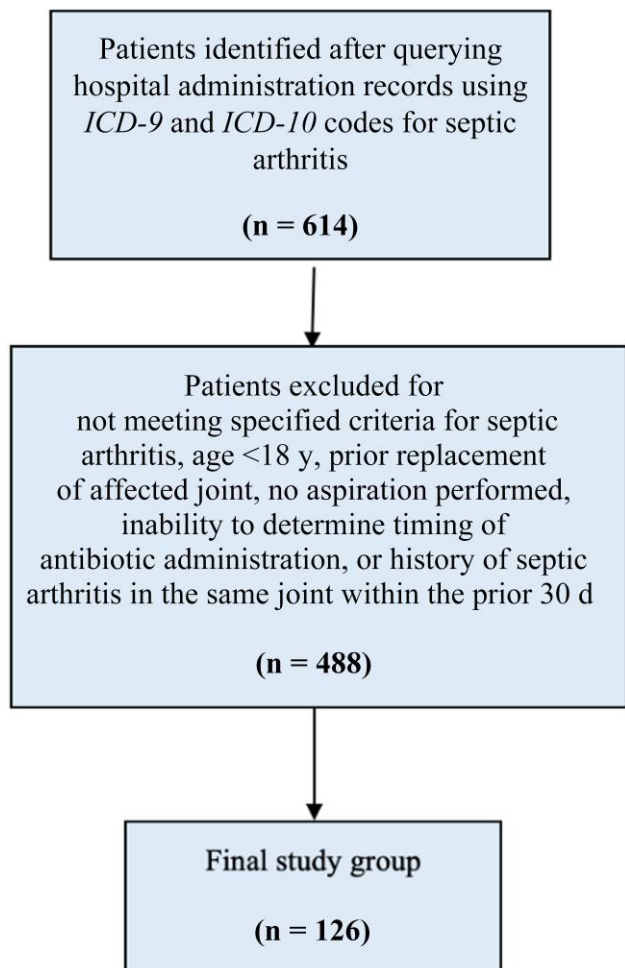
Exclusion criteria included failure to meet the above diagnostic criteria, age <18 years, prior replacement of the affected joint, inability to determine the timing sequence of antibiotic administration and joint aspiration, no joint aspiration performed, or a documented episode of septic arthritis in the same joint within 30 days before the encounter. Patients could be included multiple times as separate encounters if multiple joints were found to be septic.

After intensive record review, the cohort was split into 2 groups based on the exposure of interest: antibiotics before joint aspiration. An additional subgroup analysis was performed among only patients with positive cultures, the reference standard for diagnosis. The timing of antibiotic administration and joint aspiration were ascertained from the patient history and from time marking within the electronic medical records. It was recorded whether patients received antibiotics before presentation, while in the emergency department, or while admitted to the hospital. The following were extracted from the electronic medical record: demographic data, surgical history, laboratory and physical examination data, synovial fluid analyses, information regarding antibiotic administration, time from aspiration to surgical drainage, repeated surgery, and comorbid conditions, including history of diabetes mellitus, smoking, intravenous drug use (IVDU), and immunosuppression. Within the cohort we investigated the association of WBC count, split into groups above or below 50 000/ $\mu$ L, the historical threshold for diagnosis [1, 17], on the time elapsed from aspiration to surgery. This study did not include any factors necessitating patient consent.

Wilcoxon rank-sum, Student *t*, and  $\chi^2$  tests were used to compare joint aspiration results between groups. Two multivariable linear regressions and one multivariable logistic regression were then constructed to assess whether the administration of antibiotics before joint aspiration was independently associated with the primary outcomes: synovial fluid WBC count, percentage of PMNs, and culture positivity. These multivariable analyses each controlled for predetermined clinically meaningful predictors of the dependent variables: age, body mass index, smoking, diabetes mellitus, IVDU, and immunosuppressed or immunocompromised status. Statistical analyses were performed using SPSS statistical software (version 25).

## RESULTS

Of 614 encounters for septic arthritis during the study time frame, 126 met criteria for inclusion in the study cohort (Figure 1). Participants had a mean (standard deviation [SD])



**Figure 1.** Flow chart demonstrating patient identification and inclusion for the study. Abbreviations: *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision*.

age of 55.8 (16.4) years old (range, 21.3–92.4 years), and 57.8% were male (Table 1). The incidences of each affected joint are reported in Table 1. Nineteen patients (15.1%) had a history of prior nonarthroplasty surgery on the affected joint, and 5 (4%) had an earlier history of septic arthritis in the affected joint >30 days before their encounter. Eighty patients with septic arthritis (63.5%) received  $\geq 1$  dose of antibiotics before joint aspiration; within this group, 87.5% received  $\geq 1$  dose intravenously, 15.6% received outpatient oral antibiotics, and 8.7% received both (Table 2).

Fifty patients with septic arthritis (39.7%) had a synovial fluid WBC count  $< 50\,000/\mu\text{L}$ . Demographic characteristics and laboratory findings, other than joint aspiration results, were similar between groups (Table 1). The average synovial fluid WBC count differed between patients who received antibiotics and those who did not (mean [SD], 51 379.1/ $\mu\text{L}$  [52 576/ $\mu\text{L}$ ] vs 92 162.7/ $\mu\text{L}$  [59 330/ $\mu\text{L}$ ], respectively;  $P < .001$ ). The mean [SD] percentage of PMNs also significantly differed between the

**Table 1. Bivariate Analysis: Characteristics of the Study Population**

Parameter	Patients, No. (%) <sup>a</sup>		
	All Patients	Preaspiration Antibiotics	No Preaspiration Antibiotics
Total	126	80 (63.5)	46 (36.5)
Age, mean (SD), y	55.8 (16.4)	55.3 (17.1)	57.1 (15.3)
Female sex	54 (42.2)	34 (42.5)	26 (59.1)
BMI, mean (SD) <sup>b</sup>	28.6 (6.6)	28.8 (6.2)	28 (7.1)
Comorbid conditions			
Current Smoker	25 (19.8)	17 (21.3)	8 (18.2)
Diabetes mellitus	35 (27.8)	20 (25)	14 (31.8)
IVDU	43 (34.1)	30 (37.5)	13 (29.6)
Immunocompromised or immunosuppressed	16 (12.7)	8 (10)	6 (13.6)
Rheumatoid arthritis	3 (2.3)	1 (1.3)	2 (4.3)
Peripheral WBC count, mean (SD), cells/ $\mu\text{L}$	12.0 (5.2)	12.5 (5.7)	11.2 (11.2)
ESR, mean (SD), mm/hr	67.2 (30.3)	72.2 (29.3)	60.8 (61.9)
CRP, mean (SD), mg/L	146.8 (109)	159 (104)	129 (130)
Positive cultures other than joint aspirate <sup>c</sup>	46 (36.5)	31 (38.8)	15 (34.1)
Affected joint			
Shoulder	21 (16.7)	15 (18.8)	6 (13)
Elbow	6 (4.8)	2 (2.5)	4 (8.7)
Wrist	8 (6.3)	4 (5)	4 (8.7)
Hip	14 (11.1)	8 (10)	6 (13)
Knee	65 (51.6)	40 (50)	25 (54.4)
Ankle	12 (9.5)	11 (13.8)	1 (2.2)
Prior surgery on affected joint	19 (15.1)	16 (20)	64 (80)
History of septic arthritis in affected joint >30 d earlier	5 (4)	3 (3.8)	2 (4.3)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IVDU, intravenous drug use; SD, standard deviation; WBC, white blood cells.

<sup>a</sup>Data represent no. (%) of patients unless otherwise specified.

<sup>b</sup>BMI calculated as weight in kilograms divided by height in meters squared.

<sup>c</sup>Positive cultures from another source during encounter.

groups (83.6% [20.5%] vs 91.9% [6.0%];  $P = .01$ ). Fewer patients who received antibiotics before joint aspiration had positive cultures compared with those who had not received antibiotics (32.5% vs 59.1%, respectively;  $P = .008$ ) (Table 3). A subanalysis of only patients with positive culture results ( $n = 52$ ) demonstrated a nonsignificant trend toward lower WBC count and percentage of PMNs among patients who received antibiotics before aspiration ( $P = .28$ ) (Table 3). Methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* were the pathogens most commonly identified in aspiration cultures (in 26.1% and 30.7% of cultures, respectively). The incidences of these 2 pathogens did not differ significantly between groups ( $P = .93$  and  $P = .57$ , respectively) (Table 3).

After controlling for potential confounding factors on multivariable analysis, administration of antibiotics before joint aspiration remained associated with decreased WBC counts at

**Table 2. Descriptions of Antibiotic Administration Before Joint Aspiration**

Parameter	Patients, No. (%)
Antibiotics before aspiration	80 (62.5)
Received as an outpatient	20 (15.6)
Received in emergency department or as an inpatient	69 (53.9)
Route	
Intravenous	70 (87.5)
Oral	21 (26.3)
No. of doses received <sup>a</sup>	
1	13 (16.3)
2–4	65 (81.3)
>4	2 (2.5)
Antibiotic type	
Azithromycin	3 (3.8)
Ampicillin, augmentin, penicillin, or oxacillin	22 (27.5)
Cefazolin	10 (12.5)
Ceftriaxone	24 (30)
Ceftazidime	3 (3.8)
Cefepime	18 (22.5)
Ceftaroline	4 (5)
Ciprofloxacin	1 (1.3)
Clindamycin	6 (7.5)
Daptomycin	11 (13.8)
Doxycycline	3 (3.8)
Gentamicin	5 (6.3)
Linezolid	9 (11.3)
Meropenem-ertapenem	3 (3.8)
Piperacillin-tazobactam	6 (7.5)
Trimethoprim-sulfamethoxazole	6 (7.5)
Vancomycin	58 (72.5)

<sup>a</sup>Concomitant doses of multiple antibiotics were counted separately.

joint aspiration ( $P < .001$ ). IVDU and younger age were associated with higher WBC count at joint aspirate ( $P = .03$  and  $P = .04$ , respectively) (Table 4). Antibiotics before aspiration independently accounted for 42 785 fewer WBCs (cells/ $\mu$ L) in aspirates according to this regression model. Multivariable analysis also found antibiotics before aspiration to be associated with lower percentages of PMNs in joint aspirates, and IVDU to be associated with higher percentages of PMNs in joint aspirates ( $P = .01$  and  $P = .02$ , respectively) (Table 4). Antibiotics were associated with an absolute reduction of 7.8% PMNs. In addition, antibiotics before aspiration were the only significant predictor of culture-negative joint aspiration results on logistic regression (odds ratio, 0.39, [95% confidence interval, .18–.87];  $P = .02$ ) (Table 5). Compared with patients with WBC counts  $>50\,000/\mu$ L, those with counts  $<50\,000/\mu$ L had longer periods between joint aspiration and operative intervention (mean [SD], 10.5 [11.3] vs 17.9 [17.2] hours;  $P = .02$ ).

## DISCUSSION

Delays in diagnosis of septic arthritis may lead to irreversible joint destruction, highlighting the importance of prompt and

**Table 3. Univariate Analysis of Aspirate Results by Prior Exposure to Antibiotics**

Aspirate Results	Patients, No. (%) <sup>a</sup>		<i>P</i> Value
	Preaspiration Antibiotics (n = 80)	No Preaspiration Antibiotics (n = 46)	
WBC count, mean (SD), cells/ $\mu$ L	51 379.1 (52 576.3)	92 162.7 (593 330.6)	$<.001^b$
Neutrophil count, mean (SD), cells/ $\mu$ L	83.6 (20.5)	91.9 (6.0)	.01 <sup>b</sup>
Crystals (culture negative) <sup>c</sup>	10 (12.5)	4 (8.7)	.52
Positive Gram stain	19 (23.8)	16 (36.4)	.18
Positive culture	26 (32.5)	26 (59.1)	.008 <sup>b</sup>
WBC count, mean (SD), cells/ $\mu$ L (n = 52)	71 195.9 (66 641)	88 424 (56 600)	.49
Neutrophil count, mean (SD), cells/ $\mu$ L (n = 52)	89.9 (9.2)	92.2 (4.1)	.28
Isolated organism			
MSSA	10 (12.5)	6 (13.6)	.93
MRSA	10 (12.5)	8 (18.2)	.57
GAS	0	2 (4.6)	.13
GNR	2 (2.5)	3 (6.8)	.27
Other	4 (5)	7 (15.9)	.06

Abbreviations: GAS, group A *Streptococcus*; GNR, gram-negative rods; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S aureus*; SD, standard deviation; WBC, white blood cell.

<sup>a</sup>Data represent no. (%) of patients unless otherwise specified.

<sup>b</sup>Significant at  $P < .05$ .

<sup>c</sup>Patients who had crystals present with negative synovial fluid cultures but positive cultures from a separate site.

accurate diagnosis. In the current study, we found that the majority of patients had received  $\geq 1$  dose of antibiotics before joint aspiration. The average synovial fluid WBC count, percentage of PMNs, and rate of culture positivity were significantly lower in patients who received antibiotics than in those who did not. Patients with WBC counts  $<50\,000/\mu$ L at synovial fluid analysis had a longer time period elapse between aspiration and operative management.

Although septic arthritis is largely a clinical diagnosis, there are many alternative causes of an acutely painful and swollen joint. Therefore, joint aspiration and synovial fluid analysis is recommended to aid in diagnosis. Other than rapid identification of a pathogen in the joint aspirate, synovial fluid WBC count and percentage of PMNs are the 2 most powerful values in assessing the likelihood of septic arthritis [2]. The widely reported aspirate WBC count threshold value of  $50\,000/\mu$ L is considered a useful discriminator for diagnosis; however, up to one-third of patients with a diagnosis of septic arthritis may have a synovial fluid WBC count below this threshold [17]. There is also conflicting evidence as to whether the a WBC of  $50\,000/\mu$ L on joint aspiration can reliably distinguish between crystalline and septic arthritis [17, 18]. For these reasons, WBC counts of  $64\,000$ – $85\,000/\mu$ L have been suggested as higher thresholds to increase the specificity of this test for septic arthritis [2, 12, 18, 19].

**Table 4. Multivariable Linear Regression of Patient Factors Associated With Joint Aspirate White Blood Cell Count and Percentage of Polymorphonuclear Neutrophils**

Factor	Estimated Change in WBC Count or PMNs (95% CI)	P Value
<b>WBC count, cells/<math>\mu</math>L</b>		
Age	878.6 (53.7–1703.4)	.04 <sup>a</sup>
BMI	893.4 (–1036.3 to 2823)	.36
Current Smoker	1523.80 (–29.9715 to 33 019.10)	.92
Diabetes mellitus	4347.9 (–23 309 to 32 004.80)	.76
IVDU	35 137.80 (40 389–66 236.60)	.03 <sup>a</sup>
Immunocompromised or immunosuppressed	–9487.90 (–38 670.20 to 19 694.40)	.52
Antibiotics before aspiration	–42 784.60 (–65 355 to –20 213.90)	<.001 <sup>a</sup>
<b>PMNs, %</b>		
Age	0.15 (–.67 to .37)	.17
BMI	0.18 (–.32 to .68)	.48
Current Smoker	–3.9 (–12.4 to 4.6)	.37
Diabetes mellitus	0.53 (–6.8 to 7.9)	.89
IVDU	10.3 (1.7– 18.6)	.02 <sup>a</sup>
Immunocompromised or immunosuppressed	–1.8 (–9.5 to 5.9)	.65
Antibiotics before aspiration	–7.8 (–13.7 to –1.8)	.01 <sup>a</sup>

Abbreviations: BMI, body mass index; CI, confidence interval; IVDU, intravenous drug use; PMNs, polymorphonuclear neutrophils; WBC, white blood cell.

<sup>a</sup>Significant at  $P < .05$ .

Further complicating the differentiation of crystalline and septic arthritis is evidence demonstrating that the presence of crystals at synovial fluid analysis does not preclude the diagnosis of septic arthritis; as many as 50% of patients with septic arthritis may have crystals present at synovial fluid analysis [17, 18, 20, 21]. This collective evidence demonstrates the diagnostic conundrum when evaluating for septic arthritis, especially in the event of a symptomatic patient with borderline synovial fluid WBC results. Our presented study provides critical insight for such cases, as we found that patients who have received antibiotics before joint aspiration may have lower than expected synovial fluid WBC counts and percentages of PMNs, and higher rates of negative cultures. In this event, a high level of suspicion should be maintained, and increased emphasis should be placed on clinical history and additional laboratory findings in order to guide proper treatment.

Appropriate management of native joint septic arthritis includes prompt initiation of appropriate antibiotic therapy [11]. However, the British Society for Rheumatology Standards Guidelines and Audit Working Group, the American Academy of Family Physicians, and the American Academy of Orthopaedic Surgeons have each set forth guidelines stating that antibiotics should not be given before obtaining appropriate joint fluid cultures [11]. Interestingly, 63.5% of our cohort received  $\geq 1$  dose of antibiotics before joint aspiration, a proportion slightly higher than the range previously reported (43%–51%) [8, 13]. Although we were unable to consistently identify a rationale for the administration of antibiotics before joint aspiration, there are

**Table 5. Multivariable Logistic Regression of Patient Factors Associated With Positive Culture Results**

Predictor	OR (95% CI)	P Value
Age	0.99 (.96–1.02)	.65
BMI	1.02 (.95–1.1)	.65
Current Smoker	0.80 (.25–2.57)	.71
Diabetes mellitus	0.24 (.24– 1.86)	.44
IVDU	1.43 (.47–4.41)	.53
Immunocompromised or immunosuppressed	0.39 (.13–1.18)	.10
Antibiotics before aspiration	0.39 (.18–.87)	.02 <sup>a</sup>

Abbreviations: BMI, body mass index; CI, confidence interval; IVDU, intravenous drug use; OR, odds ratio.

<sup>a</sup>Significant at  $P < .05$ .

several plausible scenarios. A patient presenting to an outpatient clinic with a hot and swollen joint may receive immediate oral antibiotic treatment before an aspiration, especially if the clinician is not proficient or trained to perform arthrocentesis. Alternatively, an acutely septic or unstable patient may require empiric intravenous antibiotic administration without delay to perform an arthrocentesis [22].

In addition to potentially affecting the proper diagnosis of septic arthritis, preaspiration antibiotics may prevent the isolation of a causative agent, thus precluding targeted antibiotic therapy. While such deviations in the recommended sequence in management of septic arthritis may be indicated in such incidences to mitigate risks associated with developing a systemic infection, it may be consequential if knowledge of the possible effects on diagnostic laboratories is not understood. Our study found that the timing of definitive management of septic arthritis may also be affected by the receipt of preaspiration antibiotics, as patients with a synovial fluid WBC count  $< 50 000/\mu$ L were found to have waited an average of 8 hours longer for surgery from the time of their aspiration. Our study demands that obtaining a detailed history of recent antibiotic administration should be prioritized when interpreting WBC count and determining the necessity of surgical intervention.

There is a paucity of existing studies regarding the effect of antibiotics before diagnostic joint aspiration for septic arthritis, and the majority of the published literature involves PJI. Hindle et al [8] found that among 49 patients treated for septic arthritis, 25 (51%) had received antibiotics before joint aspiration. They found that these patients were significantly less likely to have an organism demonstrated on Gram stain or culture, thus decreasing the sensitivity of these tests from 58% to 12% and from 79% to 28%, respectively. Al-Mayahi et al [13] reported on 2740 cases of orthopedic infections not exclusive to septic arthritis and found that patients who received antibiotics before culture were obtained had nearly 3 times higher odds of culture-negative results (19% vs 6% in patients who had not received antibiotics).

These prior findings corroborate the results of our current study, which also found that preaspiration antibiotics significantly affect the prevalence of positive culture results. However, 44.9% of the patients in the study by Hindle et al [8], and 12% of those in the study by Al-Mayahi et al [13], were being evaluated for a PJI, which limits the applicability of their results. The intrasynovial milieu is known to be significantly altered in patients with a prosthetic joint, which changes the normal inflammatory response to an infection, further supporting the exclusion of PJIs from our study cohort [23–25].

In our investigation, 80 patients received antibiotics before joint aspiration. The vast majority of these patients (83.8%) received >1 dose, and 87.5% received  $\geq 1$  intravenous dose. The initial choice of empiric antimicrobial therapy for septic arthritis should include vancomycin, although a  $\beta$ -lactam agent may be used if methicillin-sensitive *S aureus* is identified as the causative organism [1–3]. If a gram-negative organism is identified on Gram stain or on prior cultures from a separate site, a cephalosporin should be administered [1–3]. Most patients in our series (72.5%) received vancomycin, and 73.8% received a cephalosporin. Twenty-five patients (31.3%) received neither vancomycin nor a cephalosporin, and 11.3% only received an oral antibiotic before joint aspiration.

A previous review on antibiotic penetration into bone and joints found that most antibiotics demonstrate good penetration, reaching concentrations exceeding the minimum inhibitory concentration of most common pathogens, with the exception of penicillin and metronidazole [26]. The 4 patients who received penicillin in our series had also received  $\geq 1$  dose of vancomycin before joint aspiration. Therefore, it can be assumed that each patient received an antibiotic with optimal joint penetration. However, the low number of patients who received each individual antibiotic precluded a subanalysis of the individual effect of specific antibiotics on synovial fluid markers.

Despite the relative strengths of our study, it was not without limitations. One limitation this was the relatively small sample size, a result of our strict inclusion criteria. We believe, however, that the inclusion criteria prevented the inclusion of patients who did not truly have septic arthritis but had received the incorrect billing code for this diagnosis. Even so, it is still possible that patients were wrongly excluded or included on the basis of our criteria for diagnosis of septic arthritis. However, this is a limitation in the clinical diagnosis of septic arthritis in general and not specific to our study. In addition, the retrospective nature of our study limited the availability of data regarding the nature and exact timing of prior nonarthroplasty procedures on the affected joint, prior intra-articular injections in the affected joint, and the severity of infection according to the Gachter classification for septic arthritis.

Our subanalysis demonstrated a nonsignificant association between preaspiration antibiotics and decreased WBC counts and percentages of PMNs among patients with positive culture

results (the reference standard for diagnosis;  $n = 52$ ). However, post hoc power analyses demonstrated that these comparisons had 11.7% (WBC count) and 21.3% (PMN percentage) post hoc powers. Therefore, these results are likely a type II statistical error. However, if they were accepted as valid, a potential explanation is that patients who received antibiotics and had positive cultures may have had a causative organism resistant to the antibiotic that was received. Thus, the microbial load and resulting intra-articular inflammatory response may not have been diminished to the extent otherwise caused by an antibiotic to which the pathogen was susceptible. Post hoc power analyses for our primary comparison using the proposed criteria for septic arthritis revealed post hoc powers of 87.9% (WBC count) and 92.2% (PMN percentage).

An additional limitation was that we determined the time of antibiotic administration based on electronic medical record data, which may not be truly indicative when antibiotics were actually administered. Finally, antibiotic dose and individual pharmacokinetics and pharmacodynamics were not assessed in our analysis. Future research may aim to answer the pharmacological effect of such factors on synovial fluid biomarkers.

In conclusion, we found that the administration of antibiotics before joint aspiration for suspected septic arthritis is associated with decreased synovial fluid WBC counts, percentages of PMNs, and rates of culture positivity. Judicious efforts to limit antibiotic administration before joint aspiration are important to minimize diagnostic dilemmas and circumvent treatment delays. Our findings suggest that the historical WBC count diagnostic threshold for septic arthritis of 50 000/ $\mu\text{L}$  may be misleading in patients who received preaspiration antibiotics and that detailed history about such antibiotics must be considered when making decisions about operative management.

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