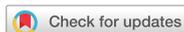


Original Article



Clinical Characteristics and Causative Pathogens of Infective Arthritis and Risk Factors for Gram-Negative Bacterial Infections

Yongseop Lee ¹, Yun Suk Cho ¹, Yu Jin Sohn ¹, Jong Hoon Hyun ¹, Sang Min Ahn ¹, Woon Ji Lee ^{1,2}, Jung Ho Kim ^{1,2}, Hye Seong^{1,2}, Junhyoung Kim ^{1,2}, Su Jin Jeong ^{1,2}, Nam Su Ku ^{1,2}, Joon Sup Yeom ^{1,2}, Jin Young Ahn ^{1,2}, and Jun Yong Choi ^{1,2}



¹Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
²AIDS research Institute, Yonsei University College of Medicine, Seoul, Korea

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Corresponding Author:
Jun Yong Choi, MD, PhD

Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: +82-2-2228-1974
Fax: +82-2-393-6884
E-mail: seran@yuhs.ac

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ORCID iDs

Yongseop Lee 
<https://orcid.org/0000-0002-0116-6710>
Yun Suk Cho 
<https://orcid.org/0000-0002-6089-876X>
Yu Jin Sohn 
<https://orcid.org/0000-0001-7018-8641>
Jong Hoon Hyun 
<https://orcid.org/0000-0002-9621-0250>
Sang Min Ahn 
<https://orcid.org/0000-0003-0641-4493>
Woon Ji Lee 
<https://orcid.org/0000-0002-3431-3633>

ABSTRACT

Background: The aim of this study was to describe the clinical and microbiological characteristics of infective arthritis and to analyze risk factors for Gram-negative bacterial infections that cause infective arthritis.

Materials and Methods: Patients admitted between 2009 - 2018 with infective arthritis in a single-tertiary hospital were evaluated retrospectively.

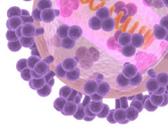
Results: A total of 181 patients were enrolled in this study. Of them, 135 were native joint infection patients and 46 were prosthetic joint infection patients. The most common site of infective arthritis was the knee (63.6%), followed by the shoulder (17.7%), and the hip (9.9%). The most frequently identified microorganisms were *Staphylococcus aureus* (51.1%), followed by *Streptococci* sp. (21.1%), *Enterobacteriaceae* (8.4%), and coagulase-negative-*Staphylococci* (CNS; 8.4%). Infections due to Gram-negative bacteria and fungi made up 13.7% and 3.2% of all cases, respectively. Additionally, 20% and 4.2% of the cases involved methicillin-resistant *S. aureus* (MRSA) and MRCNS. We found that bacteriuria, infective arthritis in the hip, and steroid use at admission are independent risk factors for Gram-negative bacterial infections.

Conclusion: Infective arthritis with methicillin-resistant microorganisms reached up to about 25% in a single-tertiary hospital in Korea. In case of suspected urinary tract infection, infective arthritis of the hip joint, or steroid use at admission time among infective arthritis patients, empirical treatment covering Gram-negative microorganisms can be considered.

Keywords: Arthritis, infectious; Gram-negative bacterial infections; Methicillin resistance; Risk factors

INTRODUCTION

Infective arthritis can rapidly destroy articular cartilage, occasionally resulting in permanent joint disabilities. Therefore, appropriate and prompt use of antibiotics is important for minimizing its sequelae. Owing to the fact that *Staphylococci* and *Streptococci* were the most common causative agents of infective arthritis, empirical antibiotic spectrum usually include *Staphylococci* and *Streptococci* [1-4]. A study in Korea also reported that 20.5% (n = 25)



Jung Ho Kim 
<https://orcid.org/0000-0002-5033-3482>
Junhyoung Kim 
<https://orcid.org/0000-0002-0595-2110>
Su Jin Jeong 
<https://orcid.org/0000-0003-4025-4542>
Nam Su Ku 
<https://orcid.org/0000-0002-9717-4327>
Joon Sup Yeom 
<https://orcid.org/0000-0001-8940-7170>
Jin Young Ahn 
<https://orcid.org/0000-0002-3740-2826>
Jun Yong Choi 
<https://orcid.org/0000-0002-2775-3315>

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Conflict of Interest

No conflict of interest.

Author Contributions

Conceptualization: YL, YSC, YJS, JHH, SMA, WJL, JHK, JK, SJJ, NSK, JSY, JYA, JYC. Data curation: YL. Formal analysis: YL. Methodology: YL, JYC. Visualization: YL. Supervision: SJJ, NSK, JSY, JYA, JYC. Validation: SJJ, NSK, JSY, JYA, JYC. Writing - original draft: YL. Writing - review & editing: YL, JYC.

of patients with culture-positive infective arthritis were due to *Staphylococcus aureus* and 1.6% (n = 2) were due to *Streptococci* [5]. However, an increased frequency of methicillin-resistant *S. aureus* (MRSA) has been reported in various parts of the world [6-10]. According to a 2017 report from the Korean Global Antimicrobial Resistance Surveillance System (Kor-GLASS), 53% of *S. aureus* infections were due to MRSA [11]. This implies that, in Korea, the antibiotic susceptibility profiles of microorganisms causing infective arthritis can change. In order to develop appropriate strategies for treating infective arthritis, data on the distributions of causative pathogens and the prevalence of antimicrobial resistance are required. However, data on the pathogen distributions and resistance patterns of pathogens involved in infective arthritis are limited in Korea. Therefore, we needed to investigate the current distribution of causative microorganisms of infective arthritis in Korean communities.

The proportion of infective arthritis with Gram-negative microorganisms ranged from 5% to 20% according to previous studies [2-4, 12, 13]. Among Gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* are frequently isolated pathogens in cases of infective arthritis. Although elderly or frail individuals, patients with recurrent urinary-tract infections, and recent abdominal surgery are considered to be risk factors for Gram-negative bacterial infections in cases with infective arthritis, the evidence was not clear [14]. Since Gram-positive bacteria are much more prevalent pathogens in infective arthritis than Gram-negative bacteria, empirical therapy for infective arthritis usually includes antibiotics for Gram-positive bacteria. The risk of inappropriate use of empirical antibiotics in Gram-negative bacterial infective arthritis is high. Thus, it is essential to verify risk factors of Gram-negative bacteria in order to successfully treat this disease.

This study aims to describe clinical manifestations and microbiological etiology of infective arthritis in a single tertiary hospital in Korea and to analyze risk factors for Gram-negative bacteria.

MATERIALS AND METHODS

1. Study population

Patients admitted with infective arthritis in a single-tertiary hospital of Korea from January 2009 to December 2018, were evaluated retrospectively. The study population only included adults older than 18 years of age. Each patient was identified with ICD-10 diagnostic codes, including M00.00-29, M00.80-99, M01.00-09, M.01.20-69, M01.80-89, and T.84.5. Only patients with microorganisms identified from either synovial fluid or blood were included and patients with culture-negative infective arthritis were not included in this study. Patients with tuberculosis arthritis and brucella arthritis were also excluded. The criteria for diagnosis of septic arthritis were derived from those of Newman [15]. Group A was defined by identification of microorganisms from synovial fluid or joint tissue, while Group B was defined by evidence of joint inflammation and pathogen isolation from blood.

2. Study design and data collection

A retrospective cohort study was conducted in order to determine the clinical characteristics and microbiologic etiology of patients with infective arthritis and risk factors for Gram-negative microorganisms among subjects with infective arthritis. Medical records of patients were retrospectively reviewed for the following variables; age at admission, sex, definition criteria, underlying immunosuppression, steroid usage (identified when the patients took

steroid at the time of admission regardless of dose and duration), comorbid conditions, previous history of infective arthritis, healthcare associated infection (defined with at least following history: recent antibiotics usage defined when antibiotics was used within 90 days, hospitalization for 2 days or more in the preceding 90 days, residence in a long term care facility, chronic dialysis within 30 days, and infective arthritis that developed more than 48 hours after admission, possible risk factors for infective arthritis (history of acupuncture and intra-articular injection, recent trauma, recent joint surgery within 90 days, prosthetic joint and other site of infections, including bacteriuria, adjacent skin and soft tissue infection, and infective endocarditis), presenting symptoms, site of infective arthritis, complications, white blood cell count (WBC), red blood cell count, platelet count, erythrocyte sedimentation rate (ESR), blood urea nitrate, serum creatinine, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, albumin concentration, C-reactive protein (CRP), analysis of synovial fluid (WBC count, protein concentration, and glucose concentration), and results of microbiological analysis.

3. Microbiological tests

Identification testing was performed using the Vitek 2 automated analyzer system (bioMérieux, Marcy l'Etoile, France) until 2013. The Bruker Biotyper matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) system (Bruker Daltonics, Bremen, Germany) was introduced in 2013 and used for identification testing from 2013 onwards. All susceptibility testing was performed using the Vitek 2 automated analyzer system with a VITEK AST2 N212 card (bioMérieux). Antibiotic susceptibility was interpreted using the Clinical and Laboratory Standards Institute (CLSI) criteria [16].

4. Statistical analysis

Pearson's chi-square test was used to compare two variables. Fisher's exact test was used instead of Pearson's chi-square test when the expected value of at least one cell is <5 . Variables of which P -value <0.1 from univariate analysis were included into multivariate logistic regression model for determining independent risk factors of infections with Gram-negative microorganisms. The results of statistical analyses were judged to be significant when the P -value was <0.05 . Variance inflation factor (VIF) was used to test multi-collinearity. VIF >10 was regarded that multi-collinearity exist. Hosmer-Lemshow's test was done to test goodness-of-fit. SPSS software, version 23.0 (SPSS, IBM Copr., Armonk, NY, USA), was used for all statistical analyses.

5. Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board at Severance Hospital (Approval No. 4-2020-1138). The need for patient consent was waived due to the retrospective nature of the study.

RESULTS

1. Demographic data

Two hundred and forty eight cases were identified by ICD-10 diagnostic codes and culture results. Patients who were not admitted ($n = 9$), patients with no microbiological confirmation ($n = 55$), and tuberculosis arthritis patients ($n = 3$) were excluded. Thus, 181 patients remained and were evaluated in this study. The median age of the subjects was 68.0 (Range: 55 – 75.5; **Table 1**). The sex ratio was approximately equal, with 53.0% males. We also

compared native joint patients to prosthetic joint patients. The prosthetic joint group was generally older than the native joint group, while more men were in the native joint group.

2. Comorbidities and potential risk factors

The most common underlying comorbidities were hypertension (n = 102; 56.4%), followed by diabetes mellitus (n = 64; 35.4%), and solid cancer (n = 21; 11.6%; **Table 1**). There were 21 cases (11.6%) of patients with previous infective arthritis. Other underlying conditions included end stage renal disease (n = 10; 5.5%), liver cirrhosis (n = 6; 3.3%), coronary artery disease (n = 16; 8.8%), rheumatologic joint disease (n = 10; 5.6%), hematologic malignancy

Table 1. Baseline characteristics of patients with septic arthritis

	Number (%)			P-value
	Total (n = 181)	Native joint (n = 135)	Prosthetic joint (n = 46)	
Demographic data				
Age [range], year	68 [55 - 75.5]	66 [54 - 74]	71.5 [63.75 - 78]	0.013
Male	96 (53.0%)	79 (58.5%)	17 (37.0%)	0.011
Comorbidities and underlying conditions				
Hypertension	102 (56.4%)	72 (53.3%)	30 (65.2%)	0.160
Diabetes mellitus	64 (35.4%)	51 (37.8%)	13 (28.3%)	0.244
Heart failure	9 (5.0%)	7 (5.2%)	2 (4.3%)	1.000
Coronary artery disease	16 (8.8%)	13 (9.6%)	3 (6.5%)	0.764
Cerebrovascular disease	15 (8.3%)	9 (6.7%)	6 (13.0%)	0.215
COPD	1 (0.6%)	1 (0.7%)	0 (0.0%)	1.000
End stage renal disease	10 (5.5%)	9 (6.7%)	1 (2.2%)	0.456
Liver cirrhosis	6 (3.3%)	6 (4.4%)	0 (0.0%)	0.340
Hepatitis	15 (8.3%)	14 (10.4%)	1 (2.2%)	0.120
Infective arthritis history	21 (11.6%)	10 (7.4%)	11 (23.9%)	0.003
Rheumatologic joint disease	10 (5.6%)	6 (4.4%)	4 (8.7%)	0.278
Solid cancer	21 (11.6%)	19 (14.1%)	2 (4.3%)	0.075
Hematologic malignancy	5 (2.8%)	5 (3.7%)	0 (0.0%)	0.331
Transplantation	5 (2.8%)	3 (2.2%)	2 (4.3%)	0.602
Immunosuppressant	9 (5.0%)	8 (5.9%)	1 (2.2%)	0.452
HIV	1 (0.6%)	1 (0.7%)	0 (0.0%)	1.000
Steroid use	19 (10.5%)	14 (10.4%)	5 (10.9%)	1.000
Long-term care facility	5 (2.8%)	3 (2.2%)	2 (4.3%)	0.602
Recent antibiotics	48 (26.5%)	31 (23.0%)	17 (37.0%)	0.067
Hospital-acquired	9 (5.0%)	8 (5.9%)	1 (2.2%)	0.452
Healthcare-associated	62 (34.3%)	41 (30.4%)	21 (45.7%)	0.059
Definition criteria for infective arthritis				
Group A	150 (82.9%)	105 (77.8%)	45 (98.8%)	0.002
Group B	31 (17.1%)	30 (22.2%)	1 (2.2%)	
Site of infection				
Knee	115 (63.6%)	75 (55.5%)	40 (87.0%)	<0.000
Shoulder	32 (17.7%)	32 (23.7%)	0 (0.0%)	<0.000
Hip	18 (9.9%)	13 (9.6%)	5 (10.9%)	0.780
Ankle	9 (5.0%)	8 (5.9%)	1 (2.2%)	0.452
Elbow	5 (2.8%)	4 (3.0%)	1 (2.2%)	1.000
Other	9 (5.0%)	9 (6.7%)	0 (0.0%)	
Potential risk factors				
Prosthetic joint	46 (25.4%)	0 (0.0%)	46 (100.0%)	
Bacteriuria	31 (17.1%)	26 (19.3%)	5 (10.9%)	0.192
Intra-articular injection	26 (14.4%)	25 (18.5%)	1 (2.2%)	0.006
Skin and soft tissue infection	22 (12.2%)	19 (14.1%)	3 (6.5%)	0.176
Recent joint surgery	21 (11.6%)	11 (8.1%)	10 (21.7%)	0.013
Acupuncture	12 (6.6%)	11 (8.1%)	1 (2.2%)	0.301
Recent trauma	8 (4.4%)	7 (5.2%)	1 (2.2%)	0.682
Infective endocarditis	7 (3.9%)	7 (5.2%)	0 (0.0%)	0.194

Rheumatologic joint diseases included 8 cases of rheumatoid arthritis, 1 case of ankylosing spondylitis, and 1 case of ulcerative colitis. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

(n = 5; 2.8%), and transplantation history (n = 5; 2.8%). The number of patients who had used any immunosuppressive agent, except steroids, at admission was nine (5.0%). The number patients who were actively using steroid was 19 (10.5%).

Healthcare-associated infection occurred in 62 cases (34.3%). Of these cases, 48 (70.6%) patients reported previous antibiotics usage, 2 (3.2%) patients had been recently admitted to hospital, and 5 (8.1%) patients had been transferred from a long-term care facility. The number of patients under chronic dialysis was 10 (16.1%), and the number of patients with infective arthritis that had developed in hospital was nine (14.5%).

In **Table 1**, we described potential risk factors of infective arthritis. The most common risk factor was a history of prosthetic joint replacement (n = 46; 25.4%). The second most common risk factor was bacteriuria (n = 31; 17.1%), followed by a history of intra-articular injection (n = 26; 14.4%), adjacent skin and soft tissue infection (n = 22; 12.2%), and recent joint surgery (n = 21; 11.6%). Bacteriuria was diagnosed upon identification of any microorganisms in urine samples that had been collected within 48 hours of admission. The number of patients who had a history of acupuncture was 12 (6.6%). There were no cases related to intravenous drug use.

There were no significant differences in comorbidities and risk factors between the native joint group and the prosthetic joint group except history of infective arthritis, intra-articular injection, and recent joint surgery. More patients with prosthetic joint had history of infective arthritis (n = 11; 23.9%) and recent joint surgery (n = 10; 21.7%) than patients with native joints (n = 10; 7.4% and n = 11; 8.1%, respectively). On the other hand, intra-articular injection history was more frequent in patients with native joint.

3. Symptoms, signs, and investigation at presentation

Median duration from onset of symptoms until admission was 5.0 days (range: 2.0 - 10.0; **Table 2**). Most patients had symptoms and signs of joint inflammation, such as arthralgia (n = 179; 100%), painful limitation of motion (n = 140; 93.3%), joint swelling (n = 143; 88.8%), and local heating sensation (n = 95; 88.8%). Fever was present in 65.7% of the patients and shock, defined as a blood pressure below 90/60 mmHg, was present in 12.7% of patients. When comparing the native joint group and the prosthetic joint group, there were no significant differences in clinical manifestations.

Leukocytosis, defined as blood WBC count above $10.8 \times 10^3/\text{mm}^3$, was recorded in 51.4% (n = 93) of patients. The average of WBC count was $12002.9 \pm 5679.1/\text{mm}^3$. Thrombocytosis was recorded in 19.9% (n = 36) of the patients, while thrombocytopenia was recorded in 18.8% (n = 34). Serum albumin levels decreased in 66.9% (n = 121) of the patients. ESR (reference range: 0.0 - 20.0 mm/hr) and CRP (reference range: 0.0 - 8.0 mg/L) were elevated in most of the cases, 96.1% and 97.8% respectively. The average of synovial WBC count was $82,138 \pm 89,448/\text{mm}^3$. The average protein level and glucose level of synovial fluid were 4.3 ± 1.3 g/dL and 52.4 ± 58.0 mg/dL, respectively.

We also compared the native joint group with the prosthetic joint group. CRP and ALT were higher in the native joint group than in the prosthetic joint group. In the native joint group, the median level of CRP and ALT were 180.6 mg/L (range: 88.6 - 276.6 mg/L) and 22.5 IU/L (range: 14.0 - 37.0 IU/L), while the median levels were 126.9 mg/L (range: 48.5 - 224.6 mg/L) and 17.0 IU/L (range: 10.5 - 30.0 IU/L) in the prosthetic joint group. Other laboratory results showed no significant differences between the two groups.

Table 2. Clinical presentation and laboratory findings of patients with infective arthritis

	Number (%)			P-value
	Total (n = 181)	Native joint (n = 135)	Prosthetic joint (n = 46)	
Clinical presentation				
Duration [range], days	5.0 [2.0 - 10.0]	5.0 [2.0 - 8.0]	4.0 [1.0 - 20.0]	0.915
Fever	119 (65.7%)	91 (67.4%)	28 (60.9%)	0.420
Shock	23 (12.7%)	20 (14.8%)	3 (6.5%)	0.145
Arthralgia	179 (100.0%)	133 (100.0%)	46 (100.0%)	
Joint swelling	143 (88.8%)	108 (89.3%)	35 (87.5%)	0.775
Local heating sensation	96 (88.9%)	71 (87.7%)	25 (92.6%)	0.726
Painful limitation of motion	140 (93.3%)	106 (93.8%)	34 (91.9%)	0.709
Laboratory findings				
WBC count (/mm ³) [range]	11,440.0 [7,810.0 - 15,275.0]	11,930.0 [7,930 - 16,050]	11,370.0 [6,825.0 - 14,535.0]	0.347
Hemoglobin (g/dL) [range]	11.5 [10.1 - 13.0]	11.5 [10.1 - 13.0]	11.4 [9.8 - 12.9]	0.647
Platelet count (× 1,000 mm ³) [range]	243.0 [169.0 - 384.5]	242.0 [155.0 - 390.0]	263.5 [202.8 - 382.0]	0.331
ESR (mm/hr) [range]	91.0 [63.0 - 116.5]	91.0 [63.0 - 120.0]	89.5 [63.3 - 113.5]	0.759
BUN (mg/dL) [range]	19.2 [13.7 - 29.8]	19.2 [13.5 - 30.8]	20.0 [13.9 - 29.5]	0.966
Creatinine (mg/dL) [range]	0.88 [0.68 - 1.20]	0.89 [0.67 - 1.27]	0.85 [0.71 - 1.14]	0.775
AST (IU/L) [range]	23.0 [16.0 - 39.0]	24.0 [17.0 - 40.0]	21.0 [14.5 - 34.0]	0.267
ALT (IU/L) [range]	21.0 [13.0 - 36.0]	22.5 [14.0 - 37.0]	17.0 [10.5 - 30.0]	0.033
Total bilirubin (mg/dL) [range]	0.6 [0.4 - 0.9]	0.6 [0.4 - 0.9]	0.6 [0.3 - 0.9]	0.265
Albumin (g/dL) [range]	3.1 [2.7 - 3.6]	3.1 [2.7 - 3.5]	3.3 [2.8 - 3.7]	0.141
CRP (mg/L) [range]	169.3 [73.4 - 273.6]	180.6 [88.6 - 276.6]	126.9 [48.5 - 224.6]	0.019
Synovial examination				
WBC (/mm ³) [range]	50,000.0 [50,000.0 - 100,687.5]	50,000.0 [50,000.0 - 101,700.0]	50,000.0 [31,500.0 - 70,500.0]	0.115
RBC (/mm ³) [range]	11,000.0 [3,000.0 - 50,000.0]	10,000.0 [3,000.0 - 46,125.0]	15,000.0 [3,000.0 - 50,000.0]	0.741
Protein (mg/dL), mean ± SD	4,309.99 ± 1,359.30	4,213.81 ± 1,420.60	4,579.31 ± 1,146.53	0.173
Glucose (mg/dL) [range]	32.0 [10.0 - 83.0]	33.0 [10.0 - 87.8]	30.0 [10.0 - 76.0]	0.261

WBC, white blood cell; RBC, red blood cell; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; SD, standard deviation.

4. Involved joints

The knees (n = 115; 63.6%) and shoulders (n = 32; 17.7%) were the joints most frequently affected, followed by hip joints (n = 18; 9.9%; **Table 1, Fig. 1**). Of the infected joints, 46 (24.5%) were prosthetic. Most of the affected prosthetic joints were knee joints (n = 40). Five infected hip joints were prosthetic and there was a case of prosthetic ankle joint infection. Other joints included sacroiliac joint (n = 4), sternoclavicular joint (n = 2), spine facet joint

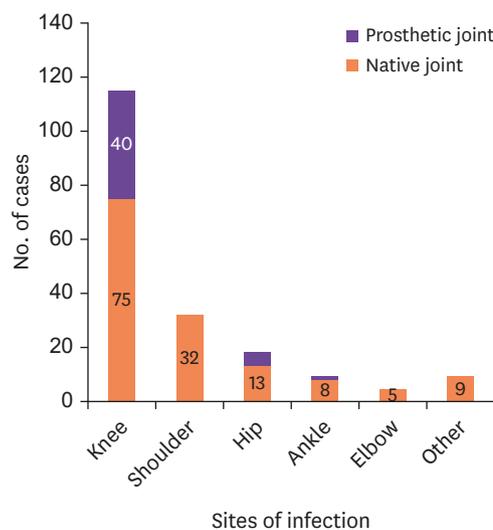


Figure 1. Site of infected joint.

(n = 1), and metacarpopharyngeal joint (n = 1). Twelve patients (6.6%) presented with multiple joints involvement.

Eighty-seven percentage (n = 40) of prosthetic joint infection patients also had knee joint infections, which was more frequent than in the native joint infection group (n = 75; 55.5%; $P < 0.001$). All shoulder joint infection cases occurred in the native joint.

5. Distributions of causative microorganisms and antibiotics susceptibility

Ninety-two cases were defined with positive synovial fluid culture alone, while in 58 cases, both synovial fluid and blood culture were positive. Additionally, 31 cases were defined with blood culture alone. Almost all prosthetic joint infections were defined with positive synovial fluid culture results (n = 45; 98.8%), while only 77.8% (n = 105) of native joint infections were defined with positive synovial fluid culture. The most commonly identified pathogen was *S. aureus* (n = 97; 51.1%; **Table 3**). The second most common pathogen was *Streptococci* (n = 40; 21.1%), followed by coagulase-negative *Staphylococci* (n = 16; 8.4%), and *Enterobacteriaceae* (n = 16; 8.4%). *Pseudomonas* sp. made up 2.1% of the cases (n = 4). The number of cases with other Gram-positive microorganisms, including *Bacillus* sp., *Enterococci* sp., and *Micrococcus* sp., was five (2.6%) and there were six (3.2%) cases of other Gram-negative microorganisms. Other Gram-negative microorganisms included *Burkholderia cepacia*, *Burkholderia pseudomallei*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Achromobacter* sp. Overall, 83.2% of the cases were caused by Gram-positive microorganisms, while 13.7% of cases were due to Gram-negative microorganisms. Only six fungal arthritis cases were identified (**Fig. 2**). We also analyzed the distribution of causative microorganisms by joint type, but there were no differences in causative microorganisms between the native joint group and prosthetic joint group.

The number of MRSA were 39.2% (n = 38) of all *S. aureus* cases and the number of MRCNS were 50% (n = 8) of all CNS cases. Among the MRSA cases, 35 cases were healthcare associated infections while 61 cases were community-acquired. We also analyzed antibiotic resistance profile in accordance with joint type, but there was no significant difference in antibiotics resistance profile between overall group, native joint patients, and prosthetic joint patients. The proportion of MRSA was higher in healthcare associated infection compared with community-acquired infection (odds ratio [OR], 3.185; 95% confidence

Table 3. Microorganisms causing septic arthritis

	Number of cases (%)						
	Total (n = 181)	Native joint (n = 135)	Prosthetic joint (n = 46)	P-value	Community (n = 119)	Healthcare (n = 62)	P-value
Gram-positive microorganisms	154 (85.1%)	114 (84.4%)	40 (87.0%)	0.680	107 (89.9%)	47 (75.8%)	0.011
<i>Staphylococcus aureus</i>	96 (53.0%)	73 (54.1%)	23 (50.0%)	0.633	61 (51.3%)	35 (56.5%)	0.507
MRSA	38 (21.0%)	27 (20.0%)	11 (23.9%)	0.574	18 (15.1%)	20 (32.3%)	0.007
CNS	16 (8.8%)	10 (7.4%)	6 (13.0%)	0.243	9 (7.6%)	7 (11.3%)	0.402
MRCNS	8 (4.4%)	5 (3.7%)	3 (6.5%)	0.421	5 (4.2%)	3 (4.8%)	1.000
<i>Streptococci</i>	40 (22.1%)	29 (21.5%)	11 (23.9%)	0.731	35 (29.4%)	5 (8.1%)	0.001
Other Gram-positive	5 (2.7%)	5 (3.7%)	0 (0.0%)	0.331	4 (3.4%)	1 (1.6%)	0.662
Gram-negative microorganisms	25 (13.8%)	19 (14.1%)	6 (13.0%)	0.861	12 (10.1%)	13 (21.0%)	0.044
<i>Enterobacteriaceae</i>	15 (8.3%)	10 (7.4%)	5 (10.9%)	0.536	8 (6.7%)	7 (11.3%)	0.290
<i>Pseudomonas</i>	4 (2.2%)	3 (2.2%)	1 (2.2%)	1.000	1 (0.8%)	3 (4.8%)	0.117
Other Gram-negative	6 (3.3%)	6 (4.4%)	0 (0.0%)	0.340	3 (2.5%)	3 (4.8%)	0.414
Fungal	6 (3.3%)	5 (3.7%)	1 (2.2%)	1.000	2 (1.7%)	4 (6.5%)	0.183

Other Gram-positive microorganisms include *E. faecalis*, *E. avium*, *E. faecium*, *Bacillus* sp., and *Micrococcus* sp.; Other Gram-negative microorganisms include *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Burkholderia pseudomallei*, *Acinetobacter maumannii*, *Achromobacter insolitus*, and *Achromobacter xylosoxidans*.

MRSA, methicillin-resistant *S. aureus*; CNS, coagulase-negative *Staphylococci*; MRCNS, methicillin-resistant coagulase-negative *Staphylococci*.

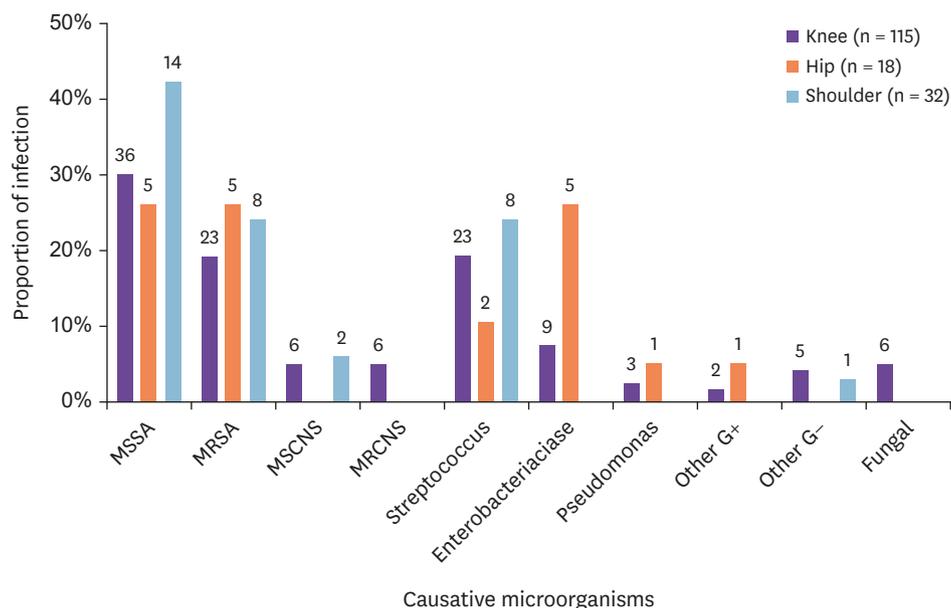


Figure 2. Distribution of causative microorganisms according to the site of infected joints. MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSCNS, methicillin-sensitive coagulase-negative *Staphylococci*; MRCNS, methicillin-resistant coagulase-negative *Staphylococci*; Other G+, other Gram-positive microorganisms; Other G-, other Gram-negative microorganisms.

internal [CI], 1.134 - 7.58; $P = 0.007$; **Table 3**). Gram-positive microorganisms were identified more frequently in community-acquired infection than in healthcare associated infection, It was mainly due to *Streptococci*. The number of cases with *Streptococci* was 29.4% ($n = 35$) of community-acquired infection cases, while the number was only 8.1% ($n = 5$) of healthcare associated infection cases. In the contrary, Gram-negative microorganisms were more frequently cultured in healthcare associated infection. Details of antibiotics susceptibility profiles are presented in **Tables 4 - 6**.

6. Risk factors for Gram-negative organism infection

Univariate analysis of risk factors for infective arthritis caused by Gram-negative microorganisms showed association with female sex, solid cancer, previous usage of

Table 4. Antibiotic resistance rates (%) of *Staphylococcus aureus* and coagulase-negative *Staphylococci* causing infective arthritis between 2009 - 2018

	Total		Native joint		Prosthetic joint	
	<i>Staphylococcus aureus</i> (n = 97)	CNS (n = 13)	<i>Staphylococcus aureus</i> (n = 74)	CNS (n = 7)	<i>Staphylococcus aureus</i> (n = 23)	CNS (n = 6)
Arbekacin	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Ciprofloxacin	17.5%	38.5%	17.6%	57.1%	17.4%	16.7%
Clindamycin	33.0%	23.1%	32.4%	42.9%	34.8%	0.0%
Linezolid	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Oxacillin	38.7%	61.5%	35.7%	71.4%	47.8%	50.0%
Cefoxitin	39.2%		36.5%		47.8%	
Penicillin G	89.7%	92.3%	89.2%	85.7%	91.3%	100.0%
Rifampin	2.2%	0.0%	2.9%	0.0%	0.0%	0.0%
TMP/SMX	2.1%	23.1%	2.7%	42.9%	0.0%	0.0%
Teicoplanin	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Vancomycin	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

The result of susceptibility test for cefoxitin among CNS was omitted, because it was rarely conducted. CNS, coagulase-negative *Staphylococci*; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 5. Antibiotic resistance rates (%) of healthcare-associated *Staphylococcus aureus* and community-acquired *Staphylococcus aureus* causing infective arthritis between 2009 – 2018

	Healthcare-associated (n = 35)	Community-acquired (n = 62)	P-value
Arbekacin	0.0%	0.0%	
Ciprofloxacin	34.3%	8.1%	0.001
Clindamycin	42.9%	27.4%	0.120
Linezolid	0.0%	0.0%	
Oxacillin	57.1%	27.6%	0.005
Cefoxitin	57.1%	29.0%	0.006
Penicillin G	97.1%	85.5%	0.089
Rifampin	6.7%	0.0%	0.326
TMP/SMX	0.0%	3.2%	0.534
Teicoplanin	0.0%	0.0%	
Vancomycin	0.0%	0.0%	

TMP/SMX, trimethoprim/sulfomethoxazole.

Table 6. Antibiotic resistance rates (%) of *Enterobacteriaceae* causing infective arthritis between 2009 and 2018

	Total (n = 16)	Native joint (n = 11)	Prosthetic joint (n = 5)
Amikacin	0.0%	0.0%	0.0%
Ampicillin	87.5%	100.0%	60.0%
Aztreonam	12.5%	9.1%	20.0%
Ceftazidime	12.5%	9.1%	20.0%
Ciprofloxacin	57.1%	66.7%	50.0%
Ertapenem	0.0%	0.0%	0.0%
Cefepime	12.5%	9.1%	20.0%
Cefoxitin	0.0%	0.0%	0.0%
Cefotaxime	25.0%	27.3%	20.0%
Gentamycin	12.5%	18.2%	0.0%
Imipenem	0.0%	0.0%	0.0%
Levofloxacin	15.4%	22.2%	0.0%
Meropenem	0.0%	0.0%	0.0%
Piperacillin/tazobactam	0.0%	0.0%	0.0%
TMP/SMX	37.5%	54.5%	0.0%
Tigecycline	16.7%	25.0%	0.0%

TMP/SMX, trimethoprim/sulfomethoxazole.

steroid, shock at presentation, hip joint infection, shoulder joint infection, bacteriuria, and healthcare associated infection (**Table 7**). A multivariate model identified the following as independent risk factors for Gram-negative organism infection: bacteriuria (OR 3.83; 95% CI, 1.42 - 10.34; $P = 0.008$), infective arthritis in hip (OR 3.84; 95% CI, 1.21 - 12.15; $P = 0.022$), and steroid use at admission (OR 3.82; 95% CI, 1.15 - 12.69; $P = 0.029$; **Table 7**). VIF showed that multi-collinearity didn't exist between each variables (bacteriuria, VIF = 1.02; hip joint involvement, VIF = 1.01; steroid use, VIF = 1.01). Hosmer-Lemshow's test showed goodness of fit for the multivariate logistic regression model ($P = 0.619$).

Table 7. Risk factors for infective arthritis due to Gram-negative microorganisms

	n	Univariate analysis		Multivariate analysis	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Male sex	9/25 (36.0%)	0.45 (0.19 - 1.07)	0.066		
Solid cancer	6/25 (24.0%)	2.97 (1.03 - 8.58)	0.048		
Steroid use	5/25 (20.0%)	2.54 (0.83 - 7.80)	0.099	3.82 (1.15 - 12.69)	0.029
Shock	6/25 (24.0%)	2.58 (0.91 - 7.36)	0.073		
Hip	6/25 (24.0%)	3.79 (1.27 - 11.28)	0.022	3.84 (1.21 - 12.15)	0.022
Shoulder	1/25 (4.0%)	0.17 (0.02 - 1.29)	0.038		
Bacteriuria	9/25 (36.0%)	3.43 (1.35 - 8.71)	0.012	3.83 (1.42 - 10.34)	0.008
Healthcare	13/25 (52.0%)	2.37 (1.01 - 5.56)	0.044		

OR, odds ratio; CI, confidence interval.

DISCUSSION

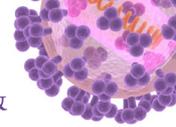
In this work, we describe the current distribution of causative microorganisms of infective arthritis in Korea. We show, as previous studies have described, that *S. aureus* and *Streptococci* are still the most common pathogens of infective arthritis [1-4]. The proportion of *Enterobacteriaceae* and CNS was also similar to the aforementioned studies.

In the case of prosthetic joint infections, the distribution of causative microorganisms was different from the previous studies. *S. aureus* and CNS were known to contribute to between 50 and 60% of prosthetic joint infections, and the proportions of prosthetic joint infections caused by *S. aureus* and CNS were almost equal [17]. In comparison with the result, our study showed that the proportion of CNS was relatively low and that of *S. aureus* and *Streptococci* was high. This difference seems to be resulted from several limitations of this study. This study was conducted in a single tertiary hospital, and since this study is a retrospective study, there can also be a possibility that diagnostic codes were missed by clinicians. Those factors seem to affect the result of microbiological distribution.

The rate of antibiotic resistance was remarkable in this study. We found that 39.2% of the *S. aureus* cases and half of the CNS cases were methicillin-resistant. Overall, methicillin-resistant pathogens comprised a quarter of identified microorganisms. Because healthcare-associated infection was as high as 34.3% in this study, the antibiotic resistance rate could be overestimated. However, 27.6% of *S. aureus* cases were methicillin-resistant even in community-acquired infections, while 57.1% of *S. aureus* cases were methicillin-resistant in healthcare associated infections. In coagulase-negative *Staphylococci* infection, 55.6% of community-acquired infections and 42.9% of healthcare associated infections were methicillin-resistant, respectively. Therefore, we can say that the proportion of methicillin-resistant pathogens is notably high in infective arthritis not only in healthcare associated infections, but also in community-acquired infections.

According to a previous study, published in 2008 in Korea, reported that only 7.4% of identified microorganisms were MRSA in 1995 - 2006 [5]. Compared to the study by Seo et al. (2008) there has been a notable change in the antibiotic susceptibility of infective arthritis in South Korea. Several studies have also reported that the proportion of MRSA in infective arthritis increased. In 2005, a study from the United States of America reported 15 out of 59 septic arthritis cases (25%) involving MRSA [9]. Furthermore, a study from France also reported that there was an increased incidence of MRSA infections in 2009 – 2013 (30.8% of *S. aureus* cases) compared to 1979 – 2013 [18]. A study conducted between 2008 and 2011 in Taiwan, reported that MRSA arthritis was found in 38 (40.9%) cases of *S. aureus* [7]. Given these data, methicillin resistance in infective arthritis seems to be on the rise domestically and globally.

Antibiotic resistance in Gram-negative microorganisms was also at a high rate. Although the third generation cephalosporins and fluoroquinolone are the commonly used antibiotics for Gram-negative microorganisms, the resistance rate of cefotaxime, ciprofloxacin, and levofloxacin were 25.0%, 57.1%, and 15.4%, respectively. This trend was especially remarkable in healthcare-associated infections. In healthcare-associated infections, the resistance rate of cefotaxime, ciprofloxacin, and levofloxacin rised as high as 57.1% (n = 4), 75.0% (n = 3) and 33.3% (n = 2).



A study conducted between 2016 to 2017 in Korea also showed high proportion of antibiotics resistance in Gram-negative microorganisms [19]. According to the study, the overall cefotaxime resistance rate was 34.7% in *E. coli* and 27.0% in *K. pneumoniae*. When it comes to healthcare-associated infections, the cefotaxime resistance rate was as high as 55.8% in *E. coli* and 48.2% in *K. pneumoniae*. Given these findings, we can say that antibiotics resistance of Gram-negative microorganisms is serious in infective arthritis, especially in healthcare-associated infections.

Significantly, in our study, we have also identified independent risk factors of Gram-negative infections in infective arthritis. These include bacteriuria, hip joint involvement, and usage of steroids. Although old age and frailty, recurrent urinary-tract infection, and recent abdominal surgery were previously known risk factors of Gram-negative infections in infective arthritis, the evidence was not clear [14]. A study, dealing with asymptomatic bacteriuria as a risk factor for prosthetic joint infection, reported that asymptomatic bacteriuria was associated with Gram-negative infection in patients with prosthetic joint infection [20]. Our study agrees with the findings made by Sousa et al. and demonstrates that bacteriuria at admission is a risk factor for Gram-negative infection in prosthetic and native joint infection. Since Gram-negative microorganisms were major pathogens of urinary tract infection, hematogenous spread of pathogens can explain the association between bacteriuria and Gram-negative infective arthritis.

Generally, it is more difficult to perform intraarticular injection in the hip joint than in the knee and shoulder joints. In our study, intraarticular injection was performed on only one patient out of 18 with hip joint involvement, while 25 of 163 patients with other joint involvement had history of intraarticular injection. This suggests that the hip joint is more often involved to infective arthritis via hematogenous spread than other joints. Different modes of pathogenesis can cause frequent involvement of Gram-negative microorganisms in the hip joints. Whereas, frequent Gram-negative infective arthritis in patients who use steroids may be due to the immunomodulatory effects of steroids. Given that immunocompromised patients are vulnerable to hematogenous spread of microorganisms living in the gastrointestinal tract and urinary tract, the immunomodulatory effect of steroids may also encourage the spread of Gram-negative microorganisms to the joints. Other immunomodulatory comorbidities and underlying conditions, including hematologic malignancy, transplantation, and uses of other immunosuppressant were too small in number to compare as risk factors. Thus, additional studies with a focus on the effects of other immunomodulatory conditions are in need.

A limitation of our study is that it was a retrospective single center study. There could, therefore, be information biased by the nature of a retrospective study. Given that patient histories of antibiotics usage were assessed only with in hospital electrical medical records, previous antibiotics usage may have been underestimated. Additionally, use of steroids were also evaluated with medicine at time of admission. The fact that our study was carried out in one tertiary hospital was also a limitation. This hospital, Severance Hospital, is one of the biggest hospitals in Korea, which has over 2,000 beds. Traditionally, there has been a tendency to refer severely ill patients to this hospital. Thus, it is possible that our study is not representative of the entire Korean population. Further prospective multicenter studies are needed to confirm the result of our work.

In conclusion, infective arthritis with methicillin-resistant microorganisms reached up to about 25% in a single-tertiary hospital in Korea. When urinary tract infection is suspected,

infective arthritis occurs in the hip joint, or in patients who are using steroids among infective arthritis patients, empirical treatment covering Gram-negative organism can be considered.

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