Journal of Microbiology, Immunology and Infection (2017) 50, 527–531

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Clinical manifestations and bacteriological features of culture-proven Gram-negative bacterial arthritis

Wei-Ting Lin [a,b], Hung-Jen Tang [c,d], Chih-Cheng Lai [e], Chien-Ming Chao [e,f,*]

[a] *Department of Trauma, Chi Mei Medical Center, Tainan, Taiwan*
[b] *Department of Physical Therapy, Shu Zen Junior College of Medicine and Management, Kaohsiung, Taiwan*
[c] *Department of Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[d] *Department of Health and Nutrition, Chia Nan University of Pharmacy and Science, Tainan, Taiwan*
[e] *Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, Tainan, Taiwan*
[f] *Department of Nursing, Min-Hwei College of Health Care Management, Tainan, Taiwan*

Received 10 June 2015; received in revised form 7 August 2015; accepted 25 August 2015
Available online 18 September 2015

KEYWORDS
antibiotic resistance;
Gram-negative bacteria;
outcome;
septic arthritis

Abstract *Background/Purpose:* To investigate the clinical manifestations and bacteriological features of culture-proven, Gram-negative bacterial arthritis.
Methods: This study was conducted at the Chi Mei Medical Center, a 1300-bed teaching hospital located in southern Taiwan. Patients with synovial fluid cultures positive for Gram-negative bacilli (GNB) during the period January 2009 to May 2014 were identified from the hospital's computerized microbiology database.
Results: During the study period, a total of 48 patients with culture-confirmed, GNB septic arthritis were identified. In the majority of patients (n = 33, 68.8%), the knee was the most commonly involved joint. The most common causative pathogen was *Pseudomonas* spp. (n = 16, 33.3%), followed by *Escherichia coli* (n = 13, 28.1%). Among the 29 clinical isolates of Enterobacteriaceae, eight (27.6%) were resistant to ceftriaxone and six (20.7%) were resistant to cefpirome. Three *E. coli* isolates and three *Klebsiella pneumoniae* isolates were extended-spectrum beta-lactamase producers (n = 6, 20.7%). Among the nonfermenting GNB (NFGNB), 21.1% were resistant to ceftazidime, 21.1% were resistant to ciprofloxacin, 26.3% were resistant to piperacillin-tazobactam, and 15.8% were resistant to imipenem. The overall mortality rate was 10.4%, and the significant risk factors for death were concomitant

* Corresponding author. Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, 201, Taikang Village, Liou Ying Township, Tainan County, 736 Taiwan, ROC.
E-mail address: ccm870958@yahoo.com.tw (C.-M. Chao).

http://dx.doi.org/10.1016/j.jmii.2015.08.026

bacteremia [odds ratio (OR): 14.6, 95% confidence interval (CI): 1.9—115.2, $p = 0.011$] and liver cirrhosis (OR: 20.0, 95% CI: 2.4—169.9, $p = 0.006$).
Conclusion: Approximately 25% of cases of septic arthritis were due to GNB and resistance to commonly used antimicrobial agents was common. Liver cirrhosis and concomitant bacteremia were significant risk factors for death.

Introduction

Septic arthritis is inflammation of a joint due to bacterial, mycobacterial, or fungal infection.[1] Without appropriate treatment, septic arthritis can lead to the irreversible destruction and dysfunction of the joint. The reported incidence ranges from four to 29 cases per 100,000 person-years.[2] Gram-positive bacteria are the most common causative pathogens, with *Staphylococcus aureus* and *Streptococcus pneumonia* being the most frequently isolated.[3—6] Septic arthritis is less commonly caused by Gram-negative bacilli (GNB), accounting for only 14—19% of septic arthritis cases.[7,8]

Treatment of septic arthritis requires appropriate antibiotics and drainage. The initial use of antibiotics should be based on knowledge of the epidemiology of the causative bacterium and its drug-resistance pattern; however, little is known about the bacteriology and associated antibiotic-resistance patterns of GNB causing septic arthritis.[4,8] The aim of this study was to investigate the clinical manifestations of patients with septic arthritis due to GNB and to evaluate the bacteriology and antibiotic-resistant patterns of GNB.

Methods

Hospital setting and patient selection

This study was conducted at the Chi Mei Medical Center, a 1300-bed hospital in southern Taiwan. All patients with synovial fluid cultures positive for GNB during the period from January 2009 to May 2014 were retrospectively identified from the computerized database of the microbiology department. Information was collected on age, gender, and underlying conditions including the history of immunosuppressant drug use, diabetes mellitus, liver cirrhosis, end-stage renal disease, and malignancy. Infections were classified as health care-associated infections in patients who acquired the disease during the course of treatment for other conditions within a health care setting. Otherwise, septic arthritis was classified as community acquired. Polymicrobial infections were diagnosed in patients from whom GNB isolates in addition to other pathogens were isolated from synovial fluid specimens. Immunocompromised status was diagnosed in patients with liver cirrhosis, diabetes mellitus, end-stage renal disease, or active cancer. Concomitant bacteremia was diagnosed in patients whose blood cultures were positive for the same species yielded from synovial fluid. In-hospital mortality was defined as death from all causes during hospitalization. The data were collected on a routine basis, and the analysis was performed retrospectively. Therefore, no informed consent was required, and the Institutional Review Board of the Chi Mei Medical Center specifically waived the need for informed consent when it approved the study.

Bacterial isolates and antimicrobial susceptibilities

All isolates were identified by conventional methods and the susceptibilities of the isolates to a battery of antimicrobial agents were determined using the disk diffusion method as described by the Clinical and Laboratory Standards Institute.

Statistical analysis

Continuous variables are expressed as means ± standard deviations and were compared using the Wilcoxon rank sum test or Student independent *t* test, as appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test. A p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the statistical package SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA).

Results

Patient demographics and clinical characteristics

Of the 194 patients with culture-confirmed septic arthritis identified during the study period, 48 (24.7%) had septic arthritis caused by GNB species. The clinical characteristics of all patients with culture-proven septic arthritis are summarized in Table 1. We found that arthritis due to Gram-positive cocci (GPC) was more likely to develop in patients with end-stage renal disease, diabetes mellitus, and prosthetic joints ($p < 0.05$), and that *S. aureus* was the most prevalent GPC species.

Of the patients with arthritis due to GNB, 30 (62.5%) were ≥65 years of age. The knee was the most commonly involved joint ($n = 34$, 70.8%), followed by hip ($n = 8$, 16.7%), ankle ($n = 4$, 8.3%), elbow ($n = 1$, 2.1%), and shoulder ($n = 1$, 2.1%). Only one (2.1%) patient had multiple joint involvement (bilateral shoulders). More than half of the infections developed in prosthetic joints, and most (24/26) of the prosthetic joint infections developed within 6 months after joint surgery. Seven (14.6%) patients had

Table 1 Demographic characteristics of 194 patients with septic arthritis.

Variable	Patients with GPC arthritis ($n = 146$)	Patients with GNB arthritis ($n = 48$)
Age (y)	66.4 ± 17.6	66.7 ± 15.7
Elderly patient with age ≥ 65 y	72 (49.3)	30 (62.5)
Male	105 (71.9)	30 (62.5)
Health care-associated infection	11 (7.3)	6 (12.5)
Presentation		
Single joint	143 (97.9)	47 (97.9)
Prosthetic joint*	110 (75.0)	26 (54.2)
Fever	40 (27.1)	13 (27.1)
Concomitant bacteremia	44 (30.2)	7 (14.6)
Underlying diseases		
Gouty arthritis	23 (15.6)	14 (29.2)
Diabetes mellitus*	62 (42.7)	12 (25.0)
Liver cirrhosis	18 (12.5)	6 (12.3)
Cancer	11 (7.3)	5 (10.4)
Rheumatoid arthritis	2 (1.0)	3 (6.3)
End stage renal disease*	40 (27.1)	2 (4.2)
Receiving systemic steroid	6 (4.2)	5 (10.4)
Recent trauma	32 (21.9)	4 (8.3)
Laboratory examinations		
C-reactive protein (mg/L, normal reference < 6 mg/L)	95.5 ± 84.5	87.8 ± 56.4
Synovial examination		
White blood cell	77,268.4 ± 85,675.5	65,865.7 ± 38,704.0
Glucose (mg/dL)	168.4 ± 85.5	153.1 ± 81.4
Positive gram stain	18 (12.5)	7 (12.3)
Surgical treatment	67 (45.8)	26 (54.2)
Drainage	64 (43.8)	25 (52.1)
Amputation	3 (2.1)	1 (2.1)
Prosthetic surgery	18 (12.5)	11 (22.9)
In-hospital mortality	8 (5.2)	5 (10.4)

Data are presented as *n* (%) or mean ± standard deviation.
*$p < 0.05$.
GNB = Gram-negative bacteria; GPC = Gram-positive cocci.

concomitant bacteremia caused by *Klebsiella pneumoniae* ($n = 3$), *Escherichia coli* ($n = 2$), *Serratia marcescens* ($n = 1$), or *Salmonella* species ($n = 1$). Polymicrobial infections were diagnosed in two patients, one with *Citrobacter koseri* and *Candida albicans* and one with *Pseudomonas aeruginosa* and *Bacteroides fragilis*. All of the other patients had monomicrobial infections. Gout and diabetes mellitus were the two most common underlying diseases, followed by liver cirrhosis and cancer. Only seven (12.3%) synovial specimens stained positive for GPC species.

Microbiological investigation

Of the 48 clinical GNB isolates recovered from synovial fluid, *P. aeruginosa* ($n = 16$, 33.3%) was the most common, followed by *E. coli* ($n = 13$, 28.1%), *K. pneumoniae* ($n = 4$, 8.3%), *Salmonella* spp. ($n = 4$, 8.3%), *Enterobacter cloacae* ($n = 3$, 6.3%), *Stenotrophomonas maltophilia* ($n = 3$, 6.3%), *Morganella morgannii* ($n = 2$, 4.2%), and one (2.1%) each of *Proteus vulgaris*, *S. marcescens*, and *C. koseri* (Table 1).

The antibiotic resistance patterns of the 48 pathogens are shown in Table 2. Among the 29 clinical isolates of Enterobacteriaceae, eight (27.6%) were resistant to ceftriaxone, six (20.7%) were resistant to cefpirome, eight (27.6%) were resistant to ciprofloxacin, and seven (24.1%) were resistant to piperacillin-tazobactam. Three of the *E. coli* isolates and three of the *K. pneumoniae* isolates were extended-spectrum beta-lactamase producers ($n = 6$, 20.7%). Among the isolates of nonfermenting GNB (NFGNB), 21.1% were resistant to ceftazidime, 21.1% were resistant to ciprofloxacin, 26.3% were resistant to piperacillin-tazobactam, and 15.8% were resistant to imipenem. In addition, NFGNB isolates also showed high rates of resistance to aminoglycosides (gentamicin, 36.8%; amikacin, 21.1%). There were no significant differences in resistance rates between pathogens causing prosthetic joint infections and those causing native joint infections.

Treatment and outcome analysis of patients with GNB arthritis

The most commonly used antibiotic was ceftazidime ($n = 28$, 58.3%), followed by ciprofloxacin ($n = 16$, 33.3%). The average duration of parenteral and oral antibiotics was 2.3 weeks and 4.7 weeks, respectively. More than half of

Table 2 Antibiotic resistance patterns of the 48 pathogens.

Antimicrobial agent	No. of resistant Enterobacteriaceae (n = 29)	No. of resistant NFGNB (n = 19)	No. of resistant bacteria causing prosthetic joint infections (n = 26)	No. of resistant bacteria causing native joint infections (n = 28)
Ampicillin	25 (86.2)		13 (50.0)	12 (42.9)
Amoxicillin-clavulanate	14 (48.3)		8 (30.8)	6 (21.4)
Gentamicin	9 (31.0)	7 (36.8)	9 (34.6)	7 (25.0)
Amikacin	1 (3.4)	4 (21.1)	3 (11.5)	2 (7.1)
Cefazolin	18 (62.1)		8 (30.8)	10 (35.7)
Cefuroxime	13 (44.8)		6 (23.1)	7 (25.0)
Ceftriaxone	8 (27.6)		5 (19.2)	3 (10.7)
Ceftazidime	8 (27.6)	4 (21.1)	7 (26.9)	5 (17.9)
Cefpirome	6 (20.7)	4 (21.1)	5 (19.2)	5 (17.9)
Ciprofloxacin	8 (27.6)	4 (21.1)	7 (26.9)	5 (17.9)
Piperacillin-tazobactam	7 (24.1)	5 (26.3)	8 (30.8)	4 (14.3)
Imipenem	1 (3.4)	3 (15.8)	2 (7.7)	2 (7.1)
ESBL	6 (20.7)		4 (15.4)	2 (7.1)

Data are presented as n (%).
ESBL = extended-spectrum beta-lactamase; NFGNB = nonfermenting gram-negative bacilli.

the patients with GNB arthritis received surgical intervention or drainage therapy (Table 1), and all of them received two-stage surgical procedures. In addition, one patient required amputation and 11 (22.9%) patients required prosthetic surgery. The overall in-hospital mortality rate was 10.4% and all five of the patients who died had underlying immunocompromising conditions. Two of the five patients who died had infections due to extended-spectrum beta-lactamase-producing *K. pneumoniae*, two had *E. coli* infections, and one had *P. aeruginosa* infection. Analysis of the outcomes showed that concomitant bacteremia (OR: 14.6, 95% CI: 1.9—115.2, p = 0.011) and liver cirrhosis (OR: 20.0, 95%, CI: 2.4—169.9, p = 0.006) were significant risk factors for death (Table 3).

Discussion

Most of the cases of septic arthritis in this study were caused by GPC (n = 146, 75.3%). We also found that GPC arthritis was more likely to develop in patients with end-stage renal disease, diabetes mellitus, or prosthetic joints. However, there were no differences in clinical presentation or outcomes between patients with arthritis due to GPC and those with arthritis due to GNB. Our findings indicate that GPC are much more prevalent pathogens than GNB, especially in patients with specific diseases or conditions. Although only about 25% of the cases of septic arthritis were caused by GNB, the incidence is markedly higher than that reported previously,[7,8] indicating that GNB species should be considered possible pathogens in patients with septic arthritis, at least in Taiwan. *Pseudomonas* spp. and *E. coli* were the most common causative pathogens, occurring in about 60% of patients with GNB septic arthritis. This finding is consistent with that reported in previous studies.[7—10] Nonetheless, clinicians must keep in mind that septic arthritis can be caused by less common GNB species, including *K. pneumoniae*, *Salmonella* spp., *E. cloacae*, *S. maltophilia*, *M. morgannii*, *P. vulgaris*, *S. marcescens*, and *C. koseri*.

Table 3 Comparison between patients who survived or died.

	Patients who survived (n = 43)	Patients who died (n = 5)	Odds ratio	p	95% CI
ESBL	4 (9.3)	2 (40.0)	6.500	0.075	0.825—51.203
Elderly	27 (62.8)	3 (60.0)	0.889	1.000	0.134—5.902
Prosthesis	25 (58.1)	1 (20.0)	0.180	0.165	0.019—1.748
Nosocomial infection	4 (9.3)	2 (40.0)	6.500	0.75	0.825—51.203
Concomitant bacteremia	4 (9.3)	3 (60.0)	14.625	0.011	1.857—115.207
Diabetes mellitus	10 (23.3)	2 (40.0)	2.200	0.587	0.321—15.066
End-stage renal disease	1 (2.3)	1 (20.0)	10.500	0.199	0.547—201.711
Liver cirrhosis	3 (7.0)	3 (60.0)	20.000	0.006	2.354—169.915
Cancer	4 (9.3)	1 (20.0)	2.438	0.438	0.217—27.436
Systemic steroid	4 (9.3)	1 (20.0)	2.438	0.438	0.217—27.436
Surgery	24 (55.8)	2 (40.0)	0.528	0.649	0.080—3.486
Drainage	23 (53.5)	2 (40.0)	0.580	0.660	0.088—3.825

Data are presented as n (%) unless otherwise indicated.
CI = confidence interval; ESBL = extended-spectrum beta-lactamase.

Initial appropriate antibiotic treatment is essential for successful management of patients with septic arthritis; however, it should be based on knowledge of the bacteriology and antibiotic-susceptibility patterns. Previous studies have shown that empirical treatment for septic arthritis should include vancomycin for GPC, ceftriaxone for Gram-negative cocci, and ceftazidime for GNB.[11–13] In our study, >25% of the Enterobacteriaceae isolates were resistant to ceftriaxone, and >20% of NFGNB isolates were resistant to ceftazidime. Among the Enterobacteriaceae isolates, six were extended-spectrum beta-lactamase producers. Overall, the rate of resistance to imipenem was 8.3%. Although *in vitro* activity does not represent *in vivo* efficacy, a large-scale clinical study is warranted to evaluate the impact of antibiotics on the outcome of patients with septic arthritis due to drug-resistant GNB. Our findings suggest that broad-spectrum antibiotic therapy should be empirically given to patients with septic arthritis in environments where antibiotic-resistant GNB is prevalent.

Previous studies have shown a close association between GNB septic arthritis and invasive urinary tract infections, old age, intravenous drug use, compromised immunity, and skin infections.[8,12] In this study, more than half ($n = 27$, 56.3%) of the patients had immunocompromising conditions, such as diabetes mellitus, liver cirrhosis, cancer, or end-stage renal disease. In addition, the majority (62.5%) of patients in this study were of advanced age. We did not investigate the association between septic arthritis and urinary tract infection or intravenous drug use. Our findings indicate that GNB should be considered possible pathogens in immunocompromised patients and in elderly patients with septic arthritis.

In this study, 14 (29.2%) patients had underlying gout. Clinically, the presentations of gout and septic arthritis may overlap, and it is difficult to differentiate them from each other without further examination of the synovial fluid. Therefore, physicians should perform arthrocentesis for differential diagnosis.

The overall mortality rate in our study was 10.4%, which is consistent with previous studies showing mortality rates ranging from 10% to 20%.[6,14,15] Moreover, we found that death was significantly associated with concomitant bacteremia (OR: 14.6, 95% CI: 1.9–115.2, $p = 0.011$) and liver cirrhosis (OR: 20.0, 95% CI: 2.4–169.9, $p = 0.006$). Morbidities including amputation, arthrodesis, and prosthetic surgery were more common in our study (>50% of patients) than in the study by Kaandorp et al[15] who reported that such morbidities were present in about 33% of patients with bacterial arthritis. The difference could be due to differences in study design and populations studied. In summary, these findings indicate that GNB septic arthritis causes significant morbidity and mortality, especially in patients with liver cirrhosis and concomitant bacteremia.

There are several limitations to this study. First, our findings are based on an investigation of patients treated at only one institution; therefore, the findings might not be generalizable to other hospital populations. Second, this study was a retrospective investigation, and bias could have been introduced by missing data. Third, we used all-cause mortality for the outcome analysis and did not evaluate mortality attributable to septic arthritis.

In conclusion, this study provides physicians with useful epidemiological information about GNB septic arthritis. We found that about one-fourth of the cases of septic arthritis were caused by GNB and that resistance to commonly used antimicrobial agents was common. Furthermore, septic arthritis due to GNB was associated with significant morbidity and mortality, and liver cirrhosis and concomitant bacteremia were significant risk factors for death.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgments

None.

References

1. García-Arias M, Balsa A, Mola EM. Septic arthritis. *Best Pract Res Clin Rheumatol* 2011;**25**:407–21.
2. Mathews CJ, Weston VC, Jones A, Field M, Coakley G. Bacterial septic arthritis in adults. *Lancet* 2010;**375**:846–55.
3. Mathews CJ, Coakley G. Septic arthritis: current diagnostic and therapeutic algorithm. *Curr Opin Rheumatol* 2008;**20**:457–62.
4. Frazee BW, Fee C, Lambert L. How common is MRSA in adult septic arthritis? *Ann Emerg Med* 2009;**54**:695–700.
5. Lin WT, Wu CD, Cheng SC, Chiu CC, Tseng CC, Chan HT, et al. High Prevalence of methicillin-resistant *Staphylococcus aureus* among patients with septic arthritis caused by *Staphylococcus aureus*. *PLoS One* 2015;**10**:e0127150.
6. Ross JJ, Saltzman CL, Carling P, Shapiro DS. Pneumococcal septic arthritis: review of 190 cases. *Clin Infect Dis* 2003;**36**:319–27.
7. Shirtliff ME, Mader JT. Acute septic arthritis. *Clin Microbiol Rev* 2002;**15**:527–44.
8. Deesomchok U, Tumravin T. Clinical study of culture-proven cases of non-gonococcal arthritis. *J Med Assoc Thai* 1990;**73**:615–23.
9. Le Dantec L, Maury F, Flipo RM, Laskri S, Cortet B, Duquesnoy B, et al. Peripheral pyogenic arthritis: a study of one hundred seventy-nine cases. *Rev Rhum Engl Ed* 1996;**63**:103–10.
10. Morgan DS, Fisher D, Merianos A, Currie BJ. An 18 year clinical review of septic arthritis from tropical Australia. *Epidemiol Infect* 1996;**117**:423–8.
11. Ohl CA. Infectious arthritis of native joints. In: Mandell GL, Bennette JE, Dolin R, editors. *Mandell, Douglas, and Bennett's principle and practice of infectious diseases*. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010. p. 1443–56.
12. Horowitz DL, Katzap E, Horowitz S, Barilla-LaBarca ML. Approach to septic arthritis. *Am Fam Physician* 2011;**84**:653–60.
13. Visser S, Tupper J. Septic until proven otherwise: approach to and treatment of the septic joint in adult patients. *Can Fam Physician* 2009;**55**:374–5.
14. Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and outcome of septic arthritis in a single UK Health District 1982–1991. *Ann Rheum Dis* 1999;**58**:214–9.
15. Kaandorp CJ, Krijnen P, Moens HJ, Habbema JD, van Schaardenburg D. The outcome of bacterial arthritis: a prospective community-based study. *Arthritis Rheum* 1997;**40**:884–92.