

Research Paper

Epidemiological, Clinical and Microbiological Characteristics of Patients with Post-Traumatic Osteomyelitis of Limb Fractures in Southwest China: A Hospital-Based Study

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Abstract

Objective To determine the epidemiological, clinical and microbiological characteristics, of patients with post-traumatic osteomyelitis of extremity fractures, and provide evidence-based guidelines for early diagnosis and treatment, including empiric antibiotic therapy.

Methods Human subject research was performed using institutional review board approved protocols. A retrospective chart review was conducted on 5,368 patients diagnosed with extremity traumatic fractures from January 1, 2012 to December 31, 2015, to identify osteomyelitis patients. Records from the Microbiology Department were reviewed, and patients with a positive wound culture, or bone biopsy culture, were selected for the study. Microbial susceptibility was determined by the M-100-S22 protocol (Clinical & Laboratory Standards Institute® (CLSI) 2012 USA). Additional clinical information, including data on patients' baseline epidemiological, clinical, and microbiological records was collected from all available charts, and reviewed using a designed protocol.

Results 84 (1.56%) patients were diagnosed with osteomyelitis based on a positive culture result. The most prevalent comorbidities in these patients were compartment syndrome, diabetes and hypertension. The most commonly involved infected site was the tibia-fibula (47.62%). 66 (78.57%) of these cases were monomicrobial, and 18 cases (21.43%) were polymicrobial. The infections were predominantly caused by Gram-positive bacteria (56, 53.85%). The most common Gram-positive bacteria were *Staphylococcus aureus* (39 cases, 37.50%) and *S. epidermidis* (6 cases, 5.77%), which were sensitive to ampicillin, synercid/ dalfopristin, linezolid, tigecycline, macrodantin, and vancomycin. *S. aureus* was the most common pathogen in both monomicrobial and polymicrobial cases. All 17 cases of MRSA infection were sensitive to Imezolid, ampicillin, synercid/ dalfopristin, linezolid, tigecycline, furadantin, piperacillin/yaz, rifampicin, and vancomycin, respectively. The most common Gram-negative bacteria were *E. coli* (16 cases, 15.38%) and *Enterobacter cloacae* (11 cases, 10.58%), which were sensitive to thienamycin.

Conclusions In this study, the overall rate of post-traumatic osteomyelitis of limb fractures (1.56%) is lower than the national average rate (2.6-7.8%), for major medical centers in China. The main medical comorbidities were compartment syndrome, diabetes mellitus and hypertension. The most common infection was monomicrobial in lower extremities. *S. aureus* was the most common pathogen, which presented in 39 (37.50%) cases, and 17 of these (43.59%) were caused by MRSA. These findings can guide empiric antibiotic therapy in Southwest China for osteomyelitis in patients with traumatic limb fractures.

Key words: Osteomyelitis; Limb fracture; Methicillin-resistant *Staphylococcus aureus* (MRSA); Antibiotic resistance, Regional characteristics.

Introduction

Osteomyelitis is a bacterial infection of the bone or bone marrow often resulting in hospital admission^[1]. Osteomyelitis may result from contiguous spread of infection from adjacent soft tissues and joints, hematogenous seeding, or direct inoculation of bacteria into the bone as a result of trauma or surgery.

There has been a remarkable increase in osteomyelitis in the USA between 1969 and 2009 for reasons that remain unclear, but could comprise a variety of host, pathogen and environmental factors^[2]. To date, little is known about changes in the epidemiological and clinical findings of osteoarticular infections over long periods of time. Conceivably, there may have been major changes in the microbiology, types of osteoarticular infections, and the characteristics of patients at risk. For example, the widespread use of medical devices in orthopaedic surgery and increased life expectancy of the population are all factors related to the increased rates of some osteoarticular infections^[3, 4]. Also, the emergence of multidrug-resistant microorganisms (e.g. methicillin-resistant *Staphylococcus aureus*, MRSA) in hospitals and other healthcare institutions has been associated with increased rates of bacterial infections caused by difficult-to-treat pathogens^[5, 6]. An increasing incidence of infections has also been related to the improvement of identification methods of microorganism^[7].

To our knowledge, there are no comprehensive studies describing the entire spectrum of osteomyelitis in Southwest China. Thus, our objective was to examine the epidemiological, clinical and microbiological characteristics of osteomyelitis in a hospital that serve for majority of this area over a four-year period from January 1, 2012 to December 31, 2015.

Materials and Methods

This study was a hospital-based investigation conducted at Affiliated Hospital of Zunyi Medical College, China, which was an investigational site participating in the AO Trauma Clinical Priority Program (AOCPP). The Ethics Committee of Affiliated Hospital of Zunyi Medical College approved all the human subject research.

We retrospectively reviewed the records of patients from January 1, 2012 to December 31, 2015, to identify osteomyelitis patients in search of patients with positive wound culture or bone biopsy culture. 84 patients were identified with confirmed bacterial bone infections and were included in the study. Bacterial susceptibility data was determined by the

M-100-S22 protocol (Clinical & Laboratory Standards Institute® (CLSI) 2012 USA. The information collected from patients with osteomyelitis included the patients' baseline characteristics, clinical presentation, and microbiological records.

Results

We identified 84 patients (58 open fracture cases and 26 closed fracture cases) with post-traumatic osteomyelitis of limb fractures. There were 69 males and 15 females, and the mean age was 43 years (range, 16-72 years).

The medical comorbidities in patients with osteomyelitis are presented in Table 1. There were 10 identified comorbidities in 84 patients, including compartment syndrome, diabetes, hypertension, hepatic dysfunction, craniocerebral trauma, closed thoracic trauma, osteoporosis, hyperuricemia, hypoproteinemia, and hyperkalemia. The most frequent accompanying conditions were compartment syndrome (4, 18.18%), diabetes (4, 18.18%) and hypertension (3, 13.64%).

Table 1. Medical comorbidities in patients with osteomyelitis

Comorbidity	n
Osteofascial compartment syndrome	4
Diabetes	4
Hypertension	3
Hepatic dysfunction	2
Craniocerebral trauma	2
Closed thoracic trauma	2
Osteoporosis	2
Hyperuricemia	1
Hypoproteinemia	1
Hyperkalemia	1
Total	22

Table 2. The Distribution and percentage of affected sites

Infection site	Single infection (%)	Mixed infection (%)	Total (%)
Tibia and Fibula	32 (38.10)	8 (9.52)**	40 (47.62)
Femur	13 (15.48)	7 (8.33)**	20 (23.81)
Radius and Ulna	9 (10.71)	2(2.38)**	11 (13.10)
Humerus	5 (5.95)	—	5 (5.95)
Patella	5 (5.95)	—	5 (5.95)
Calcaneus	2 (2.38)	1 (1.19)**	3 (3.57)
Total (%)	66 (78.57)	18 (21.43)	84 (100.00)

Notes: The superscript ** are mix infection cases which the detail is listed in table 4
 Mix infection: Sites and pathogenic bacteria.

The distribution and percentage of affected sites of the 84 patients with osteomyelitis are shown in Table 2. 66 (78.57%) cases were monomicrobial, and 18 (21.43%) cases were polymicrobial. The most commonly involved site was the tibia-fibula (40, 47.62%), including monomicrobial (32, 38.10%) and

polymicrobial (8, 9.52%), femur (20, 23.81%) and radius-ulna (11, 13.10%).

According to the proportion and cases of Gram-positive/negative bacteria (Table 3), there were 104 strains in 84 patients; 56 (53.85%) strains were Gram-positive bacteria and 48 (46.15%) were Gram-negative bacteria. The most prevalent Gram-positive bacteria were *S. aureus* (39, 37.50%) and *S. epidermidis* (6, 5.77%), and *E. coli* (16 cases, 15.38%) and *Enterobacter cloacae* (11 cases, 10.58%) were the most commonly identified Gram-negative bacteria. Overall, *S. aureus* was the most common pathogen in both monomicrobial (31, 46.97%) and polymicrobial (8, 44.44%) cases, and the breakdown of the 39 strains included MRSA (17, 43.59%) and MSSA (22, 56.41%). The mixed mix infection and pathogenic bacteria are listed in table 4. The *S. aureus* and *S. epidermidis* strains were sensitive to ampicillin, synergid/ dalfoprstin, linezolid, tigecycline, macrodantin, and vancomycin, respectively (Table 5). All 17 cases of MRSA infection were sensitive to Imezolid, ampicillin, synergid/ dalfoprstin, linezolid, tigecycline, furadantin, piperacillin/yaz, rifampicin, and vancomycin, respectively (Table 6). *E. coli* and *E. cloacae* presented as the main Gram-negative bacteria, and were all sensitive to thienamycin (Table 7).

Table 3. The proportion and cases of the Gram-positive/negative bacteria

Pathogenic bacteria	Isolate	Proportion (%)
Gram-positive bacteria		
Staphylococcus aureus **	39	37.5
Staphylococcus epidermidis**	6	5.77
Enterococcus avium **	2	1.92
Staphylococcus simulans	1	0.96
Streptococcus milleri **	1	0.96
Staphylococcus aureus subspecies**	1	0.96
Staphylococcus hominis**	1	0.96
Enterococcus faecalis **	5	4.81
Gram-negative bacteria		
Escherichia coli**	16	15.38
Enterobacter cloacae**	11	10.58
Klebsiella pneumoniae**	4	3.85
Pseudomonas aeruginosa**	4	3.85
Citrobacter koseri	2	1.92
Serratia marcescens	1	0.96
Morganella morganii	2	1.92
Baumann acinetobacter**	6	5.77
Klebsiella oxytoca **	1	0.96
Basillus **	1	0.96
Total	104	100

Note: The superscript ** are mix infection cases which the detail is listed in table 4
 Mix infection: Sites and pathogenic bacteria.

Table 4. Mix infection: Sites and pathogenic bacteria

Sites	Case No	Pathogenic bacteria			
		A	B	C	
Tibia and Fibula (44.4%)	1	S.aureus	Klebsiella pneumoniae		
	2	S.aureus	Pseudomonas aeruginosa		
	3	S.aureus	Streptococcus epidermidis	S. Hominic	
	4	S.aureus	Streptococcus milleri		
	5	S.aureus subspecies	Psiudomonas aeruginoso		
	6	S. epidermidis	Basillus		
	7	Enterobacter cloacae	Baumann acinetobacter		
	8	Enterobacter cloacae	Klebsiella oxytoca		
	Femur (38.9%)	9	S.aureus	Baumann acinetobacter	
		10	S.aureus	Escherichia coli	Baumann acinetobacter
		11	S. epidermidis	Enterococcus faecali	
		12	Enterococcus avium	Escherichia coli	
		13	Enterococcus faecalis	Enterobacter cloacae	
		14	Eschrichia coli	Baumann acinetobacter	
		15	Eschrichia coli	Baumann acinetobacter	
Radius and Ulnar (11.1%)	16	S.aureus	Enterobacter cloacae		
	17	S.aureus	Pseudomonas aeruginosa		
Calcaneus (5.60%)	18	Enterococcus faecalis	Escherichia coli		

Table 5. The rate of drug resistance of the main Gram-positive bacteria

Antibiotics	S.aureus (n=39)		S. epidermidis (n=6)	
	Cases (n)	Drug resistance rate (%)	Cases (n)	Drug resistance rate (%)
Penicillin	29	74.36	6	100
Erythrocine	24	61.54	3	50
Lincomycin	22	56.41	5	83.33
Tetracycline	21	53.85	4	66.67
Oxacillin	17	35.9	5	83.33
Cefoxitin	17	35.9	3	50
Levofloxacin	6	15.38	3	50
Inducible clindamycin	6	15.38	2	33.33
Co-trimoxazole	4	10.26	3	50
Ciprofloxacin	4	10.26	2	33.33
Moxifloxacin	2	5.13	1	16.67
Rifampicin	1	2.56	2	33.33
Vancomycin	0	0	0	0
Tigecycline	0	0	0	0
Synergid/ Dalfoprstin	0	0	0	0
Macrodantin	0	0	0	0
Linezolid	0	0	0	0
Ampicillin	0	0	0	0

Discussion

To the end of understating the incidence and clinical aspects of post-traumatic osteomyelitis in Southwest China, and deriving an empirical antibiotic regimen, we conducted a retrospective analysis of this population. The results showed that the overall rate of post-traumatic osteomyelitis of limb fractures (1.56%) seen at the Affiliated Hospital of Zunyi Medical

College is lower than the national average rate (2.6-7.8%) for major medical centers in China^[8]. This may be associated with our strict screening criteria. The majority of patients with osteomyelitis were young males, and 58 (69.05%) with open fractures. The most commonly involved site was the tibia-fibula (40, 47.62%), which may be related to the fact that these fractures are usually caused by direct trauma, and many of them are open fracture cases. Additionally, open fracture wounds are often contaminated, have long exposure times, and suffer from major soft tissue defects. At the same time, some patients have comorbidities that may delay wound healing, such as compartment syndrome, and diabetes^[9]. These factors markedly increase the risk of infection^[10, 11].

Two decades ago, Gram-negative bacteria were the main pathogens responsible for osteomyelitis in China. Since then, *S. aureus* has become the most prevalent bacteria in nosocomial infections^[12]. In this study, we found that the detection rates of MSSA and MRSA were 69.64%, 43.59%, respectively, which compares with the Chinese national average of 59.1% and 57.8%^[13]. There are regional characteristics for osteomyelitis; in the Southwest region of China, the main strains of MRSA were ST239-III-t30, ST239-037 and ST5-II-t002. In addition, we identified ST5-II, ST59-IV (a community acquired strain) and unique ST2582-III-t030 strains.

Table 6. The rate of drug resistance of *Staphylococcus aureus*

Antibiotics	MRSA(n=17)		MSSA(n=22)	
	Cases	Drug resistance rate (%)	Cases	Drug resistance rate (%)
Penicillin	17	100	22	100
Erythrocine	17	100	7	31.82
Cefoxitin	17	100	0	0
Oxacillin	17	100	0	0
Lincomycin	16	94.12	6	27.27
Tetracycline	9	52.94	13	59.09
Levofloxacin	2	11.76	4	18.75
Ciprofloxacin	2	11.76	2	9.09
Inducible clindamycin	1	5.88	5	22.73
Co-trimoxazole	1	5.88	3	13.64
Gentamicin	1	5.88	3	13.64
Moxifloxacin	1	5.88	1	4.55
Amoxicillin/Clavulanic acid	1	5.88	0	0
Cefazolin	1	5.88	0	0
Thiomycin	1	5.88	0	0
Rifampicin	0	0	1	4.55
Imezolid	0	0	0	0
Ampicillin /sulbactam	0	0	0	0
Synercid/ Dalfopristin	0	0	0	0
Linezolid	0	0	0	0
Tigecycline	0	0	0	0
Furadantin	0	0	0	0
Piperacillin/Tazo	0	0	0	0
Vancomycin	0	0	0	0

Table 7. The rate of drug resistance of the main Gram-negative bacteria

Antibiotics	E. coli (n=16)		Enterobacter cloacae (n=11)	
	Cases	Drug resistance rate (%)	Cases	Drug resistance rate (%)
Ampicillin	14	87.5	10	90.91
Cefazolin	14	87.5	7	63.64
Sulbactam	12	75	10	90.91
Ceftriaxone	11	68.75	5	45.45
Levofloxacin	11	68.75	4	36.36
Ciprofloxacin	9	56.25	4	36.36
Co-trimoxazole	9	56.25	3	27.27
ESBL	9	56.25	2	18.18
Aztreonam	6	37.5	5	45.45
Ceftazidime	6	37.5	5	45.45
Gentamicin	6	37.5	5	45.45
Cefepime	5	31.25	4	36.36
Cefotetan	1	6.25	8	72.73
Amoxicillin	1	6.25	3	27.27
Nitrofurantoin	0	0	6	54.55
Tobramycin	0	0	5	45.45
Piperacillin	0	0	4	36.36
Amikacin	0	0	4	36.36
Erythrocin	0	0	3	27.27
Piperacilin/Tazo	0	0	3	27.27
Ertapenem	0	0	2	18.18
Thienamycin	0	0	0	0

Although multidrug resistance is a major healthcare problem^[14], our research found that all 39 *S. aureus* strains detected were susceptible to imezolid, ampicillin /sulbactam, synercid/dalfopristin, linezolid, tigecycline, furadantin, piperacillin/tazo, and vancomycin. Additionally, all MRSA strains were sensitive to imezolid, ampicillin, synercid/ dalfopristin, linezolid, tigecycline, furadantin, piperacillin/tazo, rifampicin, and vancomycin. MSSA strains were sensitive to imezolid, ampicillin, synercid/ dalfopristin, amoxicillin/clavulanic acid, linezolid, tigecycline, cefoxitin, cefazolin, thiomycin, oxacillin, piperacillin/tazo, and vancomycin. Interestingly, this result differs from the drug-resistant bacteria spectrum observed in other regions in China. Additionally, while we identified common strains (ST 239, ST5, and ST59), we also found osteomyelitis patients infected with ST2582-III-t30, which appears to be unique in Southwest of China.

There are several notable limitations to this study. This is a retrospective study and the size of sample is relatively small. We were not able to save fresh specimens to extract DNA, RNA or protein to complete gene sequencing in order to screen for gene mutation and to confirm the level of protein expression. In addition, our results only represent the osteomyelitis cases seen in Zunyi and its surrounding area. Thus, a large multi-center prospective study

would be required to identify determine patient outcomes and to offer a broader assessment of osteomyelitis in Southwest China.

The overall rate of post-traumatic osteomyelitis of limb fractures in Zunyi is lower than the national average of major medical centers in China. The regional characteristics from an epidemiological, clinical and microbiological characteristics are shown by this study. These results can provide guidance for the early diagnosis and treatment including empiric antibiotic therapy for osteomyelitis.

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Competing Interests

The authors have declared that no competing interest exists.

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