

Peking University First Hospital Procedure for Culturing Pathogenic Microorganisms for Bone and Joint Infection

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Background: This retrospective cohort study explores a practical approach to acquiring pathogenic microorganisms in patients with bone and joint infections.

Methods: From Aug 2018 to Mar 2022, 68 consecutive patients (87 cultures) with bone and joint infection were recruited in this study. All cultures followed the Peking University First Hospital Procedure of Culturing Pathogenic microorganisms for bone and joint infection. Tissue samples were obtained through fluoroscopy-guided biopsy or open debridement. Tissue samples were divided into manual homogenization (MH), manual mixture (MM), and pathological examination. The baseline, antibiotic exposure, laboratory, surgical, and microbial data were reviewed. Independent sample *T*-test, Mann–Whitney *U*-test, and Chi-square test were used to detect the difference between patients who received different processing measures.

Results: The average age was 55.8±2.4 years old. Thirty-nine patients were male. The total positive culture rate of the manual homogenization group was 80.5% (70/87). Thirty-five patients had mixed infections with more than one microorganism cultured. Staphylococci accounted for 60.23% of all microorganisms. Staphylococcus aureus (18.2%) and Staphylococcus epidermidis (15.9%) were the two most common bacteria cultured in this study. Patients with positive culture in the manual mixture group had significantly higher WBC ($p = 0.006$), NE% ($p = 0.024$), ESR ($p = 0.003$), CRP ($p = 0.020$) and IL6 (0.050) compared to patients with negative culture. After tissue homogenization, only ESR is still statistically different. Patients without SIRS had a low positive culture rate (59.4%). Tissue homogenization could significantly increase the positive culture rate of patients without SIRS. Pre-culture antibiotic exposure was not an independent risk factor for culture results.

Conclusion: Peking University First Hospital Procedure for Culturing Pathogenic microorganisms for Bone and Joint Infections was a practical approach for obtaining pathogenic microorganisms.

Keywords: bone and joint infection, systemic inflammatory response syndrome, antibiotic, tissue homogenization

Background

Bone and joint infections are one of the most challenging diseases in the musculoskeletal system.¹ Although the incidence rate of hematogenous bone and joint infections is low in developed countries, it remains high in developing countries.² Bone and joint infections require long-term treatment and are prone to recurrence.³ Bone and joint infections have a high disability rate, resulting in a vast social and medical burden.

Identifying the pathogenic microorganism and using sensitive antibiotics are the cornerstones of treating patients with bone and joint infections. Several factors could affect the culture result, including the level of c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR),^{4,5} the tissue type,^{6,7} and antibiotic exposure.^{8,9} Previous literature reported that the culture-positive rate was lower than 50%.^{10–12}

Tissue homogenization, DL-dithiothreitol, and sonication can increase the quantity and viability of pathogens released from diseased tissue. These methods have been applied to improve the rate of pathogenic microorganism identification.^{13–15} However, there is currently no standardized procedure for pathogen identification in patients with bone and joint infections. Therefore, this retrospective study aims to explore a practical approach to acquiring pathogenic microorganisms in patients with bone and joint infection.

Methods

Study Design, Inclusion, and Exclusion Criteria

This study was a single-centered retrospective cohort study. From Aug 2018 to Mar 2022, 68 consecutive patients with bone and joint infection (except patients with tuberculosis) hospitalized in our department were recruited. All diagnoses were confirmed by pathology.

Data Collection

We reviewed the medical record to assess baseline, antibiotic exposure, laboratory, surgical, and microbial data among the clinical variables. Baseline data included age, gender, infection site, complications, and systemic inflammatory response syndrome (SIRS). Laboratory data included the total number of white blood cells (WBC), neutrophils (NE%), c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and interleukin-6 (IL-6).

Patients who meet two or more of the following clinical manifestations are diagnosed with SIRS. 1) Body temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; 2) Heart rate > 90 beats/minute; 3) Breathing > 20 times/minute or $\text{PaCO}_2 < 32$ mmHg; 4) The total number of WBC $> 12 \times 10^9/\text{L}$ or $< 4 \times 10^9/\text{L}$, or the proportion of immature (rod-shaped) neutrophils $> 10\%$.

Treatment Procedure in This Study

The detailed procedure of pathogenic microorganism culture for bone and joint infection in the Peking Hospital is shown in Figure 1.

Patients were first admitted to the hospital to determine whether antibiotics were consistently applied. If antibiotics were consistently applied, they were continued after hospitalization; if antibiotics were not consistently applied, the decision to apply antibiotics was based on the patient's condition. Antibiotics were applied if SIRS was present in the patient and not if SIRS was not present in the patient.

All patients underwent a physical examination, X-ray, Computer Tomography (CT), and Magnetic Resonance Imaging (MRI) to confirm the site of the infection. Their blood samples were taken for laboratory tests. Tissue specimen was obtained through fluoroscopy-guided biopsy or open debridement surgery in the operating room. Surgical methods were selected by a multidisciplinary team composed of an experienced spine surgeon and an infectious diseases specialist.

As described in our previous study, the tissues were divided into three groups: manual homogenization (MH), manual mixture (MM), and pathology. For the MH group, tissues were placed in the disposable sterile tissue grinder and grind clockwise; the homogenate was diluted to 20 mL with normal saline. For the MM group, tissues were placed in the disposable sterile bottle with 20 mL of normal saline and stirred clockwise. The infection was confirmed by pathological

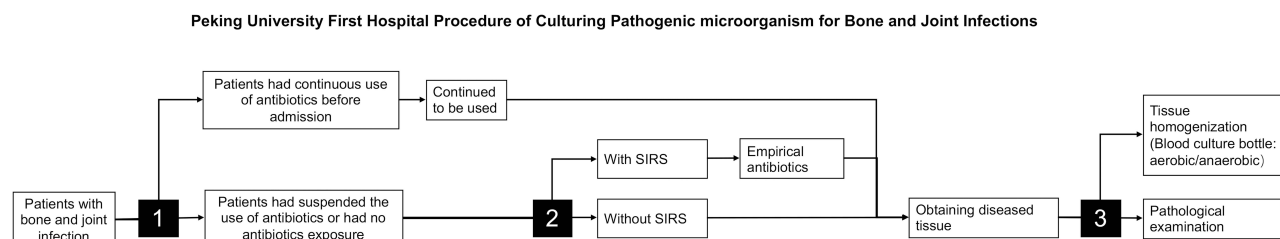


Figure 1 Peking University First Hospital Procedure of Culturing Pathogenic microorganism for Bone and Joint Infections.

examination results, which showed acute and chronic inflammatory cell infiltration and no caseous necrosis or granuloma formation. All cultures are conducted in blood culture bottles (Becton, Dickinson, and Company Spark, MD 21152 USA). Blood cultures were sent to the bacteriological laboratory for subsequent culture and bacterial identification. The identification methods were consistent across all patients studied. The criteria for culture-positive were bacterial growth in blood culture bottles within two weeks. The criteria for culture-negative were no bacterial growth in blood culture bottles within two weeks. The criteria for multi-organism positive were more than one Genus/species growth in blood culture bottles within two weeks. Detailed processing methods were described in our previous study.¹⁶

Statistical Analysis

When continuous variables conform to the standard distribution, they were expressed as mean (mean $\pm$ SE), and when they did not conform, they were expressed as median (range). Categorical variables were expressed as numbers. Independent sample *T*-test or Mann–Whitney *U*-test was used to detect the difference among continuous variables. The differences among the categorical variables were analyzed using the chi-square test. All the tests were on two sides. A *p*-value < 0.05 was considered statistically significant. We deleted cases with missing values during the statistical process. Data were analyzed with SPSS 25.0 statistical software (IBM Corporation, Armonk, NY).

Results

A total of 68 consecutive patients with 87 times pathogen cultures were recruited in this study. All patients follow the Peking University First Hospital Procedure of Culturing Pathogenic Microorganisms for Bone and Joint Infection. The baseline data of 68 patients are shown in Table 1. The average age was 55.8 ± 2.4 years old. Twenty-nine patients (42.6%) were female. Thirty-nine patients (57.4%) were involved in the spine. Thirty-six patients (52.9%) had no risk factors such as diabetes. Sixty-two patients (92.1%) had no primary infectious disease. Five patients (7.3%) performed a blood culture.

Table 1 The Baseline Information of 68 Patients

Items	N = 68
Age (years old)	55.8 $\pm$ 2.4
Gender	
Female	29 (42.6%)
Male	39 (57.4%)
Location of the lesion	
Spine	39 (57.4%)
Limb	29 (42.6%)
Risk factors	
No	36 (52.9%)
DM	16 (18.4%)
Oral hormones or immunosuppressants	4 (5.9%)
Previous internal fixation implantation	12 (22.8%)
Primary infection	
Yes	62 (91.2%)
No	6 (8.8%)

(Continued)

Table 1 (Continued).

Items	N = 68
Blood culture	
Positive	2 (3.0%)
Negative	3 (4.4%)
NA (Not performed)	63 (92.6%)

Culture results are shown in Figure 2. The positive rate of pathogen culture in the Manual homogenization and manual mixture groups was 80.5% (70/87) and 64.4% (56/87), respectively. The manual homogenization group's positive rate was significantly higher than the manual mixture group ($p = 0.018$).

About 51.47% of the patients had mixed infection with more than one microorganism cultured. About 32.35% of the patients had a single pathogen infection. Pathogenic microorganisms are predominantly Gram-positive cocci. *Staphylococci* accounted for 60.23% of all microorganisms. Gram-negative bacilli are predominantly *Escherichia coli* and *Klebsiella pneumoniae*. The top five microorganisms were *Staphylococcus aureus* (18.2%), *Staphylococcus epidermidis* (15.9%), *Staphylococcus haemolyticus* (8.0%), *Staphylococcus hominis* (5.7%), *Escherichia coli* (5.7%). Figure 3.

The characteristics of patients with different cultures, as a result of manual homogenization and manual mixture groups, are shown in Table 2. There were no significant differences in pre-culture antibiotic exposure, surgical intervention, and infection site of patients with different culture results. Patients with positive culture results in the manual mixture group had significantly higher inflammatory indicators compared to patients with negative culture results, WBC ($p = 0.006$), NE% ($p = 0.024$), ESR ($p = 0.003$), CRP ($p = 0.020$), IL6 (0.050). These differences did not reach statistical levels in manual homogenization, except ESR ($p = 0.046$). Patients with SIRS had a higher rate of positive cultures in the manual mixture group ($p = 0.059$). Thirteen culture-negative patients with spinal infection (24.5%) and 14 culture-negative patients without SIRS (20.3%) in the manual mixture group had final positive culture results after tissue homogenization. Multivariate analysis also showed that tissue homogenization would increase the positive culture rate of patients without SIRS. Figure 4.

Fourteen culture-negative patients in the manual mixture group (16.1%) had final positive culture results after tissue homogenization. The characteristics of these patients are shown in Table 3. Most patients in the moderate-risk group

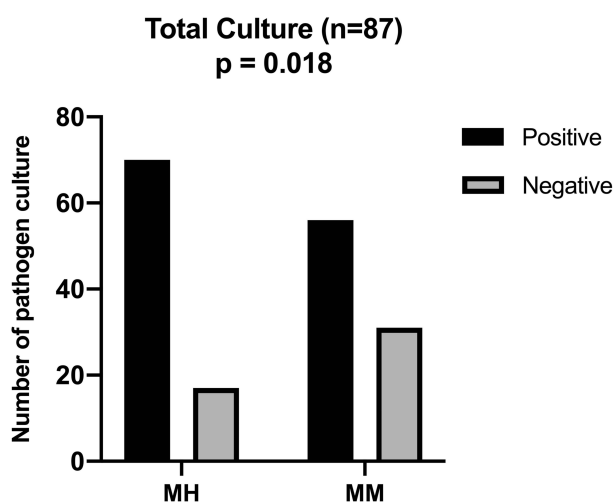


Figure 2 Total culture (n=87).

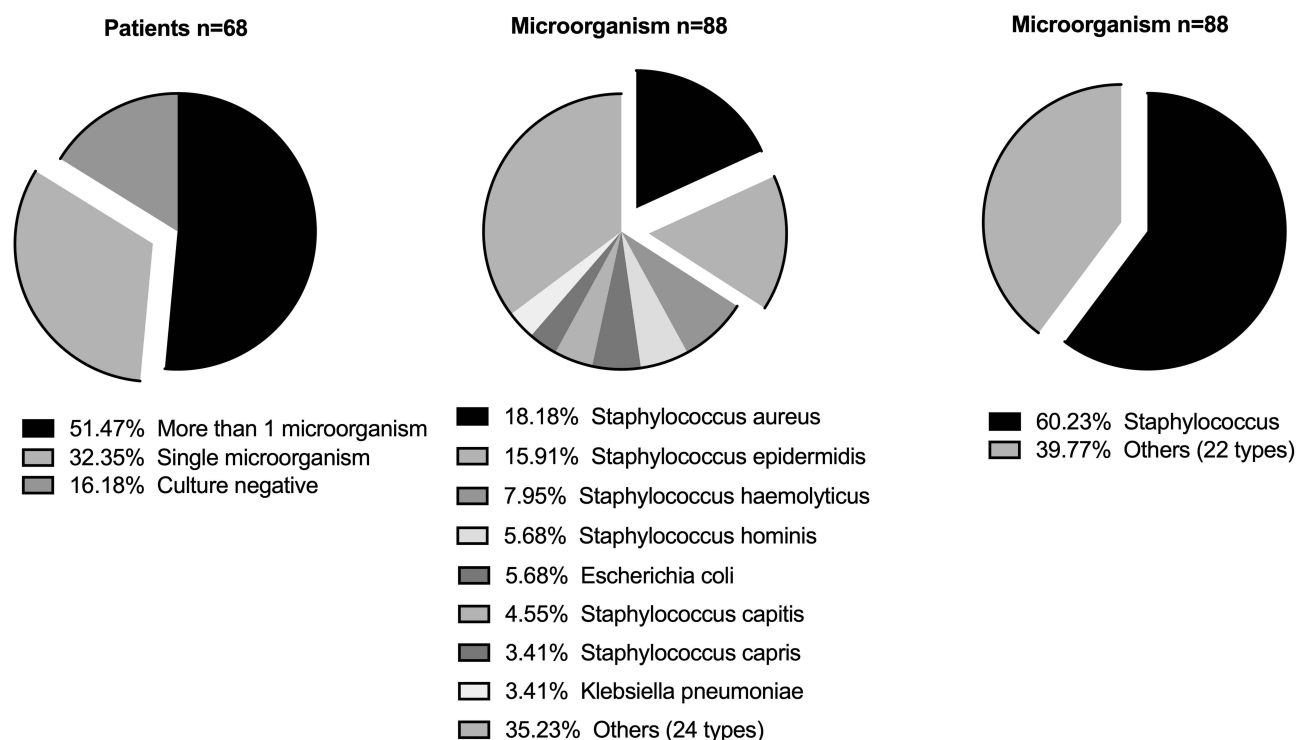


Figure 3 Microbial distribution.

had spinal infections and were without SIRS. The inflammatory indicators of the moderate-risk group (WBC, NE%, and ESR) were lower than the low-risk group.

Patients were stratified depending on the SIRS and pre-culture antibiotic exposure. [Figure 5](#). The results showed that tissue homogenization could significantly increase the positive culture rate of patients without SIRS. For patients with

Table 2 Characteristics of Patients with Different Culture Results of Manual Homogenization and Manual Mixture Group

Items	Manual Homogenization		P	Manual Mixture		P
	Positive (n = 70)	Negative (n = 17)		Positive (n = 56)	Negative (n = 31)	
Pre-culture antibiotic exposure						
Continually use	29 (80.6%)	7 (19.4%)	0.999	23 (63.9%)	13 (36.1%)	0.979
Suspend 1 week before culture	29 (80.6%)	7 (19.4%)		23 (63.9%)	13 (36.1%)	
No	12 (80.0%)	3 (20.0%)		10 (66.7%)	5 (33.3%)	
Surgical intervention						
Fluoroscopy-guided biopsy	25 (78.1%)	7 (21.9%)	0.675	18 (56.3%)	14 (43.8%)	0.228
Open surgery	45 (81.8%)	10 (18.2%)		38 (69.1%)	17 (30.9%)	
Infection site						
Spine	44 (83.0%)	9 (17.0%)	0.452	31 (58.5%)	22 (41.5%)	0.153
Limb	26 (76.5%)	8 (23.5%)		25 (73.5%)	9 (26.5%)	

(Continued)

Table 2 (Continued).

Items	Manual Homogenization		P	Manual Mixture		P
	Positive (n = 70)	Negative (n = 17)		Positive (n = 56)	Negative (n = 31)	
SIRS						
Yes	15 (83.3%)	3 (16.7%)	0.991	15 (83.3%)	3 (16.7%)	0.059
No	55 (79.7%)	14 (20.3%)		41 (59.4%)	28 (40.6%)	
WBC (10 ⁹ /L)	7.1 (5.4, 8.5)	6.2 (5.2, 7.7)	0.228	7.4 (6.2, 8.6)	5.6 (5.0, 7.1)	0.006
NE%	71.6 (63.9, 78.1)	70.4 (61.5, 74.0)	0.179	72.4 (66.1, 79.6)	70.4 (57.3, 74.3)	0.024
ESR	67.6 ± 4.7	46.4 ± 8.3	0.046	73.3 ± 4.8	48.0 ± 6.7	0.003
CRP	25.7 (8.1, 74.0)	34.6 (7.6, 90.5)	0.792	32.6 (20.7, 78.9)	11.4 (5.1, 53.0)	0.020
PCT	0.06 (0.03, 0.12)	0.06 (0.03, 0.09)	0.640	0.08 (0.03, 0.14)	0.05 (0.03, 0.09)	0.250
IL-6	15.2 (9.0, 37.6)	20.1 (8.1, 39.1)	1.000	22.1 (9.7, 39.0)	10.5 (4.0, 27.3)	0.050

continual use of antibiotics, the positive culture rate of the manual homogenization group did not reach a statistical difference when compared with that of the manual mixture.

Discussion

This study showed that strictly following the Peking University First Hospital Procedure could increase the positive rate of microorganism identification in patients with bone and joint infection. The positive rate of microorganism identification in this study was 80.5%, which was higher than in previous studies (28.0%,¹⁰ 42.0%,¹¹ 73.6%)¹⁷ More than half of the patients have mixed infections (51.5%), and the pathogenic microorganisms were mainly Gram-positive cocci (*staphylococcus aureus*: 18.2%; *staphylococcus epidermidis*: 15.91%).

Previous studies showed a correlation between the expression levels of inflammatory indicators and positive culture results. Patients with higher levels of inflammatory indicators were more likely to identify pathogenic microorganisms.^{4,5} In this study, patients with positive culture results in the manual mixture group had significantly higher inflammatory indicators compared to patients with negative culture results, WBC ($p = 0.006$), NE% ($p = 0.024$), ESR ($p = 0.003$), CRP ($p = 0.020$), IL6 (0.050). Fourteen patients with lower inflammatory indicators had final positive culture results after tissue homogenization. However, the ESR ($p = 0.046$) was still significantly higher in patients with positive culture

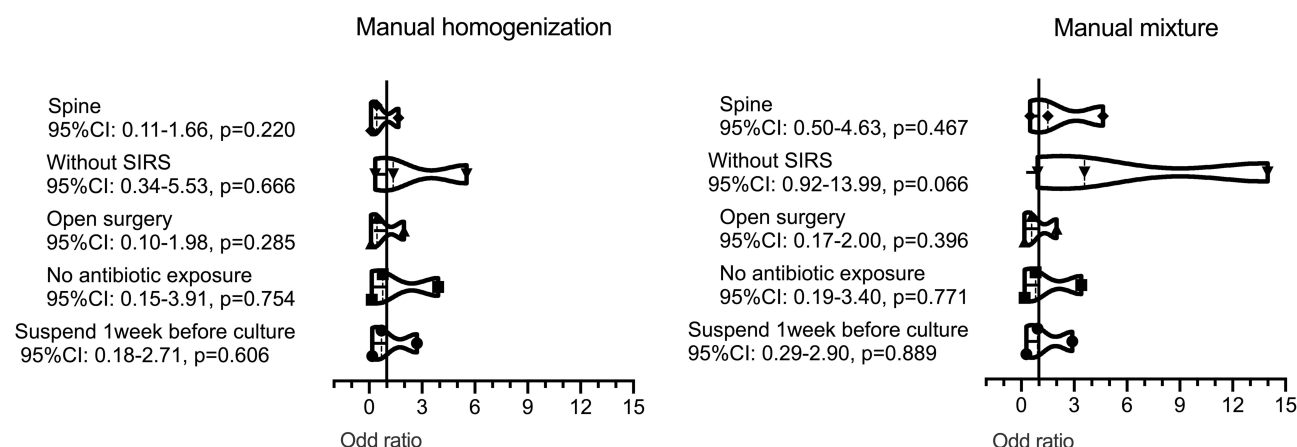
**Figure 4** Logistic regression analysis of association between culture result and clinical factors (Multivariate analysis).

Table 3 Characteristics of Patients with Different Risk Level

Items	Low Risk (n = 56)	Moderate Risk (n = 14)	High Risk (n = 17)	P
Pre-culture antibiotic exposure				
Continually use	23 (63.9%)	6 (16.7%)	7 (19.4%)	0.999
Suspend 1 week before culture	23 (63.9%)	6 (16.7%)	7 (19.4%)	
No	10 (66.7%)	2 (13.3%)	3 (20.0%)	
Surgical intervention				
Fluoroscopy-guided biopsy	18 (56.3%)	7 (21.9%)	7 (21.9%)	0.425
Open surgery	38 (69.1%)	7 (12.7%)	10 (18.2%)	
SIRS				
Yes	15 (83.3%)	0 (0.0%)	3 (16.7%)	0.081
No	41 (59.4%)	14 (20.3%)	14 (20.3%)	
Infection site				
Spine	31 (58.5%)	13 (24.5%)	9 (17.0%)	0.028
Limb	25 (73.5%)	1 (2.9%)	8 (23.5%)	
WBC (10 ⁹ /L)	7.4 (6.2, 8.6)	5.4 (4.9, 7.1)	6.2 (5.2, 7.7)	0.017
NE%	72.4 (66.1, 79.6)	69.2 (52.3, 74.3)	70.4 (61.5, 74.0)	0.077
ESR	73.3 ± 4.8	49.6 ± 10.9	46.4 ± 8.3	0.011

Notes: Low risk: Positive culture result in both Manual homogenization and Manual mixture group; medium risk: Positive culture result only in Manual homogenization; high risk: Negative culture result in both Manual homogenization and Manual mixture group.

results in the manual homogenization group. Kim CJ et al showed that soft tissue was better than bone or microbiological diagnosis. Further analysis showed that the CRP of the soft tissue group was significantly higher compared to the bone group.⁶

Sepsis is a clinical syndrome caused by a dysregulation of the host response due to infection, often accompanied by systemic inflammatory response syndrome (SIRS) and life-threatening organ dysfunction. Mohammad Anas et al study showed that PCT might be a reliable indicator of sepsis in spinal cord injury patients. Meanwhile, they found that there were positive correlations between PCT and inflammatory indicators, such as CRP ($R^2=0.673$, $p<0.05$) and WBC ($R^2=0.110$, $p < 0.05$).¹⁸ M Sauer et al also showed that serum PCT correlates with the severity of sepsis among profoundly immunocompromised patients.¹⁹ The present study showed that, like patients with high expression of inflammatory factors, patients with SIRS were more likely to identify pathogenic microorganisms. SIRS was the most significant factor affecting patient culture results. Tissue homogenization could improve the culture positivity rate of patients without SIRS Tables 2 and 3, Figures 4 and 5. Inflammatory indicators and SIRS were essential factors that predict culture results of patients with bone and joint infection.²⁰ Compared with inflammatory indicators, SIRS is more straightforward, practical, and accessible to judge.

Several studies have shown that tissue homogenization could increase the culture-positive rate by breaking down biofilm composed of bacteria, proteins, and matrices and releasing more pathogenic microorganisms into the culture medium.^{13,16,21} Consistent with previous research, our study showed that the manual homogenization group's positive rate was significantly higher than the manual mixture group (80.5% vs 64.4%). Tissue homogenization could significantly increase the positive culture rate of patients without SIRS, Figure 5.

The 2015 Infectious Diseases Society of America Clinical Practice Guidelines suggest antibiotics should be suspended for 1–2 weeks unless the patient has a hemodynamic compromise or is accompanied by neurologic

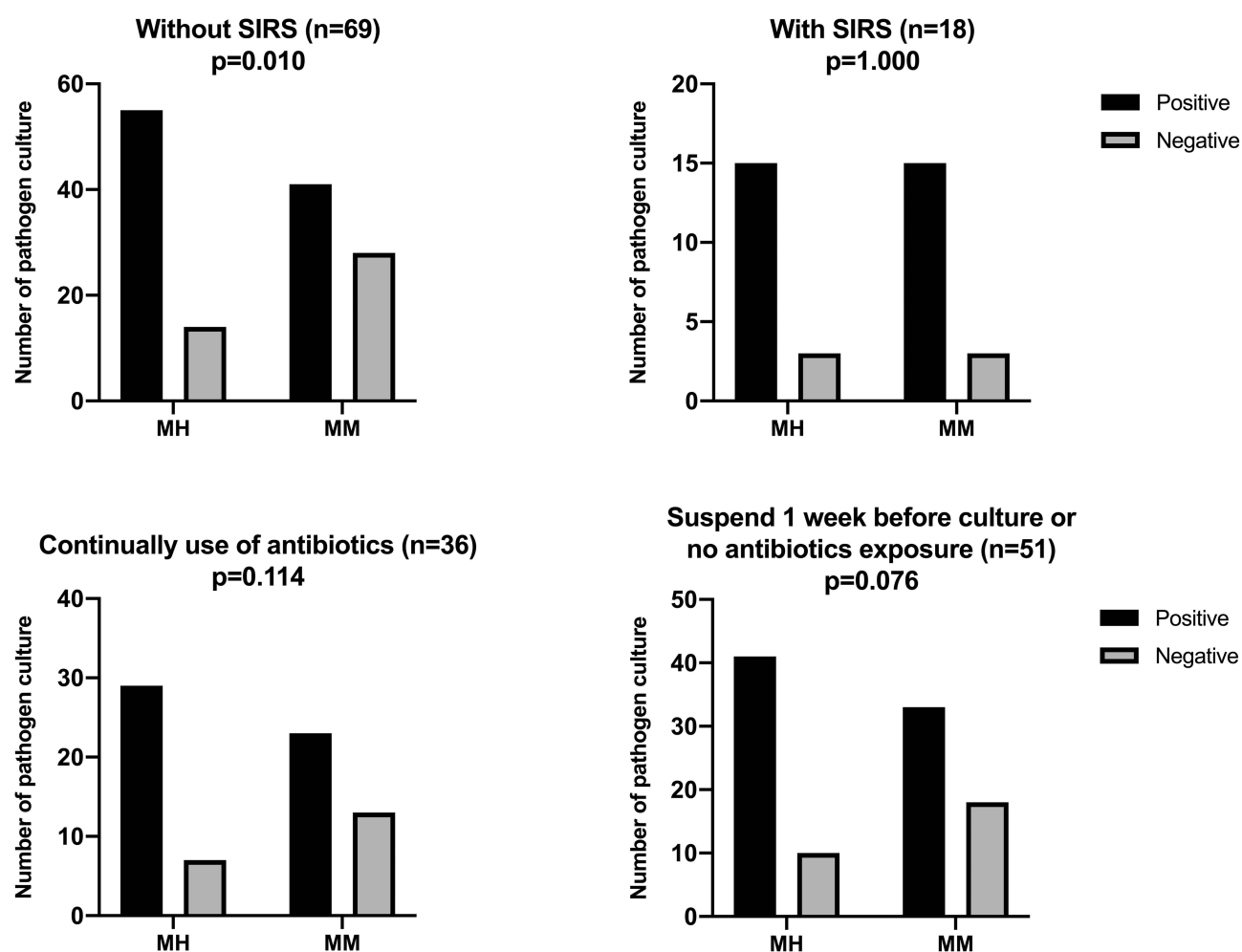


Figure 5 Subgroup analysis (Sepsis and Pre-culture antibiotic exposure).

symptoms.²² The impact of antibiotics on culture results was still controversial.^{8–10,17} Several studies showed that antibiotics can reduce the positive rate of culture.^{9,17} Russo et al's study showed that strictly following the UDIPROVE procedure could improve the positive rate of pathogenic culture. However, stopping antibiotics might lead to disease aggravation for patients with SIRS. Consistent with Lavery LA et al⁸ and Hirschfeld CB et al,¹⁰ there was no significant difference in the positive culture rate between patients with different pre-culture antibiotic exposures. This study treated patients with the following conditions with antibiotics before culture. Those who had been using antibiotics before hospitalization and those who had not used antibiotics before hospitalization but had SIRS.

Blood culture was influential for patients with bone and joint infections, especially for patients. Mylona et al's study showed that blood culture had an average positive culture rate of 58% for patients with pyogenic vertebral osteomyelitis.²³ Blood cultures play the most crucial role in pathogen identification in pyogenic vertebral osteomyelitis.²⁴

Metagenomic next-generation sequencing (NGS) was more sensitive to identifying pathogenic microorganisms. Hayder Hamad et al's study showed that polymerase chain reaction could identify pathogenic microorganisms more than blood culture.²⁵ Metagenomic next-generation sequencing was sensitive and accurate in detecting pathogenic microorganisms in prosthetic joint infection²⁶ and spinal infection.²⁷

There are limitations to this study. First, it is limited by its retrospective nature. However, our study provides valuable insight into establishing an effective procedure for identifying pathogenic microorganisms for bone and joint infection. Second, this was a single-center study with a relatively small sample size. A large-scale case should be carried out to validate these results. Third, there needs to be more in our present procedure. Some details need to be handled more

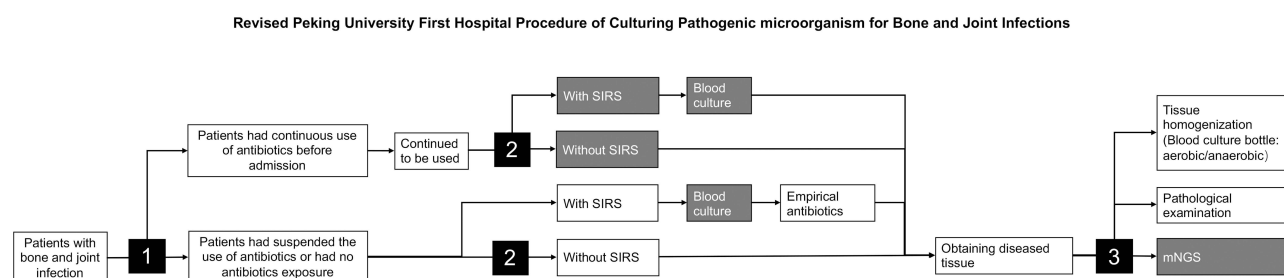


Figure 6 Revised Peking University First Hospital Procedure of Culturing Pathogenic microorganism for Bone and Joint Infections.

rigorously, such as managing antibiotic elution in patients without SIRS and ignoring blood culture and metagenomic next-generation sequencing. We propose a revision of the present procedure and validate its clinical efficacy in future studies [Figure 6](#).

Conclusions

Peking University First Hospital Procedure for Culturing Pathogenic microorganisms for Bone and Joint Infections was a practical approach for obtaining pathogenic microorganisms.

Summary

- 1) *Staphylococcus aureus* (18.2%) and *Staphylococcus epidermidis* (15.9%) were the two most common bacteria cultured in patients with bone and joint infection.
- 2) Patients with positive culture in the manual mixture group had significantly higher WBC ($p = 0.006$), NE% ($p = 0.024$), ESR ($p = 0.003$), CRP ($p = 0.020$) and IL6 (0.050) compared to patients with negative culture.
- 3) Patients without SIRS had a low positive culture rate (59.4%).
- 4) Tissue homogenization could significantly increase the positive culture rate of patients without SIRS.

Abbreviations

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

Data Sharing Statement

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics Approval and Consent to Participate

This study was a retrospective study. There was no follow-up requirement in this study. It was unnecessary to collect blood samples and other samples of the patients, and no additional examination was required. The research ethics committee of Peking University First Hospital approved the study protocol (2022 scientific research 081). The research ethics committee of Peking University First Hospital required neither patient approval nor informed consent to review patients' routine medical records in this study. Researchers would strictly keep patients' personal information confidential. Identifiable information would not be disclosed to persons other than research members unless permission was obtained from the patient. All research members were required to keep the identity of patients confidential. No patients' personal information would be disclosed when the research results were published. This study was conducted following the ethical standards in the 1964 Declaration of Helsinki.

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Disclosure

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