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ORIGINAL ARTICLE

Analysis of Pathogen Distribution and Antimicrobial Resistance in Bone and Joint Infections Among Young Children

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SUMMARY

Background: **This study aimed to analyze the distribution of pathogens and antimicrobial resistance in bone and joint infections (BJIs) among children under four years old.**
Methods: **A retrospective analysis was conducted on the clinical data of children under four years old who received inpatient treatment for BJIs at the Children's Hospital of Soochow University between January 2016 and December 2022. Results of bacterial culture and antimicrobial resistance were analyzed.**
Results: **Among the 131 patients, 52 (39.7%) showed positive bacterial culture results. There were Gram-positive (G+) bacteria detected in 38 strains (73.07%), Gram-negative (G-) bacteria in 12 strains (23.08%), and fungi in 2 strains (3.85%). Thirty-one strains of *Staphylococcus aureus* (*S. aureus*) were detected (59.62%), including 7 MRSA strains (22.58%). The resistance rate of G+ bacteria to penicillin was 72.97%, while resistance to erythromycin and clindamycin was approximately 50%. No resistance was found against linezolid, vancomycin, and teicoplanin. G- bacteria showed a sensitivity of 100% to carbapenems, including meropenem, ertapenem, and imipenem, a resistance rate of 91.67% to ampicillin-sulbactam, and relatively high resistance rates to compound sulfamethoxazole, ampicillin/sulbactam, and piperacillin.**
Conclusions: **Regional variations existed in the distribution of pathogens and antimicrobial resistance in children under four years old with BJIs. In our hospital, the most common pathogen is *S. aureus*, with MRSA accounting for approximately one-fourth of all *S. aureus* patients. Additionally, extended-spectrum β-lactamase (ESBL)-producing G- bacteria have been identified, underscoring the importance of careful consideration during empirical antibiotic therapy.**
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INTRODUCTION

Bone and joint infections (BJIs), encompass osteomyelitis and septic arthritis (SA) [1-3]. In recent years, there has been an increase in the incidence of BJIs. Clinical manifestations have become relatively atypical due to variations in causative pathogens and antibiotic usage,

especially in infants and children under four years old [4,5]. Antibiotics play a crucial role in the treatment of BJIs [6]. In recent years, due to the growing emphasis on antibiotic stewardship, there have been certain changes in the range of bacteria causing BJIs and the patterns of antibiotic resistance [7].

At present, there is a paucity of research investigating the distribution of pathogens and antibiotic resistance in infants and young children with BJIs. Therefore, this study was aimed to analyze the distribution of pathogens and antimicrobial resistance in patients with BJIs among children under four years old. The results obtained from this study offered valuable insights for the judicious use of antibiotics.

MATERIALS AND METHODS

Patients

The clinical records of patients under four years old with BJIs who were admitted to the Department of Orthopedics at the Children's Hospital of Soochow University for treatment between January 2016 and December 2022 were reviewed.

Inclusion criteria and exclusion criteria

Inclusion criteria were as follows: 1) Patients who met the diagnostic criteria of BJIs [8,9], irrespective of the affected site; 2) Patients with bacterial identification of blood, pus or tissue sample were performed.

Exclusion criteria included: 1) Patients with transient synovitis, rheumatism-related diseases or tumors; 2) Patients with postoperative iatrogenic infection; 3) Cases with incomplete antibiotic sensitivity results.

Identification of bacterial strains and testing of antibiotic susceptibility

Bacterial identification of blood, pus or tissue sample was performed using a MALDI-TOF mass spectrometer (BRUKER company). Isolated colonies were used to prepare bacterial suspensions, and antibiotic susceptibility testing was conducted either with the VITEK-2 compact fully automated system or the Kirby-Bauer method. Results were interpreted in accordance with the standards established by the Clinical and Laboratory Standards Institute (CLSI). Control strains, which were obtained from the National Clinical Testing Center of the National Health Commission, included *S. aureus* ATCC 25923, *Escherichia coli* (*E. Coli*) ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 51299 (resistant to aminoglycosides and vancomycin), and *Enterococcus faecalis* ATCC 29212 (sensitive to aminoglycosides and vancomycin).

Statistical methods

WHONET software (World Health Organization, Version 2021, http://www.whonet.org) was used for drug sensitivity analysis. Data were collected, organized, and cleaned using Microsoft Excel software (Microsoft Corporation, Version 2016, USA).

Medical ethics

This retrospective and descriptive study was approved by the Medical Ethics Committee of Children's Hospital of Soochow University (2021KS024). All data were anonymous, and the informed consent form was therefore waived.

RESULTS

Clinical data

A total of 131 children with BJIs under four years old were collected at our hospital. Among these patients, 52 (39.7%) were included in the study due to positive bacterial cultures and antibiotic sensitivity results. This group consisted of 23 patients with osteomyelitis, 15 patients with SA infection, and 14 patients with a combination of SA and osteomyelitis. There were 27 males and 25 females. The age ranged from 0.3 to 48.0 months, with a median of 11.68 months.

Microbiological analysis

A total of 38 strains were identified as Gram-positive (G+) bacteria, accounted for 73.07% of all patients. Among them, *S. aureus* was the most prevalent with 31 strains, accounting for 59.62% of all patients. There were 4 strains of *Streptococcus pneumoniae* (*S. pneumoniae*), accounting for 7.69% of all patients; while there was 1 each of *Staphylococcus epidermidis* (S. epidermidis), *Staphylococcus hominis* (*S. hominis*), and *Enterococcus faecium* (*E. faecium*), accounting for 1.92% each of all patients.

Gram-negative (G-) bacteria were found in 12 patients, accounting for 23.08% of all patients. Among the 12 patients, 5 (9.62%) were found to be positive with *Klebsiella pneumoniae* (*K. pneumoniae*); 5 (9.62%) were positive with *Salmonella*, including 2 of *Salmonella enteric* (*S. enteric*) and 1 each of *Salmonella typhi* (*S. typhi*), *Salmonella paratyphi* (*S. paratyphi*), and *Salmonella typhimurium* (*S. typhimurium*); furthermore, *E. coli* was identified in 2 patients (3.85%).

Fungi, specifically *Candida albicans* (*C. albicans*), were detected in 2 patients (3.85%).

Antibiotic resistance of pathogens

In G+ bacteria, none of the strains showed resistance to linezolid, vancomycin, and teicoplanin (Table 2). The resistance rate of G+ bacteria to penicillin was 72.97%, while approximately 50% of strains exhibited resistance to erythromycin and clindamycin. Moreover, there was a notable level of resistance observed for tetracycline, co-trimoxazole, benzylpenicillin, and levofloxacin.

For G- bacteria, carbapenems, including meropenem, ertapenem, and imipenem, demonstrated 100% sensitivity, while ampicillin-sulbactam exhibited a resistance rate of 91.67% (Table 3). Moreover, there were elevated

Table 1. Pathogens isolated from 52 children with BJIs.

Pathogen	Numbers	Age			Culture method		
		neonate	infant	young children	blood culture	biopyo-culture	both
G+ bacteria	38	10	17	11	9	23	6
S. aureus	31 (59.62%)	10	12	9	8	19	4
S. pneumoniae	4 (7.69%)	0	2	2	1	1	2
S. epidermidis	1 (1.92%)	0	1	0	0	1	0
S. hominis	1 (1.92%)	0	1	0	0	1	0
E. faecium	1 (1.92%)	0	1	0	0	1	0
G- bacteria	12	3	6	3	3	8	1
K. pneumoniae	5 (9.62%)	2	2	1	2	3	0
Salmonella	5 (9.62%)	0	3	2	1	3	1
E. coli	2 (3.85%)	1	1	0	0	2	0
Fungi	2	2	0	0	0	2	0
C. albicans	2 (3.85%)	2	0	0	0	2	0
Total	52	15	23	14	12	33	7

The bold values refer to the total number of Gram-positive bacteria, Gram-negative bacteria and fungi in the vertical direction.

Table 2. Comparison of antibiotic resistance in G+ bacteria.

Antibiotics	Resistant strains of G+ bacteria (n = 38)	Resistant strains of *S. aureus* (n = 31)	Resistant strains of *S. pneumoniae* (n = 4)	Antibiotic Resistance		
				MRSE (n = 1)	*S. hominis* (n = 1)	*E. faecium* (n = 1)
Cefoxitin screening test (positive)	8 (21.05%)	7 (22.58%)	-	P	N	-
Clindamycin	17 (44.74%)	12 (38.71%)	4 (100%)	R	S	-
Quinupristin/Dalfopristin	4 (10.53%)	0	4 (100%)	S	S	S
Linezolid	0	0	0	S	S	-
Vancomycin	0	0	0	S	S	S
Tetracycline	7 (18.42%)	3 (9.68%)	3 (75.00%)	R	S	-
Tigecycline	0	0	-	S	S	-
Levofloxacin	1 (2.63%)	0	0	S	S	R
Co-trimoxazole	8 (21.05%)	4 (12.90%)	4 (100%)	S	S	-
Penicillin G	27 (71.05%)	26 (83.87%)	0	R	S	S
Benzylpenicillin	8 (21.05%)	7 (22.58%)	-	R	S	-
Gentamicin	1 (2.63%)	0	-	S	S	R
Ciprofloxacin	5 (13.16%)	4 (12.90%)	-	R	S	-
Levofloxacin	6 (15.79%)	4 (12.90%)	0	R	S	R
Moxifloxacin	4 (10.53%)	3 (9.68%)	0	R	S	-
D test (positive)	7 (18.42%)	6 (19.35%)	-	P	N	-
Erythromycin	17 (44.74%)	11 (35.48%)	4 (100%)	R	R	-
Telithromycin	0	0	-	-	-	S

"-" - Indicates either not tested for resistance or the antibiotic is not applicable.
MRSE - methicillin-resistant Staphylococcus epidermidis, R - Resistance, S - Sensitivity, P - Positive, N - Negative.

Table 3. Comparison of antibiotic resistance in G- bacteria.

Antibiotics	Resistant strains of G- bacteria (n = 12)	Resistant strains of *K. pneumoniae* (n = 5)	Resistant strains of *E. coli* (n = 2)	Resistant strains of *Salmonella* (n = 5)
Cefoxitin screening test (positive)	0	0	0	-
Co-trimoxazole	4 (33.33%)	2 (40.00%)	2 (100%)	0
Gentamicin	8 (66.67%)	1 (20.00%)	2 (100%)	5 (100%)
Ciprofloxacin	3 (25.00%)	1 (20.00%)	2 (100%)	0
Levofloxacin	3 (25.00%)	1 (20.00%)	2 (100%)	0
Ampicillin	11 (91.67%)	5 (100%)	2 (100%)	4 (80.00%)
Cefotaxime	2 (16.67%)	1 (20.00%)	1 (50.00%)	0
ESBL test (positive)	2 (16.67%)	1 (20.00%)	1 (50.00%)	0
Ertapenem	0	0	0	0
Imipenem	0	0	0	0
Amikacin	0	0	0	-
Tobramycin	0	0	0	-
Ampicillin/Sulbactam	5 (41.67%)	1 (20.00%)	1 (50.00%)	3 (60.00%)
Piperacillin/Tazobactam	0	0	0	0
Cefotetan	0	0	0	-
Ceftazidime	0	0	0	0
Ceftriaxone	2 (16.67%)	1 (20.00%)	1 (50.00%)	0
Cefepime	1 (8.33%)	0	1 (50.00%)	0
Aztreonam	1 (8.33%)	1 (20.00%)	0	0
Cefazolin	1 (8.33%)	1 (20.00%)	0	-
Ceftizoxime	0	0	0	0
Cefuroxime	1 (8.33%)	1 (20.00%)	0	-
Cefoperazone/Sulbactam	0	0	0	0
Meropenem	0	0	0	0
Piperacillin	6 (50.00%)	1 (20.00%)	1 (50.00%)	4 (80.00%)

"-" - indicates intrinsic resistance of the strain to the class of antibiotics, and intrinsic resistant strains are not included in the total number of resistant strains.
ESBL - extended spectrum beta-lactamase, R - Resistance, S - Sensitivity, P - Positive, N - Negative.

resistance rates towards co-trimoxazole, ampicillin/sulbactam, and piperacillin. The results of *K. pneumoniae* and *E. coli* indicated relatively low resistance to aminoglycosides (such as gentamicin, amikacin, tobramycin). The resistance observed in *K. pneumoniae* and *E. coli* primarily stems from strains testing positive for Extended-Spectrum Beta-Lactamases (ESBL), namely ESBL-producing *K. pneumoniae* and ESBL-producing *E. coli*.

Antibiotic resistance of multidrug-resistant bacteria

There were 31 strains of *S. aureus* in total, out of which 7 strains were identified as methicillin-resistant Staphylococcus aureus (MRSA), accounting for 22.58% of the total. Among the 5 strains of *K. pneumoniae*, one strain was found to be ESBL-producing *K. pneumoniae*. Similarly, out of the 2 strains of *E. coli*, one strain was identified as ESBL-producing *E. coli*. Furthermore, one strain of *S. epidermidis* was classified as methicillin-resistant Staphylococcus epidermidis (MRSE). Subgroup analysis was performed specifically for the predominant *S. aureus* strains, and the findings are presented in Table 4.

DISCUSSION

Previous studies have extensively reported the distribution of pathogens and bacterial resistance in children with BJIs within local research areas. However, most of these studies included all children under 14 years old, which, although increasing the overall sample size, re-

Table 4. Comparison of antibiotic resistance between MSSA Group and MRSA group.

Antibiotics	Resistant strains of MSSA (n = 24)	Resistant strains of MRSA (n = 7)
	Number of resistant strains	Number of resistant strains
Cefoxitin screening test (positive)	0	7 (100%)
Clindamycin	7 (29.17%)	5 (71.43%)
Quinupristin/Dalfopristin	0	0
Linezolid	0	0
Vancomycin	0	0
Tetracycline	1 (4.17%)	2 (28.57%)
Tigecycline	0	0
Levofloxacin	0	0
Co-trimoxazole	4 (16.67%)	0
Penicillin G	19 (79.17%)	7 (100%)
Benzylpenicillin	0	7 (100%)
Gentamicin	0	0
Ciprofloxacin	4 (16.67%)	0
Levofloxacin	4 (16.67%)	0
Moxifloxacin	3 (12.50%)	0
D test (positive)	5 (20.83%)	1 (14.29%)
Erythromycin	7 (29.17%)	4 (57.14%)
Telithromycin	0	0

MSSA - methicillin-sensitive *Staphylococcus aureus*, MRSA - Methicillin-resistant *Staphylococcus aureus*.

sulted in relatively small sample sizes within each specific age group. Children under four years old with BJIs tend to exhibit more severe symptoms compared to their older counterparts based on our clinical practice. Consequently, this study prioritized addressing this age of group to mitigate the occurrence of sequelae.

Zhang TJ et al. [10] examined 188 children with BJIs in Zunyi over a period of 15 years. Among these patients, only 17 (9.04%) were under three years old. Similarly, Akinkugbe O el al. [11] reported only 16 (50%) children with BJIs were under five years old. We collected data from 131 patients under four years old, out of which 52 (39.7%) had positive cultures, providing a substantial advantage in terms of patient quantity. Additionally, our rate of positive cultures is similar to Filleron A et al. [12] (36.0%). However, Kao et al. [13] reported a culture positivity rate ranging from 52% to 82% in children with acute hematogenous osteomyelitis and suppurative arthritis. The age of the population included may be the main factor leading to this outcome. Bacterial resistance to antimicrobial drugs has emerged as a significant public health concern worldwide [14-16]. Our study revealed that *S. aureus* demonstrated a resistance rate exceeding 80% to penicillin, whereas resistance rates to clindamycin and erythromycin surpassed 35%. Resistance rates to moxifloxacin, levofloxacin, ciprofloxacin, co-trimoxazole, and tetracycline were approximately 10%. Notably, no resistance was observed against quinupristin/dalfopristin, linezolid, vancomycin, tigecycline, rifampin, gentamicin, and teicoplanin. These findings were consistent with the results reported by other scholars both nationally and internationally [10,17-19].

Agrawal et al. [20] found that MRSA accounted for 22% of the 61 children with BJIs caused by *S. aureus*. Our research findings were consistent with these results. Apart from MRSA, we also identified other multidrug-resistant bacteria which were rarely reported in previous literature focusing on pediatric BJI, including MRSE, ESBL-producing *K. pneumoniae*, and ESBL-producing *E. coli.* These findings indicate that despite some level of control over antibiotic misuse, there is still significant work to be done. Additionally, literature reports [21,22] have suggested the presence of vancomycin-resistant *S. aureus*. However, our study revealed that *S. aureus* strains were sensitive to vancomycin and linezolid, and no resistance to vancomycin was observed. Clinically, it is essential to enhance the detection and management of *S. aureus* resistance, promoting the rational and standardized use of antimicrobial agents [23]. Therefore, there were significant differences in the pathogenic bacteria and resistance patterns of BJIs in young

children. When prescribing empirical antibiotics, it is crucial to consider the local distribution of pathogenic bacteria and antibiotic resistance. Moreover, regular surveillance of multi-drug resistant bacteria in the local region is imperative to prevent treatment delays in children. In cases where the causative pathogen of purulent BJIs in children is uncertain, antibiotic selection can be guided by commonly encountered pathogens in the local area.

There were several limitations in our study. We only analyzed the patients in our hospital, which may not be representative enough. Therefore, caution should be exercised when generalizing the results of this study to other centers and geographical regions. Further investigation on large-scale, double-blind, high-quality randomized controlled trials to reach more comprehensive conclusions.

CONCLUSION

In summary, there were regional variations in the distribution of pathogens and antimicrobial resistance among young children with BJI. In our hospital, *S. aureus* was the predominant pathogen, with approximately one-fourth of all *S. aureus* patient infections due to MRSA. Moreover, ESBL-producing G- bacteria were also identified, underscoring the importance of careful consideration during empirical antibiotic therapy.

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Availability of Data and Material:
The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for Publication:
All authors read and approved the final manuscript.

Informed Consent:
This study was reviewed and approved by the Medical Ethics Committee of Children's Hospital of Soochow University (2021KS024). The data are anonymous, and the requirement for informed consent was therefore waived by the Medical Ethics Committee of Children's Hospital of Soochow University.

Declaration of Interest:
No potential conflict of interest was reported by the authors.

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