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ORIGINAL RESEARCH

Impact of Antibiotic Exposure Duration on Pathogen Detection in Periprosthetic Joint Infection

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Objective: Antibiotic exposure affects pathogen detection in periprosthetic joint infection (PJI). This study evaluated the impact of antibiotic duration before sampling on the diagnostic performance of microbiological cultures and metagenomic next-generation sequencing (mNGS).

Methods: We conducted a retrospective analysis of 153 patients with PJI treated at our center between January 2013 and March 2024. Patients who had discontinued antibiotics for at least 7 days before sampling and those with no history of antibiotic use were classified into the antibiotic-withdrawal group (AWD group). Based on the duration of antibiotic exposure, those who received antibiotics for ≤7 days before sampling was assigned to the short-term antibiotic group (STA group), while those with >7 days of continuous antibiotic use were included in the long-term antibiotic group (LTA group). By comparing microbiological culture and mNGS results across these groups, we analyzed how antibiotic duration before sampling affects etiological diagnosis in PJI patients.

Results: In the AWD group, microbial culture positivity (86.3%, 44/51) was comparable to mNGS (92.2%, 47/51; *P=0.338*). However, mNGS demonstrated superior positivity rates in both the STA (86.7% vs 70.0%, P=0.027) and LTA groups (76.2% vs 54.8%, P=0.039). Prolonged antibiotic use (>7 days) markedly reduced culture positivity (86.3% to 54.8%, *P=0.001*), whereas the decline in mNGS sensitivity was smaller (92.2% to 76.2%, *P=0.032*), indicating its greater resistance to antibiotic effects. Among culture-negative PJI cases, mNGS maintained robust diagnostic performance across all groups (CN-AWD: 57.1%; CN-STA: 66.7%; CN-LTA: 57.9%), with no significant differences observed.

Conclusion: Antibiotic use before sampling significantly impacts PJI pathogen detection. We recommend either: (1) sampling after ≥7 days without antibiotics, or (2) for patients on prolonged antibiotics (>7 days), combining microbial culture with routine mNGS to improve diagnostic accuracy.

Keywords: periprosthetic joint infection, microbiological cultures, metagenomic next-generation sequencing, prior use of antibiotics, pathogen diagnosis

Introduction

Periprosthetic joint infection (PJI) represents one of the most devastating complications following joint arthroplasty (JA), with reported incidence rates of 1–3% after primary procedures and 4–12% in revision cases,[1,2] accompanied by a concerning 20% mortality rate within 5 years.[3] PJI not only imposes substantial burdens on healthcare systems through prolonged hospitalizations, repeated surgical interventions, and extended antibiotic regimens, but also severely compromises patients' quality of life, frequently resulting in functional impairment and psychological distress.[4,5]

Microbial culture remains the cornerstone for PJI diagnosis and is the recommended method by major guidelines including those from the Infectious Diseases Society of America (IDSA) and the International Consensus Meeting (ICM) criteria.[6,7] However, despite the widespread use of culture-based methods, they still present several limitations. Recent

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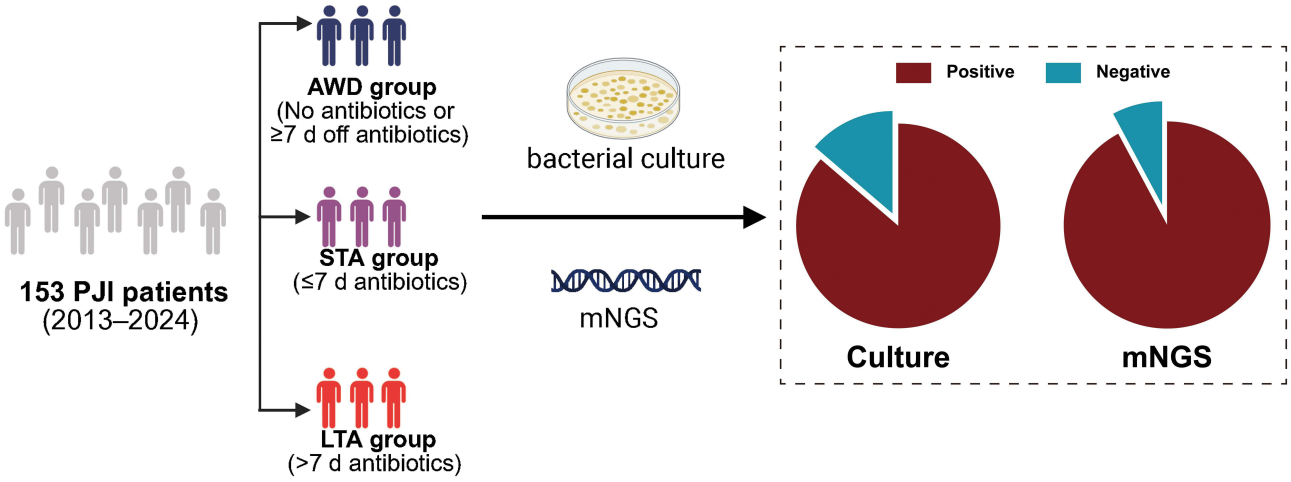
Graphical Abstract



literature reports that the prevalence of culture-negative PJI ranges between 9% and 42%,[8–10] with one significant contributing factor being prior antibiotic use before sample collection. This antibiotic exposure can temporarily reduce pathogen viability or inhibit growth, creating unfavorable conditions for accurate pathogen detection during the diagnostic window.[11,12] Studies demonstrate that even short-term antibiotic administration prior to sample collection can reduce culture positivity rates by 35.7%, significantly compromising diagnostic accuracy.[12] Consequently, current guidelines recommend discontinuing antimicrobial therapy for at least two weeks before obtaining specimens.[12] This presents a critical clinical dilemma, as many PJI patients receive empirical or prolonged antibiotic treatment before sample collection in cases where infection is suspected but not yet confirmed. Given this challenge, there is an urgent need for alternative diagnostic approaches capable of overcoming this limitation and improving pathogen detection in PJI cases.

In recent years, metagenomic next-generation sequencing (mNGS) has emerged as a promising diagnostic tool for infectious diseases.[13–15] This culture-independent approach does not rely on bacterial viability, enabling direct pathogen detection from clinical specimens through sequencing of microbial nucleic acid fragments.[14] Multiple studies have demonstrated the significant diagnostic potential of mNGS in PJI, particularly for culture-negative cases,[11,15,16] highlighting its utility in challenging diagnostic scenarios. However, despite these advantages, the performance of mNGS in patients with prior antibiotic exposure remains poorly understood. Theoretically, mNGS should be less affected by antimicrobial pretreatment since it can detect nucleic acids from nonviable microorganisms. Nevertheless, the short half-life of free microbial DNA from lysed pathogens may lead to low detectable pathogen sequences and potential false-negative results.

While existing studies have demonstrated antibiotic effects on both culture and mNGS diagnostic outcomes,[12,17] all current evidence is based on inconsistently documented antibiotic withdrawal periods prior to sampling. Crucially, a direct comparison of these methods under systematically defined durations of continuous antibiotic exposure is lacking. This gap limits the formulation of precise, evidence-based diagnostic protocols. To address this, we designed this retrospective study to specifically evaluate and compare the differential performance of culture versus mNGS across standardized antibiotic exposure intervals. Our work aims to provide the systematic evidence needed to optimize diagnostic strategies for PJI patients with a history of antibiotic therapy.

Methods

Patient Selection

Approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (Ethics No.: MRCTA, FMU ECFAH 2018 [026]), this study involved a retrospective review of 153 PJI cases treated at our institution from January 2013 to March 2024. Upon admission, all patients underwent complete diagnostic workups including serum inflammatory marker tests [white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] and synovial fluid analysis [synovial fluid polymorphonuclear neutrophil (SF-PMN) and synovial fluid WBC (SF-WBC)]. PJI diagnosis was confirmed by a multidisciplinary expert panel consisting of at least two senior infectious disease specialists, two senior orthopedic surgeons, and one senior microbiologist, following the 2018 ICM criteria.[7] The definition of rare pathogens was based on previously published studies.[18,19] All enrolled patients underwent both microbial culture and mNGS testing. The inclusion criteria were: (1) confirmed PJI diagnosis; (2) willingness to participate in the study; (3) complete clinical data; and (4) receipt of both microbial culture and mNGS testing. The exclusion criteria included: (1) concurrent malignancy; (2) coexisting other infectious diseases; (3) unclear history of prior antibiotic use; and (4) non-continuous antibiotic administration within 7 days before specimen collection (using sampling time as reference point).

Specimen Collection and Microbial Culture

All collected specimens were immediately transported to the microbiology laboratory, where different sample types underwent pretreatment prior to microbial culture. For tissue samples, they were minced and placed in an automated high-speed tissue homogenizer (JXFSTPRP24, Jingxin Industrial, Shanghai, China) with 1 mL of trypsin for thorough digestion and grinding. The homogenate was then inoculated onto Columbia blood agar plates (HBPM012415, Haibo Biotechnology, Qingdao, China) for cultivation under both anaerobic and aerobic conditions. Liquid specimens such as synovial fluid were directly injected into BACTEC Plus/F aerobic and anaerobic culture vials (Becton Dickinson, Franklin Lakes, New Jersey, USA) and incubated in an automated thermostat (Bactec 9050, Becton-Dickinson) for 14 days. For prosthetic components including intraoperative implants, we performed ultrasonic vibration treatment (40 Hz, 5 min, power density of 0.22 W/cm^2) in 400 mL of normal saline to disrupt surface biofilms. The resulting lysate was centrifuged at 10,000 × g for 15 minutes at 4°C, and the obtained precipitate was inoculated into BACTEC Plus/F aerobic and anaerobic culture bottles for 14-day incubation.

mNGS and Results Interpretation

The mNGS testing was performed according to previously described protocols,[20] with pre-analytical sample processing consistent with the microbial culture procedures. Briefly, genomic DNA was extracted and purified from specimens using the TIANamp Micro DNA Kit (DP316, Tiangen, China), followed by fragmentation into 200–300 bp short segments. Circularization amplification technology was employed to construct DNA nanoball libraries, which were then loaded onto high-throughput sequencing chips for paired-end sequencing analysis using the BGISEQ-500 platform (UWIC, China). Raw sequencing data underwent human sequence filtering (reference genome: Hg19) via the Burrows-Wheeler algorithm, with remaining data subsequently aligned and annotated against a microbial-specific database for taxonomic identification.

mNGS Interpretation in Negative Microbial Culture

For cases with negative microbial culture but positive mNGS results, the "true positive" status of mNGS findings was determined according to established validation protocols. Specifically, three criteria were sequentially applied: (1) the detected pathogen must be previously documented in literature as causally associated with osteoarticular infections, with clinical manifestations consistent with the patient's presentation; (2) verification through an independent third detection method (eg, 16S PCR) showing concordant results with mNGS; and (3) unanimous confirmation by a panel of ≥3 senior clinicians that targeted antimicrobial therapy against the identified pathogen yielded significant therapeutic improvement.

Statistical Analysis

Categorical variables were compared among the three groups using chi-square test or Fisher's exact test. One-way analysis of variance (ANOVA) was utilized for comparisons among the three groups when data were normally distributed, no post-hoc tests were performed following the non-significant ANOVA results. All analyses were completed employing SPSS software (version 26.0, IBM, USA). $P < 0.05$ signified statistical significance.

Results

Microbial Culture and mNGS results for Suspected PJIs

Our total cohort included 207 patients who were treated at our center from January 2013 to March 2024 and were diagnosed with PJI according to the 2018 ICM criteria.[7] Among these patients, 2 were excluded due to comorbid malignancies, 10 due to infections at other sites, 11 due to unclear antibiotic usage prior to sampling, and 37 due to non-continuous antibiotic use (within 7 days) before sampling as the reference point. Ultimately, 153 patients were included in this study (Figure 1). To minimize potential confounding factors, we used the sampling time as the reference point and categorized patients based on the duration of continuous antibiotic use prior to sampling. If there was an interruption in antibiotic administration exceeding 24 hours, the subsequent continuous usage period up to the sampling time was considered instead, ensuring standardized grouping criteria as much as possible. Based on the standardized antibiotic usage grouping criteria, 51 patients who had discontinued antibiotics for at least 7 days before sampling were assigned to the AWD group (including patients without any antibiotic use), 60 patients with continuous antibiotic use for ≤7 days before sampling were classified into the STA group, and 42 patients with continuous antibiotic use for >7 days were included in the LTA group (Figure 1).

No significant differences were observed among the three groups in baseline clinical characteristics, including age, sex, BMI, surgical site, CCI, ESR, CRP, SF-WBC, and SF-PMN levels ($P > 0.05$) (Table 1). Additionally, there were no statistically significant differences in the distribution of polymicrobial infections or rare pathogens among the groups ($P > 0.05$) (Table 1).

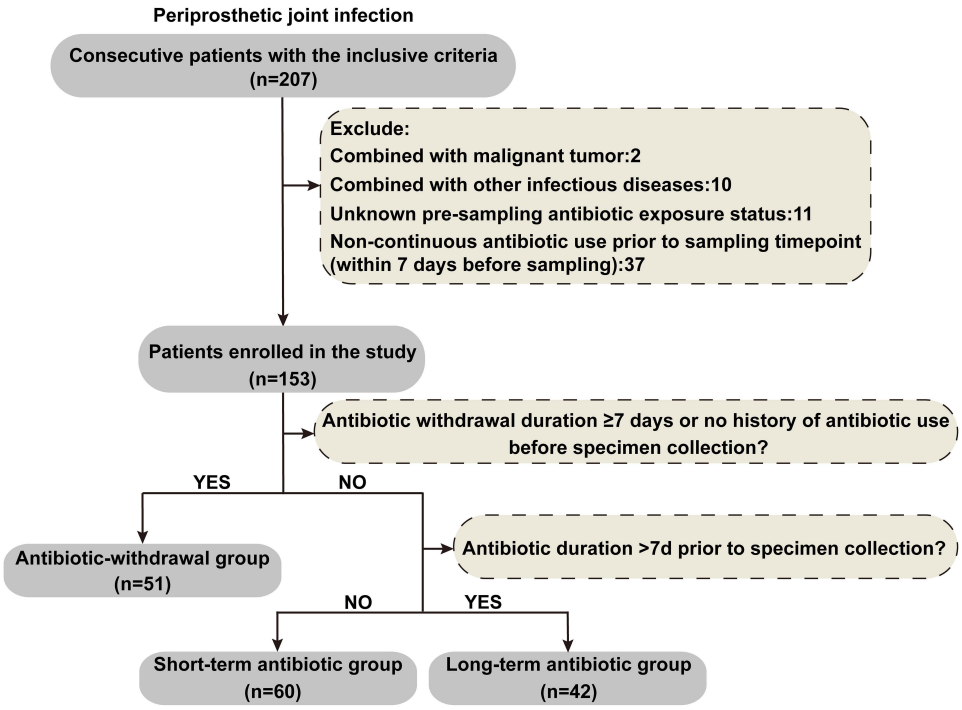


Figure 1 Flow chart of the inclusion, exclusion and grouping of PJI cases in this study.

Table 1 Comparison of Characteristics Between Culture Positive and Culture Negative Groups

Characteristics	AWD Group (n=51)	STA Group (n=60)	LTA Group (n=42)	P-Value
Age (years)	66.37±10.24	66.47±10.78	69.38±11.07	P=0.314
Gender (male/female)	20/31	25/35	17/25	P=0.966
BMI (kg/m^2)	23.98±3.02	24.68±3.55	23.98±3.39	P=0.449
Side (right/left)	27/24	33/27	24/18	P=0.921
Joint (hip/knee)	20/31	26/34	20/22	P=0.717
CCI	2.53±1.12	2.82±1.35	2.64±1.41	P=0.501
Polymicrobial infection (y/n)	16/35	18/42	13/29	P=0.987
Rare pathogen infection (y/n)	11/40	10/50	7/35	P=0.761
Laboratory data				
WBC (×10^9/l) (IQR)	6.75 (5.54,8.04)	6.15 (5.40,8.58)	7.27 (5.59,9.92)	P=0.260
ESR (mm/h) (IQR)	72.00 (34.00,91.00)	65.00 (46.25,88.75)	62.50 (43.25,83.00)	P=0.827
CRP (mg/l) (IQR)	38.00 (17.00,70.70)	35.50 (18.45,62.77)	26.57 (17.99,58.02)	P=0.057
SF-WBC (/mL) (IQR)	11119.00 (3564.00,34,392.00)	10,914.00 (6097.25,35,092.25)	8210.50 (3378.00,30,834.25)	P=0.694
SF-PMN (%) (IQR)	80.70 (70.00,89.10)	76.85 (66.25,89.38)	80.75 (69.95,90.00)	P=0.633

Abbreviations: AWD, antibiotic-withdrawal; STA, short-term antibiotic; LTA, long-term antibiotic; BMI, body mass index; CCI, Charlson comorbidity index; WBC, white blood cell count; CRP, C-reaction protein; ESR, erythrocyte sedimentation rate; SF, synovial fluid; PMN, polymorphonuclear neutrophils; IQR, interquartile range.

The Impact of Antibiotic Use on the Positivity Rates of Culture and mNGS

To evaluate the impact of preoperative antibiotic duration on microbial culture and mNGS performance, we compared the percentages of positive microbial culture and mNGS results across the three groups (Table 2 and Figure 2). As shown in Table 2 and Figure 2, in the AWD group, although mNGS demonstrated a higher detection rate (92.2%, 47/51) compared to conventional culture (86.3%, 44/51), this difference did not reach statistical significance (P=0.338). In contrast, the STA group exhibited a significant disparity, with mNGS achieving a markedly higher diagnostic positivity rate (86.7%, 52/60) compared to microbial culture (70.0%, 42/60) ($P = 0.027$). This trend remained pronounced in the LTA group, where mNGS maintained a 76.2% (32/42) positivity rate, still significantly surpassing microbial culture (54.8%, 23/42) ($P = 0.039$).

Significant differences in positivity rates were also observed across the three groups for each diagnostic method (Table 2). For microbial culture, antibiotic use ≤7 days prior to sampling significantly reduced the positivity rate (AWD vs STA: 86.3% vs 70.0%, $P = 0.041$), representing a 16.3% decline. When antibiotic duration exceeded 7 days (LTA group), the positivity rate dropped more substantially by 31.5% compared to the AWD group (86.3% vs 54.8%, $P = 0.001$). In contrast, mNGS maintained diagnostic stability with shorter antibiotic exposure: no significant difference was observed between the AWD and STA groups (92.2% vs 86.7%, $P = 0.353$). Only prolonged antibiotic use (>7 days, LTA group) significantly impacted mNGS performance, yielding a 19.6% reduction in positivity (92.2% vs 76.2%, $P = 0.032$). Critically, this decline was less pronounced than the 31.5% reduction seen with microbial culture under comparable antibiotic duration.

In summary, these findings demonstrate that mNGS exhibits greater resilience to preoperative antibiotic duration compared to conventional microbial culture.

Table 2 Comparison of Pathogen Detection Positive Rates Between Culture and mNGS

	AWD Group (n=51)	STA Group (n=60)	P-Value (*)	LTA Group (n=42)	P-Value (#)	P-Value (&)
Positive Culture, n (%)	44 (86.3%)	42 (70.0%)	P=0.041	23 (54.8%)	P=0.001	P=0.115
Positive mNGS, n (%)	47 (92.2%)	52 (86.7%)	P=0.353	32 (76.2%)	P=0.032	P=0.172
P-value	P=0.338	P=0.027		P=0.039		

Notes: *, AWD group vs STA group; #, AWD group vs LTA group; &, STA group vs LTA group.
Abbreviations: AWD, antibiotic-withdrawal; STA, short-term antibiotic; LTA, long-term antibiotic; P, positive; N, negative.

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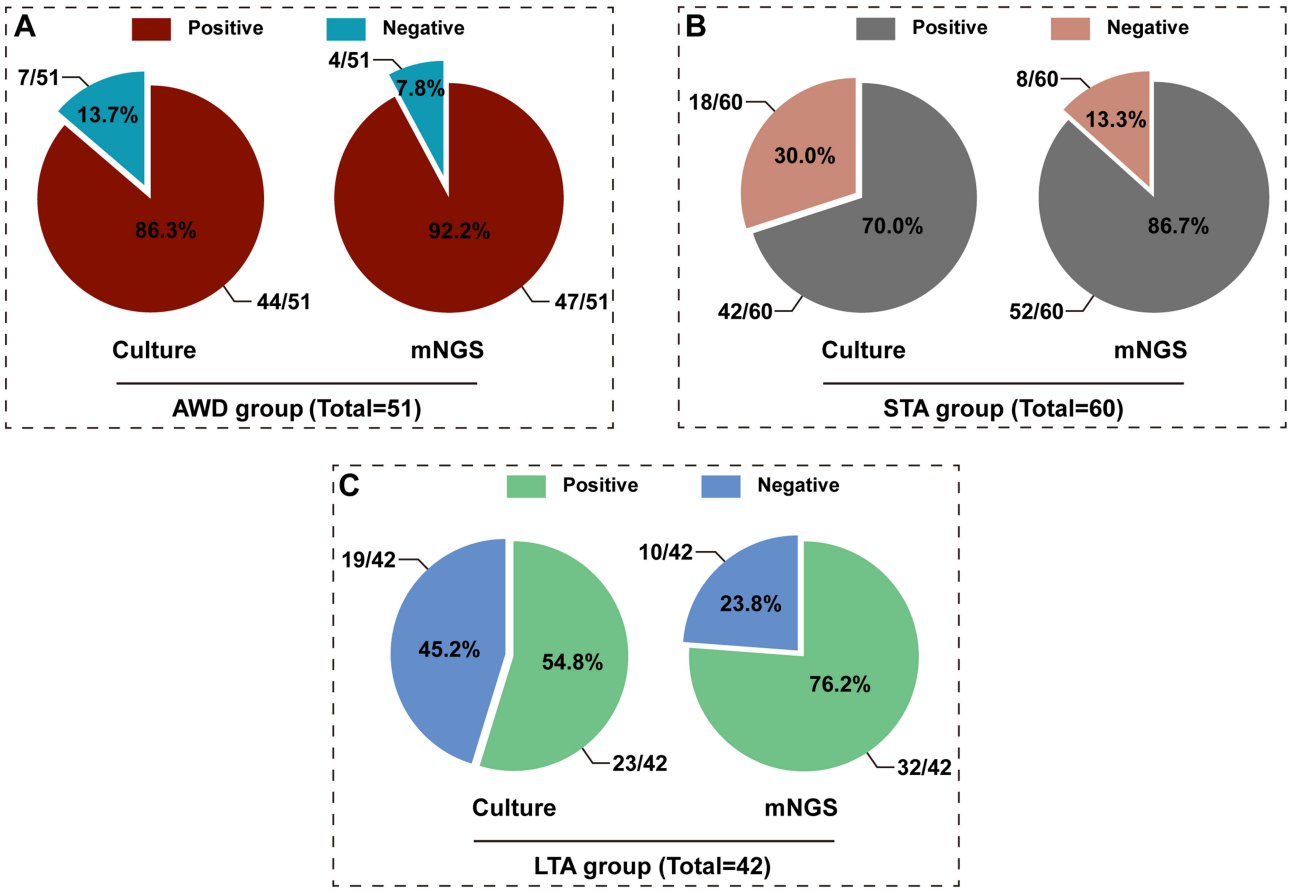

Figure 2 Comparison of pathogen detection positive rates between culture and mNGS for diagnosing PJI in the AWD (**A**), STA (**B**) and LTA group (**C**).

mNGS Results in Culture-Negative Patients Between Three Groups

Recent studies have reported that microbial cultures yield negative results in up to 42% of PJI cases, while mNGS maintains relatively high diagnostic positivity rates in culture-negative PJI (CN-PJI) patients. We therefore further investigated whether mNGS performance in CN-PJI cases was affected by the three different preoperative antibiotic exposure scenarios described above. As shown in Table 3 and Figure 3, among the 7 culture-negative patients in the AWD group (CN-AWD), mNGS demonstrated a diagnostic positivity rate of 57.1% (4/7). This did not differ significantly from the 66.7% (12/18) positivity rate observed in the 18 CN-STA patients (P = 0.673). This pattern persisted in subsequent comparisons: no significant differences were found between the CN-AWD and CN-LTA groups (57.1% vs 57.9%, P = 0.665) or between the CN-STA and CN-LTA groups (66.7% vs 57.9%, P = 0.582). We further investigated the distribution of microorganisms in mNGS-positive cases across these three CN-PJI groups (Supplementary Table 1). The analysis revealed that *Staphylococcus epidermidis* was most frequently identified in the CN-AWD group (2, 40.0%), whereas *Staphylococcus aureus* was the predominant organism in both the CN-STA (6, 42.9%) and CN-LTA (5, 41.7%) groups.

Table 3 Compare the Detection Positive Rates of mNGS in Culture-Negative Patients Among the Three Groups

	CN-AWD Group (n=7)	CN-STA Group (n=18)	P-Value (*)	CN-LTA Group (n=19)	P-Value (#)	P-Value (&)
mNGS			0.673		0.665	0.582
Positive, n (%) Negative, n (%)	4 (57.1%) 3 (42.9%)	12 (66.7%) 6 (33.3%)		11 (57.9%) 8 (42.1%)		

Notes: *, CN-AWD group vs CN-STA group; #, CN-AWD group vs CN-LTA group; &, CN-STA group vs CN-LTA group.
Abbreviations: CN, culture negative; AWD, antibiotic-withdrawal; STA, short-term antibiotic; LTA, long-term antibiotic.

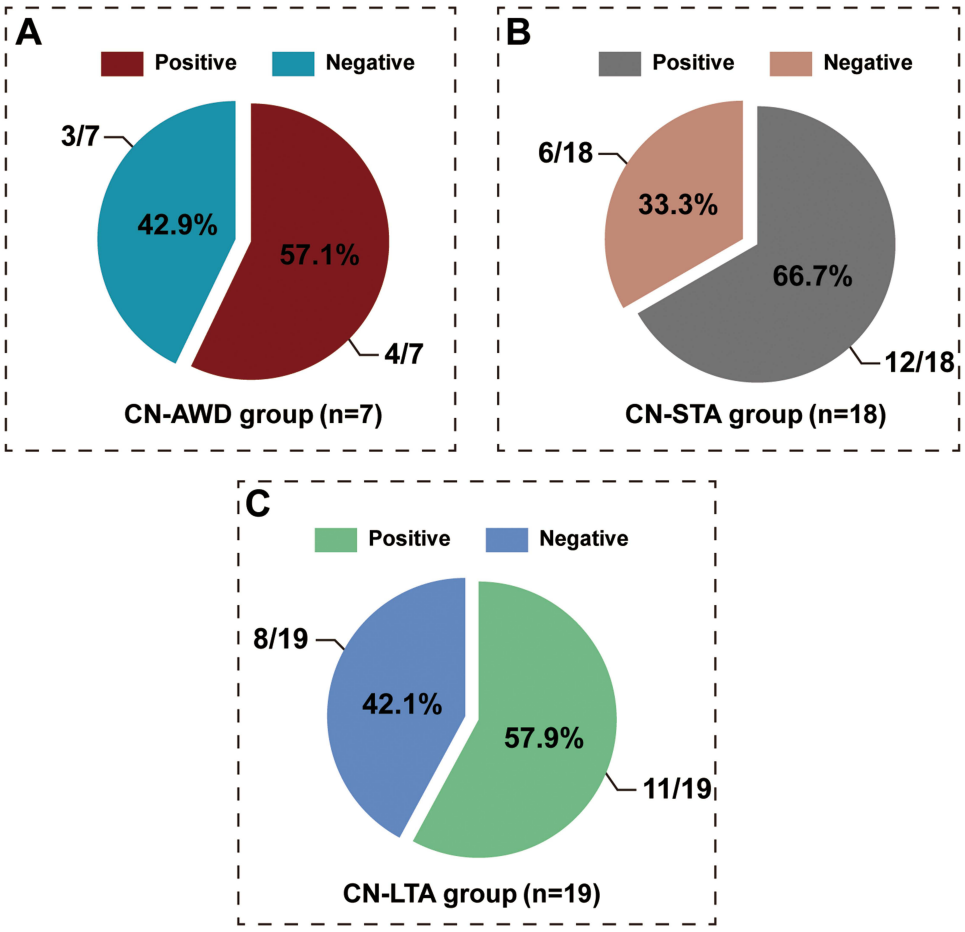

Figure 3 The detection positive rate of mNGS in culture-negative patients among the AWD (**A**), STA (**B**) and LTA group (**C**).

Overall, the above data suggest that the duration of antibiotics prior to sampling does not significantly affect the excellent diagnostic positivity rate of mNGS in patients with culture-negative PJI.

Discussion

PJI represents one of the most challenging complications following joint replacement surgery. Conventional microbial culture, regarded as the gold standard for pathogen identification, has significant limitations, including its dependence on viable pathogens and stringent culture requirements.[21,22] In recent years, mNGS, a culture-independent molecular diagnostic technique, has been widely applied for pathogen detection in PJI. Our preliminary studies demonstrated the excellent diagnostic performance of mNGS in PJI detection,[23–25] a finding consistently supported by other independent research, further validating the reliability of mNGS for PJI diagnosis.[26–28] Building upon our previous work, this study further evaluates the effectiveness of mNGS in identifying polymicrobial PJI pathogens and systematically compares its diagnostic performance with that of traditional microbial culture.

This study demonstrates that the duration of antibiotic use significantly impacts the positivity rate of conventional microbial cultures. When antibiotics were discontinued for ≥7 days before sampling (AWD group), the culture positivity rate reached 86.3%, whereas in patients with prolonged antibiotic use exceeding 7 days (LTA group), the positivity rate significantly dropped to 54.8% (P=0.001). These results suggest that antibiotic exposure may suppress pathogen growth, leading to false-negative culture results. However, mNGS maintained strong diagnostic stability and high sensitivity despite antibiotic interference. The mNGS positivity rates were 92.2% in the AWD group, 86.7% in the STA group (antibiotic use ≤7 days), and 76.2% in the LTA group. This aligns with previous research indicating that mNGS, by directly detecting microbial DNA rather than relying on viable bacteria, effectively mitigates the risk of false negatives

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caused by antibiotic intervention.[29] Furthermore, in culture-negative PJI patients, mNGS consistently achieved a detection rate of 57% to 67%, regardless of antibiotic duration, further highlighting its clinical value in diagnosing occult and challenging infections.

In terms of antimicrobial therapy, adjusting antibiotic regimens based on mNGS results in culture-negative but mNGS-positive PJI patients can significantly reduce reliance on empirical broad-spectrum treatment, minimizing unnecessary drug combinations and associated side effects. Multiple studies have demonstrated that mNGS accurately identifies mixed pathogens in complex infections, facilitating more targeted antimicrobial strategies, thereby improving infection control rates and shortening antibiotic duration.[30,31] Additionally, integrating mNGS proves particularly advantageous in high-risk populations, such as patients with prior multiple surgeries, suspected polymicrobial infections, or initially culture-negative cases.[32] Regarding turnaround time, research by Hao et al showed that traditional bacterial culture requires an average of 5.2 days, whereas mNGS takes only 1.3 days on average, contributing to faster diagnosis, improved recovery efficiency, and reduced hospital costs.[33] In clinical practice, the initiation of empiric antibiotic therapy prior to diagnostic work-up remains common in patients with suspected PJI. However, such early intervention may compromise the accuracy of microbiological cultures. Therefore, in case of suspicion of PJI, antimicrobial therapy should ideally be withheld until appropriate diagnostic sampling is completed. If withholding antibiotics is not feasible due to clinical sepsis or critical illness, microbial culture should be combined with mNGS to improve the etiological diagnosis and guide targeted antimicrobial therapy.

This study also has several limitations. First, this was a single-center retrospective study, which may introduce inherent biases such as selection bias and incomplete data recording. The retrospective design also limited our ability to control for confounding factors, and causal inferences should therefore be made with caution. Additionally, the relatively small sample size, due to the low incidence of PJI, may have reduced the statistical power for certain subgroup analyses. Second, although mNGS demonstrated a high detection rate in culture-negative cases, its sensitivity may vary across different sample types, and its resistance to antibiotic interference still requires further validation. Additionally, the high cost and technical demands of mNGS may restrict its widespread adoption in some healthcare institutions. However, with the continuous advancement of mNGS technology and the gradual reduction in costs, its application in PJI diagnosis will become more accessible. In the future, multicenter, large-scale prospective studies are needed to further evaluate the impact of antibiotic duration on mNGS diagnostic performance, thereby providing reliable evidence for optimizing antibiotic management strategies.

Conclusions

This study demonstrates that the duration of antibiotic use prior to sampling significantly impacts the positivity rate of pathogen detection in PJI patients. Compared to traditional microbial culture, mNGS maintains higher sensitivity under antibiotic interference, particularly showing crucial supplementary value in culture-negative cases. It is recommended that mNGS be adopted as a routine joint detection method in clinical scenarios where antibiotic withdrawal is not feasible. Despite a higher initial cost, the ability of mNGS to establish a definitive diagnosis can prevent more expensive downstream consequences of diagnostic uncertainty, such as extended hospitalization and revision surgery, proving cost-effective in the long term.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the First Affiliated Hospital of Fujian Medical University Ethics Committee (MRCTA, FMU ECFAH 2018 [026]).

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (Xinyu Fang, Email: fangxinyu0417@fjmu.edu.cn) upon reasonable request.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Disclosure

The authors declare that they have no conflicts of interest.

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