

EMPIRICAL ANTIBACTERIAL THERAPY FOR CULTURE-NEGATIVE PYOGENIC SPONDYLODISCITIS: FUNCTIONAL AND RADIOLOGICAL OUTCOMES AND THE ROLE OF TISSUE DIAGNOSIS

Abdul Satar¹, Muhammad Zahid Khan², Samir Khan Kabir²

How to cite this article

Satar A, Khan MZ, Kabir SK.
Empirical Antibacterial Therapy for
Culture-Negative Pyogenic
Spondylodiscitis: Functional and
Radiological Outcomes and the Role
of Tissue Diagnosis. J Gandhara Med
Dent Sci. 2026;13(4): 95-102.
<http://doi.org/10.37762/jgmids.13-4.984>

Date Submission: 21-08-2026

Date Revised: 04-09-2026

Date Acceptance: 05-09-2026

²Assistant Professor, Department of
Orthopedics and Spine Surgery,
Hayatabad Medical Complex,
Peshawar

Correspondence

¹Abdul Satar, Professor, Department of
Orthopedics and Spine Surgery,
Hayatabad Medical Complex,
Peshawar

☎: +92-333-9396005

✉: satardr@yahoo.com

INTRODUCTION

Pyogenic spondylodiscitis is an infection of the intervertebral disc and adjacent vertebral endplates that is generally considered within the clinical spectrum of native vertebral osteomyelitis. Although uncommon relative to degenerative spinal disorders, its clinical importance is disproportionate because delayed diagnosis may result in persistent pain, vertebral

ABSTRACT

OBJECTIVES

This study aimed to determine the efficacy of empirical antibacterial treatment of culture-negative pyogenic spondylodiscitis in terms of functional and radiological outcomes, with secondary assessment of pain, inflammatory response, treatment failure, recurrence, and requirement for surgery.

METHODOLOGY

A prospective observational cohort design was used at the Department of Orthopaedics and Spine Surgery, Hayatabad Medical Complex, Peshawar. Adults with clinical, biochemical, and magnetic resonance imaging findings compatible with native pyogenic spondylodiscitis, negative blood cultures, and no immediate indication for surgery were included. Patients with suspected tuberculosis, brucellosis, postoperative infection, malignancy, hemodynamic instability, or progressive neurological compromise were excluded. Empirical therapy was selected to cover staphylococci, streptococci, and aerobic Gram-negative bacilli. Functional status was measured using the Oswestry Disability Index (ODI), pain with the Visual Analogue Scale (VAS), and inflammatory response using C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Assessments were performed at baseline, 6 weeks, 3 months, and 6 months. Two readers independently classified the six-month MRI. Longitudinal outcomes were analysed using linear mixed-effects models.

RESULTS

Sixty-four patients entered the empirical-treatment cohort, and 61 completed 6-month follow-up. Mean age was 50.3 ± 12.0 years, and 39 patients (60.9%) were male. Mean ODI decreased from 62.7 ± 9.7 at baseline to 25.2 ± 13.4 at 6 months; the adjusted mean reduction was 37.38 points (95% CI 35.46–39.29; $p < 0.001$). Mean VAS decreased from 7.62 ± 0.62 to 2.23 ± 1.20 , corresponding to an adjusted reduction of 5.39 points (95% CI 5.17–5.61; $p < 0.001$). Median CRP declined from 70.4 mg/L to 5.7 mg/L, while mean ESR decreased from 75.8 ± 16.2 to 26.0 ± 17.2 mm/hour. Favorable MRI response was observed in 54/61 patients (88.5%; 95% CI 78.2–94.3), and overall treatment success was achieved in 56/61 (91.8%; 95% CI 82.2–96.4).

CONCLUSION

A structured antibacterial pathway improved patient outcome, supporting a non-biopsy approach when diagnosis is clear, blood cultures are negative, other serious conditions are excluded, and multidisciplinary monitoring is present. However, tissue diagnosis remains crucial for diagnostic uncertainty or empirical treatment failure.

KEYWORDS: Pyogenic Spondylodiscitis; Native Vertebral Osteomyelitis; Culture-Negative Infection; Empirical Antibacterial Therapy; Tissue Biopsy; Oswestry Disability Index; Magnetic Resonance Imaging

destruction, epidural extension, neurological impairment, deformity, prolonged antimicrobial exposure, and the need for operative treatment.^{1,2} Population-based data demonstrate an increasing burden of vertebral osteomyelitis, particularly among older adults and patients with diabetes, chronic kidney disease, immunosuppression, repeated healthcare exposure, or invasive procedures.³ Long-term follow-up studies further show that residual pain and neurological deficits

may persist even after infection control.⁴ The diagnosis is frequently challenging because clinical presentation is nonspecific. Severe or progressive spinal pain is the most consistent symptom, while fever may be absent and leukocytosis is neither sufficiently sensitive nor specific to exclude disease.^{1,2} ESR and CRP are more useful inflammatory markers and provide practical information during both diagnostic evaluation and treatment monitoring. MRI is the imaging modality of choice because it can identify vertebral marrow abnormalities, intervertebral disc involvement, endplate destruction, epidural extension, and paravertebral or psoas soft-tissue disease.^{1,5} Microbiological identification remains a central principle of management. The Infectious Diseases Society of America recommends obtaining appropriate blood cultures and, when a causative organism has not been established, performing image-guided aspiration or biopsy in patients with suspected native vertebral osteomyelitis whenever feasible.¹ In a hemodynamically stable patient with stable neurological findings, empirical antibacterial therapy is generally deferred while reasonable attempts are made to obtain microbiological confirmation. This strategy permits organism-directed treatment, facilitates antimicrobial stewardship, detects resistant pathogens, and assists in distinguishing bacterial infection from tuberculosis, brucellosis, fungal infection, malignancy, and inflammatory mimic.^{1,5} The practical limitation is that tissue sampling does not invariably establish an organism. In a 10-year study of image-guided biopsy, Maamari et al. demonstrated that diagnostic yield remains imperfect and is influenced by factors such as prior antimicrobial exposure and sampling characteristics.⁶ More recently, Winkler et al. evaluated 570 image-guided core biopsies and found positive microbiological cultures in 29.6%, although biopsy influenced clinical management in 37.5%.⁷ These findings demonstrate that tissue biopsy can be clinically valuable even when culture yield is modest, but they also explain why a substantial subgroup of patients remains culture-negative despite appropriate investigation. Culture-negative native vertebral osteomyelitis is therefore increasingly recognised as a distinct diagnostic and therapeutic challenge. A 2024 narrative review emphasised prior antimicrobial therapy, low pathogen burden, fastidious organisms, technical sampling limitations, and noninfectious mimics as major contributors to culture-negative disease.⁵ More recent work has highlighted the potential role of 16S ribosomal RNA polymerase chain reaction, next-generation sequencing, and microbial cell-free DNA testing in selected culture-negative cases, although accessibility, cost, interpretation, and specificity remain practical limitations.⁸ Clinical outcome data nevertheless suggest that culture negativity does not necessarily imply treatment failure. Kim et al. found that clinically

diagnosed culture-negative pyogenic vertebral osteomyelitis had outcomes broadly comparable with microbiologically confirmed disease.⁹ Yu et al. similarly reported comparable recurrence rates between culture-negative and culture-positive lumbar pyogenic vertebral osteomyelitis and emphasised the usefulness of pain, ESR, and CRP trajectories in monitoring response.¹⁰ Lee et al. subsequently reported a structured treatment protocol for 183 patients with culture-negative pyogenic vertebral osteomyelitis, including nonsurgical and surgical pathways selected according to neurological status, abscess burden, and mechanical stability.¹¹ A 2026 cohort study likewise found that culture-negative status was not independently associated with worse recurrence or mortality when patients received adequate treatment.¹² The key clinical issue is therefore not whether microbiological diagnosis is valuable. It is clear, however, whether an initial tissue diagnosis is indispensable for successful treatment in every patient with a convincing culture-negative pyogenic presentation. This question is especially relevant in resource-constrained settings, when biopsy is unavailable or delayed, when the procedure is technically difficult, when prior treatment may reduce yield, or when patients decline invasive sampling. At the same time, a non-biopsy pathway is only defensible if important alternative diagnoses are rigorously considered and predefined triggers exist for rescue biopsy or surgery when treatment response is inadequate. The study was undertaken to determine the efficacy of empirical antibacterial therapy for culture-negative pyogenic spondylodiscitis in terms of functional and radiological outcomes. Secondary objectives were to quantify longitudinal changes in pain and inflammatory markers and to determine rates of treatment success, treatment failure, recurrence, rescue tissue sampling, and unplanned surgery.

METHODOLOGY

This prospective observational cohort study was conducted in the Department of Orthopaedics and Spine Surgery, Hayatabad Medical Complex, Peshawar, Pakistan (October 2025–February 2026, with 6-month follow-up). The Institutional Research and Ethical Committee approved the study (Approval No. 2884, 30 September 2025). Sample size was based on an estimate of the favorable treatment-response proportion. Assuming an expected response of 90%, a 95% confidence level, and absolute precision of 8%, approximately 54 evaluable participants were required. Allowing for attrition, recruitment of at least 60 patients was targeted. Consecutive adults (≥ 18 years) with suspected native pyogenic spondylodiscitis were enrolled if they had new/worsening spinal pain, elevated ESR/CRP, characteristic MRI findings (disc and

adjacent endplate involvement), and ≥ 2 negative aerobic/anaerobic blood culture sets before empirical therapy. Patients with suspected tuberculous, brucellar, or fungal infection; postoperative/implant-related infection; malignancy; positive blood cultures; hemodynamic instability; uncontrolled sepsis; severe/progressive neurological deficit; major instability; or compressive epidural abscess needing urgent decompression were excluded. Demographics, symptom duration, comorbidities, prior infection/antimicrobial exposure, and neurological status were recorded, along with CBC, ESR, CRP, renal/liver function, and blood cultures. TB/brucellosis testing was added when clinically indicated; atypical cases were excluded from the pyogenic pathway. MRI of the affected region was obtained in all patients, with epidural/paravertebral involvement documented separately. Antibacterial therapy (typically IV vancomycin plus ceftriaxone, or cefepime for broader Gram-negative coverage; alternatives are available for allergy/renal impairment/resistant colonisation) targets *S. aureus* (including MRSA), streptococci, and Gram-negative bacilli, as per IDSA guidance. Patients responding clinically/biochemically were transitioned to oral therapy; total duration was ~6 weeks, extended as needed. Evidence for very early oral transition specifically in native vertebral osteomyelitis remains limited, and route changes were therefore made conservatively.¹³ Failure to improve prompted CT-guided or operative tissue sampling for microbiology/histopathology. Surgery was reserved for neurological deterioration, instability, deformity, uncontrolled infection, or intractable pain. Although early surgery may be advantageous in appropriately selected patients, the cohort was restricted to those suitable for initial conservative management. Assessments occurred at baseline, 6 weeks, 3 months, and 6 months, including ODI (0–100), VAS (0–10), ESR, and CRP.¹⁴ The primary outcomes were change in ODI and proportion with favorable MRI response at 6 months (assessed by two blinded readers as marked improvement/partial improvement/stable/progression). Secondary outcomes included VAS/ESR/CRP trends, treatment success/failure, recurrence, rescue biopsy, unplanned surgery, adverse events, and mortality.

Isolated persistent osseous MRI abnormalities did not constitute failure. Treatment success required completion of therapy without infection-related death, unplanned surgery, or recurrence at 6 months; failure was defined as progression requiring rescue diagnosis, major regimen change, unplanned surgery, or recurrence. Analyses used SPSS v27. Significance was set at $p < 0.05$.

RESULTS

Eighty-six patients with suspected pyogenic spondylodiscitis were assessed for eligibility. Twenty-two were excluded before entry into the empirical-treatment cohort: eight because tuberculosis was confirmed, three because brucellosis was identified, four because blood cultures established an organism requiring targeted treatment, two because of postoperative or implant-associated infection, three because an immediate surgical indication was present, and two because another diagnosis, including malignancy, was considered more likely. Sixty-four patients commenced the empirical-treatment pathway. All were available at the 6-week and 3-month assessments, while three were lost before final evaluation. Consequently, 61 patients (95.3%) completed the 6-month clinical and radiological assessment.

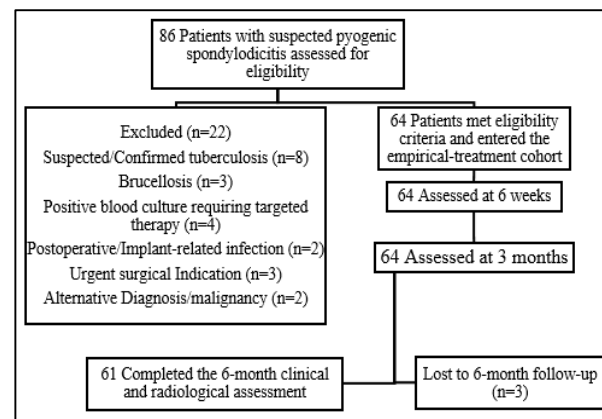
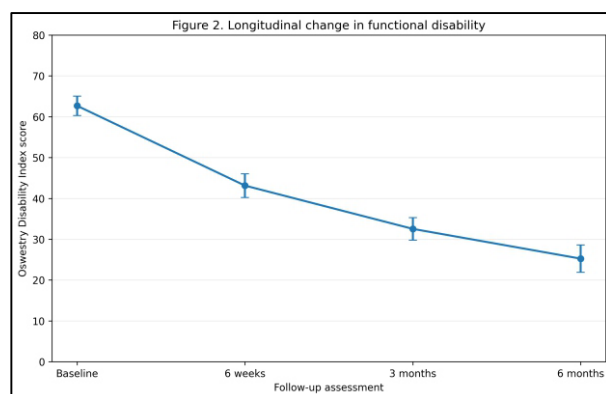


Figure 1: Participant Flow Through Screening, Empirical Treatment, and 6-Month Follow-Up.

Table 1: Baseline Demographic, Clinical, Laboratory, and Radiological Characteristics of the Empirical-Treatment Cohort (n=64).

	Characteristic	Value
Age, years, mean $\pm$ SD		50.3 $\pm$ 12.0
Gender	Male	39 (60.9)
	Female	25 (39.1)
Symptom duration, weeks, median (IQR)		4.4 (3.6 - 5.5)
Fever at presentation		14 (21.9)
Diabetes mellitus		19 (29.7)
Hypertension		28 (43.8)
Current smoking		11 (17.2)
Lumbar involvement		43 (67.2)
Thoracic involvement		16 (25.0)
Cervical involvement		05 (7.8)
Multilevel disease		12 (18.8)
Epidural inflammatory component		26 (40.6)
Paravertebral/psoas component		18 (28.1)
Baseline ODI, mean $\pm$ SD		62.7 $\pm$ 9.7
Baseline VAS, mean $\pm$ SD		7.62 $\pm$ 0.62
Baseline ESR, mm/hour, mean $\pm$ SD		75.8 $\pm$ 16.2
Baseline CRP, mg/L, median (IQR)		70.4 (49.4 - 88.7)

Abbreviations: SD, standard deviation; IQR, interquartile range; ODI, Oswestry Disability Index; VAS, Visual Analogue Scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

**Figure 2: Longitudinal change in Oswestry Disability Index. Points Represent Observed Means and Error Bars Represent Approximate 95% Confidence Intervals**

Pain severity showed a consistent decline, with mean VAS scores dropping from 7.62 $\pm$ 0.62 at baseline to 4.69 $\pm$ 0.88 at 6 weeks, 3.45 $\pm$ 1.08 at 3 months, and 2.23 $\pm$ 1.20 at 6 months. Mixed-effects analysis indicated a significant reduction of 5.39 points (95% CI 5.17–5.61; $p < 0.001$) over 6 months, reflecting meaningful improvements in function and symptoms. Mean ESR decreased from 75.77 $\pm$ 16.22 mm/hour at baseline to 42.94 $\pm$ 17.14 at 6 weeks, 32.37 $\pm$ 18.56 at 3 months, and 26.03 $\pm$ 17.18 at 6 months, yielding an adjusted reduction of 49.46 mm/hour (95% CI 47.03–51.89; $p < 0.001$). CRP levels dropped rapidly, with median values decreasing from 70.39 mg/L (IQR 49.39–88.73) at baseline to 17.25 mg/L (IQR 13.16–24.64) at 6 weeks, 9.03 mg/L (IQR 6.18–12.06) at 3 months, and 5.65 mg/L (IQR 3.81–7.85) at 6 months. Log-transformed mixed-effects modelling indicated a 6-month geometric mean ratio of 0.087 relative to baseline (95% CI 0.081–0.093; $p < 0.001$), signifying about a 91% relative reduction in CRP.

Table 2: Longitudinal Functional, Pain, and Inflammatory Outcomes

Outcome	Baseline	6 weeks	3 months	6 months	Adjusted 6 - month effect (95% CI)	p-value
ODI, mean $\pm$ SD	62.67 $\pm$ 9.71	43.13 $\pm$ 11.86	32.53 $\pm$ 11.23	25.24 $\pm$ 13.38	-37.38 (-39.29 to -35.46)	<0.001
VAS, mean $\pm$ SD	7.62 $\pm$ 0.62	4.69 $\pm$ 0.88	3.45 $\pm$ 1.08	2.23 $\pm$ 1.20	-5.39 (-5.61 to -5.17)	<0.001
ESR, mm/hour, mean $\pm$ SD	75.77 $\pm$ 16.22	42.94 $\pm$ 17.14	32.37 $\pm$ 18.56	26.03 $\pm$ 17.18	-49.46 (-51.89 to -47.03)	<0.001
CRP, mg/L, median (IQR)	70.39 (49.39 - 88.73)	17.25 (13.16 - 24.64)	9.03 (6.18 - 12.06)	5.65 (3.81 - 7.85)	GMR 0.087 (0.081 - 0.093)	<0.001

Mixed-effects models used time as a fixed effect and participant as a random intercept. CRP was log-transformed; its effect is reported as a geometric mean ratio (GMR).

At the 6-month MRI assessment, 37 of 61 patients (60.7%) demonstrated marked radiological improvement and 17 (27.9%) demonstrated partial improvement. Four patients (6.6%) had stable abnormalities without convincing evidence of active progression, while three (4.9%) demonstrated radiological progression. The combined favorable radiological response rate was therefore 54/61 patients (88.5%; 95% CI 78.2–94.3). Interobserver agreement for the four-category MRI response classification was substantial to excellent (weighted kappa=0.84). Soft-tissue inflammatory components generally resolved more clearly than

residual disc-space narrowing, endplate destruction, sclerosis, or marrow-signal abnormality. This pattern is clinically relevant because persistent osseous abnormalities may remain visible after infection control and should not be interpreted as treatment failure in isolation.^{15,16}

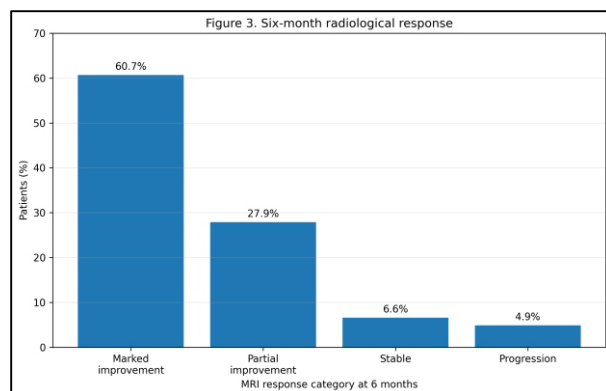


Figure 3: Distribution of Radiological Response Categories on 6 Month MRI

Overall treatment success was achieved in 56 of 61 evaluable patients (91.8%; 95% CI 82.2–96.4). Five patients met the prespecified definition of treatment failure. Three ultimately underwent operative intervention because of progressive neurological, structural, or infection-control concerns. Two underwent rescue tissue sampling because of inadequate clinical and biochemical response; outcome categories overlapped, and two of the five failures represented recurrence after an initial response. No infection-related death occurred during the 6-month follow-up period. Seven of 64 patients (10.9%) experienced an antibacterial adverse event requiring closer monitoring or regimen modification. Events consisted predominantly of reversible renal dysfunction, cutaneous drug reactions, or transient hematological abnormalities. A conservative sensitivity analysis that classified all three patients lost to final follow-up as treatment failures produced an overall success rate of 87.5% (56/64; 95% CI 77.2–93.5), indicating that the main conclusion was not dependent on complete-case classification.

Table 3: Clinical and Radiological Outcomes at 6 Months

Outcome	n/N	%age	95% CI
Overall treatment success	56/61	91.8	82.2–96.4
Favorable radiological response	54/61	88.5	78.2–94.3
Marked MRI improvement	37/61	60.7	—
Partial MRI improvement	17/61	27.9	—
Stable MRI appearance	04/61	6.6	—
MRI progression	03/61	4.9	1.7–13.5
Treatment failure	05/61	8.2	3.6–17.8
Unplanned surgical intervention	03/61	4.9	1.7–13.5
Rescue tissue sampling	02/61	3.3	0.9–11.2
Recurrence	02/61	3.3	0.9–11.2
Infection-related mortality	00/61	00	—
Antibacterial adverse event requiring modification	07/64	10.9	—
Sensitivity analysis: success with all losses treated as failures	56/64	87.5	77.2–93.5

Wilson confidence intervals are shown for principal binary outcomes. Individual failure categories may overlap.

DISCUSSION

The principal finding of this study is that a structured empirical antibacterial pathway was associated with substantial improvement in disability, pain, inflammatory activity, and MRI findings among carefully selected patients with culture-negative pyogenic spondylodiscitis. More than 90% of evaluable patients met the predefined criteria for overall treatment success, and 88.5% demonstrated a favorable MRI response at 6 months. Mean ODI improved by approximately 37 points and mean VAS by more than five points, accompanied by marked declines in CRP and ESR. These findings are consistent across functional, symptomatic, biochemical, and radiological domains. Current IDSA guidance recommends blood cultures and image-guided biopsy when the causative organism has not been established, particularly in patients who are neurologically and hemodynamically stable.¹ Tissue diagnosis can identify resistant pathogens, narrow antibacterial therapy, distinguish pyogenic disease from tuberculosis, fungal infection, or malignancy, and support antimicrobial stewardship. The present study addresses a narrower question: whether successful treatment is achievable in selected culture-negative

patients when initial tissue diagnosis is unavailable, deferred, or nondiagnostic. This distinction matters because the diagnostic yield of biopsy is variable. Winkler et al. reported positive cultures in 29.6% of 570 image-guided core biopsies, although the results altered management in 37.5% of cases.⁷ Maamari et al. similarly documented incomplete diagnostic yield and identified procedural and clinical factors influencing biopsy success.⁶ A negative or unobtained biopsy therefore does not eliminate the need to treat a convincing pyogenic infection, but imperfect culture yield likewise does not diminish the diagnostic value of sampling when it is feasible. The present findings are broadly consistent with prior culture-negative cohorts. Kim et al. reported a treatment-failure rate of 9.2% among clinically diagnosed culture-negative pyogenic vertebral osteomyelitis, compared with 17.3% among microbiologically confirmed cases, a difference that did not reach statistical significance.⁹ Yu et al. reported recurrence rates of 7.3% and 6.3% in culture-negative and culture-positive patients, respectively, and highlighted ESR, CRP, and VAS as informative markers of treatment response.¹⁰ In the present cohort, treatment failure occurred in 8.2% of patients and recurrence in 3.3%, figures that align closely with these earlier reports. Research by Lee et al. (2022) supports a stratified approach to culture-negative pyogenic vertebral osteomyelitis, successfully managing it non-surgically or surgically based on neurological deficit, abscess size, and mechanical stability.¹¹ Dogan et al. also found empirical antibiotics effective, suggesting a non-biopsy strategy for some patients.¹⁷ Sako et al. observed that while culture-negative vertebral osteomyelitis had milder inflammation, its recurrence and one-year mortality rates were similar to culture-positive cases when adequately treated; culture status did not independently predict outcomes.¹² Collectively, these studies indicate that prognosis hinges more on patient factors, anatomical severity, infection control, and treatment effectiveness than on culture status alone. This study's focus on functional recovery is critical. The significant drop in average ODI from around 63 to 25, mirrored by VAS score improvements, demonstrates substantial disability reduction. This highlights that successful treatment in spinal infection extends beyond just eradicating the infection. Gupta et al. reported persistent back pain and neurological deficits in many patients long-term, underscoring the value of patient-reported outcomes like ODI, which capture crucial clinical information beyond laboratory results.⁴ Inflammatory markers followed expected patterns, with CRP rapidly decreasing and ESR declining more gradually, consistent with previous findings supporting their use in monitoring.^{1,10} However, these markers should not be interpreted in isolation: a rising CRP with

worsening symptoms demands reassessment, while mild, persistent ESR elevation in an otherwise improving patient does not necessarily signal treatment failure. The empirical antibacterial regimen was designed to reflect the most probable bacterial spectrum. Park et al. identified methicillin-susceptible *S. aureus*, MRSA, Enterobacteriaceae, and streptococci as the predominant organisms in microbiologically confirmed hematogenous vertebral osteomyelitis and demonstrated substantial theoretical coverage with vancomycin combined with ceftriaxone, ceftazidime, or cefepime.¹⁸ This provides a rational basis for broad empirical coverage where clinically necessary, although regimens should always be adapted to local resistance patterns, renal function, prior healthcare exposure, allergy history, and individual risk of resistant organisms. The treatment-duration framework used in this study also warrants contextualisation. Bernard et al. demonstrated that 6 weeks of antibacterial therapy was noninferior to 12 weeks for clinical cure in microbiologically confirmed pyogenic vertebral osteomyelitis.¹⁹ Although this trial does not directly establish 6 weeks as optimal in culture-negative disease, it supports this duration as a reasonable initial framework when clinical and biochemical response is satisfactory. Longer durations have been used in other culture-negative cohorts, and extension remains appropriate when disease is extensive, drainage is inadequate, response is delayed, or diagnostic uncertainty persists.^{9,10,11} The radiological findings require careful interpretation. Although 88.5% of patients demonstrated a favorable MRI response, residual structural abnormalities were common. Ahn et al. showed that CRP correlates more closely with soft-tissue change and ESR with bony change during recovery, while Hecquet et al. similarly demonstrated discordance between radiological and clinical-biochemical recovery.^{15,16} Persistent endplate destruction, sclerosis, or disc-space narrowing should therefore not, in isolation, be classified as treatment failure in a patient who is otherwise improving clinically and biochemically. The 6-month MRI in this study was employed as a research outcome measure rather than as a recommendation for routine imaging in all responding patients. These findings indicate that tissue diagnosis, while important, is not indispensable for successful outcomes in every carefully selected patient, since a high proportion of patients achieved favorable outcomes without initial microbiological confirmation. Tissue diagnosis nonetheless remains essential whenever presentation is atypical, an alternative infectious or neoplastic process is plausible, resistant pathogens are a concern, or empirical therapy fails. The appropriate interpretation is therefore that an empirical pathway may be suitable for a defined subgroup of patients, not that biopsy should be routinely omitted. This position is

increasingly relevant given advances in molecular diagnostics. Pourghazi et al. (2026) described the potential of 16S rRNA PCR, next-generation sequencing, and microbial cell-free DNA assays to supplement conventional culture in native vertebral osteomyelitis.⁸ Techniques aimed at reducing culture-negative cases may improve targeted therapy after conventional diagnostic failures. Until they become standard, well-defined clinical pathways are essential when a causative organism remains unidentified. Treatment failures in five patients highlight the need for close monitoring; this pathway should not rely on a passive "treat and wait" approach. Symptoms like persistent severe pain, rising CRP, or new neurological findings should trigger swift tissue diagnosis and surgical intervention. In this group, biopsy and operative management were crucial to the treatment algorithm. These insights are particularly relevant in tertiary-care settings with limited access to image-guided biopsy, given that conditions like tuberculosis and brucellosis are significant differential diagnoses. Empirical antibacterial treatment should proceed with caution to avoid misclassifying tuberculous spondylodiscitis as culture-negative pyogenic disease, which could lead to delayed diagnosis and preventable complications. A risk-stratified approach is advisable: clinically stable patients with MRI-confirmed pyogenic spondylodiscitis and negative blood cultures may be considered for empirical therapy without immediate tissue diagnosis if closely monitored. Lack of clinical improvement should prompt tissue sampling and surgical consultation instead of continuing broad-spectrum therapy.

LIMITATIONS

This study has several limitations: its single-center, observational design limits generalizability and causal inference. The absence of a contemporaneous comparator group with systematic pretreatment biopsy means it cannot prove noninferiority of omitting tissue diagnosis. Without pretreatment tissue confirmation, diagnostic misclassification is possible, especially where atypical infections like tuberculous spondylodiscitis are common. The cohort was limited to patients suitable for initial conservative treatment, so findings may not apply to those with septic shock, neurological compromise, instability, or urgent surgical needs. The small number of treatment failures prevented reliable multivariable modeling. Finally, 6 months of follow-up may be insufficient to capture late recurrences or long-term functional issues.

CONCLUSIONS

Empirical antibacterial treatment effectively improved outcomes in select patients with culture-negative pyogenic spondylodiscitis, leading to significant reductions in disability, pain, and inflammation, along with improved MRI findings. After six months, approximately 90% of patients demonstrated overall treatment success and favorable radiological responses. This indicates that successful treatment without initial tissue diagnosis is feasible for clinically stable patients exhibiting characteristic imaging, negative blood cultures, carefully considered alternative diagnoses, and multidisciplinary monitoring. Nevertheless, tissue diagnosis remains vital when the diagnosis is uncertain, atypical infection or malignancy is suspected, resistant pathogens are a concern, or empirical treatment proves unsuccessful. Thus, while not always necessary, initial tissue confirmation remains a crucial diagnostic tool.

CONFLICT OF INTEREST: None

FUNDING SOURCES: None

REFERENCES

1. Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis.* 2015;61(6). doi:10.1093/cid/civ482. PMID: 26229122.
2. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med.* 2010;362(11):1022-1029. doi:10.1056/NEJMcp0910753. PMID: 20237348.
3. Issa K, Diebo BG, Faloony M, Naziri Q, Pourtaheri S, Paulino CB, et al. The epidemiology of vertebral osteomyelitis in the United States from 1998 to 2013. *Clin Spine Surg.* 2018;31(2). doi:10.1097/BSD.0000000000000597. PMID: 29135608.
4. Gupta A, Kowalski TJ, Osmon DR, Enzler M, Steckelberg JM, Huddleston PM, et al. Long-term outcome of pyogenic vertebral osteomyelitis: a cohort study of 260 patients. *Open Forum Infect Dis.* 2014;1(3). doi:10.1093/ofid/ofu107. PMID: 25734175.
5. Alavi SMA, Petri F, Mahmoud OK, Igwilo-Alaneme R, El Zein S, Nassr AN, et al. Culture-negative native vertebral osteomyelitis: a narrative review of an underdescribed condition. *J Clin Med.* 2024;13(19):5802. doi:10.3390/jcm13195802. PMID: 39407862.
6. Maamari JB, Tande AJ, Tai DBG, Diehn FE, Ross C, Lahr B, et al. Factors impacting the yield of image-guided biopsy in native vertebral osteomyelitis: a 10-year retrospective study. *Open Forum Infect Dis.* 2022;9(12). doi:10.1093/ofid/ofac616. PMID: 36570966.
7. Winkler WL, George IA, Gandra S, Baker JC, Tomasian A, Northrup B, et al. Diagnostic efficacy and clinical impact of image-guided core needle biopsy of suspected vertebral osteomyelitis. *Int J Infect Dis.* 2024;144:107027. doi:10.1016/j.ijid.2024.107027. PMID: 38670483.

8. Pourghazi F, Mahmoud O, Petri F, El Zein S, Suh GA, Matsuo T, et al. Integrating molecular and conventional diagnostics in native vertebral osteomyelitis: a narrative review. *J Bone Jt Infect.* 2026;11(3):373-385. doi:10.5194/jbji-11-373-2026. PMID: 42441123.
9. Kim J, Kim YS, Peck KR, Kim ES, Cho SY, Ha YE, et al. Outcome of culture-negative pyogenic vertebral osteomyelitis: comparison with microbiologically confirmed pyogenic vertebral osteomyelitis. *Semin Arthritis Rheum.* 2014;44(2):246-252. doi:10.1016/j.semarthrit.2014.04.008. PMID: 24951277.
10. Yu D, Kim SW, Jeon I. Antimicrobial therapy and assessing therapeutic response in culture-negative pyogenic vertebral osteomyelitis: a retrospective comparative study with culture-positive pyogenic vertebral osteomyelitis. *BMC Infect Dis.* 2020;20(1):939. doi:10.1186/s12879-020-05669-1. PMID: 33297994.
11. Lee SH, Kim J, Kim TH. Treatment guideline for patients with native culture-negative pyogenic vertebral osteomyelitis. *Clin Orthop Relat Res.* 2022;480(1):124-136. doi:10.1097/CORR.0000000000001866. PMID: 34128841.
12. Sako D, Sakamoto Y, Ota S, Takeuchi H, Tsukamoto Y, Yamashita S, et al. Impact of culture status on outcomes in vertebral osteomyelitis: a retrospective cohort study of 206 patients. *Global Spine J.* 2026 Jun 26:21925682261464162. doi:10.1177/21925682261464162. PMID: 42360355. [Online ahead of print].
13. Passerini M, Maamari J, Nayfeh T, Hassett LC, Tande AJ, Murad MH, et al. Early switch to oral antibiotic therapy for the treatment of patients with bacterial native vertebral osteomyelitis: a quaternary center experience, systematic review, and meta-analysis. *J Bone Jt Infect.* 2022;7(6):249-257. doi:10.5194/jbji-7-249-2022. PMID: 36532294.
14. Thavarajasingam SG, Vemulapalli KV, Vishnu SK, Ponniah HS, Sanchez-Maroto Vogel A, Vardanyan R, et al. Conservative versus early surgical treatment in the management of pyogenic spondylodiscitis: a systematic review and meta-analysis. *Sci Rep.* 2023;13(1):15647. doi:10.1038/s41598-023-41381-1. PMID: 37730826.
15. Ahn KS, Kang CH, Hong SJ, Kim BH, Shim E. The correlation between follow-up MRI findings and laboratory results in pyogenic spondylodiscitis. *BMC Musculoskelet Disord.* 2020;21(1):428. doi:10.1186/s12891-020-03446-4. PMID: 32616029.
16. Hecquet S, Verhoeven F, Aubry S, Prati C, Wendling D, Chirouze C, et al. Interest of follow-up radiological imaging in patients with pyogenic vertebral osteomyelitis. *J Clin Med.* 2021;10(12):2690. doi:10.3390/jcm10122690. PMID: 34207268.
17. Dogan M, Simsek AT, Yilmaz I, Karaarslan N. Evaluation of empirical antibiotic treatment in culture negative pyogenic vertebral osteomyelitis. *Turk Neurosurg.* 2019;29(6):816-822. doi:10.5137/1019-5149.JTN.25018-18.2. PMID: 31049918.
18. Park KH, Kim DY, Lee YM, Lee MS, Kang KC, Lee JH, et al. Selection of an appropriate empiric antibiotic regimen in hematogenous vertebral osteomyelitis. *PLoS One.* 2019;14(2). doi:10.1371/journal.pone.0211888. PMID: 30735536.
19. Bernard L, Dinh A, Ghout I, Simo D, Zeller V, Issartel B, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet.* 2015;385(9971):875-882. doi:10.1016/S0140-6736(14)61233-2. PMID: 25468170.

AUTHORS CONTRIBUTION

Abdul Satar - Concept & Design; Data Acquisition; Data Analysis/Interpretation; Drafting Manuscript; Critical Revision; Supervision; Final Approval

Muhammad Zahid Khan - Concept & Design; Data Acquisition; Data Analysis/Interpretation; Drafting Manuscript; Critical Revision; Supervision; Final Approval

Samir Khan Kabir - Concept & Design; Data Acquisition; Data Analysis/Interpretation; Drafting Manuscript; Critical Revision; Supervision; Final Approval

The authors accept responsibility for all aspects of the work and will ensure that any concerns regarding the accuracy or integrity of any part are properly investigated and resolved.



LICENSE: JGMDS publishes its articles under a Creative Commons Attribution Non-Commercial Share-Alike license (CC-BY-NC-SA 4.0).

COPYRIGHTS: Authors retain the rights without any restrictions to freely download, print, share and disseminate the article for any lawful purpose.

It includes scholarly networks such as Research Gate, Google Scholar, LinkedIn, Academia.edu, Twitter, and other academic or professional networking sites.