Infection and Drug Resistance

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SHORT REPORT

Efficacy and Safety of Contezolid as an Alternative to Linezolid for Treating MRSA Spinal Infections Following Linezolid-Induced Thrombocytopenia: A Single-Center Retrospective Study

Xiucui Zhang*, Jianrong Wang*, Xinghao Cao, Shijie Wang, Junxue Wang, Huili Huang, Bo Wei

Department of Infectious Diseases, Second Affiliated Hospital of Naval Medical University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Bo Wei, Department of infectious Disease, Second Affiliated Hospital of Naval Medical University, Shanghai, People's Republic of China, Tel +15921231996, Email weibo0816@163.com; Huili Huang, Department of Infectious Disease, Second Affiliated Hospital of Naval Medical University, Shanghai, People's Republic of China, Email huanghl1124@qq.com

Abstract: Methicillin-resistant Staphylococcus aureus (MRSA)-associated spinal infections (SI) typically require prolonged antibiotic therapy. While linezolid (LZD) demonstrates efficacy against MRSA-SI, its clinical utility is often limited by the risk of thrombocytopenia. Contezolid (CZD), a novel oral oxazolidinone, potentially presents a lower risk of myelosuppression; however, clinical evidence supporting its use in SI remains limited. This retrospective study evaluated patients with MRSA-SI who transitioned to CZD (800 mg orally twice daily) after developing LZD-induced thrombocytopenia. Clinical outcomes, adverse events, and platelet recovery were assessed. All cases were identified from the Department of Infectious Diseases at the Second Affiliated Hospital of Naval Medical University. The study period was between November 2022 and April 2024, with a follow-up period of 8 to 24 weeks. Eight patients were included (median age 61 years; range 40–78). The median LZD treatment duration was 12 days (range 7–14), resulting in a decline in platelet counts from 125–300 $\times 10^9$/L to 65–89 $\times 10^9$/L. Following transition to CZD (mean duration 66.6 ± 51.2 days; range 28–168), all patients achieved clinical success with no further platelet reduction. Platelet recovery to baseline or normal levels occurred within a mean of 8.25 ± 3.4 days (range 4–14). Three patients experienced gastrointestinal adverse events (nausea and vomiting), predominantly after the first dose. Our findings suggest that CZD may represent an effective and safe salvage therapy for patients with MRSA-SI who develop LZD-induced thrombocytopenia. Larger prospective studies are warranted to validate these preliminary findings.

Keywords: spinal infections, linezolid, thrombocytopenia, contezolid, MRSA

Introduction

SI encompass a complex and potentially debilitating spectrum of infectious pathologies, including vertebral osteomyelitis, discitis, and spinal epidural abscess. These conditions account for 2%–7% of all musculoskeletal system infections and predominantly affect adults over 50 years of age.[1,2] Without timely intervention, SI can progress to severe complications, including intractable pain, neurological deficits, and potentially paralysis, thereby significantly impairing patients' quality of life.[3]

Staphylococcus aureus represents the most commonly identified pathogen in SI. Methicillin-resistant *Staphylococcus aureus* (MRSA) accounts for approximately 45% of all *S. aureus* isolates from SI.[4] Patients with MRSA-associated SI demonstrate an increased likelihood of requiring surgical intervention and face higher rates of re-operation and complications.[5] Notably, neurological deficits occur in 53% of MRSA-associated SI cases, compared with 17% of cases involving methicillin-sensitive *Staphylococcus aureus* (MSSA).[6]

https://doi.org/10.2147/IDR.S574823
Received: 6 November 2025
Accepted: 18 March 2026
Published: 6 April 2026

The management of MRSA-associated SI typically involves a combined approach of antibiotic therapy and, when clinically indicated, surgical intervention. Although the standard treatment duration for spinal infections is six weeks, some experts advocate extended courses in high-risk patients, particularly those with MRSA infections, to optimize clinical outcomes.[7] Clinical guidelines recommend an early transition to oral antimicrobial therapy without compromising therapeutic efficacy.[3,7,8] Linezolid, characterized by high oral bioavailability, is frequently the preferred agent for sequential treatment of MRSA infections.[9] However, prolonged linezolid administration is associated with significant hematological toxicity, particularly thrombocytopenia, which has been reported in 7.5%–64.7% of treated patients.[3]

Given these limitations and adverse effects associated with current treatment options, there exists an urgent clinical need for novel oral antibacterial agents capable of effectively and safely treating MRSA-associated SI. Contezolid, a novel oxazolidinone-class antibacterial agent approved in China, has demonstrated comparable or superior in vitro antibacterial activity against S. aureus, including MRSA.[10] Phase III clinical trials have shown that contezolid is non-inferior to linezolid in treating complicated skin and skin structure infections caused by MRSA, while exhibiting a significantly lower incidence of platelet-related adverse events.[11] Consequently, the primary objective of this exploratory study was to evaluate the safety and efficacy of contezolid as a salvage therapy for patients with MRSA-associated SI who developed thrombocytopenia following linezolid treatment.

Materials and Methods

A retrospective review was conducted on patients with MRSA-associated SI who were admitted to the Department of Infectious Diseases at the Second Affiliated Hospital of Naval Medical University between November 2022 and April 2024. Written informed consent was obtained from all patients for this study before data collection. All patient data were anonymized prior to analysis.

Inclusion criteria comprised: (1) adult patients diagnosed with vertebral osteomyelitis according to Infectious Diseases Society of America (IDSA) criteria and microbiologically confirmed MRSA infection (identified through tissue/blood cultures and/or metagenomic next-generation sequencing [mNGS]); (2) initial treatment with intravenous or oral linezolid; (3) development of linezolid-associated thrombocytopenia, defined as a ≥25% decrease in platelet count from baseline or a platelet count below normal limits; and (4) subsequent transition to oral contezolid (800 mg twice daily) for at least 3 days after obtaining informed consent for contezolid treatment. Exclusion criteria were applied to patients who: (1) had confirmed co-infection with non-MRSA bacteria; or (2) presented incomplete key clinical documentation.

Treatment efficacy and adverse events were systematically documented. Magnetic resonance imaging (MRI) was utilized to evaluate therapeutic response before and after treatment. During contezolid therapy, complete blood cell counts and biochemical parameters were monitored weekly. Any adverse reactions were promptly addressed with appropriate treatment modifications. Efficacy outcomes were categorized as follows:

Treatment success: Complete resolution of clinical symptoms (fever and pain), normalization or return to baseline levels of inflammatory markers (WBC, CRP), and evident radiographic improvement compared to baseline.

Treatment failure: Occurrence, after at least 4 weeks of therapy, of persistent or worsening symptoms, unimproved or exacerbated physical signs, persistently elevated or rising systemic inflammatory markers, and absence of radiographic improvement on follow-up MRI.

Indeterminate outcome: Assigned when insufficient data precluded definitive classification.

Descriptive statistics were employed to summarize the demographic and clinical characteristics of the participants. Continuous variables were expressed as median and range or mean ± standard deviation, while categorical variables were presented as frequencies and proportions.

Results

A total of eight patients were included in this study (Figure 1), with a median age of 61 years (range 40–78 years), as summarized in Table 1. Three patients had underlying medical conditions, including two with type 2 diabetes mellitus and one with liver cirrhosis. The infection source was primarily associated with surgical procedures (4 cases) or acupuncture (2 cases). The lumbar spine was the most frequently involved site, affected in seven (87.5%) patients. Two patients underwent debridement surgery.

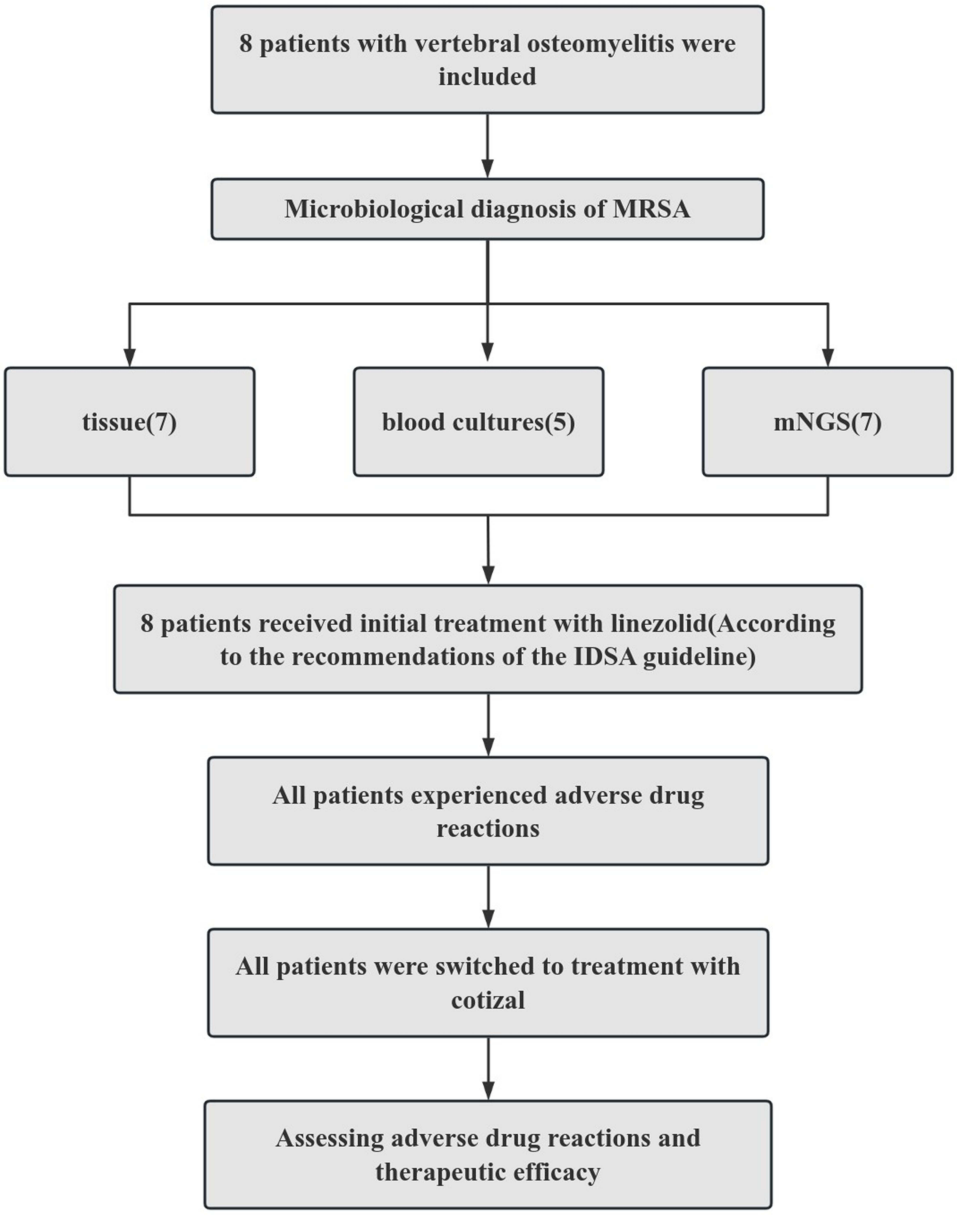

Figure 1 Flowchart of patient selection and study design.

All patients received linezolid at a standard dosage of 600 mg twice daily prior to the onset of thrombocytopenia. Of these, six patients transitioned from intravenous to oral linezolid, while the remaining two received intravenous treatment only. The median duration of linezolid therapy was 12 days (range 7–14 days), which resulted in a reduction in platelet counts from 125–300 × 10^9/L to 65–89 × 10^9/L (Table 2).

Upon detection of thrombocytopenia, treatment was switched to oral contezolid 800 mg twice daily. Contezolid was administered for a mean duration of 66.6 ± 51.2 days (range 28–168 days). All patients achieved clinical success, characterized by complete resolution of symptoms. Platelet counts stabilized following the transition to contezolid, recovering to baseline or normal levels within a mean of 8.25 ± 3.4 days (range 4–14 days). Laboratory parameters demonstrated marked improvement: white blood cell counts normalized to 2.3–7.3 × 10^9/L; CRP levels declined from 6.1–19 mg/L pre-treatment to 4.2–9.7 mg/L post-treatment; and platelet counts increased significantly from 65–89 × 10^9/L to 138–189 × 10^9/L (Table 2). MRI findings demonstrated substantial improvement compared with baseline. Three patients experienced transient gastrointestinal adverse events (primarily nausea and vomiting, CTCAE v5.0 Grade 1–2),

https://doi.org/10.2147/IDR.S574823

Table 1 Demographic of the Patients

No.	Gender	Age	Body Weight (kg)	eGFR* (mL/min/ 1.73m^2)	Underlying Disease	Classification of Vertebral Osteomyelitis	Method of MRSA Identification	Location of Infected Vertebrae	Debridement
1	Male	52	76	65	Alcoholic liver disease and cirrhosis	After acupuncture	Blood cultures	Thoracic 12	No
2	Male	65	85	92	Diabetes mellitus	After surgery for herniated disc	Tissue cultures and NGS	Thoracic 12~Lumbar 1	Yes
3	Male	78	70	65	Diabetes mellitus	None	Tissue cultures and NGS	Lumbar 3~5	No
4	Female	66	65	105	None	None	Tissue cultures and NGS	Lumbar 4~5	No
5	Male	40	82	98	None	After surgery for herniated disc	Tissue cultures and NGS	Lumbar 4~5	Yes
6	Male	51	52	116	None	After surgery for herniated disc	Tissue cultures and NGS	Lumbar 4~5	No
7	Male	64	76	97	None	After surgery for herniated disc	Tissue cultures and NGS	Lumbar 4~5	No
8	Male	58	61	123	None	After acupuncture	Blood cultures and NGS	Lumbar 3~5	No

Note: *eGFR: Estimated glomerular filtration rate prior to the administration of contezolid.
Abbreviation: NGS: Next-generation sequencing.

which typically occurred after the initial dose and resolved when contezolid was administered with food. No cases of peripheral or optic neuropathy were reported during the treatment period.

Discussion

This study suggests that for patients with MRSA spinal infections who develop thrombocytopenia during linezolid therapy despite guideline-concordant use, transitioning to contezolid may effectively mitigate adverse reactions while achieving satisfactory therapeutic outcomes.

Spinal infections account for 2–7% of musculoskeletal cases, with an incidence of 1 per 100,000–250,000 and a mortality rate of 2–4%. Major risk factors include prior spine surgery, diabetes mellitus, and immunosuppression. The incidence of SI is increasing due to the growing population of susceptible patients and improved diagnostic capabilities, with post-procedural cases now accounting for up to 30% of pyogenic spondylodiscitis.[1]

In spinal infections, *Staphylococcus aureus* emerges as the predominant pathogen identified, with MRSA comprising approximately 45% of all *S. aureus* isolates.[4] According to the clinical practice guidelines issued by the IDSA for the diagnosis and management of adult native vertebral osteomyelitis, linezolid is recommended as an appropriate anti-infective agent for spinal infections attributed to MRSA.[7]

Linezolid, an oxazolidinone antibiotic, exerts its bacteriostatic effect through specific binding to the 23S ribosomal RNA component within the 50S ribosomal subunit, thereby blocking the formation of the 70S initiation complex and halting subsequent bacterial protein synthesis.[12] Despite its therapeutic benefits, adverse events such as thrombocytopenia limit its clinical application.[13] The precise mechanisms underlying linezolid-induced thrombocytopenia remain incompletely understood. However, potential contributing factors include bone marrow suppression, inhibition of platelet release, oxidative stress, and immune-mediated reactions.[13] Monitoring platelet counts during linezolid therapy, particularly for extended durations, is critical, as evidenced by our study which demonstrated that thrombocytopenia occurred after a median of 12 days of treatment.

Table 2 Treatment Profiles and Laboratory Changes with Linezolid and Contezolid Therapy

Patient Number	Linezolid								Contezolid								Treatment Success
	Route	Linezolid Treatment Duration (day)	PLT (10^9/L)		WBC (10^9/L)		CRP (mg/L)		Contezolid Treatment Duration (day)	PLT (10^9/L)		WBC (10^9/L)		CRP (mg/L)		Time to PLT Recovery* (day)	
			Prior	After	Prior	After	Prior	After		Prior	After	Prior	After	Prior	After		
1	IV	10	125	65	8.5	2.1	125.0	19.0	120	65	139	2.1	2.3†	19.0	9.5	12	Yes
2	IV-to-Oral	14	145	73	12.3	4.9	79.3	19.1	28	73	155	4.9	5.6	19.1	9.7	7	Yes
3	IV-to-Oral	14	167	69	12.3	5.1	124.9	12.0	28	69	175	5.1	5.6	12.0	6.5	7	Yes
4	IV-to-Oral	14	244	75	9.9	4.7	118.5	11.0	42	75	142	4.7	5.8	11.0	7.3	5	Yes
5	IV	10	165	70	11.2	4.0	97.6	8.5	56	70	185	4.0	4.3	8.5	6.5	9	Yes
6	IV-to-Oral	7	171	69	11.9	8.5	102.4	8.2	63	69	138	8.5	7.3	8.2	7.9	4	Yes
7	IV-to-Oral	10	240	66	11.6	6.8	120.1	9.6	28	66	162	6.8	7.1	9.6	4.2	8	Yes
8	IV-to-Oral	14	299	89	10.9	5.3	13.1	6.1	168	89	189	5.3	6.7	6.1	8.5	14	Yes

Notes: * PLT recovery is defined as the return of platelet counts to baseline or normal levels. †Patient #1 had alcoholic cirrhosis (Child-Pugh B) with portal hypertension and hypersplenism. Before this spinal infection he was already leukopenic (lowest WBC 1.8 × 10^9/L); during SI treatment his WBC fell to 2.1 × 10^9/L prior to contezolid. After switching to contezolid his WBC gradually improved, though it remained below normal. ‡ prior, pre-treatment; after, post-treatment.

Abbreviations: PLT, platelet; WBC, white blood cell; RBC, red blood cell; CRP, C-reactive protein; bid, twice daily; IV, intravenous; PO, oral.

Contezolid, characterized by its trifluorinated non-coplanar structure, has been associated with a lower incidence of hematological side effects compared to linezolid.[14] The phase III clinical study of contezolid demonstrated a significantly lower incidence of hematological adverse events, with only 0.9% of patients experiencing hematological abnormalities and no reported cases of thrombocytopenia, compared to 8.8% in the linezolid group.[11] Pharmacokinetic studies have demonstrated substantial tissue penetration by contezolid. Studies in patients undergoing joint replacement surgery have shown adequate penetration of contezolid into bone and joint tissues following oral administration of 800 mg twice daily. In patients receiving total hip arthroplasty, the mean tissue-to-plasma concentration ratio measured 2 hours after dosing ranged from 0.21 ± 0.17 to 0.91 ± 0.37.[15] Similarly, Similarly, in patients undergoing total knee arthroplasty, the ratio ranged from 0.10 (±0.07) to 0.57 (±0.22) at the corresponding time point. These findings align with the drug's high oral bioavailability and volume of distribution of 0.61 L/kg.[16] In vitro susceptibility testing has shown that contezolid exhibits comparable antimicrobial potency to linezolid, vancomycin, and teicoplanin against clinical MRSA isolates, with a minimum inhibitory concentration (MIC) range of 0.5–4 mg/L.[10] Clinical reports have documented successful use of contezolid in treating severe MRSA infections, including pneumonia, bloodstream infections, and infective endocarditis.[17–19]

In the present study, transitioning patients from linezolid to contezolid due to thrombocytopenia resulted in significant improvement in platelet count recovery, with all patients eventually achieving normal platelet levels. Furthermore, only three patients reported transient gastrointestinal adverse events, suggesting a favorable safety profile for contezolid. All patients experienced complete resolution of pain, with normalization of white blood cell counts and CRP levels. MRI findings demonstrated significant absorption of lesions. These outcomes indicate excellent efficacy of contezolid therapy. Based on the findings of this study, contezolid may serve as a promising and valuable therapeutic alternative for MRSA-SI.

Several limitations of our study should be acknowledged. First, as a single-center study with a small sample size (n=8), this study is inherently subject to selection bias and its findings should be interpreted with caution regarding generalizability to broader populations. Second, substantial therapeutic heterogeneity was observed, including variations in treatment duration and concurrent use of surgical interventions with anti-infective regimens, which may have impacted observed outcomes. Finally, the lack of a comparator group, combined with its retrospective case-series design, precludes definitive conclusions about causality and complicates efforts to attribute therapeutic effects solely to contezolid.

Despite these limitations, our findings suggest the potential of contezolid as a possibly safe and effective alternative for the treatment of MRSA-associated SI in patients who have developed linezolid-induced thrombocytopenia, though further validation in larger cohorts is warranted. Future investigations should involve large-scale prospective studies to further determine whether contezolid can serve as a first-line treatment for patients with MRSA spinal infections, thereby providing new therapeutic options for this challenging patient population.

Conclusions

In this study, patients receiving linezolid for MRSA-associated SI who developed thrombocytopenia were transitioned to contezolid. Following this therapeutic switch, platelet counts improved and spinal infections resolved successfully. These findings suggest that contezolid may serve as an effective alternative for managing MRSA-associated SI in this high-risk population. Larger prospective studies are needed to confirm these preliminary observations and establish the role of contezolid in the therapeutic armamentarium against MRSA spinal infections.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Statement of Ethics

The research was conducted in compliance with the ethical guidelines set forth in the Declaration of Helsinki. This retrospective study was approved by the Medical Ethics Committee of Second Affiliated Hospital of Naval Medical University (2023-01-20). Written informed consent was obtained from the patients for the publication of their case details and any accompanying images.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

Xiucui Zhang and Jianrong Wang are co-first authors for this study. Huili Huang and Bo Wei are co-correspondence authors for this study. The authors declare that they have no conflicts of interest regarding this work.

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