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ORIGINAL RESEARCH

Hematological Safety of Contezolid versus Linezolid in Stage 5 Chronic Kidney Disease: An Active-Comparator New-User Retrospective Cohort Study

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Introduction: Contezolid is a novel oxazolidinone antibiotic approved for treating Gram-positive bacterial infections. Unlike linezolid, it lacks myelosuppressive toxicity, a potential advantage in patients with renal failure who are prone to anemia. However, data on hematologic safety of contezolid in this population remains limited. This study evaluates the hematological effects of contezolid in patients with renal failure.

Methods: This two-center retrospective cohort study employed an active-comparator new-user design to compare the hematological safety of contezolid versus linezolid in patients with renal failure. The primary outcome was the impact of contezolid and linezolid on hemoglobin levels. The secondary outcomes included microbial eradication, clinical cure rate and adverse reaction. Propensity score matching and multivariate logistic regression were used to adjust for confounding factors.

Results: A total of 290 patients were enrolled, with 122 in the contezolid group and 168 in the linezolid group. Severe anemia occurred in 14.75% of patients receiving contezolid versus 46.43% with linezolid ($P < 0.001$). No significant differences in platelet count ($P = 0.072$), clinical cure rate ($P = 0.878$), procalcitonin levels ($P = 0.432$), or microbial eradication rates ($P = 0.411$) were observed between the contezolid and linezolid groups after treatment. Multivariate-adjusted logistic analysis further illustrated that, compared to contezolid, linezolid was associated with a higher risk of severe anemia (adjusted odds ratio: 2.29; 95% CI: 1.64–3.35), with a treatment duration cutoff of 7 days.

Conclusion: Compared with linezolid, contezolid was associated with a lower risk of clinically significant hemoglobin decline among patients with renal failure.

Keywords: contezolid, linezolid, renal failure, myelosuppression, hemoglobin

Introduction

Staphylococcus aureus and group A *Streptococcus* are important Gram-positive bacterial pathogens in community-acquired pneumonia (CAP) and SSTI.[1,2] According to the China Antimicrobial Surveillance Network, approximately 30% of *Staphylococcus aureus* are resistant to methicillin. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is associated with prolonged hospital stays and increased mortality.[3] Methicillin-resistant coagulase-negative *Staphylococci* and

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Enterococci are clinically important multidrug-resistant Gram-positive bacteria. Currently, the drugs that are often used to treat multidrug-resistant Gram-positive bacteria include vancomycin, linezolid, and daptomycin. However, for patients with renal failure with Gram-positive bacteria infection, linezolid may be an optimal choice, as it is not excreted through the kidneys. Furthermore, patients can receive treatment at home because the bioavailability of linezolid tablets is reportedly almost 100%.[4]

Linezolid is the first oxazolidinone class of antibiotics that exerts its antibacterial effect by binding to the 23S site on ribosomal RNA of the bacterial 50S subunit, inhibiting the connection between mRNA and ribosomes and thus suppressing bacterial protein synthesis. Currently, linezolid is widely used for the treatment of infections initiated by multidrug-resistant Gram-positive bacteria, including methicillin-resistant coagulase-negative *Staphylococci*, penicillin-resistant *Streptococcus pneumoniae* (PRSP), vancomycin-resistant *Staphylococcus aureus*, and MRSA. Although linezolid has shown good efficacy in treating the related infections, its hematologic toxicity (thrombocytopenia and anemia) has raised concerns among physicians.[5,6]

Patients with renal failure are often anemic because of their primary disease.[7] These patients may experience worsening anemia with the use of linezolid. Although vancomycin does not cause anemia, it is challenging to determine the appropriate dosage in the absence of therapeutic drug monitoring. In China, vancomycin concentrations cannot be measured at most hospitals. Therefore, for patients with renal failure, physicians prefer to consider the risk of hematological toxicity and choose linezolid over vancomycin.

Patients with renal failure, particularly those with end-stage renal disease (ESRD), represent a high-risk population for SSTIs due to immune dysfunction, frequent vascular access, and comorbidities such as diabetes and peripheral vascular disease. A retrospective study of 433 ESRD patients from 1992–2000 reported an overall infection rate of 5.7 episodes per 1000 dialysis-days, with SSTIs accounting for 9% of all infections; below-knee infections—often classified as a subtype of SSTIs—contributed an additional 19.3%.[8] More recent US data from 2010–2020 show that patients with chronic kidney disease experience an SSTI incidence of 204.3 per 1000 person-years, one of the highest among major comorbidities.[9] These infections carry substantial clinical and economic consequences, including recurrent episodes, increased hospitalization, and elevated mortality, underscoring the need for safer antimicrobial options in this vulnerable population.

As a new type of oxazolidinone antibiotic, contezolid (generally called MRX-I) was approved for complicated skin and soft tissue infection in China in 2021. It has a higher therapeutic index for MRSA and PRSP than does linezolid and has a good post-antibiotic effect on MRSA and PRSP.[10] The development of contezolid was aimed at improving the safety of oxazolidinone antibacterial agents, especially to mitigate the problem of bone marrow cytotoxicity. Clinical studies and case series suggest that contezolid is not associated with an increased risk of thrombocytopenia or anemia.[11–13] Pre-clinical work has demonstrated that structural modifications in contezolid reduce its off-target inhibition of mitochondrial protein synthesis and myelosuppression in human hematopoietic progenitor cell assays compared with linezolid.[14,15] This mitochondrial-sparing profile provides a plausible mechanistic explanation for the lower incidence of hematologic toxicity observed in early clinical studies of contezolid.[16] Contezolid is excreted by the kidneys in less than 5% of cases, and dosage adjustment is not required in patients with renal insufficiency.[11,16] This pharmacokinetic profile suggests that contezolid may be suitable for use in patients with renal impairment. However, its potential impact on anemia in this population remains unclear. Although Xiong et al reported improved hematological safety after switching from linezolid to contezolid in five cases of drug-resistant tuberculosis, systematic evidence in patients with renal failure is still limited.[12] To date, no studies have been reported on contezolid in patients with renal failure. Thus, we aimed to compare the safety and efficacy of contezolid and linezolid treatment among patients with renal failure.

Materials and Methods

Study Design and Patient Selection

An active-comparator new-user designed cohort study was conducted at the Second Hospital of Shanxi Medical University and Shanxi Provincial People's Hospital. We identified all patients with chronic kidney disease (CKD) stage 5 between February 2020 and June 2024 who initiated treatment for a complicated skin and soft tissue infection with either contezolid (the study drug) or linezolid (the active comparator). All patients were treated in general wards and

none were admitted to the ICU. The Ethics Committee of the Second Hospital of Shanxi Medical University (2022–280) approved the study protocol. Owing to the retrospective nature of the study, the Ethics Committee of the Second Hospital of Shanxi Medical University waived the need to obtain informed consent.

The primary study outcome was the effects of contezolid/linezolid on hemoglobin level in patients with CKD. The secondary outcomes were the effects of contezolid/linezolid on platelet counts, clinical cure rates, microbial eradication rates, and adverse reactions. Our primary analysis was to emulate an intention-to-treat (ITT) analysis to assess any exposure effects of antibiotics use on the risk of severe anemia. The enrolled patients were divided into linezolid and contezolid groups. Treatment regimens included contezolid tablets (800 mg every 12 hours) or linezolid administered intravenously or orally (600 mg every 12 hours), without dose adjustments, as therapeutic drug monitoring was not available. The index date was defined as the date of the first dose of either contezolid or linezolid. Follow-up continued until 48 hours after the last dose. To establish a new-user cohort, we required that patients had not received any oxazolidinone antibiotics (including linezolid or contezolid) within a 30-day washout period prior to the index date. This was to ensure we captured incident, rather than prevalent, users and to minimize confounding by indication and severity.

The inclusion criteria were as follows: patients with chronic kidney disease (CKD) stage 5, were diagnosed with skin and soft tissue infection and administered linezolid injections/tablets or contezolid tablets, were aged ≥18 years, and had no alcoholic or viral hepatitis. The exclusion criteria were applied to patients with macrocytic/microcytic anemia, current sepsis, bleeding events, or hepatic failure; those with treatment duration shorter than 5 days; those who had received blood products during or within 1 week before linezolid/contezolid treatment; those undergoing treatment in combination with other antibiotics or simultaneous use of drugs impacting bone marrow, liver function or coagulation.

Treating physicians selected contezolid or linezolid according to routine clinical considerations; linezolid (IV/oral) was typically used when parenteral therapy was required, whereas contezolid (oral only) was used mainly in clinically stable patients. To mitigate confounding by indication we applied an active-comparator new-user design with propensity-score matching and multivariable adjustment.

Definition

CKD 5: glomerular filtration rate < 15 mL/min/1.73 m^2. Severe anemia was defined as hemoglobin < 60 g/L or a >20% decline from baseline. The absolute threshold was selected to represent a clinically consequential level of anemia, and the relative-decline criterion was included to capture substantial within-patient deterioration in a population with heterogeneous baseline hemoglobin levels.[17,18] To focus specifically on drug-induced normocytic anemia, patients with baseline microcytic anemia (mean corpuscular volume [MCV] < 80 fL) or macrocytic anemia (MCV > 100 fL) were excluded from the primary analysis. Reticulocyte count was analyzed to assess bone marrow erythropoietic activity, with reticulocyte production index calculated to account for the degree of anemia. The frequency of dialysis for patients undergoing peritoneal dialysis was 3–5 times per day, while for patients undergoing hemodialysis was three times per week. Clinical cure was defined as the resolution of infection-related symptoms (such as fever, pain, cough), while microbial eradication was defined as a negative culture (wound culture) following treatment.

Data Collection

Clinical information collected from the hospital information system included sex, age, underlying diseases, site of infection, responsible pathogens, length of linezolid/contezolid treatment, concomitant drugs administered, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, international normalized ratio (INR), white blood cell count, neutrophil count, platelet count, hemoglobin level, total bilirubin level, transaminase level, creatinine level, C-reactive protein level, and procalcitonin level. All laboratory tests were performed from 48 hours prior to linezolid/contezolid administration and were repeated every 2–3 days during therapy. The baseline was defined as 48 hours before the initiation of contezolid or linezolid treatment, and post-treatment values were defined as the last available measurements obtained within a standardized window of 48 hours after the final dose. To minimize the influence of hemodilution, hemoglobin measurements were obtained prior to hemodialysis or when patients were at their clinical dry weight.

Statistical Analysis

Statistical descriptions on quantitative variables were shown as medians and interquartile ranges or means and standard deviations. On a case-by-case basis, the chi-square test was adopted to perform univariate comparisons for qualitative variables. Similarly, Student's *t* test or the Kruskal–Wallis *H*-test was used for continuous variables. Multiple imputation was used to impute the missing C-reactive protein, procalcitonin (PCT), transaminase level, PT, APTT, fibrinogen and INR (The proportion of missing data was below 10%). To compare parameters pre- and post- medication, the paired samples Wilcoxon test was performed. Propensity score matching (PSM) method was used to adjust for demographic data (age, sex and baseline hemoglobin level) between the linezolid group and contezolid group, using a 1:2 match ratio. A caliper was set of 0.02. Balance was assessed using standardized mean differences (SMD), with values less than 0.1 indicating adequate balance. We intentionally used a parsimonious propensity-score model for matching to avoid overfitting and excessive loss of sample size in this retrospective cohort. Additional clinically relevant variables (eg, CRP, dialysis modality, and other treatment-related factors) were evaluated in post-matching regression models to improve robustness while maintaining match quality. Multivariate-adjusted logistic analysis was used to calculate the odds ratio (OR), with a 95% confidence interval (CI), of the association between medication and the risks of severe anemia. Dummy variables were created to represent the treatment regimens, with contezolid therapy serving as the reference category. The multivariable models were adjusted for the following variables: Model 1 was adjusted for treatment duration and C-reactive protein levels. Model 2 was adjusted for model 1 plus baseline hemoglobin level and renal replacement therapy (peritoneal dialysis or hemodialysis). Multicollinearity among independent variables in the multivariate logistic regression models was assessed using the variance inflation factor (VIF), with values >10 indicating severe multicollinearity requiring model adjustment.

Two sensitivity analyses were conducted. First, to minimize the impact of acute, non-drug-related hemoglobin fluctuations, including those due to bleeding or hemodialysis-related factors (eg, residual blood in the dialysis circuit or hemolysis), and considering that most patients in the cohort underwent routine blood testing every 2–3 days, individuals with a ≥10% reduction in hemoglobin levels within a 3-day period were excluded. Second, as older age is a well-established risk factor for renal anemia, we repeated the analysis after excluding participants aged < 55 years.[19,20] Adjustments for multiple testing were not applied in the subgroup analyses; accordingly, these findings should be regarded as exploratory. The optimal cutoff point of occurrence of severe anemia was determined using the receiver operating characteristic (ROC) curve.

All statistics were calculated using xsmartanalysis software (retrieved from https://www.xsmartanalysis.com). $P < 0.05$ was considered statistically significant.

Results

A total of 290 eligible patients were included in the study, comprising 122 in the contezolid group and 168 in the linezolid group, which together constituted the primary (unmatched) cohort. To reduce potential confounding, PSM was conducted, yielding a matched cohort of 272 patients (122 contezolid and 150 linezolid). After PSM, all matched covariates (age, sex, baseline hemoglobin) achieved good balance (post-match SMD range 0.02–0.03, Supplementary Table S1). The initial comparative analysis of outcomes (Primary and Secondary Outcome in the Primary Cohort and 3.2) was performed using the primary cohort to maximize data utilization. All subsequent analyses, ie, multivariate regression, and sensitivity analyses (Propensity Score-Matched Cohort onward), were conducted using the matched cohort to ensure robustness and group comparability. The study flow is illustrated in Figure 1. The baseline information of the groups is described in Table 1.

Primary and Secondary Outcome in the Primary Cohort

Comparisons between the two groups after treatment are shown in Table 2. The hemoglobin level was much higher in the contezolid group than that in the linezolid group (87.03 ± 15.06 vs 80.06 ± 10.93, $P = 0.002$). Consequently, the incidence of severe anemia was significantly lower in the contezolid group (14.75%) than in the linezolid group (46.43%) ($P < 0.001$). Analysis of bone marrow response markers revealed significantly better preserved reticulocyte counts in the contezolid group compared to the linezolid group (64.1 ± 15.3 vs 51.2 ± 12.7, $P = 0.026$). The reticulocyte production index, which

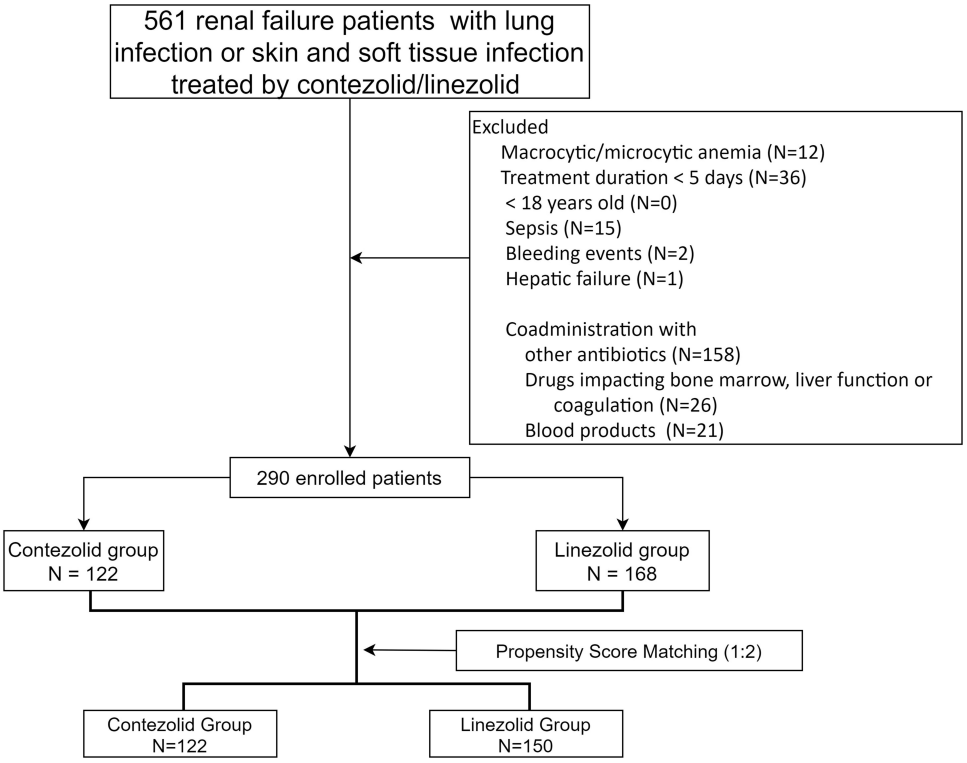

Figure 1 Study profile.

adjusts for the severity of anemia, was also higher in the contezolid group (1.12 ± 0.31 vs 0.88 ± 0.25, $P = 0.023$), indicating more robust bone marrow erythropoietic activity in patients receiving contezolid. No difference was observed in platelet count, white blood cell count, C-reactive protein, procalcitonin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, clinical cure rates, or rate of microbial eradication.

Table 1 Baseline Information in the Primary Cohort

Parameter	Contezolid Group n = 122	Linezolid Group n = 168	*P*
Sex, n (%)			0.157
Female	58 (47.54)	94 (55.95)	
Male	64 (52.46)	74 (44.05)	
Age, years	66 [57, 74]	65 [57, 68]	0.309
Treatment duration, days	10 [7, 10]	8 [6, 10]	0.205
Peritoneal dialysis/Hemodialysis, n	90/32	124/44	0.790
Fe, μmol/L	15.7 [11.1, 18.6]	17.3 [11.9, 19.4]	0.081
Ferritin, ng/mL	175 [82, 303]	200 [101, 332]	0.093
Transferrin, mg/dL	1.9 [1.6, 2.2]	2.0 [1.7, 2.2]	0.103
Erythropoietin, mU/mL	9.1 [7.5, 12.8]	9.6 [7.7, 13.2]	0.080
Erythropoietin use, n (%)	71 (58.2)	103 (61.3)	0.572
Responsible pathogens, n (%)			
MSSA	12 (9.84)	16 (9.52)	
MRSA	6 (4.92)	6 (3.57)	
CoNS	16 (13.11)	30 (17.86)	
Streptococcus spp.	14 (11.48)	22 (13.10)	
Negative	74 (60.66)	94 (55.95)	

(*Continued*)

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Table 1 (Continued).

Parameter	Contezolid Group n = 122	Linezolid Group n = 168	*P*
White blood cell, *10^9/L	9.0 [6.3, 11.8]	8.4 [5.7, 10.7]	0.052
Hemoglobin, g/L	85.49±17.48	83.18±13.97	0.124
Reticulocyte count, *10^9/L	65.32 ± 18.26	63.81 ± 16.54	0.634
Platelet, *10^9/L	239.79±109.13	253.17±91.86	0.188
CRP, mg/L	43.73±18.56	50.58±29.81	0.243
PCT, ng/mL	1.40±0.86	1.57±0.70	0.064

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; CoNS, Coagulase-negative *staphylococci*; CRP, C-reactive protein; PCT, procalcitonin.

Table 2 Univariate Comparison Between Contezolid and Linezolid Groups After Treatment in the Primary Cohort

Parameter	Contezolid Group N = 122	Linezolid Group N = 168	*P*
White blood cell (*10^9/L)	9.36±2.55	8.85±1.16	0.106
Hemoglobin (g/L)	87.03±15.06	80.06±10.93	0.002*
Reticulocyte count	64.10 ± 15.36	51.28 ± 12.72	0.026*
Reticulocyte production index	1.12 ± 0.31	0.88 ± 0.25	0.023*
Platelet (*10^9/L)	226.20±78.82	204.84±81.51	0.072
CRP (mg/L)	36.59±7.24	34.66±11.91	0.058
PCT (ng/mL)	1.60±0.75	1.53±0.34	0.432
ALT (U/L)	41.09±19.24	38.07±22.23	0.313
AST (U/L)	36.13±28.92	28.87±36.22	0.292
Total bilirubin (μmol/L)	16.42±14.07	17.94±10.22	0.303
PT (seconds)	11.1±3.3	13.3±2.6	0.270
APTT (seconds)	32.1±5.0	31.0±6.1	0.551
Fibrinogen (g/L)	3.83±1.12	3.96±1.48	0.738
INR	1.29±0.29	1.33±0.48	0.752
Clinical cure rates, %	93.44 (114/122)	92.86 (156/168)	0.878
Microbial eradication, %	93.75 (45/48)	94.60 (70/74)	0.411
Severe anemia, n (%)	18 (14.75)	78 (46.43)	< 0.001*
Thrombocytopenia, n (%)	3 (2.46)	9 (5.36)	0.212

Note: *, $P < 0.05$.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; PCT, procalcitonin; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio.

To assess the robustness of our primary finding, a post-hoc power analysis was conducted based on the observed incidence of severe anemia in the contezolid (14.75%) and linezolid (46.43%) groups. With sample sizes of 122 and 168 in the contezolid and linezolid groups, respectively, and a two-sided alpha of 0.05, the achieved statistical power exceeded 95%, indicating that the study was sufficiently powered to detect the association between antibiotic choice and severe anemia.

Comparisons Between Pre- and Post-Medication in Each Group

We also compared the changes in laboratory test results before and after contezolid/linezolid administration (Table 3). The hemoglobin level (83.18 ± 13.97 vs 80.06 ± 10.93, $P = 0.011$) and platelet count (253.17 ± 91.86 vs 204.84 ± 81.51, $P = 0.031$) declined in the linezolid group. Notably, reticulocyte counts remained stable in the contezolid group throughout treatment (65.3 ±

Table 3 Comparisons Between Pre- and Post-Medication in Each Group (Primary Cohort)

Parameter	Contezolid Group			Linezolid Group		
	Pre-Medication	Post-Medication	*P*	Pre-Medication	Post-Medication	*P*
Hemoglobin (g/L)	85.49±17.48	87.03±15.06	0.346	83.18±13.97	80.06±10.93	0.011*
Reticulocyte count	65.32 ± 18.26	64.10 ± 15.36	0.486	63.81 ± 16.54	51.28 ± 12.72	0.007*
Platelet (*10^9/L)	239.79±109.13	226.20±78.82	0.107	253.17±91.86	204.84±81.51	0.031*
Total bilirubin (μmol/L)	13.54±4.59	16.42±14.07	0.022*	15.80±9.56	17.94±10.22	0.128
ALT (U/L)	32.44±18.38	41.09±19.24	0.115	27.11±22.60	38.07±22.23	0.053
AST (U/L)	44.05±16.53	36.13±28.92	0.516	27.92±26.55	28.87±36.22	0.116
PT (seconds)	11.2±2.2	11.1±3.3	0.600	12.7±2.2	13.3±2.6	0.163
APTT (seconds)	31.4±5.7	32.1±5.0	0.169	30.4±5.6	31.0±6.1	0.133
Fibrinogen (g/L)	4.05±1.38	3.83±1.12	0.106	3.89±1.63	3.96±1.48	0.970
INR	1.31±0.20	1.29±0.29	0.588	1.26±0.20	1.33±0.48	0.275

Note: *, $P < 0.05$.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio.

18.2 to 64.1 ± 15.3, $P = 0.486$), while declining significantly in the linezolid group (63.8 ± 16.5 to 51.2 ± 12.7, $P = 0.007$). This differential effect on reticulocyte production provides direct hematological evidence supporting the bone marrow-sparing properties of contezolid. No differences were observed in hemoglobin level, platelet count, alanine aminotransferase, aspartate aminotransferase, fibrinogen, activated partial thromboplastin time, prothrombin time, or international normalized ratio in the contezolid group. In the contezolid group, total bilirubin increased from 13.54±4.59 to 16.42±14.07 μmol/L ($P = 0.022$), whereas no significant change was observed in the linezolid group.

Propensity Score-Matched Cohort

After PSM, 272 cases remained in the study cohort (122 in the contezolid group and 150 cases in the linezolid group) (Figure 1). Supplementary Table S2 shows the comparison of both groups in the PSM cohort. All baseline variables were well-balanced between two groups (SMD < 0.1 for all covariates).

Association Between Contezolid/Linezolid and Severe Anemia

Table 4 shows the association between treatment regimen and severe anemia. Compared with that of individuals who received contezolid treatment, those who received linezolid treatment showed an elevated risk of severe anemia: OR (95% CI) was 2.29 (1.64–3.35, $P < 0.001$) in the multivariable-adjusted model. VIFs for model covariates are reported in Supplementary Table S3 and ranged from 1.001 to 1.010, indicating no evidence of problematic multicollinearity.

Sensitivity Analysis

In the sensitivity analysis which excluded participants who experienced a hemoglobin level reduction of ≥10% within 3 days of treatment initiation, the results remained robust. Subsequently, we reanalyzed the data after excluding participants under 55 years of age. For patients undergoing treatment with linezolid, the pattern of severe anemia risk remained similar in the treatment duration- and C-reactive protein-adjusted model and the multivariable-adjusted mode (Table 5).

Table 4 Association Between Contezolid/Linezolid and Severe Anemia in Patients with Renal Failure (Matched Cohort, n = 272)

Variable	No. of Patients		Crude OR		Model 1[a]		Model 2[b]	
	Severe Anemia Group	Control Group	OR	95% CI	OR	95% CI	OR	95% CI
Contezolid	18	104	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Linezolid	68	82	4.79	2.65–8.70	2.33	1.89–4.01	2.29	1.64–3.35

Notes: [a] Model 1 was adjusted for treatment duration and C-reactive protein. [b] Model 2 was adjusted for model 1 plus baseline hemoglobin level and renal replacement therapy (peritoneal dialysis or hemodialysis).

Table 5 Association Between Treatment Regimen and Severe Anemia in Sensitivity Analyses (Matched Cohort)

Therapy	Excluding Participants with ≥10% Hemoglobin Level Reduction within Three Days (n = 259)			Excluding Participants < 55 years (n = 225)		
	Crude OR	Model 1[a]	Model 2[b]	Crude OR	Model 1[a]	Model 2[b]
Contezolid	1.00 (*ref.*)	1.00 (*ref.*)	1.00 (*ref.*)	1.00 (*ref.*)	1.00 (*ref.*)	1.00 (*ref.*)
Linezolid	5.36 (3.31–7.98)	2.71 (1.91–3.86)	2.02 (1.73–3.29)	4.75 (2.66–5.18)	2.82 (2.54–4.79)	2.15 (1.77–3.30)

Notes: [a] Model 1 was adjusted for treatment duration and C-reactive protein. [b] Model 2 was adjusted for model 1 plus baseline hemoglobin level and renal replacement therapy (peritoneal dialysis or hemodialysis).

The results of stratification analyses according to sex, dialysis modality and age were similar to the main findings (Supplementary Table S4, Supplementary Figure S1).

Evaluation of the Optimal Length of Treatment

The cutoff for treatment duration for severe anemia was 7 days (AUC: 0.82, 95% CI: 0.74–0.89, sensitivity: 0.76, specificity: 0.85).

Discussion

Contezolid is an oxazolidinone antibiotic that has been newly approved in China. To the best of our knowledge, this study is the first to compare the efficacy and safety of contezolid and linezolid in patients with renal failure using an active-comparator new-user design, an approach that minimizes key biases such as prevalence bias and confounding by indication. Our principal finding is that while clinical efficacy was comparable between the two oxazolidinones, contezolid demonstrated a significantly superior hematological safety profile, with a substantially lower incidence of severe anemia (14.75% vs 46.43%).

Definitions of anemia severity differ across oxazolidinone safety studies (eg, CTCAE-based grading, absolute hemoglobin cutoffs, or relative declines), which can materially influence event rates and effect estimates.[17,18,21] Our combined definition prioritizes clinical relevance and within-patient change, but may limit direct quantitative comparability with studies using alternative thresholds; results should therefore be interpreted in the context of outcome-definition heterogeneity.

The non-inferior efficacy of contezolid observed in our cohort is consistent with prior evidence. Our findings align with the Phase III trial by Zhao et al, which demonstrated comparable clinical cure and microbial eradication rates between contezolid and linezolid in patients with complicated skin and soft tissue infections.[22] This equivalent efficacy is underpinned by pharmacodynamic studies showing that contezolid exhibits similar or slightly superior in vitro antibacterial activity against Gram-positive pathogens, including MRSA and PRSP.[23,24] Thus, contezolid remains a highly effective therapeutic option for renal failure patients.

The markedly reduced risk of hematological toxicity represents the most significant advantage of contezolid. This is likely attributable to its unique properties that mitigate the off-target effects of oxazolidinones on human mitochondria and hematopoietic progenitor cells.[14–16,25,26] Furthermore, contezolid undergoes minimal renal excretion and produces no known toxic metabolites, limiting systemic accumulation—a particular advantage in renal impairment where linezolid's metabolite may accumulate.[5] Our data provide direct clinical support for these mechanisms: reticulocyte counts and the reticulocyte production index remained stable in the contezolid group but declined significantly with linezolid, indicating superior preservation of bone marrow erythropoietic activity.

In this study, 33.10% (96/290) patients developed severe anemia. Multivariate analysis suggested that linezolid regimen was an independent risk factor for severe anemia. To address potential reverse causality, we reanalyzed the data after excluding participants with a hemoglobin reduction ≥ 10% within the first 3 days of treatment onset. The association between linezolid and severe anemia remained robust ($P < 0.001$). Further sensitivity analyses excluding participants aged < 55 years yielded consistent results. These findings indicate that reverse causality is unlikely to explain the observed associations. To evaluate potential confounding effects, stratified analyses by sex, age, and renal replacement

therapy modality were performed. The relationship between linezolid use and severe anemia persisted across subgroups, demonstrating its independence from sex and age.

After oral administration of contezolid, the unmetabolized drug is excreted in the urine at less than 5% of the administered dose. It is primarily metabolized in the liver and eliminated from the body as a metabolite in the urine and feces.[11] No statistically significant differences were found in the levels of aspartate aminotransferase, alanine aminotransferase, or total bilirubin between the two groups, indicating that contezolid exhibits hepatic safety similar to that of linezolid.

The superior hematological safety of contezolid observed in our cohort is supported by evidence from other clinical contexts. For example, a recent randomized trial in rifampicin-resistant tuberculosis reported a substantially lower incidence of overall adverse events with contezolid than with linezolid (14.3% vs 92.3%), and no contezolid-treated patients developed anemia or neuropathy during the two-month treatment period.[27] These findings contribute to a consistent pattern: contezolid provides comparable antimicrobial efficacy while causing markedly less bone-marrow suppression.

This hematologic advantage appears more pronounced than that reported for another oxazolidinone, tedizolid. In the pooled ESTABLISH trials, thrombocytopenia occurred in 3.2% of tedizolid-treated patients versus 5.6% with linezolid.[28] In real-world use beyond 6 days, thrombocytopenia and anemia were reported in 7.4% and 1.2% of patients, respectively; among patients with chronic renal failure, myelotoxicity was reported in 17.4%.[29] While these studies differ from our cohort in design, patient population, and treatment duration, they provide a useful reference point for interpreting anemia and thrombocytopenia in renal-impaired patients receiving oxazolidinones. In our advanced renal failure cohort, contezolid was associated with a substantially lower incidence of thrombocytopenia (2.46% vs 5.36%) compared with linezolid, supporting a clinically meaningful hematologic safety advantage in this high-risk subgroup. The favorable safety profile of contezolid is plausibly explained by its distinct chemical structure and metabolic pathway, which together reduce off-target effects on mitochondrial translation and on hematopoietic progenitor cells.

The lower risk of severe anemia observed with contezolid carries clear clinical implications: it may reduce the need for interventions such as blood transfusions and erythropoiesis-stimulating agents, thereby improving patient comfort and conserving healthcare resources. Importantly, this safety advantage was not accompanied by a loss of antimicrobial efficacy. Although routine hematologic monitoring remains advisable, our data — together with the identified 7-day risk threshold — suggest that the clinical burden of severe hematologic events is substantially lower with contezolid.

According to Phase III clinical trials, contezolid may lead to an increase in total bilirubin; however, the incidence of this change was low (1.1%, N = 354) [11]. In our study, 12.3% (15/122, data not shown) of patients showed a significant increase in total bilirubin after contezolid treatment, yet no severe liver damage occurred, without concomitant transaminase elevation. The mechanism underlying total bilirubin elevation remains unclear. One plausible explanation is a transient alteration in hepatobiliary bilirubin handling, potentially through effects on hepatic transporters involved in bilirubin uptake and/or biliary excretion (eg, OATP-mediated uptake and canalicular efflux transporters such as MRP2), which could reduce bilirubin clearance and result in a modest total bilirubin rise.[30] A reversible effect on bilirubin conjugation (eg, UGT1A1-mediated glucuronidation) is another possibility.[31,32] While hemolysis is a theoretical consideration, the absence of a corresponding decline in hemoglobin or reticulocyte indices in our cohort makes it less likely. Future prospective studies with bilirubin fractionation (direct vs indirect bilirubin) and mechanistic evaluation of transporter/conjugation pathways are warranted to clarify this finding.

Generalizability should be considered in light of the study setting and case-mix. First, our cohort was derived from centers in Asia; differences in practice patterns, baseline anemia burden, and supportive care may limit extrapolation to other regions and ethnicities. Second, these findings reflect the infection syndromes captured in our dataset and may not extend to conditions with different severity profiles or treatment pathways (eg, pneumonia or bacteremia). Third, because we focused on advanced CKD (stage 5), extrapolation to earlier stages should be made cautiously, as baseline anemia risk, comorbidity profiles, and drug exposure/dosing/monitoring may differ across CKD stages.

We recognize several limitations. First, this was a retrospective cohort study, so causality cannot be definitively established. For example, because treatment route may influence prescribing decisions, patients receiving oral-only contezolid could have been perceived as clinically more stable than those receiving IV linezolid. Although we used an active-comparator new-user design and adjusted for available baseline severity proxies, residual confounding by infection severity cannot be fully excluded. Second, we attempted to mitigate reverse causality (sicker patients switching

to contezolid after an early hemoglobin drop) by excluding early decliners and still found robust results. Nonetheless, residual bias cannot be excluded. Third, data on important factors such as PCT, C-reactive protein were incomplete. Fourth, our cohort size limits power to detect rare events and subgroup effects. Fifth, the cutoff of 7 days for toxicity is data-driven and may not generalize; it should be validated prospectively. Sixth, the exclusion of critical care patients (eg, those with sepsis, receiving blood products) was necessary to minimize confounding but consequently limits the generalizability of our findings to a more stable renal failure population. The safety profile of contezolid in more critically ill patients warrants further investigation. Finally, our follow-up was limited to the treatment period and immediate test-of-cure; long-term outcomes were not captured.

Conclusions

Compared with linezolid, contezolid was associated with a lower risk of clinically significant hemoglobin decline among patients with renal failure; prospective randomized studies are needed to confirm causality.

Abbreviations

MRSA, Methicillin-Resistant *Staphylococcus aureus*; CKD, Chronic Kidney Disease; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; INR, International Normalized Ratio; PSM, Propensity Score Matching; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; CoNS, Coagulase-Negative *Staphylococci*; PRSP, Penicillin-Resistant *Streptococcus pneumoniae*; VRE, Vancomycin-Resistant *Enterococci*; PD/HD, Peritoneal Dialysis / Hemodialysis.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are publicly available in the Zenodo repository at https://doi.org/10.5281/zenodo.18168231.

Ethics Approval and Informed Consent

The protocol of this study received approval from the Ethics Committee of the Second Hospital of Shanxi Medical University (2022-280). In addition, this study was implemented in conformity with the moral standards formulated in the 1964 Declaration of Helsinki and its subsequent amendments or similar moral standards. Owing to the retrospective nature of the study, the Ethics Committee of the Second Hospital of Shanxi Medical University waived the need of obtaining informed consent. This retrospective study used de-identified data and that patient confidentiality was maintained.

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Disclosure

The authors report no conflicts of interest in this work.

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