Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

Efficacy of Contezolid in the Treatment of Catheter-Related Bloodstream Infections Caused by Methicillin-Resistant *Staphylococcus aureus* in a Patient with Hepatorenal Syndrome and Acute Kidney Injury: A Case Report

Xiucui Zhang*, Huili Huang*, Jianrong Wang, Bo Wei

Department of Infectious Disease, Changzheng Hospital, Navy Medical University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Bo Wei, Department of infectious disease, Changzheng Hospital, Navy Medical University, Shanghai, People's Republic of China, Email weibi0816@163.com

Abstract: The Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI) patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) urgently require safe and effective treatment options due to their compromised hepatic and renal functions, as well as thrombocytopenia resulting from hypersplenism. In our case, an HRS-AKI patient who underwent continuous renal replacement therapy for fluid overload developed fever with chills. His blood tests indicated elevated C-reactive protein and neutrophils, low platelet count, and bilateral lung infiltrates. Subsequently, his blood culture and catheter culture confirmed a catheter-related MRSA bloodstream infection. To address this complex clinical challenge, a novel oxazolidinone antibiotic, contezolid (800mg orally every 12 hours), was introduced into the patient's anti-infection regimen. Notably, the patient exhibited remarkable improvements and responded favorably to this treatment. During subsequent follow-up, no recurrence of the infection or drug-related adverse events was observed. The successful utilization of contezolid in this case underscores its potential as a novel therapeutic option for treating MRSA infections in patients with HRS-AKI.

Keywords: Hepatorenal syndrome-acute kidney injury, methicillin-resistant *Staphylococcus aureus*, bloodstream infection, contezolid

Introduction

The Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI) represents a serious complication in patients with cirrhosis in the decompensated stage, often leading to a dismal prognosis.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) infection further complicates the situation, negatively impacting on prognosis of patients with decompensated cirrhosis.[2] The mortality rate associated with MRSA bloodstream infections is approximately 32%.[3] Patients with cirrhosis exhibit an increased mortality risk in the context of MRSA bloodstream infections, with a 1.9-fold higher likelihood of fatality compared to those without cirrhosis.[4] Furthermore, it is estimated that only about two-thirds of these cases receive appropriate initial therapeutic interventions.[3] Timely initiation of treatment against MRSA is crucial upon establishing a diagnosis. However, the employment of first-line agents, such as vancomycin and linezolid, for MRSA infections in HRS-AKI patients is hindered by compromised hepatic and renal functions, as well as thrombocytopenia resulting from hypersplenism.[5,6] Although daptomycin has demonstrated efficacy in treating MRSA bloodstream infections, its use is contraindicated in patients with pneumonia.[7] Therefore, HRS-AKI patients with MRSA infection urgently need safe and effective therapeutic agents. Herein, we present a case of a continuous renal replacement therapy (CRRT) catheter-related

Received: 18 October 2024
Accepted: 25 December 2024
Published: 16 January 2025

MRSA bloodstream infection in an HRS-AKI patient with stage 3 AKI, concurrent thrombocytopenia and suspected pneumonia, who achieved favorable clinical outcomes after receiving a new oxazolidinone antibiotic contezolid.

Case Details

A 58-year-old male patient was admitted to our department with a 10-day history of nausea, abdominal distension, and oliguria. He had a 30-year history of heavy alcohol consumption and hepatitis C virus treated 3 years ago and denied recent kidney-damaging drug use. Prior to admission, the patient had received i.v. albumin for 48 hours without satisfactory response and presented with dyspnea and chest tightness.

On admission, his body temperature was 36.2°C, pulse was 82/min, respirations were 25/min, and blood pressure was 154/78 mmHg. Physical examination revealed abdominal distension with positive shifting dullness, bilateral lower extremity edema, and decreased breath sounds in both lungs. The abdominal computed tomography (CT) confirmed liver cirrhosis, splenomegaly, and ascites. Chest CT showed pleural effusion and left atelectasis. The renal ultrasound revealed no evidence of structural damage. Laboratory examination indicated an increase in serum creatinine (Scr) levels (from 850umol/L two days before admission to 1181umol/L at admission), elevated liver enzymes (glutamyl transferase at 126U/L and alkaline phosphatase at 206U/L) and normal coagulation test. Proteinuria was present, but no pathological casts. The patient was diagnosed with HRS-AKI, AKI stage 3.

Albumin and CRRT were initiated to optimize renal function and mitigate fluid overload. Cefazolin was administered. The patient's Scr levels gradually decreased from 1181umol/L to 419umol/L (Figure 1), while urine volume increased from 500mL/d to 1650mL/d. However, on the 11th day of hospitalization, his temperature rose to 39°C with chills. Tests showed elevated C-reactive protein and neutrophils, as well as a decrease in platelet count (67×10^9/L). The chest CT revealed bilateral lung infiltrates accompanied by pleural effusion. Based on the hypothesis of a bacterial infection, empirical treatment with Piperacillin-tazobactam (PTZ) (2.5g I.V. every 12 hours) was initiated. The blood culture at 24 hours returned positive for Gram-positive cocci, leading to the removal of the CRRT catheter as the suspected source. Further blood cultures confirmed the presence of MRSA in both blood and CRRT catheter samples, with drug sensitivity tests revealing susceptibility to vancomycin, linezolid, and rifampin. A diagnosis of catheter-related MRSA bloodstream infection was established. Despite negative sputum culture results, the presence of pulmonary infection cannot be excluded based on the findings from the CT scan of the lungs. Considering the patient's history of HRS-AKI and

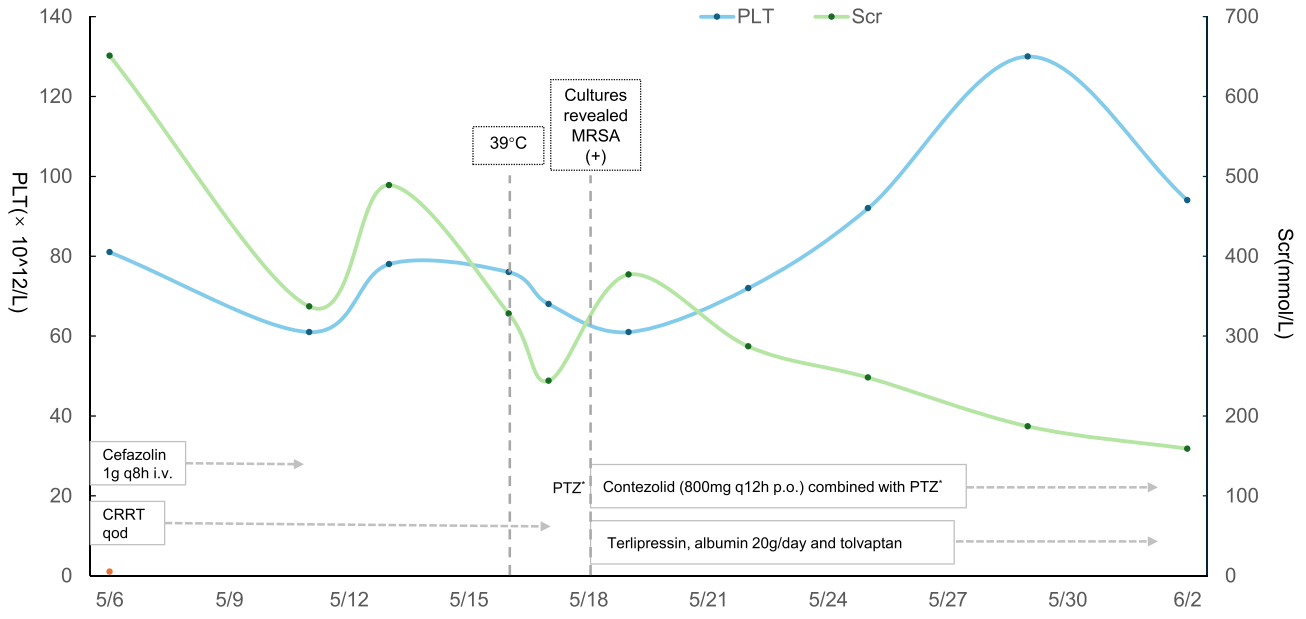

Figure 1 Antibiotics used in the patient and correlated changes with the progress of the clinical condition.
Abbreviations: Plt, platelets; Scr, serum creatinine; MRSA, methicillin-resistant *Staphylococcus aureus*; CRRT, continuous renal replacement therapy; PTZ, piperacillin-tazobactam.

 https://doi.org/10.2147/IDR.S501604

stage 3 AKI, along with concurrent thrombocytopenia and the potential for pulmonary infection, treatment with vancomycin, linezolid or daptomycin were pending. An alternative oxazolidinone antibiotic called contezolid (800mg orally every 12 hours) was introduced to the anti-infection regimen with informed consent. Terlipressin, albumin, and tolvaptan were administered for HRS-AKI management. The patient's temperature gradually returned to normal, serum creatinine levels decreased, and urine output significantly increased (2400mL/d) (see Figure 1). Liver function improved as shown by normalized bilirubin and liver enzyme levels. By day 7, infection markers had returned to normal. Contezolid and PTZ were administered for another seven days without any significant changes in platelet count (refer to Figure 1). Additionally, the patient did not report any significant adverse reactions throughout this period. The intake of medication was closely monitored by the nursing staff to ensure adherence. No infection recurrence or drug-related adverse events was observed during his follow-up. At the six-month consultation, bilirubin and transaminase levels were normal, while creatinine level was 127umol/L.

Discussion

This patient presented with a catheter-related infection caused by MRSA, which was further complicated by stage 3 AKI, HRS-AKI, concurrent thrombocytopenia, and suspected pneumonia. Therefore, the use of first-line agents such as vancomycin, linezolid, and daptomycin was limited. Consequently, combination therapy involving contezolid and piperacillin-tazobactam was administered, which led to complete recovery.

HRS-AKI is a functional renal failure that occurs due to renal vascular constriction in patients with end-stage liver disease, acute liver failure, or alcoholic hepatitis. The first-line therapy for HRS-AKI is the combination of terlipressin and albumin, which effectively reduces plasma renin and serum creatinine levels, thereby enhancing the reversal rate of HRS.[8] Renal replacement therapy (RRT) is often used as a transitional treatment before liver transplantation, but its use in HRS-AKI patients who are not suitable for liver transplantation is controversial. However, for patients with severe acidosis, hyperkalemia, or volume overload, the decision to initiate RRT should be made on an individual basis.[9] In this case, our patient presented with severe manifestations of fluid overload upon admission, necessitating the initiation of CRRT. However, during CRRT treatment, the patient's temperature and infection markers increased.

According to a report, patients with cirrhosis have a 5–6 times higher prevalence of bacterial infections compared to the general population.[10] Hospitalization is a known risk factor for bacterial infections in cirrhotic patients.[10] Furthermore, AKI can have a negative impact on immune functions, leading to persistent immune paralysis and an increased risk of subsequent infections. A large-scale retrospective study involving over 3 million patients with cirrhosis found that individuals with AKI had a higher risk of developing infections (34.6% vs 22.2%, $p<0.001$) and sepsis (19.3% vs 6.1%, $p<0.001$) compared to those without AKI.[11] Prompt diagnosis and treatment of infections are crucial for HRS-AKI patients. Therefore, our group immediately conducted blood, sputum, urinary, and ascitic fluid cultures to detect any possible infections. The diagnosis of catheter-related bloodstream MRSA infection was confirmed by detecting MRSA in the blood culture and in the catheter culture after removing the CRRT catheter.

MRSA is a leading nosocomial pathogen and ranks second in terms of infection-related mortality rate in China.[12] Currently, there are few available reports on the treatment of MRSA infection in patients with HRS-AKI. The presence of AKI and persistent baseline thrombocytopenia in those patients may limit the choice of antibiotics.

Glycopeptides, such as vancomycin and teicoplanin, are effective against gram-positive bacteria, including MRSA. However, they are renal toxic. It was reported that among the various comorbidities and clinical factors examined, the highest risk of vancomycin-associated AKI is posed by kidney disease (OR 2.19), followed by liver disease (OR 1.82).[13] Considering the patient's hepatic and renal injury, it was crucial to avoid exacerbating renal impairment by excluding glycopeptides from his treatment regimen.

It is reported that patients with impaired renal function have an increased risk of linezolid exposure.[14] Those with renal insufficiency are significantly more likely to develop linezolid-related thrombocytopenia compared to those with normal renal function.[14] Therefore, linezolid was not considered as the initial treatment for this patient.

Daptomycin is an alternative to vancomycin for treating MRSA bacteremia. In cases of persistent MRSA bloodstream infections, the concurrent administration of daptomycin and ceftaroline has demonstrated superior cure rates and comparatively shorter treatment durations.[15] It is primarily eliminated through renal excretion, with approximately 78% being excreted

in urine. In patients with impaired kidney function, daptomycin exhibits a prolonged half-life.[16] However, its use for pneumonia treatment is not recommended due to inactivation by pulmonary surfactant. Therefore, daptomycin was not included in the treatment regimen as pneumonia was suspected.

Contezolid, a novel oxazolidinone antibiotic, has exhibited antibacterial activity comparable to or exceeding that of linezolid, vancomycin, and daptomycin against clinical isolates of MRSA, in vitro. The The minimum inhibitory concentration 90 (MIC_{90}) values for contezolid, linezolid, vancomycin, and daptomycin were 0.5 mg/L, 0.5 mg/L, less than 1 mg/L, and 0.5 mg/L, respectively.[17] In a murine model of systemic S. aureus infection, the median effective dose of contezolid is either lower or equivalent to that of linezolid.[18] The Phase III clinical trial of contezolid for treating complex skin and soft tissue infections demonstrated comparable efficacy to linezolid. Additionally, there was a low incidence of hematologic toxicity, with only 3 out of 354 cases affected.[19] Contezolid also showed similar major pharmacokinetic parameters in patients with mild to moderate renal impairment (estimated creatinine clearance (CLcr) 30-<90 mL/min) and mild to moderate liver impairment compared to those with normal kidney and liver function.[20,21] The efficacy of contezolid in individuals with mild or moderate renal impairment was similar to that in individuals with normal renal function, and the rates of adverse drug events during treatment observed in both Phase 2 and 3 trials were also comparable.[22] Currently, successful treatment of adult MRSA infective endocarditis with contezolid has been reported.[23] After thorough consultation with the patient, contezolid was administered for treatment. The patient demonstrated satisfactory clinical efficacy following treatment with contezolid, and no significant drug-related adverse effects were observed.

This case report has certain limitations. The patient exhibited substantial clinical improvement after contezolid therapy and the removal of the indwelling catheter, which effectively addressed the source of infection. It is crucial to understand that these results may not apply to all cases, particularly for patients who are unable to have their catheters removed or those with ongoing bloodstream infections. Therefore, the conclusions from this single case should not be broadly applied to all instances of MRSA-related bloodstream infections. Given these considerations, future research efforts should be directed towards large-scale, prospective clinical trials to further investigate the efficacy and safety of contezolid in the treatment of MRSA-related bloodstream infections.

Conclusion

The successful use of contezolid in this case highlights its potential as an innovative therapeutic option for treating MRSA infections in patients with HRS-AKI.

Ethics Approval and Informed Consent

The study was conducted in accordance with the declaration of Helsinki. Written informed consent was provided by the patient to allow the case details and any accompanying images to be published, and this report was approved by the Medical Ethics Committee, Shanghai Changzheng Hospital.

Funding

There is no funding to report.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Musunuri B, Gopal S, Tantry BV, Shenoy S, Shetty AJ. Predictors of Short-term Mortality in Patients of Cirrhosis of Liver Presenting as Acute Kidney Injury: an In-hospital Prospective Observational Study. *J Clini Experim Hep*. 2023;13(6):989–996. doi:10.1016/j.jceh.2023.05.017
2. Fernández J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. *J Hepatol*. 2019;70(3):398–411. doi:10.1016/j.jhep.2018.10.027
3. Gasch O, Camoez M, Dominguez MA, et al. Predictive factors for mortality in patients with methicillin-resistant staphylococcus aureus bloodstream infection: impact on outcome of host, microorganism and therapy. *Clin Microbiol Infect*. 2013;19(11):1049–1057. doi:10.1111/1469-0691.12108

4. Ju M, Huang Y, Xu X, et al. Predictors of mortality in adult patients with methicillin-resistant staphylococcus aureus bloodstream infection: a meta-analysis and systematic review. *Ann Palliat Med*. 2021;10(8):8617–8627. doi:10.21037/apm-21-932
5. Cattaneo D, Marriott DJE, Gervasoni C. Hematological toxicities associated with linezolid therapy in adults: key findings and clinical considerations. *Expert Rev Clin Phar*. 2023;16(3):219–230. doi:10.1080/17512433.2023.2181160
6. Fernández J, Bert F, Nicolas-Chanoine M-H. The challenges of multi-drug-resistance in hepatology. *J Hepatol*. 2016;65(5):1043–1054. doi:10.1016/j.jhep.2016.08.006
7. Richard HB. Daptomycin: mechanisms of action and resistance, and biosynthetic engineering. *Curr Opin Chem Biol*. 2009;13(2):144–151. doi:10.1016/j.cbpa.2009.02.031
8. Uriz J, Ginès P, Cárdenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J Hepatol*. 2000;33(1):43–48. doi:10.1016/s0168-8278(00)80158-0
9. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74(2):1014. doi:10.1002/hep.31884
10. Fernández J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. *Gut*. 2018;67(10):1870–1880. doi:10.1136/gutjnl-2017-314240
11. Desai AP, Knapp SM, Orman ES, et al. Changing epidemiology and outcomes of acute kidney injury in hospitalized patients with cirrhosis – a US population-based study. *J Hepatol*. 2020;73(5):1092–1099. doi:10.1016/j.jhep.2020.04.043
12. CHINET数据云/抗生素耐药性. Available from: https://www.chinets.com/Data/AntibioticDrugFast. Accessed April 11, 2024.
13. Yun Kim JY, Yee J, Young Yoon HY, Min Han JM, Sun Gwak HS. Risk factors for vancomycin-associated acute kidney injury: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2022;88(9):3977–3989. doi:10.1111/bcp.15429
14. Nukui Y, Hatakeyama S, Okamoto K, et al. High plasma linezolid concentration and impaired renal function affect development of linezolid-induced thrombocytopenia. *J Antimicrob Chemother*. 2013;68(9):2128–2133. doi:10.1093/jac/dkt133
15. Alsowaida YS, Alsolami A, Almangour TA. Daptomycin and ceftaroline combination for the treatment of persistent methicillin-resistant *staphylococcus aureus* bloodstream infections: a case series and literature review. *J Chemother*. 2024;36(7):540–545. doi:10.1080/1120009X.2024.2340877
16. Murray KP, Zhao JJ, Davis SL, et al. Early Use of Daptomycin Versus Vancomycin for Methicillin-Resistant Staphylococcus aureus Bacteremia With Vancomycin Minimum Inhibitory Concentration >1 mg/L: a Matched Cohort Study. *Clinl Infect Dis*. 2013;56(11):1562–1569. doi:10.1093/cid/cit112
17. Wang S, Cai C, Shen Y, et al. In vitro Activity of Contezolid Against Methicillin-Resistant Staphylococcus aureus, Vancomycin-Resistant Enterococcus, and Strains With Linezolid Resistance Genes From China. *Front Microbiol*. 2021;12:729900. doi:10.3389/fmicb.2021.729900
18. Gordeev MF, Yuan ZY. New Potent Antibacterial Oxazolidinone (MRX-I) with an Improved Class Safety Profile. *J Med Chem*. 2014;57(11):4487–4497. doi:10.1021/jm401931e
19. Zhao X, Huang H, Yuan H, et al. A Phase III multicentre, randomized, double-blind trial to evaluate the efficacy and safety of oral contezolid versus linezolid in adults with complicated skin and soft tissue infections. *J Antimicrob Chemoth*. 2022;77(6):1762–1769. doi:10.1093/jac/dkac073
20. Fang E, Yang H, Yuan H. 1701. Pharmacokinetics in Subjects with Renal Impairment in a Contezolid Complicated Skin and Soft Tissue Infection Phase 3 Clinical Trial. *Open Forum Infect Diseases*. 2022;9(Supplement_2):ofac492.1331. doi:10.1093/ofid/ofac492.1331
21. Wu J, Yang X, Wu J, et al. Dose adjustment not required for contezolid in patients with moderate hepatic impairment based on pharmacokinetic/pharmacodynamic analysis. *Front Pharmacol*. 2023;14:1135007. doi:10.3389/fphar.2023.1135007
22. Fang E, Yang H, Yuan H. 1700. Efficacy and Safety in Subjects with Renal Impairment in Contezolid and Contezolid Acefosamil Phase 2 and Phase 3 Skin Infection Clinical Trials. *Open Forum Infect Diseases*. 2022;9(Supplement_2):ofac492.1330. doi:10.1093/ofid/ofac492.1330
23. Zhao S, Zhang W, Zhang L, et al. Use of Contezolid for the Treatment of Refractory Infective Endocarditis in a Patient with Chronic Renal Failure: case Report. *Infec Drug Resista*. 2023;16:3761–3765. doi:10.2147/IDR.S413452