Ref: Ro Med J. 2024;71(2)
DOI: 10.37897/RMJ.2024.2.15

Effectiveness of ceftazidime/avibactam as a continuous infusion in critically ill patients with OXA-48-producing *Klebsiella pneumoniae* infection

Ivan Šitum[1], Dora Karmelić[1], Anja Mandarić[1], Ante Erceg[1], Daniel Lovrić[2], Marko Siroglavić[3], Slobodan Mihaljević[1], Mirabel Mažar[1]

[1]Department of Anesthesiology and ICU, University Hospital Centre Zagreb, Croatia
[2]Department of Cardiovascular Diseases, University Hospital Centre Zagreb, Croatia
[3]Department of Clinical Microbiology, Infection Prevention and Control, University Hospital Centre Zagreb, Croatia

Ivan Šitum **ORCID ID:** 0000-0002-4113-2400
Dora Karmelić **ORCID ID:** 0000-0003-2328-7764
Anja Mandarić **ORCID ID:** 0000-0002-0344-9028
Daniel Lovrić **ORCID ID:** 0000-0002-5052-6559
Marko Siroglavić **ORCID ID:** 0000-0003-2582-747X
Slobodan Mihaljević **ORCID ID:** 0000-0001-8228-8914
Mirabel Mažar **ORCID ID:** 0000-0002-4589-2490

ABSTRACT

Introduction. Ceftazidime/avibactam, a novel beta-lactam antibiotic, demonstrates time-dependent bacterial killing; thus, new reports advocate its administration as a continuous infusion, as opposed to bolus or prolonged infusion application.

Methods. Critically ill COVID-19 patients (n=10) superinfected with OXA-48-producing *Klebsiella pneumoniae* susceptible to ceftazidime/avibactam were treated with ceftazidime/avibactam as a continuous infusion for an average of 10 days. The treatment regimen included an initial loading dose, followed by a continuous infusion of ceftazidime/avibactam. These patients were immunocompromised because of severe COVID-19, treatment with corticosteroids, and some solid organ transplant recipients (n=2), all with high disease severity scores.

Discussion. Considering the published literature to this date, this is the one of first reports describing the real-life results of using a continuous infusion of ceftazidime/avibactam in the treatment of OXA-48-producing *K. pneumoniae* superinfection in critically ill COVID-19 patients. Microbiological effectiveness of treatment, evidenced by negativization of microbiological samples, was achieved in eight cases (80%) overall, but in patients with sepsis and urinary tract infection, the cure rate was 100%.

Conclusion. The reasons for the low treatment success rates in pneumonia caused by OXA-48-producing *K. pneumoniae* could be explained by the concurrent severe COVID-19 pneumonia.

Keywords: COVID-19, sepsis, intensive care unit, antibiotics, *Klebsiella pneumoniae*

INTRODUCTION

Patients with coronavirus 2019 disease (COVID-19) often suffer from co- or superinfection with various pathogens, especially critically ill patients hospitalized in intensive care units (ICUs). *Klebsiella pneumoniae* emerged as the most frequent cause of bacterial co-infection, and the third most frequent cause of bacterial superinfection [1], often causing pneumonia, urinary tract infection, or sepsis. In our

Corresponding authors:
Anja Mandarić
E-mail: anja.mandaric2@gmail.com

Article History:
Received: 28 May 2024
Accepted: 29 June 2024

patient population, there were multiple cases of OXA-48-producing *K. pneumoniae* isolated from microbiological samples obtained from severely ill COVID-19 patients with bacterial superinfections. These Gram-negative bacteria were multidrug-resistant but susceptible to a novel beta-lactam antibiotic, ceftazidime/avibactam.

Ceftazidime is a third-generation cephalosporin with broad-spectrum gram-negative activity that causes bacterial cell lysis and death by binding to penicillin-binding proteins and inhibiting cell wall biosynthesis. Avibactam is a β-lactamase inhibitor that protects ceftazidime from degradation by β-lactamase enzymes, including class D β-lactamases (such as OXA-48) [2]. Most manufacturers recommend ceftazidime/avibactam dosing three times daily (or less, in renal compromise) in a two-hour-long infusion.

An important feature of beta-lactam antibiotics is time-dependent bacterial killing, their efficacy is associated with the percentage of the dosing interval in which the unbound concentration remains higher than the minimum inhibitory concentration (MIC) of the targeted pathogen. Therefore, many authors suggest administering them as either prolonged or continuous infusions to achieve an aggressive pharmacokinetic/ pharmacodynamics (PK/PD) target and maximize the efficacy of the drug, particularly in critically ill and immunocompromised patients [3].

METHODS

A retrospective analysis of the effectiveness of continuous infusion of ceftazidime/avibactam was conducted in all patients with proven OXA-48-producing *K. pneumoniae* infection and confirmed susceptibility to ceftazidime/avibactam who were treated according to this protocol from November 2021 to November 2022 in the COVID ICU at the University Hospital Centre Zagreb in Croatia.

Considering this rationale, for the newly established COVID-19 Intensive Care Unit (ICU), a treatment for patients with confirmed OXA-48-producing *K. pneumoniae* infection with proven ceftazidime/avibactam sensitivity was created. The treatment regimen included an initial loading dose of 2.5 g (2 g ceftazidime+0.5 g avibactam) over 2 hours, followed by a continuous infusion of ceftazidime/avibactam of 5 g over 12 hours. The dose should be adjusted for renal insufficiency based on the estimated glomerular filtration rate (eGFR).

Susceptibility to ceftazidime/avibactam was ascertained according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint definitions. Laboratory and clinical data were extracted from the patients' electronic records. A demographic analysis of our patients was conducted, with comorbidity burden assessed by the Charlson Comorbidity Index and the severity of index illness using the Apache score, SOFA score, and Pitt bacteremia score for patients with bacteremia. The rate of microbiological and clinical effectiveness of the treatment regimen and the rate of side effects and survival at 30 and 90 days were analyzed.

RESULTS

The patient cohort included 10 patients with confirmed COVID-19 infection and OXA-48-producing *K. pneumoniae* superinfection who were treated with a continuous ceftazidime/avibactam infusion regimen.

The patients were predominantly male (80%), with a mean age of 62.3 years (range 37-76 years), and most of them (60%) had two or more comorbidities prior to hospital admission. The Charlson Comorbidity Index was 4.4 (range 2-8). Of note, two patients were recipients of a solid organ transplant (the kidney or heart).

At admission to the ICU, the majority of the patients were critically ill, with a median Apache score of 17.5 (range 11-23) and a mean SOFA score of 5.0 (range 2-11). For patients with bacteremia (n=5), the average Pitt bacteremia score was 4.07.

K. pneumoniae is usually present at more than one microbiological site. The most frequent infections were sepsis (n=5), lower respiratory tract infection (n=3), and urinary tract infection (n=2). All but one patient had previously isolated *K. pneumoniae* from surveillance cultures, mostly from rectal swabs (58%).

The median time from sampling of relevant microbiological samples to the initiation of treatment was 2 days (0–6 days). The mean treatment duration was 10 days (range 4-25 days).

Microbiological effectiveness of treatment, evidenced by negativization of microbiological samples, was achieved in eight cases (80%). Microbiological negativization was achieved in 100% of the patients with septicemia (n=5) and urinary tract infection (n=2). A low rate of microbiological negativization was observed in patients with bacterial pneumonia superinfection (one of three patients). Recurrent infection was noted in three of the cases. The all-cause mortality at 30 days was 80%, while the mortality at 90 days was 100%.

Considering adverse reactions to the drug, no patients developed allergic reactions to the drug. One patient developed renal failure and was treated with continuous renal replacement therapy (CRRT), although the causal relationship with ceftazidime/avibactam therapy could not be determined because of a plethora of confounding factors. No other side effects were observed.

DISCUSSION

Considering the published literature to this date, this is the one of first reports describing the real-life results of using a continuous infusion of ceftazidime/avibactam in the treatment of OXA-48-producing *K. pneumoniae* superinfection in critically ill COVID-19 patients.

The first studies comparing the treatment of carbapenem-resistant *Klebsiella pneumoniae* bacteremia with ceftazidime/avibactam with other antibiotic regimens cited higher clinical success and survival rates in the ceftazidime/avibactam group than in comparators (carbapenem plus aminoglycoside or colistin, or other therapies such as aminoglycoside, carbapenem, colistin, tigecycline, and ciprofloxacin monotherapy or combination therapy), with clinical success for ceftazidime/avibactam regimen of 85%, 30 and 90 days survival of 92%, and acute kidney injury rates of 25% at the end of treatment [4].

Only a few studies have described the application of a therapeutic regimen of prolonged or continuous infusions of ceftazidime/avibactam, and even fewer have been used for the treatment of multidrug-resistant Klebsiella pneumoniae. Most are summarized in a review article by Gatti and Pea [3]. These are three case reports, one retrospective case series of 10 patients (four of which had multidrug-resistant *Klebsiella pneumoniae* infection) by Goncette et al. [5], and a multicenter retrospective cohort study by Tumbarello et al. on 577 patients [6]. Tumbarello et al. applied ceftazidime/avibactam in the regime of prolonged three-hour-long infusion and managed to prove a survival benefit. Goncetta et al. used a continuous infusion of ceftazidime/avibactam and achieved a PK/PD target of 100%T>5×MIC (median 13.3-fold the MIC) in 100% of patients, a clinical cure of 80%, microbiological eradication of 90%, and a 30-day mortality rate of 10%. Another report by Venutti et al. [11], published in 2023, summarized the available pharmacological and clinical data regarding prolonged infusion. It was found to protect beta-lactams and concluded that the suggested administration is supported because it optimizes therapeutic activity by increasing the probability of attaining maximal bactericidal activity.

Using a continuous infusion regimen of ceftazidime/avibactam, we achieved a 100% cure rate in patients with sepsis and urinary tract infection, which is higher than that previously reported.

Unfortunately, despite the physiological and pharmacological plausibility of the continuous infusion treatment regimen, microbiological and clinical success rates were not observed (33% vs. 85%, or 80-90%) in patients with COVID-19 and lower respiratory tract OXA-48-producing *K. pneumoniae* superinfection.

In theory, the low efficacy of this treatment regimen could be explained by the potential simultaneous presence of lung microthrombosis, a frequent feature of severe COVID-19 [7], for which we did not screen our patient population. A systematic review of microthrombi in COVID-19 autopsies found that microthrombi in the lungs appeared in up to 73% of patients who died of severe COVID-19 [8]. One could assume that the presence of non-perfused tissue presents a microbiological site even though continuously high antibiotic concentrations cannot be overcome; however, this assumption requires separate investigation.

The interpretation of the mortality results in this study remains inconclusive due to the unfavorable clinical course of patients with severe COVID-19 infection.

All the investigated patients were immunocompromised, in part as a consequence of the immune dysregulation caused by COVID-19, and in part due to the concurrent treatment with corticosteroids, a mainstay treatment for severe COVID-19. Twenty% of the patients were receiving chronic corticosteroid therapy because they had received an organ transplant. This report highlights the need for a careful approach in the treatment of immunocompromised patients with ceftazidime-avibactam. Due to strained healthcare resources during the pandemic, the measurement of plasma antibiotic concentration in our case was not possible. Currently, therapeutic drug monitoring for ceftazidime/avibactam is not widely recommended. However, some reports have shown that it can help avoid under- and over-dosing, thus ensuring the attainment of PK/PD targets while minimizing the risk of ceftazidime/avibactam side effects [9], especially in patients undergoing CRRT [10]. It would seem wise to implement therapeutic drug monitoring for ceftazidime/avibactam in immunocompromised patients.

The extrapolation of these conclusions to the general population of all critically ill patients should be approached with caution. The retrospective, single-center design and relatively small sample size of this study should be considered.

Further studies are needed, with a more rigorous study design of the continuous infusion of ceftazidime-avibactam in susceptible infections.

Authors' contribution:

Ivan Šitum: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft; Dora Karmelić: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft; Ante Erceg: Investigation, Writing-review and editing; Anja Mandarić: Conceptualization, Investigating, writing–review and editing; Lovrić, Daniel: Conceptualization, Investigation, Writing -review & editing; Marko Siroglavić: Conceptualization, Investigation, Writing -review & editing; Mhaljević, Slobodan: Writing-review and editing; Mažar, Mirabel: Writing-review and editing

REFERENCES

1. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PLoS One*. 2021;16(5):e0251170. Published 2021 May 6. doi: 10.1371/journal.pone.0251170.
2. Shirley M. Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative *Bacterial Infections. Drugs.* 2018;78(6):675-692. doi: 10.1007/s40265-018-0902-x.
3. Gatti M, Pea F. Continuous versus intermittent infusion of antibiotics in Gram-negative multidrug-resistant infections. *Curr Opin Infect Dis.* 2021;34(6):737-747. doi: 10.1097/QCO.0000000000000755.
4. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. *Antimicrob Agents Chemother.* 2017;61(8):e00883-17. Published 2017 Jul 25. doi: 10.1128/AAC.00883-17.
5. Goncette V, Layios N, Descy J, Frippiat F. Continuous infusion, therapeutic drug monitoring and outpatient parenteral antimicrobial therapy with ceftazidime/avibactam: a retrospective cohort study. *J Glob Antimicrob Resist*. 2021;26:15-19. doi: 10.1016/j.jgar.2021.04.015.
6. Tumbarello M, Raffaelli F, Giannella M, Mantengoli E, Mularoni A, Venditti M, et al. Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase-Producing K. pneumoniae Infections: A Retrospective Observational Multicenter Study. C*lin Infect Dis.* 2021;73(9):1664-1676. doi: 10.1093/cid/ciab176.
7. McFadyen JD, Stevens H, Peter K. The Emerging Threat of (Micro) Thrombosis in COVID-19 and Its Therapeutic Implications. *Circ Res.* 2020;127(4):571-587. doi: 10.1161/CIRCRESAHA.120.317447.
8. Parra-Medina R, Herrera S, Mejia J. Systematic Review of Microthrombi in COVID-19 Autopsies. *Acta Haematol.* 2021;144(5):476-483. doi: 10.1159/000515104.
9. Fresan D, Luque S, Benítez-Cano A, Sorlí L, Milagro Montero M, De-Antonio M, et al. Pharmacokinetics/pharmacodynamics and therapeutic drug monitoring of ceftazidime/avibactam administered by continuous infusion in patients with MDR Gram-negative bacterial infections. *J Antimicrob Chemother.* 2023;78(3):678-683. doi: 10.1093/jac/dkac439.
10. Gatti M, Rinaldi M, Gaibani P, Siniscalchi A, Tonetti T, Giannella M, et al. A descriptive pharmacokinetic/ pharmacodynamic analysis of continuous infusion ceftazidime-avibactam for treating DTR gram-negative infections in a case series of critically ill patients undergoing continuous veno-venous haemodiafiltration (CVVHDF). *J Crit Care.* 2023;76:154301. doi: 10.1016/j.jcrc.2023.154301.
11. Venuti F, Trunfio M, Martson AG, Lipani F, Audagnotto S, Di Perri G, Calcagno A. Extended and Continuous Infusion of Novel Protected β-Lactam Antibiotics: A Narrative Review. *Drugs*. 2023; 83:967–83. doi: 10.1007/s40265-023-01893-6.

Acknowledgements:
The authors would like to thank Ana-Marija Šarušić, Katarina Kovač, Ivan Đureković, and David Palijan for their assistance with data collection.

Conflicts of interest and source of funding:
We declare no conflict of interest.
This research has received no funding.

Ethical statement:
All patients included in this study signed an informed consent form, and permission to collect and edit data was granted to the researchers.