

Real-World Effectiveness and Cost-Effectiveness of Ceftazidime–Avibactam versus Colistin–Meropenem for ICU-Acquired MDR Gram-Negative Infections in Liver Transplant Recipients

Adem Kose

adem.kose@inonu.edu.tr

Inonu University

Nisa Candas

Inonu University

Seyma Yasar

Inonu University

Sibel Altunisik Toplu

Inonu University

Funda Memisoglu

Inonu University

Elif Seren Tanriverdi

Inonu University

Huseyin Kocaaslan

Inonu University

Esin Gunay

Inonu University

Research Article

Keywords: liver transplantation, ceftazidime–avibactam, multidrug-resistant Gram-negative infections, antimicrobial stewardship, cost-effectiveness

Posted Date: August 6th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10541663/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at European Journal of Clinical Microbiology & Infectious Diseases on September 26th, 2026. See the published version at <https://doi.org/10.1007/s10096-026-05677-0>.

Abstract

Background

Novel β -lactam/ β -lactamase inhibitor combinations have expanded treatment options for carbapenem-resistant Gram-negative infections; however, comparative real-world evidence in critically ill liver transplant recipients remains limited. We compared the clinical effectiveness and cost-effectiveness of ceftazidime–avibactam (CAZ/AVI) with colistin–meropenem for intensive care unit (ICU)-acquired multidrug-resistant (MDR) Gram-negative infections in adult liver transplant recipients.

Materials and Methods

In this retrospective comparative cohort study, 190 adult liver transplant recipients treated between October 2021 and April 2025 received definitive therapy with either CAZ/AVI monotherapy (n = 100) or colistin–meropenem combination therapy (n = 90). The primary outcome was clinical response. Secondary outcomes included microbiological eradication, sepsis-related mortality, 30-day all-cause in-hospital mortality, ICU and hospital length of stay, and pharmacoeconomic outcomes. Cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs), non-parametric bootstrap resampling, cost-effectiveness planes, and cost-effectiveness acceptability curves.

Results

Clinical response was significantly higher with CAZ/AVI than with colistin–meropenem (87.5% vs 57.6%, $p < 0.001$). CAZ/AVI also achieved higher microbiological eradication (95.8% vs 72.9%, $p < 0.001$) and substantially lower sepsis-related mortality (11.1% vs 42.4%, $p < 0.001$), whereas 30-day all-cause in-hospital mortality did not differ significantly between groups ($p = 0.377$). Although antimicrobial acquisition costs were higher with CAZ/AVI, pharmacoeconomic analyses demonstrated favorable cost-effectiveness, with an ICER of 54,442.13 TL per additional clinical success, supported by bootstrap and acceptability analyses.

Conclusions

CAZ/AVI was associated with superior clinical response, greater microbiological eradication, lower sepsis-related mortality, and favorable cost-effectiveness compared with colistin–meropenem. These findings support CAZ/AVI as an effective definitive treatment option for critically ill liver transplant recipients with ICU-acquired MDR Gram-negative infections.

INTRODUCTION

Liver transplantation (LT) has substantially improved survival for patients with end-stage liver disease; however, infectious complications remain a major cause of early postoperative morbidity and mortality despite advances in surgical techniques, perioperative care, and immunosuppressive therapy [1]. The burden of infection is particularly high among recipients requiring intensive care unit (ICU) support, in whom severe healthcare-associated infections continue to compromise graft function, prolong hospitalization, and adversely affect survival.

Recipients requiring intensive care unit (ICU) support represent the most vulnerable subgroup among liver transplant recipients because prolonged critical illness, invasive supportive interventions, and extensive antimicrobial exposure substantially increase the risk of healthcare-associated infections and multidrug-resistant (MDR) pathogen acquisition [2]. Consequently, prompt recognition of ICU-acquired infections and timely initiation of appropriate antimicrobial therapy are essential for improving clinical outcomes, preserving graft function, and reducing infection-related mortality in this high-risk population [3].

Among healthcare-associated infections, multidrug-resistant (MDR) Gram-negative bacteria have emerged as one of the greatest therapeutic challenges in liver transplant recipients. Carbapenem-resistant *Klebsiella pneumoniae*, difficult-to-treat *Pseudomonas aeruginosa*, and MDR *Escherichia coli* are increasingly encountered in transplant ICUs and are associated with limited therapeutic options, prolonged hospitalization, graft-related complications, and excess mortality [4]. The global spread of carbapenem-resistant Enterobacterales has further restricted effective treatment options, highlighting the urgent need for active targeted antimicrobial therapies [5].

Successful treatment of MDR Gram-negative infections depends largely on the prompt administration of an active antimicrobial agent, whereas delays in appropriate therapy are consistently associated with poorer clinical outcomes [6]. Although colistin-based combination regimens remained one of the few therapeutic options for carbapenem-resistant Gram-negative infections for many years, their clinical use has been increasingly limited by nephrotoxicity, suboptimal pharmacokinetic properties, and the emergence of polymyxin resistance [7]. Consequently, ceftazidime–avibactam (CAZ/AVI) has emerged as an important therapeutic alternative because of its potent activity against many carbapenem-resistant Gram-negative pathogens and its more favorable safety profile [8].

Although observational studies have reported favorable outcomes with CAZ/AVI, most available evidence has been derived from heterogeneous patient populations in which liver transplant recipients represent only a small proportion of enrolled patients [9]. Furthermore, comparative studies simultaneously evaluating both clinical effectiveness and cost-effectiveness of CAZ/AVI specifically in critically ill liver transplant recipients remain scarce, despite the increasing economic burden associated with novel antimicrobial therapies [10]. Consequently, high-volume liver transplant centers provide a unique opportunity to generate clinically meaningful real-world evidence in a homogeneous population at exceptionally high risk for MDR Gram-negative infections [11].

Accordingly, we compared ceftazidime–avibactam monotherapy with colistin–meropenem combination therapy in adult liver transplant recipients with ICU-acquired MDR Gram-negative infections treated at a high-volume liver transplantation center. We aimed to compare clinical effectiveness, microbiological eradication, sepsis-related mortality, and cost-effectiveness, thereby addressing an important evidence gap in the management of MDR Gram-negative infections in transplant critical care.

MATERIALS AND METHODS

Study Design and Setting

This retrospective comparative cohort study was conducted at the Liver Transplant Institute of İnönü University Faculty of Medicine, Malatya, Türkiye, a high-volume liver transplant center in Türkiye, between October 2021 and April 2025. The study compared the real-world clinical and pharmacoeconomic outcomes of ceftazidime–avibactam (CAZ/AVI) monotherapy and colistin–meropenem combination therapy in adult liver transplant recipients with ICU-acquired multidrug-resistant (MDR) Gram-negative infections. A single-center design was adopted to ensure uniformity in surgical practice, perioperative management, microbiological procedures, antimicrobial stewardship, and intensive care management throughout the study period.

Study Population

Adult liver transplant recipients (≥ 18 years) admitted to the transplant intensive care unit (ICU) between October 2021 and April 2025 were screened for eligibility. Patients were included if they developed microbiologically confirmed ICU-acquired MDR Gram-negative infections and received definitive treatment with either CAZ/AVI monotherapy or colistin–meropenem combination therapy.

Included patients had microbiologically confirmed infections caused by MDR *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, or *Escherichia coli* isolated from clinically significant specimens. Only the first eligible infectious episode during each ICU admission was included. Patients receiving alternative definitive antimicrobial regimens, those with polymicrobial infections requiring additional Gram-negative therapy, incomplete clinical or microbiological data, or death within 72 hours from non-infectious causes were excluded.

Data Collection

Demographic, clinical, microbiological, therapeutic, and pharmacoeconomic data were retrospectively collected using a standardized data extraction form. Information was obtained from the electronic medical record system, microbiology laboratory database, pharmacy dispensing records, hospital billing system, and daily physician and nursing documentation. Data from all sources were cross-checked

before analysis, and only infectious episodes with complete clinical, microbiological, treatment, and cost data were included. All data were anonymized before statistical analysis.

Microbiological Procedures

Clinical specimens were processed in the Department of Medical Microbiology according to routine laboratory procedures. Blood culture bottles were incubated in an automated blood culture system and positive cultures were subcultured onto appropriate media for organism isolation.

Bacterial identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) with the VITEK MS system (bioMérieux, Marcy-l'Étoile, France) according to the manufacturer's instructions [12].

Antimicrobial susceptibility testing was performed using the VITEK 2 Compact automated system (bioMérieux, Marcy-l'Étoile, France). Results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints applicable during the study period. Colistin susceptibility was determined by the reference broth microdilution method in accordance with current EUCAST recommendations [13, 14].

Definitions

MDR Gram-negative bacteria were defined as isolates exhibiting acquired non-susceptibility to at least one antimicrobial agent in three or more antimicrobial categories according to the international expert proposal by Magiorakos et al [15].

The primary outcome was clinical response at completion of definitive antimicrobial therapy, defined as complete resolution of infection-related signs and symptoms without escalation or modification of definitive antimicrobial therapy or initiation of additional Gram-negative antimicrobial agents. Secondary outcomes included microbiological eradication, sepsis-related mortality, 30-day all-cause in-hospital mortality, ICU length of stay, hospital length of stay, and direct antimicrobial treatment costs. Microbiological eradication was defined as the absence of the initial pathogen in clinically indicated follow-up cultures. Outcomes were assessed using predefined study criteria, and only patients with complete follow-up data were included in the final analyses.

Ethical Approval

The study protocol was approved by the Malatya Clinical Research Ethics Committee (Approval No. 8816/2025). The study was conducted in accordance with the Declaration of Helsinki. Because of the retrospective design and use of anonymized routinely collected clinical data, the requirement for written informed consent was waived by the Ethics Committee.

Pharmacoeconomic Evaluation

Direct medical costs were obtained from institutional pharmacy dispensing records and hospital billing databases. Cost-effectiveness analysis was performed from the hospital perspective using clinical response as the primary measure of effectiveness. Mean treatment costs and clinical effectiveness were calculated before estimation of incremental cost (Δ Cost), incremental effectiveness (Δ Effect), and the incremental cost-effectiveness ratio (ICER).

Parameter uncertainty was assessed using non-parametric bootstrap resampling with 5,000 iterations. Cost-effectiveness was evaluated using the cost-effectiveness plane, cost-effectiveness acceptability curves (CEACs), and the net monetary benefit (NMB) framework across a range of willingness-to-pay thresholds.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), as appropriate, whereas categorical variables were summarized as frequencies and percentages. Between-group comparisons were performed using the independent-samples *t* test or Mann–Whitney *U* test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA) and R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and a *p* value <0.05 was considered statistically significant.

Because important baseline ICU severity indices (e.g., SOFA and APACHE II) were unavailable or incompletely recorded, multivariable regression analysis was not performed. A post hoc power analysis was conducted using G*Power version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany). Based on the final study sample and a two-sided α level of 0.05, the estimated statistical power was approximately 80%. The post hoc power analysis was performed for descriptive purposes only and was not used to determine the study sample size.

RESULTS

Patient Characteristics and Clinical Outcomes

A total of 190 adult liver transplant recipients with microbiologically confirmed ICU-acquired MDR Gram-negative infections met the study eligibility criteria, including 100 patients treated with ceftazidime–avibactam (CAZ/AVI) monotherapy and 90 treated with colistin–meropenem combination therapy. No significant differences were observed in baseline demographic and clinical characteristics between treatment groups, although antimicrobial acquisition costs were significantly higher in the CAZ/AVI group (Table 1).

Despite higher antimicrobial acquisition costs, patients receiving CAZ/AVI achieved significantly better clinical outcomes. Clinical response was observed in 87.5% of patients treated with CAZ/AVI compared

with 57.6% of those receiving colistin–meropenem ($p<0.001$). Likewise, microbiological eradication rates were significantly higher in the CAZ/AVI group (95.8% vs 72.9%, $p<0.001$). Most importantly, sepsis-related mortality was markedly lower among patients receiving CAZ/AVI (11.1% vs 42.4%, $p<0.001$). In contrast, no statistically significant difference was observed in 30-day all-cause in-hospital mortality between treatment groups ($p = 0.377$) (Table 1).

Table 1. Baseline characteristics and selected clinical outcomes of liver transplant recipients with ICU-acquired multidrug-resistant Gram-negative infections treated with ceftazidime–avibactam or colistin–meropenem.

Variable	Colistin– Meropenem (n=90)Mean ± SD	Median (IQR)	CAZ/AVI (n=100)Mean ± SD	Median (IQR)	P value
Age	53.36 ± 12.45	56 (17)	51.08 ± 12.91	52.5 (15.5)	0.238
Hospital stay (days)	55.15 ± 28.53	52 (44)	52.17 ± 27.88	49.5 (39.5)	0.480
Antimicrobial acquisition cost (TL)	5747.57 ± 4955.03	4628.96 (5231.64)	22080.21 ± 11510.44	17546.89 (15670.92)	<0.001

Variable	Colistin–Meropenem (n=90)n (%)	CAZ/AVI (n=100)n (%)	P value
Gender			0.506
Male	54 (60.0)	42 (42.0)	
Female	31 (34.4)	30 (30.0)	
Missing	5 (5.6)	28 (28.0)	
Microbiological eradication			<0.001
No	23 (27.1)	3 (4.2)	
Yes	62 (72.9)	69 (95.8)	
In-hospital mortality within 30 days			0.377
No	46 (54.1)	44 (61.1)	
Yes	39 (45.9)	28 (38.9)	
Clinical response			<0.001
No	36 (42.4)	9 (12.5)	
Yes	49 (57.6)	63 (87.5)	
Sepsis-related mortality			<0.001
No	49 (57.6)	64 (88.9)	
Yes	36 (42.4)	8 (11.1)	

Footnotes: Baseline demographic and clinical characteristics of patients receiving ceftazidime–avibactam (CAZ/AVI) monotherapy or colistin–meropenem combination therapy are presented. Gender data were unavailable for 33 patients and were therefore analyzed using available cases. Continuous variables are expressed as median (interquartile range) or mean ± standard deviation as appropriate, and categorical variables are presented as number and percentage. Outcome analyses were performed using available cases with complete follow-up data.

Microbiological Characteristics

Microbiological characteristics of 169 infectious episodes are summarized in Table 2. Intra-abdominal infections were the most common infection source among patients receiving CAZ/AVI, whereas pneumonia and ventilator-associated pneumonia predominated in the colistin–meropenem group. *Klebsiella pneumoniae* was the most frequently isolated pathogen in both treatment groups, followed by *Pseudomonas aeruginosa* and *Escherichia coli*.

Among carbapenem-resistant isolates, OXA-48 was the predominant resistance mechanism in both treatment groups, whereas NDM, KPC, IMP, and VIM carbapenemases were identified less frequently. Overall, resistance mechanism profiles were broadly comparable between treatment groups. However, significant differences were observed in infection source distribution and in the relative frequencies of *K. pneumoniae* and *P. aeruginosa* (Table 2).

Table 2. Microbiological Characteristics of ICU-Acquired MDR Gram-Negative Infections

Variable	CAZ/AVI (n=85)	Colistin–Meropenem (n=84)	P value
Infection source			
Intra-abdominal infection	54 (63.5)	37 (44.0)	0.014
Pneumonia/VAP	12 (14.1)	32 (38.1)	<0.001
Urinary tract infection	18 (21.2)	11 (13.1)	0.221
Other	1 (1.2)	4 (4.8)	0.210
Pathogen distribution			
<i>Klebsiella pneumoniae</i>	41 (48.2)	56 (66.7)	0.020
<i>Pseudomonas aeruginosa</i>	23 (27.1)	37 (44.0)	0.025
<i>Escherichia coli</i>	7 (8.2)	5 (6.0)	0.766
Carbapenemase detected			
OXA-48-like	47 (55.3)	59 (70.2)	0.056
NDM	8 (9.4)	8 (9.5)	1.000
OXA-48-like + NDM	17 (20.0)	7 (8.3)	0.046
KPC	4 (4.7)	2 (2.4)	0.682
IMP	2 (2.4)	2 (2.4)	1.000
VIM	2 (2.4)	0 (0.0)	0.497

Data are presented as n (%). CAZ/AVI, ceftazidime–avibactam; MDR, multidrug-resistant; VAP, ventilator-associated pneumonia. Carbapenemase data refer to isolates from patients included in the study cohort.

Pharmacoeconomic Outcomes

Cost-effectiveness analysis demonstrated that the superior clinical effectiveness of CAZ/AVI was achieved at a higher antimicrobial acquisition cost. The absolute improvement in clinical response was 0.299 ($\Delta\text{Effect} = 0.299$), corresponding to an incremental cost-effectiveness ratio (ICER) of 54,442.13 TL per additional clinical success (Table 3).

Table 3. Incremental cost-effectiveness analysis comparing ceftazidime–avibactam and colistin–meropenem therapy.

Parameter	Value
Average cost – Colistin–Meropenem (TL)	5,747.57
Average cost – CAZ/AVI (TL)	22,080.21
Incremental cost (Δ Cost) (TL)	16,332.64
Clinical response – Colistin–Meropenem	57.6%
Clinical response – CAZ/AVI	87.5%
Incremental effectiveness (Δ Effect)	0.299
ICER (TL per additional clinical success)	54,442.13

ICER (Incremental cost-effectiveness ratio) (TL per additional clinical success) was calculated as the incremental cost divided by the incremental effectiveness (clinical response rate). Clinical response was used as the primary effectiveness outcome. Costs are presented in Turkish Lira (TL).

Bootstrap-based pharmacoeconomic analysis confirmed the robustness of the base-case findings (Table 4).

Table 4. Base-case cost and effectiveness results with bootstrap-derived 95% confidence intervals

Outcome	Colistin–Meropenem	CAZ/AVI	Increment (CAZ/AVI – Colistin–Meropenem)
Clinical effectiveness	0.576 (0.470–0.684)	0.875 (0.791–0.945)	0.299
Mean cost (TL)	5,747.57 (4,796.23–6,906.42)	22,080.21 (19,577.20–24,816.83)	16,332.64
ICER (TL per additional clinical success)	—	—	54,442.13

Values are presented as mean (95% bootstrap confidence interval), unless otherwise indicated. Base-case estimates of treatment cost and clinical effectiveness were derived from bootstrap resampling. ICER, incremental cost-effectiveness ratio; TL, Turkish Lira.

Across 5,000 bootstrap replications, CAZ/AVI consistently demonstrated greater clinical effectiveness than colistin–meropenem while remaining associated with higher antimicrobial acquisition costs. Accordingly, all bootstrap estimates were located in the northeast quadrant of the cost-effectiveness plane (Figure 1).

Cost-effectiveness acceptability curve (CEAC) analysis demonstrated that the probability of CAZ/AVI being cost-effective increased substantially at willingness-to-pay thresholds above approximately 50,000–60,000 TL, approaching nearly 100% at thresholds exceeding 100,000 TL (Figure 2).

DISCUSSION

The management of ICU-acquired multidrug-resistant (MDR) Gram-negative infections in liver transplant recipients remains one of the greatest therapeutic challenges in contemporary transplant medicine because treatment decisions must balance antimicrobial efficacy, toxicity, emerging resistance, and healthcare costs in an exceptionally vulnerable patient population. In this comparative cohort, ceftazidime–avibactam (CAZ/AVI) was associated with substantially higher clinical response and microbiological eradication rates, together with markedly lower sepsis-related mortality, than colistin–meropenem therapy. Although CAZ/AVI was associated with higher antimicrobial acquisition costs, pharmacoeconomic analysis demonstrated favorable cost-effectiveness. Collectively, these findings suggest that optimizing definitive antimicrobial therapy can improve both clinical outcomes and the overall value of care in critically ill liver transplant recipients.

The favorable outcomes observed with CAZ/AVI in our cohort are consistent with the evolving therapeutic landscape for carbapenem-resistant Gram-negative infections, in which novel β -lactam/ β -lactamase inhibitor combinations have progressively replaced polymyxin-based regimens as preferred definitive therapy when in vitro susceptibility is confirmed. Recent international guidelines recommend CAZ/AVI for susceptible carbapenem-resistant Enterobacterales because of its superior efficacy and improved safety profile compared with polymyxin-based therapies [16]. These recommendations are supported by systematic reviews and meta-analyses demonstrating higher clinical success, improved microbiological eradication, and lower mortality with CAZ/AVI than with colistin-containing regimens [17]. Similarly, multicenter observational studies have confirmed survival benefits in critically ill patients with severe carbapenem-resistant Gram-negative infections [18]. Our findings extend this evidence by demonstrating that these advantages are maintained in a homogeneous cohort of liver transplant recipients, supporting early administration of an active and well-tolerated antimicrobial agent as a key determinant of successful management in transplant-associated MDR Gram-negative infections [19].

The substantial reduction in sepsis-related mortality observed with CAZ/AVI represents one of the most clinically important findings of this study and is consistent with evidence showing that timely administration of an active antimicrobial agent is a key determinant of survival in carbapenem-resistant Gram-negative infections [20]. Previous comparative studies have likewise demonstrated lower infection-attributable mortality and higher survival rates with CAZ/AVI than with colistin-containing regimens, supporting the link between improved microbiological eradication and better clinical outcomes [21]. In contrast, the absence of a significant difference in 30-day all-cause mortality should be interpreted cautiously because early mortality after liver transplantation is influenced by multiple competing factors, including graft dysfunction, surgical complications, rejection, severe immunosuppression, and non-infectious organ failure [22]. Therefore, infection-specific outcomes such as sepsis-related mortality may

provide a more appropriate measure of antimicrobial effectiveness than all-cause mortality in critically ill liver transplant recipients receiving targeted therapy for multidrug-resistant pathogens [23].

The significantly higher microbiological eradication rate achieved with CAZ/AVI provides an important explanation for its superior clinical performance. Durable eradication of carbapenem-resistant Gram-negative pathogens is particularly important in liver transplant recipients because persistent infection may lead to recurrent bacteremia, prolonged ICU stay, repeated antimicrobial exposure, and emergence of further resistance [24]. In contrast, the clinical utility of polymyxin-based regimens has become increasingly limited by suboptimal pharmacokinetics, poor tissue penetration, and dose-dependent nephrotoxicity, particularly during prolonged treatment [25]. Recent studies have further demonstrated that the improved efficacy of CAZ/AVI is accompanied by a more favorable safety profile, allowing optimization of definitive antimicrobial therapy while reducing the toxicity concerns associated with colistin-containing regimens [26]. These advantages are especially relevant in liver transplant recipients, in whom preservation of renal function and avoidance of treatment-related adverse events are essential for successful postoperative management and long-term graft outcomes [27].

The pharmacoeconomic findings further strengthen the clinical advantages of CAZ/AVI by demonstrating favorable economic value despite its higher acquisition cost. Although CAZ/AVI required greater antimicrobial expenditure than colistin–meropenem, the incremental cost-effectiveness ratio (ICER) remained economically acceptable when interpreted alongside the substantial improvement in clinical response. Bootstrap analysis confirmed the robustness of these findings, while both the cost-effectiveness plane and cost-effectiveness acceptability curve consistently supported the favorable economic profile of CAZ/AVI across clinically relevant willingness-to-pay thresholds [28]. These findings are consistent with previous economic evaluations demonstrating that the higher acquisition cost of CAZ/AVI may be offset by improved clinical outcomes, lower treatment failure rates, and reduced downstream healthcare utilization [29]. From a healthcare system perspective, antimicrobial selection should therefore be guided not only by acquisition cost but also by overall treatment value, incorporating effectiveness, safety, and resource utilization [30]. This approach may be particularly important in high-volume liver transplant centers, where preventing recurrent infections, reducing ICU resource utilization, and preserving graft function have important clinical and economic implications beyond the index hospitalization [31].

The findings of this study have important implications for antimicrobial stewardship in transplant critical care. As antimicrobial resistance continues to increase globally, optimizing definitive therapy requires consideration not only of microbiological activity but also of clinical effectiveness, treatment-related toxicity, and healthcare resource utilization [32]. In high-risk populations such as liver transplant recipients, selection of an effective targeted antimicrobial regimen may reduce exposure to nephrotoxic agents, minimize recurrent infections, and preserve graft function while improving patient outcomes [33]. These considerations are particularly relevant in high-volume transplant centers, where the clinical and economic burden of MDR Gram-negative infections remains substantial [34]. Future prospective multicenter studies with standardized antimicrobial stewardship strategies and long-term follow-up are

needed to validate these findings and further define the role of CAZ/AVI in transplant-associated MDR Gram-negative infections [35].

Strengths and Limitations

A major strength of this study is its exclusive focus on adult liver transplant recipients with ICU-acquired MDR Gram-negative infections while simultaneously evaluating clinical effectiveness, microbiological eradication, sepsis-related mortality, and pharmacoeconomic outcomes within a standardized transplant setting.

This study has several limitations. First, its retrospective single-center design may limit the generalizability of the findings. Second, the relatively small sample size may have limited the statistical power for some secondary outcomes. Finally, incomplete ICU severity data precluded multivariable regression analysis, leaving the possibility of residual confounding.

Conclusions

CAZ/AVI was associated with improved clinical response, higher microbiological eradication, lower sepsis-related mortality, and favorable cost-effectiveness compared with colistin–meropenem in adult liver transplant recipients with ICU-acquired MDR Gram-negative infections. These findings support CAZ/AVI as an effective definitive treatment option for this high-risk population. Prospective multicenter studies are needed to validate these findings.

Declarations

Ethics approval and consent to participate

The study was approved by the Malatya Clinical Research Ethics Committee (Approval No. 8816/2025). The study was conducted in accordance with the Declaration of Helsinki. Because of the retrospective study design and the use of anonymized routinely collected clinical data, the requirement for written informed consent was waived by the Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

A.K. conceived the study, supervised the research, interpreted the data, and drafted the manuscript. N.C., S.Y., and S.A.T. contributed to data collection, data verification, and manuscript revision. E.S.T. performed microbiological analyses and contributed to data interpretation. H.K. provided surgical and liver transplantation expertise and critically revised the manuscript. E.G. contributed to pharmacoeconomic data collection, cost analysis, and interpretation of the economic findings. All authors critically reviewed the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Acknowledgements

The authors thank the intensive care unit staff and the microbiology laboratory personnel of the Liver Transplant Institute, İnönü University Faculty of Medicine, for their continuous support in patient care and assistance with clinical data collection.

Use of artificial intelligence

Artificial intelligence–based tools were used only to support language refinement, reference cross-checking, and preparation of preliminary manuscript drafts. All scientific content, study design, data analysis, interpretation of the results, and the final version of the manuscript were independently reviewed, verified, and approved by the authors, who accept full responsibility for the accuracy and integrity of the work.

References

1. European Association for the Study of the Liver (2024) EASL Clinical Practice Guidelines on liver transplantation. *J Hepatol* 81(6):1040–1086
2. Fishman JA (2017) Infection in organ transplantation. *Am J Transpl* 17(4):856–879
3. Shbaklo N, Tandoi F, Lupia T, Corcione S, Romagnoli R, De Rosa FG (2022) Bacterial and viral infections in liver transplantation: new insights from clinical and surgical perspectives. *Biomedicines* 10(7):1561
4. Boutzoukas AE, Dai W, Cober E, Abbo LM, Komarow L, Chen L et al (2025) Carbapenem-resistant Enterobacterales in solid organ transplant recipients. *Am J Transpl* 25(4):848–859
5. Park SY, Baek YJ, Kim JH, Seong H, Kim B, Kim YC et al (2024) Guidelines for antibacterial treatment of carbapenem-resistant Enterobacterales infections. *Infect Chemother* 56(3):308–328
6. Falcone M, Bassetti M, Tiseo G, Giordano C, Nencini E, Russo A et al (2020) Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-

- producing *Klebsiella pneumoniae*. Crit Care 24(1):29
7. Nation RL, Rigatto MHP, Falci DR, Zavascki AP (2019) Polymyxin acute kidney injury: dosing and other strategies to reduce toxicity. Antibiot (Basel) 8(1):24
 8. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F et al (2018) Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis 66(2):163–171
 9. Pérez-Nadales E, Fernández-Ruiz M, Natera AM, Gutiérrez-Gutiérrez B, Mularoni A, Russelli G et al (2023) Efficacy of ceftazidime-avibactam in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae*. Am J Transpl 23(7):1022–1034
 10. Kong W, Yang X, Shu Y, Li S, Song B, Yang K (2023) Cost-effectiveness analysis of ceftazidime-avibactam as definitive treatment for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection. Front Public Health 11:1118307
 11. Varón-Vega FA, Lemos E, Castaño GN, Reyes JM (2022) Cost-utility analysis of ceftazidime-avibactam versus colistin-meropenem in the treatment of infections due to carbapenem-resistant *Klebsiella pneumoniae* in Colombia. Expert Rev Pharmacoecon Outcomes Res 22(2):235–240
 12. Patel R (2015) MALDI-TOF MS for the diagnosis of infectious diseases. Clin Chem 61(1):100–111
 13. The European Committee on Antimicrobial Susceptibility Testing (2020) EUCAST guidance document on routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Clin Microbiol Infect 26(8):1039–1044
 14. The European Committee on Antimicrobial Susceptibility Testing (2025) Breakpoint tables for interpretation of MICs and zone diameters. Version 15.0. EUCAST, Basel
 15. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG et al (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18(3):268–281
 16. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ (2024) Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant Gram-negative infections. Clin Infect Dis 79(3):e91–e116
 17. Fiore M, Alfieri A, Di Franco S, Pace MC, Passavanti MB, Leone S et al (2024) Ceftazidime-avibactam combination therapy compared with other active antimicrobial regimens for the treatment of carbapenem-resistant Gram-negative infections: a systematic review and meta-analysis. Clin Microbiol Infect 30(2):170–180
 18. Shields RK, Nguyen MH, Chen L, Press EG, Kreiswirth BN, Clancy CJ (2017) Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. Clin Infect Dis 65(9):1462–1469
 19. Ackley R, Roshdy D, Meredith J, Minor S, Anderson WE, Capraro GA et al (2020) Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant

- Enterobacterales infections: clinical outcomes and antimicrobial stewardship implications. Open Forum Infect Dis 7(4):ofaa084
20. Castón JJ, Cano A, Pérez-Camacho I, Aguado JM, Carratalà J, Torre-Cisneros J et al (2022) Impact of ceftazidime-avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study). J Antimicrob Chemother 77(5):1452–1460
 21. King M, Heil EL, Kuriakose S, Bias T, Huang V, El-Beyrouy C et al (2017) Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother 61(7):e00449–e00417
 22. Yang P, Chen Y, Jiang S, Shen P, Lu X, Xiao Y (2023) Efficacy and safety of ceftazidime-avibactam versus polymyxins for the treatment of carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis. Int J Antimicrob Agents 61(6):106793
 23. Satlin MJ, Chen L, Patel G, Gomez-Simmonds A, Weston G, Kim AC et al (2017) Multicenter Clinical and Molecular Epidemiological Analysis of Bacteremia Due to Carbapenem-Resistant Enterobacteriaceae (CRE) in the CRE Epicenter of the United States. Antimicrob Agents Chemother 61(4):e02349–e02316
 24. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR et al (2017) Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT study). Antimicrob Agents Chemother 61(8):e00179–e00117
 25. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A et al (2019) International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 39(1):10–39
 26. Jorgensen SCJ, Trinh TD, Zasowski EJ, Lagnf AM, Bhatia S, Melvin SM et al (2019) Real-world experience with ceftazidime-avibactam for multidrug-resistant Gram-negative bacterial infections. Open Forum Infect Dis 6(12):ofz522
 27. Pouch SM, Patel G, AST Infectious Diseases Community of Practice (2019) Multidrug-resistant bacterial infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transpl 33:e13594
 28. Hu N, Xiao F, Chen Y, Zhang X, Wang L, Zhou H et al (2025) Efficacy, safety, and cost-effectiveness analysis of ceftazidime-avibactam versus polymyxin B in the treatment of carbapenem-resistant Enterobacteriaceae infections: a target trial emulation. Infect Dis Ther 14:1419–1437
 29. Kong W, Yang X, Shu Y, Li S, Song B, Yang K (2023) Cost-effectiveness analysis of ceftazidime-avibactam as definitive treatment for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection. Front Public Health 11:1118307

30. Gutiérrez M, Fandiño C (2021) Cost-effectiveness of ceftazidime/avibactam versus colistin plus meropenem in the treatment of infections caused by carbapenem-resistant Enterobacteriaceae in Chile. *Rev Chil Infectol* 38(1):7–15
31. Solante RM, Buehrle DJ, Lodise TP, Yu HT, Albarillo FS, Mould-Quevedo J et al (2025) Cost-effectiveness analysis comparing ceftazidime-avibactam with colistin for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia caused by multidrug-resistant Gram-negative pathogens in the Philippines. *Clin Drug Investig* 45(9):917–930
32. Bassetti M, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, Dimopoulos G et al (2018) Management of KPC-producing *Klebsiella pneumoniae* infections. *Clin Microbiol Infect* 24(2):133–144
33. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL et al (2018) Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 18(3):318–327
34. Tamma PD, Cosgrove SE, Maragakis LL (2012) Combination therapy for treatment of infections with Gram-negative bacteria. *Clin Microbiol Rev* 25(3):450–470
35. Bassetti M, Vena A, Sepulcri C, Giacobbe DR, Peghin M (2024) Treatment of bloodstream infections due to Gram-negative bacteria with difficult-to-treat resistance. *Clin Microbiol Infect* 30(Suppl 2):S23–S32

Figures

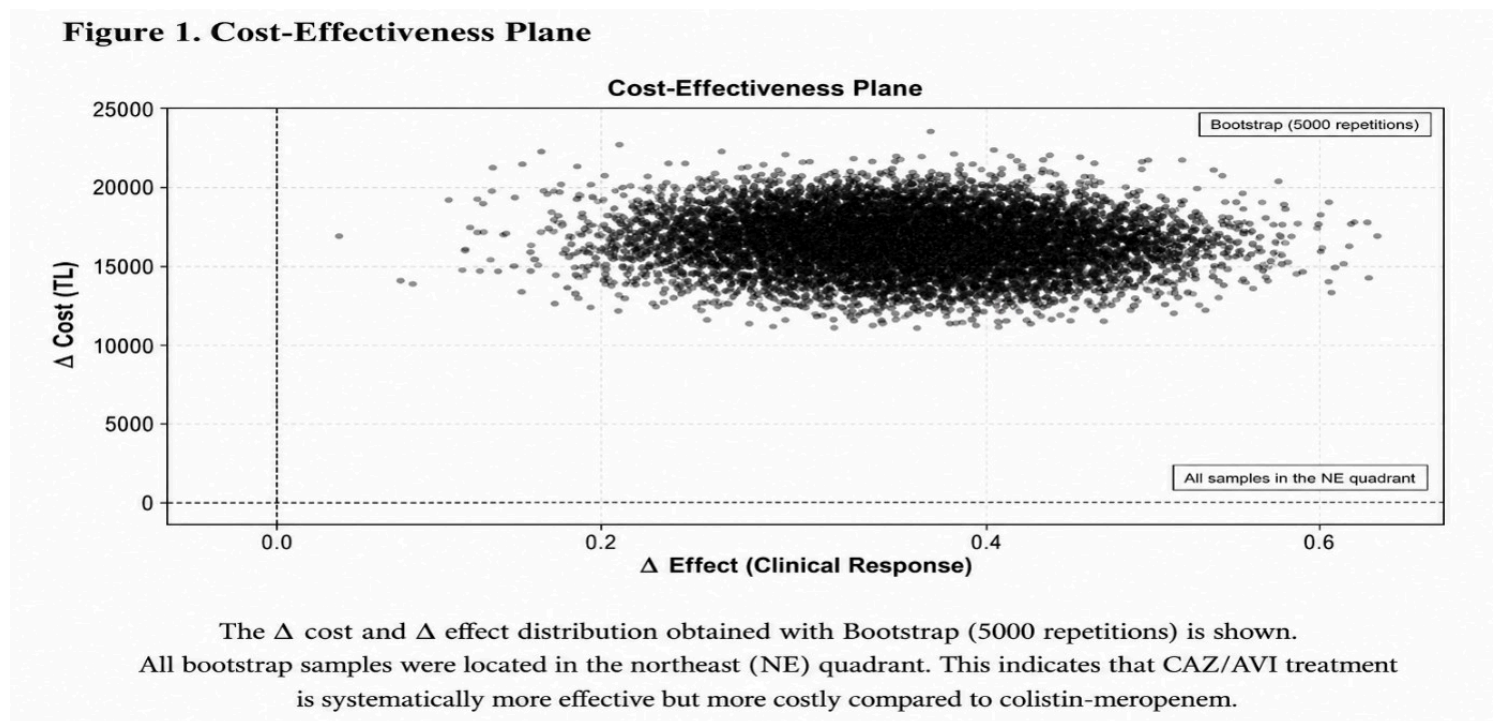
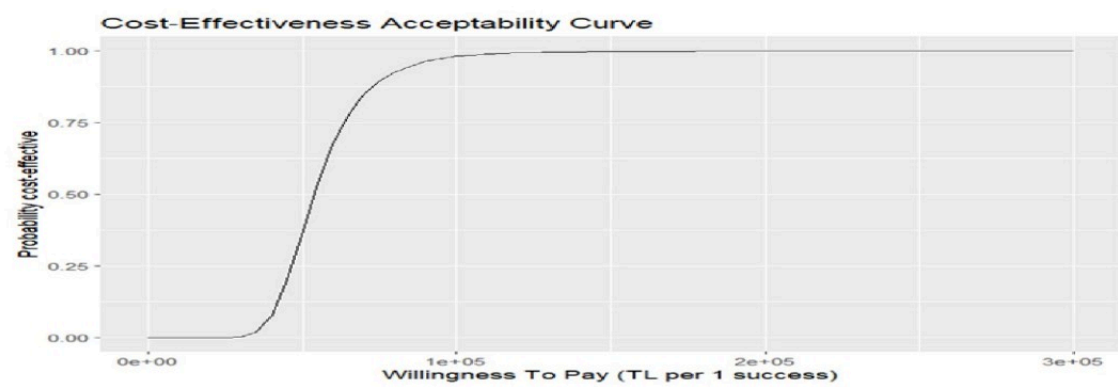


Figure 1

See image above for figure legend.

Figure 2. Cost-Effectiveness Acceptability Curve (CEAC)



The probability of CAZ/AVI treatment being cost-effective at different willingness-to-pay thresholds is shown. At thresholds above approximately 50,000–60,000 TL, the probability of CAZ/AVI treatment being cost-effective increases significantly and reaches nearly 100% above 100,000 TL. In the cost-effectiveness plane analysis, all bootstrap samples were observed to be in the NE region.

Figure 2

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SUPPLEMENTARYDATA.docx](#)