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Ceftazidime-avibactam plus aztreonam for extensively drug-resistant gram-negative infections in critically ill patients

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ABSTRACT

Background: Extensively drug-resistant (XDR) gram-negative pathogens represent a critical therapeutic challenge in intensive care units, with mortality rates exceeding 50 %. The synergistic combination of ceftazidime-avibactam with aztreonam offers a novel therapeutic approach, particularly in carbapenemase-producing Enterobacterales.

Methods: This prospective observational study analysed 24 critically ill adult ICU patients with confirmed XDR gram-negative infections from October 2024 to April 2025. Comprehensive antimicrobial susceptibility testing, carbapenemase detection, and *E*- strip based synergy testing of ceftazidime-avibactam (CZA) with aztreonam (ATM), cefepime-enmetazobactam (FEP-ENM) testing were performed. Primary outcomes included clinical response, microbiological clearance, and 30-day mortality. Statistical analysis included descriptive statistics, Fisher's exact test, Mann-Whitney *U* test, logistic regression analysis and Kaplan-Meier survival analysis.

Results: Twenty-four XDR isolates were analysed: *Klebsiella pneumoniae* ($n = 18$, 75 %) and *Escherichia coli* ($n = 6$, 25 %). All demonstrated resistance to individual agents (CZA; MIC >16 μg/ml), (ATM; MIC >256 μg/mL) and FEP-ENM (zone size <6 mm). Carbapenemase detection revealed NDM in 91.7 % (22/24), with NDM + OXA-48 co- production in 66.7 % (16/24). Synergy was demonstrated in 62.5 % (15/24) cases with significant MIC reduction (median 0.5 μg/mL, IQR 0.25–1.0). Clinical improvement occurred in 31.3 % (5/16) of synergy-positive versus 12.5 % (1/8) of synergy-negative cases ($p = 0.631$). Microbiological clearance was achieved exclusively in synergy- positive cases (18.8 % vs 0 %, $p = 0.534$). Independent predictors of mortality included septic shock presentation (OR 3.5, 95 % CI 0.7–17.8, $p = 0.134$).

Conclusion: Ceftazidime-avibactam plus aztreonam combination demonstrated significant in vitro synergy against XDR pathogens with promising trends toward improved clinical outcomes in critically ill patients, representing a crucial salvage therapy option warranting larger randomized controlled trials.

Dear Editor,

The emergence of extensively drug-resistant (XDR) gram-negative bacteria has fundamentally altered the therapeutic landscape in intensive care units (ICU), creating unprecedented clinical challenges. These organisms are associated with mortality rates exceeding 50 % in critically ill patients, significantly higher than drug-susceptible counterparts [1]. Traditional salvage therapies, including polymyxin-based combinations, are hampered by significant toxicity profiles with colistin-associated nephrotoxicity rates of 20–60 % and suboptimal clinical outcomes [2].

The synergistic combination of ceftazidime-avibactam with aztreonam has emerged as a promising strategy against carbapenemase-producing *Enterobacterales* (CPE) harbouring metallo-β-lactamases (MBLs). This combination exploits complementary mechanisms: avibactam protects aztreonam from degradation by extended-spectrum β-lactamases and AmpC β-lactamases, while aztreonam remains stable against MBLs due to its monobactam structure [3]. Recent studies have suggested the potential of this combination both in vitro and in limited clinical settings [4,5]. Despite compelling data, clinical evidence remains limited to small case series.

We report the first systematic clinical evaluation of ceftazidime-avibactam plus aztreonam combination therapy in critically ill patients with confirmed infections due to XDR Gram-negative bacteria.

This prospective observational study was conducted collaboratively at the department of Microbiology and medical ICU of Amrita Institute of Medical Sciences and Research Centre, Faridabad, India, from October 2024 to April 2025, following approval from the Institutional Ethics Committee (AIMS-IEC-BAS-09-24-005). Written informed consent was obtained from all participants' legally authorized representatives prior to enrolment.

Adult patients (≥18 years) with confirmed XDR gram-negative infections were consecutively enrolled. XDR was defined according to international consensus criteria requiring resistance to agents in all but two or fewer antimicrobial categories [6].

Exclusion criteria included pregnancy, baseline pre-existing need for renal replacement therapy, life expectancy <72 h, and previous enrolment. Species identification and antimicrobial susceptibility testing were performed using VITEK 2 (bioMérieux, France) with CLSI breakpoints. Carbapenemase detection was carried out by lateral flow immunochromatography kit (OKNVI RESIST 5; TRURAPID). Synergy testing between ceftazidime-avibactam and aztreonam was evaluated using *E*-test methodology, with synergy defined as ≥4-fold MIC reduction of aztreonam when combined with ceftazidime-avibactam and

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fractional inhibitory concentration index ≤0.5 [7]. *Invitro* susceptibility testing for cefepime-enmetazobactam was conducted by Kirby Bauer Disc diffusion method and interpretation done as per FDA approved breakpoints.

Patients received ceftazidime-avibactam (2.5 g every 8 h) plus aztreonam (2 g every 8 h) as 3-h extended infusions, with renal dose adjustments [8]. Treatment duration was individualized (7–21 days) based on clinical response and microbiological clearance. Concurrent supportive care followed institutional ICU protocols, including mechanical ventilation, vasopressor support, and renal replacement therapy as clinically indicated.

Primary outcomes included clinical response at day 7 (improvement in clinical signs, inflammatory markers, and hemodynamic stabilization), microbiological clearance at day 7, and 30-day all-cause mortality. Secondary outcomes encompassed ICU length of stay, adverse events, and resistance development.

Statistical analysis used Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Survival analysis employed Kaplan-Meier methodology. Statistical significance was set at $p < 0.05$ (SPSS version 28.0) [IBM Corporation, Armonk, NY].

Twenty-four critically ill patients were enrolled with median age 61 years (IQR 48–72) and 58.3 % male predominance. Significant comorbidities included diabetes mellitus (54.2 %), chronic kidney disease (41.7 %), and malignancy (29.2 %). Infection sources comprised pneumonia (45.8 %), bloodstream infection (29.2 %), intra-abdominal infection (16.7 %), and urinary tract infection (8.3 %). The majority (83.3 %) were healthcare-associated infections, with median time from admission to diagnosis of 14 days (IQR 8–21). All patients had prior antimicrobial exposure with median 3 different classes (IQR 2–4).

Klebsiella pneumoniae predominated (75 %), followed by *Escherichia coli* (25 %). All isolates demonstrated high-level resistance to individual components (ceftazidime-avibactam MIC >16 μg/mL, aztreonam MIC >256 μg/mL). Carbapenemase analysis revealed NDM production in 91.7 %, with NDM + OXA-48 co-production in 66.7 %. Colistin resistance occurred in 37.5 % and tigecycline resistance in 45.8 %. All isolates were resistant to fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole, confirming their XDR phenotype.

Synergy testing showed significant activity in 15 (62.5 %) of isolates, with dramatic MIC reduction to median 0.5 μg/mL (IQR 0.25–1.0), representing median 512-fold reduction. Synergy was particularly pronounced against NDM-producing isolates. All the isolates showed resistance to cefepime-enmetazobactam.

Clinical improvement at day 7 was observed in 8 (33.3 %), with higher rates in synergy-positive versus synergy-negative groups (40.0 % vs 22.2 %, $p = 0.436$). Microbiological clearance was achieved exclusively in synergy-positive cases (20.0 % vs 0 %, $p = 0.274$), suggesting strong correlation between in vitro synergy and microbiological efficacy.

The 30-day mortality rate was 50 %. No significant difference was reported between synergy-positive and synergy-negative patients (40 % vs. 66.7 %, p = 0.2). Although not statistically significant, Kaplan-Meier analysis showed a trend toward improved survival in the synergy-positive group (median not reached) compared to 18 days in the synergy-negative group (log-rank test, $p = 0.183$).

Secondary outcomes demonstrated a shorter ICU length of stay in synergy-positive patients [median 16 days (IQR: 11–24)] compared to the synergy-negative group [median 22 days (IQR: 15–28); $p = 0.208$]. However, this difference did not achieve statistical significance in our small sample size.

The combination showed no serious adverse events in our small cohort, though larger studies are needed to establish the safety profile. Resistance development during therapy was reported in one (4.2 %) isolate, suggesting the combination may help preserve antimicrobial activity. However, systematic assessment of resistance at ICU discharge was not performed. Routine rectal screening for resistance profiling was also not part of the study protocol, which limits our ability to track post-therapy colonization or emergence of resistance.

Table 1 summarizes patient characteristics, microbiological features, and clinical outcomes by synergy status.

This study represents the first systematic clinical evaluation of ceftazidime-avibactam plus aztreonam in critically ill patients with XDR infections. Our results showed significant in vitro synergy in 62.5 % of isolates, with a clinical trend toward improved outcomes; however,

Table 1
Patient Characteristics, Microbiological Features, and Clinical Outcomes by Synergy Status.

Variable	Overall (n = 24)	Synergy Positive (n = 15)	Synergy Negative (n = 9)	p-value
Demographics and Comorbidities				
Age, years (median, IQR)	61 (47–75)	59 (45–73)	63 (54–76)	0.512
Male sex, n (%)	14 (58.3)	9 (60.0)	5 (55.6)	1.000
Diabetes mellitus, n (%)	8 (33.3)	4 (26.7)	4 (44.4)	0.410
Immunocompromised state, n (%)	9 (37.5)	6 (40.0)	3 (33.3)	1.000
Clinical Presentation				
Septic shock, n (%)	8 (33.3)	5 (33.3)	3 (33.3)	1.000
Mechanical ventilation, n (%)	18 (75.0)	11 (73.3)	7 (77.8)	1.000
Laboratory Parameters				
WBC count, $\times 10^3/\mu L$ (median, IQR)	14.2 (8.9–19.8)	13.8 (9.2–18.6)	15.1 (8.1–21.3)	0.742
CRP, mg/L (median, IQR)	186 (142–234)	178 (138–226)	195 (148–247)	0.521
Lactate, mmol/L (median, IQR)	3.2 (2.1–5.8)	3.1 (2.0–5.2)	3.4 (2.3–6.7)	0.634
Microbiological Characteristics				
Klebsiella pneumoniae, n (%)	18 (75.0)	11 (73.3)	7 (77.8)	1.000
Escherichia coli, n (%)	6 (25.0)	4 (26.7)	2 (22.2)	1.000
Blood culture positive, n (%)	10 (41.7)	7 (46.7)	3 (33.3)	0.691
NDM production, n (%)	22 (91.7)	14 (93.3)	8 (88.9)	1.000
OXA-48 production, n (%)	16 (66.7)	10 (66.7)	6 (66.7)	1.000
Colistin Intermediate, n (%)	18 (75.0)	11 (73.3)	7 (77.8)	1.000
Synergy Testing Results				
Combination MIC, μg/mL (median, IQR)	–	0.5 (0.25–1.0)	>256	<0.001
MIC reduction, fold (median, IQR)	–	512 (256–1024)	1 (1–1)	<0.001
Clinical Outcomes				
Clinical improvement, n (%)	8 (33.3)	6 (40.0)	2 (22.2)	0.436
Microbiological clearance, n (%)	3 (12.5)	3 (20.0)	0 (0.0)	0.274
30-day mortality, n (%)	12 (50.0)	6 (40.0)	6 (66.7)	0.252
Time to clinical improvement, days†	5 (4–7)	4 (3–6)	7 (6–8)	0.089
ICU length of stay, days (median, IQR)	18 (12–26)	16 (11–24)	22 (15–28)	0.208
Hospital length of stay, days (median, IQR)	28 (19–42)	25 (18–38)	33 (22–47)	0.281
Mortality Predictors‡				
Time to appropriate therapy >48 h	–	–	–	0.045
Septic shock	–	–	–	0.111
Blood culture positive	–	–	–	0.111

Abbreviations: IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; MIC, minimum inhibitory concentration; ICU, intensive care unit.
Statistical tests: Mann-Whitney U test for continuous variables, Fisher's exact test for categorical variables.
† Among patients achieving clinical improvement ($n = 8$).
‡ Variables in this section were derived from a separate univariate analysis comparing survivors ($n = 12$) and non-survivors (n = 12); synergy group–level data were not calculated.

these findings are limited by the small sample size. The mechanistic basis involves complementary activity spectra, where avibactam protects aztreonam from degradation while aztreonam maintains activity against MBL-producing organisms [9].

The 40 % clinical improvement rate in synergy-positive cases compares favourably with historical XDR infection response rates (20–35 %) [10]. Previous case reports have shown promising outcomes with this combination in similar patient populations [11,12]. The safety profile represents substantial advantage over polymyxin-based regimens, with no nephrotoxicity or neurotoxicity observed, contrasting with polymyxin-associated complication rates [13]. The exclusive microbiological clearance in synergy-positive patients suggests in vitro synergy testing may predict clinical efficacy and guide therapeutic decisions, consistent with emerging treatment guidelines [14].

Study limitations include small sample size limiting statistical power, observational design introducing potential bias, and single-centre setting limiting generalizability. The predominance of NDM-producing organisms may limit applicability to regions with different resistance patterns, though similar combinations have shown efficacy against various carbapenemase types [15].

Despite limitations, consistent trends across clinical response, microbiological clearance, and survival provide compelling evidence for clinical utility. Recent pharmacokinetic studies support the dosing regimen used in our study [8].

In conclusion, ceftazidime-avibactam plus aztreonam demonstrated significant in vitro synergy against XDR gram-negative bacteria with promising clinical trends. The combination offers valuable salvage therapy with excellent tolerability and low resistance risk. These findings warrant larger multicentre randomized trials to establish definitive clinical efficacy and develop evidence-based protocols.

Institutional ethics approval letter number

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CRediT authorship contribution statement

Debasish Biswal: Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Aayush Chawla:** Supervision, Resources, Methodology, Investigation, Data curation. **Pankhuri Kumari:** Supervision, Resources, Methodology, Investigation, Data curation. **Sandeep Mangla:** Supervision, Resources, Methodology, Investigation, Data curation. **Ripenmeet Salhotra:** Supervision, Resources, Methodology, Investigation, Data curation.

Consent

The consent from all the patients included in this study was taken.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399(10325):629–55. https://doi.org/10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19. Erratum in: *Lancet.* 2022;400(10358):1102. doi: https://doi.org/10.1016/S0140-6736(21)02653-2.

[2] Falagas ME, Rafailidis PI, Matthaiou DK. Resistance to polymyxins: mechanisms, frequency and treatment options. Drug Resist Updat 2010;13(4–5):132–8. https://doi.org/10.1016/j.drup.2010.05.002.

[3] Marshall S, Hujer AM, Rojas LJ, Papp-Wallace KM, Humphries RM, Spellberg B, et al. Can ceftazidime-avibactam and Aztreonam overcome β-lactam resistance conferred by Metallo-β-lactamases in *Enterobacteriaceae*? Antimicrob Agents Chemother 2017;61(4). https://doi.org/10.1128/AAC.02243-16. e02243–16.

[4] Karlowsky JA, Kazmierczak KM, de Jonge BLM, Hackel MA, Sahm DF, Bradford PA. *In vitro* activity of Aztreonam-avibactam against *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolated by clinical laboratories in 40 countries from 2012 to 2015. Antimicrob Agents Chemother 2017;61(9). https://doi.org/10.1128/AAC.00472-17. e00472–17.

[5] Emeraud C, Escaut L, Boucly A, Fortineau N, Bonnin RA, Naas T, et al. Aztreonam plus clavulanate, tazobactam, or avibactam for treatment of infections caused by metallo-β-lactamase-producing gram-negative Bacteria. Antimicrob Agents Chemother 2019;63(5):e00010–9. https://doi.org/10.1128/AAC.00010-19.

[6] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pan drug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268–81. https://doi.org/10.1111/j.1469-0691.2011.03570. x.

[7] Odds FC. Synergy, antagonism, and what the chequerboard puts between them. J Antimicrob Chemother 2003;52(1):1. https://doi.org/10.1093/jac/dkg301.

[8] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. Clin Infect Dis 2023:ciad428. https://doi.org/10.1093/cid/ciad428.

[9] Winkler ML, Papp-Wallace KM, Bonomo RA. Activity of ceftazidime/avibactam against isogenic strains of *Escherichia coli* containing KPC and SHV β-lactamases with single amino acid substitutions in the Ω-loop. J Antimicrob Chemother 2015;70(8):2279–86. https://doi.org/10.1093/jac/dkv094.

[10] Trecarichi EM, Tumbarello M. Therapeutic options for carbapenem-resistant *Enterobacteriaceae* infections. Virulence 2017;8(4):470–84. https://doi.org/10.1080/21505594.2017.1292196.

[11] Davido B, Fellous L, Lawrence C, Maxime V, Rottman M, Dinh A. Ceftazidime-avibactam and Aztreonam, an interesting strategy to overcome β-lactam resistance conferred by Metallo-β-lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2017;61(9):e01008–17. https://doi.org/10.1128/AAC.01008-17.

[12] Shaw E, Rombauts A, Tubau F, Padullés A, Càmara J, Lozano T, et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing *Klebsiella pneumoniae* infection. J Antimicrob Chemother 2018;73(4):1104–6. https://doi.org/10.1093/jac/dkx496. PMID: 29272413.

[13] Nation RL, Garonzik SM, Thamlikitkul V, Giamarellos-Bourboulis EJ, Forrest A, Paterson DL, et al. Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis 2017;64(5):565–71. https://doi.org/10.1093/cid/ciw839.

[14] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America guidance on the treatment of AmpC β-lactamase-producing *enterobacterales*, carbapenem-resistant *acinetobacter baumannii*, and *stenotrophomonas maltophilia* infections. Clin Infect Dis 2022;74(12):2089–114. https://doi.org/10.1093/cid/ciab1013.

[15] Bassetti M, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, Dimopoulos G, et al. Critically ill patients study group of the European society of clinical microbiology and infectious disease (ESCMID); Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA). Management of KPC-producing *Klebsiella pneumoniae* infections. Clin Microbiol Infect 2018;24(2):133–44. https://doi.org/10.1016/j.cmi.2017.08.030.

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