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HIGHLIGHTS

- Fixed ATM-AVI co-exposure reduces risk of PK asynchrony.
- Standardized MIC testing for ATM-AVI; none validated for CAZ-AVI+ATM.
- PK/PD supports q6h 3-h infusions; adequate AVI exposure is critical.
- Clinical data are promising, but direct comparative studies are lacking.
- PBP3 alterations can raise ATM-AVI MICs and impact treatment choices.

A Comparative Evaluation of Aztreonam-Avibactam and Ceftazidime-Avibactam Plus Aztreonam for Infections Due to MBL-Producing Enterobacterales

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ABSTRACT

Aztreonam-avibactam (ATM-AVI) and ceftazidime-avibactam plus aztreonam (CAZ/AVI-ATM) represent therapeutic strategies for infections caused by metallo-β-lactamase (MBL)-producing Enterobacterales. This perspective synthesizes mechanistic rationale, microbiologic determinants of activity, pharmacokinetic/pharmacodynamic principles, and available clinical outcomes to compare these regimens and identify knowledge gaps. Both approaches are expected to provide activity against MBL-producing organisms; however, important distinctions exist. ATM-AVI ensures fixed and predictable co-exposure of aztreonam and avibactam, minimizing the risk of pharmacokinetic asynchrony inherent to administering CAZ/AVI with separate aztreonam. The efficacy of ATM-AVI may nevertheless be influenced by organism-specific resistance mechanisms and pharmacologic variables. CAZ/AVI-ATM offers a pragmatic alternative but introduces logistical complexity and potential variability in inhibitor exposure. Observational data appear more favorable for ATM-AVI, although direct comparisons are not available. In the absence of direct comparative trials, regimen selection should consider renal function, infection syndrome, and the feasibility of sustaining adequate inhibitor exposure.

KEYWORDS

Aztreonam, Avibactam, Ceftazidime, Metallo-β-lactamase-producing Enterobacterales.

Perspective

Aztreonam-avibactam (ATM-AVI) has recently become available as a therapeutic option for infections caused by metallo-β-lactamase (MBL)-producing Enterobacterales. The combination is currently approved and available in the European Union, the United Kingdom, and the United States, with regulatory expansion anticipated in parts of Asia and Latin America. However, despite regulatory approvals and encouraging early data, direct head-to-head comparative clinical evidence versus ceftazidime-avibactam plus aztreonam (CAZ/AVI-ATM) remains limited, and comparative effectiveness cannot yet be established.

Before the introduction of ATM-AVI, ceftazidime-avibactam plus aztreonam (CAZ/AVI-ATM) was commonly used to treat infections due to MBL-producing Enterobacterales. Owing to accumulated clinical experience and established prescribing familiarity, this regimen remains widely used. However, it remains uncertain whether one strategy is associated with superior clinical outcomes in patients with MBL-producing Gram-negative infections. This perspective synthesizes the microbiologic, pharmacokinetic/pharmacodynamic (PK/PD), and clinical evidence supporting ATM-AVI and contextualizes these data in comparison with CAZ/AVI-ATM. It also highlights the remaining evidentiary gaps that need to be addressed to inform optimal therapeutic selection for patients with MBL-producing Enterobacterales infections.

Comparative Microbiologic Activity and Resistance Determinants

Both ATM-AVI and CAZ/AVI-ATM are designed to overcome the complex β-lactamase profile characteristic of MBL-producing Enterobacterales. More specifically, ATM is intrinsically stable to MBL-mediated hydrolysis but can be compromised by co-produced serine β-lactamases, which are inhibited by AVI [1,2].

Across large contemporary surveillance collections, ATM-AVI shows a high likelihood of *in vitro* activity against Enterobacterales, including MBL producers. In the ATLAS Global Surveillance Program (2016–2020), ATM-AVI retained potent antimicrobial activity against MBL-producing Enterobacterales (MIC_{50}/MIC_{90} 0.12/1 mg/L) [3]. Using EUCAST/CLSI 2024 interpretive criteria, pooled susceptibility among carbapenem-non-susceptible and/or carbapenemase-producing Enterobacterales was 99.5%, with only a modest decrease among MBL-producers (96.9%) and NDM-producers (95.6%) [4]. In addition, in a nationwide collection of double-carbapenemase-producing Enterobacterales, including isolates co-producing an MBL with a class A carbapenemase (n = 14) or an MBL with a class D carbapenemase (n = 35), ATM-AVI retained excellent activity (MIC_{50}/MIC_{90} ≤0.25/0.5 mg/L) [5].

The emergence of PBP3 modifications that reduce ATM target engagement can compromise the activity of ATM-AVI. In NDM-producing *E. coli*, four-amino-acid insertions in PBP3 (e.g., YRIK/YRIN) have been associated with elevated ATM-AVI MICs and reduced ATM affinity. This effect is further amplified when acquired AmpC enzymes (e.g., CMY-42) are co-expressed, consistent with a multi-mechanism, stepwise erosion of activity [1]. Additional mechanisms, particularly porin loss and potentially enhanced efflux, may further increase ATM-AVI MICs by limiting periplasmic drug access, compounding the impact of altered PBP3 binding [6]. These PBP3 four–amino-acid insertions were first described in *E. coli* lineages reported from Asia and the Middle East (notably including India), and have since been documented across multiple countries, consistent with broader dissemination [7,8]. Reports of very high prevalence (including >90% among NDM-producing *E. coli* in some single-center cohorts) should be interpreted as context-specific, reflecting local epidemiology and study design, and may not be generalizable across regions or time periods [8].

From a pragmatic perspective, a pivotal benefit of ATM-AVI lies in the accessibility and feasibility of direct susceptibility testing employing MIC-based methodologies and associated diffusion surrogates. This feature enhances the reproducibility of interpretations within clinical microbiology workflows. Conversely, no universally validated, standardized MIC-testing approach for the co-administration strategy exists for CAZ/AVI-ATM. Pragmatic methods such as disk/broth disk elution may provide only a crude estimate of activity and are inherently less informative than a formal MIC for a fixed combination [9].

In this context, the rationale sometimes cited for CAZ/AVI-ATM is not limited to “AVI protection of ATM,” but also includes the possibility of broader PBP engagement. While both CAZ and ATM primarily target PBP3, CAZ is reported to have additional, though variable, affinity for other PBPs (including PBP1a and PBP1b), which could theoretically provide partial buffering when PBP3 is altered [10]. Moreover, although CAZ is generally susceptible to MBL hydrolysis, a small fraction of CAZ molecules may escape hydrolysis by NDM enzymes, potentially allowing residual antibacterial activity and supporting the plausibility of two β-lactams [2]. This represents a biologically plausible but unproven, hypothesis-generating concept and should be considered speculative pending dedicated experimental and clinical validation.

Pharmacokinetic/Pharmacodynamic Profiles and Exposure Considerations

The fixed 3:1 formulation of ATM-AVI ensures synchronized exposure to both components, allowing AVI to inhibit co-produced serine β-lactamases while ATM, intrinsically stable to MBL hydrolysis, binds its primary target, PBP3 [11,12]. Accordingly, population PK/PD models incorporate joint target attainment: ≥60% fT>MIC for ATM and ≥50% fT>2.5 mg/L for AVI [12]. With a loading dose followed by

3-hour infusions every 6 hours, simulations demonstrate high joint probability of target attainment across renal function strata, including augmented renal clearance, with AVI exposure emerging as the principal determinant of success [11,12]. Recommended dosing therefore includes a 2000/670 mg loading dose followed by 1500/500 mg every 6 hours (3-hour infusion) for creatinine clearance >50 mL/min, with renal adjustment as needed [11]. In accordance with the significance of exposure synchronisation, hollow-fibre infection model (HFIM) experiments assessing the co-administration strategy (ceftazidime/avibactam plus aztreonam) revealed that staggered dosing was less effective than simultaneous administration, and that prolonged/continuous infusions augmented bacterial killing and resistance suppression against NDM-producing *E. coli* and *K. pneumoniae* [13]. These HFIM-informed regimens were subsequently subjected to evaluation in a phase I study, which provided support for the feasibility of clinically relevant exposure profiles. However, this evaluation also served to highlight the necessity for laboratory monitoring (e.g. hepatic enzymes) when high-dose aztreonam strategies are employed [14]. EUCAST and CLSI use the same susceptible cutoff for aztreonam–avibactam (S ≤4 mg/L). However, interpretive categorisation beyond susceptibility differs (eg, CLSI includes an intermediate category at 8/4 mg/L and resistance at ≥16/4 mg/L, whereas EUCAST defines non-susceptibility as >4 mg/L and uses an ATU approach for disk diffusion) [9,15].

Finally, CAZ/AVI-ATM is pharmacologically and operationally complex because ATM and AVI are delivered as separate products, potentially with differing dosing schedules and infusion parameters. Simultaneous administration is technically feasible under specific conditions: compatibility studies suggest no physical incompatibility between CAZ-AVI and ATM during simulated and actual Y-site co-infusion over 2-hour infusions, supporting strategies designed to preserve inhibitor-substrate overlap [16].

Nonetheless, CAZ/AVI-ATM requires greater coordination than ATM-AVI and may be less practical outside the inpatient setting.

Clinical Outcomes

Comparative effectiveness studies directly evaluating clinical outcomes between ATM-AVI and CAZ/AVI-ATM are not currently available. Clinical data for ATM-AVI remain limited and derive from two prospective cohorts involving patients with MBL-producing Gram-negative infections. The first is the phase 3 REVISIT trial in hospitalised adults with complicated intra-abdominal infection or HAP/VAP, which included ten patients with MBL-positive baseline pathogens (seven in the ATM-AVI group and three in the meropenem group). [17]. The second study enrolled 15 hospitalized adults with confirmed MBL-producing Gram-negative infections randomized in a 2:1 ratio to ATM-AVI (± metronidazole for complicated intra-abdominal infection) or alternative therapy [18]. Clinical cure occurred in 43% (5/12) of those receiving ATM-AVI compared with 0% (0/3) in the alternative therapy arm. Twenty-eight-day survival was likewise higher with ATM-AVI (92% [11/12] vs 33% [2/3]).

In contrast, most clinical data supporting CAZ/AVI-ATM are observational. In a cohort of bloodstream infections caused by MBL-producing Enterobacterales, 30-day survival approached 80% with CAZ/AVI-ATM compared with 56% among patients receiving alternative regimens, predominantly polymyxin-based therapy [19]. In addition, several observational experiences describe outcomes with CAZ/AVI-ATM in MBL-producing Enterobacterales infections. Because available studies are highly heterogeneous and not directly comparable, reported cure rates should be considered descriptive. In aggregated CAZ/AVI–ATM reports, cure has been described in ~84% (67/80), whereas in the limited ATM-AVI reports, cure has been reported in 42% (7/17). No

inference of superiority can be drawn from these non-comparable datasets. Much of the CAZ/AVI-ATM experience derives from case reports and small series, which are susceptible to publication bias favoring positive outcomes. Furthermore, substantial heterogeneity exists across studies with respect to patient populations, infection syndromes, MBL genotypes, dosing strategies, and outcome definitions. While these numerical differences are hypothesis-generating, the absence of controlled comparative data precludes definitive conclusions regarding any incremental benefit from adding ceftazidime.

Comparative Safety Data

From a safety standpoint, both regimens appear to be generally well tolerated. In a phase 1 study conducted in healthy volunteers, elevations in alanine aminotransferase and/or aspartate aminotransferase were observed in approximately 40% of participants receiving CAZ/AVI-ATM [14]. These abnormalities were asymptomatic and resolved following treatment discontinuation, with no evidence of persistent hepatotoxicity. In contrast, aminotransferase elevations with ATM-AVI have been reported in approximately 5% of treated patients, without a signal suggestive of severe drug-induced liver injury in available clinical datasets [17]. Although cross-study comparisons should be interpreted cautiously, the available data suggest a lower frequency of transient hepatic laboratory abnormalities with ATM-AVI.

Looking Ahead

Future research priorities are clear. Studies prioritizing clinically actionable stratification strategies, including standardized phenotypic susceptibility testing for both regimens and rapid molecular assays capable of detecting PBP3 mutations within

clinically relevant timeframes are needed. The presence of such mutations may compromise the activity of both CAZ/AVI-ATM and ATM-AVI (as well as cefiderocol), necessitating consideration of alternative agents such as tigecycline or polymyxins pending the availability of newer β-lactam/β-lactamase inhibitor combinations.

In parallel, well-designed animal infection models are needed to translate preclinical PK/PD findings into clinically relevant contexts. These models would enable exposure-response evaluation across infection compartments and support dose optimization under controlled conditions.

Prospective clinical trials - or, where infeasible, rigorously matched comparative cohort studies - are required to determine whether the theoretical advantages of CAZ/AVI-ATM, including potential PBP target redundancy, translate into superior clinical outcomes. Although therapeutic drug monitoring (TDM) may refine dosing in select settings, β-lactam/β-lactamase inhibitor TDM is not widely available and is unlikely to serve as a practical differentiator between regimens in most centers. Accordingly, near-term efforts should focus on pragmatic, broadly applicable dosing and administration guidance that accounts for renal function and common clinical scenarios, complemented by prospective pharmacometric substudies in specialized centers to inform future refinement.

In summary, ATM-AVI represents a PK/PD-informed strategy for MBL-producing Enterobacterales supported by a coherent mechanistic rationale, encouraging - though still limited - clinical data, and feasibility advantages. CAZ/AVI-ATM remains a viable alternative, underpinned by experimental PK/PD evidence, early-phase safety data, and favorable observational outcomes.

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.

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Ethical approval statement

As this work is a perspective and does not involve new data collection or research involving human participants or animals, the requirement for ethical approval and informed consent is not applicable.

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Declaration of Interest Statement

☒ 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.

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