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Consultation name: Proposed revision of breakpoints for carbapenems with and without inhibitors, and for ceftazidime-avibactam

Closing Date: 2026-03-15

Please send comments to the EUCAST Scientific Secretary at Mandy.Wootton@wales.nhs.uk

Comment from (name, contact details)	Comments	EUCAST Responses
Katie Hopkins (katie.hopkins@ukhsa.gov.uk) on behalf of UKHSA AMR&HCAI Division	Revisions of carbapenem breakpoints may result in an apparent increase in carbapenem and BL/BLI non-susceptibility in national surveillance datasets	Since typically there are very few isolates at the former R breakpoints, surveillance data should not change significantly. If these isolates are more common in certain regions this should cause an alert for Public Health and may even be considered an argument in favour of lowered breakpoints. Also knowing MIC distributions, impact of breakpoints change can be tracked.
Dr Paurus Irani Senior Director, Global Medical Affairs Anti-infectives, Speciality Care, Pfizer	The totality of available pharmacokinetic/pharmacodynamic (PK/PD), microbiological surveillance, exposure–response modelling and real-world clinical data supports retention of the current EUCAST susceptibility breakpoint of ≤ 8 mg/L for ceftazidime–avibactam (CAZ–AVI) against Enterobacterales. Lowering the breakpoint to 4 mg/L would:	The initial interpretations of the PK-PD data when CAZ-AVI was introduced on the market suggested that a breakpoint at 8 mg/L might work. However, there was at that point limited real-life clinical data and knowledge about resistance mechanisms.



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<p>Paurus.Irani@pfizer.com</p>	<ul style="list-style-type: none"> • Reclassify isolates with demonstrated PK/PD target attainment and reported clinical effectiveness as resistant • Not be supported by contemporary joint PK/PD probability of target attainment (PTA) modelling • Not be supported by exposure–response analyses demonstrating no loss of efficacy between 4 mg/L and 8 mg/L • Introduce discordance between EUCAST susceptibility categorisation (S/I/R), quantitative PK/PD modelling and reported clinical outcomes <p>1. Surveillance Data and MIC Distributions</p> <p>Although EUCAST notes the absence of a formally defined ECOFF for CAZ–AVI, global surveillance programs (e.g., ATLAS, the Antimicrobial Testing Leadership and Surveillance global surveillance program) demonstrate a unimodal MIC distribution for Enterobacterales, with the majority of isolates at ≤ 4 mg/L and MIC90 values remaining stable over multiple years of monitoring (see accompanying figures). This stability suggests no evidence of progressive susceptibility erosion that may necessitate breakpoint revision.</p> <p>However, when clinically important subpopulations such as KPC-producing carbapenem-resistant Enterobacterales (CRE) are evaluated separately, the MIC distribution shifts closer to the current breakpoint. As illustrated in Figure 1, the overall Enterobacterales population demonstrates a distribution well below the current susceptibility breakpoint. In contrast, Figure 2 shows that the MIC distribution for KPC-2- and KPC-3-producing isolates</p>	<p>Given these aspects, which have been mentioned in the consultation document, the total body of evidence suggests it would be a safer approach to decrease the breakpoint by one MIC dilution. There is very limited evidence (e.g., animal data or hollow fiber) suggesting that the killing of KPC-strains with MICs of 8 mg/L is efficient. While PK-PD will always play an important role initially for setting of breakpoints there is no rule about discordance between different methods, and this will also as always depend on the model, the underlying dataset and the desired target attainment.</p> <p>1. Since the role of avibactam is to restore susceptibility of the parent beta-lactam, the ECOFF of CAZ-AVI should be regarded 1 mg/L for Enterobacterales. As you correctly point out even for producers of KPC there are few isolates at the MIC of 8. It is therefore not surprising that there is little clinical data for such strains and lowering the breakpoint cannot increase the resistance rate beyond this fraction. Understandably, during development of the current breakpoints no KPC-producing strains with an MIC of 8 mg/L were used for determination of the PD target. As pointed out in the Consultation some authors</p>
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	<p>extends into the 4–8 mg/L range. In this context, lowering the breakpoint from 8 mg/L to 4 mg/L would reclassify a proportion of isolates within this clinically relevant population as resistant despite PK/PD evidence and clinical experience supporting favourable treatment outcomes.</p> <p>2. PK/PD Evidence</p> <p>2.1. Foundational and Contemporary Joint PK/PD Modelling: The current breakpoint was derived using validated joint PK/PD targets (ceftazidime $\geq 50\%$ $fT > MIC$ and avibactam $\geq 50\%$ $fT > 1$ mg/L), supported by preclinical models and human PK/PD simulations (Das et al. 2019). Approved dosing (2.5 g every 8 h with a 2-h infusion) was selected based on quantitative PTA analyses demonstrating adequate joint target attainment up to an MIC of 8 mg/L. Exposure–response analyses evaluating clinical outcomes relative to baseline MIC have not demonstrated reduced efficacy within the susceptible range up to 8 mg/L, supporting the robustness of the current PK/PD-derived breakpoint.</p> <p>2.2. Critically Ill Patients and Augmented Renal Clearance: Population PK data and Monte Carlo simulations in critically ill patients, including those with augmented renal clearance and mechanical ventilation, demonstrate high probability of joint PK/PD target attainment at MIC ≤ 8 mg/L (Stein et al. 2019). These findings directly counter concerns that critically ill patients may not achieve adequate exposure at the currently accepted breakpoint of ≤ 8 mg/L.</p>	<p>suggest (Gatti et al) that clinical response is impaired at MIC ≥ 4 mg/L.</p> <p>2. It is true that the current breakpoints were set on the assumption that a $\geq 50\%$ T>MIC was correct. As pointed out, this is no longer generally accepted. The paper you cite (Stein et al) did not determine the target for critically ill patients but looked if (and how) the 50% target could be reached. The conclusion was that at 16 mg/L 50% T>MIC can be reached; however, the value for 8 mg/L is not given.</p> <p>The argument about ELF depends again on what your target values are for ceftazidime. A lot more is known today than when the breakpoints were set about mechanisms of resistance in KPC-producers and most of the arguments made initially when the antimicrobial was new was based on either ESBL-producers or KPC-producers without elevated MICs.</p> <p>3. We agree that the data is not conclusive about clinical outcomes, although many studies report favourable outcome with CAZ-AVI. Unfortunately, many of the studies did not report MIC values but used</p>
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	<p>2.3. Lung Exposure and Pneumonia (ELF Modelling): Concerns regarding pneumonia and deep-seated infections are particularly important in breakpoint deliberations. Population PK modelling of plasma and epithelial lining fluid (ELF) concentrations has directly evaluated this issue. Dimelow et al. (2018) developed compartmental PK models linking plasma and ELF exposures of ceftazidime and avibactam. Their simulations demonstrated that, at the approved dosing regimen:</p> <ul style="list-style-type: none"> • ELF concentrations for both agents achieve exposures exceeding predefined joint PK/PD targets • ELF:plasma penetration ratios are approximately 52% for ceftazidime and 42% for avibactam, demonstrating infection-site exposure consistent with clinical success at MIC values of 8 mg/L • ELF exposures frequently exceed plasma PK/PD thresholds predictive of clinical efficacy <p>These infection-site exposure simulations directly address EUCAST’s concerns regarding pneumonia and other deep-seated infections by demonstrating that standard dosing achieves PD targets in the lung compartment even at MIC values of 8 mg/L.</p> <p>3. Real-World Clinical Outcomes, Including MIC Context</p> <p>Robust real-world experience supports clinical and microbiological effectiveness of CAZ–AVI when used according to current susceptibility criteria. Multicentre analyses (e.g., Aktuğ-Demir et al. 2025) involving 1,245 patients in an OXA-48-dominant region</p>	<p>other, derivative tests to estimate susceptibility (Aktuğ-Demir et al. https://pmc.ncbi.nlm.nih.gov/articles/PMC12805475/).</p> <p>4. We agree that the mechanisms of resistance are complex and not directed magically to a given MIC-value, but the risk increases with increasing MICs that there is an accumulation of resistance mechanisms that will ultimately result in risk for therapeutic failure. Clearly there has over time been quite a lot of development of resistance to CAZ-AVI in areas where the antimicrobial has been used extensively vs KPC-producers, and this calls for caution when pushing the limits of the antimicrobial too much, with resulting suboptimal exposure in selected cases. A recent paper (Yang F, et al, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC13055305/) suggests that suboptimal exposure is a driver for development of resistance.</p> <p>5. We disagree that the breakpoint change would lead to reliance of polymyxins – there are certainly also other alternatives, and as Pfizer pointed out themselves, it is already clear that the value 8 mg/L is a rare one</p>
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	<p>demonstrated high microbiological cure (~82%) and mortality rates aligned with severity of illness (higher WHO severity scores, mechanical ventilation, CRRT) rather than MIC category.</p> <p>Importantly, systematic meta-analyses (focusing on bacteraemia and nosocomial pneumonia) report significantly lower mortality and higher clinical cure with CAZ–AVI relative to comparators (Shields et al. 2024), reinforcing observed clinical effectiveness across severe infection types.</p> <p>Where MIC data were available, outcomes did not deteriorate for isolates between 4 mg/L and 8 mg/L. Mortality and treatment failure were driven by illness severity indices rather than MIC category (for it would have been highlighted). In other real-world studies, no clinically validated efficacy threshold at 4 mg/L has been identified, and the absence of such reporting suggests no clinically significant deterioration across the susceptible range.</p> <p>Interpretation of single retrospective analyses should be done with caution due to potential confounding factors, including disease severity, treatment selection bias, dosing heterogeneity and source control.</p> <p>4. Resistance Development Is Not MIC Dependent</p> <p>Mechanistically, resistance to CAZ–AVI emerges through defined molecular changes (e.g., Ω-loop mutations in the clinically important KPC enzyme, porin alterations and efflux changes), rather than simply crossing a specific MIC threshold. Resistance selection is associated with prolonged therapy and suboptimal exposures, irrespective of MIC within the susceptible range.</p>	<p>and the most important is that strains with MICs ≤ 4 mg/L will still be regarded susceptible.</p> <p>6. As pointed out, breakpoints need to be specific for the active antibiotic; however, in current BL/BLI combinations the activity is that of the active combination partner and thus should reflect the breakpoint of that compound. The EUCAST Rationale Document shows that at 4 mg/L the curves for T>MIC drop and therefore the attained T>MIC at 8 mg/L is less safe than that at 4 mg/L.</p> <p>The burden of evidence should always focus on patient safety. Thus, if we were to retain the breakpoint at 8 mg/L, there needs to be compelling evidence that this would be a safe alternative. There is no need to prove that 8 mg/L is associated with a significantly worse outcome. Rather it is a safety measure to lower the breakpoint to the level of I/R breakpoint for ceftazidime alone vs Enterobacterales in the absence of strong evidence supporting a higher breakpoint. The breakpoint was driven initially by PK/PD, and with few strains with complex resistance mechanisms. Thus, we would need to see data with strains having MICs of 8 mg/L that would demonstrate</p>
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	<p>5. Clinical and Stewardship Implications</p> <p>Reducing the breakpoint may restrict access to effective therapy for carbapenem-resistant Enterobacterales infections and increase reliance on alternative agents with less favourable safety profiles such as colistin and polymyxin B. The observed safety profile of CAZ–AVI across infection types is consistent with the established safety profile of ceftazidime monotherapy, and no new safety findings have been identified since EMA approval in 2016. Breakpoint changes should be supported by demonstrated exposure–response failure at the higher MIC boundary; such evidence is not present in current PK/PD or clinical outcome data.</p> <p>6. Alignment With Newer BL/BLIs</p> <p>While consistency across β-lactam/β-lactamase inhibitor (BL/BLI) combinations may be desirable for interpretive simplicity, breakpoints should remain drug specific and evidence driven. Each BL/BLI combination has unique intrinsic antibiotic activity, spectrum of activity, PK, joint PK/PD targets and resistance profiles. For example, ceftazidime penetration to ELF exceeds cefepime penetration, and avibactam PK/PD targets differ from enmetazobactam targets. Breakpoints for related compounds appropriately differ based on their pharmacology.</p> <ul style="list-style-type: none">• Carbapenems: Meropenem ≤ 2 mg/L; ertapenem ≤ 0.5 mg/L; imipenem ≤ 2 mg/L (reflects distinct PK)• Cephalosporins: Ceftriaxone < 1 mg/L; ceftazidime < 1–2 mg/L; cefepime ≤ 1 mg/L (reflects distinct penetration and activity)	<p>outcomes comparable to those of strains with lower MICs.</p>
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	<p>Extrapolating CAZ–AVI breakpoint criteria by analogy with other BL/BLI agents assumes equivalent joint PK/PD behaviour not supported by current comparative evidence.</p> <p>Across microbiological surveillance distributions, quantitative PK/PD modelling (including infection-site simulations) and large real-world clinical outcome datasets, there is no demonstrated microbiological or clinical inflection at an MIC value of 4 mg/L that would justify lowering the CAZ–AVI breakpoint. The available evidence continues to support retention of the EUCAST susceptibility breakpoint at ≤ 8 mg/L for ceftazidime–avibactam against Enterobacterales.</p> <p>References</p> <ol style="list-style-type: none">1. Antimicrobial Testing Leadership and Surveillance (ATLAS). Available at https://atlas-surveillance.com2. Demir NA, et al. <i>Infect Dis Clin Microbiol</i> 2025;15;7(4):411-425.3. Stein GE, et al. <i>Surg Infect (Larchmt)</i> 2019;20(1):55-61.4. Dimelow R, et al. <i>Drugs R D</i> 2018;18(3):221-230. <p>Das S, et al. <i>Antimicrob Agents Chemother</i> 2019;63(4):e02187-18.</p>	
NWGA Christoffer Lindemann	The NWGA fully supports the proposed carbapenem and ceftazidime-avibactam breakpoint changes.	Thank you.
Christian Giske, SRGA	For <i>P. aeruginosa</i> and <i>Acinetobacter</i> spp. versus meropenem it seems as if the most suitable S-breakpoint would normally be 1 mg/L, while the ECOFFs are 2 mg/L. Both of these microorganisms cause ICU-infections and are difficult to treat. Rather than accepting a lower T>MIC and increasing the S-bp to avoid splitting the wild-type, it might be good instead to consider putting the wild type in the I-group with breakpoints of <0.001/4 mg/L. There could also be some antimicrobial stewardship benefits from this strategy, as meropenem would be among the many agents reported as “I” in <i>P. aeruginosa</i> .	We agree that this is a strategy to avoid many misunderstandings and make therapy of severe infections safer.