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Letter to the Editor

# Response to Author Comments on "Clinical, microbiological characteristics and predictors of mortality in patients with carbapenemase-producing Enterobacterales blood stream infections"

*Dear Sir/Madam,*

Thank you for your letter and your interest and feedback on our publication titled "*Clinical, microbiological characteristics and predictors of mortality in patients with carbapenemase-producing Enterobacterales bloodstream infections: a multi-centre study*" [1]. We agree with the need for faster treatment of bacteraemia and the need for optimised and rapid diagnostic pathways.

You discuss the use of the definitions in this report and in particular the use of the words "effective" and "definitive". We would first note that there are, as yet, no standard terms or definitions used in describing timings in research in the treatment of bacteraemia. For example, the different terms of "discordant empiric antibiotic therapy" [2] and "time to appropriate antibiotic" [3] are used in the papers quoted in your letter. As long as terms are clearly defined, readers can interpret their impact on the patient outcomes described in our report.

We agree that the outcome of patients treated for bacteraemia is determined by factors including the *in-vitro* sensitivity of the infecting organism to the antibiotic used, time to antibiotic therapy, clinical condition of the patient, species of infecting organism, route of administration and dose of antibiotic used. Although we understand an optimal outcome in any individual episode of bacteraemia is only achieved if the correct antibiotic therapy is given as soon as possible, this does not mean that antibiotics are not effective if there is a delay in therapy. All studies quoted show reduction in efficacy of therapy if treatment is delayed — but not that therapy becomes completely ineffective. For example, a recent retrospective study concluded that delays in appropriate antimicrobial treatment were associated with increased 30-day mortality after 12 hours from blood culture collection. The risk of death further increased with inappropriate treatment at 24, 48, and 72 hours [4]. We would be concerned to propose a definition that could lead people to assume that antibiotics become completely ineffective if given too late.

We chose to differentiate between early and definitive antibiotic treatment as the usual management of bacteraemia recommends early treatment with broad-spectrum empiric agents with a later switch to narrower spectrum therapy once the results of antibiotic susceptibilities become available. This treatment strategy reduces use of broad-spectrum agents to reduce chance of antibiotic resistance, but it means there is a need to differentiate between early and definitive therapy.

We agree that the time of collection of blood culture, along with time onset of fever or onset of symptoms are reasonable times from which to measure the starting point for delay to initiation of therapy. However, in practice it can be difficult to determine the time of collection of blood cultures, particularly in retrospective multicentre studies. In fact, neither study quoted in your letter use the time of blood culture collection. *Lee et al.* [3] use the time of admission to the emergency department and *Khadri et al.* [2] use the day of collection and not the time of collection of blood cultures. In keeping with these other studies, we have used a practical and measurable time to start measuring the time until antibiotic therapy.

We agree with the importance of optimising diagnostics and pre-analytical pathways in bacteraemia. As outlined in a recent national review of blood culture pathway processes which proposed several measures to improve the pre-analytical phase of the blood culture pathway, including reducing the collection-to-load time into the incubator to minimise delays [5]. More importantly, to date, rapid susceptibility testing is only available for blood culture specimens following one or two days of incubation, rather than directly on a person's blood sample. This delay may interfere with the actual clinical impact of rapid testing for bloodstream infections. Therefore, greater efforts are required to reduce the overall blood culture incubation time [6].

There is a need to further improve management and diagnostics of bacteraemia and we hope this report contributes to further improvements in the management of bacteraemia with carbapenemase-producing Enterobacterales bloodstream infections. Agreement on standardised terms and definitions used in such studies of antimicrobial outcomes will also speed this field of research.

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## References


[1] Anton-Vazquez V, Evans TJ, Fernando S, Somasunderam D, David K, Melzer M, et al. Clinical, microbiological characteristics and predictors of mortality in patients with carbapenemase-producing Enterobacterales bloodstream infections: a multi-centre study. Infect Prev Pract 2023;5(3):100298.

[2] Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis 2021;21(2):241—51.

[3] Lee CC, Lee CH, Hong MY, Tang HJ, Ko WC. Timing of appropriate empirical antimicrobial administration and outcome of adults with community-onset bacteremia. Crit Care 2017;21(1):119.

[4] Van Heuverswyn J, Valik JK, Desiree van der Werff S, Hedberg P, Giske C, Naucler P. Association Between Time to Appropriate Antimicrobial Treatment and 30-day Mortality in Patients With Bloodstream Infections: A Retrospective Cohort Study. Clin Infect Dis 2023;76(3):469—78.

[5] NHS_England, Improving the blood culture pathway - A national review of blood culture pathway processes to support better antimicrobial stewardship and improved patient safety, https://www.england.nhs.uk/wp-content/uploads/2022/06/B0686-improving-the-blood-culture-pathway-executive-summary-v1-1.pdf.pdf. 2023: UK.

[6] Anton-Vazquez V, Hine P, Krishna S, Chaplin M, Planche T. Rapid versus standard antimicrobial susceptibility testing to guide treatment of bloodstream infection. Cochrane Database Syst Rev 2021;5(5):CD013235.



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