

Cover letter

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To:

Editor-in-Chief

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Dear Editor,

On behalf of my co-authors, I am pleased to submit for consideration in the *International Journal of Infectious Diseases* two closely related manuscripts that together address one of the most pressing challenges in contemporary infectious diseases: the optimal clinical use of **cefiderocol** in the treatment of infections caused by carbapenem-resistant Gram-negative bacteria (CR-GNB).

The first manuscript, entitled “**Exploring the evidence for use of cefiderocol as part of combination therapies: a systematic review of in vitro, in vivo, and clinical studies**”, provides the most comprehensive synthesis to date of all available preclinical and clinical data on cefiderocol-based combinations. By integrating *in vitro* synergy studies, *in vivo* infection models, and real-world clinical outcomes, this review offers a translational framework to understand where combination therapy may be biologically plausible and where current clinical practice may be unsupported by evidence.

The second manuscript, “**CLEARER study: a global survey on cefiderocol use in multidrug-resistant infections**”, captures real-world prescribing behaviour, stewardship constraints, microbiological practices, and clinicians’ perceptions of cefiderocol across 31 countries. It highlights major geographic inequities in access, substantial heterogeneity in microbiological testing, and a frequent reliance on combination therapy—particularly for carbapenem-resistant *Acinetobacter baumannii* (CRAB) and metallo- β -lactamase producers—despite limited supporting clinical data.

Together, these two studies provide **complementary and highly synergistic perspectives**:

- the **systematic review** defines what the science and clinical evidence currently support;
- the **global survey** shows how cefiderocol is actually being used at the bedside.

Strikingly, our meta-analysis demonstrates that cefiderocol combination therapy is not associated with improved clinical outcomes compared with monotherapy, while the survey reveals that combination regimens are widely adopted in high-risk scenarios, largely to mitigate concerns about resistance and uncertain efficacy in CRAB. This gap between evidence and practice has immediate relevance for clinicians, antimicrobial stewardship teams, and guideline developers worldwide.

We believe that *IJID* is the ideal forum for disseminating these findings. Both manuscripts have been conducted in accordance with PRISMA and STROBE principles where applicable, have not been published elsewhere, and are not under consideration by another journal.

All authors have approved the submitted versions and declare no conflicts of interest. These studies were conducted as part of the GARDP-supported CLEARER project.

We sincerely thank you for considering our work and would be pleased to respond to any questions or revisions.

Yours sincerely,

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