Exploring the evidence for use of cefiderocol as part of combination therapies: a systematic review and meta-analysis of in vitro, in vivo, and clinical studies

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REVIEW TITLE AND BASIC DETAILS

Review title
Exploring the evidence for use of cefiderocol as part of combination therapies: a systematic review and meta-analysis of in vitro, in vivo, and clinical studies

Condition or domain being studied
Cefiderocol; Combination Therapy; Infection Due To Carbapenem Resistant *Acinetobacter baumannii* (CRAB); Infection Due To Carbapenem Resistant Enterobacterales (CRE); Infection due to difficult-to-treat *Pseudomonas Aeruginosa* (DTR-PA)

Rationale for the review
Cefiderocol is increasingly used for the treatment of infections caused by carbapenem Gram-negative bacteria, yet there is substantial uncertainty regarding when and how it should be combined with other antimicrobial agents. Combination therapy is frequently adopted in clinical practice—particularly for CRAB and metallo-β-lactamase–producing organisms—despite limited and heterogeneous supporting evidence. Existing data are fragmented across *in vitro* synergy studies, in vivo experimental models, and observational clinical cohorts, with no integrated synthesis across translational and clinical domains.

Review objectives
To determine whether cefiderocol-based combination therapy improves clinical outcomes compared with cefiderocol monotherapy in patients with infections caused by carbapenem-resistant Gram-negative bacteria.

Keywords
Cefiderocol; Combination therapy; In vitro studies; In vivo studies; Clinical studies

Participant countries
Italy; Spain; Switzerland

ELIGIBILITY CRITERIA

Population
Patients with infections caused by multi drug resistant Gram-negative bacteria (MDR-GNB).

Additionally, experimental in vitro and in vivo models involving MDR-GNB

Intervention(s) or exposure(s)
Cefiderocol-based combination therapy, defined as cefiderocol administered together with any companion antimicrobial or adjuvant agent

Comparator(s) or control(s)
Cefiderocol monotherapy

Study design
Both randomized and nonrandomized study types will be included.

Context
All patient populations and infection types are eligible. Preclinical studies using any validated synergy-testing methodology are included

TIMELINE OF THE REVIEW

Review timeline
Start date: 1 July 2025. End date: 1 January 2026.

SEARCHING AND SCREENING

Search for unpublished studies
Both published and unpublished studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *MEDLINE/PubMed*. Additionally, ESCMID library and Open Forum Infectious Diseases website will be screened for abstract retrieval.

Search language restrictions
The review will only include studies published in English.

Search date restrictions
Databases will be searched for articles published from 1 January 2015 and before 31 January 2025.

Other methods of identifying studies
Other studies will be identified by backward citation searching.

Search strategy
“cefiderocol[tw]” or “S-649266[tw]”

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted by one person (or a machine) and checked by at least one other person (or machine).

Authors will not be contacted for further information.

Study risk of bias or quality assessment
Risk of bias will be assessed using: *Cochrane RoB-2* and *Newcastle-Ottawa*

Data will be assessed by one person and checked by at least one other person.

Additional information will **not** be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment
Risk of bias due to missing results will not be assessed

OUTCOMES TO BE ANALYSED

Main outcomes
For clinical studies, the outcomes analysed will include 30-day all-cause mortality, as well as clinical cure and microbiological cure in patients treated with cefiderocol combination therapy compared with cefiderocol monotherapy.

For *in vitro* studies, the main outcomes will include measures of antibacterial activity such as synergistic effects, bacterial killing, and changes in minimum inhibitory concentrations.

For *in vivo* studies, outcomes will be summarised narratively and will include treatment efficacy in experimental infection models, such as survival, bacterial burden reduction, and other relevant microbiological or pathological endpoints.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

In vitro and *in vivo* studies will be summarised narratively, and their main findings will be described and critically commented on.

For clinical studies effect sizes will be calculated as odds ratios (ORs) with 95% confidence intervals (CIs). When available, adjusted effect sizes will be pooled using the inverse variance method. Heterogeneity across studies will be assessed using the Chi- squared test and the I^2 statistic. A subgroup analysis will be performed based on the type of infection, distinguishing between CRAB infections only and mixed MDR infections.

Only clinical studies with more than 25 patients will be included in the meta-analysis. Case series will be excluded.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	✓
Screening search results against inclusion criteria	✓	✓
Data extraction or receipt of IPD	✓	✓
Risk of bias/quality assessment	✓	✓
Data synthesis	✓	✓

Review status

The review is currently ongoing.

Publication of review results

Results of the review will be published in English.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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Funding source

Additional non-commercial funding information
Global Antibiotic Research and Development Partnership (GARDP)

ADDITIONAL INFORMATION

Review conflict of interest

No conflict interests are recorded for this review.