

INPLASY PROTOCOL

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Conflicts of interest:
None declared.

INTRODUCTION

Review question / Objective: What is the benefit stemming from meropenem add-on treatment to colistin against Carbapenem-Resistant strains of *Acinetobacter baumannii*?

Colistin plus meropenem versus colistin alone for invasive infections caused by Carbapenem-Resistant *Acinetobacter baumannii*: a rapid systematic review of randomized controlled trials using Bayesian meta-analysis

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Review question / Objective: What is the benefit stemming from meropenem add-on treatment to colistin against Carbapenem-Resistant strains of *Acinetobacter baumannii*?

Condition being studied: Invasive infections caused by extensively drug-resistant (XDR) *Acinetobacter baumannii*, specifically carbapenem-resistant *Acinetobacter baumannii* (CRAB), are associated with high mortality above 50%, especially in critically ill patients. Often colistin is the only active agent in vitro and, although its safety issues, remains the cornerstone of therapy. Nevertheless, considering the relevant mortality rate when resorting to colistin alone, an intriguing idea is to exploit the potent in vitro synergy of colistin when combined with carbapenems.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 January 2023 and was last updated on 17 January 2023 (registration number INPLASY202310055).

Rationale: Two randomized controlled trials (RCTs), AIDA and OVERCOME, have addressed the question: according to their results, the addition of meropenem does not improve patients' outcomes in patients with Carbapenem-Resistant strains of *Acinetobacter baumannii*. Nevertheless,

confidence intervals did not exclude a potential benefit, that could be better explored by the means of a Bayesian analysis. As matter of fact, thanks to Bayesian analyses, researchers can capture if there is high probability that combination therapy may be associated with even a small decrease in 28/30- day mortality (absolute difference of 1%/2%/5% for instance), that can be clinically significant, especially in settings without easy access to new drugs.

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METHODS

Search strategy: A rapid review will be implemented and therefore only two databases will be screened: MEDLINE and EMBASE, from inception to 31/12/2022, specifically focusing on RCTs.

Participant or population: Adult patients affected by invasive infections (especially pneumonia and bloodstream infections) caused by CRAB.

Intervention: Colistin and meropenem combination therapy.

Comparator: Colistin monotherapy.

Study designs to be included: RTCs.

Eligibility criteria: RCTs reporting on mortality associated with the two aforementioned different therapeutic strategies. RCTs.

Information sources: MEDLINE, EMBASE.

Main outcome(s): All-cause Mortality.

Additional outcome(s): If feasible, meta-analysis of secondary outcomes (clinical failure, microbiological cure, adverse events) will be performed.

Quality assessment / Risk of bias analysis: The ROB2 tool devised by the Cochrane will be used.

Strategy of data synthesis: Main statistical analyses will be carried out in a Bayesian framework to obtain posterior probabilities on the log Relative Risk (RR) scale by resorting to vague priors. Bayesian meta-analyses show several advantages over frequentist approaches, including more rigorous assessment of overall uncertainty, especially between-study heterogeneity; more reliable analyses of smaller sample sizes; and the ability to yield direct probability statements conditional on current and prior data. Probabilities of any association ($RR < 1$) and moderate association ($RR \leq 0.9$) will be estimated. Moreover, simulations will be used to calculate the posterior probability of any decrease in mortality, and whether the decrease in mortality exceeded 1 in 100 (1%), 1 in 50 (2%) and 1 in 20 (5%): indeed, absolute risk differences are easier for clinicians to conceptualize than hazard or risk ratios, and have more meaning for public health decisions.

All analyses will be performed by using the bayesmeta and metafor packages in the R environment.

Subgroup analysis: If feasible, analyses will be conducted according to type of infections.

Sensitivity analysis: As a sensitivity analysis, we will also run a frequentist restricted maximum likelihood (REML) random effects meta-analysis on the log RR scale.

Language restriction: English.

Country(ies) involved: Italy; The Netherlands.

Keywords: Acinetobacter baumannii; XDR; Colistin; Carbapenem; Combination therapy; Monotherapy; Mortality.

Dissemination plans: The manuscript will be submitted to an impacted ID Journal.

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