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Cefiderocol versus best available therapy for treatment of carbapenem-*resistant A. baumannii* infections: A hypothetical target trial emulation study

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Significance & Background

In July 2024, the Centers for Disease Prevention and Control published new antimicrobial resistance surveillance data which demonstrated a significant increase in the number of hospital-onset carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CR-ABC) infections from 2019 to 2022[1]. This statistic is quite alarming given the high mortality associated with CR-ABC infections even among patients who

receive *in vitro* active antibiotic therapy within 72 hours of culture collection[2]. Guidelines for treatment of severe CR-ABC infections remain broad, varied across professional societies, and based on limited high-quality clinical trial data[3, 4]. As of recent, the Infectious Diseases Society of America (IDSA) suggested the optimal treatment regimen for severe CR-ABC is the combination of sulbactam-durlobactam with imipenem-cilastatin[4]. This recommendation comes from findings of a recent randomized controlled trial comparing this combination to colistin and imipenem-cilastatin[5], a regimen which was previously demonstrated not to be superior to colistin alone[6]. Despite this revised recommendation, sulbactam-durlobactam is relatively new to the commercial market and not necessarily available at all institutions. Consequently, clinicians must rely on alternative treatment regimens which include combination antibiotic treatment with ampicillin-sulbactam and a second agent (i.e., polymyxin b, minocycline, tigecycline, or cefiderocol). However, much of the existing literature investigating the optimal regimen for CR-ABC is derived from observational studies and are biased by small sample sizes, heterogenous patient populations, inadequate antibiotic dosing, and variable combination regimens among comparison groups[7-12].

Cefiderocol demonstrates *in vitro* activity against CR-ABC and a more favorable side effect profile compared to traditional CR-ABC agents such as tigecycline and polymyxin b. However, given the findings from CREDIBLE-CR trial a black box warning was issued by the Food and Drug Administration due to a concern for an increased risk of mortality for the subgroup of patients with CR-ABC. These findings have not been confirmed in subsequent observational studies[13-18], but uncertainty remains regarding the clinical effectiveness of cefiderocol in this target population. While a large randomized controlled trial comparing cefiderocol to best available therapy would provide definitive answers, recruitment into a study of this type is often challenging due to the rarity of disease and severity of illness upon presentation. The use of large, observational databases in combination with causal inference techniques offer a powerful tool to investigate relevant clinical questions for which traditional randomized controlled trials are not possible.

This study aims to use a target trial emulation framework to compare 28-day mortality among patients with CR-ABC infection randomized to a hypothetical target trial to receive at least 7 days of a cefiderocol-based treatment strategy or at least 7 days of best available therapy if and when they receive an empiric gram-negative antibiotic following culture collection using patient data collected from the PINC-AI healthcare database between 2018 and 2024.

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Eligibility
Hospitalized adult (≥18 years of age) with clinical culture positive for carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CR-ABC) in the PINC AI database[19] between 2018-2024 are be eligible for inclusion in the hypothetical target trial.

Inclusion Criteria
- Adult hospitalized patients (≥18 years of age)
- Any clinical culture positive for carbapenem resistant *A. baumannii-calcoaceticus* complex

Exclusion Criteria
- Antibiotic susceptibility results are not available for *A. baumannii-calcoaceticus* complex culture
- *A. baumannii-calcoaceticus* complex diagnosed by molecular testing only (i.e., multiplex polymerase chain reaction [PCR]

Treatment strategy
- Best available therapy: Patients will receive at least 7 days of best available therapy (i.e., any monotherapy or combination of ampicillin/sulbactam, minocycline, tigecycline, polymyxin B, colistin, aminoglycosides, fluoroquinolones, eravacycline, and/or trimethoprim/sulfamethoxazole) if and when they receive an empiric gram-negative antibiotic following culture collection.
- Cefiderocol: Patients will receive at least 7 days of cefiderocol (as monotherapy or in combination) if and when they receive an empiric gram-negative antibiotic following culture collection.

Primary Outcome measure
- In-hospital mortality defined as death during hospitalization or discharge to hospice.

Secondary outcome measures

- Length of stay among survivors: duration of hospitalization among surviving patients
- Recurrent carbapenem resistant *A. baumannii* infection: clinical culture positive for carbapenem resistant *A. baumannii* infection within the same encounter downstream of the index episode and within 30 days.
- Development of antibiotic resistance to initial antibiotic treatment: development of antibiotic resistance on a subsequent positive clinical culture to an antibiotic administered during prior infectious episode

Statistical Analysis Plan

We will use a target trial emulation framework to reduce confounding bias. In the hypothetical target trial, patients will be randomized to a hypothetical treatment strategy of receiving at least 7 days of best available therapy or at least 7 days of cefiderocol if and when a patient received an empiric gram-negative antibiotic following culture collection. This target trial will assume no loss to follow up. Under perfect adherence to the assigned treatment strategy, we will use a longitudinal g-computation formula [20] to estimate the per protocol average treatment effect between the two treatment strategies on 28-day mortality (defined as death or discharge to hospice) under standard causal assumptions (consistency, positivity, and exchangeability). The g-computation formula determines the average treatment effect by estimating outcomes that would occur under the counterfactual treatment strategies. A sequentially doubly robust (SDR) estimator[21] will be used to estimate the g-computation formula. This method uses the probability of receiving a hypothetical treatment strategy, the probability of experiencing the outcome, and the probability of censoring at each time point (day 0-day 28) to estimate a survival curve under each hypothetical treatment strategy. If at least one model is correctly specified at each time point, the average treatment effect estimate will remain correct and is, therefore, doubly robust against model misspecification. This method will minimize the presence of confounding that occurs in the absence of random allocation to either treatment strategy. Time-independent variables including age, gender, race, Elixhauser co-morbidity score[22], eSOFA (simplified sequential organ failure assessment simplified for use in observational data from electronic health records)[23], infection site, and polymicrobial culture will be included in baseline adjustments as well as time-dependent variables such as receipt of mechanical ventilation, receipt of vasopressors, ICU admission, and receipt of renal replacement therapy will be used for model specification. Subgroup analyses comparing cefiderocol-based antibiotic regimens to distinct combinations of BAT (i.e., ampicillin/sulbactam in combination with either minocycline, tigecycline, or polymyxins) will be performed to examine the heterogeneity of treatment effect.

Statistical analysis will be performed using R version 4.5.0 within Rstudio version 2025.05.1+513 (R Foundation for Statistical Computing, Vienna, Austria). The reporting of the study will be in line with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Missing Data Plan

Less than 5% missingness across key variables is expected. If >5% of missingness across key variables is identified, then predictors of missingness will be evaluated and hospitals which display a significant amount of missingness that does not conform to expectations may be excluded. We will impute missing data elements using multiple imputation approach for some variables, when feasible. Sensitivity analyses using only complete case records would be reported for analyses requiring multiple imputation for missing data elements.

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