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Cefiderocol versus standard therapy for hospital-acquired and health-care-associated Gram-negative bacterial bloodstream infection (the GAME CHANGER trial): an open-label, parallel-group, randomised trial

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Abstract

Background: Bloodstream infections caused by bacteria with carbapenem resistance are associated with high mortality. Cefiderocol has broad in vitro activity against carbapenem-resistant Gram-negative bacilli. We aimed to assess whether cefiderocol was non-inferior or superior to standard-of-care antibiotics in preventing mortality in patients with bloodstream infection caused by Gram-

negative bacilli. Methods: The GAME CHANGER trial was an open-label, parallel-group, randomised clinical trial in which patients with health-care-associated or hospital-acquired Gram-negative bloodstream infection were recruited from 17 tertiary hospitals with more than 500 beds in Australia, Malaysia, Singapore, Taiwan, Thailand, and Türkiye. Adult patients (aged ≥21 years in Singapore or ≥18 years elsewhere) with positive blood cultures and Gram-negative bacilli seen on Gram stain were eligible. Participants were randomly assigned in a 1:1 ratio to cefiderocol (2 g intravenously every 8 h) or standard of care (chosen by the patient's clinical team) using an online randomisation tool with strata defined by severity of comorbidities and region, with random permuted blocks of unequal size. Patients, treating clinicians, and site investigators were not masked to treatment. The primary outcome was all-cause mortality at 14 days after randomisation. All outcomes were analysed in participants who received at least one dose of assigned antibiotic, grew an aerobic Gram-negative bacillus from the index blood culture, and did not withdraw consent before day 14. The non-inferiority margin was 10%; superiority was to be assessed if non-inferiority was shown, and was evaluated in both the main analysis population and in patients with at least one carbapenem-resistant organism causing bloodstream infection. Missing data were handled by imputing data. The trial was registered on ClinicalTrials.gov (NCT03869437) and is closed to new participants. Findings: 513 participants were enrolled between Nov 12, 2019, and Oct 31, 2023 (210 [42%] female and 294 [58%] male). 256 patients were randomly assigned to cefiderocol and 257 were assigned to standard of care. Nine patients (six in the cefiderocol group and three in the standard-of-care group) were excluded from further analysis because they withdrew consent or their blood cultures did not grow an aerobic Gram-negative bacillus. Thus, 504 participants were included in the main analysis population. 20 (8%) of 250 patients in the cefiderocol group had died at 14 days compared with 17 (7%) of 254 patients in the standard-of-care group (absolute risk difference 1%, 95% CI −3 to 6). 127 (25%) of 504 patients had an infection with a carbapenem-resistant organism; at 14 days, nine (14%) of 64 patients in the cefiderocol group had died compared with six (10%) of 63 patients in the standard-of-care group (5%, −7 to 16). There were five treatment-emergent serious adverse events that were either probably or possibly related to the study drug (all i
group): delirium, stupor, rigors, abnormal liver chemistry, and rash, all of which re
treatment (except for the rash, which required hydrocortisone and anti-histamines). Interpretation: Among patients with a hospital-acquired or health-care-associated Gram-negative bloodstream infection, cefiderocol resulted in non-inferior 14-day mortality compared with standard of care. Adverse events were similar between groups, although those thought to be related to the study drug only occurred in the cefiderocol group. In both the main analysis population and the carbapenem-resistant subset, cefiderocol was not superior to standard of care. This evidence suggests that cefiderocol is efficacious in patients with health-care-associated Gram-negative bloodstream infection who are at high risk of antibiotic resistance, but more evidence is required to define its efficacy when carbapenem-resistant organisms are the cause. Funding: The University of Queensland, Shionogi, The Henderson Foundation, and the National Medical Research Council (Singapore).

Indexed keywords

MeSH

Adult; Aged; Anti-Bacterial Agents; Bacteremia; Cefiderocol; Cephalosporins; Cross Infection; Female; Gram-Negative Bacteria; Gram-Negative Bacterial Infections; Humans; Male; Middle Aged; Treatment Outcome

EMTREE drug terms

antibiotic agent; antihistaminic agent; avibactam plus ceftazidime; azathioprine; carbapenem derivative; cefiderocol; cyclosporine; cytotoxic agent; etanercept; everolimus; hydrocortisone; infliximab; inotropic agent; methotrexate; mycophenolic acid; polymyxin; prednisolone; rituximab; tacrolimus; third generation cephalosporin; antiinfective agent; cefiderocol; cephalosporin derivative

EMTREE medical terms

abdominal infection; Acinetobacter; Acinetobacter baumannii; Acinetobacter baumannii infection; Acinetobacter infection; Acinetobacter nosocomialis; Acinetobacter pittii; Acinetobacter ursingii; acquired immune deficiency syndrome; acute kidney failure; adult; Aeromonas; all cause mortality; antibiotic therapy; Article; artificial ventilation; Atlantibacter hermannii; attributable risk; Australia; bacterial skin disease; bacteriuria; blood culture; bloodstream infection; broth dilution; carbapenem resistance; carbapenem-resistant Enterobacteriaceae; cephalosporin resistance; Charlson Comorbidity Index; chronic lung disease; Citrobacter freundii; Citrobacter koseri; Citrobacter werkmanii; clinical outcome; Clostridioides difficile; coinfection; comorbidity; comparative effectiveness; congestive heart failure; controlled study; corticosteroid therapy; delirium; diabetes mellitus; disability; disk diffusion; drug megadose; Enterobacter; Enterobacteriaceae infection; Escherichia coli; Escherichia coli infection; Escherichia fergusonii; female; follow up; Gram negative infection; Gram staining; health care quality; healthcare associated infection; hematologic malignancy; hospital discharge; hospital infection; hospital mortality; human; immunosuppressive treatment; in vitro study; infection prevention; Klebsiella oxytoca; Klebsiella pneumoniae; Klebsiel

infection; Klebsiella variicola; Leclercia adecarboxylata; major clinical study; Malaysia; male; minimum inhibitory concentration; monoclonal antibody therapy; Morganella morganii; neutropenia; non-fermenting Gram-negative bacterium; non-inferiority trial; nonhuman; open study; palliative therapy; Pantoea agglomerans; Pantoea dispersa; parallel design; Proteus mirabilis; Proteus mirabilis infection; Providencia stuartii; Pseudomonas aeruginosa; Pseudomonas infection; Pseudomonas putida; randomized controlled trial; rash; rigor; Salmonella enterica serovar Enteritidis; Sequential Organ Failure Assessment Score; Serratia infection; Serratia marcescens; severe renal impairment; side effect; Singapore; soft tissue infection; solid tumor; Stenotrophomonas maltophilia; stupor; Taiwan; tertiary care center; Thailand; treatment duration; treatment outcome; Turkey (republic); typhoid fever; ventilator associated bacterial pneumonia; aged; bacteremia; clinical trial; cross infection; drug effect; drug therapy; Gram negative bacterium; Gram negative infection; microbiology; middle aged; mortality; multicenter study

Chemicals and CAS Registry Numbers

Unique identifiers assigned by the Chemical Abstracts Service (CAS) to ensure accurate identification and tracking of chemicals across scientific literature.

avibactam plus ceftazidime	1393723-27-7
azathioprine	446-86-6, 55774-33-9
cefiderocol	1225208-94-5, 2009350-94-9, 2135543-94-9
cyclosporine	59865-13-3, 63798-73-2, 79217-60-0

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Details about financial support for research, including funding sources and grant numbers as provided in academic publications.

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Pranita Tamma		
George B. Henderson Foundation See opportunities		
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Funding text 1
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