Infect Dis Ther (2024) 13:1929–1948
https://doi.org/10.1007/s40121-024-01016-y

ORIGINAL RESEARCH

Use of Cefiderocol in Adult Patients: Descriptive Analysis from a Prospective, Multicenter, Cohort Study

Daniele Roberto Giacobbe · Laura Labate · Chiara Russo Artimagnella · Cristina Marelli · Alessio Signori · Vincenzo Di Pilato · Chiara Aldieri · Alessandra Bandera · Federica Briano · Bruno Cacopardo · Alessandra Calabresi · Federico Capra Marzani · Anna Carretta · Annamaria Cattelan · Luca Ceccarelli · Giovanni Cenderello · Silvia Corcione · Andrea Cortegiani · Rosario Cultrera · Francesco Giuseppe De Rosa · Valerio Del Bono · Filippo Del Puente · Chiara Fanelli · Fiorenza Fava · Daniela Francisci · Nicholas Geremia · Lucia Graziani · Andrea Lombardi · Angela Raffaella Losito · Ivana Maida · Andrea Marino · Maria Mazzitelli · Marco Merli · Roberta Monardo · Alessandra Mularoni · Chiara Oltolini · Carlo Pallotto · Emanuele Pontali · Francesca Raffaelli · Matteo Rinaldi · Marco Ripa · Teresa Antonia Santantonio · Francesco Saverio Serino · Michele Spinicci · Carlo Torti · Enrico Maria Trecarichi · Mario Tumbarello · Malgorzata Mikulska · Mauro Giacomini · Anna Marchese · Antonio Vena · Matteo Bassetti · CEFI-SITA investigators

Received: May 22, 2024 / Accepted: June 27, 2024 / Published online: July 12, 2024

ABSTRACT

Introduction: Cefiderocol is a siderophore cephalosporin showing activity against various carbapenem-resistant Gram-negative bacteria (CR-GNB). No data currently exist about real-world use of cefiderocol in terms of types of therapy (e.g., empirical or targeted, monotherapy or combined regimens), indications, and patient characteristics.

Methods: In this multicenter, prospective study, we aimed at describing the use of cefiderocol in terms of types of therapy, indications, and patient characteristics.

Results: Cefiderocol was administered as empirical and targeted therapy in 27.5% (55/200) and

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-024-01016-y.

D. R. Giacobbe (✉) · L. Labate · C. Russo Artimagnella · M. Mikulska · A. Vena · M. Bassetti
Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy
e-mail: danieleroberto.giacobbe@unige.it

D. R. Giacobbe · C. Russo Artimagnella · C. Marelli · M. Mikulska · A. Vena · M. Bassetti
Clinica Malattie Infettive, IRCCS Ospedale Policlinico San Martino, L.go R. Benzi, 10, 16132 Genoa, Italy

A. Signori
Section of Biostatistics, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

V. Di Pilato · A. Marchese
Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy

C. Aldieri · V. Del Bono
Infectious Diseases Unit, S. Croce e Carle Hospital, Cuneo, Italy

A. Bandera · A. Lombardi
Department of Pathophysiology and Transplantation, University of Milano, Milan, Italy

72.5% (145/200) of cases, respectively. Overall, it was administered as monotherapy in 101/200 cases (50.5%) and as part of a combined regimen for CR-GNB infections in the remaining 99/200 cases (49.5%). In multivariable analysis, previous isolation of carbapenem-resistant *Acinetobacter baumannii* odds ratio (OR) 2.56, with 95% confidence interval (95% CI) 1.01–6.46, $p = 0.047$] and previous hematopoietic stem cell transplantation (OR 8.73, 95% CI 1.05–72.54, $p = 0.045$) were associated with administration of cefiderocol as part of a combined regimen, whereas chronic kidney disease was associated with cefiderocol monotherapy (OR 0.38 for combined regimen, 95% CI 0.16–0.91, $p = 0.029$). Cumulative 30-day mortality was 19.8%, 45.0%, 20.7%, and 22.7% in patients receiving targeted cefiderocol for infections by Enterobacterales, *A. baumannii*, *Pseudomonas aeruginosa*, and any metallo-β-lactamase producers, respectively.

Conclusions: Cefiderocol is mainly used for targeted treatment, although empirical therapies account for more than 25% of prescriptions, thus requiring dedicated standardization and guidance. The almost equal distribution of cefiderocol monotherapy and cefiderocol-based combination therapies underlines the need for further study to ascertain possible differences in efficacy between the two approaches.

A. Bandera · A. Lombardi
Infectious Diseases Unit, IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation, Milan, Italy

F. Briano
SC Malattie Infettive e Tropicali, Ospedale San Paolo Savona, Savona, Italy

B. Cacopardo · A. Marino
Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, ARNAS Garibaldi Hospital, University of Catania, Catania, Italy

A. Calabresi
AOU SS Antonio, Biagio e Cesare Arrigo di Alessandria, Alessandria, Italy

F. Capra Marzani
SC AR1-Terapia Intensiva Generale, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

A. Carretta · T. A. Santantonio
Department of Medical and Surgical Sciences, Infectious Diseases Unit, University of Foggia, Foggia, Italy

A. Cattelan · M. Mazzitelli
Infectious and Tropical Diseases Unit, Padua University Hospital, Padua, Italy

L. Ceccarelli · M. Rinaldi
Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

L. Ceccarelli · M. Rinaldi
Department of Integrated Management of Infectious Risk, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico Sant'Orsola, Bologna, Italy

G. Cenderello
Department of Infectious Diseases, Sanremo Hospital, Sanremo, Italy

S. Corcione · F. G. De Rosa
Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy

S. Corcione
Tufts University School of Medicine, Boston, MA, USA

A. Cortegiani
Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.), University of Palermo, Palermo, Italy

A. Cortegiani
Department of Anesthesia, Analgesia, Intensive Care and Emergency, University Hospital Policlinico Paolo Giaccone, Palermo, Italy

R. Cultrera
Department of Translational Medicine, University of Ferrara, Ferrara, Italy

R. Cultrera
Infectious Diseases, Azienda Unità Sanitaria Locale of Ferrara, Ferrara, Italy

F. Del Puente · E. Pontali
Department of Infectious Diseases, Galliera Hospital, Genoa, Italy

C. Fanelli · I. Maida
Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy

F. Fava
Anestesia e Terapia Intensiva Cardiotoracica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

D. Francisci · C. Pallotto
Infectious Diseases Clinic, Santa Maria della Misericordia Hospital, Department of Medicine and Surgery, University of Perugia, Perugia, Italy

N. Geremia
Unit of Infectious Diseases, Department of Clinical Medicine, Ospedale "dell'Angelo", Venice, Italy

Keywords: Cefiderocol; Antimicrobial resistance; Clinical practice; Carbapenem resistance; Carbapenemases

Key Summary Points

In a real-life, observational, multicenter study, cefiderocol was mostly administered as targeted therapy (72.5%), although the proportion of empirical therapy was non-negligible (27.5%).

Cefiderocol was mainly administered for lower respiratory tract infections and bloodstream infections caused by *Acinetobacter baumannii*, followed by *Pseudomonas aeruginosa.*

Notably, in a real-life scenario, cefiderocol was administered almost equally as monotherapy or as combination therapy (50.5% vs. 49.5%).

The almost equal distribution of cefiderocol monotherapy and cefiderocol-based combination therapies underlines the need for further study to ascertain possible differences in efficacy between the two approaches.

INTRODUCTION

Cefiderocol is a catechol-substituted siderophore cephalosporin showing in vitro rapid bactericidal activity against various carbapenem-resistant Gram-negative bacteria (CR-GNB) [1, 2].

Based on the results of phase-3 randomized controlled trials (RCT), cefiderocol was approved in Europe for the treatment of GNB infections with limited therapeutic options [3–5]. Various studies have described the use of cefiderocol for treatment of CR-GNB infections, including those caused by carbapenem-resistant *Acinetobacter baumannii* and CR-GNB producing metallo-β-lactamases (MBL) for which cefiderocol is usually among the very few active options [6–35]. However, such studies were designed mostly to evaluate cefiderocol for targeted treatment of specific infections and/or pathogens, while no data currently exist about the real-world use of cefiderocol in terms of types of therapy (e.g., empirical or targeted, monotherapy or in combination with other agents), indications, and

N. Geremia
Unit of Infectious Diseases, Department of Clinical Medicine, Ospedale Civile "S.S. Giovanni e Paolo", Venice, Italy

L. Graziani · M. Spinicci
Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

A. R. Losito · F. Raffaelli · C. Torti
Dipartimento di Scienze Mediche e Chirurgiche, UOC Malattie Infettive, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

M. Merli · C. Oltolini
ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

R. Monardo · M. Ripa
Università Vita-Salute San Raffaele, Milan, Italy

R. Monardo · M. Ripa
Department of Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy

A. Mularoni
IRCCS-ISMETT, Palermo, Italy

F. S. Serino
Azienda ULSS4 Veneto Orientale, UOS Malattie Infettive, UOC Medicina Generale Portogruaro, Portogruaro, Italy

M. Spinicci
Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy

C. Torti
Dipartimento di Sicurezza e Bioetica, Università Cattolica del Sacro Cuore, Sez. Malattie Infettive, Rome, Italy

E. M. Trecarichi
Department of Medical and Surgical Sciences, University "Magna Graecia", Catanzaro, Italy

E. M. Trecarichi
"R. Dulbecco" Teaching Hospital, Catanzaro, Italy

M. Tumbarello
Department of Medical Biotechnologies, University of Siena, Siena, Italy

characteristics of the treated patients. These data could be useful to improve the development of empirical and targeted therapeutic algorithms of cefiderocol in real life, ultimately aiming at better patient care.

In this multicenter, observational, prospective study, we primarily aimed at describing how cefiderocol is used in Italian hospitals, in terms of types of therapy, indications, and patient characteristics.

METHODS

Setting and Objectives

The MULTI-SITA project is a novel platform developed by the Italian Society of Anti-Infective Therapy (SITA) and dedicated to conducting observational studies on invasive bacterial and fungal diseases. CEFI-SITA is an ongoing observational, prospective, multicenter study conducted in Italian hospitals within the MULTI-SITA project, registering use of cefiderocol in consecutive adult patients according to clinical practice. The prospective study period of the CEFI-SITA study is from 1 August 2022 to 31 December 2025. Here, in a pre-planned analysis, we report the preliminary descriptive results of the CEFI-SITA study. The primary objective of this preliminary analysis was to describe the characteristics of patients and infections treated with cefiderocol in the first 200 enrolled patients (see sample size calculation below) from 17 hospitals. Secondary objectives were: (1) to exploratorily describe factors associated with use of cefiderocol as part of a combined regimen versus monotherapy; and (2) to describe clinical cure rates and 30-day mortality in patients with GNB infections receiving targeted cefiderocol therapy. Patients receiving at least one dose of cefiderocol for any reason according to local practice were included in the study, in line with its observational nature. Exclusion criteria were (1) age less than 18 years and (2) already included in the study for a previous cefiderocol administration.

Microbiological Procedures

Identification of bacterial isolates from clinical specimens was performed by means of matrix-assisted laser desorption ionization time of flight mass spectrometry (Vitek MS MALDI-TOF mass spectrometer, bioMérieux, Craponne, France; or MALDI Biotyper, Bruker Daltonics, Billerica, MA, USA) or automated systems, depending on standard local procedures. Antimicrobial susceptibility testing (AST) for antibiotics other than cefiderocol was also performed by means of automated systems (Vitek 2, bioMérieux; MicroScan, Beckman Coulter, Brea, CA, USA; or Phoenix, Becton Dickinson Diagnostics, Sparks, MD, USA) according to local standard procedures. Cefiderocol AST was performed by means of disk diffusion or broth microdilution methods, including either the reference broth microdilution MIC determination using iron-depleted cation-adjusted Mueller Hinton Medium [36] or commercial broth microdilution tests, according to local practice. Cefiderocol AST by gradient test was reported for one isolate. Results of susceptibility testing were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints, version 14.0 http://www.eucast.org/), also for cefiderocol. In more detail, resistance to cefiderocol was defined as: (1) for Enterobacterales, minimum inhibitory concentration (MIC) > 2 mg/L for broth microdilution and zone diameter < 23 mm for disk diffusion; and (2) for *P. aeruginosa*, MIC > 2 mg/L for broth microdilution and zone diameter < 22 mm for disk diffusion). For other GNB currently lacking sufficient evidence for defining cefiderocol breakpoints

M. Tumbarello
Infectious and Tropical Diseases Unit, Azienda Ospedaliero Universitaria Senese, Siena, Italy

M. Giacomini
Department of Informatics, Bioengineering, Robotics and System Engineering (DIBRIS), University of Genoa, Genoa, Italy

A. Marchese
UO Microbiologia, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

according to EUCAST, isolates were defined as non-wild-type based on EUCAST ECOFF breakpoints for cefiderocol (MIC > 0.5 mg/L for broth microdilution). For disk diffusion, zone diameters < 17 mm (for *A. baumannii*) and < 19 mm (for *S. maltophilia*), corresponding to MIC values below the EUCAST PK-PD breakpoint of cefiderocol, were also deemed as defining non-wild-type isolates in this study. An MIC > 2 mg/L and an MIC > 0.5 mg/L were also considered as the cut-off for defining resistant and non-wild-type isolates by gradient test, respectively. For the purpose of the study, carbapenem resistance was defined as resistance to any of the carbapenems not intrinsically inactive against the given GNB species. Presence of carbapenemase-encoding gene/s was detected using Verigene BC-GN (Nanosphere, Northbrook, IL, USA) or Xpert Carba-R (Cepheid, Sunnyvale, CA, USA), or inferred by means of the BioFire BCID2 or Pneumonia Plus syndromic panels (bioMérieux), whereas the production of carbapenemase/s was assessed by NG-test Carba 5 (NG Biotech, Guipry, France), depending on standard local procedures at the time the study was conducted.

Definitions and Data Collected for the Study

The following demographic and clinical variables were collected at the time of cefiderocol initiation: age in years; sex; previous hospitalization (within 6 months); admission from a long-term care facility (LTCF); diabetes mellitus; chronic obstructive pulmonary disease (COPD); previous myocardial injury; New York Heart Academy (NYHA) score; chronic liver disease (defined histologically as liver cirrhosis or in presence of a clinical diagnosis supported by laboratory, endoscopy, and radiologic findings [37]); chronic kidney disease (defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2); chronic intermittent hemodialysis; solid neoplasm; metastatic solid neoplasm; hematological malignancy; previous hematopoietic stem cell transplantation (HSCT); previous solid organ transplantation (SOT); human immunodeficiency virus (HIV) infection; autoimmune disease; age-adjusted Charlson Comorbidity Index [38]; previous therapy with cefiderocol (within 6 months); previous antibiotic therapy with agents other than cefiderocol (within 6 months); previous chemotherapy (within 6 months); previous steroid therapy (within 6 months); previous therapy with other immunosuppressants (within 6 months); previous major surgery (within 3 months); previous isolation of carbapenem-resistant GNB (within 6 months); days from admission to cefiderocol initiation; intensive care unit (ICU) stay; sequential organ failure assessment (SOFA) score [39]; presence of central venous catheter (CVC); presence of urinary catheter; presence of septic shock [40]; presence of at least mild acute respiratory distress syndrome (ARDS) [41]; estimated creatine clearance (CL_{Cr}) and presence of at least stage 1 of acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcome (KDIGO) criteria [42]; concomitant coronavirus disease 2019 (COVID-19); total parenteral nutrition; neutropenia (defined as blood absolute neutrophil count < 500 cell/mm^3); continuous renal replacement therapy (CRRT); extracorporeal membrane oxygenation (ECMO); absolute blood white cell count; serum C-reactive protein; serum procalcitonin; type of cefiderocol therapy, defined as monotherapy or combined therapy based on the anti-carbapenem-resistant GNB (CR-GNB) activity of agents administered concomitantly with cefiderocol (more in detail, combination of cefiderocol with at least one of the following agents was considered as a combined anti-CR-GNB therapy: aminoglycosides; fosfomycin; tigecycline, with the exception of targeted therapy of *Pseudomonas aeruginosa* infections; polymyxins; sulbactam or ampicillin/sulbactam, as empirical treatment or as targeted therapy for *Acinetobacter baumannii* infections); timing of cefiderocol therapy (empirical vs. targeted after identification of the causative agent); initial cefiderocol dosage according to estimated CL_{Cr} or hemodialytic treatment; type of infection treated with cefiderocol (according to the US Centers for Disease Control and Prevention/National Healthcare Safety Network [CDC/NHSN] surveillance definitions [43]; if CDC/NHSN criteria were not satisfied, local investigators indicated the diagnosis registered in the clinical chart, e.g., sepsis provided Sepsis-3

criteria were satisfied [40]); causative agent/s of the infection treated with targeted cefiderocol therapy. The following information was also collected during follow-up: causative agent/s of the infection initially treated with empirical cefiderocol, if subsequently identified; change of cefiderocol dosage during therapy due to changes in CL_{Cr}; clinical cure, defined as resolution of clinical signs and symptoms of infection, at day 7, 14, and 28 after cefiderocol initiation; cumulative mortality at day 30 after cefiderocol initiation; adverse events (AE), including serious AE (SAE), occurring during cefiderocol therapy, if any.

Sample Size Calculation

A sample size of 200 patients was considered an acceptable compromise regarding the external validity of study results when considering the primary descriptive endpoint (i.e., use of cefiderocol in terms of indications and characteristics of treated patients). In more detail, by assuming normal distribution of the estimates of population parameters measured in the study sample (e.g., proportion of patients receiving cefiderocol as empirical therapy/all patients receiving cefiderocol), a sample size of 200 patients would guarantee a maximum error margin (confidence interval) of ± 7% with $\alpha = 0.05$.

Statistical Analysis

The characteristics of patients and infections treated with cefiderocol were described through median (interquartile range, IQR) and absolute frequency (relative frequency, %) for continuous and categorical variables, respectively. The 95% confidence interval (CI) was calculated for both proportions [44] and median values [45] estimates. To assess factors associated with cefiderocol combination therapy, we performed Rubin's multiple imputation as a preliminary step [46]. Then, the association of demographic/clinical variables with cefiderocol combination therapy (vs. cefiderocol monotherapy as reference) was first assessed through univariable logistic regression (LR) models. Subsequently, all variables showing a p value < 0.10 in univariable comparisons were included in an initial multivariable LR model, and further selected for inclusion in the final multivariable LR model (model A) by means of a stepwise backward procedure. Finally, as sensitivity analysis, variables included in model A were also included in an additional multivariable LR model that also included center as random effect (model B). The crude 30-day mortality from the initiation of cefiderocol therapy was summarized graphically using the Kaplan–Meier method in patients receiving (1) targeted cefiderocol therapy for Enterobacterales infection, (2) targeted cefiderocol therapy for *Acinetobacter baumannii* infection, (3) targeted cefiderocol therapy for *Pseudomonas aeruginosa* infection, and (4) targeted cefiderocol therapy for MBL-producing Gram-negative bacteria.

The analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA) and R Statistical Software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

The MULTI-SITA project was approved by the ethics committee of the coordinating center (Liguria Region Ethics Committee, registry number 390/2020). The amendment authorizing the conduct of the CEFI-SITA study within the MULTI-SITA project was approved by the Liguria Region Ethics Committee on 12 April 2022. The other participating centers followed the local ethical committees' requirements and started to prospectively enroll patients once activated. All conscious patients at time of enrollment signed an informed consent to participate in the study. A waiver of informed consent for data collection from unconscious patients at the time of enrollment due to severe clinical conditions was obtained within the ethics committee approval, in line with the observational nature of the analyses and in order not to bias research results towards high cure rates and low mortality prejudicing scientific validity.

Table 1 Demographic and clinical characteristics of adult patients treated with cefiderocol

Variables	No. of patients	%	95% CI
Demographics			
Age in years, median (IQR)	66 (52–75)	–	50–68
Female sex	48/200	24	18.4–30.4
Comorbidities and medical history			
Previous hospitalization	94/193	48.7	41.7–56.0
Admission from LTCF	14/198	7.0	4.1–11.4
Diabetes mellitus	35/199	17.6	12.6–23.5
COPD	23/197	11.7	7.7–16.9
Previous myocardial injury	27/192	14.1	9.7–19.6
NYHA score, median (IQR)	1 (1–2)	–	1–1
Chronic liver disease	13/200	6.5	3.5–10.8
Chronic kidney disease	32/198	16.2	11.4–21.8
Chronic intermittent hemodialysis	7/197	3.6	1.6–7.2
Solid neoplasm	29/197	14.7	10.2–20.4
Metastatic solid neoplasm	10/196	5.1	2.6–9.0
Hematological malignancy	29/198	14.6	10.2–20.3
Previous HSCT	9/198	4.5	2.3–8.4
Previous SOT	12/198	6.1	3.4–10.2
HIV infection	3/187	1.6	0.4–4.6
Autoimmune disease	21/198	10.6	6.9–15.7
Age-adjusted Charlson Comorbidity Index, median (IQR)	4 (2–6)	–	2–4
Previous therapy with cefiderocol	4/194	2.1	0.7–5.2
Monotherapy	0/194	0.0	0.0–1.8
Combination therapy	4/194	2.1	0.7–5.2
Previous antibiotic therapy other than cefiderocol	129/186	69.4	62.4–75.7
Previous piperacillin/tazobactam	85/186	45.7	38.6–53.0
Previous ceftazidime/cefepime	11/186	5.9	3.1–10.3
Previous ceftolozane/tazobactam	16/186	8.6	5.2–13.5
Previous carbapenems	56/186	30.1	23.8–37.0
Previous ceftazidime/avibactam	14/186	7.5	4.4–12.2
Previous meropenem/vaborbactam	1/186	0.5	0.0–2.7
Previous imipenem/relebactam	0/186	0.0	0.0–1.9

Table 1 continued

Variables	No. of patients	%	95% CI
Previous polymyxins	5/186	2.7	1.1–6.0
Previous chemotherapy	23/197	11.7	7.7–16.9
Previous steroid therapy	65/187	34.8	28.0–41.9
Previous therapy with immunosuppressants	26/193	13.5	9.2–19.0
Previous major surgery	75/199	37.7	31.1–44.7
Previous isolation of CR-GNB	67/186	36.0	29.2–43.2
Previous CRE	37/186	19.9	14.6–26.2
Previous CRPA	9/186	4.8	2.4–8.9
Previous CRAB	27/186	14.5	10.0–20.3
Previous MBL-producing CR-GNB	17/186	9.1	5.4–14.1
Variables at cefiderocol initiation			
Days from admission to cefiderocol initiation, median (IQR)	22 (10–40)	–	9–25
ICU stay	102/200	51.0	44.0–58.0
SOFA score, median (IQR)	5 (3–7)	–	2–5
Presence of CVC	140/194	72.2	65.5–78.2
Presence of urinary catheter	155/195	79.5	73.2–84.8
Presence of septic shock	51/198	25.8	20.0–32.2
Presence of ARDS	21/192	10.9	7.1–16.0
Presence of AKI	68/199	34.2	27.8–41.2
Concomitant COVID-19	16/197	8.1	4.9–12.8
Total parenteral nutrition	55/191	28.8	22.7–35.5
Neutropenia	10/200	5.0	2.6–8.8
CRRT	26/198	13.1	8.9–18.5
ECMO	5/198	2.5	1.0–5.6
White blood cell $\times 10^{-3}/mm^3$, median (IQR)	10.26 (5.58–15.34)	–	4.9–12.0
Serum C-reactive protein in mg/L, median (IQR)	84.3 (22.8–154.0)	–	69–104
Serum procalcitonin in ng/mL, median (IQR)	1.4 (0.3–5.1)	–	0.9–1.9

Results are presented as No. of patients/Total of patients unless otherwise indicated. Number of missing values per variable were as follows: SOT (n = 2/200); hematological malignancy (n = 2/200); HSCT (n = 2/200); solid neoplasm (n = 3/200); metastatic solid neoplasm (n = 4/200); HIV infection (n = 13/200); previous chemotherapy (n = 3/200); COPD (n = 3/200); autoimmune disease (n = 2/200); diabetes mellitus (n = 1/200); chronic kidney disease (n = 2/200); previous myocardial injury (n = 8/200); previous hospitalization (n = 7/200); previous cefiderocol therapy (n = 6/200): previous antibiotic therapy other than cefiderocol (n = 14/200); previous steroid therapy (n = 13/200); previous therapy with immunosuppressants (n = 7/200); previous major surgery (n = 1/200); Previous isolation of CR-GNB (n = 14/200); admission from LTCF (n = 2/200); presence of CVC (n = 6/200); presence of urinary catheter (n = 5/200; ECMO

Table 1 continued

(*n* = 2/200); chronic intermittent hemodialysis (*n* = 3/200); CRRT (*n* = 2/200); presence of septic shock (*n* = 2/200); presence of ARDS (*n* = 8/200); presence of AKI (*n* = ½00); concomitant COVID-19 (*n* = 3/200); total parenteral nutrition (*n* = 9/200); serum C-reactive protein (*n* = 12/200); serum procalcitonin (*n* = 43/200); HIV infection (*n* = 13/200). No missing values were registered for all other remaining variables

AKI acute kidney injury, *ARDS* acute respiratory distress syndrome, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *COVID-19* coronavirus disease 2019, *CR-GNB* carbapenem-resistant gram-negative bacteria, *CRAB* carbapenem-resistant *Acinetobacter baumannii*, *CRE* carbapenem-resistant Enterobacterales, *CRPA* carbapenem-resistant *Pseudomonas aeruginosa*, *CRRT* continuous renal replacement therapy, *CVC* central venous catheter, *ECMO* extracorporeal membrane oxygenation, *HIV* human immunodeficiency virus, *HSCT* hematopoietic stem cell transplantation, *ICU* intensive care unit, *IQR* interquartile range, *MBL* metallo β-lactamases, *NYHA* New York Heart Association, *LTCF* long-term care facility, *SOFA* sequential organ failure assessment, *SOT* solid organ transplantation

RESULTS

The demographic and clinical characteristics at time of cefiderocol initiation of the 200 included patients (enrolled from August 2022 to September 2023) are displayed in Table 1. Their median age was 66 years (IQR 52–75) and 76% were male (152/200). The characteristics of cefiderocol treatments are reported in Table 2. Overall, cefiderocol was started as empirical and targeted therapy in 27.5% (55/200) and 72.5% (145/200) of cases, respectively.

Empirical Therapy

As shown in Supplementary Table S1, the most frequently reported indications for empirical cefiderocol therapy were sepsis (33/55, 65.5%) and lower respiratory tract infection (10/55, 18.2%). In 28/55 cases of empirical therapy (50.9%), GNB grew from cultures collected at the time of treatment initiation, of which 14/26 (54%, missing = 2/28) were CR-GNB, mostly *A. baumannii*, *P. aeruginosa*, and *Klebsiella* spp. (all 4/14 each, 28.6%). Among identified CR-GNB, production of carbapenemase/presence of carbapenemase-encoding genes was assessed in 12/14 cases (85.7%), resulting positive in 5/12 cases (41.7%), of which 3/5 were positive for MBL (60.0%). Identified MBL-producers were 1 VIM-producing *Escherichia* spp., 1 NDM-producing *Escherichia* spp., and 1 NDM-producing *K. pneumoniae*. The other identified carbapenemase-producing organisms were 1 KPC-producing *K. pneumoniae* and 1 OXA-producing *A. baumannii*. Cefiderocol AST was performed among 8/14 identified CR-GNB (including 2/3 MBL-producers), with one *A. baumannii* isolate being non-wild-type (production of carbapenemase/presence of carbapenemase-encoding genes investigated but not detected). The other 7 isolates were all wild-type/susceptible to cefiderocol.

Targeted Therapy

Regarding targeted cefiderocol therapy (Supplementary Table S1), the most frequently reported indications were lower respiratory tract infection (63/145, 43.4%) and bloodstream infection (56/145, 38.6%). Overall, 170 GNB causative agents were retrieved from 145 infections treated with targeted cefiderocol therapy (see details in the legend of Supplementary Table S1). Infections treated with targeted cefiderocol therapy were most frequently monomicrobial (122/145, 84.1%), mainly caused by *A. baumannii* (67/122, 54.9%), *P. aeruginosa* (25/122, 20.5%), and *Klebsiella* spp. (18/122, 14.8%). Rates of carbapenem resistance among these infections were 91.9% (57/62 tested isolates), 95.5% (21/22 tested isolates), and 93.8% (15/16 tested isolates) for *A. baumannii*, *P. aeruginosa*, and *Klebsiella* spp., respectively. Production of carbapenemase/presence of carbapenemase-encoding genes was

Table 2 Characteristics of cefiderocol therapy

Variables[a]	No. of patients	%	95% CI
Type of anti-CR-GNB therapy[b]			
Cefiderocol monotherapy	101/200	50.5	43.5–57.5
Combination therapy[c,d,e,f,g]	99/200	49.5	42.5–56.5
Timing of cefiderocol therapy			
Empirical therapy[h]	55/200	27.5	21.6–34.2
Empirical cefiderocol monotherapy	23/55	41.8	28.7–55.5
Empirical combination therapy	32/55	58.2	44.5–71.3
Targeted therapy[I]	145/200	72.5	65.8–78.4
Targeted cefiderocol monotherapy	69/145	47.6	39.2–55.9
Targeted combination therapy	76/145	52.4	44.1–60.8
Targeted therapy for Enterobacterales infection[j]			
Cefiderocol monotherapy	14/26	53.8	34.1–71.8
Combination therapy	12/26	46.2	28.2–65.9
Targeted therapy for *Pseudomonas aeruginosa* infection[j]			
Cefiderocol monotherapy	14/25	56.0	35.5–74.8
Combination therapy	11/25	44.0	25.2–64.5
Targeted therapy for *Acinetobacter baumannii* infection[j]			
Cefiderocol monotherapy	29/67	43.3	31.9–55.3
Combination therapy	38/67	56.7	44.7–68.1
Targeted therapy for *Stenotrophomonas maltophilia* infection[j]			
Cefiderocol monotherapy	3/4	75.5	24.9–98.7
Combination therapy	1/4	25.5	1.3–75.1
Targeted therapy for MBL-producing Gram-negative infection[j,k,l]			
Cefiderocol monotherapy	13/22	59.1	38.3–78.3
Combination therapy	9/22	40.9	21.7–61.7
Initial cefiderocol dosage according to estimated CL_{Cr} or hemodialytic treatment			
CL_{Cr} > = 120 mL/min	34/200	17.0	12.1–22.9
CL_{Cr} 60 to 119 mL/min	97/200	48.5	41.5–55.5
CL_{Cr} 30 to 59 mL/min	37/200	18.5	13.6–24.4
CL_{Cr} 15 to 29 mL/min	18/200	9.0	5.6–13.8
CL_{Cr} < 15 mL/min	6/200	3.0	1.3–6.3
IHD	3/200	1.5	0.4–4.3

Table 2 continued

Variables[a]	No. of patients	%	95% CI
CRRT	5/200	2.5	1.0–5.6
Change of dosage during therapy due to changes in CL_{Cr}[m]	11/196	5.6	2.9–9.8

CI confidence interval, CL_{Cr} creatinine clearance, *CR-GNB* carbapenem-resistant gram-negative bacteria, *IHD* intermittent haemodialysis, *MBL* metallo β-lactamases, *CRRT* continuous renal replacement therapy

[a]Results are presented as No. of patients/Total of patients unless otherwise indicated

[b]Anti-CR-GNB combination was defined as treatment with cefiderocol in combination with at least one of the following agents: aminoglycosides; fosfomycin; tigecycline (with the exception of targeted therapy of *P. aeruginosa* infections); polymyxins; sulbactam or ampicillin/sulbactam (as empirical treatment of as targeted therapy for *A. baumannii* infections)

[c]Agents combined with cefiderocol for empirical therapy: fosfomycin (*n* = 9); tigecycline (*n* = 6); colistin (*n* = 3); colistin plus tigecycline (*n* = 2); aminoglycoside (*n* = 1); aminoglycoside plus fosfomycin (*n* = 1); ampicillin/sulbactam plus tigecycline (*n* = 1)

[d]Agents combined with cefiderocol for targeted therapy of Enterobacterales infection: fosfomycin (*n* = 5); tigecycline (*n* = 4); aminoglycoside (*n* = 2); aminoglycoside plus tigecycline (*n* = 1)

[e]Agents combined with cefiderocol for targeted therapy of *Pseudomonas aeruginosa* infections: fosfomycin (*n* = 8); aminoglycosides (*n* = 2); colistin (*n* = 1)

[f]Agents combined with cefiderocol for targeted therapy of *Acinetobacter baumannii* infections: fosfomycin (*n* = 13); ampicillin/sulbactam (*n* = 8); colistin (*n* = 8); tigecycline (*n* = 5); aminoglycosides (*n* = 1); aminoglycosides plus tigecycline (*n* = 1); ampicillin/sulbactam plus tigecycline (*n* = 1); colistin plus tigecycline (*n* = 1)

[g]Agents combined with cefiderocol for targeted therapy of *Stenotrophomonas maltophilia* infections: colistin plus tigecycline (*n* = 1)

[h]In 28/55 cases of empirical therapy (51%), a Gram-negative etiological agent grew from cultures collected at the time of treatment initiation, of which 14/26 (54%, missing = 2/28) were carbapenem-resistant (of them 3/12, 25%, were MBL producers, missing = 2/14)

[I]Cefiderocol therapy started after identification of the causative agent

[j]Analyses limited to Infection by only one Gram negative genus (with the exception of Enterobacterales infection, for which concomitant infection by more than one member of the Enterobacterales order was also considered)

[k]Type of MBL enzyme (*n* = 20): NDM (*n* = 12); VIM (*n* = 19); NDM (*n* = 3)

[l]Type of MBL-producing causative agent: *P. aeruginosa* (*n* = 12); Enterobacterales (*n* = 10)

[m]Changes in CL_{Cr} deemed as not related to cefiderocol therapy. Presence of missing values (*n* = 4/200)

assessed in 121/170 isolates (71.2%), resulting positive in 51/121 cases (42%), of which 26/51 (51.0%) were MBL-producing (21.5%), mostly VIM-producing *P. aeruginosa* (12/26, 46.2%), followed by NDM-producing *Klebsiella* spp. (5/26, 19.2%) and VIM-producing *Enterobacter* spp. (4/26, 15.4%). Other detected carbapenemases were KPC-type (*n* = 11), OXA-type (*n* = 11), and not specified (*n* = 3). Cefiderocol AST was performed in 74/170 isolates (43.5%) from infections receiving targeted cefiderocol therapy (including 13/26 MBL producers, 50.0%), with 3/57 tested *A. baumannii* isolates (5.3%) being non-wild-type (production of carbapenemase/presence of carbapenemase-encoding genes was investigated but not detected in all three isolates). No other isolates were resistant/non-wild-type. The demographic and clinical characteristics at time of targeted cefiderocol initiation, stratified according to the different causative agents of infection, are available in supplementary Table S2.

Monotherapy and Combined Therapy

Cefiderocol was administered as monotherapy and as combined therapy for CR- GNB infections in 101/200 (50.5%) and 99/200 (49.5%) cases, respectively (Table 2). Supplementary Table S3

reports the results of univariable analyses of factors associated with administration of cefiderocol as a combined therapy for CR-GNB infections, whereas factors retaining an independent association with combined therapy for CR-GNB infections in the final multivariable models are presented in Table 3. In model A, previous isolation of carbapenem-resistant *Acinetobacter baumannii* [odds ratio (OR) 2.56, 95% CI 1.01–6.46, $p = 0.047$) and previous hematopoietic stem cell transplantation (OR 8.73, 95% CI 1.05–72.54, $p = 0.045$) were associated with administration of cefiderocol within a combined regimen, whereas chronic kidney disease was associated with cefiderocol monotherapy (OR 0.38 for combined regimen, 95% CI 0.16–0.91, $p = 0.029$). In model B, including the same variables of model A plus center as a random effect, the direction of fixed effects was the same registered in model A.

Cure Rates and Tolerability

Cure rates at days 14, 21, and 28 are descriptively summarized in supplementary Table S4, divided by pathogen and combination or monotherapy. As shown in Fig. 1, the cumulative 30-day mortality was 19.8% (95% CI 7.0–37.4) in patients receiving targeted cefiderocol therapy for Enterobacterales infection (panel A), 45.0% (95% CI 32.4–56.8) in those receiving targeted cefiderocol therapy for *A. baumannii* infection (panel B), 20.7% (95% CI 7.3–38.7) in patients receiving targeted cefiderocol therapy for *P. aeruginosa* infection (panel C), and 22.7% (95% CI 8.0–41.9) in patients receiving targeted cefiderocol therapy for MBL-producing GNB (panel D). Overall, 4/200 patients (2.0%) experienced a suspected drug-related AE during cefiderocol administration. Two patients developed mild skin rash, one patient experienced hyperchromic urine and moderate increase in liver enzymes values, and one patient developed status epilepticus categorized as SAE. Cefiderocol was discontinued in 2/4 patients (50.0%) experiencing AE.

Table 3 Multivariable analysis of factors associated with use of cefiderocol in combination with other anti-CR-GNB agents [a]

Model A (AIC 265.28)	**OR (95% CI)**	***P***
Chronic kidney disease	0.38 (0.16–0.91)	**0.029**
Previous HSCT	8.73 (1.05–72.54)	**0.045**
Previous CRAB	2.56 (1.01–6.46)	**0.047**
ICU stay	1.57 (0.83–2.98)	0.168
Presence of septic shock	1.77 (0.86–3.62)	0.120
Urinary tract infection	0.21 (0.02–1.99)	0.174
Model B [b] (AIC 289.36)	**OR (95% CI)**	***P***
Chronic kidney disease	0.81 (0.68–0.97)	**0.024**
Previous HSCT	1.50 (1.09–2.07)	**0.013**
Previous CRAB	1.21 (0.99–1.48)	0.062
ICU stay	1.12 (0.97–1.30)	0.124
Presence of septic shock	1.13 (0.96–1.33)	0.137
Urinary tract infection	0.77 (0.53–1.11)	0.156

Analyses conducted after multiple imputation (see study methods). Values in bold are significant, $p < 0.05$

AIC Akaike information criterion, *CI* confidence interval, *CR-GNB* carbapenem-resistant Gram-negative bacteria, *OR* odds ratio, *HSCT* hematopoietic stem cell transplantation, *CRAB* carbapenem-resistant *Acinetobacter baumannii*, *COVID-19* coronavirus disease 2019

[a]Anti-CR-GNB combination was defined as treatment with cefiderocol in combination with at least one of the following agents: aminoglycosides; fosfomycin; tigecycline (with the exception of targeted therapy of *P. aeruginosa* infections); polymyxins; sulbactam or ampicillin/sulbactam (as empirical treatment of as targeted therapy for *A. baumannii* infections)

[b]Model B also included center as a random effect. For complete details, see Methods

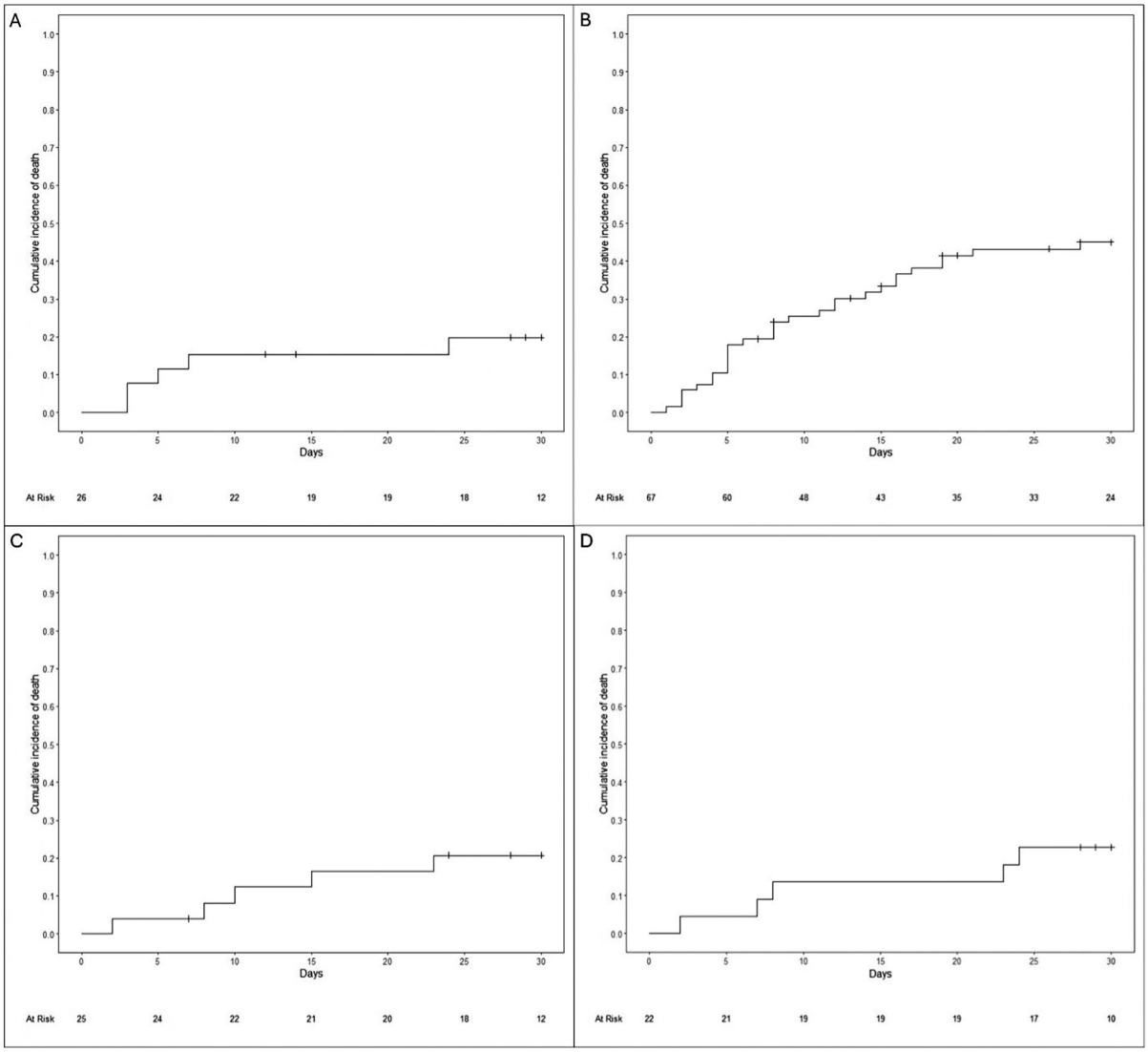
DISCUSSION

In this multicenter study, cefiderocol was mostly administered as targeted therapy (72.5% vs. 27.5% as empirical therapy), mainly for lower respiratory tract infections and bloodstream infections caused by *A. baumannii*, followed by

P. aeruginosa. Cefiderocol was almost equally administered as monotherapy or as combination therapy (50.5% vs. 49.5%).

Most available studies on the use of cefiderocol in real life are focused on the targeted treatment of infections caused by various or specific CR-GNB [7, 10–15, 17, 18, 21–24, 26–35]. While useful for reporting cure rates in specific infections, these studies were unable to generally depict how cefiderocol is currently used by physicians, having been designed for other purposes. In our opinion, this topic is of interest considering the following: (1) current international and national guidelines/guidance documents provide recommendations on the use of cefiderocol for targeted treatment, while there is still no clear guidance regarding its empirical use [47–51]; and (2) various studies have reported use of cefiderocol either in combination or as monotherapy, thus we deemed it of interest to descriptively explore their relative frequency [30, 52]. Regarding the first point, in our study, cefiderocol was mainly administered as targeted therapy. However, the proportion of empirical therapies was not negligible, representing more than one-quarter of all cefiderocol prescriptions. This could reflect the physicians' willingness to prescribe an active therapy without delay in patients with severe infections and risk factors for CR-GNB, in areas where the prevalence rate of CR-GNB, especially MBL producers, is high. Overall, these results suggest the need for standardized consensus regarding the use of cefiderocol within empirical therapeutic algorithms, in order to maximize proper indications in line with antimicrobial stewardship principles, but also to not perilously delay treatment in patients with infections caused by cefiderocol-susceptible CR-GNB.

Regarding the use of cefiderocol as monotherapy or within combined regimens, our results could reflect the current lack of solid evidence on this aspect. Against this background, the possible perception of some clinicians of potential reduced activity of cefiderocol in patients with severe *A. baumannii* infections could have prompted to consider combination therapy in some cases. This is in line with the independent association we found in multivariable models between previous isolation of carbapenem-resistant *A. baumannii* and use of cefiderocol in combined regimens, although it is also of note that no association was found between targeted treatment of *A. baumannii* infections and use of cefiderocol within combined regimens. Furthermore, in our opinion, this controversial point merits some additional considerations. First, it should be considered that the apparently higher mortality rates (50% [21/42] vs. 18% [3/17] for best available therapy, as 49-day mortality) in patients with *A. baumannii* infections treated with cefiderocol in the CREDIBLE-CR RCT were possibly confounded by factors such as severity of presentation and baseline diseases (e.g., severe renal dysfunction, ongoing shock, shock 31 days before randomization, and ICU stay at randomization were more frequent in patients treated with cefiderocol than in those receiving best available therapy) [5]. A similar situation was present in our study, in which mortality of *A. baumannii* infection was higher than mortality of infections caused by other organisms. Indeed, severe clinical presentation was more frequent in patients with *A. baumannii* infections than in those with infections caused by other organisms (e.g., septic shock was present in 29% of patients receiving cefiderocol for the targeted treatment of *A. baumannii* infections vs. 15.4% and 16.0% in patients receiving cefiderocol for the targeted treatment of Enterobacterales infections and *P. aeruginosa* infections, respectively, as shown in supplementary Table S2). Second, it should also be noted that, although mortality rates of cefiderocol-treated *A. baumannii* infections in some other studies were in line with our results [13, 15, 18, 23, 24, 33], in many other studies, including the APEKS-NP randomized controlled trial, they were far lower, ranging from 18 to 37% [3, 7, 12, 14, 16, 27, 29, 32, 53]. Third, lower mortality of cefiderocol-treated *A. baumannii* infections in comparison with non-cefiderocol-based regimens was suggested by recent meta-analyses including data from both CREDIBLE-CR and observational studies [54–56]. Lastly, among isolates subjected to cefiderocol AST, non-susceptibility (i.e., non-wild-type) was exclusively detected in *A. baumannii*, a finding consistent with that of a recent meta-analysis reporting the highest prevalence of cefiderocol non-susceptibility for



A. baumannii, compared to other major Gram-negative pathogens [57]. Overall, considering all the above, in our opinion, the relevant research question for future studies should regard which subgroups of patients with *A. baumannii* infections could benefit the most from cefiderocol monotherapy versus combination therapy (in turn possibly influencing the choice of combined regimens). Regarding other results, the significant association between previous HSCT and administration of cefiderocol within a combined regimen deserves further investigations. Indeed, while the perception of severe baseline conditions and increased mortality due to immunosuppression connected to baseline disease and/or its treatment could have played a role in influencing the choice of combination, also for targeted treatment, the subgroup of patients who underwent HSCT was small in this preliminary analysis ($n = 9$), thus a spurious association due to chance alone cannot be definitely ruled out pending further dedicated data. By contrast, the association between chronic kidney disease and cefiderocol monotherapy could reflect the physicians' decision, at least in some cases, not to administer cefiderocol together with potentially nephrotoxic agents (e.g., polymyxins, aminoglycosides) in patients with already impaired renal function, or the fact that these patients are at increased risk of urinary tract infections

◂**Fig. 1** Cumulative mortality up to day 30 in patients receiving targeted cefiderocol therapy for Enterobacterales infection (panel **A**), *Acinetobacter baumannii* infection (panel **B**), *Pseudomonas aeruginosa* infection (panel **C**), and MBL-producing Gram-negative bacteria (panel **D**). *MBL* metallo-β-lactamases. Analyses limited to Infection by only one Gram negative genus (with the exception of Enterobacterales infection, for which concomitant infection by more than one member of the Enterobacterales order was also considered). The time of origin was set at the day of cefiderocol initiation. Death was the event of interest and right-censoring was applied at the end of follow-up (hospital discharge or day 30, whichever came first). Site/s of Enterobacterales infection: bloodstream infection (n = 12); lower respiratory tract infection (n = 7); urinary tract infection (n = 2); skin and soft tissue infection (n = 1); intra-abdominal infection (n = 1); intra-abdominal infection plus bloodstream infection (n = 1); lower respiratory tract infection plus bloodstream infection (n = 1); urinary tract infection plus bloodstream infection (n = 1). Site/s of *P. aeruginosa* infection (n = 25): lower respiratory tract infection (n = 12); bloodstream infection (n = 6); urinary tract infection (n = 2); bone and joint infection plus bloodstream infection (n = 1); intra-abdominal infection (n = 1); lower respiratory tract infection plus bloodstream infection (n = 1); skin and soft tissue infection (n = 1); skin and soft tissue infection plus bloodstream infection (n = 1). Site/s of *A. baumannii* infection (n = 67): lower respiratory tract infection (n = 30); bloodstream infection (n = 29); bone and joint infection (n = 2); urinary tract infection (n = 2); intra-abdominal infection (n = 1); lower respiratory tract infection plus bloodstream infection (n = 1); skin and soft tissue infection (n = 1); site/s not reported (n = 1). Site/s of MBL-producing Gram-negative infection (n = 22): lower respiratory tract infection (n = 8); bloodstream infection (n = 5); urinary tract infection (n = 3); intra-abdominal infection (n = 2); skin and soft tissue infection (n = 2): lower respiratory tract infection plus bloodstream infection (n = 1); skin and soft tissue infection plus bloodstream infection (n = 1). Type of MBL enzyme (n = 20): NDM (n = 12); VIM (n = 19); NDM (n = 3). Type of MBL-producing causative agent: *P. aeruginosa* (n = 12); Enterobacterales (n = 10)

(for which a trend towards preference of monotherapy was observed in our study, albeit not statistically significant, as reported in Supplementary Table S3).

This present preliminary analysis of the CEFI-SITA study has some limitations to be acknowledged. The first is that, while we reported cumulative mortality in patients receiving cefiderocol in subgroups according to different causative organisms, the analysis was not primarily designed with this aim, thus the resulting unadjusted estimates (e.g., not adjusted for appropriateness of targeted therapy based on in vitro activity) should be interpreted with caution pending further data. However, the low cumulative mortality registered in infections by Enterobacterales, *P. aeruginosa*, and MBL producers is worth mentioning, and is in line with our previous findings of the possibly changing landscape in the treatment of CR-GNB registered in the past few years [58]. A second limitation is connected to the small sample size of patients treated with empirical cefiderocol. Indeed, although the registered 27.5% proportion of patients receiving empirical cefiderocol is solidly based on sample size estimates, subgroup proportions (within empirical therapy) have a larger degree of uncertainty and may require confirmation in further dedicated studies. Of note, this also includes the analysis of either crude or adjusted mortality in patients receiving empirical cefiderocol with subsequent isolation of CR-GNB as etiological agents, which has been deferred to a later phase of CEFI-SITA due to the limited sample size of this subgroup in this preliminary analysis. Third, no standardized microbiological approach was used for cefiderocol AST across participating centers, due to the observational, descriptive representation of daily routine practice. Fourth, owing to the expression of genes not commonly included among targets of rapid molecular tests, production of carbapenemases might have not been thoroughly evaluated in some cases (e.g., OXA-23 in *A. baumannii*). Additional studies employing WGS are therefore needed to decipher the molecular bases of carbapenem resistance in study isolates.

CONCLUSIONS

Cefiderocol is mainly used for targeted treatment in Italian hospitals, although empirical therapies account for more than 25% of prescriptions and should require dedicated standardization and guidance. The almost equal distribution of

cefiderocol monotherapy and cefiderocol-based combination therapies underlines the need for further study to ascertain possible differences in efficacy between the two approaches.

ACKNOWLEDGEMENTS

CEFI-SITA investigators (collaborators): Ylenia Murgia, Gabriele Di Meco, Alice Cappello, Sabrina Guastavino, Cristina Campi, Michele Piana, Sara Mora, Nicola Rosso, Antonio Di Biagio, Giulia Viglietti, Iole Brunetti, Chiara Robba, Lorenzo Ball, Denise Battaglini, Federica Portunato, Maddalena Giannella, Pierluigi Viale, Giulia Viero, Cecilia Azzarà, Alessandro Bartoloni, Benedetta Casciato, Chiara Grillo, Donatella Cibelli, Silvia Boni, Marcello Feasi, Paola Del Giacomo, Gianmaria Baldin, Federico D'Amico, Giovanna Travi, Teresa Fasciana, Giulia Catalisano, Antonino Giarratano, Elena Baranello, Margherita Albagini, Chiara Maci, Antonella Castagna, Cecilia Grosso, Nour Shbaklo, Elena Momesso, Nicoletta Boffa, Elena Potenza, Vincenzo Scaglione, Daniele Mengato, Alessandro Russo, Ludovica Corsello, Francesca Serapide, Monica Rizzo, Erika Asperges, Francesco Truffelli, Margherita Sambo, Gabriele Giuliano, Francesco Fele, Chiara Gullotta, Edoardo Campanella, Maria Chiara Meloni, Sabrina Boraso, Sandro Panese, Aurora Bonazza, Kristian Scolz, Erika Coppo, Marco Berruti.

Author Contributions. Conceptualization: Daniele Roberto Giacobbe, Matteo Bassetti; methodology: Daniele Roberto Giacobbe, Cristina Marelli, Alessio Signori; formal analysis: Cristina Marelli, Daniele Roberto Giacobbe; data curation:Daniele Roberto Giacobbe, Cristina Marelli, Laura Labate, Chiara Russo Artimagnella, Chiara Aldieri, Alessandra Bandera, Federica Briano, Bruno Cacopardo, Alessandra Calabresi, Federico Capra Marzani, Anna Carretta, Annamaria Cattelan, Luca Ceccarelli, Giovanni Cenderello, Silvia Corcione, Andrea Cortegiani, Rosario Cultrera, Francesco Giuseppe De Rosa, Valerio Del Bono, Filippo Del Puente, Emanuele Pontali, Chiara Fanelli, Fiorenza Fava, Daniela Francisci, Nicholas Geremia, Lucia Graziani, Andrea Lombardi, Angela Raffaella Losito, Ivana Maida, Andrea Marino, Maria Mazzitelli, Marco Merli, Roberta Monardo, Alessandra Mularoni, Chiara Oltolini, Carlo Pallotto, Francesca Raffaelli, Matteo Rinaldi, Marco Ripa, Teresa Antonia Santantonio, Francesco Saverio Serino, Michele Spinicci, Carlo Torti, Enrico Maria Trecarichi, Mario Tumbarello, Malgorzata Mikulska, Mauro Giacomini, Antonio Vena; writing—original draft preparation: Daniele Roberto Giacobbe, Cristina Marelli, Vincenzo Di Pilato; writing—review and editing: Daniele Roberto Giacobbe, Vincenzo Di Pilato, Cristina Marelli, Laura Labate, Chiara Russo Artimagnella, Chiara Aldieri, Alessandra Bandera, Federica Briano, Bruno Cacopardo, Alessandra Calabresi, Federico Capra Marzani, Anna Carretta, Annamaria Cattelan, Luca Ceccarelli, Giovanni Cenderello, Silvia Corcione, Andrea Cortegiani, Rosario Cultrera, Francesco Giuseppe De Rosa, Valerio Del Bono, Filippo Del Puente, Emanuele Pontali, Chiara Fanelli, Fiorenza Fava, Daniela Francisci, Nicholas Geremia, Lucia Graziani, Andrea Lombardi, Angela Raffaella Losito, Ivana Maida, Andrea Marino, Maria Mazzitelli, Marco Merli, Roberta Monardo, Alessandra Mularoni, Chiara Oltolini, Carlo Pallotto, Francesca Raffaelli, Matteo Rinaldi, Marco Ripa, Teresa Antonia Santantonio, Francesco Saverio Serino, Michele Spinicci, Carlo Torti, Enrico Maria Trecarichi, Mario Tumbarello, Malgorzata Mikulska, Mauro Giacomini, Anna Marchese, Antonio Vena, Matteo Bassetti;supervision, Daniele Roberto Giacobbe, Mauro Giacomini, Anna Marchese, Matteo Bassetti. All authors have read and agreed to the submitted version of the manuscript.

Funding. The CEFI-SITA project was funded by an investigator-initiated research grant (2021-IIR-000047) from Shionogi & Co., Ltd. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No funding or sponsorship was received for the publication of this article.

Data Availability. The data presented in this study will be available from the corresponding author on reasonable request and provided

all regulatory and privacy requirements are fulfilled.

Declarations

Conflict of Interest. Outside the submitted work, Daniele Roberto Giacobbe reports investigator-initiated grants from Pfizer, BioMérieux, and Gilead Italia, and speaker/advisory board fees from Pfizer, Menarini, and Tillotts Pharma. Outside the submitted work, Matteo Bassetti has received funding for scientific advisory boards, travel, and speaker honoraria from Angelini, Astellas, Bayer, bioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer, Shionogi, Tetraphase, and Nabriva. Outside the submitted work, Vincenzo di Pilato reports travel grants from Arrow Diagnostic, and speaker honoraria from A.D.A. Outside the submitted work, Emanuele Pontali has received funding for scientific advisory boards, travel, and/or speaker honoraria from Abbvie, Angelini, Gilead, Janssen, MSD, and Viiv. Outside the submitted work, Andrea Lombardi reports travel grants from Shionogi. Outside the submitted work, Rosario Cultrera has received funding for scientific advisory boards, travel, and speaker honoraria from Angelini, Menarini, MSD, Pfizer, Shionogi, and TRX Italy. Outside the submitted work, Andrea Cortegiani reports fees for lectures/ advisory board membership from Gilead, MSD, Mundipharma, Pfizer, Shionogi. The other authors have no conflicts of interests to disclose.

Ethical Approval. The MULTI-SITA project was approved by the ethics committee of the coordinating center (Liguria Region Ethics Committee, registry number 390/2020). The amendment authorizing the conduct of the CEFI-SITA study within the MULTI-SITA project was approved by the Liguria Region Ethics Committee on 12 April 2022. The other participating centers followed the local ethical committees requirements and started to enroll patients prospectively once activated. All conscious patients at time of enrollment signed an informed consent to participate in the study. A waiver of informed consent for data collection from unconscious patients at the time of enrollment due to severe clinical conditions was obtained within the ethics committee approval, in line with the observational nature of the analyses and in order not to bias research results towards high cure rates and low mortality prejudicing scientific validity.

REFERENCES

1. Ong'uti S, Czech M, Robilotti E, et al. Cefiderocol: a new cephalosporin stratagem against multidrug-resistant gram-negative bacteria. Clin Infect Dis. 2022;74(7):1303–12.

2. Giacobbe DR, Ciacco E, Girmenia C, et al. Evaluating cefiderocol in the treatment of multidrug-resistant gram-negative bacilli: a review of the emerging data. Infect Drug Resist. 2020;13:4697–711.

3. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2021;21(2):213–25.

4. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2018;18(12):1319–28.

5. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2021;21(2):226–40.

6. Timsit JF, Paul M, Shields RK, et al. Cefiderocol for the treatment of infections due to metallo-B-lactamase-producing pathogens in the CREDIBLE-CR and APEKS-NP Phase 3 randomized studies. Clin Infect Dis. 2022;75(6):1081–4.

7. Falcone M, Tiseo G, Leonildi A, et al. Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2022;66(5): e0214221.

8. Falcone M, Tiseo G. Cefiderocol for the treatment of metallo-beta-lactamases producing gram-negative bacilli: lights and shadows from the literature. Clin Infect Dis. 2022;75(6):1085–7.

9. Bassetti M, Di Pilato V, Giani T, et al. Treatment of severe infections due to metallo-beta-lactamases-producing Gram-negative bacteria. Future Microbiol. 2020;3:1489–505.

10. Zingg S, Nicoletti GJ, Kuster S, et al. Cefiderocol for Extensively Drug-Resistant Gram-Negative Bacterial Infections: real-world Experience From a Case Series and Review of the Literature. Open Forum Infect Dis. 2020;7(6): ofaa185.

11. Wicky PH, Poiraud J, Alves M, et al. Cefiderocol treatment for severe infections due to difficult-to-treat-resistant non-fermentative gram-negative bacilli in ICU patients: a case series and narrative literature review. Antibiotics (Basel). 2023;12(6):991.

12. Russo A, Bruni A, Gulli S, et al. Efficacy of cefiderocol- vs colistin-containing regimen for treatment of bacteraemic ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter* baumannii in patients with COVID-19. Int J Antimicrob Agents. 2023;62(1): 106825.

13. Rando E, Cutuli SL, Sangiorgi F, et al. Cefiderocol-containing regimens for the treatment of carbapenem-resistant *A. baumannii* ventilator-associated pneumonia: a propensity-weighted cohort study. JAC Antimicrob Resist. 2023;5(4): dlad085.

14. Piccica M, Spinicci M, Botta A, et al. Cefiderocol use for the treatment of infections by carbapenem-resistant Gram-negative bacteria: an Italian multicentre real-life experience. J Antimicrob Chemother. 2023;78(11):2752–61.

15. Pascale R, Pasquini Z, Bartoletti M, et al. Cefiderocol treatment for carbapenem-resistant Acinetobacter baumannii infection in the ICU during the COVID-19 pandemic: a multicentre cohort study. JAC Antimicrob Resist. 2021;3(4): dlab174.

16. Palermo G, Medaglia AA, Pipito L, et al. Cefiderocol efficacy in a real-life setting: single-centre retrospective study. Antibiotics (Basel). 2023;12(4):746.

17. Meschiari M, Volpi S, Faltoni M, et al. Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P) infections. JAC Antimicrob Resist. 2021;3(4): dlab188.

18. Mazzitelli M, Gregori D, Sasset L, et al. Cefiderocol-based versus colistin-based regimens for severe carbapenem-resistant *Acinetobacter baumannii* infections: a propensity score-weighted, retrospective cohort study during the first two years of the COVID-19 pandemic. Microorganisms. 2023;11(4):984.

19. Lupia T, Carnevale-Schianca F, Vita D, et al. *Stenotrophomonas maltophilia* infections in haematological malignancies and hematopoietic stem cell transplantation: a case series including cefiderocol-based regimens. Medicina (Kaunas). 2024;60(1):88.

20. Larcher R, Laffont-Lozes P, Roger C, et al. Last resort beta-lactam antibiotics for treatment of New-Delhi Metallo-Beta-Lactamase producing Enterobacterales and other Difficult-to-Treat Resistance in Gram-negative bacteria: a real-life study. Front Cell Infect Microbiol. 2022;12:1048633.

21. Karruli A, Massa A, Andini R, et al. Clinical efficacy and safety of cefiderocol for resistant Gram-negative infections: a real-life, single-centre experience. Int J Antimicrob Agents. 2023;61(2): 106723.

22. Hoellinger B, Simand C, Jeannot K, et al. Real-world clinical outcome of cefiderocol for treatment of multidrug-resistant non-fermenting, gram negative bacilli infections: a case series. Clin Microbiol Infect. 2023;29(3):393–5.

23. Giannella M, Verardi S, Karas A, et al. Carbapenem-resistant Acinetobacter spp infection in critically ill patients with limited treatment options: a descriptive study of cefiderocol therapy during the COVID-19 pandemic. Open Forum Infect Dis. 2023;10(7): ofad329.

24. Gavaghan V, Miller JL, Dela-Pena J. Case series of cefiderocol for salvage therapy in carbapenem-resistant Gram-negative infections. Infection. 2023;51(2):475–82.

25. Fendian AM, Albanell-Fernandez M, Tuset M, et al. Real-life data on the effectiveness and safety of cefiderocol in severely infected patients: a case series. Infect Dis Ther. 2023;12(4):1205–16.

26. Falcone M, Tiseo G, Nicastro M, et al. Cefiderocol as rescue therapy for *Acinetobacter baumannii* and other carbapenem-resistant gram-negative infections in intensive care unit patients. Clin Infect Dis. 2021;72(11):2021–4.

27. El Ghali A, Kunz Coyne AJ, Lucas K, et al. Cefiderocol: early clinical experience for multi-drug resistant gram-negative infections. Microbiol Spectr. 2024;12(2): e0310823.

28. de la Fuente C, Rodriguez M, Merino N, et al. Real-life use of cefiderocol for salvage therapy of severe infections due to carbapenem-resistant Gram-negative bacteria. Int J Antimicrob Agents. 2023;62(1): 106818.

29. Dalfino L, Stufano M, Bavaro DF, et al. Effectiveness of first-line therapy with old and novel antibiotics in ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*: a real life, prospective, observational, single-center study. Antibiotics (Basel). 2023;12(6):1048.

30. Corcione S, De Benedetto I, Pinna SM, et al. Cefiderocol use in Gram negative infections with limited therapeutic options: Is combination therapy the key? J Infect Public Health. 2022;15(9):975–9.

31. Chou A, Ramsey D, Amenta E, et al. Real-world experience with cefiderocol therapy for *Pseudomonas aeruginosa* and other multidrug resistant gram-negative infections within the Veterans Health Administration, 2019–2022. Antimicrob Steward Healthc Epidemiol. 2023;3(1): e90.

32. Campogiani L, Crea AMA, Minardi ML, et al. Real-life data on cefiderocol efficacy and safety to treat multidrug-resistant *Acinetobacter baumannii* infections. Open Forum Infect Dis. 2023;10(12): ofad627.

33. Calo F, Onorato L, De Luca I, et al. Outcome of patients with carbapenem-resistant *Acinetobacter baumannii* infections treated with cefiderocol: a multicenter observational study. J Infect Public Health. 2023;16(9):1485–91.

34. Bavaro DF, Papagni R, Belati A, et al. Cefiderocol versus colistin for the treatment of carbapenem-resistant *Acinetobacter baumannii* complex bloodstream infections: a retrospective, propensity-score adjusted. Monocentric Cohort Study Infect Dis Ther. 2023;12(8):2147–63.

35. Balandin B, Pintado V, Perez-Pedrero MJ, et al. Multicentre study of cefiderocol for treatment of Gram-negative bacteria infections in critically ill patients. Int J Antimicrob Agents. 2024;63(5): 107121.

36. Hackel MA, Tsuji M, Yamano Y, et al. Reproducibility of broth microdilution MICs for the novel siderophore cephalosporin, cefiderocol, determined using iron-depleted cation-adjusted Mueller-Hinton broth. Diagn Microbiol Infect Dis. 2019;94(4):321–5.

37. Bartoletti M, Giannella M, Lewis R, et al. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. Clin Microbiol Infect. 2018;24(5):546e1–8.

38. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245–51.

39. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.

40. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.

41. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33.

42. Kellum JA, Lameire N, Group KAGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204.

43. CDC/NHSN Surveillance Definitions for Specific Types of Infections [last accessed 24 March 2024]. https://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf.

44. Blaker H. Confidence curves and improved exact confidence intervals for discrete distributions. Can J Statistics. 2000;28:783–98.

45. Pereira CA de B, Polpo A. MedOr: Order of Medians Based on Confidence Statements. arXiv.org 2012. http://arxiv.org/abs/1212.5405.

46. Yuan YC. Multiple Imputation for Missing Data: Concepts and New Development (Version 9.0). SAS Institute Inc.; 2010 [last accessed 27 Mar 2023]. Available at: https://support.sas.com/rnd/app/stat/papers/multipleimputation.pdf.

47. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America guidance on the treatment of ampc beta-lactamase-producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clin Infect Dis. 2022;74(12):2089–114.

48. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America 2022 guidance on the treatment of extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2022;75(2):187–212.

49. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022;28(4):521–47.

50. Cortegiani A, Ingoglia G, Ippolito M, et al. Empiric treatment of patients with sepsis and septic shock and place in therapy of cefiderocol: a systematic review and expert opinion statement. J Anesth Analg Crit Care. 2022;2(1):34.

51. Tiseo G, Brigante G, Giacobbe DR, et al. Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM). Int J Antimicrob Agents. 2022;60(2): 106611.

52. Onorato L, de Luca I, Monari C, et al. Cefiderocol either in monotherapy or combination versus best available therapy in the treatment of carbapenem-resistant *Acinetobacter baumannii* infections: a systematic review and meta-analysis. J Infect. 2024;88(3): 106113.

53. Oliva A, Liguori L, Covino S, et al. Clinical effectiveness of cefiderocol for the treatment of bloodstream infections due to carbapenem-resistant Acinetobacter baumannii during the COVID-19 era: a single center, observational study. Eur J Clin Microbiol Infect Dis. 2024;43(6):1149–60.

54. Gatti M, Cosentino F, Giannella M, et al. Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: a systematic review with meta-analysis. Int J Antimicrob Agents. 2024;63(2): 107047.

55. Gill K, Takamichi B, Cooper A. Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: new data from CREDIBLE-CR with an updated meta-analysis. International Journal of Antimicrobial Agents. 2024 2024/04/04/:107167.

56. Gatti M, Cosentino F, Giannella M, et al. In reply to the Letter to the Editor regarding "Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: a systematic review with meta-analysis". Int J Antimicrob Agents. 2024:107168.

57. Karakonstantis S, Rousaki M, Vassilopoulou L, et al. Global prevalence of cefiderocol non-susceptibility in Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. Clin Microbiol Infect. 2024;30(2):178–88.

58. Giacobbe DR, Marelli C, Cattardico G, et al. Mortality in KPC-producing Klebsiella pneumoniae bloodstream infections: a changing landscape. J Antimicrob Chemother. 2023;78(10):2505–14.