Supplementary material

Use of cefiderocol in adult patients:

descriptive analysis from a prospective, multicenter, cohort study

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Supplementary table S1. Infections treated with empirical and targeted cefiderocol

Variables [a]	No. of patients	%	95% CI
Reported indication for empirical therapy			
Sepsis	36/55	65.5	51.8-77.8
Lower respiratory tract infection	10/55	18.2	9.4-30.6
Intra-abdominal infection	6/55	10.9	4.9-22.2
Surgical site infection	2/55	3.6	0.7-12.1
Other indication (not further specified)	1/55	1.8	0.1-9.3
Infections treated with targeted cefiderocol [b]			
Lower respiratory tract infection	63/145	43.4	35.4-51.7
Bloodstream infection	56/145	38.6	30.9-46.9
Urinary tract infection	7/145	4.8	2.2-9.4
Lower respiratory tract infection plus bloodstream infection	4/145	2.8	1.0-6.7
Bone and joint infection	3/145	2.1	0.6-5.9
Intra-abdominal infection	3/145	2.1	0.6-5.9
Skin and soft-tissue infection	3/145	2.1	0.6-5.9
Bone and joint infection plus bloodstream infection	1/145	0.7	0.0-3.5
Intra-abdominal infection plus bloodstream infection	1/145	0.7	0.0-3.5
Skin and soft-tissue infection plus bloodstream infection	1/145	0.7	0.0-3.5

Surgical site infection	1/145	0.7	0.0-3.5
Urinary tract infection plus bloodstream infection	1/145	0.7	0.0-3.5
Other indication (not further specified)	1/145	0.7	0.0-3.5

CI, confidence interval.

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

[b] Cefiderocol therapy started after identification of the causative agent. Causative agents: *Acinetobacter baumannii* (n = 67); *Pseudomonas aeruginosa* (n = 25); *Klebsiella* spp. (n = 18); *Enterobacter* spp. (n = 7); *A. baumannii* plus *Klebsiella* spp. (n = 5); *A. baumannii* plus *P. aeruginosa* (n = 4); *Stenotrophomonas maltophilia* (n = 4); *Klebsiella* spp. plus *P. aeruginosa* (n = 3*); A. baumannii* plus *Enterobacter* spp. (n = 1); *A. baumannii* plus *Enterobacter* spp. plus *S. maltophilia* (n = 1); *A. baumannii* plus *Klebsiella* spp. plus *P. aeruginosa* (n = 1); *A. baumannii* plus *S. maltophilia* (n = 1); *Achromobacter xylosoxidans* (n = 1); *A. xylosoxidans* plus *Escherichia coli* plus *P. aeruginosa* (n = 1); *A. xylosoxidans* plus *P. aeruginosa* (n = 1); *A. xylosoxidans* plus *Elizabethkingia miricola* plus *S. maltophilia* (n= 1); *Elizabethkingia miricola* plus *S. maltophilia* (n = 1); *Enterobacter* spp. plus *P. aeruginosa* (n = 1); *Enterobacter* spp. plus *Klebsiella* spp. (n = 1); *P. aeruginosa* plus *S. maltophilia* (n = 1).

Supplementary table S2. Demographic and clinical characteristics of adult patients treated with targeted cefiderocol and stratified according to causative agents

Variables*	Enterobacterales infection** (N=26)	*Acinetobacter baumannii* infection** (N=67)	*Pseudomonas aeruginosa* infection** (N=25)	MBL-producing GNB infection**, *** (N = 22)
Demographics				
Age in years, median (IQR)	68 (58-74)	68 (53-75)	63 (51-73)	63 (57-74)
Male sex	7/26 (26.9%)	12/67 (17.9%)	7/25 (28.0%)	6/22 (27.3%)
Comorbidities and medical history				
Previous hospitalization	15/25 (60.0%)	26/64 (40.6%)	8/25 (32.0%)	9/21 (42.9%)
Admission from LTCF	2/26 (7.7%)	5/67 (7.5%)	2/25 (8.0%)	1/22 (4.6%)
Diabetes mellitus	7/25 (28.0%)	17/67 (25.4%)	3/25 (12.0%)	2/22 (9.1%)
COPD	4/25 (16.0%)	4/66 (6.1%)	4/25 (16.0%)	3/22 (13.6%)
Previous myocardial injury	3/25 (12.0%)	16/64 (25.0%)	1/24 (4.2%)	0/22 (0.0%)
NYHA score, median (IQR)	1 (1-2)	2 (1-2)	1 (1-1)	1 (1-1)
Chronic liver disease	2/26 (7.7%)	4/67 (6.0%)	2/25 (8.0%)	2/22 (9.1%)
Chronic kidney disease	6/24 (25.0%)	11/67 (16.4%)	3/25 (12.0%)	4/22 (18.2%)
Chronic intermittent hemodialysis	1/25 (4.0%)	1/65 (1.54%)	0/25 (0.0%)	0/22 (0.0%)
Solid neoplasm	6/25 (24.0%)	5/66 (7.6%)	3/25 (12.0%)	6/22 (27.3%)
Metastatic solid neoplasm	1/25 (4.0%)	2/65 (3.1%)	1/25 (4.0%)	2/22 (9.1%)
Hematological malignancy	5/25 (20.0%)	6/67 (9.0%)	3/25 (12.0%)	6/22 (27.3%)

Previous HSCT	1/25 (4.0%)	3/67 (4.5%)	2/25 (8.0%)	3/22 (13.6%)
Previous SOT	0/25 (0.0%)	5/67 (7.5%)	3/25 (12.0%)	1/22 (4.6%)
HIV infection	0/24 (0.0%)	1/62 (1.6%)	1/23 (4.4%)	0/21 (0.0%)
Autoimmune disease	2/25 (8.0%)	11/67 (16.4%)	2/25 (8.0%)	2/22 (9.1%)
Age-adjusted Charlson Comorbidity Index, median (IQR)	4 (3-6)	4 (2-6)	3 (2-5)	4 (2-6)
Previous therapy with cefiderocol	0/25 (0.0%)	1/66 (1.6%)	1/25 (4.0%)	0/21 (0.0%)
Previous antibiotic therapy other than cefiderocol	16/23 (69.6%)	36/59 (61.0%)	17/25 (68.0%)	17/21 (81.0%)
Previous piperacillin/tazobactam	7/23 (30.4%)	26/59 (44.1%)	10/25 (40.0%)	7/21 (33.3%)
Previous ceftazidime/cefepime	1/23 (4.4%)	2/59 (3.4%)	1/25 (4.0%)	1/21 (4.8%)
Previous ceftolozane/tazobactam	2/23 (8.7%)	0/59 (0.0%)	4/25 (16.0%)	5/21 (23.8%)
Previous carbapenems	7/23 (30.4%)	14/59 (23.7%)	6/25 (24.0%)	5/21 (23.8%)
Previous ceftazidime/avibactam	4/23 (17.4%)	2/59 (3.4%)	2/25 (8.0%)	3/21 (14.3%)
Previous meropenem/vaborbactam	1/23 (4.4%)	0/59 (0.0%)	0/25 (0.0%)	0/21 (0.0%)
Previous imipenem/relebactam	0/23 (0.0%)	0/59 (0.0%)	0/25 (0.0%)	0/21 (0.0%)
Previous colistin	0/23 (0.0%)	1/59 (1.7%)	0/25 (0.0%)	0/21 (0.0%)
Previous chemotherapy	5/26 (19.2%)	3/65 (4.6%)	4/25 (16.0%)	8/22 (36.4%)
Previous steroid therapy	8/25 (32.0%)	22/57 (38.6%)	10/25 (40.0%)	10/22 (45.5%)
Previous therapy with immunosuppressants	3/25 (12.0%)	8/64 (12.5%)	5/25 (20.0%)	5/22 (22.7%)
Previous major surgery	11/26 (42.3%)	21/67 (31.3%)	9/25 (36.0%)	8/22 (36.4%)
Previous isolation of CR-GNB	9/24 (37.5%)	15/59 (25.4%)	5/24 (20.8%)	5/21 (23.8%)

Previous CRE	9/24 (37.5%)	7/59 (11.9%)	1/24 (4.2%)	4/21 (19.1%)
Previous CRPA	0/24 (0.0%)	0/59 (0.0%)	4/24 (16.7%)	1/21 (4.8%)
Previous CRAB	0/24 (0.0%)	9/59 (15.3%)	0/24 (0.0%)	0/21 (0.0%)
Previous MBL-producing CR-GNB	5/24 (20.8%)	1/59 (1.7%)	3/24 (12.5%)	4/21 (19.1%)
Variables at cefiderocol initiation				
Days from admission to cefiderocol initiation, median (IQR)	19 (10-31)	19 (10-35)	25 (9-42)	12 (4-38)
ICU stay	13/26 (50.0%)	35/67 (52.2%)	14/25 (56.0%)	10/22 (45.5%)
SOFA score, median (IQR)	4 (2-5)	5 (3-8)	4 (2-5)	4 (2-4)
Presence of CVC	14/23 (60.9%)	43/64 (67.2%)	18 (72.0%)	15/21 (71.4%)
Presence of urinary catheter	19/25 (76.0%)	49/64 (76.6%)	21/24 (87.5%)	16/21 (76.2%)
Presence of septic shock	4/26 (15.4%)	20/67 (29.9%)	4/25 (16.0%)	3/22 (13.6%)
Presence of ARDS	1/24 (4.2%)	6/64 (9.4%)	5/25 (20.0%)	3/21 (14.3%)
Presence of AKI	10/25 (40.0%)	24/67 (35.8%)	10/25 (40.0%)	10/22 (45.5%)
Concomitant COVID-19	0/26 (0.0%)	6/67 (9.0%)	1/24 (4.2%)	0/22 (0.0%)
Total parenteral nutrition	7/25 (28.0%)	16/66 (24.2%)	6/21 (28.6%)	6/19 (31.6%)
Neutropenia	1/26 (3.9%)	2/67 (3.0%)	1/25 (4.0%)	1/22 (4.6%)
CRRT	6/26 (23.1%)	5/65 (7.7%)	3/25 (12.0%)	3/22 (13.6%)
ECMO	0/25 (0.0%)	2/66 (3.0%)	0/25 (0.0%)	0/22 (0.0%)
White blood cell x $10^{-3}/mm^3$, median (IQR)	9.66 (4.50-19.36)	10.00 (6.59-13.48)	21.01 (9.42-15.10)	12.00 (5.47-17.80)
Serum C-reactive protein in mg/L, median (IQR)	33.4 (16.8-90.8)	69.8 (11.2-134.8)	98.1 (32.6-155.4)	84.0 (23.7-127.0)

Serum procalcitonin in ng/mL, median (IQR)	2.1 (0.8-5.1)	0.9 (0.4-5.2)	0.9 (0.2-1.8)	1.4 (0.3-2.9)

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 are presented as No. of patients/Total of patients unless otherwise indicated.

** 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).

*** Not mutually exclusive with the other subgroups

Supplementary table S3. Univariable analysis of factors associated with use of cefiderocol in combination with other anti-CR-GNB agents [a]

Variables [b]	OR (95% CI)	*P*
Demographics		
Age in years	0.99 (0.97-1.00)	0.102
Female sex	1.28 (0.67-2.45)	0.459
Comorbidities and medical history		
Previous hospitalization	1.25 (0.71-2.19)	0.435
Admission from LTCF	2.66 (0.80-8.81)	0.109
Diabetes mellitus	1.26 (0.61-2.62)	0.534
COPD	0.47 (0.19-1.15)	0.097
Previous myocardial injury	1.31 (0.58-2.95)	0.516
NYHA score	1.04 (0.72-1.50)	0.851
Chronic liver disease	0.62 (0.20-1.96)	0.414
Chronic kidney disease	0.37 (0.17-0.83)	**0.016**
Chronic intermittent hemodialysis	0.55 (0.12-2.59)	0.451
Solid neoplasm	0.55 (0.24-1.23)	0.143
Metastatic solid neoplasm	0.41 (0.10-1.65)	0.211
Hematological malignancy	1.31 (0.59-2.88)	0.510
Previous HSCT	8.79 (1.08-71.66)	**0.042**

Previous SOT	0.71 (0.22-2.33)	0.577
HIV infection	0.77 (0.08-7.64)	0.823
Autoimmune disease	0.92 (0.37-2.27)	0.856
Age-adjusted Charlson Comorbidity Index	0.91 (0.83-1.00)	0.059
Previous therapy with cefiderocol	1.79 (0.32-10.02)	0.510
Previous antibiotic therapy other than cefiderocol	0.90 (0.48-1.68)	0.749
Previous piperacillin/tazobactam	0.62 (0.35-1.12)	0.115
Previous ceftazidime/cefepime	0.84 (0.27-2.63)	0.764
Previous ceftolozane/tazobactam	1.91 (0.70-5.18)	0.203
Previous carbapenems	0.82 (0.44-1.54)	0.543
Previous ceftazidime/avibactam	2.32 (0.77-6.94)	0.133
Previous meropenem/vaborbactam*	-	-
Previous imipenem/relebactam**	-	-
Previous polymyxins	3.68 (0.39-37.76)	0.255
Previous chemotherapy	1.04 (0.44-2.46)	0.925
Previous steroid therapy	0.88 (0.49-1.59)	0.674
Previous therapy with immunosuppressants	0.67 (0.30-1.53)	0.345
Previous major surgery	1.03 (0.58-1.83)	0.912
Previous isolation of CR-GNB	1.08 (0.61-1.91)	0.797
Previous CRE	0.78 (0.40-1.55)	0.471
Previous CRPA	1.09 (0.30-4.00)	0.894

Previous CRAB	2.08 (0.91-4.77)	0.083
Previous MBL-producing CR-GNB	0.67 (0.26-1.72)	0.411
Variables at cefiderocol initiation		
Days from admission to cefiderocol initiation	1.00 (0.99-1.01)	0.730
ICU stay	1.69 (0.97-2.96)	0.066
SOFA score	1.03 (0.97-1.10)	0.350
Presence of CVC	1.56 (0.83-2.94)	0.166
Presence of urinary catheter	1.66 (0.82-3.38)	0.160
Presence of septic shock	2.02 (1.05-3.89)	**0.035**
Presence of ARDS	0.75 (0.30-1.88)	0.543
Presence of AKI	0.83 (0.46-1.48)	0.522
Concomitant COVID-19	0.39 (0.13-1.16)	0.089
Total parenteral nutrition	1.05 (0.57-1.94)	0.880
Neutropenia	1.57 (0.43-5.72)	0.499
CRRT	1.02 (0.45-2.33)	0.956
ECMO	0.67 (0.11-4.12)	0.669
White blood cell x $10^{-3}/mm^3$	1.01 (0.97-1.04)	0.772
Serum C-reactive protein in mg/L	1.00 (1.00-1.00)	0.328
Serum procalcitonin in ng/mL	1.00 (0.99-1.01)	0.950
Type of therapy		
Targeted therapy (vs. empirical therapy as ref.)	1.53 (0.82-2.87)	0.182

Targeted therapy for *Enterobacterales* infection [c]	0.86 (0.38-1.96)	0.715
Targeted therapy for *Pseudomonas aeruginosa* infection [c]	0.78 (0.33-1.81)	0.557
Targeted therapy for *Acinetobacter baumannii* infection [c]	1.55 (0.86-2.79)	0.149
Targeted therapy for *Stenotrophomonas maltophilia* infection [c]	0.33 (0.03-3.26)	0.345
Targeted therapy for MBL-producing Gram-negative infection [c]	0.68 (0.28-1.66)	0.395
Indication [d]		
Sepsis/bloodstream infection	0.88 (0.51-1.54)	0.662
Lower respiratory tract infection	1.52 (0.85-2.72)	0.154
Intra-abdominal infection	0.50 (0.12-2.04)	0.330
Urinary tract infection	0.16 (0.02-1.37)	0.094
Other indication	1.24 (0.37-4.20)	0.732
More than one indication	1.02 (0.25-4.20)	0.977

Analyses conducted after multiple imputation (see study methods). 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.

* Algorithm does not converge due to too few cases.

** No cases.

[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] Results are presented as No. of patients (%) unless otherwise indicated.

[c] 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).

[d] Mutually exclusive.

Supplementary table S4. Clinical outcomes in patients receiving targeted cefiderocol therapy

Infection [a]	7-day clinical cure	14-day clinical cure	28-day clinical cure	Adjusted 28-day clinical Cure [b]
Enterobacterales infection [c,e]	17/26 (65)	18/25 (72)	17/23 (74)	20/26 (77)
Cefiderocol monotherapy	11/14 (79)	11/13 (85)	10/12 (83)	12/14 (86)
Combination therapy [d]	6/12 (50)	7/12 (58)	7/11 (64)	8/12 (67)
***Pseudomonas aeruginosa* infection [c,f]**	21/25 (84)	20/24 (83)	19/23 (83)	21/25 (84)
Cefiderocol monotherapy	12/14 (86)	11/13 (85)	10/12 (83)	12/14 (86)
Combination therapy [d]	9/11 (82)	9/11 (82)	9/11 (82)	9/11 (82)
***Acinetobacter baumannii* infection [c,g]**	35/65 (54)	32/61 (52)	25/55 (45)	35/65 (54)
Cefiderocol monotherapy	17/29 (59)	15/28 (54)	15/27 (56)	17/29 (59)
Combination therapy [d]	18/36 (50)	17/33 (52)	10/28 (36)	18/36 (50)
MBL-producing Gram-negative infection [c,h,i,l]	16/22 (73)	17/22 (77)	17/22 (77)	17/22 (77)
Cefiderocol monotherapy	10/13 (77)	11/13 (85)	11/13 (85)	11/13 (85)
Combination therapy [d]	6/9 (67)	6/9 (67)	6/9 (67)	6/9 (67)

MBL, metallo-β-lactamases.

[a] Results are presented as No. of patients/Total of patients (%). Discharged patients excluded from denominator with the exception of the sensitivity analysis for adjusted 28-day mortality (for details, see methods). Missing information excluded from denominator.

[b] Sensitivity analysis considering also discharged patients as clinically cured at day 28.

[c] 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).

[d] 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).

[e] 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).
[f] 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).
[g] 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).
[h] 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).
[i] 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).