ECCMID: infezioni da batteri gram negativi

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New data on G- epidemiology and risk factors

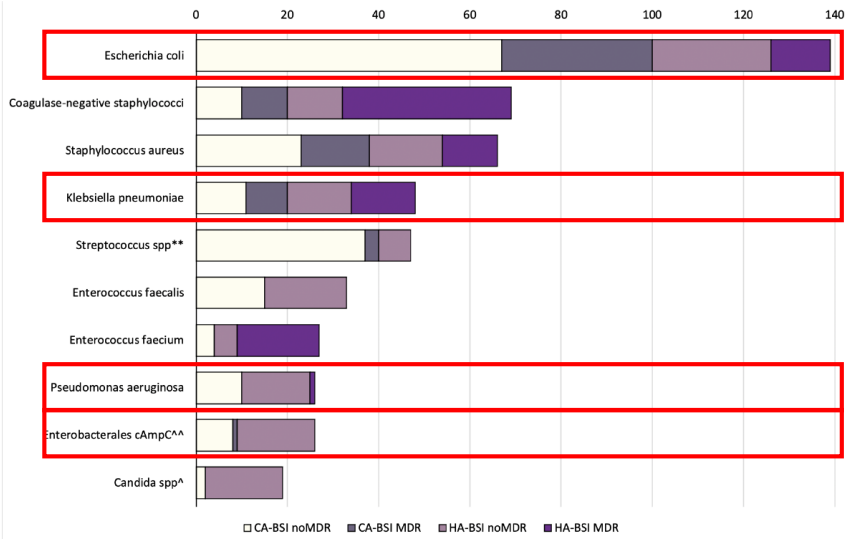
New data on G- epidemiology (i)

Characterization of community-acquired and hospital-acquired bloodstream infections and factors associated to multi-drug resistance in a high–antibiotic resistance setting

AIM: To assess **factors associated with infection by multi-drug-resistant organisms.**

METHODS: Preliminary analysis from patient registry BSI-REG, which collects clinical and microbiological data of adult patients with BSI in Policlinico Hospital (Milan, Italy). Episodes from 08/2022 to 08/2023 were included.

RESULTS: MDROs: 168/515 **(32.6%) BSI**, more frequently **HA-BSI 96/239 (40.2%)** than **CA-BSI 72/276 (26.1%)**



A. CA-BSI

	MDROs N=72	No MDROs N=204	OR (95% CI)	p-value	OR_{adj}* (95% CI)	p-value
CHRONIC CONDITIONS						
Charlson age adjusted ≥ 4	43 (61.4)	118 (60.2)	1.05 (0.60-1.84)	0.857	0.85 (0.47-1.55)	0.603
KDIGO [a]						
G 3a-3b	23 (32.9)	71 (36.4)	1.13 (0.59-2.18)	0.707	1.10 (0.57-2.14)	0.776
G 4-5	23 (32.9)	40 (20.5)	**2.01 (1.02-3.99)**	**0.045**	**2.03 (1.01-4.08)**	**0.047**
Neutropenia	1 (1.4)	4 (2.0)	0.70 (0.08-6.37)	0.752	0.64 (0.07-5.94)	0.690
Transplant	7 (9.9)	16 (8.0)	1.25 (0.49-3.18)	0.638	1.18 (0.45-3.08)	0.741
Orthopedic prosthesis	9 (12.7)	14 (7.0)	1.93 (0.80-4.67)	0.146	1.74 (0.68-4.46)	0.248
Vascular prosthesis	7 (9.9)	15 (7.5)	1.35 (0.53-3.46)	0.533	1.04 (0.39-2.73)	0.944
Ureteral stent	6 (8.5)	15 (7.5)	1.14 (0.42-3.06)	0.797	0.99 (0.36-2.75)	0.989
Pacemaker	3 (4.2)	19 (9.6)	0.42 (0.12-1.46)	0.171	0.32 (0.09-1.14)	0.078
Any hospitalization in the last year [b]	45 (63.4)	88 (43.8)	**2.22 (1.27-3.88)**	**0.005**	**2.36 (1.34-4.18)**	**0.003**
Any MDROs isolates in the last year	27 (38.0)	13 (6.5)	**8.87 (4.24-18.57)**	**<0.001**	**7.12 (3.31-15.30)**	**<0.001**
CLINICAL EVENTS IN THE LAST 30 DAYS						
Invasive procedures	12 (16.9)	32 (16.2)	1.06 (0.51-2.18)	0.885	1.16 (0.55-2.47)	0.692
Parenteral nutrition	1 (1.4)	3 (1.5)	0.94 (0.10-9.22)	0.960	0.72 (0.07-7.52)	0.787
ICU admission	3 (4.2)	7 (3.5)	1.21 (0.30-4.81)	0.787	1.32 (0.31-5.67)	0.710
Dialysis	6 (8.5)	10 (5.0)	1.76 (0.61-5.02)	0.294	0.93 (0.29-3.02)	0.906
Broad spectrum antibiotics	27 (38.6)	49 (24.6)	**1.92 (1.08-3.43)**	**0.027**	1.57 (0.85-2.91)	0.152
SETTING & CHARACTERISTICS AT BSI DIAGNOSIS						
Nursing home or long-term care facilities before hospitalization	11 (15.5)	16 (8.0)	2.12 (0.93-4.82)	0.073	1.39 (0.58-3.34)	0.461
Immunosuppressive therapy	14 (19.7)	40 (20.1)	0.98 (0.50-1.93)	0.945	0.98 (0.48-1.99)	0.960
Short term catheter	4 (5.6)	10 (5.0)	1.14 (0.35-3.76)	0.829	1.17 (0.34-4.02)	0.804
Long term catheter	15 (21.1)	33 (16.4)	1.36 (0.69-2.70)	0.372	1.09 (0.54-2.22)	0.812
Urinary catheter [c]	27 (38.0)	53 (26.4)	1.71 (0.98-3.04)	0.065	1.79 (0.98-3.24)	0.057

Only variables with less than 10% of missing values were analysed. * factors included in the adjusted model (KDIGO G4-5, Any hospitalization in the last year) are based on their univariate relationship with the outcome of interest (p<0.05) or for being known confounders with respect to the outcome studied. If Pearson/Spearman correlation coefficient was greater than 0.20, the variable with the greatest clinical relevance was retained in the model. Legend: KDIGO Kidney Disease Improving Global Outcomes (G1 GFR >=90ml/min, G2 GFR 60-89ml/min, G3a GFR 45-59ml/min, G3b 30-44ml/min, G4 GFR 15-29ml/min, G5 GFR <15ml/min), ICU intensive care unit. [a] reference category G1-2, [b] 48/133 (36.1%) patients were hospitalized in the last 30 days before BSI, [c] 51/80 (63.8%) had indwelling catheter, 29/81 (36.3%) had urinary catheter placed during hospitalization before BSI event.

B. HA-BSI

	MDROs N=96	No MDROs N=143	OR (95% CI)	p-value	OR_{adj}* (95% CI)	p-value
CHRONIC CONDITIONS						
Charlson age adjusted ≥ 4	54 (52.2)	80 (56.7)	0.90 (0.53-1.53)	0.689	1.01 (0.57-1.79)	0.969
KDIGO [a]						
G 3a-3b	22 (22.9)	36 (25.5)	0.93 (0.50-1.73)	0.823	1.41 (0.71-2.83)	0.330
G 4-5	13 (13.5)	12 (8.5)	1.65 (0.71-3.86)	0.246	1.81 (0.70-4.68)	0.218
Neutropenia	16 (16.7)	28 (19.9)	0.81 (0.41-1.59)	0.536	0.48 (0.21-1.09)	0.078
Transplant	28 (29.2)	29 (20.4)	1.60 (0.88-2.92)	0.123	0.90 (0.41-2.00)	0.801
Orthopedic prosthesis	8 (8.3)	8 (5.6)	1.52 (0.55-4.21)	0.417	1.78 (0.60-5.29)	0.300
Vascular prosthesis	9 (9.5)	5 (3.5)	2.87 (0.93-8.84)	0.067	3.11 (0.95-10.17)	0.060
Ureteral stent	1 (1.1)	3 (2.1)	0.49 (0.05-4.81)	0.543	0.43 (0.04-4.69)	0.492
Pacemaker	2 (2.1)	2 (1.4)	1.49 (0.21-10.76)	0.693	4.17 (0.31-55.66)	0.280
Any hospitalization in the last year [b]	52 (54.7)	60 (42.3)	1.65 (0.98-2.79)	0.060	1.40 (0.77-2.56)	0.272
Any MDROs isolates in the last year	44 (45.8)	32 (22.5)	**2.91 (1.66-5.10)**	**<0.001**	**2.60 (1.43-4.71)**	**0.002**
CLINICAL EVENTS IN THE LAST 30 DAYS						
Invasive procedures	51 (53.1)	64 (45.4)	1.36 (0.81-2.29)	0.243	1.35 (0.77-2.38)	0.295
Endoscopic procedure	15 (16.0)	13 (9.1)	1.88 (0.85-4.17)	0.118	1.92 (0.80-4.58)	0.144
Parenteral nutrition	15 (15.6)	14 (9.9)	1.68 (0.77-3.66)	0.192	1.76 (0.75-4.15)	0.194
ICU admission	23 (24.0)	28 (19.9)	1.27 (0.68-2.38)	0.451	0.89 (0.44-1.80)	0.748
Dialysis	8 (8.4)	9 (6.3)	1.36 (0.51-3.66)	0.544	1.17 (0.40-3.39)	0.771
Broad spectrum antibiotics	64 (68.1)	73 (52.5)	**1.93 (1.12-3.33)**	**0.019**	1.52 (0.85-2.72)	0.156
SETTING & CHARACTERISTICS AT BSI DIAGNOSIS						
Nursing home or long-term care facilities before hospitalization	8 (8.4)	7 (5.0)	1.75 (0.61-4.99)	0.298	2.49 (0.82-7.61)	0.109
Immunosuppressive therapy	47 (49.5)	48 (34.0)	**1.90 (1.11-3.23)**	**0.018**	1.58 (0.89-2.81)	0.116
Short term catheter	40 (41.7)	35 (24.8)	**2.16 (1.24-3.78)**	**0.007**	**2.03 (1.12-3.68)**	**0.019**
Long term catheter	31 (32.3)	42 (29.8)	1.12 (0.64-1.97)	0.682	1.11 (0.56-2.23)	0.761
Urinary catheter [c]	49 (51.6)	52 (37.4)	**1.78 (1.05-3.03)**	**0.032**	**1.96 (1.06-3.61)**	**0.032**

Only variables with less than 10% of missing values were analysed. * Factors included in the adjusted model (Any MDROs isolates in the last year, Broad spectrum antibiotics, Immunosuppressive therapy, Short term catheter) are based on their univariate relationship with the outcome of interest (p<0.05) or for being known confounders with respect to the outcome studied. If Pearson/Spearman correlation coefficient was greater than 0.20, the variable with the greatest clinical relevance was retained in the model. Legend: KDIGO Kidney Disease Improving Global Outcomes (G1 GFR >=90ml/min, G2 GFR 60-89ml/min, G3a GFR 45-59ml/min, G3b 30-44ml/min, G4 GFR 15-29ml/min, G5 GFR <15ml/min), ICU intensive care unit. [a] reference category G1-2, [b] 41/112 (36.6%) patients were hospitalized in the last 30 days before BSI, [c] 62/101 (62.4%) had indwelling catheter, 38/101 (34.6%) had urinary catheter placed during hospitalization before BSI event.

CONCLUSIONS: **Patient's medical history has a relevance in development of CA BSI, in HA BSI, in addition to medical history, the single episode acquires relevance.**

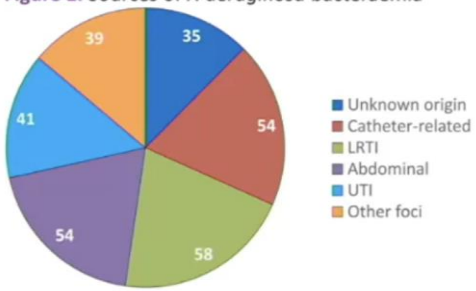
New data on G- epidemiology (ii)

Predictors of mortality of *Pseudomonas aeruginosa* bacteraemia and the role of early source control: a retrospective cohort study

AIM: To determine **predictors of mortality in patients with *P. aeruginosa* bacteraemia.**
METHODS: **Retrospective study** (2015-21) at the Lausanne University Hospital, Switzerland. Inclusion: adult patients with *P. aeruginosa* bacteraemia. A cut-off of 48h was used to define early interventions (ID consultation, source control, appropriate antimicrobial treatment)
RESULTS: **278 episodes** of *P. aeruginosa* bacteraemia, 20 (7%) multi-drug-resistant isolates. The overall **30-day mortality rate was 22%** (60 episodes).
Cox multivariable regression model for 30-day mortality:

- CC >4 (P 0.001; aHR 2.83, CI 1.58-5.09)
- Sepsis (P 0.002; aHR 7.48, CI 1.52-6.84)
- LRTI (P<0.001; aHR 4.60, CI 2.15-9.81)
- Early ID consultation (P 0.049; HR 0.59, CI 0.35-0.99)
- **Early source control (P 0.009; aHR 0.29, CI 0.11-0.74)**

Figure 1. Sources of *P. aeruginosa* bacteraemia



ure 2. Mortality based on focus of infection

Figure 3. Mortality based on early interventions

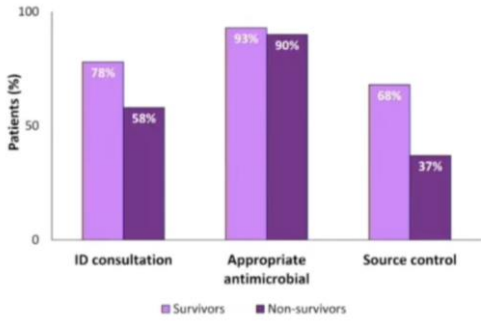
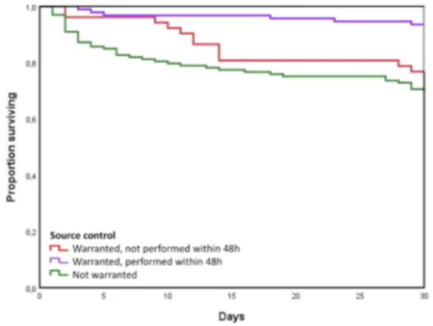


Figure 4. Kaplan-Meier curves on 30-day mortality based on timing of source control interventions



CONCLUSIONS: **Beneficial role of timely ID consultation. Positive impact of timely source control interventions.**

New data on *P. aeruginosa* DTR/XDR

Cactus study (i)

- C/T and CZA are recommended as preferred treatment options for difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa* (Tamma PD, et al. CID 2023 Jul 18)
  - Based on in vitro activity, observational reports, and clinical trials
  - Both agents studied for pneumonia in clinical trials => Few patients infected with multidrug-resistant (MDR) or DTR P. aeruginosa
  - Real-world evidence has shown both agents are superior to aminoglycoside- or polymyxin-based combinations (Pogue JM, et al. CID 2020;71(2):1801, Chen J, et al. Infect Drug Res 2022;15:655)
- There are no randomized clinical trial data to compare agents
- Observational comparative data are lacking
  - Recently published multicenter study from Saudi Arabia (Almangour, T et al. AAC 2023;67(8))
  - Non-matched analysis subject to indication biases and confounding
  - Minority of cases were from patients with pneumonia or bloodstream
- Ceftolozane vs ceftazidime= enhanced stability against ampC, lower affinity to efflux pumps, improved binding to PBPs, better ELF penetration

Cactus study (ii)

A multicenter, observational study to compare the effectiveness of Ceftazidime-Avibactam versus Ceftolozane-Tazobactam for multidrug-resistant Pseudomonas aeruginosa infections in the United States (CACTUS)

- **Objective:** To compare the clinical efficacy of C/T vs. CZA for the treatment of MDR P. aeruginosa **pneumonia and bloodstream infections**
- **Study design:** Retrospective, matched cohort study
  - Patients matched by study site, severity of illness, infection site, and time to initiation of treatment
  - Conditional logistic regression analysis
- **Targeted sample size:** 420 patients (210 pairs)
- **Hypothesis:** Treatment with C/T will result in higher rates of clinical success for patients with pneumonia and/or bacteremia due to MDR Pseudomonas

PRECEDENT NETWORK STUDY SITES

28 U.S. based sites – all major academic medical centers where MDR *P. aeruginosa* is prevalent

www.precedentnetwork.com

Cactus study (iii)

INCLUSION CRITERIA

- Adult patients treated with C/T or CZA for >48h within 7 days of index MDR *P. aeruginosa* blood or respiratory culture

EXCLUSION CRITERIA

- Death or transition to comfort measures within 48 hours of treatment initiation
- Cystic fibrosis
- COVID-19 within 90 days
- Concomitant infection with carbapenem-resistant *A. baumannii* or MRSA bacteremia
- Documented resistance to study treatment by the local laboratory
- Infectious complications including empyema, osteomyelitis, septic arthritis

Cactus study (iv)

ENDPOINTS

- Primary endpoint of **clinical success on day 30** was defined as:
  - Survival and absence of recurrent infections
  - Completion of the intended treatment course without needing to extend treatment due to clinical response or toxicity
- Secon

	Time to improvement
Hemodynamics	Among patients on vasopressors or with a MAP <65 at baseline, time to improvement was defined as the first of 2 consecutive days off pressors and a MAP ≥65 while remaining off pressors up to day 7
Febrile	Among febrile patients at baseline (T≥38°C), time to fever resolution was defined as the first of 2 consecutive afebrile days (T<38°C)
Leukocytosis	Among patients with leukocytosis at baseline (WBC ≥12k), time to improvement was defined as the first of 2 consecutive days with a WBC <12k OR a ≥30% decrease from baseline
Oxygenation	Among patients with pneumonia with a SpO2/FiO2 <300 at baseline, time to improvement will be defined as the first of 2 consecutive days with a >100 improvement from baseline OR a ratio ≥300 For ventilated patients, the first of two consecutive days off the ventilator will also meet this criteria

Cactus study (v)

Patient demographics

	C/T (n=210)	CZA (n=210)	P-value
Median age in years (IQR)	63 (51 – 70)	60 (49 –69)	0.10
Age ≥65 years, n (%)	93 (44)	70 (33)	0.02
Male sex, n (%)	132 (63)	133 (63)	0.92
Race			
• **Caucasian**	119 (57)	126 (60)	0.70
• **Black/African American**	63 (30)	61 (29)	
• **Other**	28 (13)	23 (11)	
Median body mass index (IQR)	24.8 (21.5 – 30.3)	25.2 (21.1 – 30.1)	0.54
Solid-organ transplant recipient, n (%)	**40 (19)**	**32 (15)**	0.30
Any immunocompromising condition*, n (%)	68 (32)	51 (24)	0.07
Origin of hospital admission, n (%)			
• **Home**	101 (48)	103 (49)	0.16
• **LTAC/SNF**	51 (24)	64 (30)	
• **Outside hospital**	58 (28)	43 (20)	
Median Charlson Comorbidity Index (IQR)	5 (3 – 7)	4 (3 – 6)	0.16

*Other conditions included bone-marrow transplant, chronic steroid use, neutropenia and AIDS

Cactus study (vi)

Severity of illness

PRECEDENT NETWORK

	C/T (n=210)	CZA (n=210)	P-value
Median SOFA score (IQR)	7 (4 – 10)	7 (4 – 10)	0.98
Bloodstream Infections, n (%) • **Median Pitt Bacteremia Score** (IQR)	35 (17) 4 (2 – 8)	35 (17) 4 (2 – 6)	0.75
Receipt of renal replacement therapy, n (%) • **Continuous renal replacement**, n (%) • **Intermittent hemodialysis**, n (%)	64 (30) 32 (15) 32 (15)	61 (29) 30 (14) 31 (15)	0.75
Residence in the ICU, n (%)	171 (81)	165 (79)	0.46
Severe sepsis/septic shock, n (%)	123 (59)	123 (59)	1.00
Receipt of vasopressors, n (%)	82 (39)	86 (41)	0.69
Mechanical ventilation, n (%)	149 (71)	145 (69)	0.67
Median SpO2/FiO2 ratio at baseline among patients with pneumonia (IQR)	235 (164 – 267)	238 (167 – 263)	0.95

A total of 80% of patients were in the ICU at the time of treatment initiation and 70% of patients that were receiving mechanical ventilation

Shields R. ESCMID Global 2024

Cactus study (vii)

Treatment characteristics

	C/T (n=210)	CZA (n=210)	P-value
Bacteremia, n (%)	35 (17)	35 (17)	1.00
Pneumonia, n (%)	175 (83)	175 (83)	1.00
• **CAP**	21 (10)	23 (11)	
• **HAP**	26 (12)	21 (10)	
• **VAP**	97 (46)	103 (49)	
• **vHAP**	31 (15)	28 (13)	
Median time to study drug in hours (IQR)	71.8 (45.1 – 94.9)	70.9 (30.2 – 95.9)	0.52
Active treatment before study drug, n (%)	43 (20)	34 (16)	0.26
Time to active treatment initiation in hours (range)	65.2 (22.9 – 88.8)	65.3 (20.9 – 92.8)	0.84
Receipt of prolonged infusion, n (%)	65 (31)	44 (21)	0.02
Suboptimal dosing regimen, n (%)	42 (20)	15 (7)	<0.001
Median treatment duration, (IQR)	8.75 (6.3 – 13.3)	7.8 (6.1 – 12.5)	0.23
Combination treatment, n (%)	59 (28)	57 (27)	0.83
• **Inhaled antibiotics**	35 (17)	28 (13)	
• **Intravenous antibiotics**	20 (10)	24 (11)	
• **Both inhaled and intravenous**	4 (2)	5 (2)	
Co-infection, n (%)	83 (40)	97 (46)	0.27
• **Co-infection appropriately treated**, n (%)	76 (92)	90 (93)	
Baseline isolate not tested for susceptibility, n (%)	45 (21)	39 (19)	0.46

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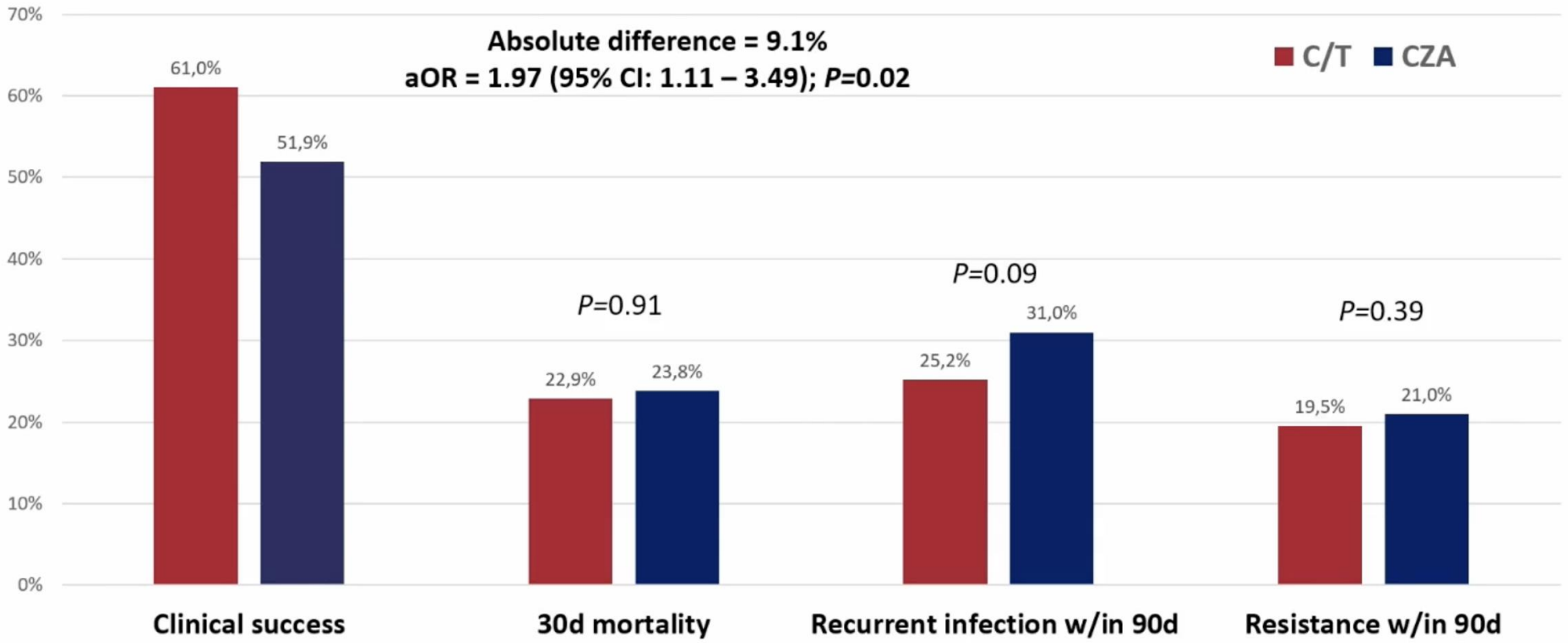
Cactus study (viii)

Clinical outcomes



Conditional logistic regression performed controlling for age, immunocompromising conditions, infection site, suboptimal dosing, SOFA score, Charlson Comorbidity Index, time to treatment initiation, co-infection, prolonged infusions, and receipt of renal replacement therapy

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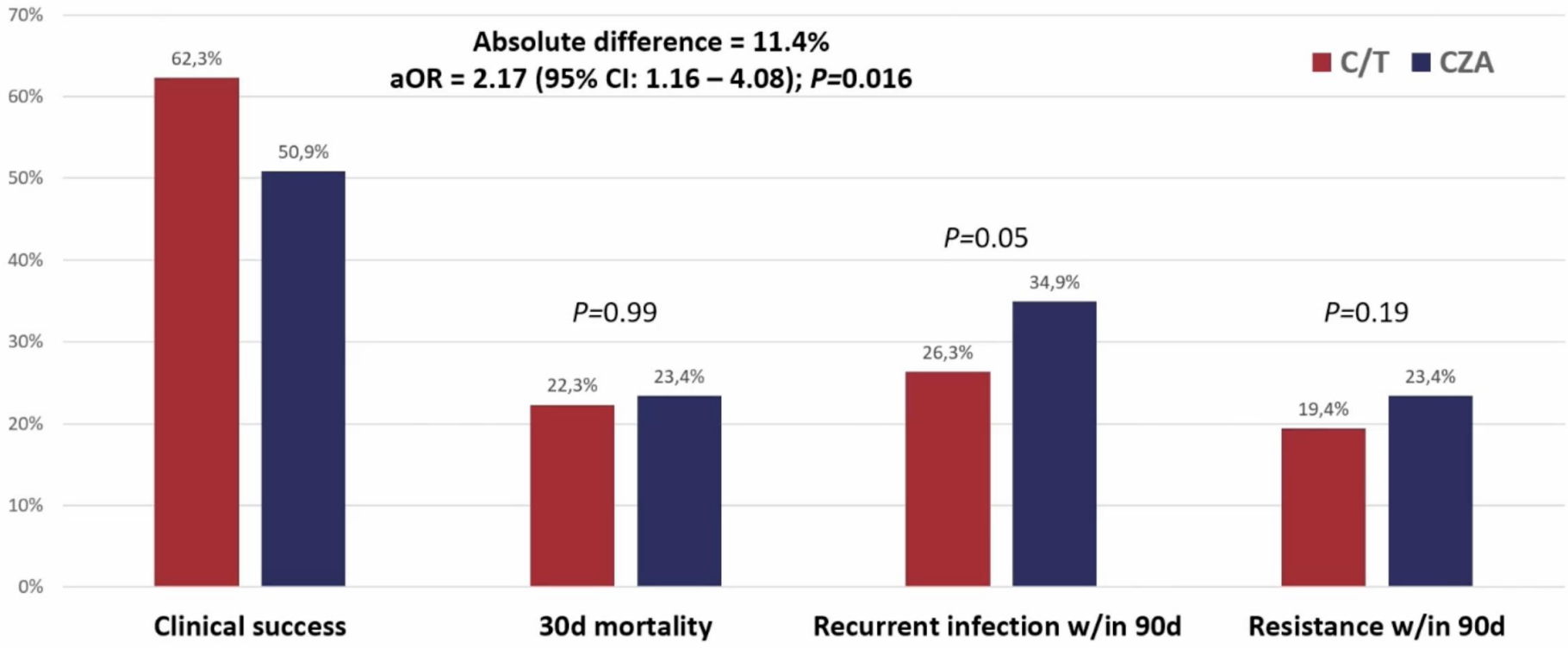
Cactus study (ix)

Clinical outcomes (pneumonia)



Conditional logistic regression performed controlling for age, immunocompromising conditions, infection site, suboptimal dosing, SOFA score, Charlson Comorbidity Index, time to treatment initiation, co-infection, prolonged infusions, and receipt of renal replacement therapy

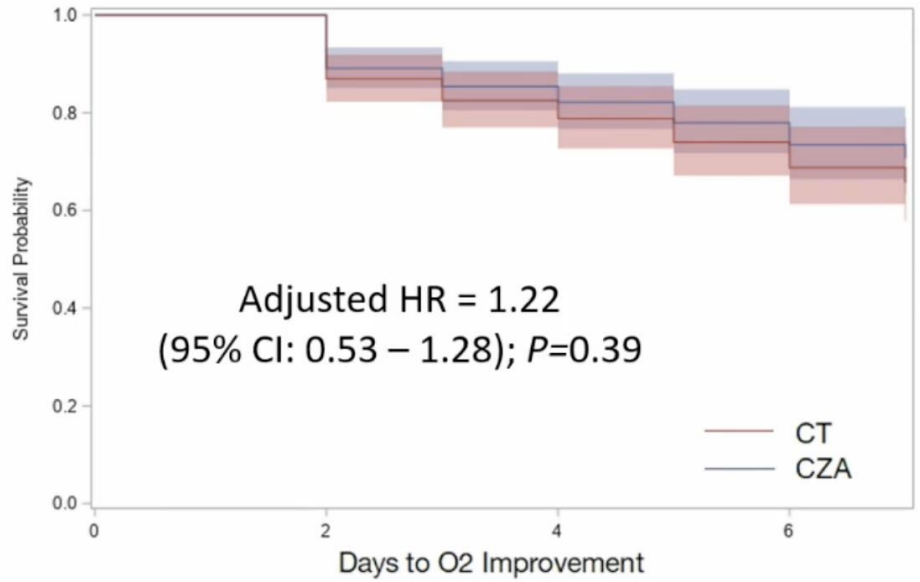
Shields R. ESCMID Global 2024

Cactus study (x)

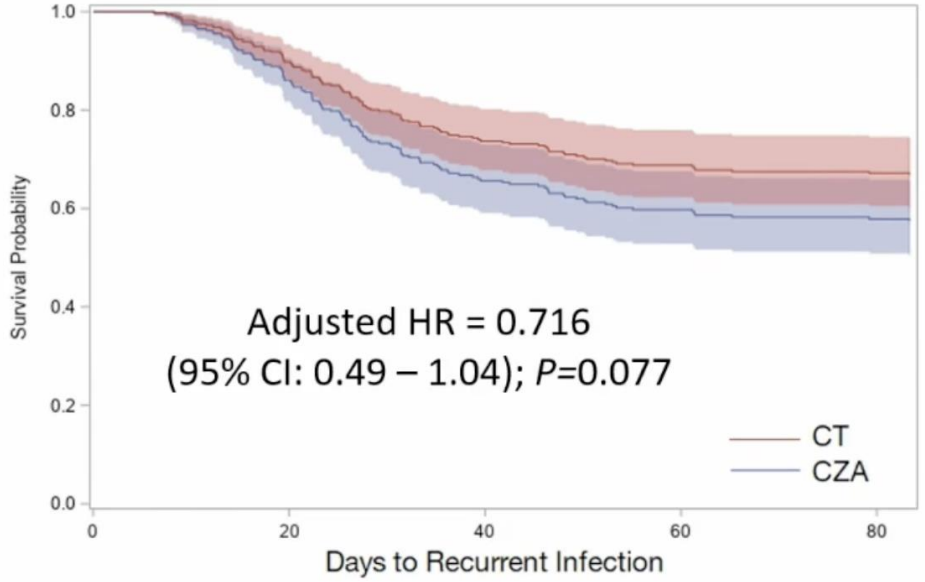
Secondary clinical outcomes (All patients)

- No difference in time to hemodynamic stability, defervescence, or normalization of leukocytosis

Time to improved oxygenation



Time to recurrent infection



Cactus study (xi)

- In a multicenter, retrospective matched study, **treatment with C/T resulted in a higher rate of clinical success compared to treatment with CZA**
  - Differential response rates driven by recurrent infections among patients with pneumonia
- Robust retrospective, multicenter comparative-effectiveness studies are feasible
  - Groups were well-balanced by severity of illness and time to treatment initiation
  - Subtle differences in Charlson score, immunocompromised patients and dosing practices that were adjusted for in conditional logistic regression analyses
- CACTUS represents real-world patients infected by MDR *P. aeruginosa*, for which outcomes can still be improved
  - 23% of patients died within 30 days of treatment initiation

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4891722

Perseus study (i)

CREDIBLE-CR + APEKS-NP[e]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]
Overall	70.8 (17/24)	40.0 (4/10)	58.3 (14/24)	30.0 (3/10)	12.5 (3/24)	50.0 (5/10)
Type of infection						
Pneumonia	71.4 (10/14)	50.0 (3/6)	42.9 (6/14)	33.3 (2/6)	21.4 (3/14)	33.3 (2/6)
Other diagnoses[b]	70.0 (7/10)	25.0 (1/4)	80.0 (8/10)	25.0 (1/4)	0 (0/10)	75.0 (3/4)
MBL type						
NDM	56.3 (9/16)	33.3 (2/6[a])	62.5 (10/16)	16.7 (1/6[a])	18.8 (3/16)	50.0 (3/6[a])
Non-NDM	100 (8/8)	40.0 (2/5[a])	50.0 (4/8)	40.0 (2/5[a])	0 (0/8)	40.0 (2/5[a])
Pathogen type						
Enterobacterales	73.3 (11/15)	20.0 (1/5)	66.7 (10/15)	20.0 (1/5)	13.3 (2/15)	60.0 (3/5)
Non-fermenters	66.7 (6/9)	60.0 (3/5)	44.4 (4/9)	40.0 (2/5)	11.1 (1/9)	40.0 (2/5)

- Non-fermenters were underrepresented in FDC pivotal trials
- Apparently, numerically higher clinical cure and microbiological eradication rates than comparators against MBL-producing pathogens

Perseus study (ii)

- **PERSEUS study**: retrospective analysis (2018-2022) of real-world use of cefiderocol in the management of G- infections
- Spanish **Early Access Program**
- Collected data from treatment start to day 28 (or death or discharge)
- Excluding *Acinetobacter* spp.
- **Shionogi sponsored**

Geographical location

50 centres participated

314 patients recruited

~90 HPCs participated

52 isolates collected

Perseus study (iii)

INCLUSION CRITERIA

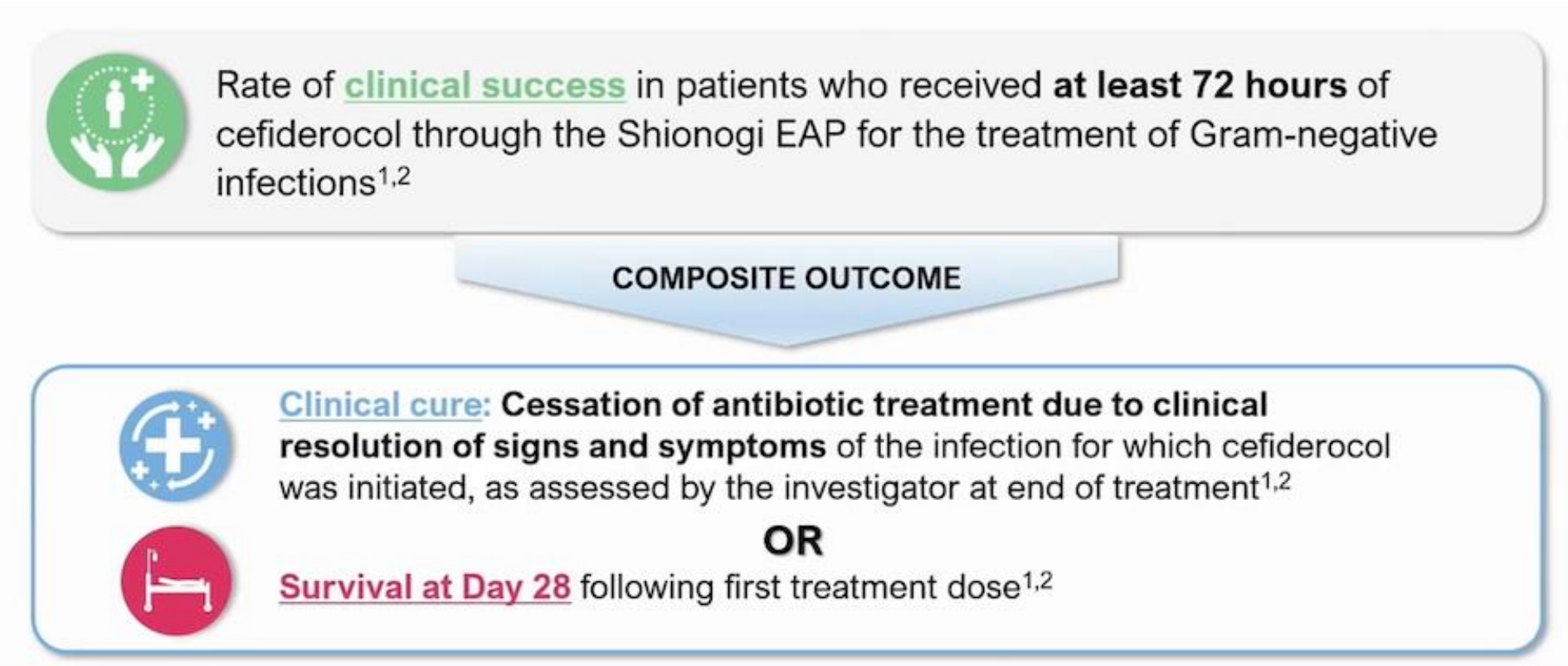
- Age > 18 years of age
- Confirmed G- infection
- Isolate FDC-Sn
- First FDC treatment
- At least 72h of treatment

EXCLUSION CRITERIA

- Patient enrolled in RCT
- *Acinetobacter* spp. infection
- Incomplete medical records for:
  - FDC use
  - Data on clinical success
- Coinfection with a GNB FDC-R within 28 days of the first FDC dose

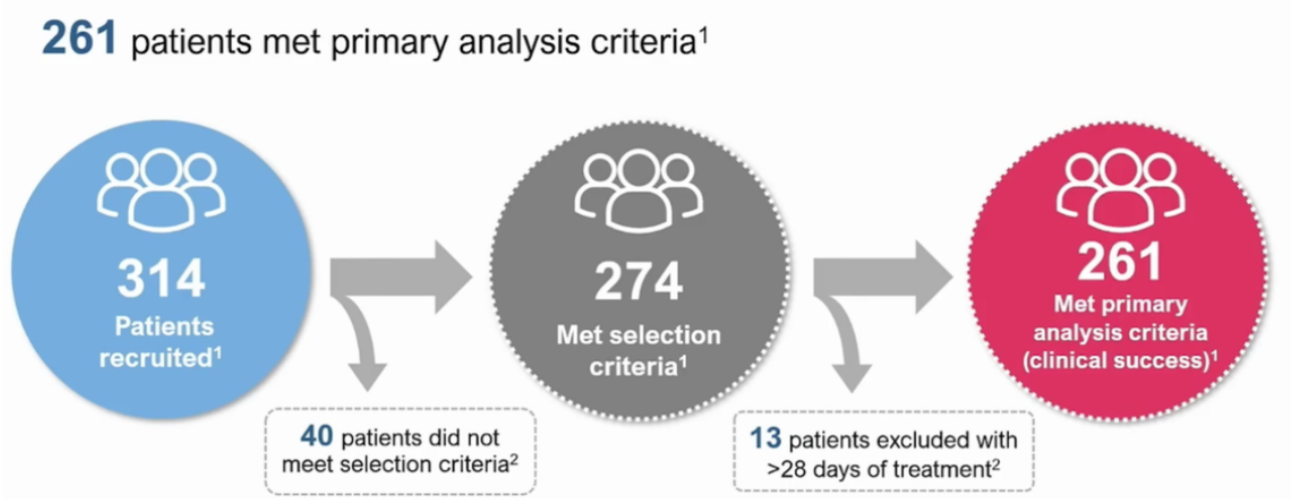
Perseus study (iv)

PRIMARY OUTCOME

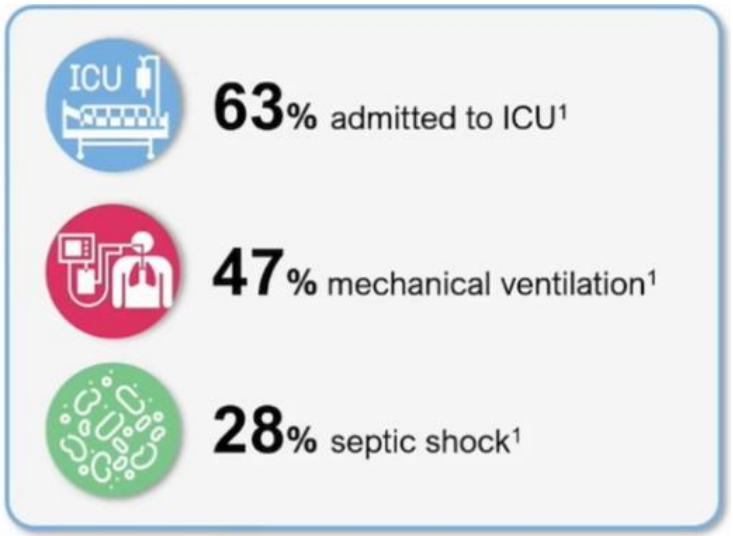


Perseus study (v)

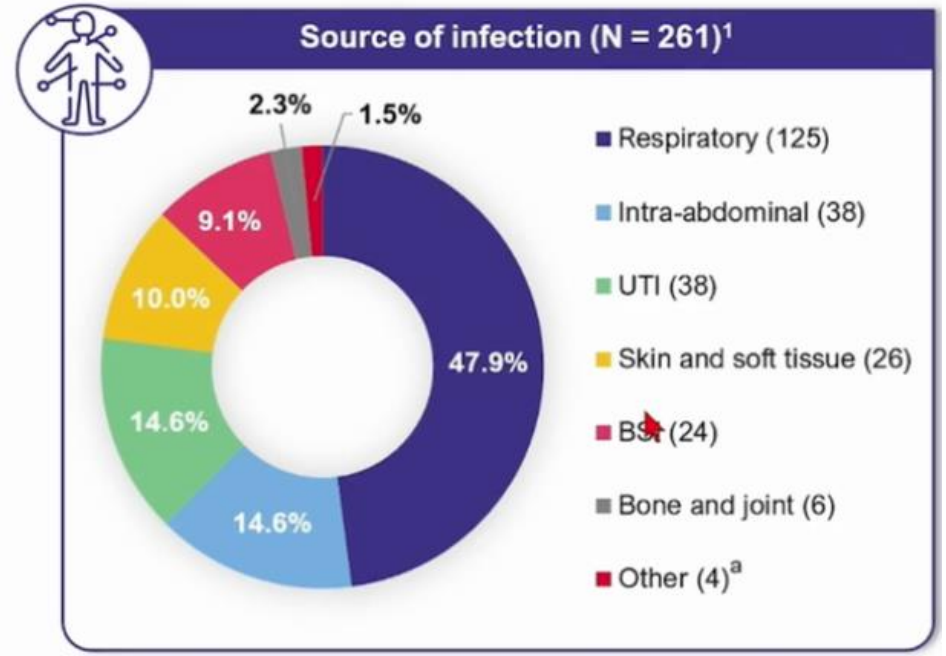
PATIENTS RECRUITED

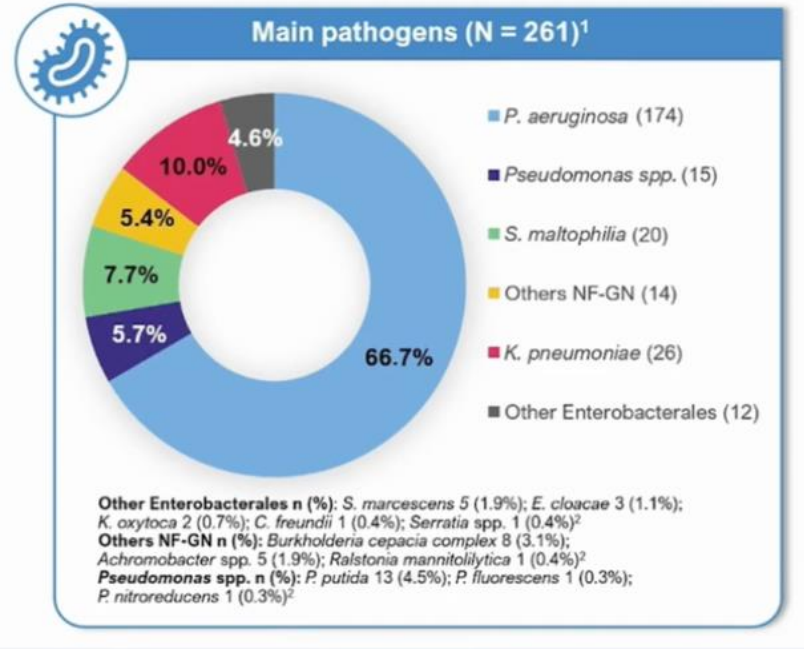


Clinical status[1]	Overall (N = 261)
ICU	165 (63.2%)
Mechanical ventilation	123 (47.1%)
Septic shock	73 (28.0%)
APACHE II (median, IQR)	15.0 (10.5, 22.0)
Charlson Comorbidity Index (median, IQR)	3.0 (2.0, 4.0)
SOFA Day 0 (median, IQR)[2]	8.0 (4.0, 11.0)
Immunosuppression[a]	79 (30.3%)
ECMO	12 (4.6%)
Creatine clearance <60 mL/min[b] (N = 177)[2]	54 (30.5%)
Renal replacement therapy[c]	71 (27.2%)
Symptomatic COVID-19	63 (24.1%)



Perseus study (vi)





Bacteraemia[1]	Overall (N = 69)
Catheter related	15
Unknown source	9
Secondary BSI[2]	45

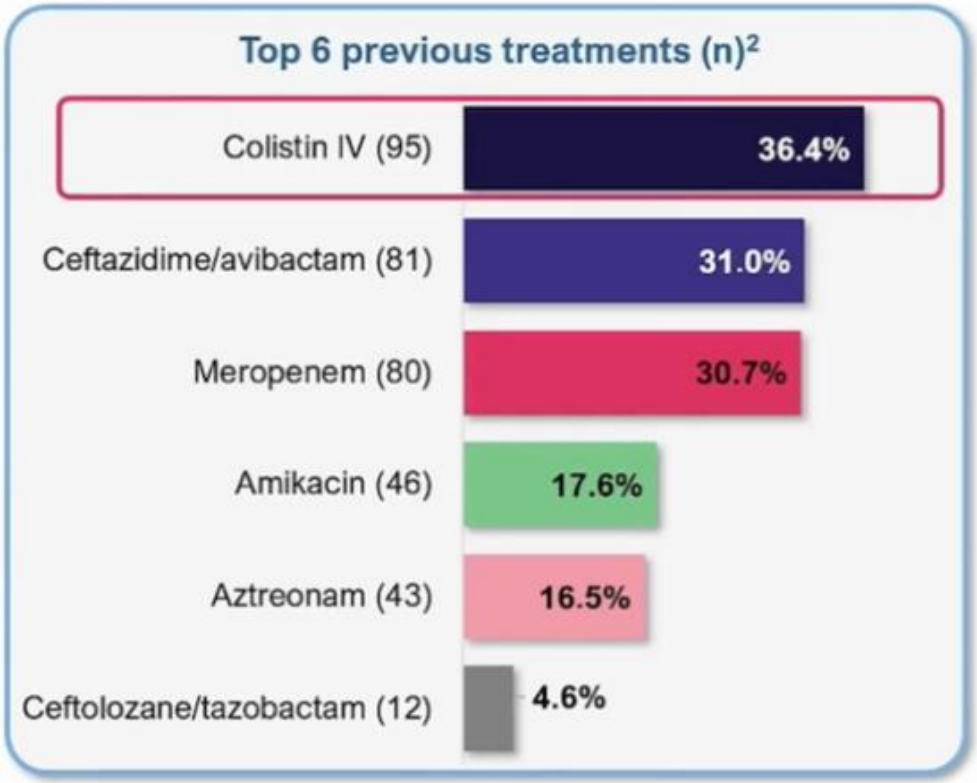
Characteristics[2]	Overall (N = 261)
Resistance to C/T and CZA (N = 129)	99/129 (76.7%)

Mechanism of resistance[2]	Overall (N = 261)
Class B β-lactamase	98 (37.5%)[a]
VIM	60 (61.0%)
IMP	22 (22.4%)
NDM	12 (12.2%)
Unknown MBL	4 (4.0%)

Perseus study (vii)

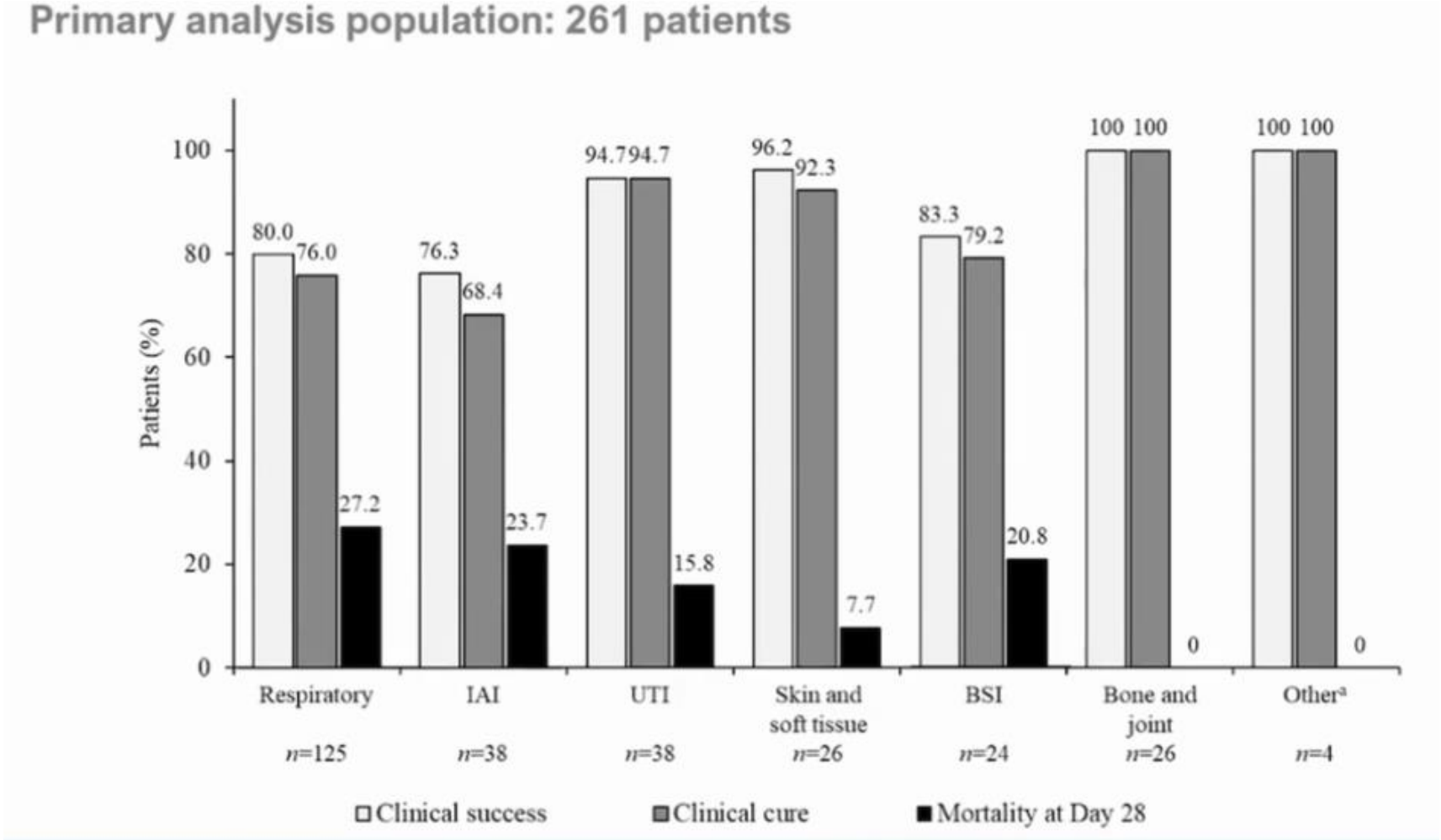
PREVIOUS TREATMENTS

	Overall (N = 261)
Cefiderocol as first line[1]	**42 (16.1%)**
Number of days with previous ATB[a] (median, IQR)[1]	6.0 (3.0,10.1)
Number of days with previous ATB (range)[1]	
≤3	55 (25.9%)
4–7	70 (33.0%)
>7	87 (41.0%)
Number of previous ATB (range)[2]	
1	54 (25.5%)
2	62 (29.2%)
≥3	96 (45.3%)



Perseus study (viii)

OUTCOMES OVERALL



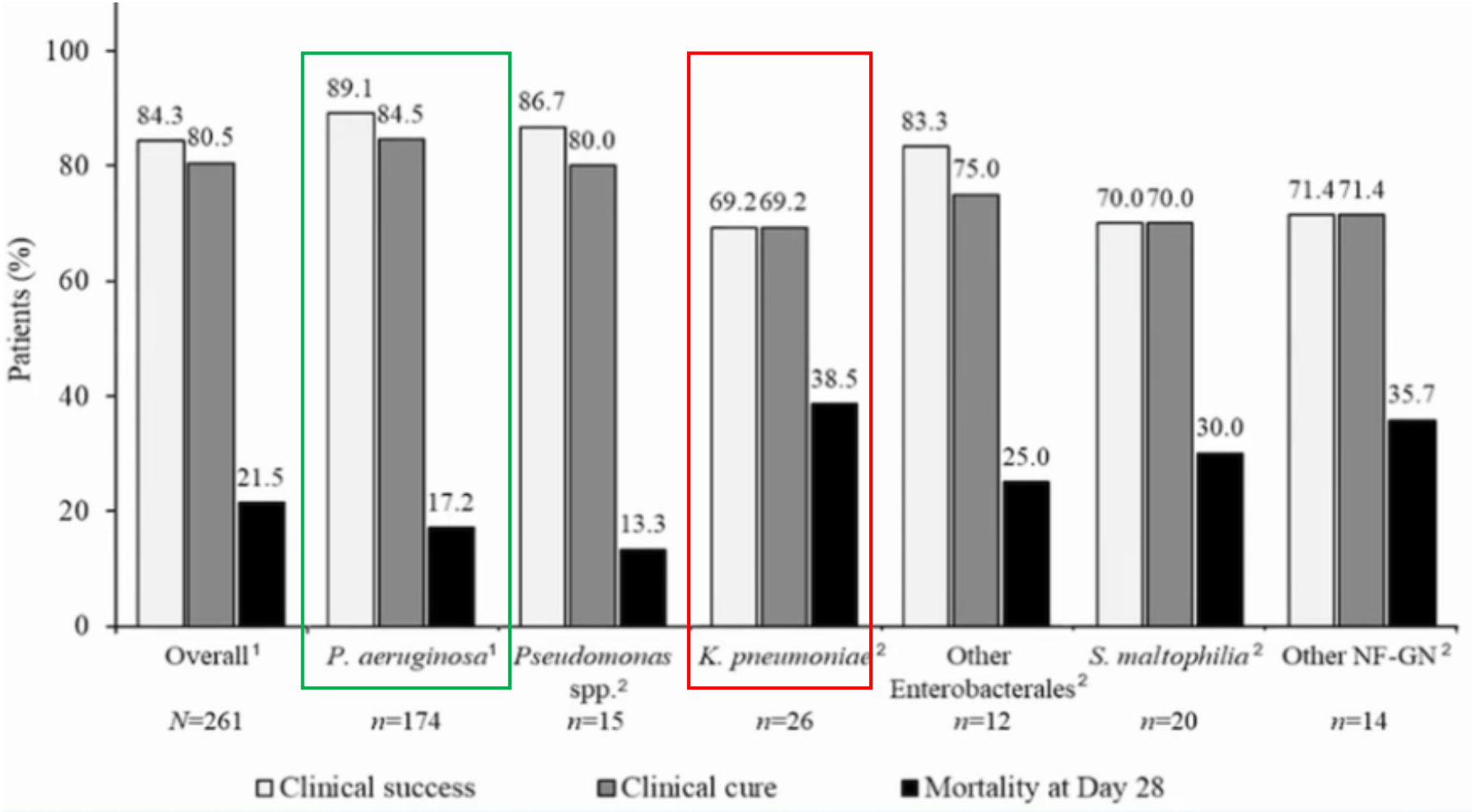
Perseus study (ix)

OUTCOMES BY PREVIOUS TREATMENT

Treatment with cefiderocol[1]	Overall (N =261)	Clinical success	Clinical cure	Mortality Day 28
Cefiderocol as first line				
Yes	42 (16.1%)	38 (90.5%)	38 (90.5%)	6 (14.3%)
No	219 (83.9%)	182 (83.1%)	172 (78.5%)	50 (22.8%)
Number of previous ATB (range)[2]	**N = 219[a]**			
1	54 (25.5%)	48 (88.9%)	47 (87.0%)	9 (16.7%)
2	62 (29.2%)	54 (87.1%)	52 (83.9%)	10 (16.1%)
≥3	96 (45.3%)	76 (79.2%)	69 (71.9%)	28 (29.2%)
Number of days with previous ATB (range)				
≤3	55 (25.9%)	49 (89.1%)	49 (89.1%)	9 (16.4%)
4–7	70 (33.0%)	62 (88.6%)	59 (84.3%)	13 (18.6%)
>7	87 (41.0%)	67 (77.0%)	60 (69.0%)	25 (28.7%)
Previous treatment with colistin[2]	95 (36.4%)	78 (82.1%)	74 (77.9%)	25 (26.2%)
Previous treatment with CZA[2]	81 (31.0%)	62 (76.5%)	59 (72.8%)	23 (28.4%)
Previous treatment with meropenem[2]	80 (30.7%)	63 (78.8%)	58 (72.5%)	23 (28.8%)
Previous treatment with C/T[2]	12 (4.6%)	10 (83.3%)	9 (75.0%)	2 (16.7%)
Combined treatment				
Yes	91 (34.9%)	70 (76.9%)	67 (73.6%)	26 (28.6%)
No	170 (65.1%)	150 (88.2%)	143 (84.1%)	30 (17.6%)

Perseus study (xi)

OUTCOMES BY PATHOGEN



Perseus study (xii)

PATIENT CHARACTERISTICS BY PATHOGEN

	P. aeruginosa (N = 174)	*Pseudomonas* spp. (N = 15)	*S. maltophilia* (N = 20)	Other NF-GN (N = 14)	*K. pneumoniae* (N = 26)	Other Enterobacterales (N = 12)
Male[2]	138 (79.3%)	11 (73.3%)	14 (70.0%)	9 (64.3%)	21 (80.8%)	9 (75%)
Age, median (IQR)[2]	61 (52, 68)	59 (54, 67)	60.5 (48, 65.5)	49.5 (33, 59)	64.5 (49, 70)	51 (44.5, 58.5)
CCI, median (IQR)[2]	3.0 (2.0, 5.0)	4.00 (2.0, 4.0)	3.0 (2.0, 5.0)	2.0 (1.0, 3.0)	3.0 (2.0, 4.0)	2.5 (1.0, 4.0)
Septic shock[2]	47 (27.0%)	1 (6.7%)	6 (30.0%)	3 (21.4%)	13 (50.0%)	3 (25.0%)
Immunosuppression[2]	41 (23.6%)	9 (60.0%)	11 (55.0%)	9 (64.3%)	5 (19.2%)	4 (33.3%)
Transplant[2]	23 (13.2%)	6 (40.0%)	9 (45.0%)	8 (57.1%)	4 (15.4%)	4 (33.3%)
Solid	17 (73.9%)	1 (16.7%)	3 (33.3%)	7 (87.5%)	4 (100%)	1 (25.0%)
Haematopoietic	6 (26.1%)	5 (83.3%)	6 (66.7%)	1 (12.5%)	0 (0.0%)	3 (75.0%)
Site of infection[2]						
Respiratory	81 (46.6%)	2 (13.3%)	11 (55.0%)	10 (71.4%)	16 (61.5%)	5 (41.7%)
IAI	23 (13.2%)	3 (20.0%)	2 (10.0%)	1 (7.1%)	7 (26.9%)	2 (16.7%)
UTI	28 (16.1%)	6 (40.0%)	1 (5.0%)	2 (14.3%)	0 (0.0%)	1 (8.3%)
Skin and soft tissue	22 (12.6%)	3 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
BSI (unknown source and catheter)	11 (6.3%)	1 (6.7%)	5 (25.0%)	1 (7.1%)	3 (11.5%)	3 (25.0%)
Bone/joint	6 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other[a]	3 (1.7%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinical success at Day 28[2]	156 (89.1%)	13 (86.7%)	14 (70.0%)	10 (71.4%)	18 (69.2%)	10 (83.3%)
Clinical cure at Day 28[2]	147 (84.5%)	12 (80%)	14 (70.0%)	10 (71.4%)	18 (69.2%)	9 (75.0%)
Mortality at Day 28[2]	30 (17.2%)	2 (13.3%)	6 (30.0%)	5 (35.7%)	10 (38.5%)	3 (25.0%)

Perseus study (xiii)

Safety analysis	Overall (N = 314)
Any adverse drug reactions, n (%)	7 (2.7)
SADRs, n (%)	3 (1.1)
Discontinuation due to ADR, n (%)	3 (1.1)
Discontinuation due to SADR, n (%)	3 (1.1)
Death due to SADR, n (%)[a]	1 (0.4)

New data on CRE

Gamechanger study (i)

- Multicentre, randomised, non-inferiority, open-label trial **comparing cefiderocol with standard of care antibiotics for Gram negative bacterial bloodstream infection** that is hospital-acquired or healthcare-associated

Gamechanger study (ii)

INCLUSION CRITERIA

- Adult patients
- Bloodstream infection with a Gram-negative organism from at least one blood culture draw.
- No more than 48 hours has elapsed from the time of positive blood culture's

EXCLUSION CRITERIA

- Refractory shock or comorbid condition such that not expected to survive more than 7 days
- History of moderate to severe hypersensitivity reaction to a cephalosporin
- Polymicrobial bloodstream infection with a significant Gram-positive pathogen
- Line-related and line unable to be removed
- Treatment is not with intent to cure the infection
- Pregnancy or breast-feeding
- On peritoneal dialysis
- Prior inclusion in the trial

Gamechanger study (iii)

- **Cefiderocol** dosage regimen: 2 grams IV over 3 hours, every 8 hours for 5-14 days
  - Dosage adjustment for ARC and decreased renal function
- **Standard of Care** (SOC)
  - One, two or three antibiotics with activity against Gram negative bacteria
  - Could be adjusted according to susceptibility results or changes in the patient's condition
- For both arms, additional antibiotics can be given for Gram positive or anaerobic organisms or fungi

Gamechanger study (iv)

ENDPOINTS

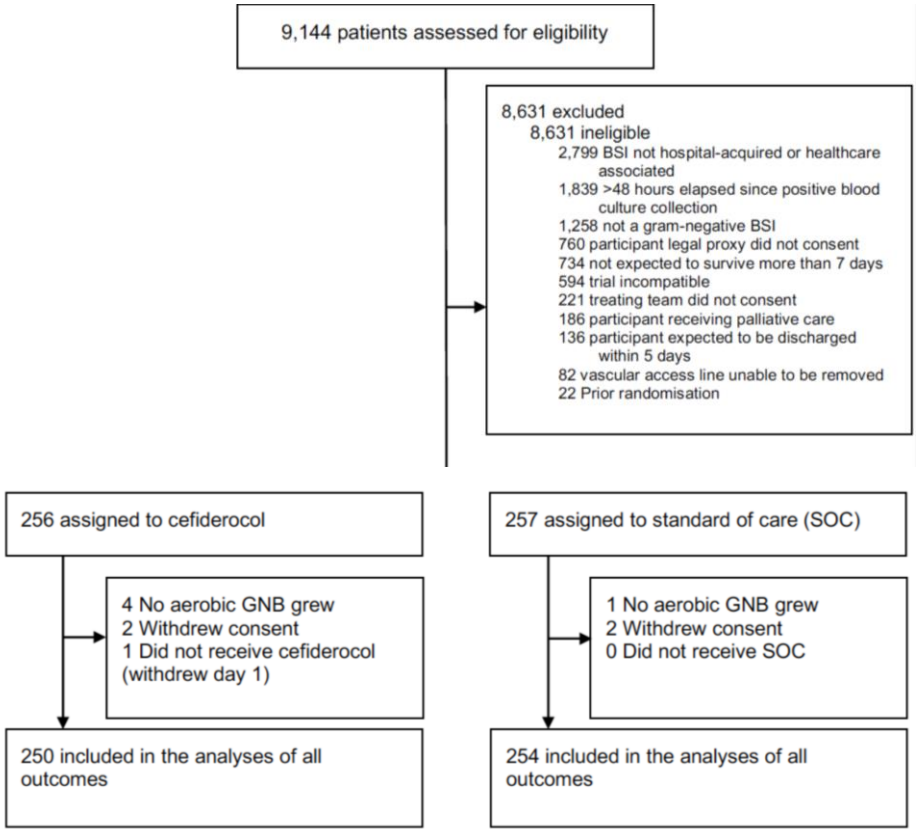
- **14-day all-cause mortality**, with day 1 being the day of randomisation
- Hypothesis: Cefiderocol is non-inferior to SOC
- Non-inferiority margin of 10%
- Superiority analysis if non-inferiority met

MAIN ANALYSIS POPULATION

- All patients randomised except where:
  - No aerobic Gram-negative bacilli grew from a patient's index blood culture
  - Post-randomisation, patient did not receive at least one dose of cefiderocol (if randomised to cefiderocol arm) or an agent with activity against GNBs (if randomised to SOC)
  - Patient withdrew consent before day

Gamechanger study (v)

RESULTS



	Cefiderocol	SOC
Australia	8%	8%
Malaysia	30%	24%
Singapore	16%	12%
Taiwan	15%	22%
Thailand	20%	23%
Turkey	11%	11%

	Cefiderocol		SOC	
Escherichia coli	36%		30%	
Klebsiella pneumoniae	29%	84%	31%	82%
Enterobacter spp.	8%		7%	
Other Enterobacterales	11%		14%	
Pseudomonas spp.	11%		9%	
Acinetobacter baumannii	7%	24%	10%	25%
Stenotrophomonas	2%		1%	
Other Non-fermenter	4%		5%	
Other Gram negative bacilli	3%		1%	

*Columns may not add to 100% because of polymicrobial infections

Gamechanger study (v)

RESULTS

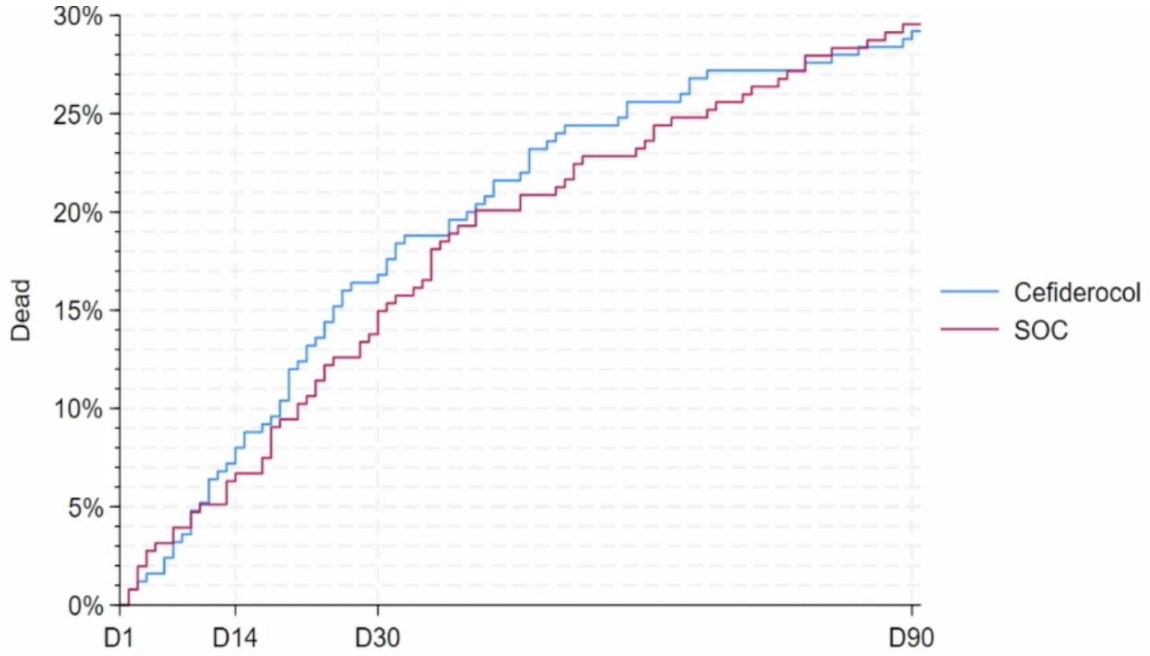
	Cefiderocol	SOC
Age (median)	62	61
Female	43%	40%
BMI (median)	23.4	23.7
ICU	17%	20%
Hospital-acquired	62%	60%
Charlson (median, IQR)	5 (3-7)	5 (3-7)
Baseline SOFA (median, IQR)	4 (2-6)	4 (3-7)

	Cefiderocol	SOC
UTI	21%	18%
Intra-abdominal	16%	19%
Line-related	16%	21%
Pneumonia	13%	12%
Skin/soft tissue/burns	5%	4%
Other	10%	6%
Unknown/not recorded	18%	20%

Gamechanger study (v)

RESULTS (mortality)

	Cefiderocol N=250 (%)	SOC N=254 (%)	RD (95% CI), % Cef. – SOC	RR (95% CI) Cef./SOC
All				
Day 14	20 (8.0%)	17 (6.7%)	1.3 (-3.2 to 5.9)	1.20 (0.64 to 2.23)
Day 30	42 (16.8%)	38 (15.0%)	1.8 (-4.5 to 8.2)	1.12 (0.75 to 1.68)
Day 90	73 (29.2%)	75 (29.5%)	-0.3 (-8.3 to 7.6)	0.99 (0.75 to 1.30)



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Gamechanger study (v)

RESULTS (AEs)

	Cefiderocol	SOC
Not related to study drug	76	83
Unlikely related	1	0
Possibly related	0	0
Probably related	0	0
Definitely related	0	0

Gamechanger study (v)

RESULTS (Carbapenem resistant population)

- Carbapenem resistance was defined as recorded at the UQCCR central laboratory by broth microdilution using EUCAST (2024) definitions
- For organisms not arriving (or non-viable) at the central laboratory, carbapenem resistance was defined as recorded by the site microbiology laboratories*

	Cefiderocol	**SOC**
14 day ACM	10 / 57* (18%)	7 / 60 (12%)

Risk difference 5.8% (95% CI -6.9% to 18.7%)
Risk Ratio 1.5 (95% CI 0.6 to 3.7)

Superiority was not achieved.

*42 patients received monotherapy and 15 received combination therapy

	Cefiderocol	SOC
Day 30	20 / 57 (35%)	17 / 60 (28%)
Day 90	28 /57 (49%)	31 / 60 (52%)

	D14 deaths	D30 deaths
CRE		
Cefiderocol	6/31 (19%)	10/31 (32%)
SOC	2/30 (7%)	7/30 (23%)
CRAB		
Cefiderocol	1/11 (9%)	5/11 (45%)
SOC	3/14 (21%)	7/14 (50%)

*Organisms with chromosomally encoded carbapenemases (e.g., *Stenotrophomonas maltophilia*) were be defined as carbapenem resistant regardless of the in vitro susceptibility

New data on combination therapy

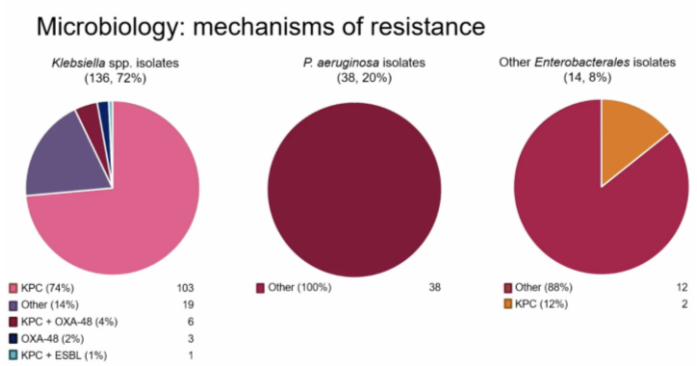
New data on combination therapy

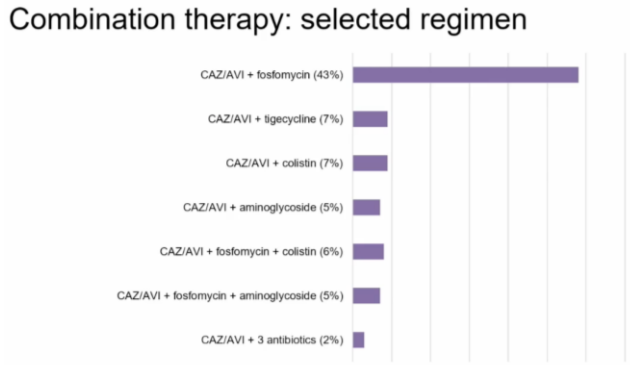
Ceftazidime/avibactam combination therapy does not impact on patient's mortality in carbapenem-resistant Gram-negative bacilli infections

AIM: To assess the impact of **CZA combination therapy.**
METHODS: Analysis of **SUSANA (Surveillance of Safety and outcome of New Antibiotics) database**, a retrospective, multicentric cohort study started in November 2019 on the use of new antibiotics for patients with suspected or microbiologically documented CRE/CRPA infections.
RESULTS: MDROs: 188 patients, median age 57 years

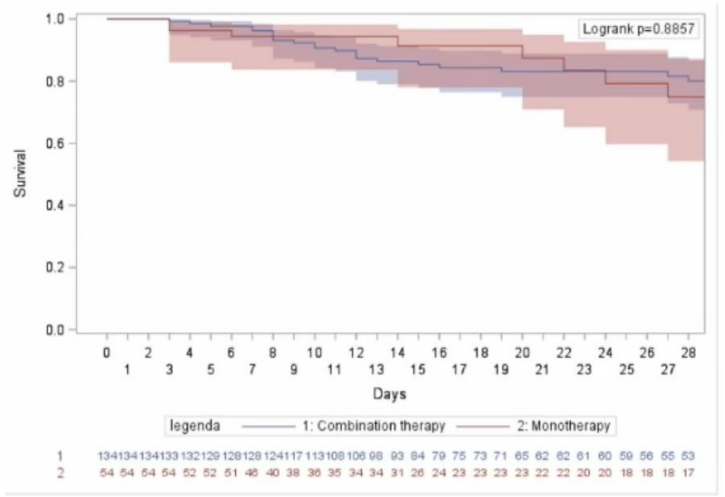
	Monotherapy (n=54) (No, %)	Combination therapy (n=134) (No, %)	Total (n=188) (No, %)	*p* value
Ward of CAZ/AVI prescription				0.17
• Medical wards	32 (59.2%)	59 (44%)	91 (48%)	
• Intensive care units (ICUs)	15 (27.8%)	52 (38.8%)	67 (36%)	
• Surgical wards	7 (13%)	23 (17.2%)	30 (16%)	
Hospitalization within the previous 12 months	23 (42.6%)	68 (50.8%)	91 (48%)	0.19
Antibiotic therapy within the previous 90 days	37 (68.5%)	66 (49.2%)	103 (54.8%)	0.054
Immunodepression status	8 (14.8%)	26 (19.4%)	34 (18%)	0.08
Central venous catheter	24 (44.4%)	95 (70.9%)	119 (63%)	0.0007
Urinary catheter	42 (77.8%)	111 (82.8%)	153 (81%)	0.24
Endotracheal tube	16 (29.6%)	57 (42.5%)	73 (40%)	0.24

	Monotherapy (n=54) (No, %)	Combination therapy (n=134) (No, %)	*p* value
Main sites of infection			
• Lower respiratory tract infections (LRTIs)	16 (29.6%)	62 (46.3%)	0.04
• Urinary tract infections (UTIs)	17 (31.5%)	29 (21.6%)	0.16
• Intra-abdominal infections (IAIs)	3 (5.5%)	23 (17.2%)	0.04
• Skin and soft tissue infections (SSTIs)	5 (9.2%)	7 (5.2%)	0.31
Bloodstream infections (BSIs)	27 (50%)	68 (50.8%)	0.93
Sepsis	34 (63%)	91 (68%)	0.67
Septic shock	8 (14.8%)	18 (13.4%)	0.57
CR-*Klebsiella* spp. infections	46 (85.2%)	90 (48%)	0.01
CR-*P. aeruginosa* infections	7 (13%)	31 (16%)	0.12
CR-*Enterobacterales* infections	4 (7.4%)	10 (7.5%)	0.99





IV FOSFOMYCIN WAS THE MOST COMMON ANTIBIOTIC USED IN COMBINATION THERAPY WITH CAZ/AVI



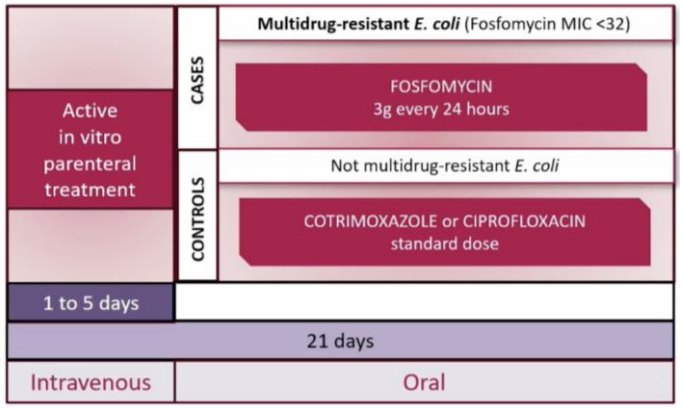
CONCLUSIONS: **Among patients treated with CAZ/AVI, combination therapy did not impact significantly on 14- and 28-day mortality rates.**

New data on oral therapy

New data on oral therapy (i)

Oral fosfomycin as sequential oral treatment for multidrug-resistant Escherichia coli in acute bacterial prostatitis: the FOS-PROST study

AIM: to evaluate fosfomycin **efficacy and safety in ABP caused by MDR *E. coli***
METHODS: adult patients with *E. coli* ABP, between January 2022-October 2023. Patients were prospectively included in two groups: **case**: MDR *E. coli* ABP, treated with sequential oral fosfomycin (3g/24h); **control**: not-MDR *E. coli* ABP treated with cotrimoxazole or ciprofloxacin as sequential oral treatment.
RESULTS: Forty-seven patients were included, 12 with MDR *E. coli* ABP (25.5%); 14 (29%) of the total cohort had bacteraemia.



Characteristics	Cases (n=12)	Controls (n=35)	p
Age	72.5 (3.11)	66.1 (2.13)	0.14
Charlson Index	0.5 (0-2.75)	0 (0-1)	0.47
Pitt score	0 (0-0)	0 (0-1)	0.49
qSOFA >2	0 (0)	0 (0)	NA
Community-acquired infection	10 (83.3)	34 (97.1)	0.16
Active empiric treatment	3 (25)	35 (100)	<0.001
Parenteral treatment duration (days)	3 (2-5)	3 (2-3.5)	0.23

	Cases (n=12)	Controls (n=35)	p
END OF TREATMENT (21 +/- 3 days)			
Microbiological cure	8 (66.7)	28 (80)	0.44
Clinical cure	11 (91.7)	33 (94.3)	1
TWO WEEKS AFTER END OF TREATMENT (57 +/- 7 days)			
Microbiological cure	7 (70)	26 (92.9)	0.1
Clinical cure	12 (100)	34 (97.1)	1

CONCLUSIONS: **Fosfomycin is safe and has shown a high clinical efficacy, displaying a 100% clinical cure rate and an almost 70% microbiological cure rate**

Conclusions

- Early ID consultation and source control are beneficial in *P. aeruginosa* bacteraemia
- In patients with *P. aeruginosa* infections treatment with C/T resulted in a higher rate of clinical success compared to treatment with CZA
- FDC appears as a promising agent for *P. aeruginosa* infections, less bright data on CRE infections
- CZA alone is probably effective as combination therapy against CRE/CRPA infections
- Consider OS FOF for the treatment of ABP due to MDR *E. coli*