Infezioni e terapia da *Acinetobacter baumannii* MDR

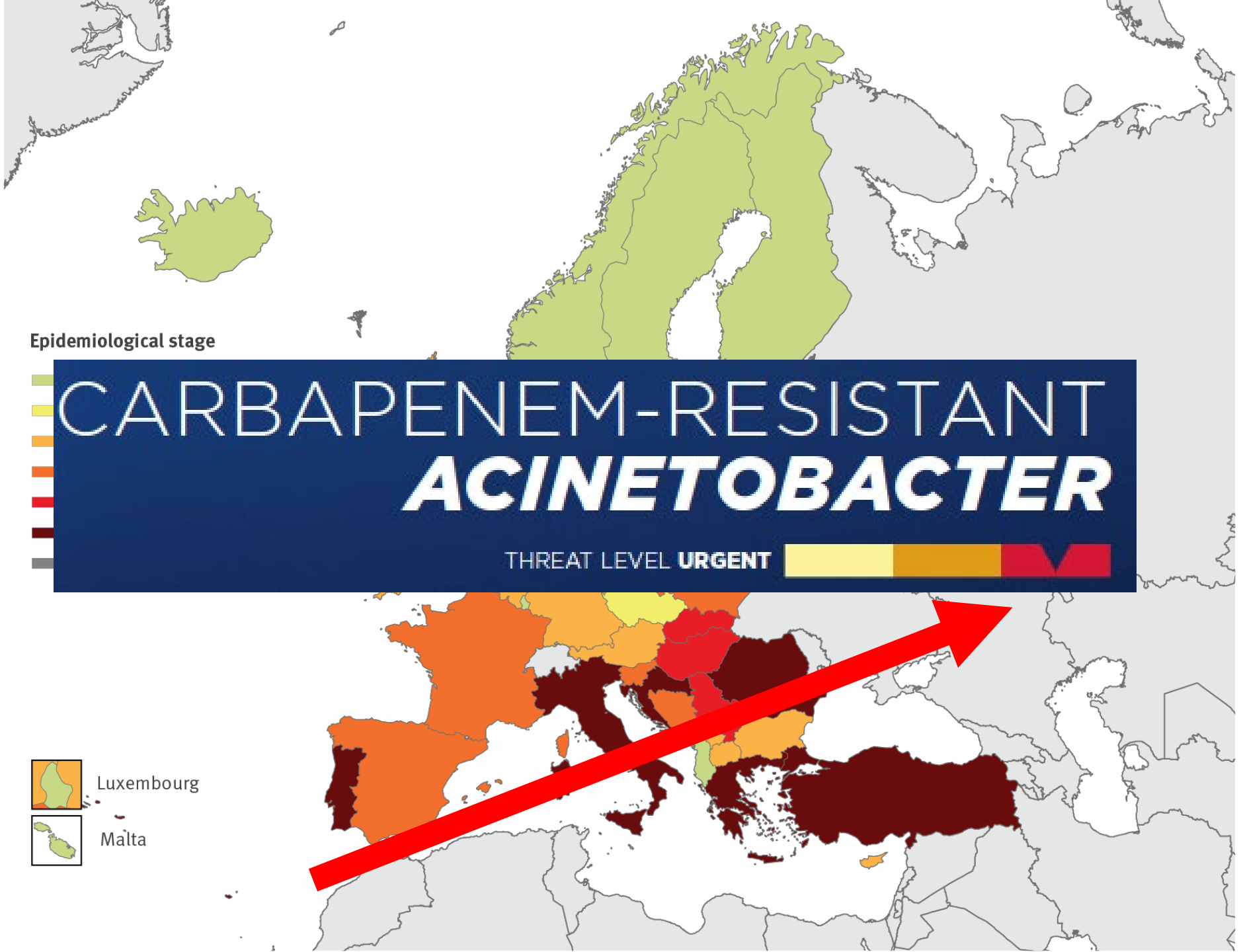
Prof. Alessandro Russo

Infectious and Tropical Diseases Unit

Department of Medical and Surgical Sciences

«Magna Graecia» University of Catanzaro

a.russo@unicz.it


Epidemiological stage
CARBAPENEM-RESISTANT
ACINETOBACTER
THREAT LEVEL URGENT
Luxembourg
Malta

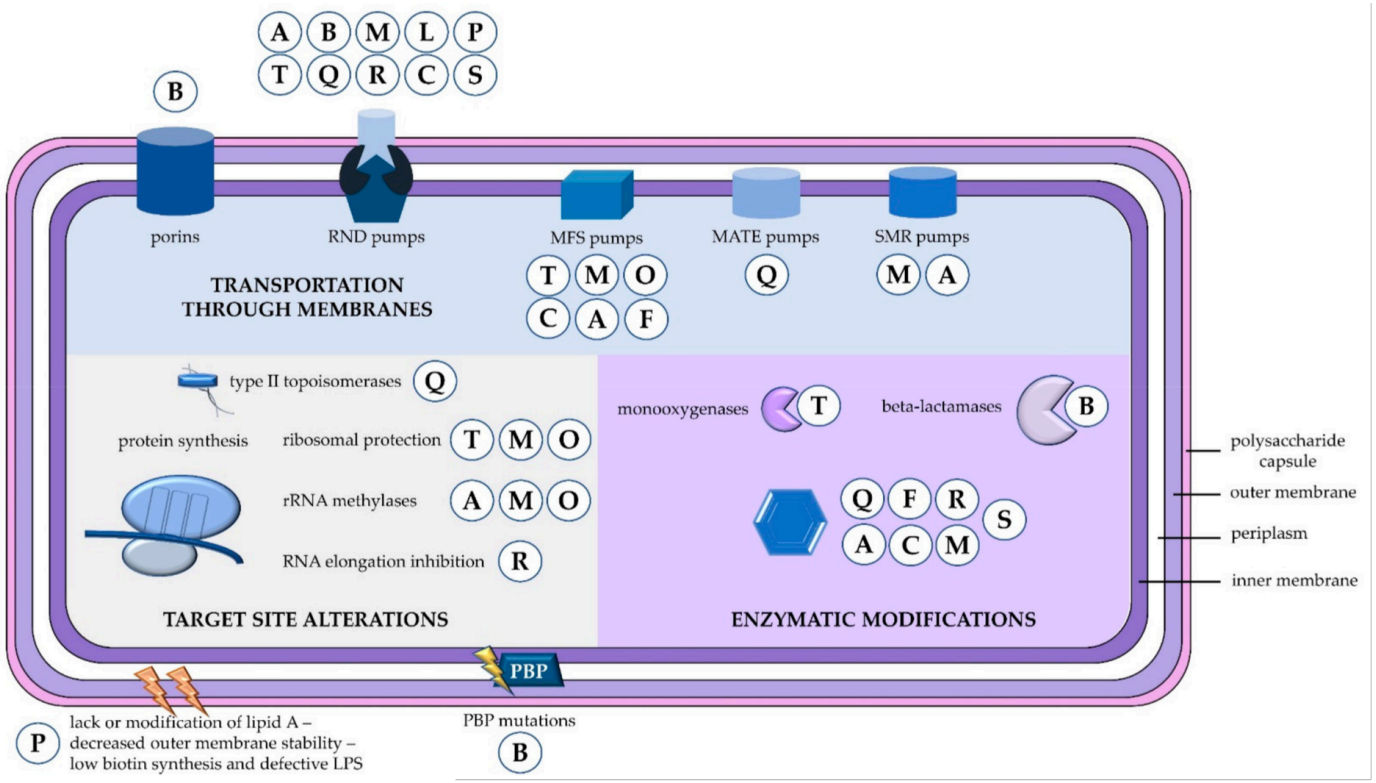


Figure 1. Mechanisms of antibiotic resistance in *A. baumannii*. Antibiotic resistance can be conferred through three main mechanisms, i.e., control of antibiotic transportation through membranes (reduction of porin permeability or increased efflux), modification of antibiotic targets, and enzymatic inactivation of the antibiotics. A = aminoglycosides; B = beta-lactams; C = chloramphenicol; F = fosfomycin; L = lincosamides; M = macrolides; MATE = multidrug and toxic compound extrusion; MFS = major facilitator superfamily; O = oxazolidinones; P = polymyxins; PBP = penicillin binding protein; Q = fluoroquinolones; R = rifamycins; RND = resistance-nodulation-division; S = diaminopyrimidines and sulfonamides; SMR = small multidrug resistance family; T = tetracyclines.

Kyriakidis et al, Pathogens 2021

Comparison of Septic Shock Due to Multidrug-Resistant *Acinetobacter baumannii* or *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* in Intensive Care Unit Patients

Alessandro Russo,[a] Simone Giuliano,[b] Giancarlo Ceccarelli,[a] Francesco Alessandri,[c] Alessandra Giordano,[a] Grazia Brunetti,[a] Mario Venditti[a]

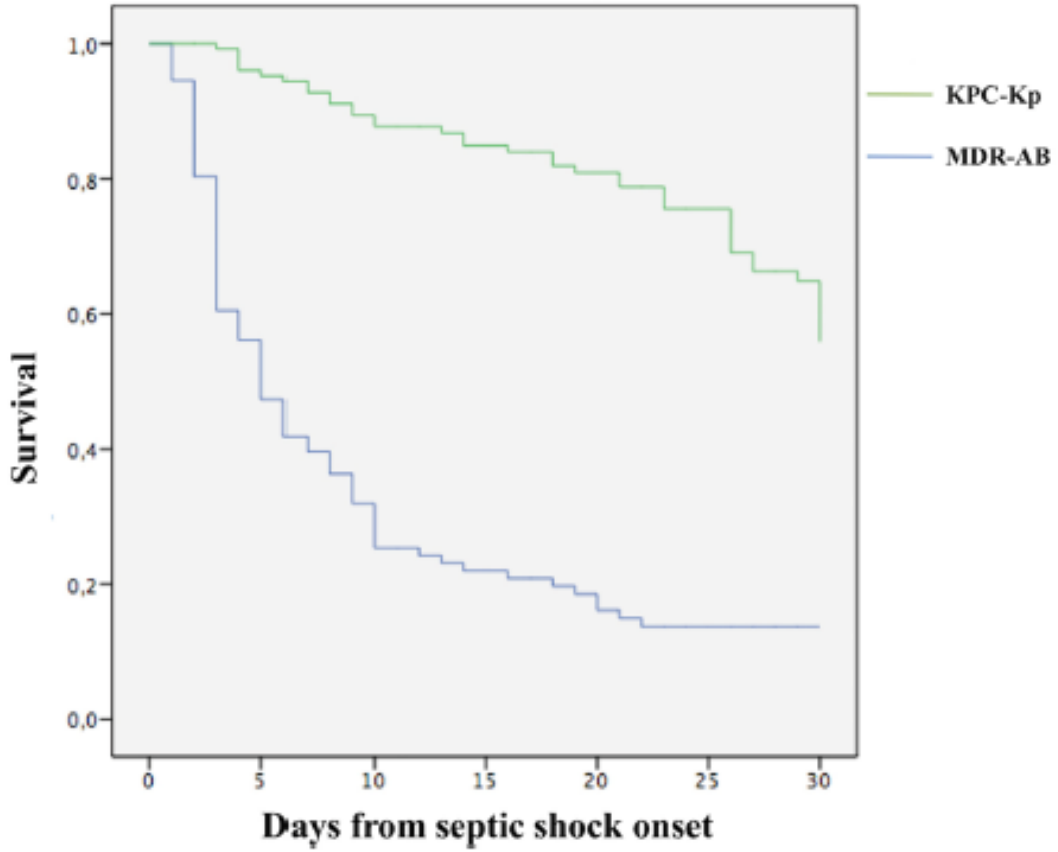
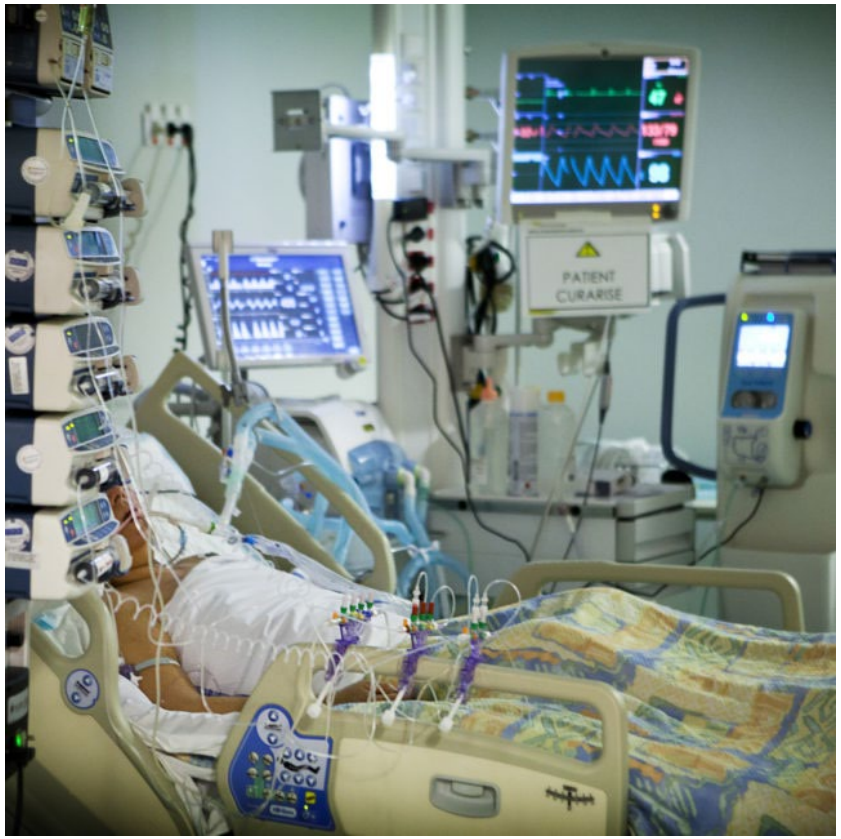


FIG 1 Kaplan-Meier curves for 30-day survival of KPC-Kp or MDR-AB infections. *, $P < 0.001$. KPC-Kp, *Klebsiella pneumoniae* carbapenem-resistant *K. pneumoniae*; MDR-AB, multidrug-resistant *Acinetobacter baumannii*.

Russo et al. AAC 2018

Host Status or CRAB?



It is challenging to determine if poor clinical outcomes are attributable to suboptimal antibiotic therapy or to underlying host factors

Multidrug-resistant *Acinetobacter baumannii* infections in COVID-19 patients hospitalized in intensive care unit

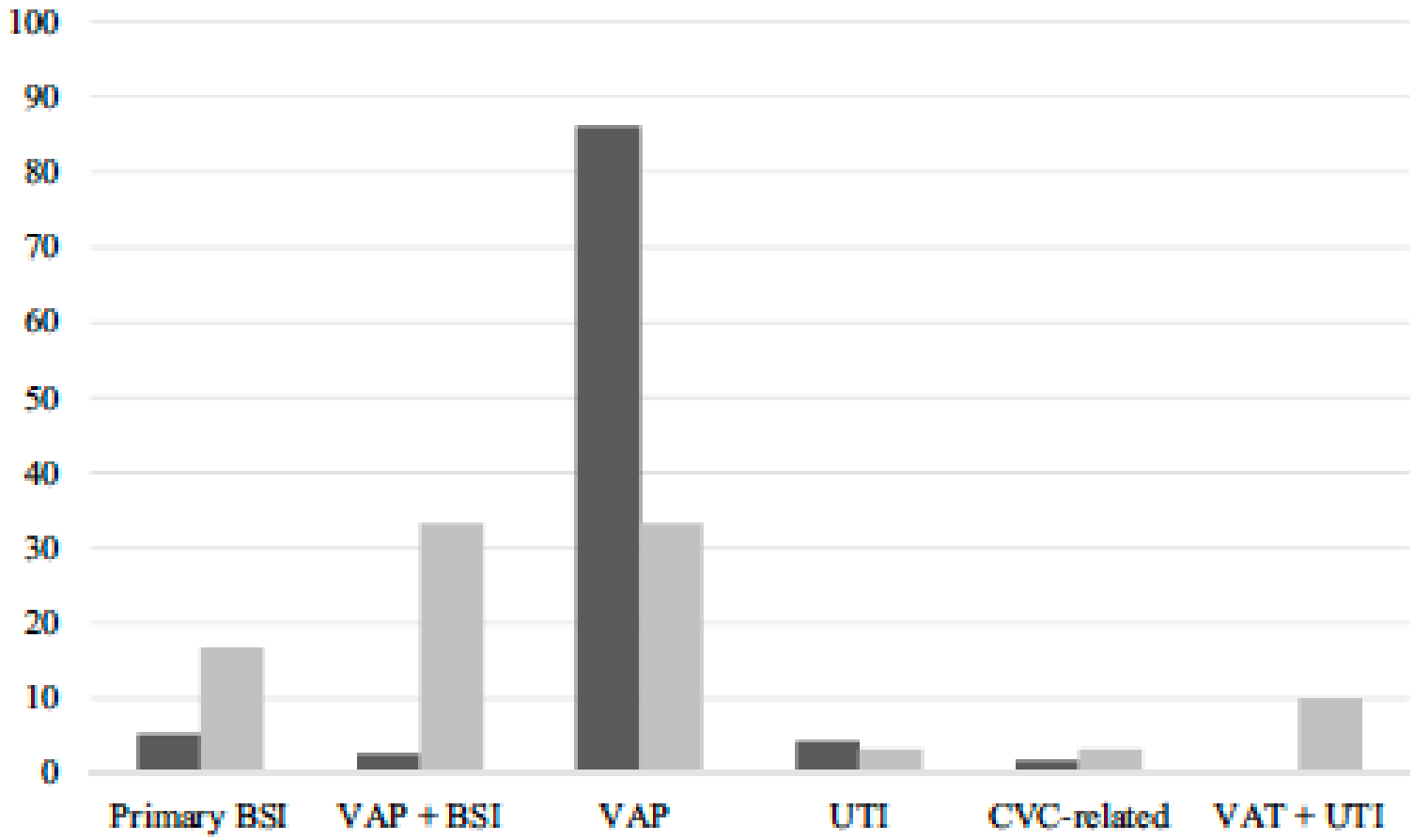


Fig. 1 Sites of MDR-AB infection in COVID-19 (gray line) or non-COVID-19 (black line).

Russo et al, Infection 2021

- Ventilator-associated pneumonia (VAP) caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) in patients hospitalized in intensive care units (ICU) is an important and challenging complication, including in COVID-19 patients

- Considering the poor lung penetration of most antibiotics, the choice of the best antibiotic regimen is still being debated

Russo A. et al, Infectious Diseases and Therapy 2021

- Real-life experiences from case series including patients with CR-GNB were not completely focused only on CRAB

- Thus, a gap between the results from the CREDIBLE-CR study and real-world observations continues to exist and data on the efficacy of cefiderocol in patients with CRAB infections are still lacking, with there being few observations about patients with VAP

- Moreover, data about the efficacy of cefiderocol are mandatory

Russo A. et al, Antimicrobial Agents and Chemotherapy 2018
Russo A. et al, Journal of Infection 2019
Russo A. et al, Infection 2022

Multidrug-resistant *Acinetobacter baumannii* infections in COVID-19 patients hospitalized in intensive care unit

Table 2 Relative risk* associated or not with MDR-AB infection in patients affected or not by COVID-19

Variables	RR	CI 95%	*p* value
Previous hospitalization (90 days)	0.4	0.2–0.9	0.031
COPD	0.3	0.1–0.9	0.029
Chronic steroid therapy	0.1	0.0–0.9	0.041
Infection at time of ICU admission	0.1	0.0–0.4	0.001
Serum lactate levels > 2 mmol/l	1.8	1.3–2.5	0.001
Acinetobacter baumannii colonization	7.9	4.0–15.7	< 0.001
Bloodstream infection	6.5	3.2–13.3	< 0.001
Steroid therapy	18.4	7.6–44.1	< 0.001

Table 3 Logistic regression analysis about risk factors associated with 30-days mortality

Variables	OR	CI 95%	*p* value
Serum lactate levels > 2 mmol/l	4.9	2.1–11.3	< 0.001
Acinetobacter baumannii colonization	17.1	5.5–53.3	< 0.001
Bloodstream infection	13.6	4.8–38.2	< 0.001
Steroid therapy	46.9	13.9–157.5	< 0.001

Table 5 Multivariate analysis about risk factors associated with development of bloodstream infection

Variables	OR	CI 95%	*p* value
Severe COVID-19	15.1	3.7–40.1	< 0.001
WBC > 11,000 mm^3	5.2	2.1–11.5	< 0.001
Serum lactate levels > 2 mmol/l	2.7	1.2–6.4	0.022
Infections at time of ICU admission	0.4	0.2–1	0.030
Acinetobacter baumannii colonization	4.8	1.9–12.1	< 0.001
Steroid therapy	8.8	3.5–22.1	< 0.001

Russo et al, Infection 2021

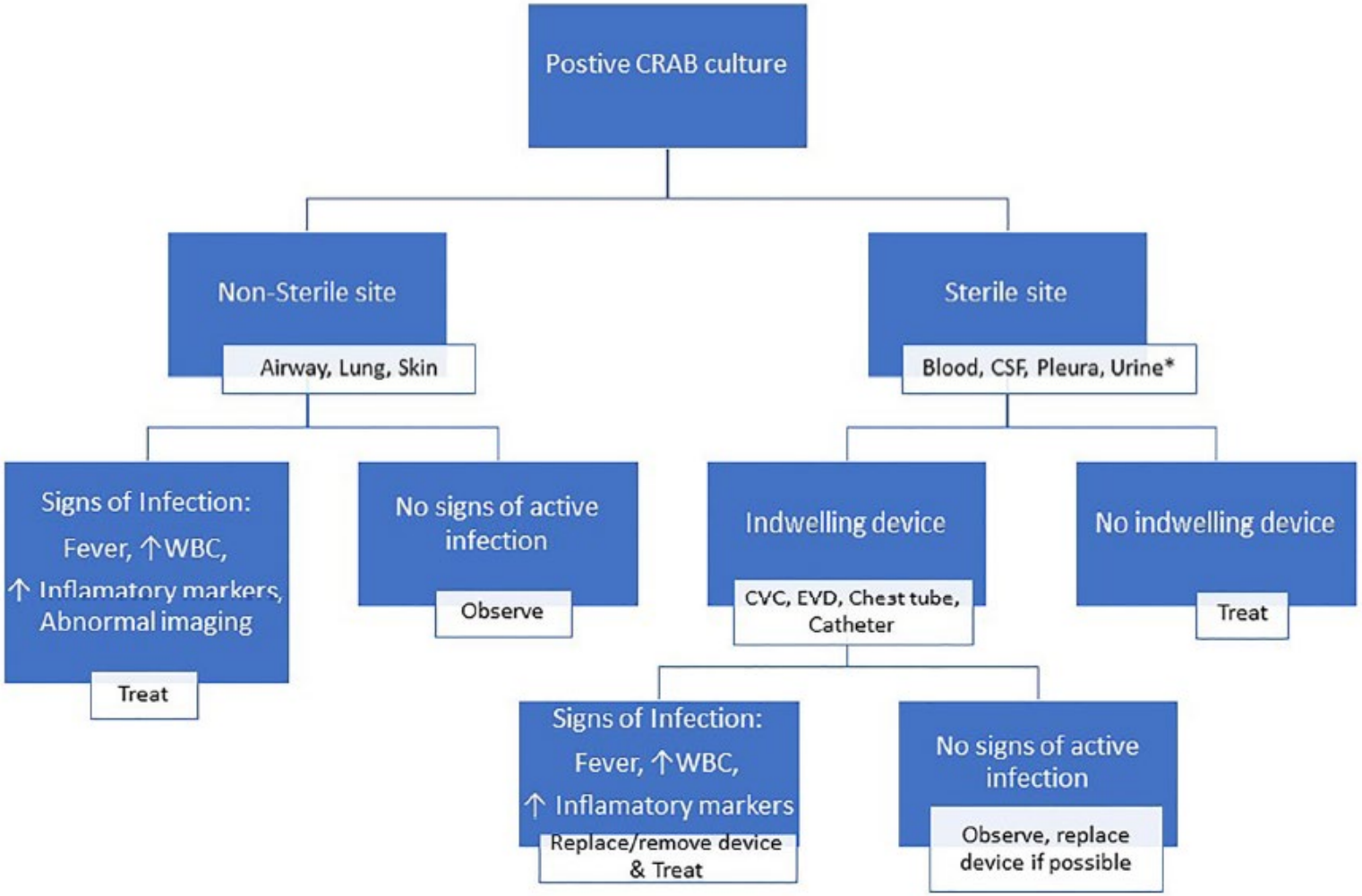
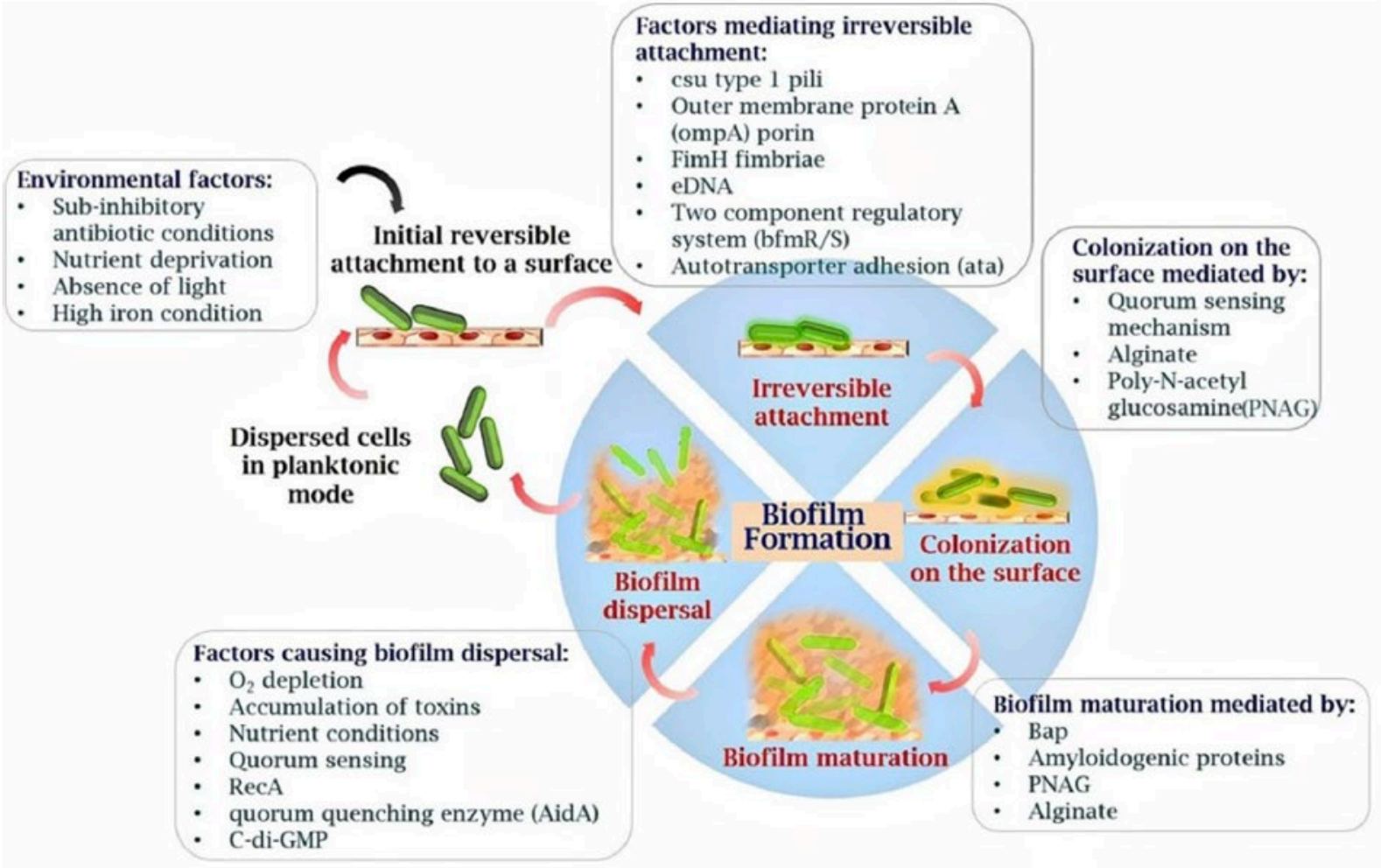


Fig. 1 Management algorithm of patients with a positive CRAB culture. *Most cultures in this setting represent colonization and not infection

Bartal et al, Infect Dis Ther 2022



Upmanyu et al, CRMS 2022

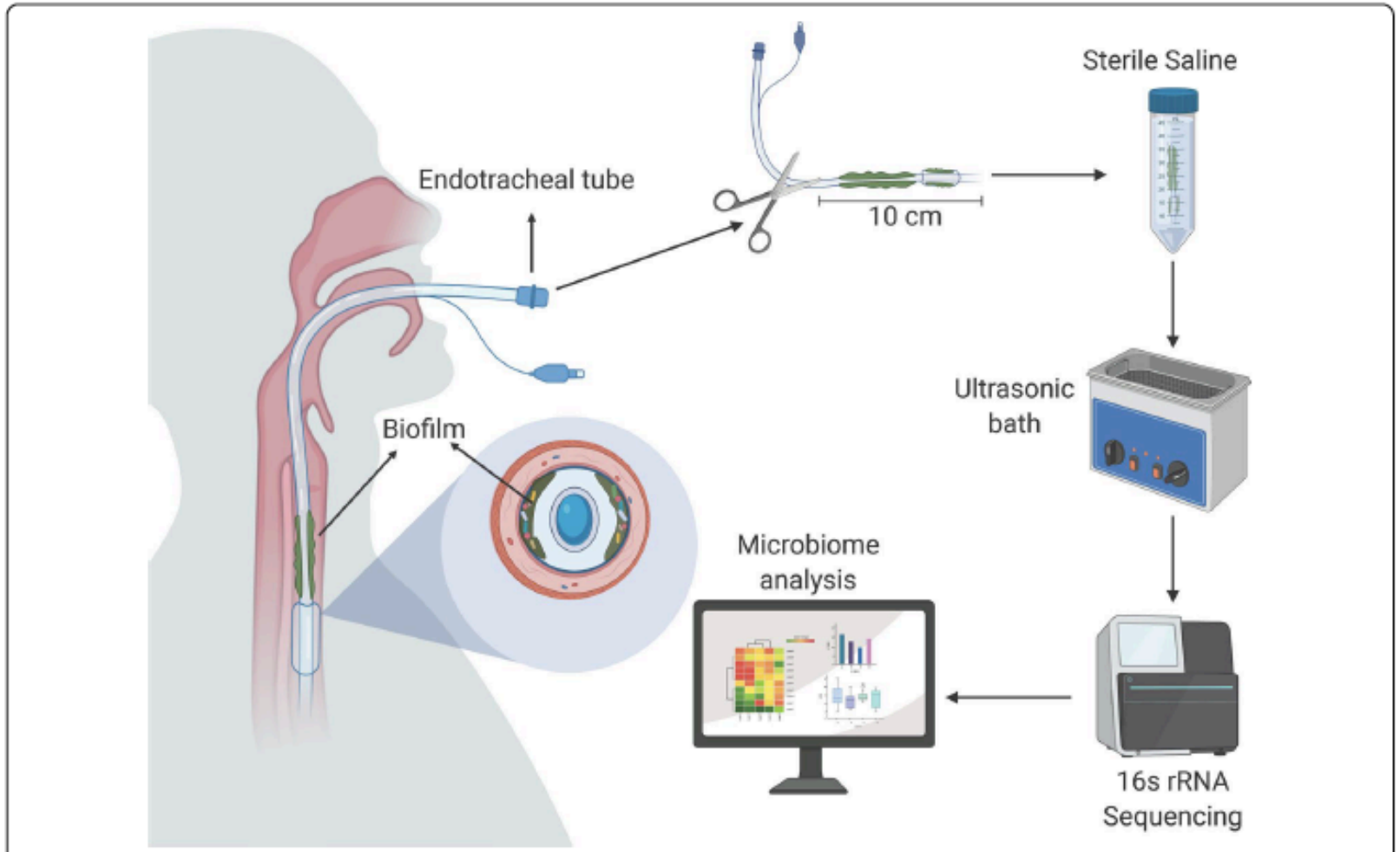


Fig. 1 Sampling strategy. ETT samples were collected and used for both analysis of microbial communities by sequencing of the 16S rRNA gene and for culturing in laboratory media. A section of the endotracheal tube was cut and immediately placed in 0.85% NaCl. Associated bacteria were dislodged by three cycles of vortex followed by sonication. DNA was extracted and the V3-V4 hypervariable region of the 16S rRNA gene was amplified and sequenced on the Illumina MiSeq platform

Cifuentes et al, Respiratory Research 2022

Comparative *In Vitro* Study of Biofilm Formation and Antimicrobial Susceptibility in Gram-Negative Bacilli Isolated

TABLE 2 Comparison between EB and NFGBN biofilm formation[a]

Family group	No. of strains			Total
	Biofilm formation (Q1 to Q3) (*n*-fold OD_c)	Nonbiofilm producer (%)	Biofilm producer (%)	
EB	3.28 (1.72 to 5.68)	1 (2.1%)	37 (97.9%)	38
NFGNB	10.06 (5.60 to 22.78)	0	8 (100%)	8

[a]EB, Enterobacteriaceae; NFGBN, nonfermenting Gram-negative bacilli; OD_c, cutoff value three standard deviations (SD) above the mean optical density; Q, quartile.

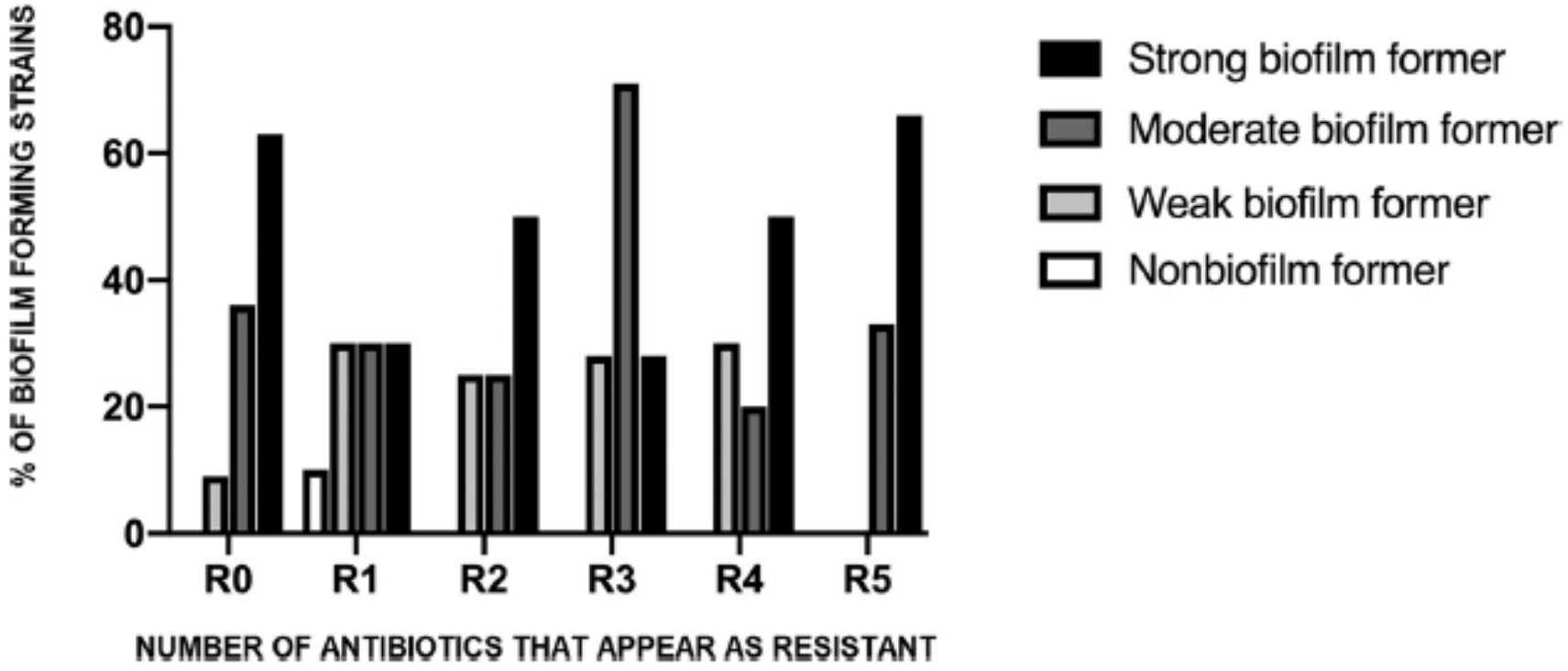
TABLE 3 GNB biofilm formation[a]

Strain (*n*)	Biofilm formation (Q1 to Q3) (*n*-fold OD_c)	Percentage biofilm producer (%)			
		Strong	Moderate	Weak	No producer
A. baumanii (1)	2.5 (1.9 to 4)	0	1 (100%)	0	0
C. freundii (1)	3.4 (1.9 to 3.9)	0	1 (100%)	0	0
C. koseri (1)	1.3 (0.7 to 1.6)	0	0	1 (100%)	0
E. cloacae (2)	7.2 (5.6 to 8.4)	2 (100%)	0	0	0
E. hormaechei (2)	1.7 (0.7 to 3.6)	0	1 (50%)	1 (50%)	0
E. coli (8)	2.1 (1.2 to 3.3)	1 (12.5%)	4 (50%)	3 (37.5%)	0
K. pneumoniae (7)	4.9 (2.3 to 7.4)	4 (71.4%)	2 (14.3%)	1 (14.3)	0
M. morganii (3)	5.9 (2.1 to 13.45)	2 (66.7%)	0	1 (33.3%)	0
P. mirabilis (8)	3.3 (2.2 to 5)	2 (25%)	5 (62.5%)	1 (12.5%)	0
P. vulgaris (1)	1.3 (1.1 to 2.4)	0	0	1 (100%)	0
P. stuartii (1)	2.9 (2.3 to 4.6)	0	1 (100%)	0	0
P. aeruginosa (7)	10.2 (6.4 to 19.6)	7 (100%)	0	0	0
R. ornithinolytica (1)	0.9 (0.7 to 1.3)	0	0	0	1 (100%)
S. marcescens (3)	2.6 (1.7 to 5)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0
Total	3.6 (1.8 to 6.8)	19 (41.3%)	16 (34.8%)	10 (21.8%)	1 (2.1%)

[a]GNB, Gram-negative bacilli; OD_c, cutoff value three standard deviations (SD) above the mean optical density; Q, quartile.

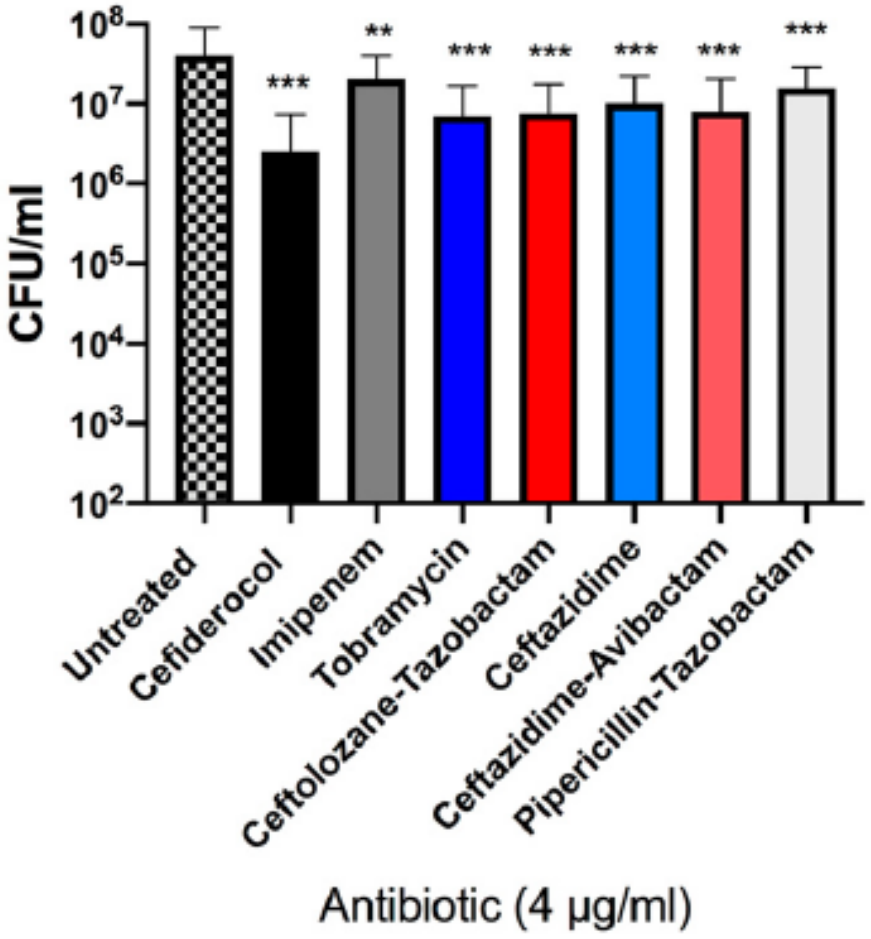
Macias-Valcajo et al, Microbiology Spectrum 2022

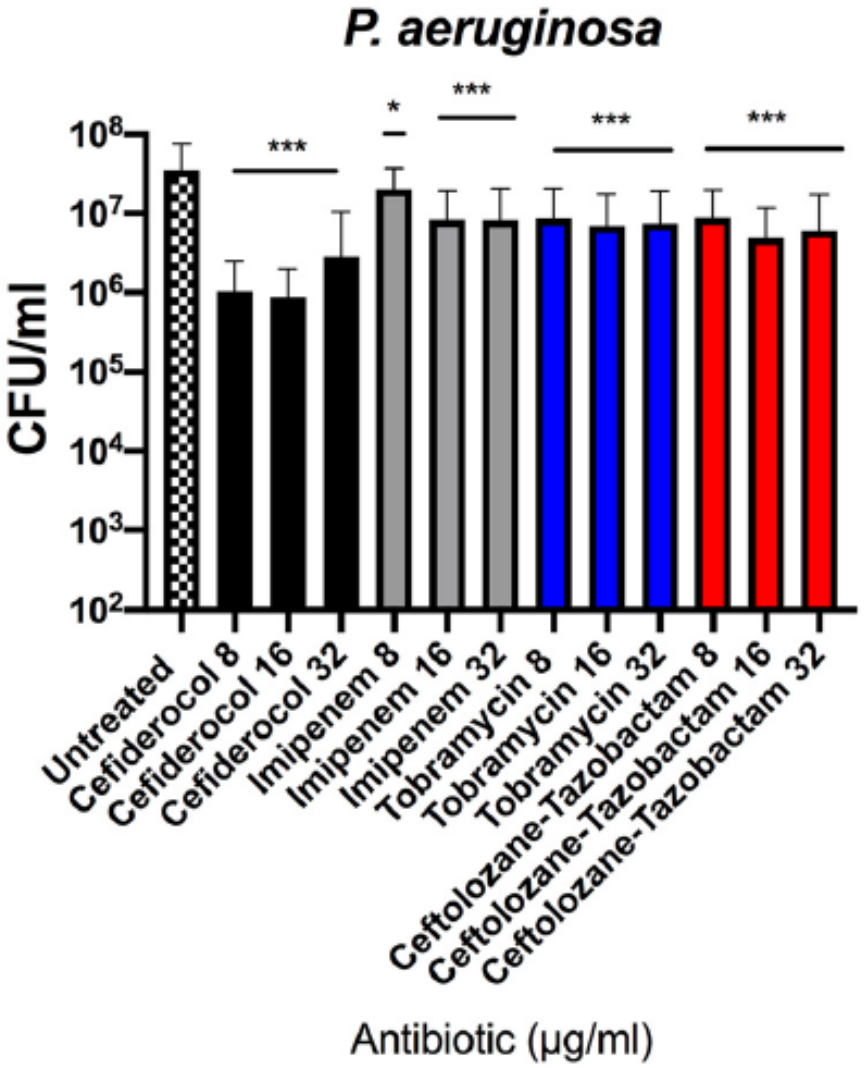
Comparative *In Vitro* Study of Biofilm Formation and Antimicrobial Susceptibility in Gram-Negative Bacilli Isolated



Macias-Valcajo et al, Microbiology Spectrum 2022

Biofilm and Gram-negative





Pybus et al, AAC 20[illegible]

Clinical Infectious Diseases

IDSA FEATURES

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

[1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Department of Pharmacy, University of Michigan Health, Ann Arbor, Michigan, USA; [3]Medical Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA; [4]Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA; [5]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA; and [6]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

MODERATE TO SEVERE INFECTIONS

Combination antibiotic therapy

Which ones?

Ampicillina/Sulbactam

Tetracycline
(+ Minocycline)

Polymyxin B

Extended-infusion Meropenem

Cefiderocol

AVOID
Fosfomycin
Rifampin

Meropenem +
Polimyxyns
witouth third
agent

AVOID NEBULIZED ANTIBIOTICS

- The combination of ampicillin-sulbactam, meropenem, and polymyxin B remains a consideration (keeping in mind the potential for toxicities from two high-dose β-lactam agents).
- As previously stated, because of the increased risk of toxicities with multiple β-lactam agents, if high-dose ampicillin-sulbactam is administered, minocycline, tigecycline, or polymyxin B are preferred as additional agents to choose amongst.

High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant Acinetobacter baumannii.
Scand J Infect Dis. 2007;39:38-43.

Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. *J Infect. 2008 Jun;56(6):432-6.*

MODERATE TO SEVERE INFECTIONS

Combination antibiotic therapy with at least 2 active agents is suggested fot the tratment of moderate to severe CRAB infection

Seven RCTs have investigated the role of combination therapy for CRAB infections

Only 1 of the 7 trials indicated a potential benefit with combination therapy

- Lack of robust clinical data supporting the treatment of CRAB infections with any single agent demonstrating in vitro activity against CRAB
- High bacterial burdens
- Chronically and critically ill with potentially impaired immune systems
- Combination therapy increases the likelihood that at least 1 active agent is being administered.

Clinical Microbiology and Infection 28 (2022) 521–547

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journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

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)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25], Johan W. Mouton [26, †], Evelina Tacconelli [3, 27, 28, *, §], Jesús Rodríguez-Baño [4, 5, §]

[1] *Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel*
[2] *Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel*
[3] *Division of Infectious Diseases, Department of Diagnostic and Public Health, University of Verona, Verona, Italy*
[4] *Departamento de Medicina, Universidad de Sevilla, Sevilla, Spain*
[5] *Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena/Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain*
[6] *Department of Medical Sciences, Uppsala University, Uppsala, Sweden*
[7] *Department of Medicine, Pharmacology, Molecular Biology and Microbiology, Biochemistry, Proteomics and Bioinformatics, Case Western Reserve University School of Medicine, Cleveland, OH, USA*
[8] *Medical Service, Research Service, and GRECC, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH, USA*
[9] *VAMC Center for Antimicrobial Resistance and Epidemiology, Cleveland, OH, USA*
[10] *Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium*
[11] *First Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece*
[12] *Hacettepe University School of Medicine, Department of Infectious Diseases, Ankara, Turkey*
[13] *Infection Control Programme, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland*

Table 1 (*continued*)

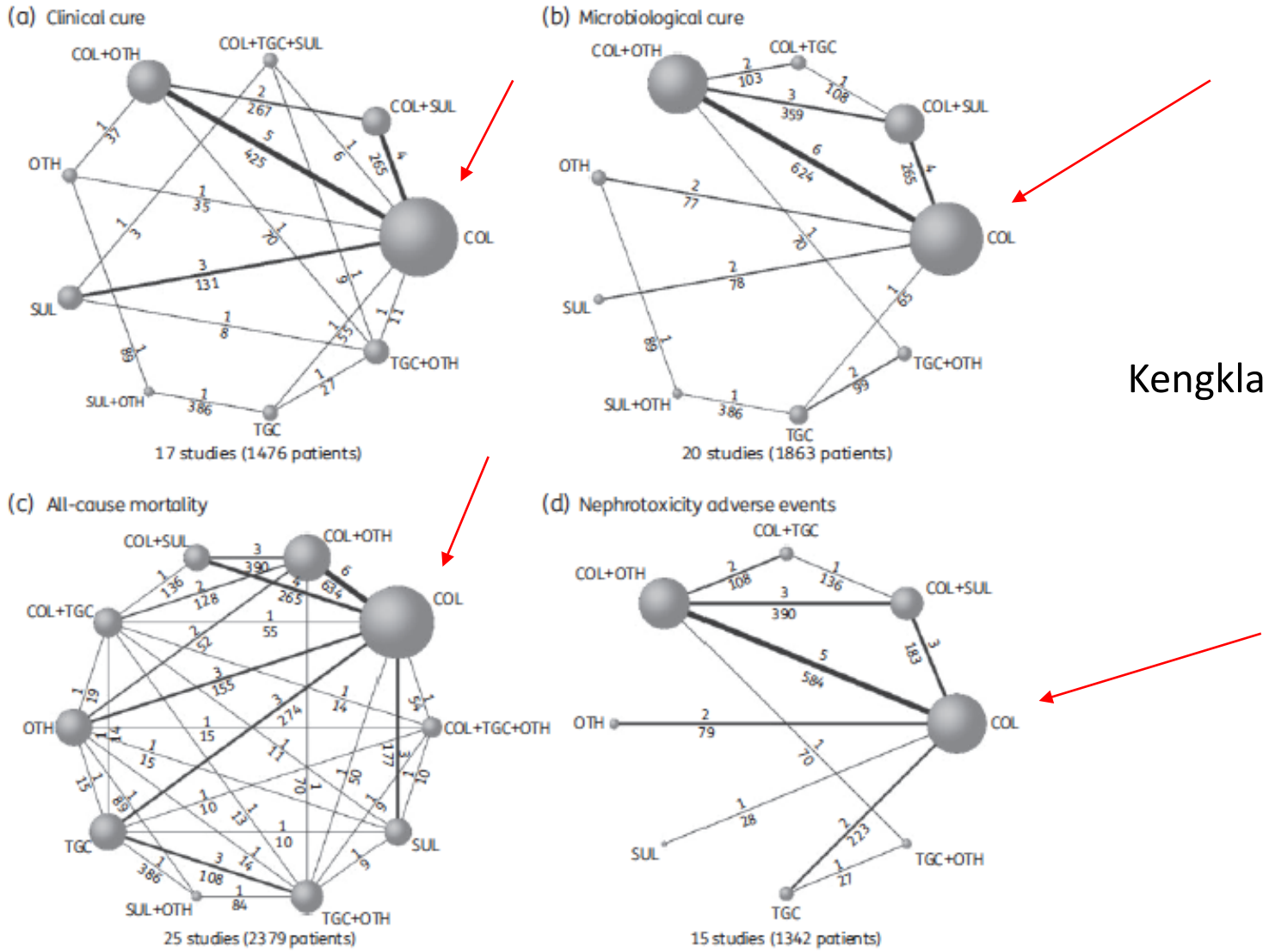
Recommendation	Strength of recommendation	Level of evidence
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)		
Recommendations on the choice of antibiotic treatment for CRAB		
For patients with CRAB susceptible to sulbactam and HAP/VAP, we suggest ampicillin-sulbactam.	Conditional	Low
For patients with CRAB resistant to sulbactam, a polymyxin or high-dose tigecycline can be used if active *in vitro*. Lacking evidence, we cannot recommend on the preferred antibiotic.	No recommendation	
We conditionally recommend against cefiderocol for the treatment of infections caused by CRAB.	Conditional	Low
Recommendations on combination therapy for CRAB		
For all patients with CRAB infections, we do not recommend polymyxin-meropenem combination therapy or polymyxin-rifampin combination therapy.	Strong	High/moderate
For patients with severe and high-risk CRAB infections, we suggest combination therapy including two *in vitro* active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations).	Conditional	Very low
For patients with CRAB infections with a meropenem MIC $\leq$8 mg/L, we consider carbapenem combination therapy, using high-dose extended-infusion carbapenem dosing, as good clinical practice.	Good practice statement	Expert opinion

Differences between CRAB treatment guidelines

	ESCMID guidelines	IDSA guidance
Combination antibiotic regimen	For severe and high-risk CRAB infection	For moderate-severe CRAB infection
Ampicillin/sulbactam	For patients with CRAB susceptible to sulbactam and HAP/VAP (1 g sulbactam component q6h)	Back-bone treatment for all CRAB infection (6-9 g sulbactam component daily)
Polymyxins	Either colistin or polymyxin B: for patients with CRAB resistant to sulbactam susceptible to polymyxins; in combination with one other *in-vitro* active agent for severe, susceptible to polymyxins, CRAB infection	Polymyxin B in combination with at least one other agent for the treatment of CRAB infections (Colistin only for CRAB UTIs)
Tetracycline derivatives	High-dose tigecycline: for patients with CRAB resistant to sulbactam susceptible to tigecycline; in combination with one other *in-vitro* active agent for severe, susceptible to tigecycline, CRAB infection	High-dose minocycline (preferred option) or high-dose tigecycline in combination with at least one other agent for the treatment of CRAB infections
Cefiderocol	Not recommended	In combination with at least one other agent for the treatment of CRAB infections
Aminoglycosides	In combination with one other *in-vitro* active agent for severe, susceptible to aminoglycosides, CRAB infection	Not recommended
Meropenem	In combination with one other *in-vitro* active agent for severe CRAB infections with a meropenem MIC <8 mg/L (2 g q8h over 3 hrs infusion)	Not recommended

Personal view

Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis



Kengkla et al. JAC 2017

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

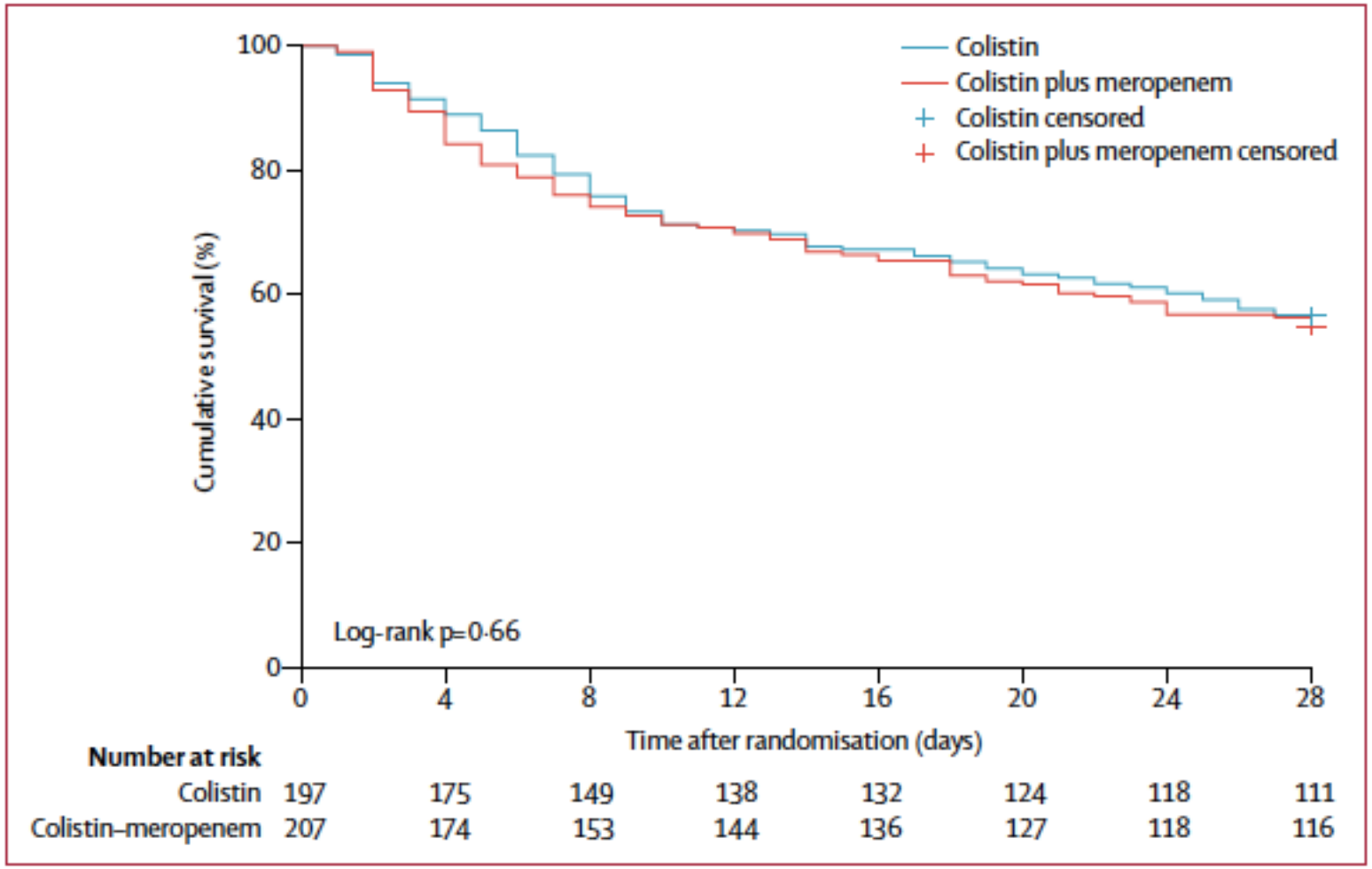


Figure 2: **Survival analysis to day 28 after randomisation**

Paul et al. LID 2018

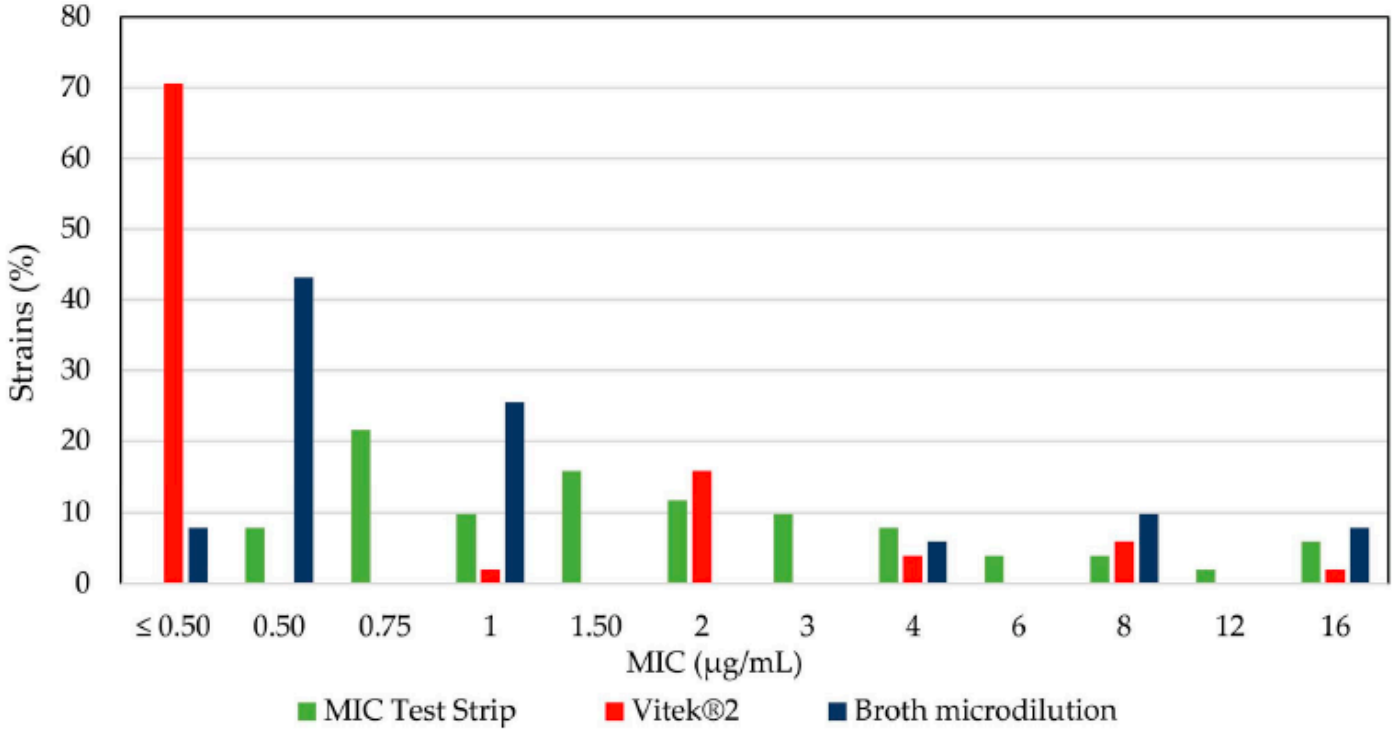
Colistin

Potential false susceptibility to colistin in approximately 50% of *Acinetobacter baumanni*i strains using automated systems or an E-test.

Therefore, the very high rates of mortality observed in published studies might also be attributed to a reported false susceptibility to colistin in patients for whom physicians were confident in prescribing a colistin-based regimen?

EUCAST 2020

Colistin



Sacco et al, Antibiotics 2020

Treatment outcomes of colistin and carbapenem-resistant *Acinetobacter baumannii* infections: an exploratory subgroup analysis of a randomized clinical trial

Several *in vitro* and animal model studies have demonstrated that colistin-resistance in *A. baumannii* isolates may result in fitness cost [21-23] with the degree to which fitness and virulence are reduced correlating with mechanism of resistance [21, 24, 25]. Our finding of lower mortality among patients with colistin-resistant isolates may be explained by a loss of fitness and virulence relative to colistin-susceptible strains. That patients with colistin-resistant isolates had lower mortality compared with patients with colistin-susceptible isolates, despite the former apparently receiving no effective antibiotic therapy, likely reflects both on the inherently limited effectiveness of colistin in patients with severe infection caused by extremely-drug-resistant Gram-negative bacteria (XDR GNB) [26-28] and the fitness cost of colistin-resistance. Indeed, even patients with colistin MIC≤0.5 in our study had no difference in 28-day mortality compared with patients with MIC>0.5 (23/43 vs. 112/223, p=0.74).

Surprisingly, we found that colistin monotherapy was associated with lower mortality in patients with colistin-resistant CRAB compared with colistin-meropenem combination

Dickstein et al. CID 2018

What happened to Cefiderocol?

Question 7: What Is the Role of Cefiderocol Therapy for the Treatment of Infections Caused by CRAB?

Suggested Approach

Cefiderocol should be limited to the treatment of CRAB infections refractory to other antibiotics or in cases where intolerance to other agents precludes their use. When cefiderocol is used to treat CRAB infections, the panel suggests prescribing the agent as part of a combination regimen.

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

Numerically more deaths occurred in the cefiderocol group, primarily in the patient subset with *Acinetobacter* spp infections, particularly in patients with nosocomial pneumonia or bloodstream infection or sepsis with *Acinetobacter* spp at baseline.

	Cefiderocol (n=101)	Best available therapy (n=49)
Acinetobacter spp*	21/42 (50%)	3/17 (18%)
Acinetobacter baumannii	19/39 (49%)	3/17 (18%)
Klebsiella pneumoniae	8/34 (24%)	4/16 (25%)
Without *Acinetobacter* spp	6/28 (21%)	4/15 (27%)
Pseudomonas aeruginosa	6/17 (35%)	2/12 (17%)
Without *Acinetobacter* spp	2/11 (18%)	2/11 (18%)
Escherichia coli	1/6 (17%)	0/3
Without *Acinetobacter* spp	0/3	0/1
Stenotrophomonas maltophilia	4/5 (80%)	NA
Without *Acinetobacter* spp	2/3 (67%)	NA

Data are n/N (%). NA=not available. *Includes *Acinetobacter baumannii* (for 39 patients assigned cefiderocol and 17 assigned best available therapy), *Acinetobacter nosocomialis* (for two patients assigned cefiderocol), and *Acinetobacter radioresistens* (for one patient assigned cefiderocol).

Table 6: **All-cause mortality at the end of study by most frequent baseline pathogen in the safety population**

For patients with *Acinetobacter* spp infections was observed, at baseline, an increased rate of:

- moderate or severe renal dysfunction
- ICU at randomisation
- ongoing shock
- shock within 31 days before randomisation

in the cefiderocol group than in the best available therapy group

Bassetti et al, LID 2021

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journal homepage: www.elsevier.com/locate/ijantimicag

Review

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)

Giusy Tiseo[a,1], Gioconda Brigante[b,1], Daniele Roberto Giacobbe[c,d,1], Alberto Enrico Maraolo[e,1], Floriana Gona[f,1], Marco Falcone[a], Maddalena Giannella[g,h], Paolo Grossi[i], Federico Pea[h,j], Gian Maria Rossolini[k], Maurizio Sanguinetti[l], Mario Sarti[m], Claudio Scarparo[n], Mario Tumbarello[o], Mario Venditti[p], Pierluigi Viale[g,h], Matteo Bassetti[c,d,2], Francesco Luzzaro[q,2], Francesco Menichetti[a,2,*], Stefania Stefani[r,2], Marco Tinelli[s,2]

Recommendation 7.3:

Cefiderocol represents a promising antibiotic option for patients with carbapenem-resistant Acinetobacter baumannii (CRAB) infections. Further studies are needed to consolidate this recommendation and to evaluate the use of cefiderocol as monotherapy or in combination with other antibiotics.

Strength of recommendation:	**STRONG**	Certainty of evidence:	**LOW**

Several aspects regarding the use of cefiderocol in patients with CRAB infections remain unresolved:

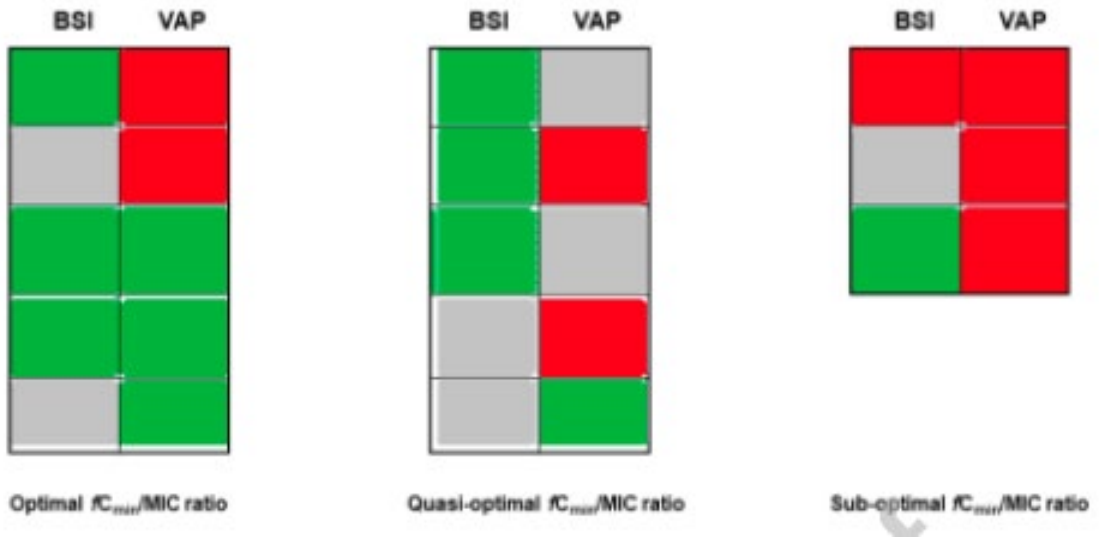
- PK/PD characteristics in patients with renal impairment and in critically ill patients;
- use of cefiderocol as monotherapy or in combination with other drugs;
- penetration into the ELF and pulmonary concentrations in patients with VAP.

Thus, consultation with an infectious diseases specialist should be recommended before its use.

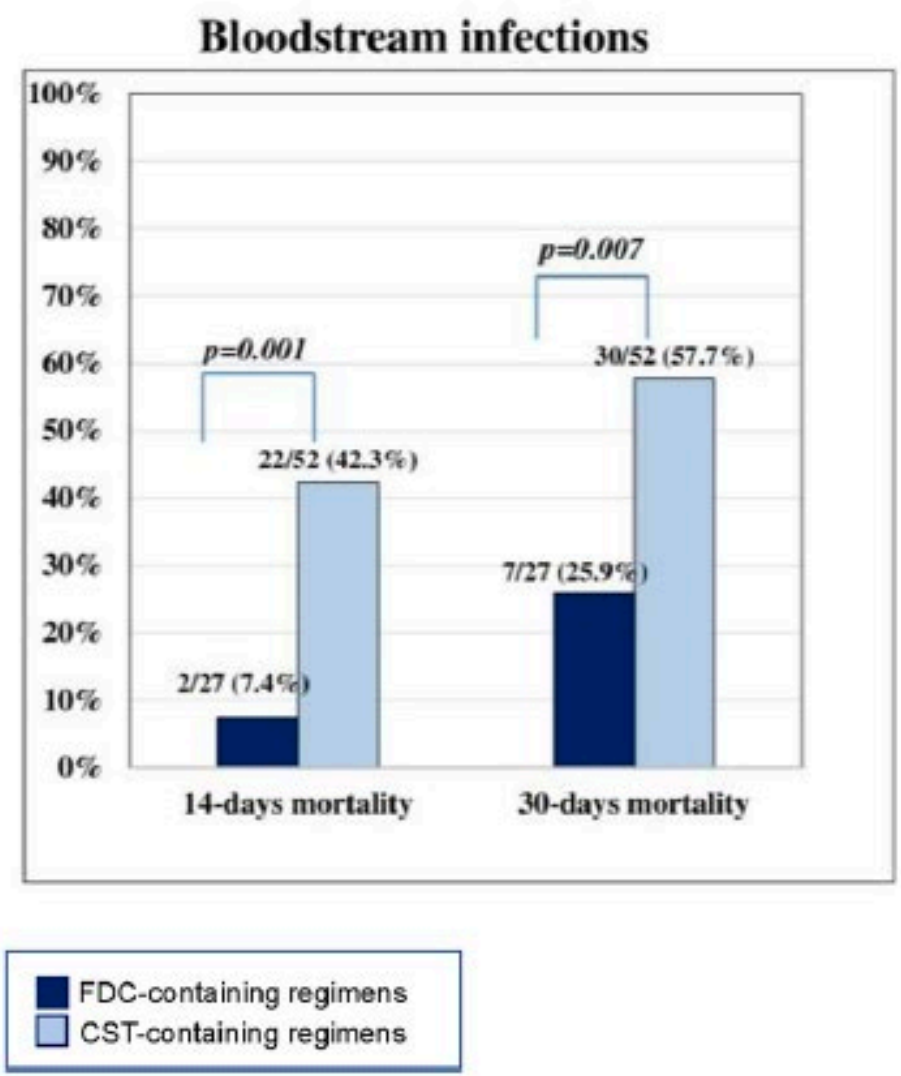
In conclusion, despite low-quality of evidence, cefiderocol may be considered a promising therapeutic option for patients with CRAB in- fections. Further RCTs comparing cefiderocol-containing regimens vs. colistin-containing regimens are urgently warranted for an ap- propriate use of this new siderophore cephalosporin.

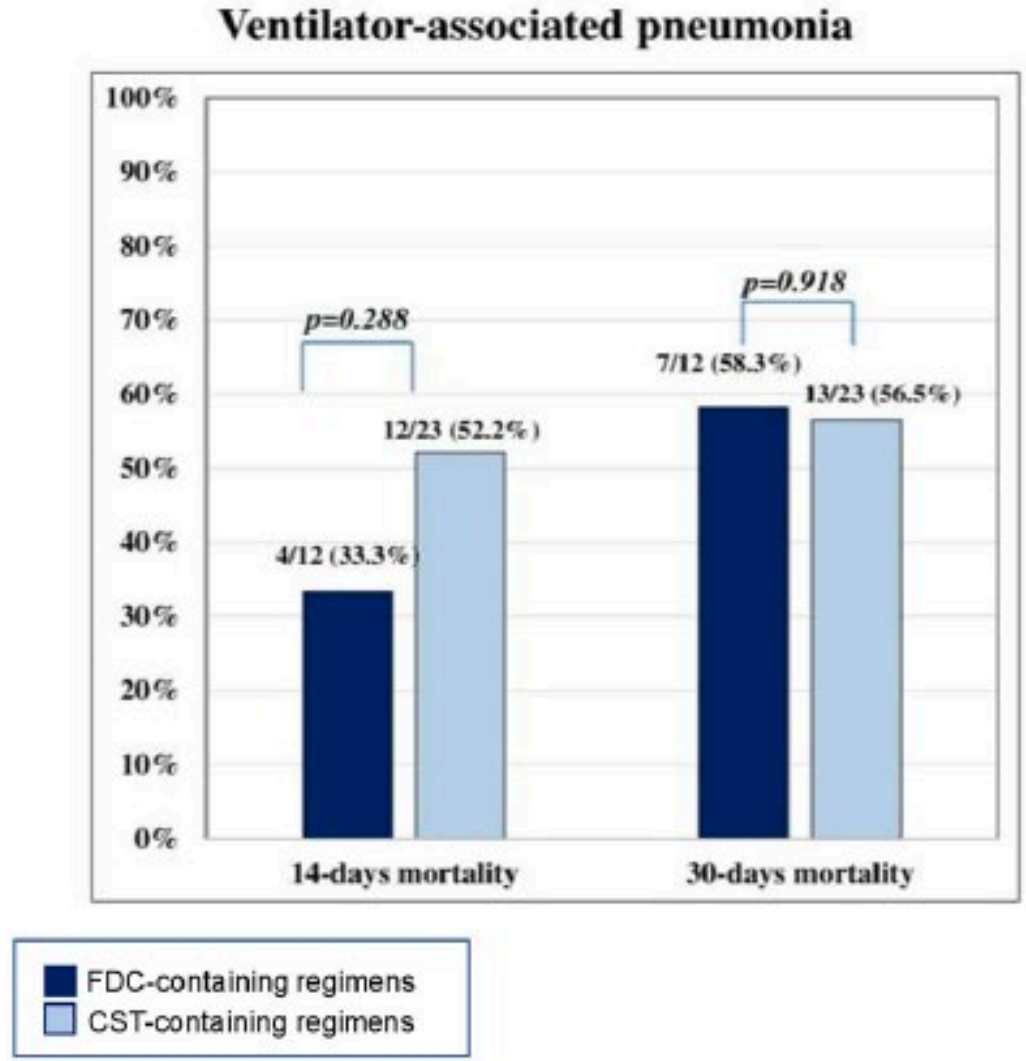
A descriptive case series of PK/PD target attainment and microbiological outcome in critically ill patients with documented severe XDR *Acinetobacter baumannii* BSI and/or VAP treated with cefiderocol

fCmin/MIC ratio was defined as optimal if ≥ 4, quasi-optimal if between 1 and 4, and suboptimal if < 1.

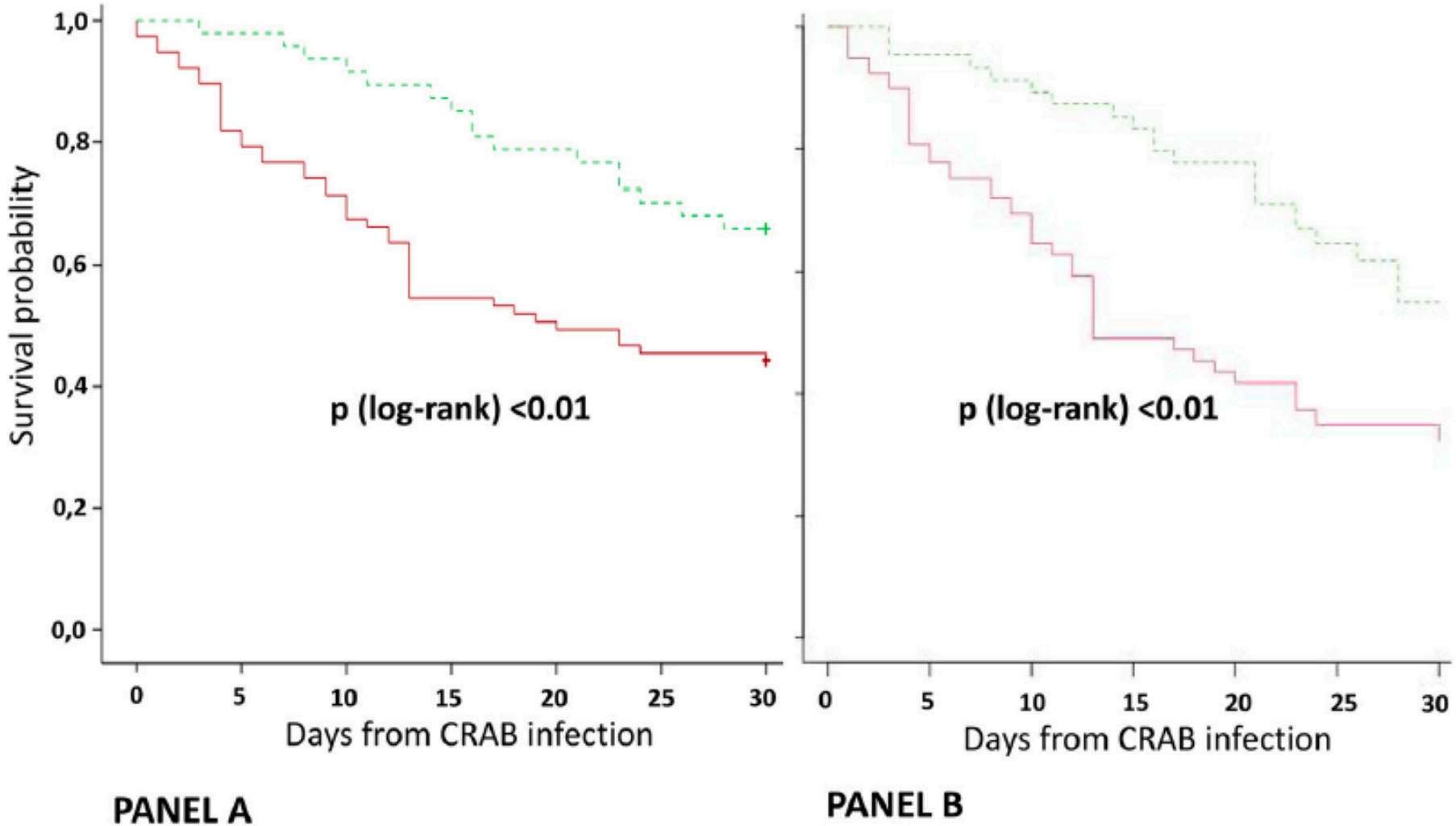


Gatti et al, JGAR 2021





Falcone et al, AAC 2022



Falcone et al, AAC 2022

	Clinical Resolution (n = 56)	Clinical Failure (n = 34)
Age (years)	62 (52–69)	71 (64–78) *
Male sex	38 (68)	16 (47)
Surgical admission	30 (54)	18 (53)
Immunodepression	12 (21)	15 (44) *
Charlson comorbidity index	4 (2–6)	8 (6–8) *
Main comorbidities		
Diabetes mellitus	8 (14)	17 (50) *
Cardiovascular disease	13 (23)	18 (53) *
Chronic respiratory disease	6 (11)	15 (44) *
Chronic kidney disease	4 (7)	6 (18)
Chronic liver disease	2 (4)	3 (9)
Solid cancer	6 (11)	5 (15)
Active hematologic malignancies	2 (4)	5 (15)
Solid organ transplantation	3 (5)	6 (18)
Obesity (BMI > 30 kg/m^2)	5 (9)	4 (12)
APACHE II score upon ICU admission	22 (20–25)	23 (20–25)
VAP onset from ICU admission (days)	8 (6–11)	9 (7–11)
SOFA score at VAP onset	9 (7–11)	10 (9–11) *
Oxygenation at VAP onset		
PaO_2 to FiO_2 ratio >200	9 (16)	4 (12)
PaO_2 to FiO_2 ratio >100 and <200	41 (73)	26 (76)
PaO_2 to FiO_2 ratio <100	6 (11)	4 (12)
Infection severity at VAP onset		
Uncomplicated infection	13 (23)	2 (6) *
Sepsis	19 (34)	10 (29)
Septic shock	25 (45)	22 (65)
Bacteraemic VAP	15 (26.8)	14 (41.2)
Augmented renal clearance	10 (18)	5 (15)
CRRT	8 (14)	8 (24)
vv-ECMO	3 (5)	1 (3)
Known respiratory CRAB colonization	34 (61)	18 (53)
Fast molecular diagnostics at VAP onset	17 (30.3)	3 (8.8) *
Timely (≤24 h) targeted therapy	50 (89)	22 (65) *
Cefiderocol-based regimens	30 (54)	10 (29) *
Cefiderocol–inhaled colistin	10 (17.8)	9 (26.5)
Cefiderocol–fosfomycin–inhaled colistin	20 (35.7)	1 (3) *
Colistin-based regimens	26 (46)	24 (71) *
Colistin–tigecycline–inhaled colistin	11 (20)	16 (47) *
Colistin–ampicillin/sulbactam–inhaled colistin	8 (14)	7 (21)
Colistin–meropenem–inhaled colistin	7 (13)	1 (3)
14-day mortality	0 (0)	14 (41) *
28-day mortality	12 (21)	24 (71) *
ICU length of stay (days)	24 (21–28)	21 (17–25) *

Dalfino et al, Antibiotics 2023

Table 3. Cox proportional hazard model for investigating predictors of clinical failure with first-line antimicrobial therapy.

	Univariable Analysis			Multivariable Analysis		
	aHR	**95% CI**	***p*-Value**	**aHR**	**95% CI**	***p*-Value**
Immunodepression	1.97	0.98–3.83	0.06	1.56	0.76–3.19	0.23
Charlson comorbidity index	1.28	1.12–1.47	<0.0001	1.21	1.04–1.42	0.01
SOFA score	1.15	1.02–1.30	0.02	1.07	0.92–1.25	0.35
Septic shock	1.91	0.93–3.87	0.07	1.52	0.69–3.33	0.29
Bacteremic VAP	1.46	0.74–2.90	0.28	/		
Augmented renal clearance	1.07	0.41–2.76	0.41	/		
CRRT	1.10	0.50–2.47	0.81	/		
Timely targeted therapy	0.44	0.22–0.90	0.02	0.40	0.19–0.84	0.01
Cefiderocol-based first-line regimens	0.37	0.17–0.79	0.01	0.38	0.17–0.85	0.02

Dalfino et al, Antibiotics 2023

- ✓ In un’ampia coorte di pazienti con VAP monomicrobica causata da CRAB, il fallimento clinico dopo la terapia mirata di prima linea ha coinvolto quasi il 40% dei pazienti ed è stato associato a tassi di mortalità in terapia intensiva a 14 e 28 giorni pari al 41% e al 71%. rispettivamente.
- ✓ I tassi di fallimento clinico sono stati pari al 48% nei pazienti che avevano ricevuto regimi a base di colistina e al 25% in quelli trattati con regimi a base di cefiderocol
- ✓ la terapia mirata tempestiva e i regimi di prima linea a base di cefiderocol hanno ridotto fortemente il rischio di fallimento
- ✓ quasi il 90% dei pazienti che hanno avuto una risoluzione dell’infezione hanno ricevuto agenti attivi CRAB entro 24 ore dall’insorgenza della VAP e una terapia mirata tempestiva si è rivelata in grado di ridurre in modo indipendente il rischio di fallimento clinico del 60%.
- ✓ Il 58% dei pazienti è stato colonizzato da CRAB e, di conseguenza, sono state intraprese strategie terapeutiche empiriche guidate
- ✓ I tassi rilevanti di terapia attiva tempestiva, che hanno portato alla risoluzione della VAP, sono stati raggiunti grazie al contributo significativo della diagnostica molecolare rapida eseguita in pazienti ad alto rischio. Questa scoperta conferma il valore dei pannelli respiratori multiplex RT, che includono, oltre alla sospensione degli antibiotici, l’aiuto ai medici a indirizzare tempestivamente la terapia nei pazienti con VAP grave.

Dalfino et al, Antibiotics 2023

In vitro activities of carbapenems in combination with amikacin, colistin or fosfomycin against carbapenem-resistant *Acinetobacter baumannii* clinical isolates

Table 3
Results of the activity of antibiotic combinations against *A. baumannii* by checkerboard assay.

Strain	ST type	FICI of antibiotic combinations (interpretation)					
		IPM + AK	IPM + CT	IPM + FOF	MEM + AK	MEM + CT	MEM + FOF
AB2	195	ND	0.63 (N)	0.31 (S)	ND	0.75 (N)	0.75 (N)
AB5	195	ND	2.00 (N)	0.56 (N)	ND	1.00 (N)	1.00 (N)
AB6	195	ND	2.00 (N)	0.50 (S)	ND	0.63 (N)	1.00 (N)
A7	195	ND	0.63 (N)	1.00 (N)	ND	0.75 (N)	2.00 (N)
AB29	542	0.31 (S)	2.00 (N)	0.31 (S)	0.38 (S)	0.75 (N)	0.53 (N)
AB58	542	0.75 (N)	2.00 (N)	0.38 (S)	0.38 (S)	0.63 (N)	2.00 (N)
AB97	542	0.50 (S)	2.00 (N)	0.31 (S)	0.50 (S)	0.63 (N)	1.00 (N)
AB13	542	0.75 (N)	0.75 (N)	0.75 (N)	0.38 (S)	1.00 (N)	0.75 (N)
AB35	1417	0.75 (N)	0.50 (S)	0.50 (S)	0.50 (S)	0.56 (N)	0.75 (N)
A4	1417	ND	0.75 (N)	0.50 (S)	ND	1.00 (N)	1.00 (N)
AB4	1423	ND	2.00 (N)	0.50 (S)	ND	1.00 (N)	1.00 (N)
AB354	1423	ND	0.50 (S)	0.53 (N)	ND	0.75 (N)	0.75 (N)
AB1	806	ND	0.63 (N)	0.56 (N)	ND	0.75 (N)	0.75 (N)
AB3	1415	0.75 (N)	0.63 (N)	0.31 (S)	0.50 (S)	2.00 (N)	0.75 (N)
AB9	514	0.75 (N)	0.63 (N)	0.31 (S)	1.00 (N)	0.75 (N)	0.53 (N)
AB55	1166	ND	0.50 (S)	1.00 (N)	ND	0.63 (N)	0.75 (N)
A5	229	0.63 (N)	0.75 (N)	2.00 (N)	0.63 (N)	1.00 (N)	1.00 (N)
A8	1418	0.50 (S)	0.75 (N)	0.75 (N)	0.75 (N)	2.00 (N)	2.00 (N)
A9	551	ND	0.50 (S)	0.50 (S)	ND	0.75 (N)	0.56 (N)
AB227	208	0.75 (N)	0.75 (N)	0.31 (S)	1.00 (N)	0.63 (N)	0.75 (N)
A6	1001	0.38 (S)	1.00 (N)	0.50 (S)	0.75 (N)	0.75 (N)	0.75 (N)
AB250	1416	0.75 (N)	2.00 (N)	0.50 (S)	1.00 (N)	0.63 (N)	1.00 (N)
A10	1426	0.75 (N)	0.75 (N)	0.50 (S)	1.00 (N)	1.00 (N)	0.75 (N)

FICI = fractional inhibitory concentration index; ND = not determined (isolates with amikacin MIC>256 mg/L were excluded); N = no interaction; S = synergy; IPM = imipenem; MEM = meropenem; CT = colistin; AK = amikacin; FOF = fosfomycin.

Singkham-In et al. DMID 2018

Efficacy of a Fosfomycin-Containing Regimen for Treatment of Severe Pneumonia Caused by Multidrug-Resistant *Acinetobacter baumannii*: A Prospective, Observational Study

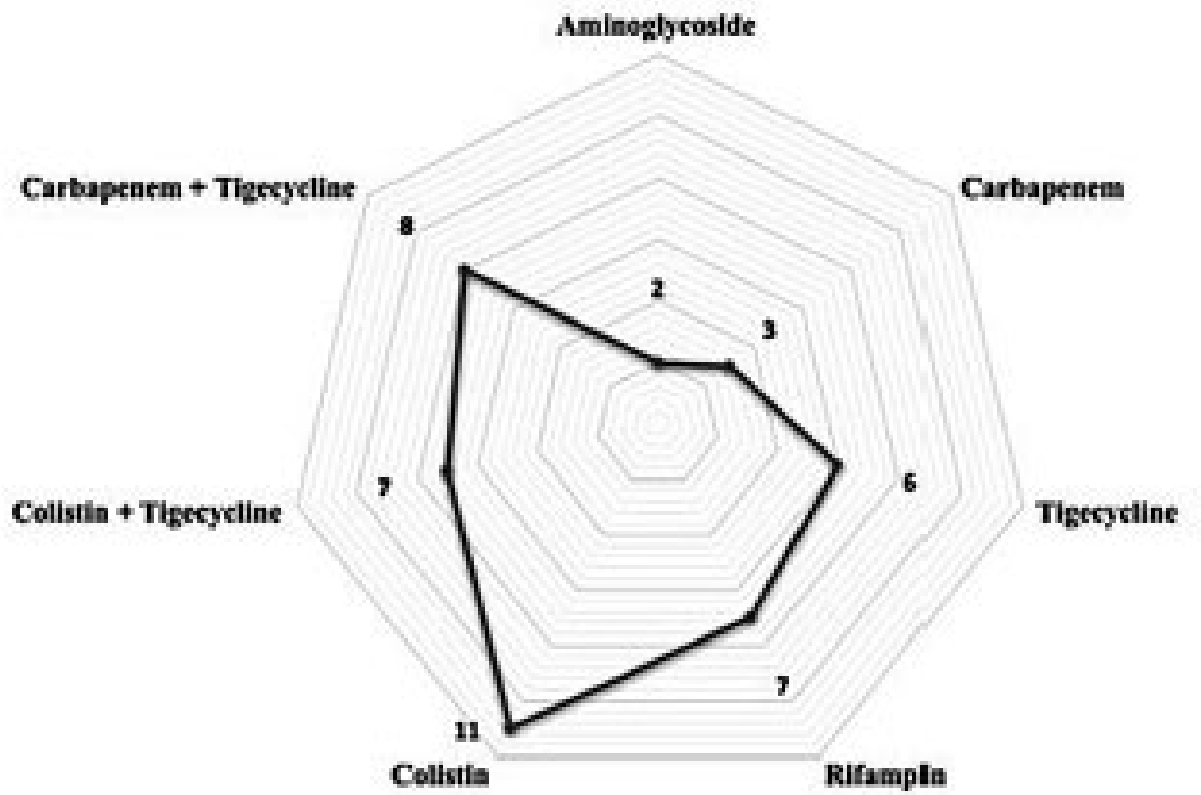
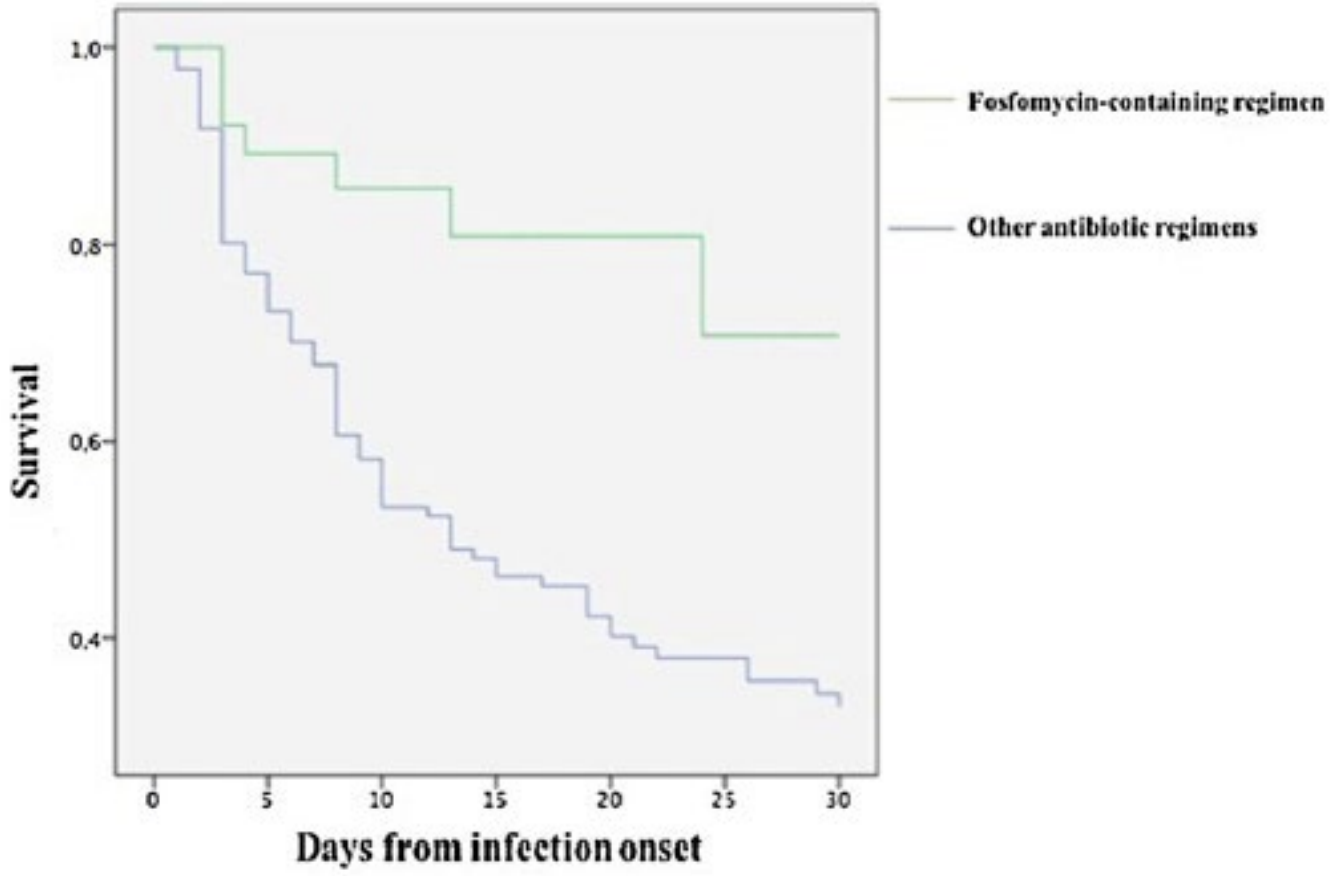


Fig. 1 Antibiotics in combination with fosfomycin in definitive therapy (no. of patients treated)

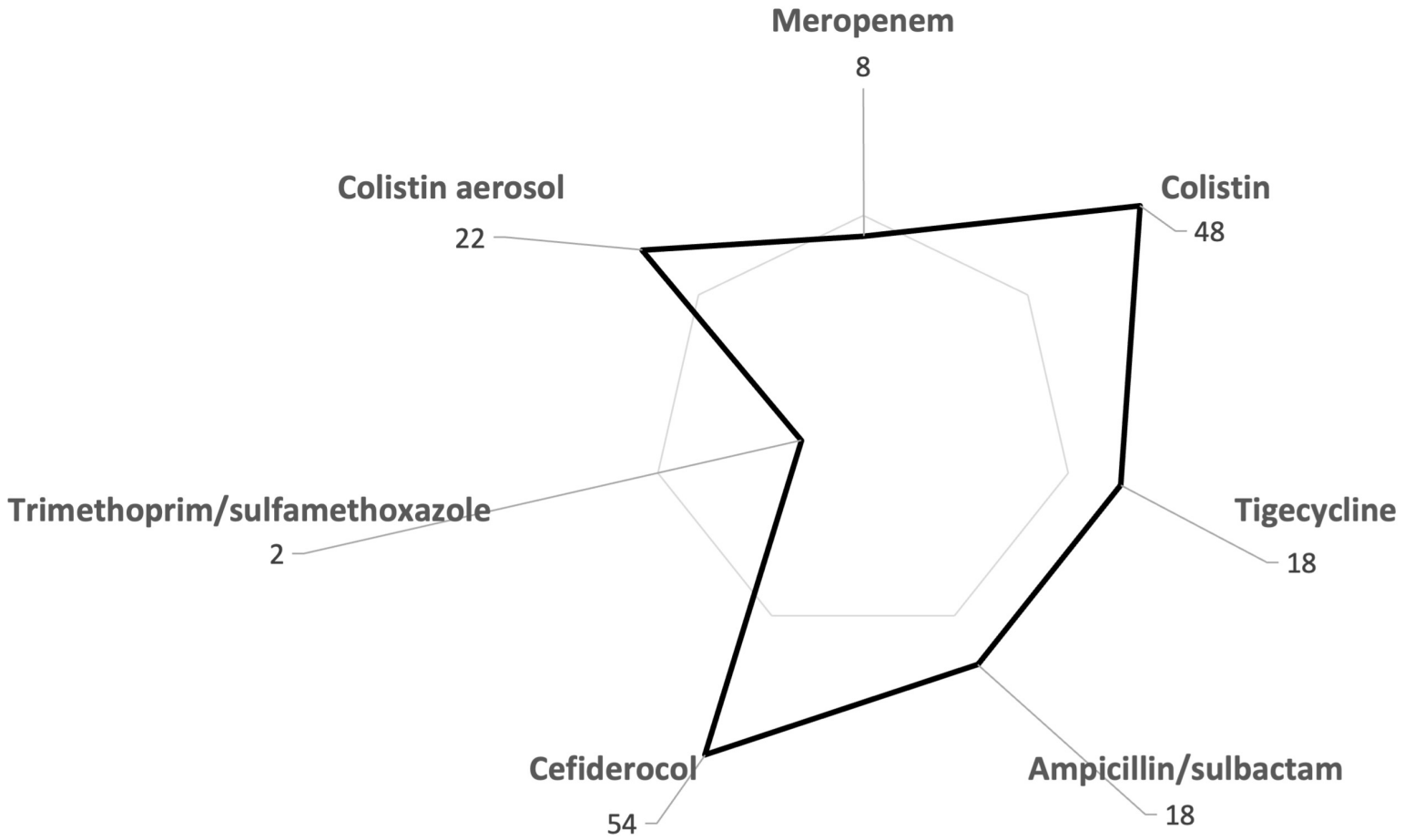
Russo et al, IDT, 2020

Efficacy of a Fosfomycin-Containing Regimen for Treatment of Severe Pneumonia Caused by Multidrug-Resistant *Acinetobacter baumannii*: A Prospective, Observational Study



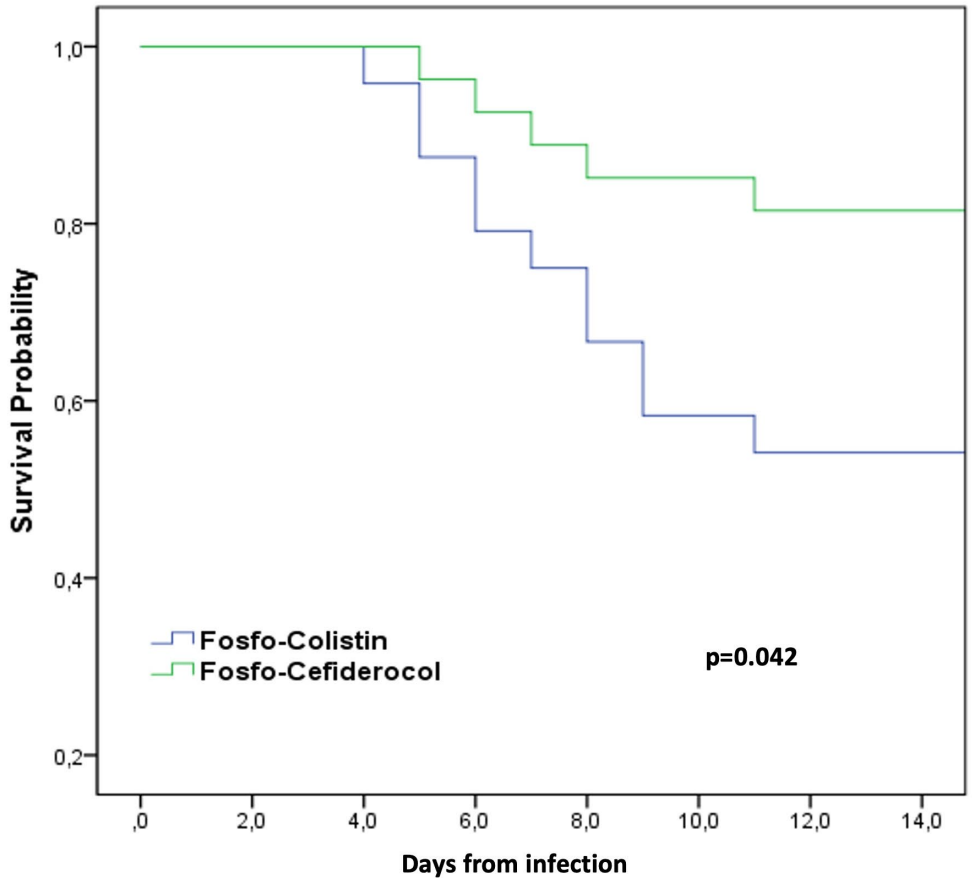
Russo et al, IDT, 2020

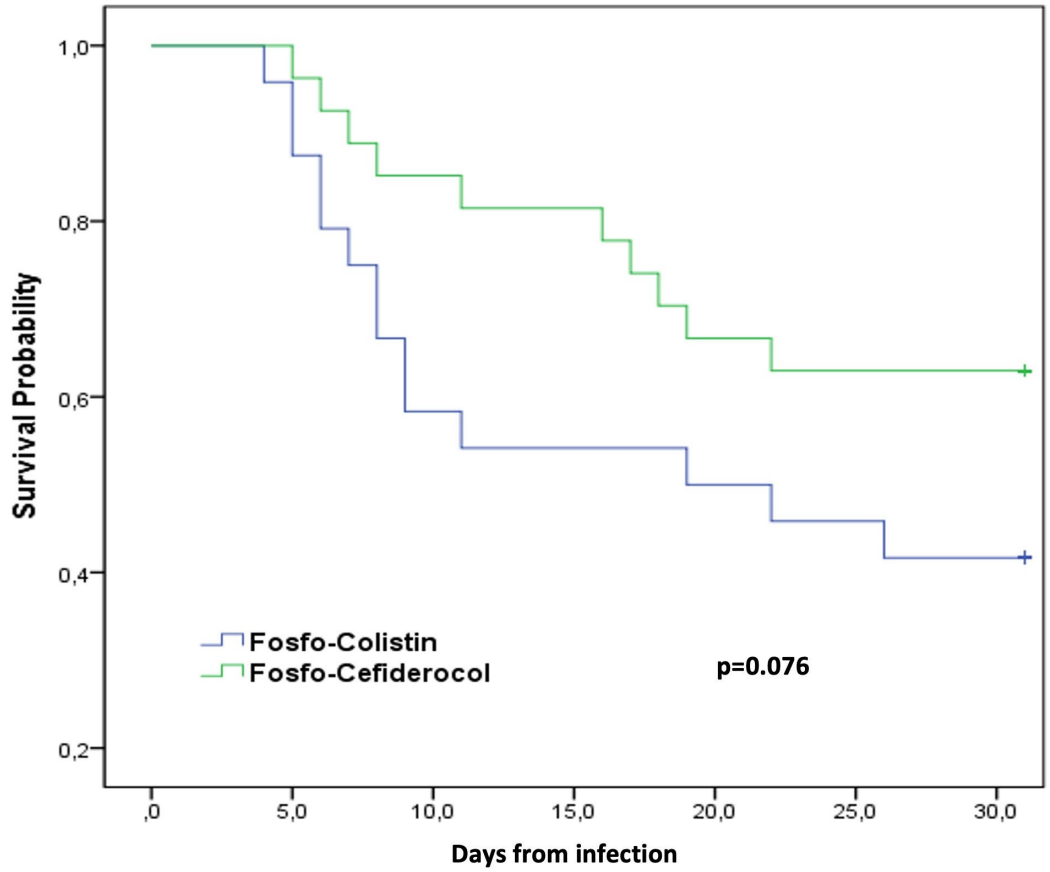
Intravenous fosfomycin for treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*: a multicenter clinical experience



Russo et al, submitted

Intravenous fosfomycin for treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*: a multicenter clinical experience





Russo et al, submitted

Synergistic Activity of Cefiderocol in Combination withFosfomycin against CRAB

Isolates	MIC (mg/L) [1]							
	CFD [2]	SULB [3]	PIP-TAZ [4]	IMI-REL [5]	MER-VAB [6]	CAZ-AVI [7]	AMP-SULB [8]	FOS [9]
CRE 1	16	>256	>256 [a]	4 [b]	16 [c]	48 [d]	>256 [e]	>256
CRE 2	0.032	>256	>256 [a]	0.25 [b]	4 [c]	3 [d]	>256 [e]	8
CR-Ab 1	>256	>256	>256 [a]	>32 [b]	>256 [c]	>256 [d]	>256 [e]	32
CR-Ab 2	0.125	64	>256 [a]	>32 [b]	>256 [c]	48 [d]	>256 [e]	>256
CR-Pa 1	0.5	>256	12 [a]	2 [b]	16 [c]	24 [d]	>256 [e]	>256
CR-Pa 2	0.125	>256	8 [a]	>32 [b]	32 [c]	8 [d]	>256 [e]	>256

Isolates	CFD/PIP-TAZ [1]	CFD/FOS [2]	CFD/CAZ-AVI [3]	CFD/IMI-REL [4]	CFD/MER-VAB [5]	CFD/AMP-SULB [6]
CRE 1	1.25	**0.50**	**0.38**	0.63	0.63	0.88
CRE 2	1.00	0.86	0.83	1.00	0.75	1.47
CR-Ab 1	2.00	**0.44**	2.00	2.00	2.00	2.00
CR-Ab 2	1.50	1.01	1.75	2.00	2.00	1.50
CR-Pa 1	1.00	1.00	**0.50**	0.63	1.25	**0.50**
CR-Pa 2	2	1.75	2	0.63	1.26	2

Palombo et al, Antibiotics 2023

Fosfomycin may be an effective adjunctive therapy for pneumonia caused by MDR/XDR *A. baumannii* strains, considering the synergistic effect of colistin and fosfomycin reported in *in vitro* studies.

Fosfomycin achieves effective concentrations in infected lung tissue, and in association with colistin showed bactericidal and synergistic effects at 8 h, reducing the bacterial load in the lungs at 48 h as recently showed in clinical studies

A combination regimen containing fosfomycin showed significantly better microbiologic responses with trends toward more favorable treatment outcomes and lower mortality

Russo et al, IDT, 2020

In vitro activity of sulbactam/durlobactam against global isolates of carbapenem-resistant *Acinetobacter baumannii*

Table 1. MIC distributions, MIC_{50} and MIC_{90} values, MIC ranges and antimicrobial susceptibilities of 246 carbapenem-resistant *A. baumannii* isolates

	MIC																		
Antimicrobial agent	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
Amikacin				3	9	14	6	9	**9**[d]	25	20	25	126	256	≥512	0.5 to ≥512	20.3	10.2	69.5
Colistin		3	52	159	20	**2**[d]		2		3	4		1	0.5	1	0.125 to ≥256	95.9	–	4.1
Imipenem						**0**[d]		8	5	49	121	57	6	64	128	8 to ≥256	0.0	0.0	100.0
Imipenem/sulbactam/ durlobactam[a,b]			4	36	125	66	9	3		3				1	2	0.25–32	–	–	–
Meropenem						**0**[d]		2	10	55	99	58	22	64	128	8 to ≥256	0.0	0.0	100.0
Minocycline	4	6	24	38	29	23	**27**[d]	35	52	4	4			2	16	≤0.06–64	61.4	14.2	24.4
Sulbactam[a]						2	11	43	68	80	36	3	3	16	64	2 to ≥256	–	–	–
Sulbactam/ durlobactam[a,c]			7	56	97	66	11	3	2	1	1	2		1	2	0.25–128	–	–	–

Seifert et al, JAC 2020

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

The aim of this study was to evaluate the impact of cefiderocol-containing regimens compared to colistin-containing regimens on the outcome of patients with VAP and concomitant bloodstream infection (BSI) caused by CRAB infection in COVID-19 patients

Russo et al, IJAA 2023

- During the study period, 73 patients who developed VAP and concomitant positive blood cultures caused by CRAB were enrolled in the COVID-ICU. Of these patients, 67 (91.7%) developed septic shock, 42 (57.5%) died at 14 days and 59 (80.8%) died at 30 days. All *Acinetobacter baumannii* strains were classified as XDR or PDR.

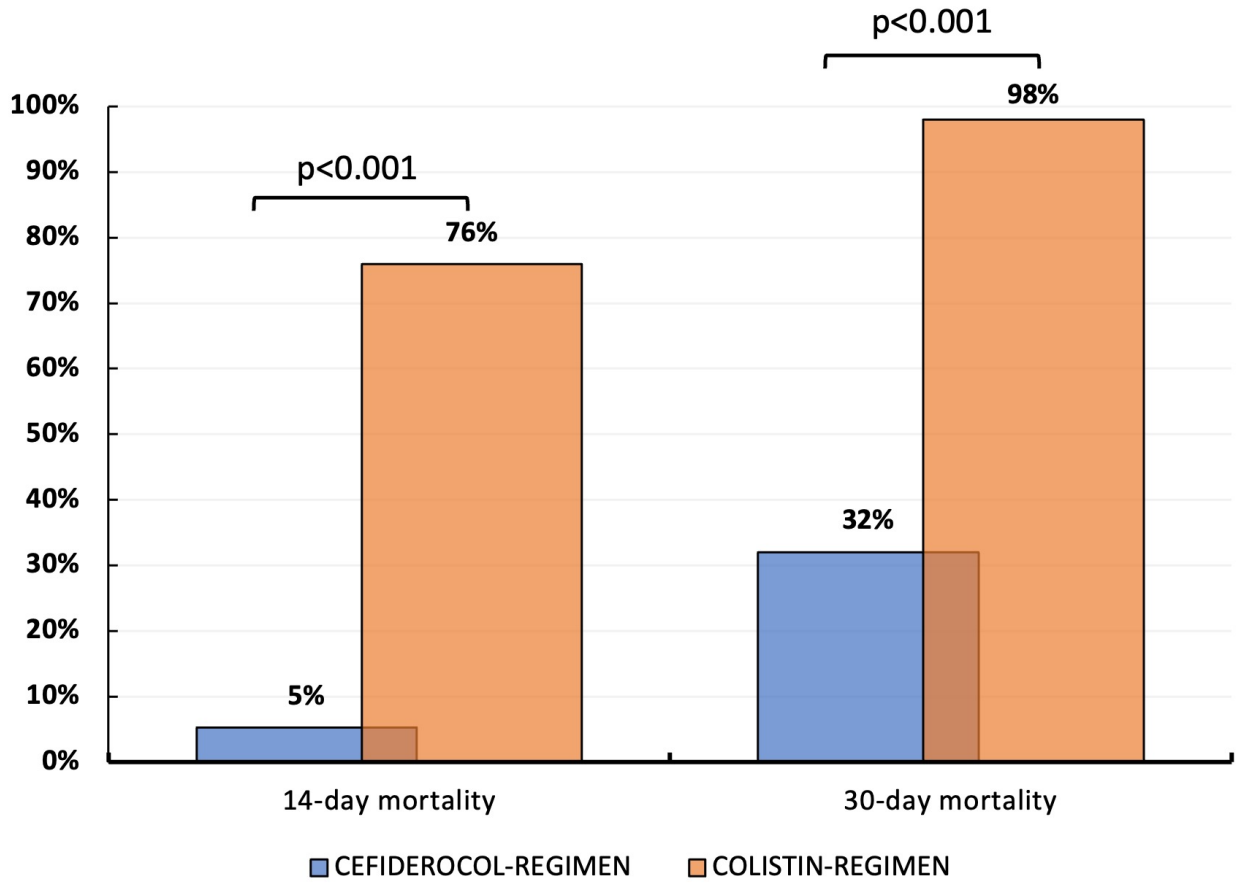
- Overall, 54 (74%) patients were treated using a colistin-containing regimen: 12 (22.2%) patients with colistin monotherapy, 12 (22.2%) with colistin plus meropenem plus tigecycline, and 9 (16.6%) with colistin plus meropenem.

- Nineteen (26%) patients were treated with a cefiderocol-containing regimen: no patients were treated with cefiderocol as monotherapy, six (31.5%) with cefiderocol plus fosfomycin, three (15.8%) with cefiderocol plus fosfomycin plus tigecycline, and three (15.8%) with cefiderocol plus meropenem plus fosfomycin plus tigecycline.

- Finally, 33 (45.2%) were treated with colistin aerosol as adjunctive therapy.

Russo et al, IJAA 2023

No differences were observed in relation to sex, age, comorbidities, septic shock or length of ICU stay. Patients treated with colistin-containing regimens showed higher rates of 14-day (75.9% Vs 5.2%, p < 0.001) and 30-day mortality (98.1% Vs 31.5%, p < 0.001) compared to patients in the cefiderocol group



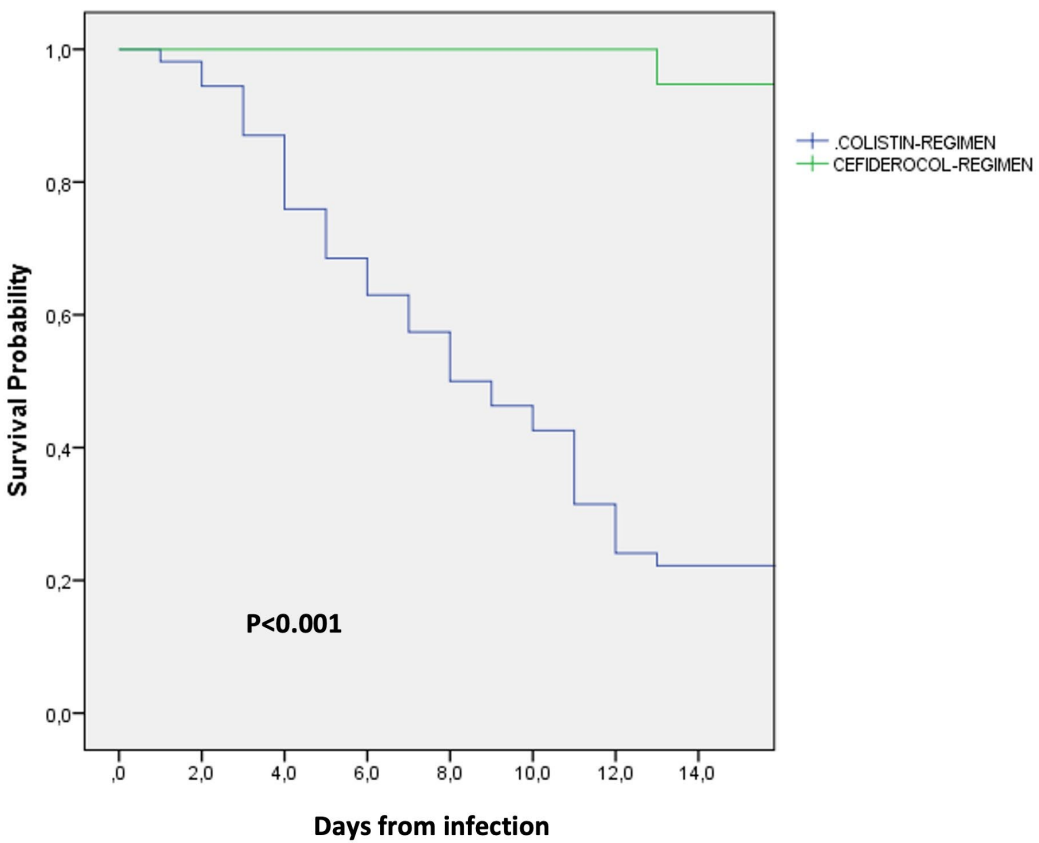
Russo et al, IJAA 2023

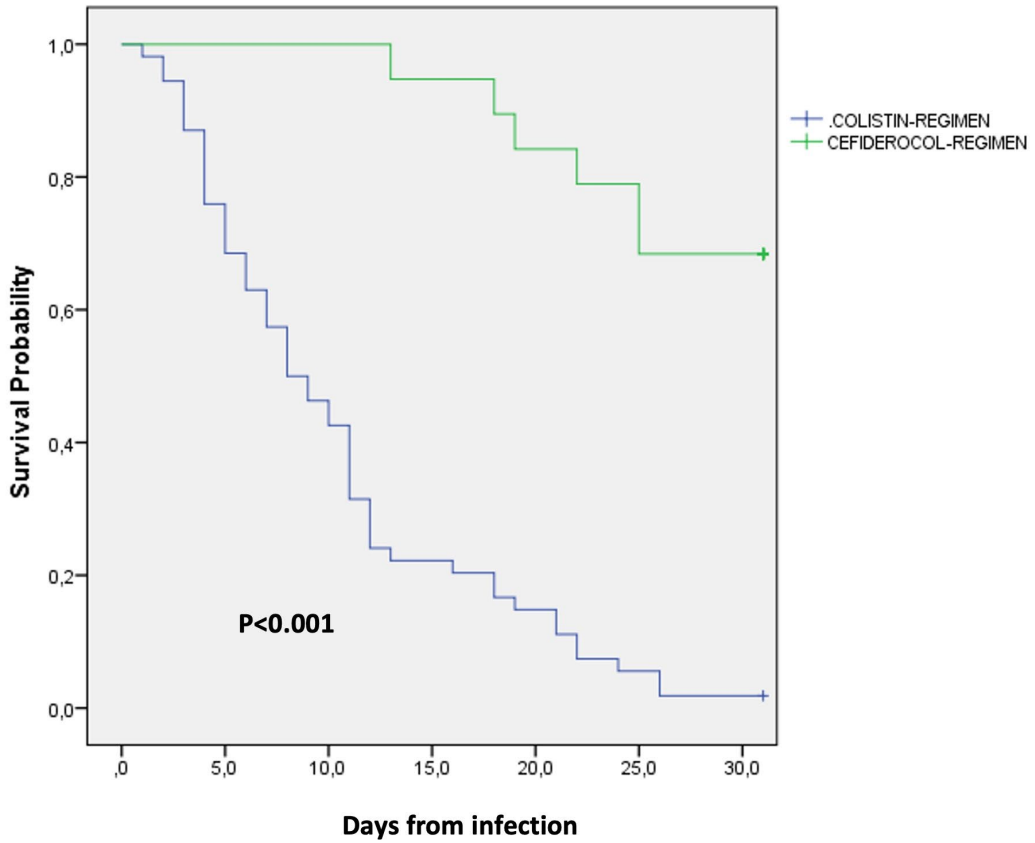
COX regression analysis on risk factors associated with death at 30 days and propensity-score analysis

Variables	Adjusted-HR (95% CI)	p-value
COPD	1.4 (1.3-12.2)	0.022
Age	1.12 (1.01–1.1)	0.001
Cefiderocol-containing regimens (colistin-containing regimens as reference variable)	0.34 (0.18–0.56)	< 0.001
Cefiderocol – fosfomycin	0.22 (0.1-0.55)	< 0.001
Propensity score analysis		
Cefiderocol-containing regimens (IPTW-adjusted)	0.44 (0.22–0.66)	< 0.001
Cefiderocol – fosfomycin (IPTW-adjusted)	0.33 (0.12-0.54)	< 0.001

Russo et al, IJAA 2023

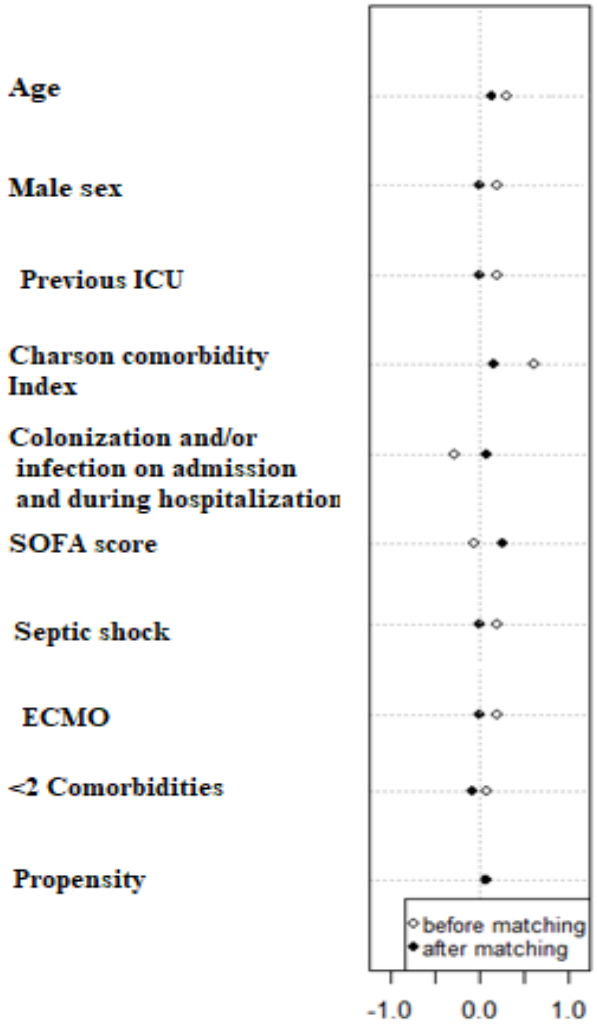
Kaplan-Meier curves for 14- and 30-day survival in patients treated with cefiderocol-or colistin-containing regimens

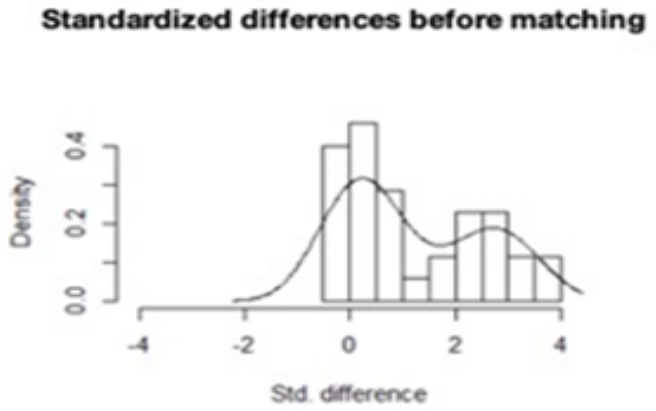


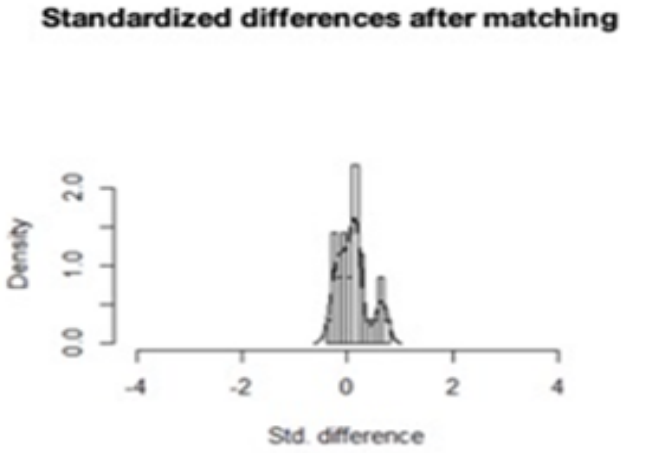


Russo et al, IJAA 2023

Standardized differences before and after propensity score matching







Russo et al, IJAA 2023

- An important strength of this study is that we considered only patients who developed VAP with concomitant isolation of CRAB from blood cultures.
- The diagnosis of VAP in COVID-19 patients can be challenging, considering clinical and radiological findings in severe COVID-19 with or without superinfection (including VAP).
- Moreover, the exact role of colonization of the lower respiratory tract by CRAB is not well defined. The analysis of bacteremic VAP only can therefore reduce this bias and makes this population more homogenous, especially in patients affected by COVID-19.

- This real-life clinical experience about the therapeutic approach in bacteremic VAP caused by CRAB provides useful suggestions for clinicians about the management of this difficult-to-treat infection

- VAP, especially in COVID-19 patients, represents a challenge for physicians, considering the high rates of septic shock and mortality associated with this infection

- Our data reveal the clinical features and usage outcomes of different antibiotic regimens in this infection setting, assigning a predominant role for cefiderocol and its possible use in combination with fosfomycin

- Further randomized clinical trials comparing different cefiderocol regimens with different dosages (i.e., septic patients) are necessary to confirm these observations

4 punti critici

Precedente Isolamento CRAB :

Che ruolo?

Multiplex PCR:

Infezione Vs Colonizzazione

Clinica:

Infezione clinicamente in atto

Antibiotico

Biofilm e Microbioma

Personal view

- ✓Tamponi di sorveglianza per germi MDR
- ✓Multiplex-PCR per agenti respiratori
- ✓Multiplex-PCR su emocolture
- ✓Source control
- ✓Terapia antibiotica empirica
- ✓Terapia antibiotica mirata

+

CLINICA!!!

Unmeet needs

- What role for colonization?
- More clinical data about fosfomycin
- Cefiderocol in mono or combo?
- Increased dosage of cefiderocol in critically ill patients and continuous infusion?
- What role for ampicillin-sulbactam?

Fattori predittivi di mortalità precoce e tardiva e valutazione dell'efficacia terapeutica in pazienti con batteriemia associata ad isolamento di *Acinetobacter baumannii* MDR

ITACA
(ITalian Advances on Carbapenem-resistant *Acinetobacter*)

Tipo di studio	**Studio osservazionale, prospettico, multicentrico**
Disegno dello studio	Saranno arruolati prospetticamente i pazienti ospedalizzati che svilupperanno una infezione clinicamente significativa da *A. baumannii* MDR, con il riscontro di emocolture positive.
Obiettivi dello studio	<u>Obiettivo primario:</u> Analisi dei fattori clinici e terapeutici in grado di prevedere la mortalità a 30 giorni (tardiva) dallo sviluppo dell'infezione associata a batteriemia da *A. baumannii* MDR. <u>Obiettivi secondari:</u> - Mortalità precoce a 14 giorni dallo sviluppo dell'infezione associata a batteriemia da *A. baumannii* MDR - Mortalità a 14 e 30 giorni nei pazienti con shock settico - Analisi genotipica dei ceppi di *A. baumannii* MDR - Predittori di sviluppo di infezione *da A. baumannii* MDR - Efficacia schemi di terapia antibiotica in terapia mirata

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