09:30 - 09:45 **Cefiderocol** - *C. Tascini (Udine)*

Prof Carlo Tascini

Direttore Clinica Malattie infettive

ASUFC – Università di Udine

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Il sottoscritto Carlo Tascini
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

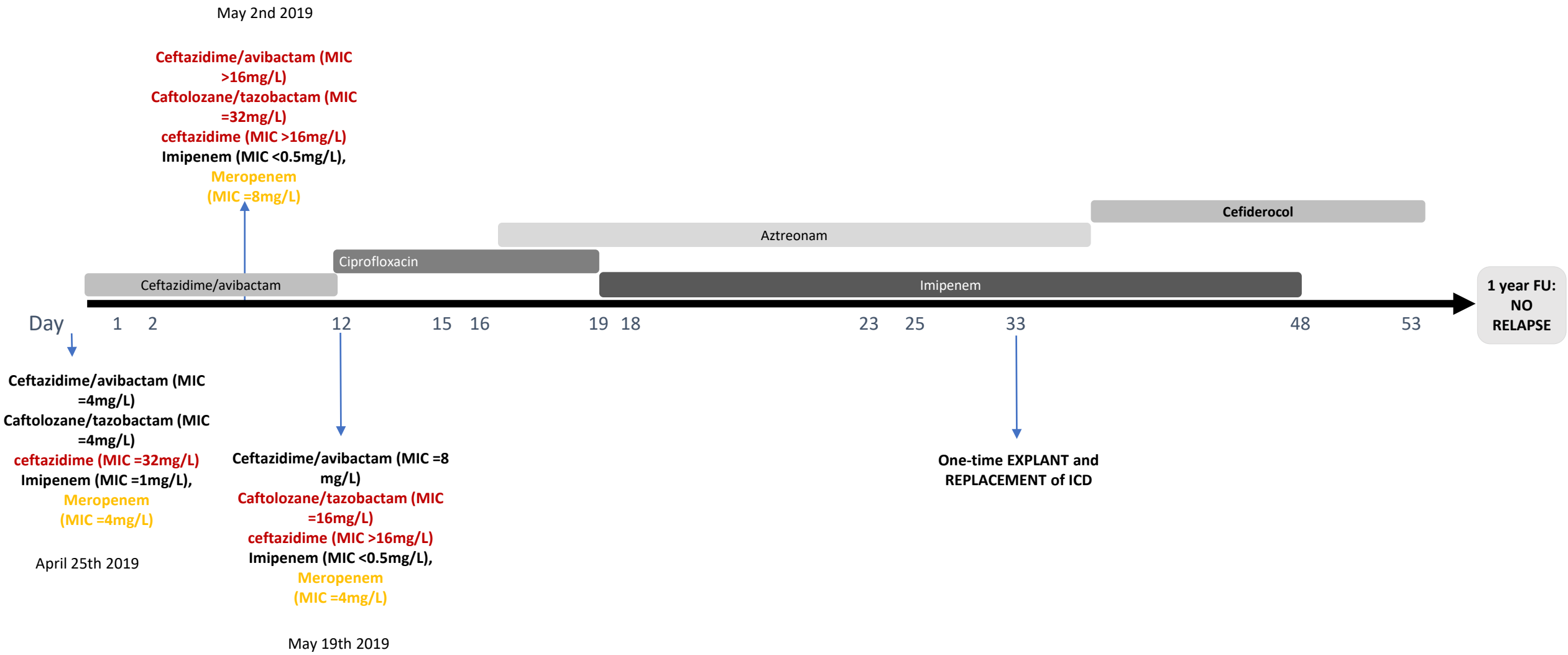
che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Astra*
- *Merck*
- *Pfizer*
- *Angelini*
- *Gilead*
- *Novartis.*
- *Biomeriex*
- *Thermofischer*
- *Zambon*
- *Hikma*
- *Avir Pharma*
- *Shionogi*
- *Biotest*

Cotugno Hospital experience

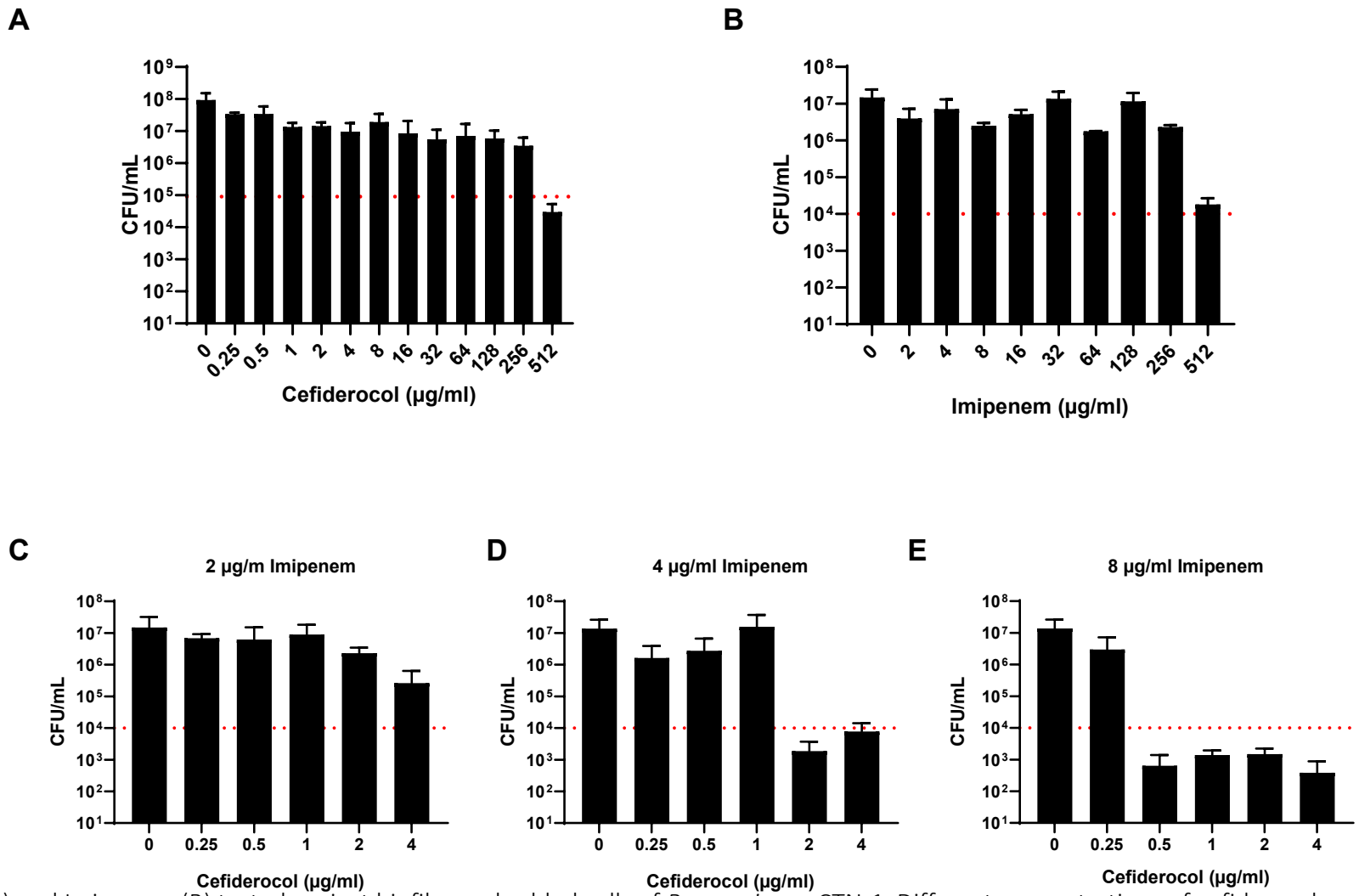
- Transvenous extraction of infected CIED started in march 2018
- 30 patients extracted
- Reimplantation of a new CIED performed on same day of the extraction, at another body site, using a biofilm active drug (e. g. daptomycin in combination, more cumbersome for gram negative)
- No relapse of infection
- Follow-up time: 1 year

ONe-stage re-implantation of CIED endocarditis, due to VIM *P. aeruginosa*, relapsed with ceftolozane/tazobactam and ceftazidime/avibactam and treated with imipenem and cefiderocol, in vitro activity of cefiderocol alone or in combination with impenem(Prof Di Luca)



Antonelli et al submitted for pub
Biofilm exp by Prof Di Luca

Antimicrobial activity of cefiderocol versus biofilm-embedded cells of *P. aeruginosa* CTN-1. CFU/ml obtained after incubation of different concentrations of cefiderocol and imipenem



Cefiderocol (A) and Imipenem (B) tested against biofilm-embedded cells of *P. aeruginosa* CTN-1. Different concentrations of cefiderocol were also tested in combination with 2 µg/ml (C), 4 µg/ml (D) e 8 µg/ml (E) imipenem. Dashed red line indicated a reduction of 3 $\log_{10}$ CFU/ml number in comparison to the untreated control (0µg/ml).

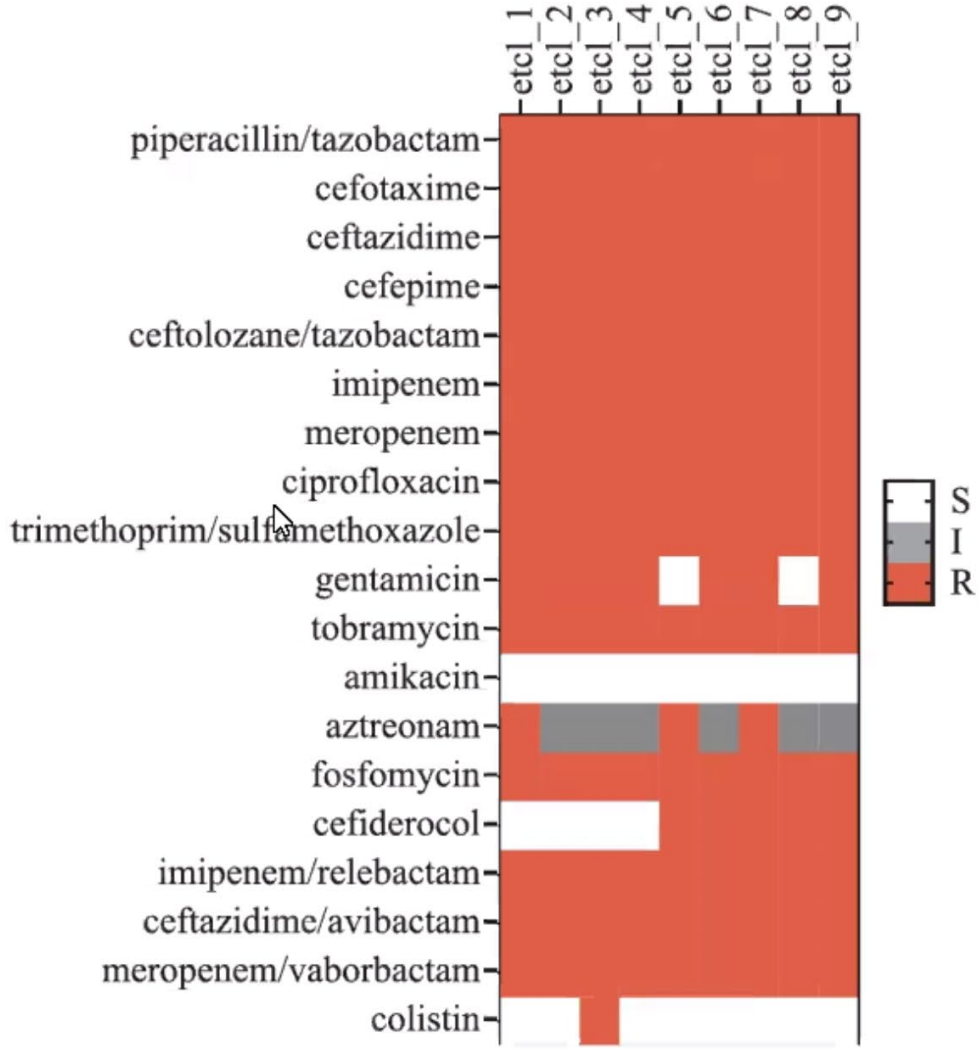
Antonelli et al submitted for pub
Biofilm exp by Prof Di Luca

Clinical Infectious Diseases

BRIEF REPORT 2022

Rapid Development of Cefiderocol Resistance in Carbapenem-resistant *Enterobacter cloacae* During Therapy Is Associated With Heterogeneous Mutations in the Catecholate Siderophore Receptor *cirA*

Sabrina Klein,[1,a] Sébastien Boutin,[1,a] Kaan Kocer,[1] Mascha O. Fiedler,[2] Dominic Störzinger,[3] Markus A. Weigand,[2] Benjamin Tan,[2] Daniel Richter,[2] Christian Rupp,[4] Markus Mieth,[5] Arianeb Mehrabi,[5] Thilo Hackert,[5] Stefan Zimmermann,[1] Klaus Heeg,[1] and Dennis Nurjadi[1]



K. pneumoniae

bla_{NDM-1}, $bla_{CTX-M-15}$, $\Delta cirA$

Antibiogr. molecolare	
CTX-M	RILEVATO
KPC	Non rilevato
OXA-48	Non rilevato
IMP	Non rilevato
VIM	Non rilevato
NDM	RILEVATO

Fenotipo atteso:

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Clav	(R)
Pip/Tazob	(R)
Ceftriaxone	(R)
Ceftazidime	(R)
Cefepime	(R)
Meropenem	(R)
Ceftol/Tazob	(R)
Fosfomicina	?
Amikacina	?
Gentamicina	?
Ciprofloxacina	?
Colistina	?
CAZ/AVI	(R)
MER/VBR	(R)
IMI/REL	(R)
FDC	(S)

Fenotipo riscontrato:

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	128 R
Ceftriaxone	>4 R
Ceftazidime	>64 R
Cefepime	>16 R
Meropenem	>16 R
Ceftol/Tazob	>32 R
Fosfomicina	16 S
Amikacina	>16 R
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>4 R
CAZ/AVI	>64 R
MER/VBR	ND
IMI/REL	ND
FDC	128 R

AOUC Lab + Tascini - unpublished results

Paziente trapiantato di fegato, colonizzato da *K. Pneumoniae* NDM con MIC al cefiderocol 2 mg/L. Durante il trattamento sviluppo di resistenza al cefiderocol

Cortesia Prof Tommaso Giani

Mutante *CirA*

- Nello stesso periodo (agosto 2021) due altri pazienti con stesso germe: uno con infezione urinaria e batteriemia e compagno di stanza colonizzato
- Da allora nessun altro isolamento

K. pneumoniae

bla_{NDM-1}, $bla_{CTX-M-15}$, Δ*cirA*

Antibiogr. molecolare	
CTX-M	RILEVATO
KPC	Non rilevato
OXA-48	Non rilevato
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Fenotipo atteso:

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Clav	(R)
Pip/Tazob	(R)
Ceftriaxone	(R)
Ceftazidime	(R)
Cefepime	(R)
Meropenem	(R)
Ceftol/Tazob	(R)
Fosfomicina	?
Amikacina	?
Gentamicina	?
Ciprofloxacina	?
Colistina	?
CAZ/AVI	(R)
MER/VBR	(R)
IMI/REL	(R)
FDC	(S)

Fenotipo riscontrato:

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
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Meropenem	>16 R
Ceftol/Tazob	>32 R
Fosfomicina	16 S
Amikacina	>16 R
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>4 R
CAZ/AVI	>64 R
MER/VBR	ND
IMI/REL	ND
FDC	128 R

AOUC Lab + Tascini - unpublished results

Fenotipo riscontrato:

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	128 R
Ceftriaxone	>4 R
Ceftazidime	>64 R
Cefepime	>16 R
Meropenem	>16 R
Ceftol/Tazob	>32 R
Fosfomicina	16 S
Amikacina	>16 R
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	<= 0.5 S
CAZ/AVI	>64 R
MER/VBR	>32 R
IMI/REL	>32 R
FDC	128 R

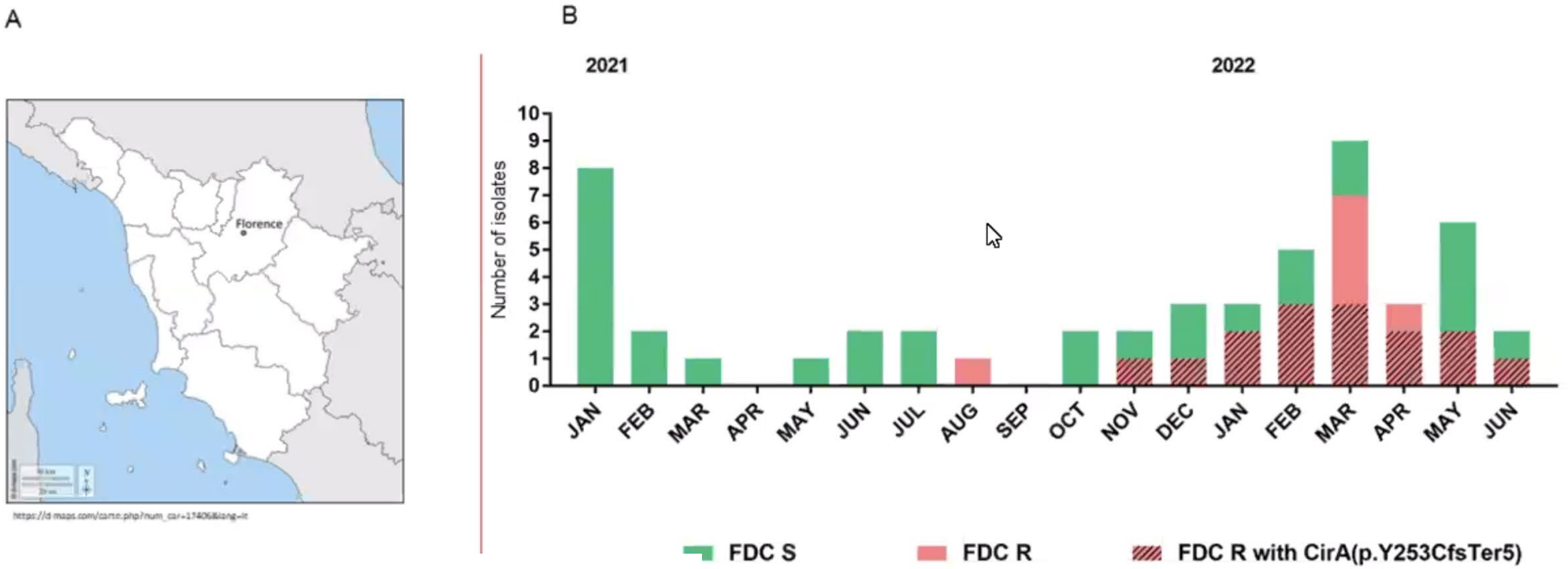
AOUC Lab - unpublished results

Cortesia Prof Tommaso Giani

Ceppo sensibile alla tigeciclina

K. pneumoniae NDM+ resistenti al cefiderocol

Cortesia Prof Tommaso Giani



RAPID COMMUNICATIONS

Nosocomial outbreak by NDM-1-producing *Klebsiella pneumoniae* highly resistant to cefiderocol, Florence, Italy, August 2021 to June 2022

Marco Coppi[1,2], Alberto Antonelli[1,2], Claudia Niccolai[1], Andrea Bartolini[1], Laura Bartolini[2], Maddalena Grazzini[3], Elisabetta Mantengoli[3,4], Alberto Farese[4], Filippo Pieralli[5], Maria Teresa Mechi[3], Vincenzo Di Pilato[2,6], Tommaso Giani[1,2], Gian Maria Rossolini[1,2]

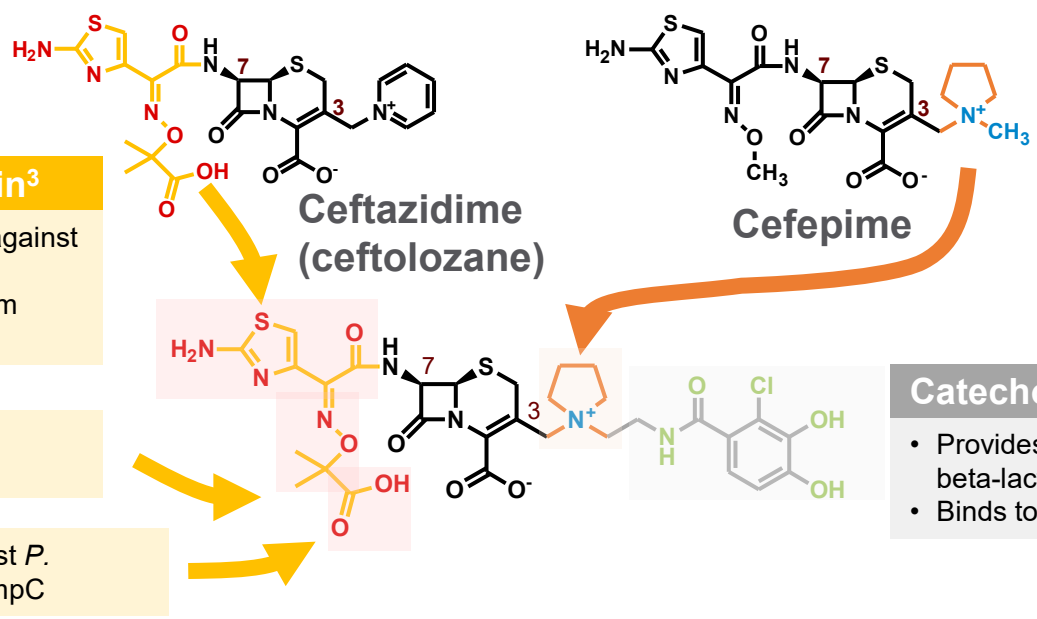
1. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
2. Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy
3. Hospital Infection Prevention and Control Unit, Florence Careggi University Hospital, Florence, Italy
4. Infectious and Tropical Diseases Unit, Florence Careggi University Hospital, Florence, Italy
5. Subintensive Care Unit, Florence Careggi University Hospital, Florence, Italy
6. Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy

Correspondence: Gian Maria Rossolini (gianmaria.rossolini@unifi.it)

Coppi M.- manuscript in preparation

Unique structure of cefiderocol

Cefiderocol incorporates features of other cephalosporin antibiotics, but is distinct from other beta-lactam antibiotics due to its beta-lactamase resistance and iron chelation[1]



R2 C-7 side chain[3]

- Enhances stability against beta-lactamases
- Activity against Gram Negatives

- Stability against penicillinases

- Stability against *P. aeruginosa* AmpC

R1 C-3 side chain[2]

- Facilitates penetration of the Gram-negative outer membrane
- Confers low affinity for beta-lactamases
- Stability to AmpC

Catechol moiety

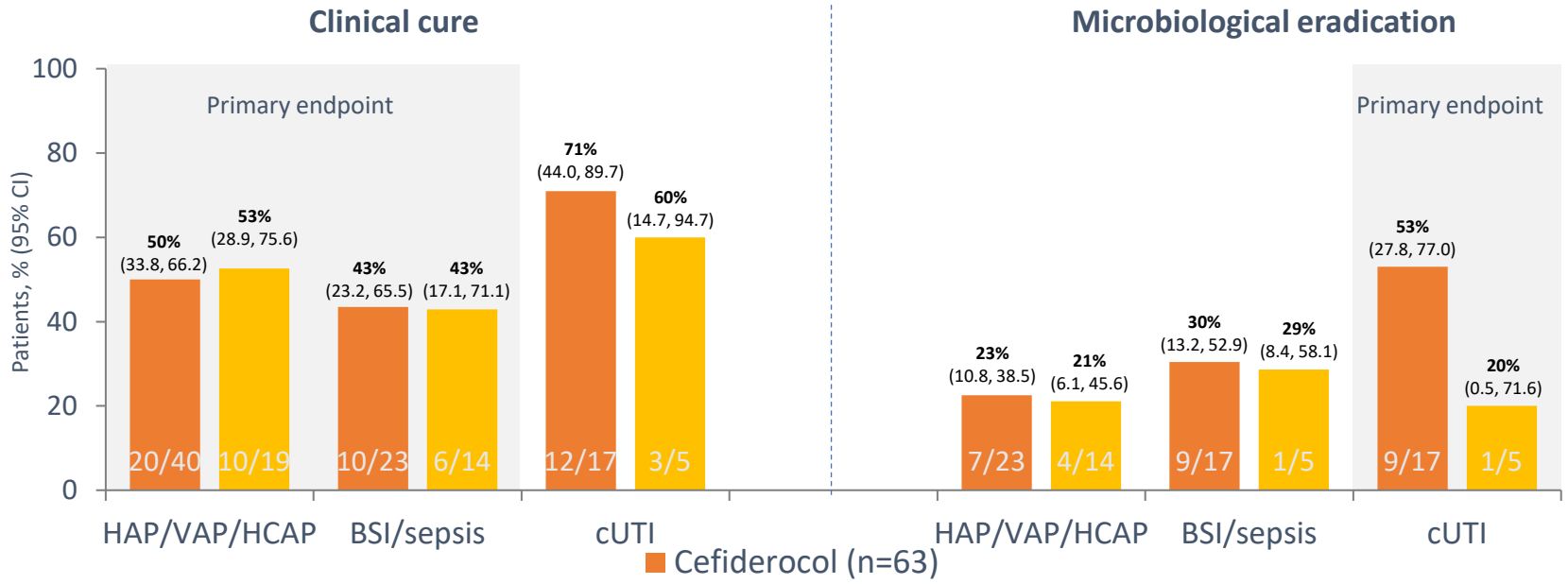
- Provides additional stability against beta-lactamases[4]
- Binds to free iron[5]

Ito A, et al. *Antimicrob Agents Chemother* 2016;60:7396–40; 2. Hancock RE, et al. *J Chemother* 1996;8 Suppl 2:31–6;
3. Craig WA et al. *Principles and Practice of Infectious Diseases (Eighth Edition)* 2015; Chapter 21:278–292;
4. Ito-Horiyama T, et al. *Antimicrob Agents Chemother* 2016;60:4384–6; 5. Ito A, et al. *J Antimicrob Chemother* 2016;71:670–7.
6. Zhanel et alDrugs 2014

Outcomes at TOC by infection site

CR Micro-ITT population (N=118); HAP/VAP/HCAP n=59, BSI/sepsis n=37, cUTI n=23

Clinical cure and microbiological eradication were numerically higher with cefiderocol in cUTI, but similar in both treatment arms for HAP/VAP/HCAP and BSI/sepsis



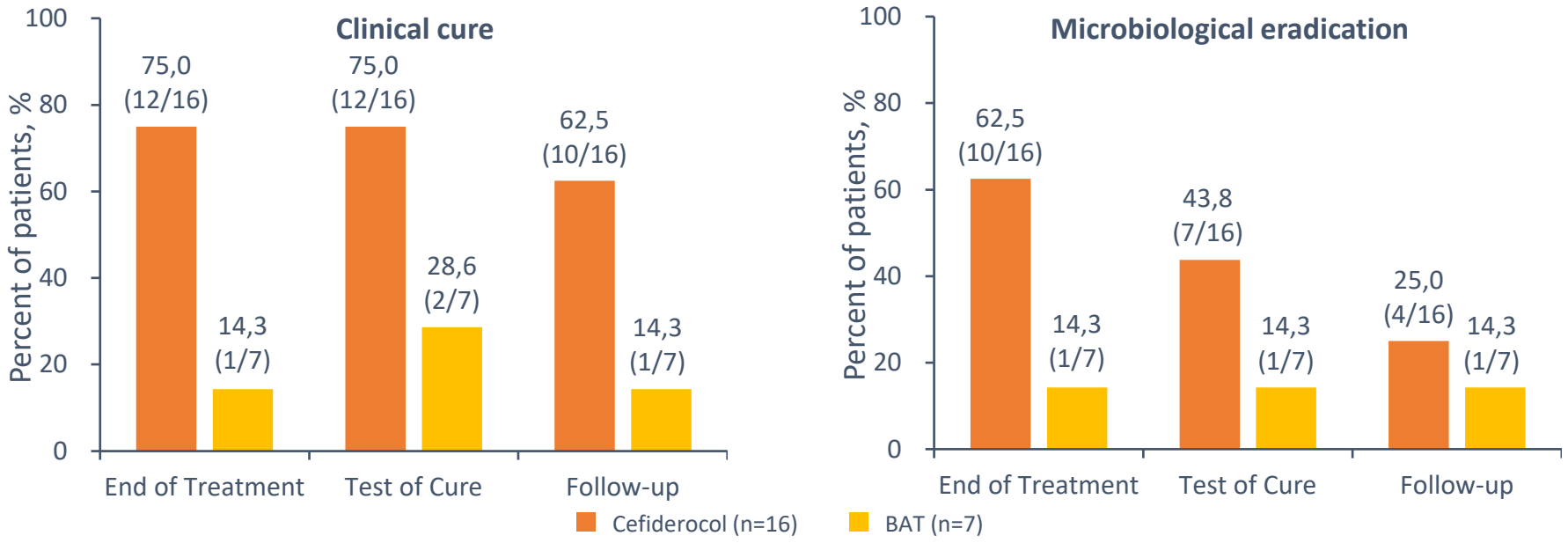
BAT, best available therapy; BSI, bloodstream infection; CI, confidence interval; CR, carbapenem-resistant; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; Micro-ITT, microbiological intent-to-treat; TOC, test of cure; VAP, ventilator-associated pneumonia

Bassetti M, et al. *Lancet Infect Dis.* 2020.

Efficacy outcomes in metallo-β-lactamase-producers

(CR Micro-ITT Population)

At all time points, clinical cure and microbiological eradication were higher in the cefiderocol arm compared with BAT for difficult to treat pathogens producing metallo-β-lactamases such as VIM and IMP



Bassetti M, et al. *Lancet Infect Dis.* 2020.

All-cause mortality to EOS

Safety population (N=150)

No additional patients in BAT died after Day 28 to EOS, while nine additional deaths occurred in the cefiderocol arm

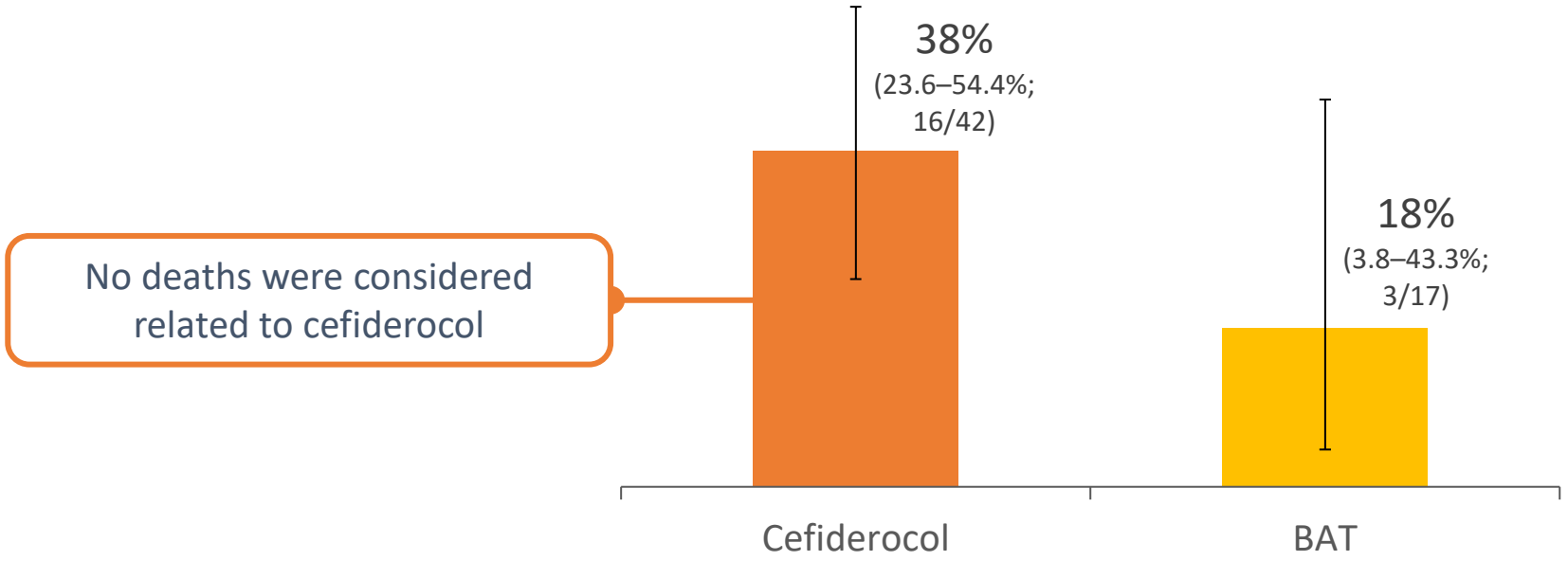
ACM, n (%)	Cefiderocol (n=101)	BAT (n=49)
Day 14	19 (18.8)	6 (12.2)
Day 28	25 (24.8)	9 (18.4)
EOS	34 (33.7)	9 (18.4)

ACM, all-cause mortality; BAT, best available therapy; EOS, end of study; EOT, end of treatment
Bassetti M, et al. *Lancet Infect Dis.* 2020.

Patients with *Acinetobacter* spp. infections treated with cefiderocol had higher mortality than those treated with BAT (CREDIBLE-CR)

Safety population

Day 28 all-cause mortality, % (95% CI; n/N')



No mortality imbalance was observed in monomicrobial *P. aeruginosa* or *K. pneumoniae* infections; however, a mortality difference was seen in patients with *Acinetobacter* spp. co-infection

CI, confidence interval; BAT, best available therapy
Bassetti M, et al. *Lancet Infect Dis* 2020;21:226–40.

CREDIBLE-CR: all-cause mortality at the end of study by most frequent baseline pathogen in the safety population (N=150)

	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

- For patients with *Acinetobacter* spp infections, moderate or severe renal dysfunction (33% [14 of 42] and 18% [three of 17]), ICU at randomisation (81% [34 of 42] and 47% [eight of 17]), ongoing shock (19% [eight of 42] and 6% [one of 17]), or shock within 31 days before randomisation (26% [11 of 42] and 6% [one of 17]) occurred more frequently at baseline in the cefiderocol group than in the best available therapy group,
- In patients without *Acinetobacter* spp infection, there were no differences in mortality rates for any of the variables between the cefiderocol and best available therapy groups

. *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).
Bassetti et al Lancet Infect Dis 2020

A higher proportion of patients with *Acinetobacter* infection were very severely ill at randomisation in the cefiderocol arm compared with BAT (CREDIBLE-CR)

Safety population

Parameter	Cefiderocol n=42	BAT n=17
Age		
Median (range), years	69 (23–91)	62 (19–83)
≥65 years, n (%)	26 (62)	7 (41)
Clinical diagnosis, n (%)		
NP	29 (69)	10 (59)
BSI/Sepsis	12 (29)	7 (41)
cUTI	1 (2)	0
Severity, n (%)		
Mild	2 (5%)	2 (12%)
Moderate	17 (40%)	8 (47%)
Severe	23 (55%)	7 (41%)
Total APACHE II score		
Median	17	15
≥16, n (%)	24 (57)	8 (47)
Median SOFA score	6	6
Median CPIS score	5	5
Creatinine clearance		
Median, mL/min	68.6	84.6
Grading group ≤50 mL/min, n (%)	14 (33)	3 (18)
Treatment failure to prior therapy, n (%)	27 (64)	13 (76)
Shock at screening or <1 month prior to randomisation, n (%)	11 (26)	1 (6)
ICU at randomisation	34 (81)	8 (47)

A higher proportion of patients had APACHE II score ≥16 at randomisation in the cefiderocol arm vs BAT

Median APACHE II score was higher in the cefiderocol arm vs BAT

A higher proportion of patients had prior shock and/or were in ICU at randomisation in the cefiderocol arm vs BAT

APACHE, Acute Physiology and Chronic Health Evaluation; BAT, best available therapy; BSI, bloodstream infection; CPIS, clinical pulmonary infection score; cUTI, complicated urinary tract infection; ICU, intensive care unit; NP, nosocomial pneumonia; SOFA, sequential organ failure assessment

Bassetti M, et al. *Lancet Infect Dis* 2020;21:226–40.

Baseline drug regimens (

CR Micro-ITT population (N=118)

There was an imbalance in treatment regimens: cefiderocol included 82.5% (66/80) monotherapy, while BAT was 28.9% (11/38) monotherapy (colistin, amikacin, ceftazidime/avibactam, doripenem, fosfomycin or gentamicin)

Study drug regimen, n (%)	Cefiderocol(n =80)
Cefiderocol	66 (82.5)
Cefiderocol + adjunctive therapy	14 (17.5)
Cefiderocol	66 (82.5)
Cefiderocol, tigecycline	4 (5.0)
Cefiderocol, fosfomycin	2 (2.5)
Cefiderocol, amikacin	1 (1.3)
Cefiderocol, ampicillin-sulbactam	1 (1.3)
Cefiderocol, ciprofloxacin	1 (1.3)
Cefiderocol, colistin	1 (1.3)
Cefiderocol, gentamicin	1 (1.3)
Cefiderocol, gentamicin, tigecycline	1 (1.3)
Cefiderocol, levofloxacin	1 (1.3)
Cefiderocol, piperacillin-tazobactam	1 (1.3)

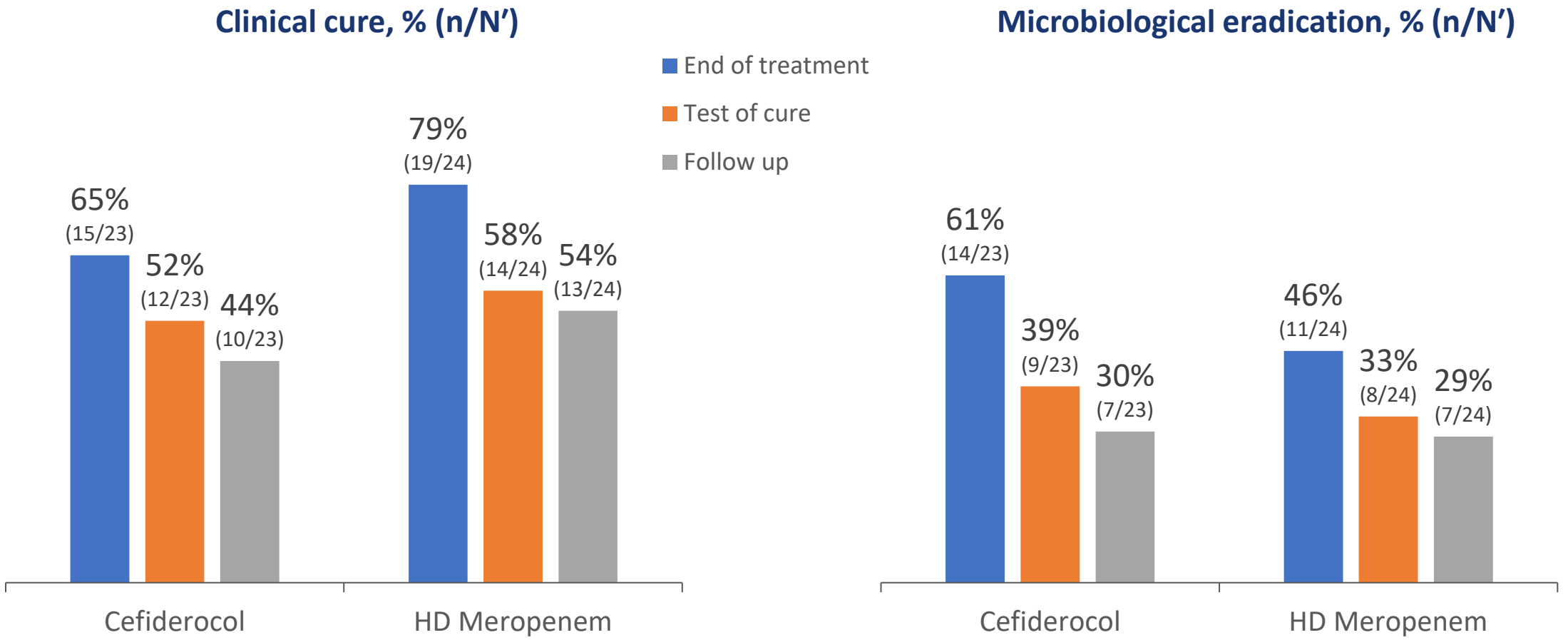
Study drug regimen, n (%)[1]	BAT (n=38)
Colistin-based regimen[a]	25 (65.8)
Non-colistin-based regimen	13 (34.2)
Colistin	6 (15.8)
Colistin, tigecycline	3 (7.9)
Colistin, ampicillin-sulbactam	2 (5.3)
Colistin, fosfomycin	2 (5.3)
Colistin, amikacin	1 (2.6)
Colistin, amikacin, levofloxacin	1 (2.6)
Colistin, cefipime	1 (2.6)
Colistin, cefipime, tigecycline	1 (2.6)
Colistin, cefoperazone-sulbactam	1 (2.6)
Colistin, ceftolozane-tazobactam	1 (2.6)
Colistin, ertapenem	1 (2.6)
Colistin, imipenem-cilastin	1 (2.6)
Colistin, meropenem	1 (2.6)
Colistin, piperacillin	1 (2.6)
Colistin, piperacillin-tazobactam	1 (2.6)
Polymyxin B, ampicillin-sulbactam, fosfomycin	1 (2.6)

Study drug regimen, n (%)[1]	BAT (n=38)
Amikacin	1 (2.6)
Amikacin, ceftazidime-avibactam	1 (2.6)
Amikacin, doripenem	1 (2.6)
Ceftazidime, ciprofloxacin	1 (2.6)
Ceftazidime-avibactam	1 (2.6)
Ceftazidime-avibactam, gentamicin	1 (2.6)
Ciprofloxacin, trimethoprim-sulfamethoxazole	1 (2.6)
Doripenem	1 (2.6)
Doripenem, gentamicin	1 (2.6)
Doripenem, tobramycin	1 (2.6)
Fosfomycin	1 (2.6)
Gentamicin	1 (2.6)
Imipenem-cilastin, tigecycline	1 (2.6)

[a]Includes one Polymyxin B-based combination
BAT, best available therapy; CR, carbapenem-resistant; Micro-ITT, microbiological intent-to-treat
Bassetti M, et al. *Lancet Infect Dis.* 2020.

Cefiderocol efficacy was comparable to high-dose meropenem against *A. baumannii* in patients with pneumonia (APEKS-NP)

mITT population



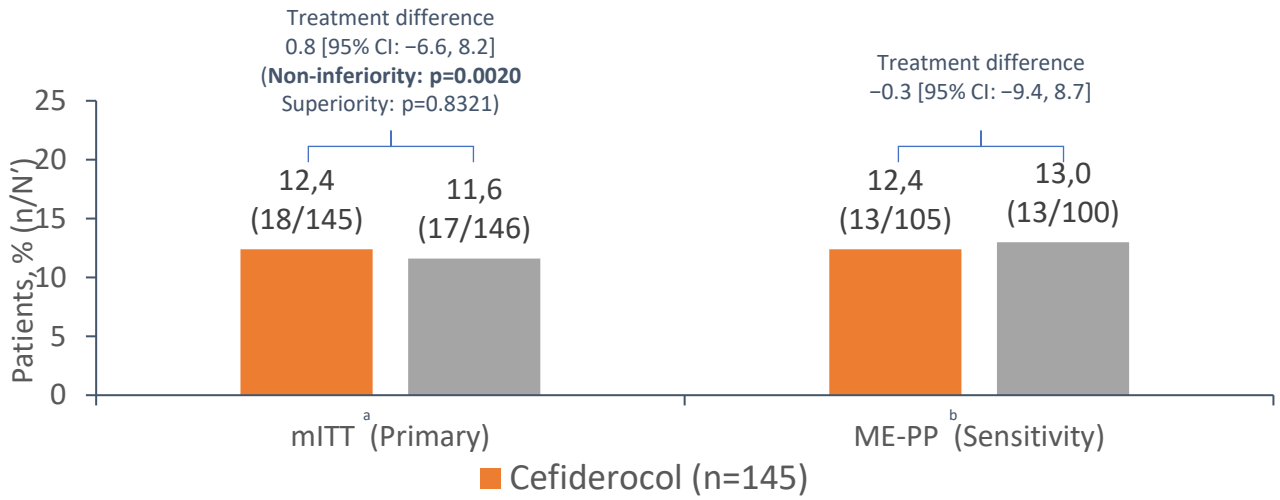
HD, high dose; mITT, modified intent-to-treat
Wunderink RG, et al. *Lancet Infect Dis* 2020;21:213–25.

Primary endpoint: Day 14 all-cause mortality

The Day 14 all-cause mortality non-inferiority margin of 12.5% was met

Results also met the standard FDA guidance non-inferiority margin of 10% (not prespecified for this study)

- The 12.5% non-inferiority margin required fewer patients than the conventional FDA Day 28 10% non-inferiority margin (~300 vs ~540)



[a]All treated patients except those with Gram-positive pathogens only identified at baseline; [b]Baseline pathogen was either Gram-negative or mixed pathogen (Gram-negative + Gram-positive pathogen)
CI, confidence interval; CR, carbapenem-resistant; CS, carbapenem-sensitive; FDA, US Food and Drug Administration; HD, high dose;
ME-PP, microbiologically evaluable per-protocol population; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat population
Wunderink RG, et al. Lancet Infect Dis. 2020;

TABLE 4. PRE- AND POST-CEFIDEROCOL MIC CHANGES, RESISTANCE CRITERIA, IDENTIFIED β-LACTAMASES, AND POST-TREATMENT WHOLE-GENOME SEQUENCING-IDENTIFIED MUTATIONS IN MULTILOCUS SEQUENCE TYPING-CONFIRMED ISOGENIC ISOLATES WITH A ≥4-FOLD POST-TREATMENT INCREASE IN MIC: DATA FROM CREDIBLE-CR

				Cefiderocol MIC retests				*Resistance according to established criteria, based on median MIC*						
Species and site of infection	*Time point for MIC increase*	*Original MIC (μg/mL)*	*Fold of baseline MIC*	*MIC #2 (μg/mL)*	*MIC #3 (μg/mL)*	*Median MIC (μg/mL)*	*Fold of median baseline MIC*	*CLSI S/I/R ≤4/8/≥16*	*FDA S/I/R ≤4/8/≥16 ENT & ≤1/2/≥4 NF*	*EUCAST S/R ≤2/>2 (ENT, PA)*	*fT >4× MIC (%)*	*C_{min} (μg/mL)*	*β-Lactamase identified at baseline and post-treatment (WGS)*	*Post-treatment mutation identified (WGS)*
Acinetobacter baumannii Lung (VAP)	Baseline	0.25		1	1	1		S	S	S	NA	NA	ADC-25-like[d]; OXA-23; OXA-66[a]; TEM-1D	
	Day 14	4	16×	2	4	4	4×	S	R	R			ADC-25-like[d]; OXA-23; OXA-66[a]; TEM-1D	PBP3 (H370Y)
A. baumannii Lung (VAP)	Baseline	1		1	2	1		S	S	S	100	26.4	ADC-25-like[d]; OXA-23; OXA-69[d]	
	EOT	8	8×	64	64	64	64×	R	R	R			ADC-25-like[d]; OXA-23-like; OXA-69[d]	OXA-23 (N85I and P225S)
A. baumannii Lung (VAP)[a]	Baseline	1		0.25	1	1		S	S	S	100	26.7	ADC-25-like[d]; OXA-23; OXA-71[a]	
	Unscheduled (Day 10)	8	8×	8	8	8	8×	I	R	R			ADC-25-like[d]; OXA-23; OXA-71[a]	Not identified
K. pneumoniae Lung (VAP)	Baseline	0.06		≤0.03	0.06	0.06		S	S	S	100	8.24	SHV-61-like[e]	
	Unscheduled (Day 8)	0.5	8×	1	1	1	16×	S	S	S			SHV-61-like[e] partial CDS; TEM-18	Not identified
K. pneumoniae Lung (HAP)[b]	Baseline	0.25		0.12	0.25	0.25		S	S	S	NA	NA	KPC-2; SHV-1	
	Day 14	2	8×	4	2	2	8×	S	S	S			KPC-2; SHV-1	Not identified
Pseudomonas aeruginosa Urine (cUTI)	Baseline	0.12		0.12	0.12	0.12		S	S	S	100	7.3	OXA-847[f]; PDC-11; VIM-2	
	EA	16	128×	16	16	16	128×	R	R	R			OXA-847[f]; PDC-11; VIM-2	Not identified
***P. aeruginosa* Lung (HAP)**	**EA**	**0.25**		**0.12**	**0.12**	**0.12**		**S**	**S**	**S**	**NA**	**NA**	**OXA-488[f]; PDC-30**	

(*continued*)

J Antimicrob Chemother 2022; **77**: 1662–1669
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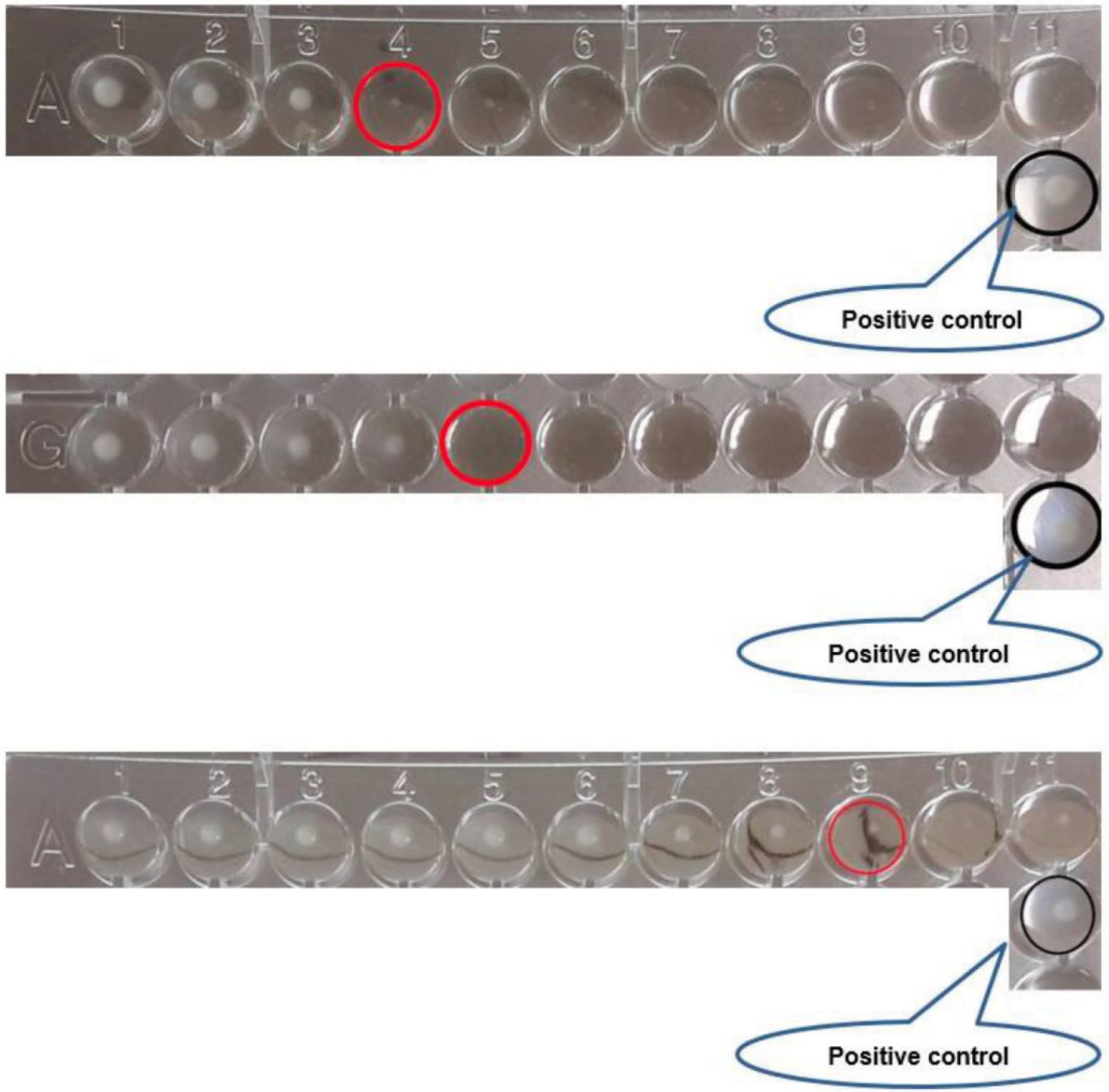
Journal of Antimicrobial Chemotherapy

Cefiderocol: EUCAST criteria for disc diffusion and broth microdilution for antimicrobial susceptibility testing

Erika Matuschek[1]*, Christopher Longshaw[2], Miki Takemura[3], Yoshinori Yamano[4] and Gunnar Kahlmeter[1]

[1]EUCAST Development Laboratory, Växjö, Sweden; [2]Infectious Diseases, Shionogi B.V., London, UK; [3]Laboratory for Drug Discovery and Disease Research, Shionogi & Co., Ltd., Osaka, Japan; [4]Research Planning Department, Shionogi & Co., Ltd., Osaka, Japan



Examples of reading cefiderocol endpoints when trailing occurs; examples from the EUCAST Reading Guide. This figure appears in

Clinical Microbiology and Infection xxx (xxxx) xxx

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Research note

Comparison of disk diffusion, MIC test strip and broth microdilution methods for cefiderocol susceptibility testing on carbapenem-resistant enterobacterales

Rémy A. Bonnin [1, 2], Cécile Emeraud [1, 2, 3], Agnès B. Jousset [1, 2, 3], Thierry Naas [1, 2, 3], Laurent Dortet [1, 2, 3, *]

[1)] *Team "Resist" UMR1184 "Immunology of Viral, Auto-Immune, Hematological and Bacterial Diseases (IMVA-HB), INSERM, Paris-Saclay University, Faculty of Medicine, Le Kremlin-Bicêtre, France*
[2)] *Associated French National Reference Center for Antibiotic Resistance: Carbapenemase-Producing Enterobacteriales, Le Kremlin-Bicêtre, France*
[3)] *Department of Bacteriology-Hygiene, Bicêtre Hospital, Assistance Publique des Hôpitaux de Paris, Le Kremlin-Bicêtre, France*

Results: Compared to reference method, CE-IVD BMD plate gave 95.0% (95% CI, 88.8–97.9) categorisation agreement (CA), 2.8% (95% CI, 0.4–14.2) very major errors (VME), and 1.6% (95% CI, 0.3–8.7) major errors (ME) with high reproducibility. MIC strip gave only 63% (95% CI, 53.2–71.8) of CA and 94.9% (95% CI, 83.1–98.6) of VME due to critical underestimation of the MICs. Disk diffusion gave 77% (95% CI, 67.9–84.2) CA with additional 8% of the isolates within the area of technical uncertainty of 18–22 mm. Prospectively, disk diffusion gave 81.7% (95% CI, 79.0–84.2) CA, 23.3% (95% CI, 15.1–34.2%)VME, and 4.9% (95% CI, 3.6–6.7) ME. Additionally, 21.3% (95% CI, 18.6–24.2) of CRE were within the area of technical uncertainty. *Discussion:* Commercial CE-IVD BMD (ThermoFisher) is accurate for cefiderocol MIC determination in difficult-to-treat Enterobacterales whereas MIC test strip (Liofilchem), that was formulated for *Pseudomonas aeruginosa* only, should be avoided. Disk diffusion might be useful for screening, but many of these CRE have to be re-tested using BMD to assess definitive categorization. **Rémy A. Bonnin, Clin Microbiol Infect 2022;■:1**

J Antimicrob Chemother 2022; **77**: 1662–1669
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Cefiderocol: EUCAST criteria for disc diffusion and broth microdilution for antimicrobial susceptibility testing

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[1]EUCAST Development Laboratory, Växjö, Sweden; [2]Infectious Diseases, Shionogi B.V., London, UK; [3]Laboratory for Drug Discovery and Disease Research, Shionogi & Co., Ltd., Osaka, Japan; [4]Research Planning Department, Shionogi & Co., Ltd., Osaka, Japan

EUCAST to correspond to the PK/PD BPs.[16,17] When using BMD as a method of AST for cefiderocol, iron-depleted-CAMHB (ID-CAMHB) media are needed to ensure MICs used for determining clinical breakpoints and PK/PD assessment are predictive of *in vivo* activity.[18] DD does not require iron-depleted media and standard Mueller–Hinton agar can be used,[3,17] meaning DD is potentially a simpler, cheaper, and a more widely accessible method of AST for cefiderocol.[3]

Results: MIC and ZD distributions for cefiderocol against WT isolates were established. Cefiderocol ZD BPs were set at susceptible ≥22 mm, resistant <22 mm for Enterobacterales and *Pseudomonas aeruginosa* and ATUs were decided. For *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*, ZD cut-off values of ≥17 mm and ≥20 mm corresponded to MIC values of ≤2 and ≤0.5 mg/L, respectively. Cefiderocol ZDs for *Escherichia coli* ATCC 25922 (target 27 mm) and *P. aeruginosa* ATCC 27853 (target 26 mm) were within ±3 mm of the target values. For DD, there was no problematic variation between discs, media or laboratories.

Conclusions: DD is a robust and easy-to-perform method for cefiderocol susceptibility testing. For isolates with results in the ATU, an MIC test should be performed to confirm the results.

observed. Areas of Technical Uncertainty (ATU) were introduced to increase the robustness of the test: ATU for Enterobacterales, 18–22 mm; ATU for *P. aeruginosa*, 14–22 mm.

Expert Review of Anti-infective Therapy

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All-cause mortality rates in adults with carbapenem-resistant Gram-negative bacterial infections: a comprehensive review of pathogen-focused, prospective, randomized, interventional clinical studies

Thomas P. Lodise, Matteo Bassetti, Ricard Ferrer, Thierry Naas, Yoshihito Niki, David L. Paterson, Markus Zeitlinger & Roger Echols

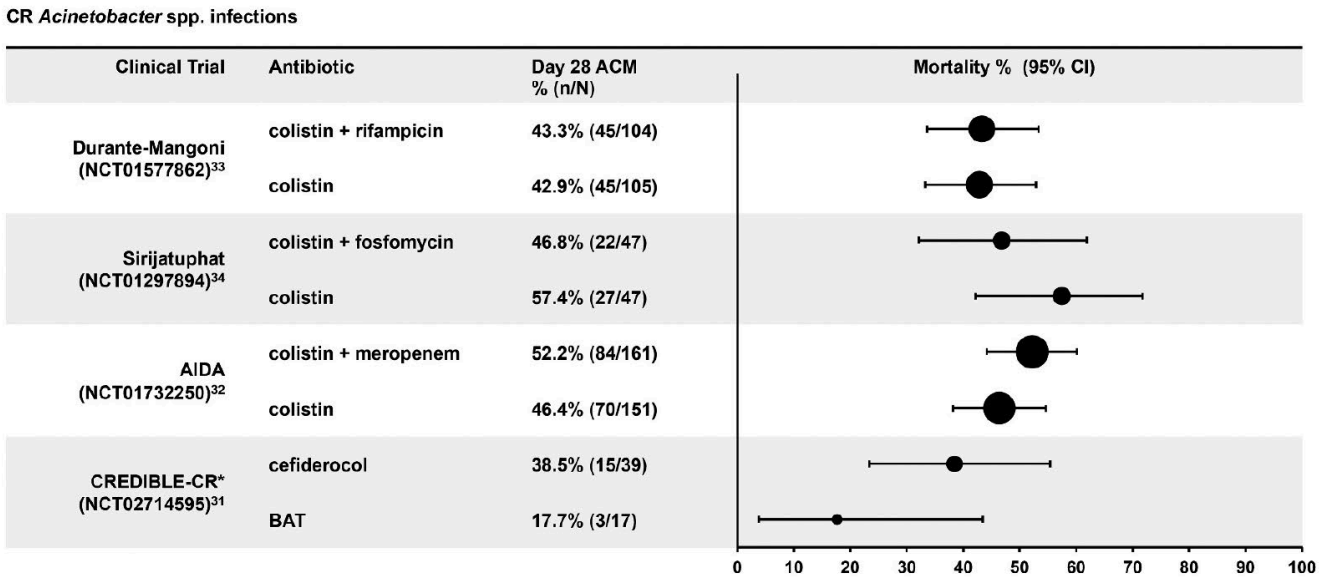

Figure 2. Day 28 all-cause mortality rates in carbapenem-resistant *Acinetobacter* spp. infections. ACM: all-cause mortality, BAT: best-available therapy, CI: confidence interval, CR: carbapenem resistant. In the CREDIBLE-CR study, patients were randomized 2:1 (cefiderocol:BAT). *Acinetobacter* spp. include: *A. baumannii; A. nosocomialis.*

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CLINICAL THERAPEUTICS

Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*

Marco Falcone,[a] Giusy Tiseo,[a] Alessandro Leonildi,[b] Leonardo Della Sala,[a] Alessandra Vecchione,[b] Simona Barnini,[b] Alessio Farcomeni,[c] Francesco Menichetti[a]

TABLE 1 Type of infection and relative treatment regimens in 47 patients with CRAB infections treated with cefiderocol-containing regimens[a]

Type of infection	Treatment regimen	
BSI N = 27 (57.4%)	Cefiderocol monotherapy	*n* = 12
	Cefiderocol + tigecycline	*n* = 10
	Cefiderocol + fosfomycin	*n* = 3
	Cefiderocol + ertapenem	*n* = 1
	Cefiderocol + ampicillin/sulbactam	*n* = 1
VAP N = 12 (25.5%)	Cefiderocol monotherapy	*n* = 2
	Cefiderocol + tigecycline	*n* = 6
	Cefiderocol + fosfomycin	*n* = 3
	Cefiderocol + meropenem-vaborbactam	*n* = 1
Other infections N = 8 (17%)	Cefiderocol monotherapy	*n* = 1
	Cefiderocol + tigecycline	*n* = 5
	Cefiderocol + fosfomycin	*n* = 2

TABLE 2 Type of infection and relative treatment regimens in 77 patients with CRAB infections treated with colistin-containing regimens[a]

Type of infection	Treatment regimen	
BSI *N* = 52 (67.5%)	Colistin-containing regimens	*N* = 52
	Colistin alone	*n* = 11
	Colistin + tigecycline	*n* = 30
	Colistin + tigecycline + meropenem	*n* = 5
	Colistin + tigecycline + rifampin	*n* = 2
	Colistin + tigecycline + fosfomycin	*n* = 1
	Colistin + meropenem + fosfomycin	*n* = 1
	Colistin + rifampin	*n* = 1
	Colistin + aminoglycosides	*n* = 1
VAP *N* = 23 (29.9%)	Colistin-containing regimens	*N* = 23
	Colistin alone	*n* = 1
	Colistin + tigecycline	*n* = 9
	Colistin + tigecycline + rifampin	*n* = 1
	Colistin + tigecycline + meropenem	*n* = 2
	Colistin + tigecycline + fosfomycin	*n* = 2
	Colistin + meropenem + fosfomycin	*n* = 1
	Colistin + tigecycline + ampicillin/sulbactam	*n* = 6
	Colistin + ampicillin/sulbactam	*n* = 1
Other infections	Colistin-containing regimens	*N* = 2
N = 2 (2.6%)	Colistin alone	*n* = 1
	Colistin + tigecycline	*n* = 1

[a]BSI, bloodstream infection; CRAB, carbapenem-resistant *A. baumannii*; VAP, ventilator-associated pneumonia; other infections were 1 urinary tract infection and 1 surgical site infection.

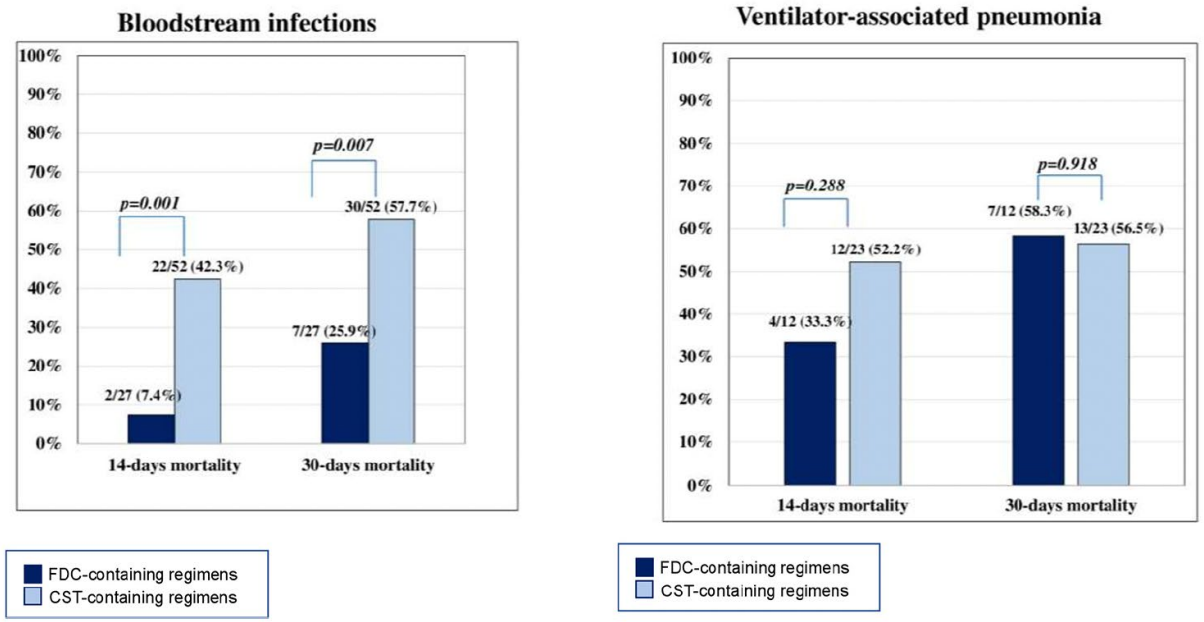
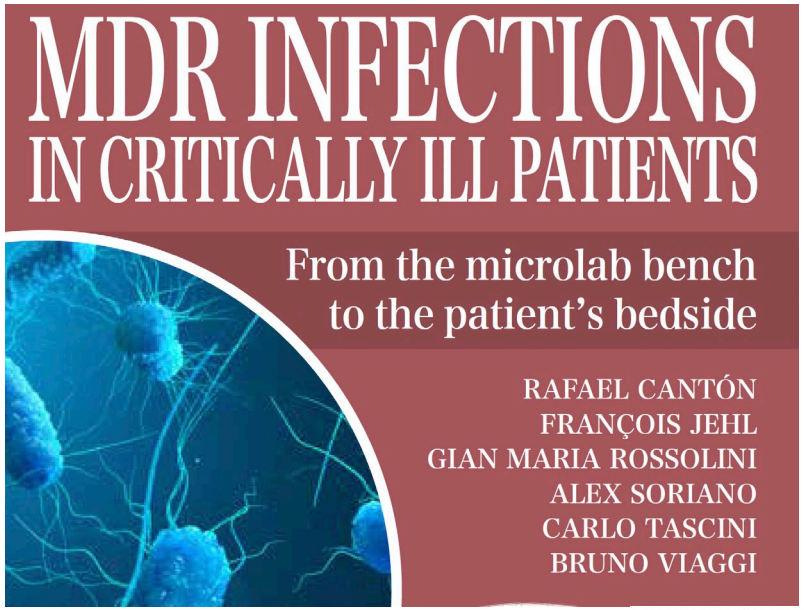
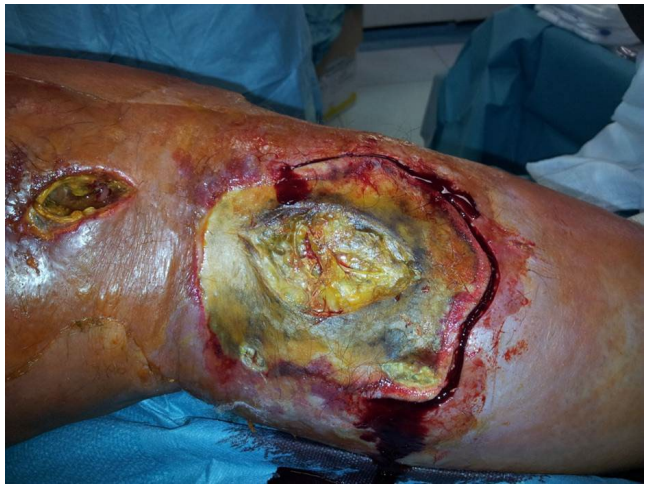
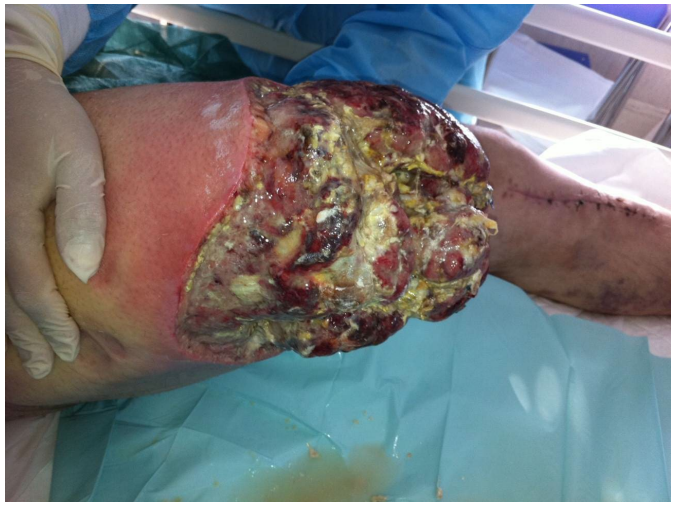


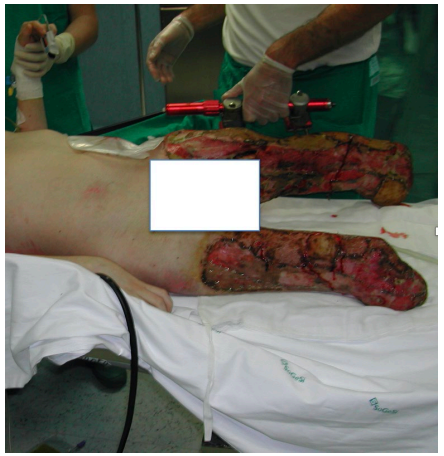
FIG 2 Fourteen- and 30-days mortality in patients with bloodstream infection (BSI) and ventilator-associated pneumonia (VAP). FDC cefiderocol.







Cortesia Dr Giovanni Riccio



Fascite post-traumatica

virulence factors within a single species. Despite its different virulence factors, *A. baumannii* is closely correlated to *A. pittii* and *A. nosocomialis* and is phenotypically indistinguishable from these species. Strains from the Acb complex are furthermore often confused with *Acinetobacter lwoffii* and *Acinetobacter radioresistant* strains that are typically considered as skin colonizers (that may, however, cause infections in immuno-compromised patients). *Acinetobacter calcoaceticus* and *A. johnsonii*, on the other hand, are considered to be environmental *Acinetobacter* species.

Colistina: mai da sola, *Enterobacterales*

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Chloramphenicol[1]	8	8		30	17	17	
Colistin[2]	(2)[3]	(2)[3]			Note[A]	Note[A]	
Daptomycin	-	-			-	-	
Fosfomycin iv	32[4]	32[4]		200[B]	21[C,D]	21[C,D]	
Fosfomycin oral (uncomplicated UTI only), *E. coli*	8[4]	8[4]		200[B]	24[D]	24[D]	
Fusidic acid	-	-			-	-	
Lefamulin	-	-			-	-	
Metronidazole	-	-			-	-	
Nitrofurantoin (uncomplicated UTI only), *E. coli*	64	64		100	11	11	
Nitroxoline (uncomplicated UTI only), *E. coli*	16	16		30	15	15	
Rifampicin	-	-			-	-	
Spectinomycin	-	-			-	-	
Trimethoprim (uncomplicated UTI only)	4	4		5	15	15	
Trimethoprim-sulfamethoxazole[5]	2	4		1.25-23.75	14	11	

Notes

Numbered notes relate to general comments and/or MIC breakpoints.
Lettered notes relate to the disk diffusion method.

1. The clinical efficacy of chloramphenicol in meningitis has been questioned and breakpoints are currently under rev
For chloramphenicol treatment in meningitis, see table of dosages.
2. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with b
susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 1
(*mcr-1* positive).
3. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/.
4. Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems.
5. Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.

A. Use an MIC method (broth microdilution only).
B. Fosfomycin 200 µg disks must contain 50 µg glucose-6-phosphate.
C. Zone diameter breakpoints apply to *E. coli* only. For other *Enterobacterales*, use an MIC method.
D. Ignore isolated colonies within the inhibition zone (**see pictures below**).

Tra parentesi, terapia di combinazione

Evaluation of the activities of two-drug combinations of rifampicin, polymyxin B and ampicillin/sulbactam against *Acinetobacter baumannii*

J Antimicrob Chemother 1998; **42:** 270–271

Carlo Tascini[a]*, Francesco Menichetti[b], Silvia Bozza[a], Albano Del Favero[c] and Francesco Bistoni[a]

Pseudomonas spp.

EUCAST Clinical Breakpoint Tables v. 12.0, valid from 2022-01-01

Expert Rules and Intrinsic Resistance Tables

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Chloramphenicol	-	-			-	-		**1.** Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr-1* positive).
Colistin[1]	(4)[2]	(4)[2]			Note[A]	Note[A]		**2.** For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/.
Daptomycin	-	-			-	-		**3.** Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems. Infections caused by wild-type isolates (ECOFF: MIC 128 mg/L; corresponding zone diameter 12 mm using the disk potency and reading instructions for *E. coli*) have been treated with fosfomycin in combination with other agents.
Fosfomycin iv[3]	-	-			-	-		
Fosfomycin oral[3]	-	-			-	-		**A.** Use an MIC method (broth microdilution only).
Fusidic acid	-	-			-	-		
Lefamulin	-	-			-	-		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only)	-	-			-	-		
Nitroxoline (uncomplicated UTI only)	-	-			-	-		
Rifampicin	-	-			-	-		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	-	-			-	-		
Trimethoprim-sulfamethoxazole	-	-			-	-		

Acinetobacter spp.

EUCAST Clinical Breakpoint Tables v. 12.0, valid from 2022-01-01

Expert Rules and Intrinsic Resistance Tables

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Chloramphenicol	-	-			-	-		**1.** Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr-1* positive).
Colistin[1]	(2)[2]	(2)[2]			Note[A]	Note[A]		**2.** For information on how to use breakpoints in brackets, see hhttps://www.eucast.org/eucastguidancedocuments/.
Daptomycin	-	-			-	-		**3.** Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.
Fosfomycin iv	-	-			-	-		
Fosfomycin oral	-	-			-	-		**A.** Use an MIC method (broth microdilution only).
Fusidic acid	-	-			-	-		
Lefamulin	-	-			-	-		
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only)	-	-			-	-		
Nitroxoline (uncomplicated UTI only)	-	-			-	-		
Rifampicin	-	-			-	-		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	-	-			-	-		
Trimethoprim-sulfamethoxazole[3]	2	4		1.25-23.75	14	11		

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlab174

JAC-Antimicrobial Resistance

Cefiderocol treatment for carbapenem-resistant *Acinetobacter baumannii* infection in the ICU during the COVID-19 pandemic: a multicentre cohort study

Renato Pascale[1], Zeno Pasquini[1], Michele Bartoletti[1], Luca Caiazzo[2], Giacomo Fornaro[1], Linda Bussini[1], Francesca Volpato[1], Elisa Marchionni[1], Matteo Rinaldi [1], Filippo Trapani[1], Chiara Temperoni[2], Paolo Gaibani [3], Simone Ambretti[3], Francesco Barchiesi[2,4], Pierluigi Viale[1] and Maddalena Giannella[1]*

Table 2. Multivariable analysis of independent risk factors for 28 day mortality adjusted for male sex, SOFA score, septic shock, steroid treatment for COVID-19, bloodstream infection and cefiderocol as the variable of interest

	HR (95% CI)	*P*
SOFA score	1.24 (1.15–1.38)	<0.001
Cefiderocol	0.64 (0.38–1.08)	0.10

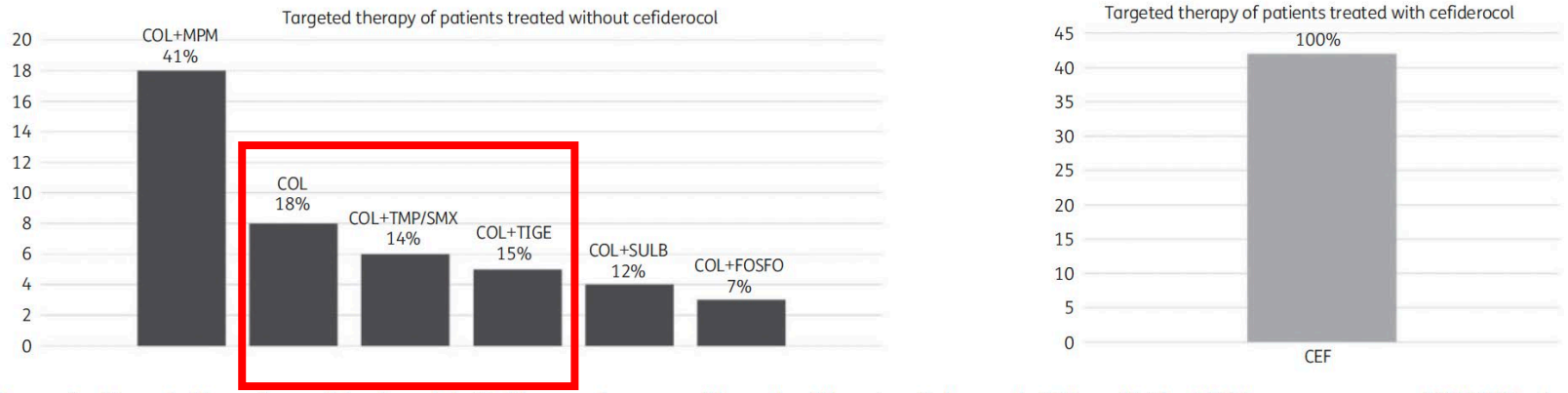
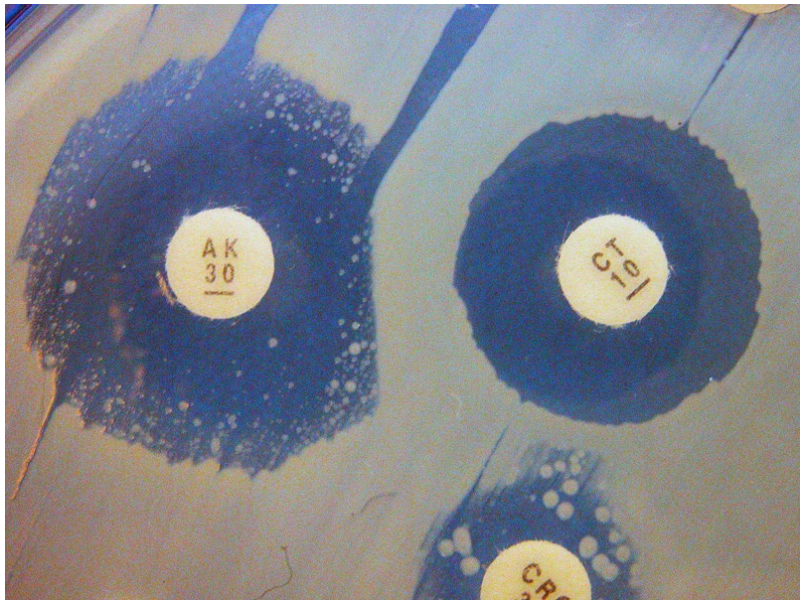
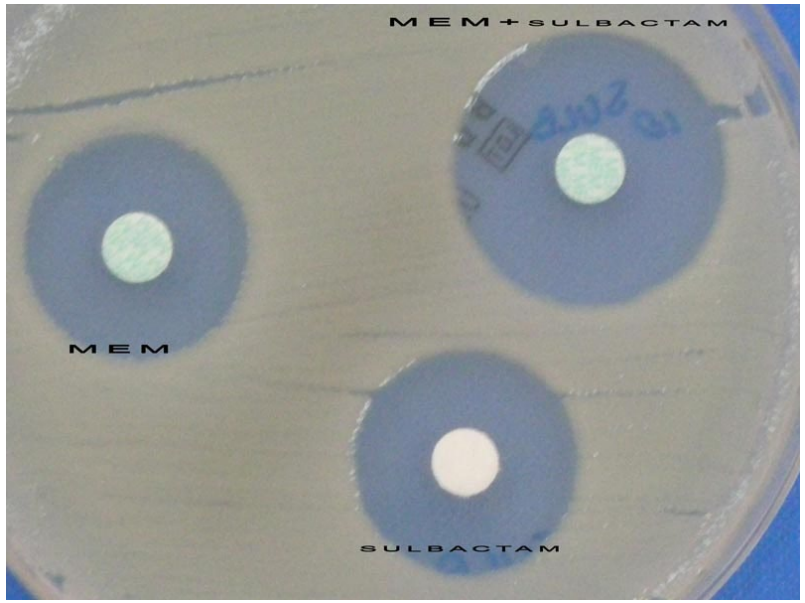


Figure 2. Description of empirical and definitive regimens with and without cefiderocol. COL, colistin; MPM, meropenem; PIP/TZB, piperacillin/tazobactam; CAZ, ceftazidime; AVI, avibactam; TIGE, tigecycline; FOSFO, fosfomycin; TMP/SMX, trimethoprim/sulfamethoxazole; SULB, sulbactam; CEF, cefiderocol.

A. baumannii: antagonismo e sinergismo





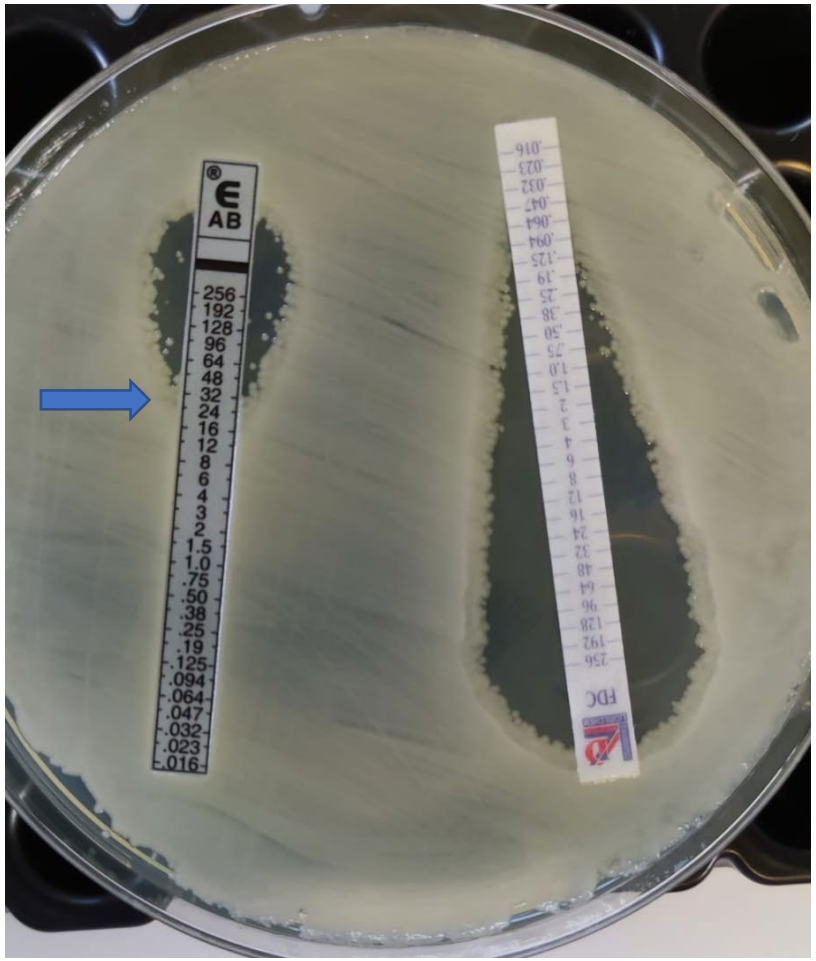
A.baumannii sustained nosocomial meningitis and ventriculitis in a 16 year old boy after major trauma

- Cefiderocol 2 g every 6 hrs, continuous infusion + ampicillin sulbactam 20 g /day, Intrathecal administration of colistin 8 mg
- Cefiderocol CSF concentration: 20 m/L,
- Cefiderocol serum concentration: 200 mg/L
- Antibiogram can provide helpful information only with MICs for cefiderocol and colistin
- Ampicillin/sulbactam MICs?

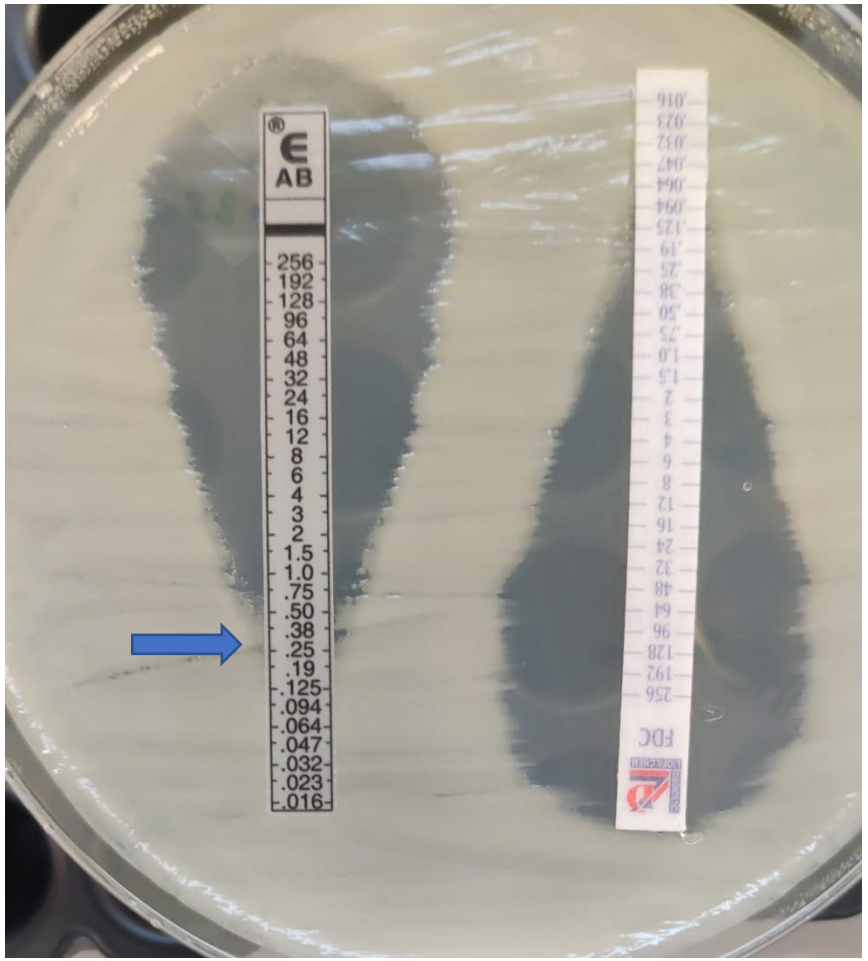
ANTIBIOTICI	MIC mg/l
Imipenem	>8 R
Meropenem	>8 R
Amikacina	>16 R
Gentamicina	>4 R
Trimetoprim/ sulfam	>4 R
Levofloxacina	>2 R
Colistina	1 S

Courtesy of Dr Gambardella

Acinetobacter



MIC alone



MIC in combination

Clinical evidence supporting cefiderol for serious *Acinetobacter baumannii* infections

Matteo Bassetti[a,b], *Antonio Vena*[a,b], *Nadia Castaldo*[c], *Daniele Roberto Giacobbe*[a,b], *Maddalena Peghin*[d] *and Paolo Antonio Grossi*[d]

Tigeciclina potrebbe non essere sinergica con FDC
Sulbactam con colistina sinergico perché arriva meglio al target
Sulbactam e FDC per inibizione di PBP (1 e 3)

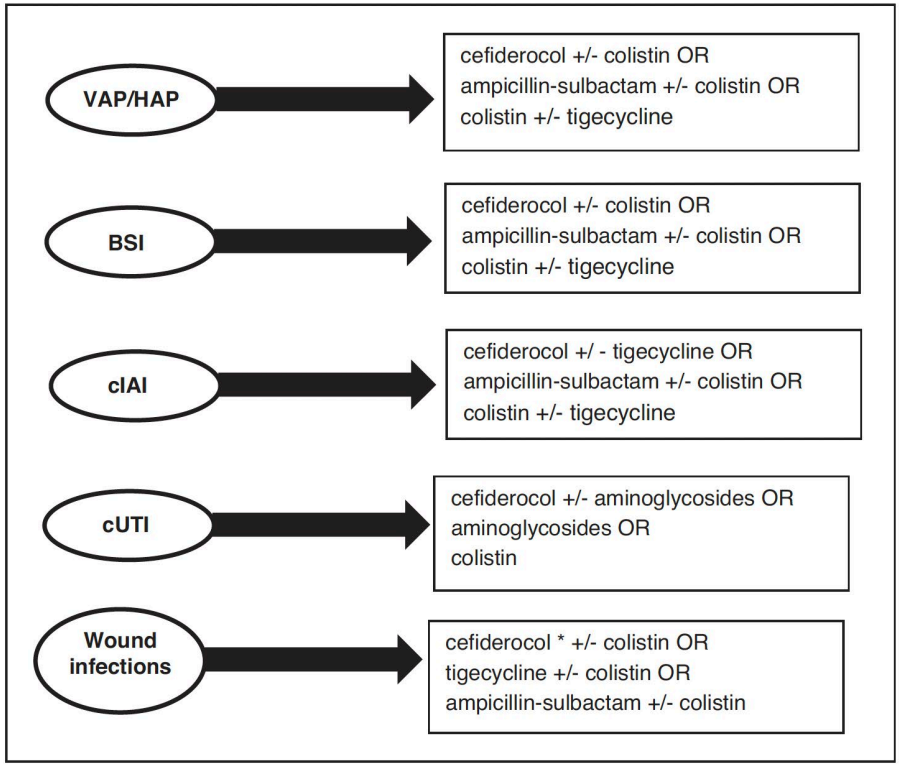


FIGURE 1. Suggested targeted treatment of carbapenem-resistant- *A. baumannii* infections. Recommended dosages and infusion for patients without renal adjustment. Ampicillin-sulbactam: 9 g of sulbactam: 6 g ampicillin/3 g sulbactam q8 h IV over 4 h. Aminoglicosides: gentamicin 3–5 mg/kg q24 h IV or amikacin 15–20 mg/kg q24 h IV. Cefiderocol: 2 g q8 h IV over 3 h. Colistin: loading dose 9 MU followed by maintenance doses with 4.5 MU q12 h. Tigecycline: loading dose 200 mg in h followed by maintenance dose 100 mg q12 h. BSI, bloodstream infections; cIAI complicated intra-abdominal infections; cUTI complicated urinary tract infections HAP Hospital acquired pneumonia; VAP ventilator associated pneumonia; ^ poor activity of cefiderocol against anaerobes: consider anaerobes coverage in association * poor activity of cefiderocol against aerobic Gram-positive organisms: consider Gram-positives coverage in association.

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Evidence for Efficacy of Cefiderocol against OXA-48-Containing Isolates from the APEKS-NP and CREDIBLE-CR Trials

Christopher Longshaw,[a] Echols Roger,[b] Anne Santerre Henriksen,[c] Takamichi Baba,[d] Sean Nguyen,[e] Yoshinori Yamano[d]

TABLE 1 Summary of CREDIBLE-CR and APEKS-NP database results for *Klebsiella pneumoniae*

Clinical study	Cefiderocol MIC (μg/mL)	Meropenem MIC (μg/mL)	Site of infection[a]	Country	Clinical outcome at TOC	Beta-lactamase profile[b]
CREDIBLE-CR	2	4	BSI/sepsis	Spain	Clinical failure	CTX-M-15; SHV-OSBL; TEM-OSBL; **OXA-48**
	4	>64	cUTI	Turkey	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; **OXA-48; NDM-1**
	0.12	32	cUTI	Turkey	Clinical cure	CTX-M-9-group; SHV-OSBL; TEM-OSBL; **OXA-48**
	1	16	cUTI	Turkey	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; **OXA-232**
	1	8	cUTI	Turkey	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; **OXA-48**
	4	>64	cUTI	Korea	Indeterminate	CTX-M-55; SHV-OSBL; **OXA-232; NDM-1**
	1	>64	BSI/sepsis	Thailand	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; **OXA-232; NDM-1**
APEKS-NP	2	64	RTI	Ukraine	Clinical cure	CTX-M-1-TYPE; SHV-OSBL; TEM-OSBL; **OXA-48**
	1	64	RTI	Russia	Clinical cure	CTX-M-15; SHV-OSBL; **OXA-48**
	0.5	32	RTI	Georgia	Indeterminate	CTX-M-15; SHV-OSBL; TEM-OSBL; **OXA-48**

[a]BSI, bloodstream infection; cUTI, complicated urinary tract infection; RTI, respiratory tract infection.
[b]Beta-lactamases in bold type are carbapenemases.

Conclusioni

- Cefiderocol farmaco rescue per Metallo enzimi sia negli *Enterobacterales* e *P. aeruginosa*; attenzione nelle NDM
- Alternativa a Ceftazidime/avibactam nell'OXA-48: epidemiologia del nord-est
- Farmaco rescue per *Acinetobacter*, da solo? In compagnia, con chi? La mia risposta doppio beta lattamico……. e colistina!!!!!