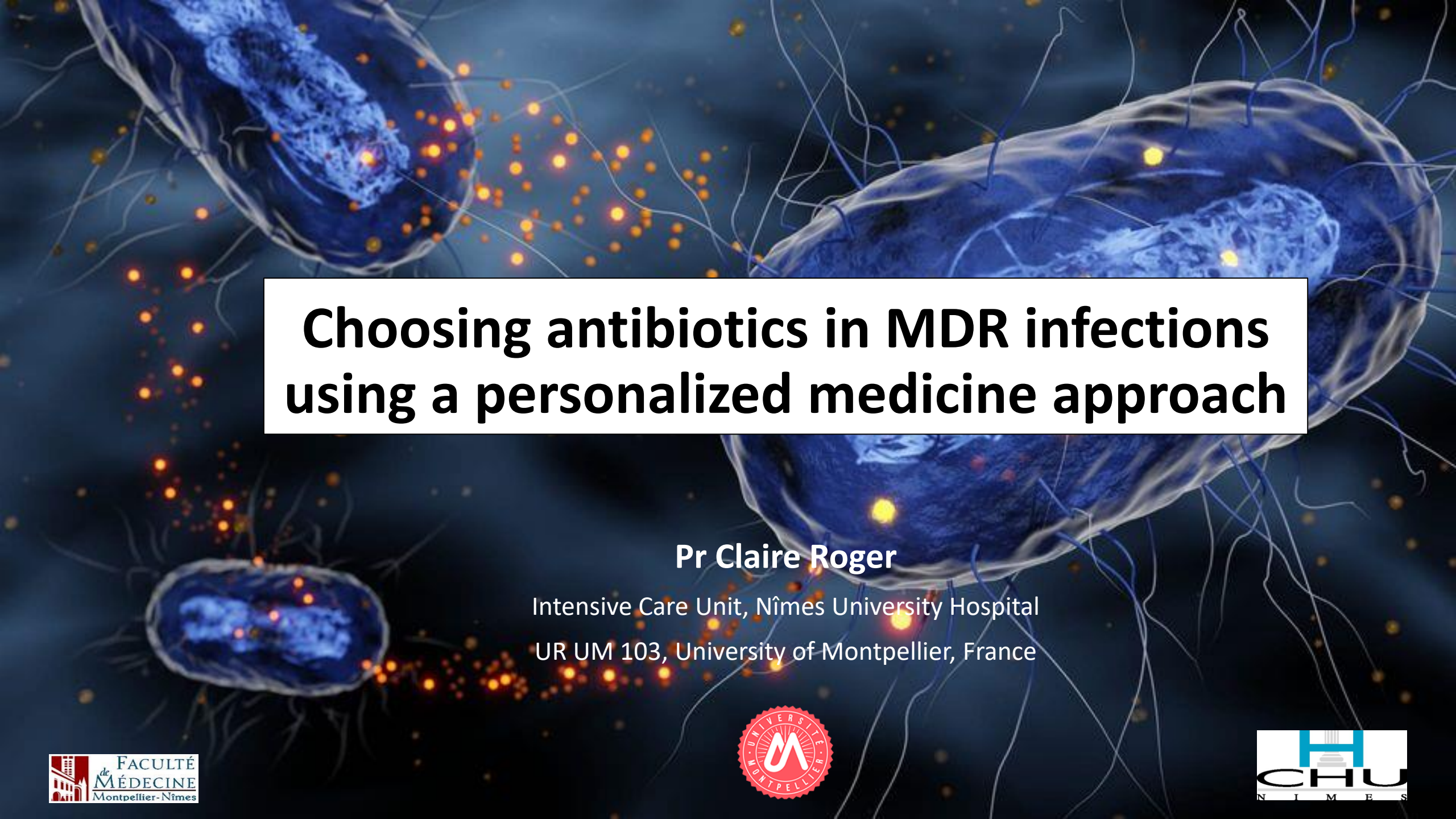

Choosing antibiotics in MDR infections using a personalized medicine approach

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Disclosures

- Speaker fees:
  - MSD
  - Pfizer
  - Shionogi
  - bioMerieux
  - Advanz pharma
- Scientific advisory board:
  - bioMerieux
  - Viatris

Risk of inappropriate empirical antimicrobial treatment in immunocompromised patients

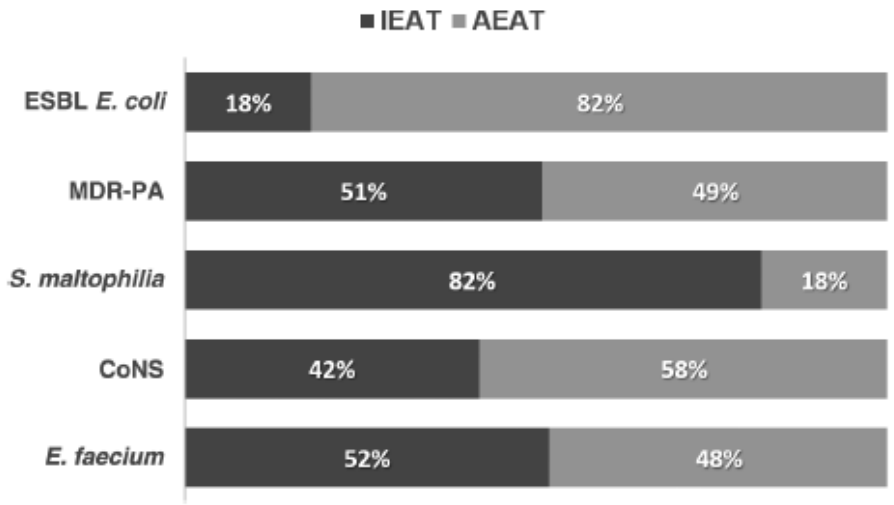
Inappropriate Empirical Antibiotic Treatment in High-risk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance

Gemma Martinez-Nadal,[1,a] Pedro Puerta-Alcalde,[2,a] Carlota Gudiol,[3,4] Celia Cardozo,[2] Adaia Albasanz-Puig,[3] Francesc Marco,[5,6] Júlia Laporte-Amargós,[3] Estela Moreno-García,[2] Eva Domingo-Doménech,[7] Mariana Chumbita,[2] José Antonio Martínez,[2,8] Alex Soriano,[2,8] Jordi Carratalà,[3,4] and Carolina Garcia-Vidal[2,8]

1615 infectious episodes

14% MDR GNB infections

24% inappropriate empirical antimicrobial therapy



High Rate of Inappropriate Antibiotics in Patients with Hematologic Malignancies and *Pseudomonas aeruginosa* Bacteremia following International Guideline Recommendations

Mariana Chumbita,[a] Pedro Puerta-Alcalde,[a] Lucrecia Yáñez,[b] Maria Angeles Cuesta,[c] Anabelle Chinea,[d] Ignacio Español-Morales,[e] Pascual Fernandez-Abellán,[f] Carlota Gudiol,[g] Pedro González-Sierra,[h] Rafael Rojas,[i] José María Sánchez-Pina,[j] Irene Sánchez Vadillo,[k] Miguel Sánchez,[k] Rosario Varela,[l] Lourdes Vázquez,[m] Manuel Guerreiro,[n] Patricia Monzo,[a] Carlos Lopera,[a] Tommaso Francesco Aiello,[a] Oliver Peyrony,[a,p] Alex Soriano,[a,o] Carolina Garcia-Vidal[a,o]

TABLE 2 Resistance profiles among bloodstream infections caused by *Pseudomonas aeruginosa* in hematologic patients with febrile neutropenia[a]

Antibiotic	N = 280 (%)
Quinolones	82 (29.3)
Piperacillin-tazobactam	61 (21.8)
Cefepime	72 (25.7)
Meropenem	70 (25)
Amikacin	41 (14.6)
MDR-*P. aeruginosa*	59 (21.1)
XDR-*P. aeruginosa*	32 (11.4)
Resistance to at least 1 of the β-lactam antibiotics recommended in the international guidelines	101 (36.1)

[a]EUCAST MIC breakpoints R> (mg/L): Ciprofloxacin: >0.5; Piperacillin-tazobactam: >16; Cefepime: >8; Meropenem: >8; Amikacin: >16. Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant.

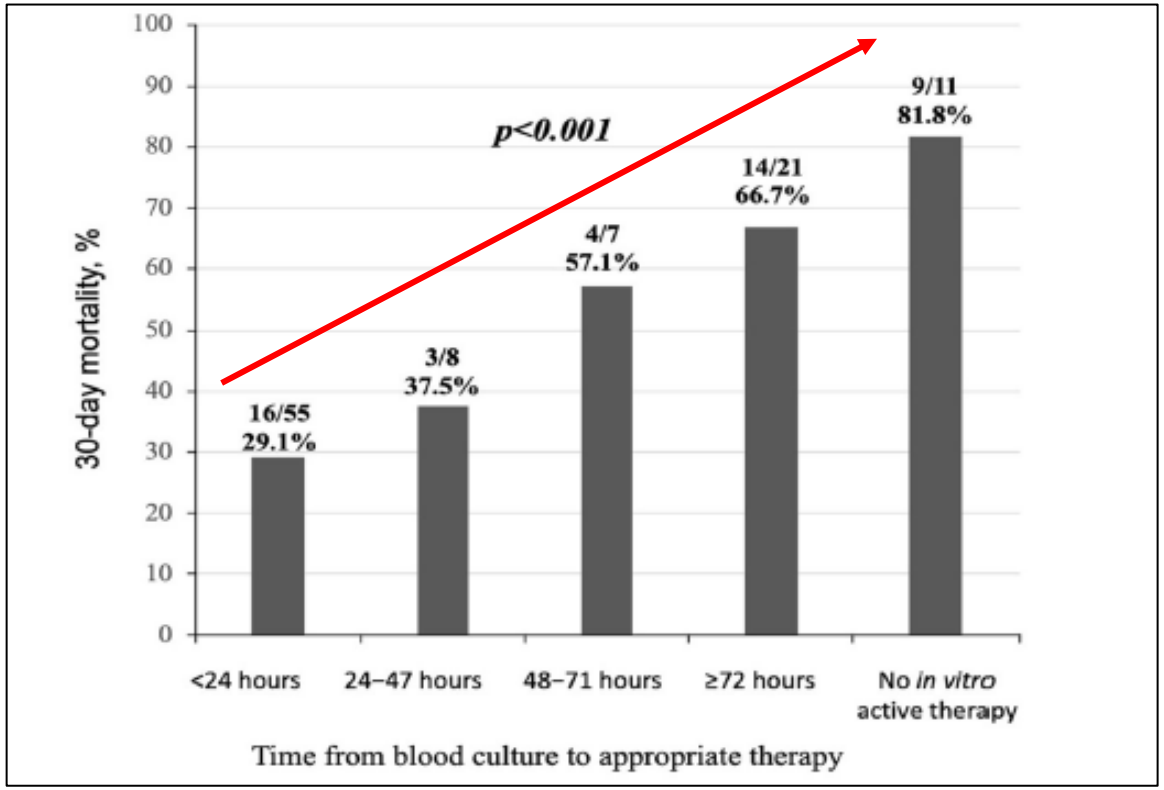
Chumbita et al. Microbiol Spectr 2023

Martinez-Nadal et al. CID 2020; 70: 1068-74.

RESEARCH Open Access

Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae*

Marco Falcone[1*], Matteo Bassetti[2], Giusy Tiseo[1], Cesira Giordano[3], Elia Nencini[4], Alessandro Russo[1], Elena Graziano[5], Enrico Tagliaferri[1], Alessandro Leonildi[3], Simona Barnini[3], Alessio Farcomeni[6] and Francesco Menichetti[1]



How to shorten the time to appropriate antimicrobial therapy?

Falcone et al. Crit Care 2020

Original Investigation | Infectious Diseases

Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use

Chanu Rhee, MD, MPH; Sameer S. Kadri, MD, MSc; John P. Dekker, MD, PhD; Robert L. Danner, MD; Huai-Chun Chen, PhD; David Fram, BA; Fang Zhang, PhD; Rui Wang, PhD; Michael Klompas, MD, MPH; for the CDC Prevention Epicenters Program

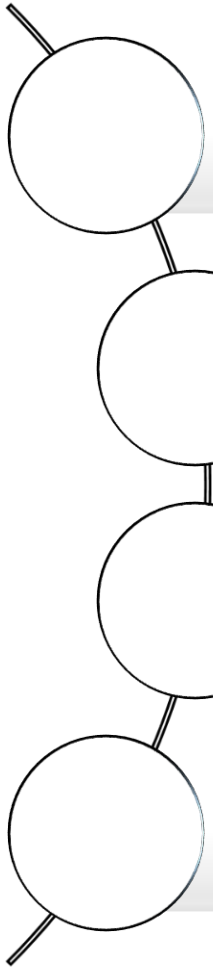
How to improve antibiotics selection?

Table 2. Outcomes Associated With Inadequate and Unnecessarily Broad Empiric Antibiotic Therapy[a]

	Inadequate vs adequate empiric therapy						Unnecessarily broad vs not unnecessarily broad empiric therapy[b]					
	No./total No. (%)						No./total No. (%)					
Outcome	Inadequate	Adequate empiric therapy	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Unnecessarily broad	Not unnecessarily broad	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
In-hospital death	488/2785 (17.5)	2011/12 388 (16.3)	1.10 (0.98-1.22)	.09	1.19 (1.03-1.37)	.02	1575/8405 (18.7)	436/3993 (10.9)	1.88 (1.68-2.11)	<.001	1.22 (1.06-1.40)	.007
Hospital-onset acute kidney injury	486/2785 (17.5)	2196/12 398 (17.7)	0.98 (0.88-1.09)	.74	1.02 (0.90-1.16)	.72	1641/8405 (19.5)	555/3993 (13.9)	1.50 (1.35-1.67)	<.001	1.12 (1.00-1.26)	.05
Clostridioides difficile	207/2785 (7.4)	498/12 398 (4.0)	1.92 (1.63-2.27)	<.001	1.19 (0.98-1.45)	.09	367/8405 (4.4)	131/3993 (3.3)	1.34 (1.10-1.65)	.004	1.26 (1.01-1.57)	.04

Rhee et al. JAMA Network Open 2020; 3: e202899.

Agenda



- MDR risk factors assessment
- Resistance mechanisms identification
- New therapeutic options
- Dosing optimization

Identify patients at risk of MDR infections

Article

Risk Factors and Outcomes for Multidrug Resistant *Pseudomonas aeruginosa* Infection in Immunocompromised Patients

Pilar Hernández-Jiménez [1,2,*], Francisco López-Medrano [1,2,3], Mario Fernández-Ruiz [1,2,3], J. Tiago Silva [1,2], Laura Corbella [1,2], Rafael San-Juan [1,2,3], Manuel Lizasoain [1,2], Jazmín Díaz-Regañón [4], Esther Viedma [5] and José María Aguado [1,2,3]

Variable	Univariate			Multivariate		
	OR	95% CI	*p*	aOR	95% CI	*p*
Diabetes mellitus with no target organ damage	2.45	1.08–5.59	0.033	4.74	1.63–13.79	0.004
Previous receipt of antibiotics	5.81	2.53–13.33	<0.001	5.32	1.93–14.73	0.001
Previous surveillance for MDR colonization	2.06	1.02–4.16	0.043	1.29	0.48–3.43	0.616
Previous MDR colonization	4.2	1.81–9.74	<0.001	0.29	0.05–1.64	0.161
Previous MDR *P. aeruginosa* colonization	23.5	5.12–107.8	<0.001	42.1	4.49–394.8	0.001
Septic shock at diagnosis	3.28	1.49–7.21	0.003	3.73	1.36–10.21	0.010

Hernandez-Jimenez et al. Antibiotics 2022; 11: 1459.

Role of previous carbapenem exposure in neutropenic patients

Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis

Elda Righi[1,2]*, Anna Maria Peri[2,3], Patrick N. A. Harris[2], Alexander M. Wailan[2], Mariana Liborio[4], Steven W. Lane[5-7] and David L. Paterson[2]

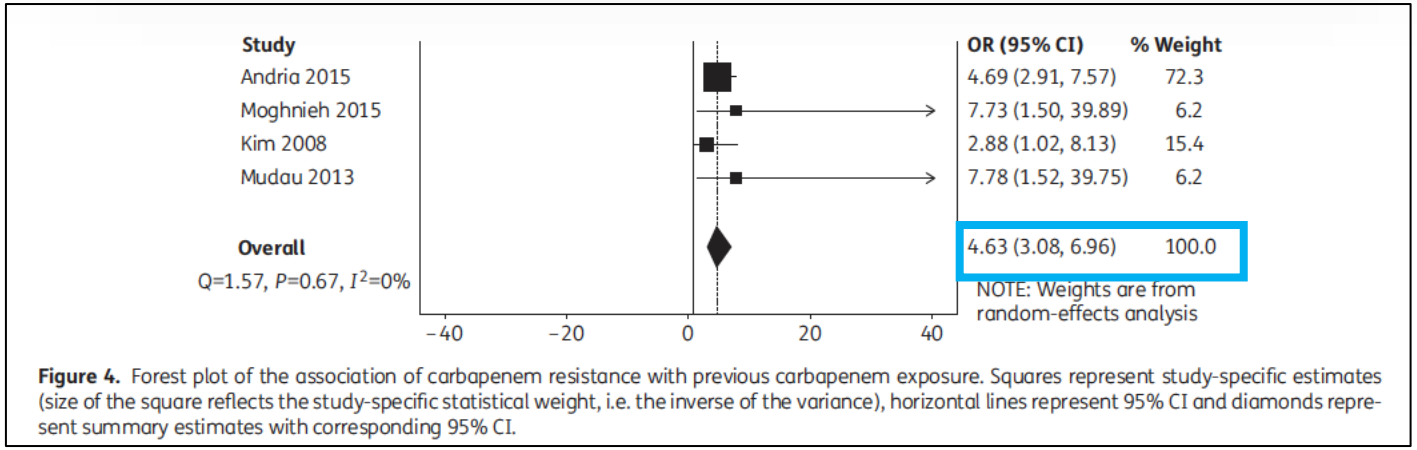


Figure 4. Forest plot of the association of carbapenem resistance with previous carbapenem exposure. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance), horizontal lines represent 95% CI and diamonds represent summary estimates with corresponding 95% CI.

Righi et al. JAC 2017; 72:668-677.

Prior colonization as risk factor for MDR infections

Risk factors for carbapenem-resistant *Acinetobacter baumannii* (CRAB) bloodstream infections and related mortality in critically ill patients with CRAB colonization

Francesco Cogliati Dezza[1], Sara Covino[1], Flavia Petrucci[1], Federica Sacco[2], Agnese Viscido[2], Francesca Gavaruzzi[1], Giancarlo Ceccarelli[1], Gianmarco Raponi[2], Cristian Borrazzo[3], Francesco Alessandri[4], Claudio Maria Mastroianni[1], Mario Venditti[1] and Alessandra Oliva[1*]

Risk factors	OR (95% CI)	*P* value
Risk factors for BSI onset in patients with CRAB colonization		
CCI	1.34 (1.02–15.2)	**0.026**
COVID-19	2.32 (1.72–15.8)	**<0.001**
Hypertension	1.87 (0.91–3.87)	0.089
SAPS II	2.5 (0.88–11.5)	0.091
Timing of ICU to colonization	1.2 (0.84–9.9)	0.122
Multisite >1	2.4 (1.2–4.90)	**0.016**
Mechanical ventilation	2.34 (1.1–5.02)	**0.024**

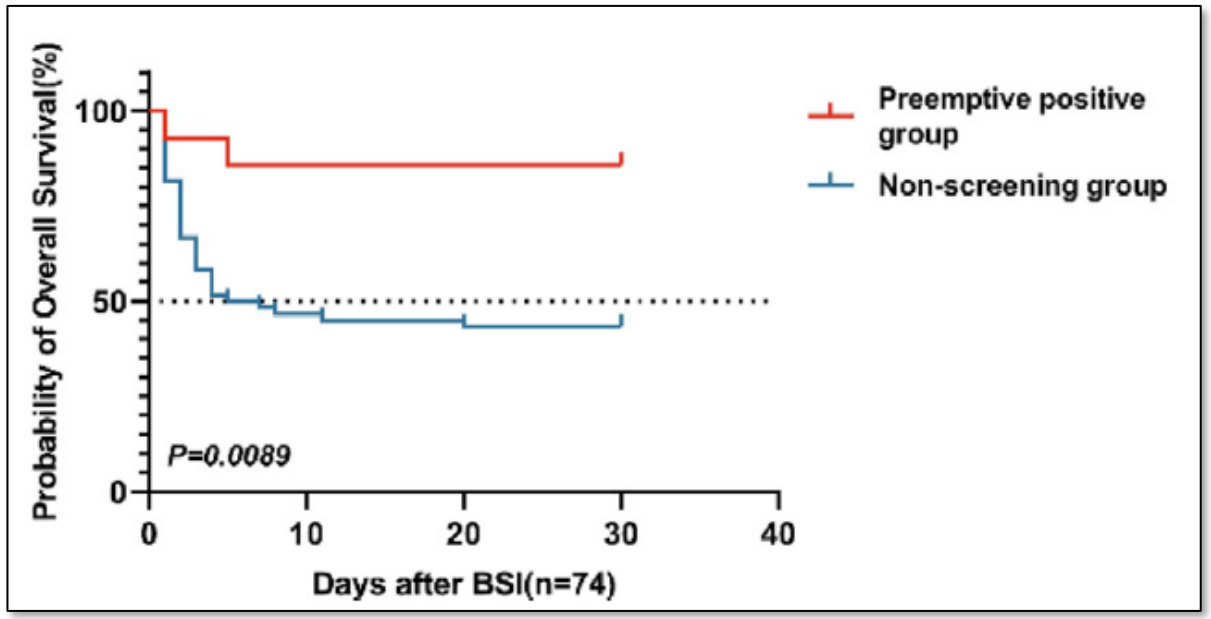
129 patients with CRAB colonization
44% developed BSI

JAC Antimicrob Resist 2023

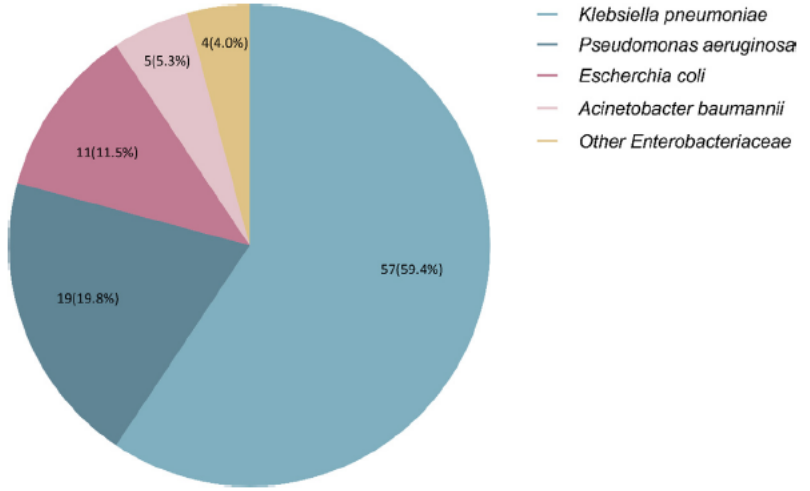
Rectal culture could predict carbapenem-resistant organism bloodstream infection and reduce the mortality in haematological patients: A retrospective cohort study

Siyu Gao[#], Ran Yan[#], Suping Zhang, Li Li, Ran Zhang, Jinpeng Fan, Jing Qin, Yingnan Peng, Dingming Wan[*], Weijie Cao, Zhilei Bian[*]

Department of Hematology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou University, Zhengzhou, People's Republic of China



434 hematological patients with BSI
98 with CRO BSI
75% with positive rectal swab



Gao et al. J Glob Antimicrob Resist 2024; 36:96-104.

MDR colonisation guides empirical antimicrobial therapy

Treatment of Community-Acquired Pneumonia in Immunocompromised Adults

A Consensus Statement Regarding Initial Strategies

Check for updates

CHEST

In which immunocompromised patients should the initial empirical therapy be extended to cover MDR pathogens?

We suggest that in patients with a recent history of colonization or infection with MDR gram-negative bacilli, the initial empirical therapy should cover the possibility of infection due to the colonizing MDR gram-negative bacilli.

We suggest that initial empirical therapy to cover for MRSA should be started in patients with a history of colonization or infection with MRSA in the previous 12 months.

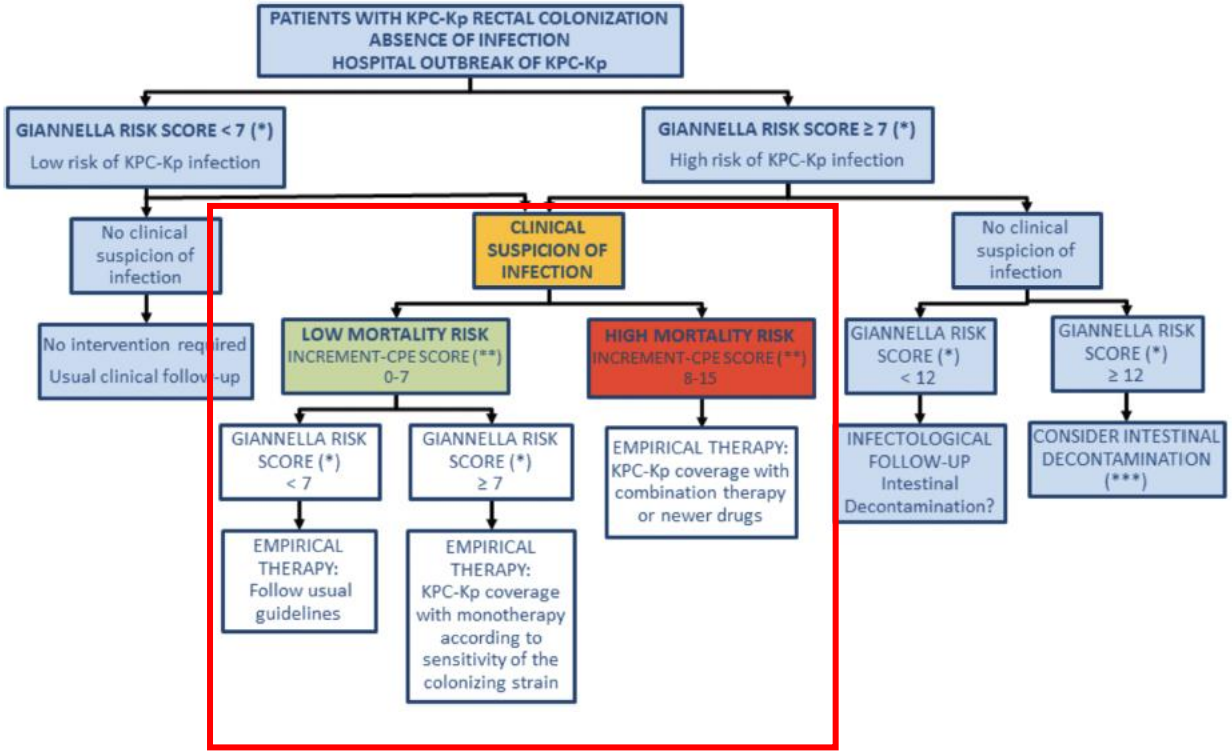
Ramirez et al. Chest 2020; 158: 1896-1911.

MDR risk score may guide empirical KPC-Kp coverage

Giannella risk score

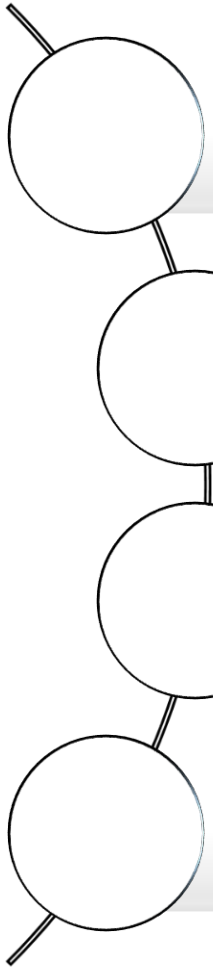
Table 3. Giannella risk score. Risk factors for CR-KP BSI development in rectal carriers.[7]

Risk factors	Risk score point
Admission to ICU	2
Invasive abdominal procedures	3
Chemotherapy/radiation therapy	4
Colonization at site besides stool (risk per each additional site)	5 per site



Giannella et al. CMI 2014
Cano et al. CID 2018

Agenda



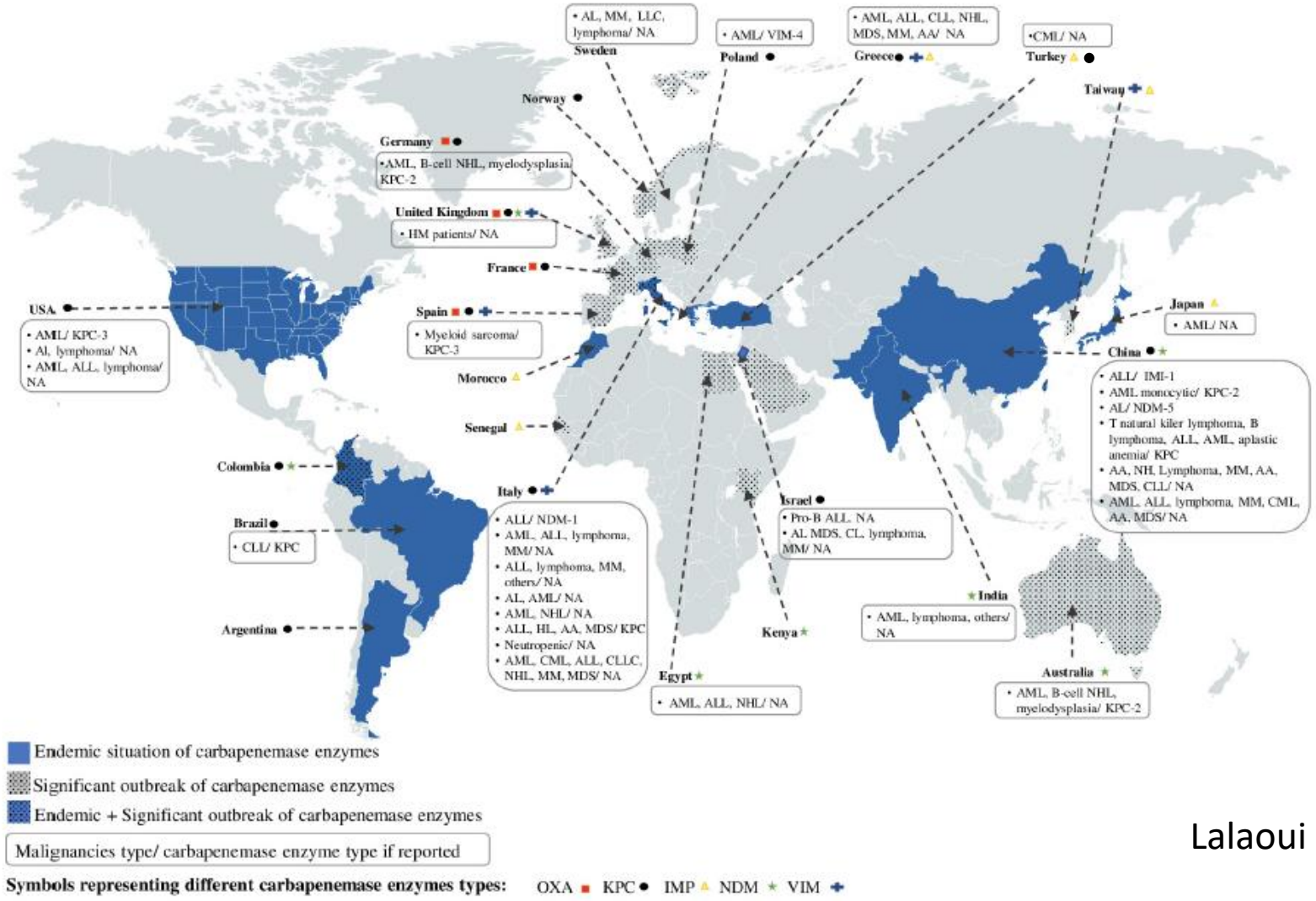
MDR risk factors assessment

Resistance mechanisms identification

New therapeutic options

Dosing optimization

Consider the local epidemiology



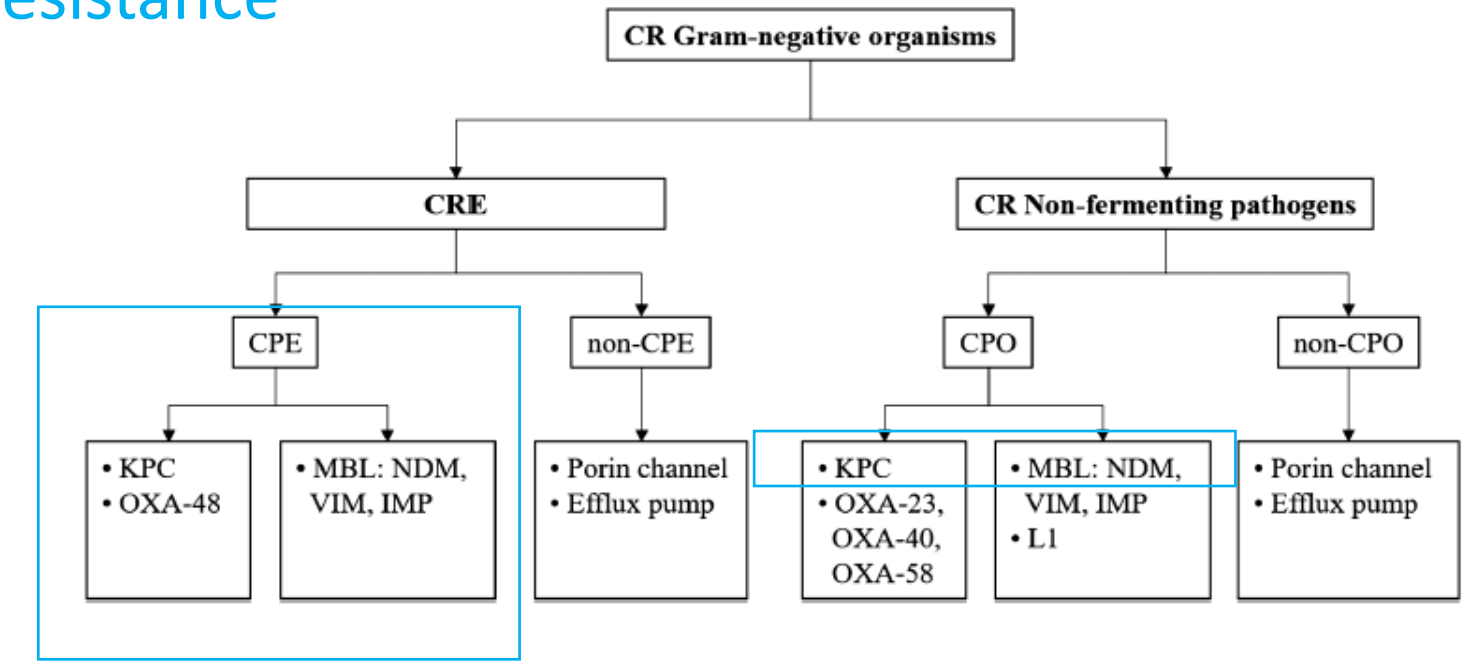
Worldwide distribution of carbapenemase enzymes in hematological patients.

OXA-48
KPC
NDM
IMP
VIM

Lalaoui et al. Front Microbiol 2020; 11: 1422.

Early determination of underlying multidrug resistance mechanisms

1. Rapid identification of the pathogen
2. Rapid identification of resistance mechanisms
   - Genotypic tests
   - Phenotypic tests



Nordmann et al. CID 2019

The Evolving Role of the Clinical Microbiology Laboratory in Identifying Resistance

BCs' MALDI-TOF direct ID

NG-Test Carba 5

FILMARRAY system (ME,BC, pneumonia, GI)

T2Dx Instrument (Bacteria, candida, AMR)

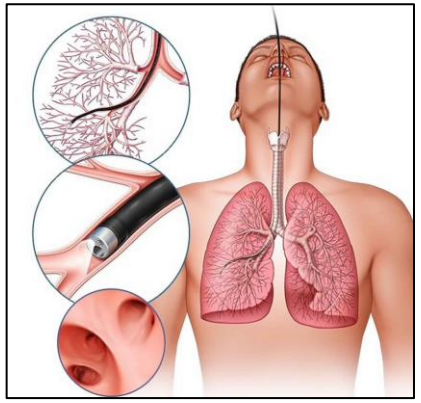
NG-Test CTX-M Multi

Eazyplex MRSAplus

Unyvero System (tissue, fluids, urine)

WGS

Role of molecular rapid diagnostic testing to inform optimal treatment decisions ?



Recherche de pathogènes respiratoires par amplification génique

Nature du prélèvement: LBA

Chlamydia pneumoniae	Négative
Mycoplasma pneumoniae	Négative
Legionella pneumophila	Négative
Staphylococcus aureus	Négative
Recherche de méticillino-résistance (mecA/C et MREJ)	Non applicable
Streptococcus pneumoniae	Négative
Streptococcus agalactiae	Négative
Streptococcus pyogenes	Négative
Haemophilus influenzae	Négative
Moraxella catarrhalis	Négative
Escherichia coli	Négative
Klebsiella pneumoniae group	POSITIVE: ADN détecté à 10^6 copies/mL (quantification non équivalente à CFU/mL)
Klebsiella oxytoca	Négative
Klebsiella aerogenes	Négative
Enterobacter cloacae complex	Négative
Proteus spp.	Négative
Serratia marcescens	Négative
Pseudomonas aeruginosa	Négative
Acinetobacter calcoaceticus-baumannii complex	Négative

Rapid identification of the pathogen

Multiplex PCR

Rapid identification of resistance mechanisms

Recherche de bétalactamase à spectre étendu (BLSE) de type CTX-M	Négative
Recherche de carbapénémase de type IMP	Négative
Recherche de carbapénémase de type KPC	Négative
Recherche de carbapénémase de type NDM	Négative
Recherche de carbapénémase de type OXA48	POSITIVE
Recherche de carbapénémase de type VIM	Négative
Adénovirus	Négative
Enterovirus/Rhinovirus	Négative
MERS CoV	Négative
Coronavirus (autres que SARS-CoV1/2)	Négative
Virus de la grippe A	Négative
Virus de la grippe B	Négative
Virus parainfluenza	Négative
Metapneumovirus	Négative
Virus respiratoire syncitial	Négative

FilmArray Pneumonia Panel plus, Biomérieux

Diagnosis and Treatment of Bacterial Pneumonia in Critically Ill Patients with COVID-19 Using a Multiplex PCR Assay: A Large Italian Hospital's Five-Month Experience

Brunella Posteraro,[a,b] Venere Cortazzo,[a] Flora Marzia Liotti,[a,c] Giulia Menchinelli,[a,c] Chiara Ippoliti,[a] Giulia De Angelis,[a,c] Marilena La Sorda,[c] Gennaro Capalbo,[d] Joel Vargas,[a] Massimo Antonelli,[a,e] Maurizio Sanguinetti,[a,c] Gennaro De Pascale,[a,e] Teresa Spanu[a,c]

Microbial target	No. positive by FA-PP and SoC/no. positive by SoC	PPA (%) (95% CI)	No. negative by FA-PP and SoC/no. negative by SoC	NPA (%) (95% CI)	No. positive only by FA-PP for samples from patients who were[b]:	
					Under antimicrobial therapy	Not under antimicrobial therapy
Bacterial species						
Acinetobacter calcoaceticus-baumannii complex	53/53	100 (93.2–100)	159/159	100 (97.7–100)		
Enterobacter cloacae complex	4/4	100 (39.8–100)	206/207	99.5 (97.4–100)	1	
Escherichia coli	15/15	100 (78.2–100)	195/196	99.5 (97.2–100)	1	
Haemophilus influenzae	2/2	100 (15.9–100)	208/209	99.5 (97.4–100)		1
Klebsiella aerogenes	5/5	100 (47.8–100)	207/207	100 (98.2–100)		
Klebsiella oxytoca	2/2	100 (15.8–100)	204/207	98.6 (95.9–99.7)	1	2
Klebsiella pneumoniae group	23/23	100 (85.2–100)	189/189	100 (98.1–100)		
Proteus spp.	2/2	100 (15.9–100)	210/210	100 (98.3–100)		
Pseudomonas aeruginosa	19/19	100 (82.4–100)	185/189	97.9 (94.8–99.4)	4	
Serratia marcescens	6/6	100 (54.1–100)	200/203	98.5 (95.8–99.7)	2	1
Staphylococcus aureus	45/45	100 (92.1–100)	155/161	96.4 (92.3–98.7)	5	1
Streptococcus agalactiae	0/0	NC	208/210	99.1 (96.6–99.9)		2
Streptococcus pneumoniae	4/4	100 (39.8–100)	206/207	99.5 (97.4–100)		1
Total species	180/180	100 (98.0–100)	2,532/2,554	99.2 (98.7–99.5)	14	8
Antimicrobial resistance genes						
CTX-M	12/12	100 (73.5–100)	200/200	100 (98.2–100)		
KPC	10/10	100 (69.2–100)	202/202	100 (98.2–100)		
mecA/-C and MREJ[c]	23/23	100 (85.2–100)	185/187	98.9 (96.2–99.9)	2	
Total genes	45/45	100 (92.1–100)	587/589	99.7 (98.8–100)	2	

150 ICU patients
SARS Cov-2
pneumonia

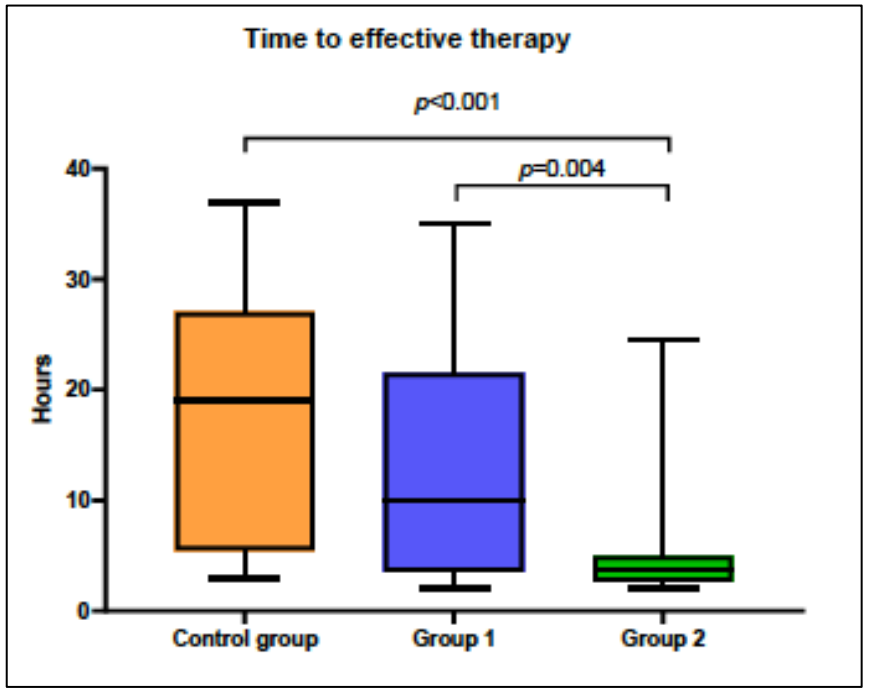
Posteraro et al. Microbiol Spectr 2021

Rapid PCR-based blood culture reduces time to effective therapy in neutropenic patients

Article

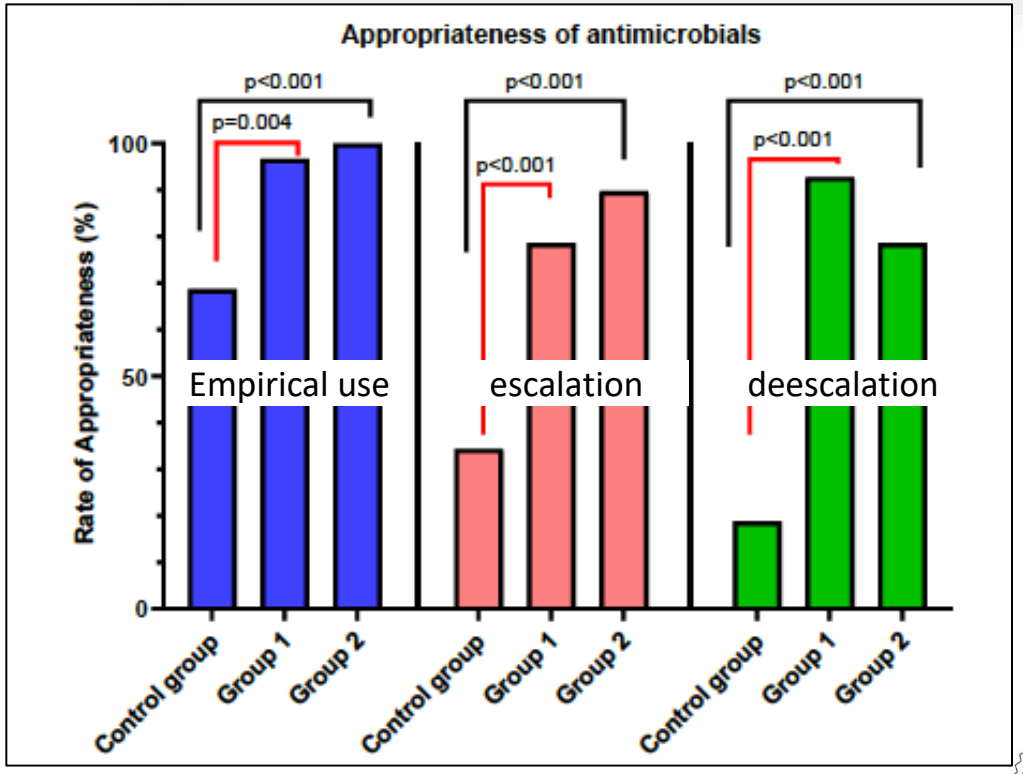
Impact of Adding a Rapid PCR-Based Blood Culture Identification Panel to the Antimicrobial Stewardship Program of Patients with Febrile Neutropenia in a Peruvian Referral Hospital

Reduce time to effective therapy



Group 1: ASP

Group 2: mPCR+ ASP



Perez-Lazo et al. Antibiotics 2023; 12:648.

Rapid diagnostic tools allow rapid selection of appropriate antibiotics

Retrospective study
5 centres in US

N=854
Bacteremia

Rapid AST vs
conventional technique

Table 4. Antimicrobial Modifications and Clinical Outcomes

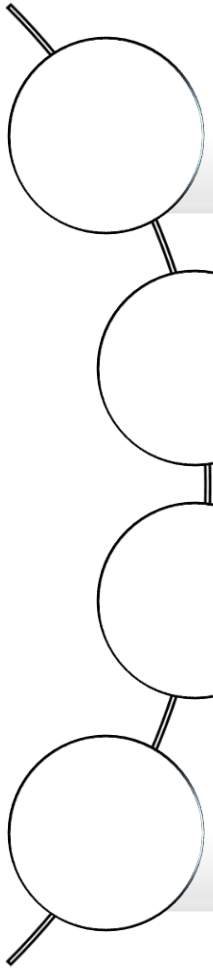
	All[a]			Gram-Negative[b]		
Endpoint	Pre-AXDX	Post-AXDX	*P* Value	Pre-AXDX	Post-AXDX	*P* Value
Antimicrobial modification[c]						
Time to first antimicrobial modification[d]	24.2 (7.3–46.2)	13.9 (5.0–31.1)	**<.0001**	22.8 (7.0–45.3)	13.6 (5.8–30.9)	**.01**
Time to first gram-positive antimicrobial modification[e]	30.1 (11.2–52.8)	18.3 (6.7–41.8)	**.0013**	28.1 (10.5–51.7)	18.6 (9.4–42.1)	.11
Time to first gram-negative antimicrobial modification[f]	34.6 (9.2–53.4)	18.6 (8.2–36.8)	**<.0001**	30.2 (7.6–52.8)	16.7 (8.6–35.2)	**.003**
Time to first antimicrobial escalation[g]	9.5 (3.4–28.9)	9.0 (3.7–18.4)	.22	9.5 (3.7–31.6)	9.6 (3.9–18.4)	.44
Time to first antimicrobial deescalation[h]	36.0 (17.1–54.5)	27.2 (13.5–43.6)	**.0004**	34.5 (16.6–52.8)	25.4 (12.0–42.5)	**.003**
Time to effective therapy[i]	13.3 (3.1–35.9)	6.7 (3.1–16.2)	**.02**	13.7 (3.3–38.1)	10.0 (3.6–18.6)	.10

Median time to ID: 2.5h vs 24.8h
Median time to AST: 7.9h vs 39.5h

MDR pathogens: 16%
Pathogens identified: ESBL-E, MDR P. aeruginosa, MDR A. baumannii, MRSA, VRE

Balhodi et al. CID 2022; 75:269-77.

Agenda



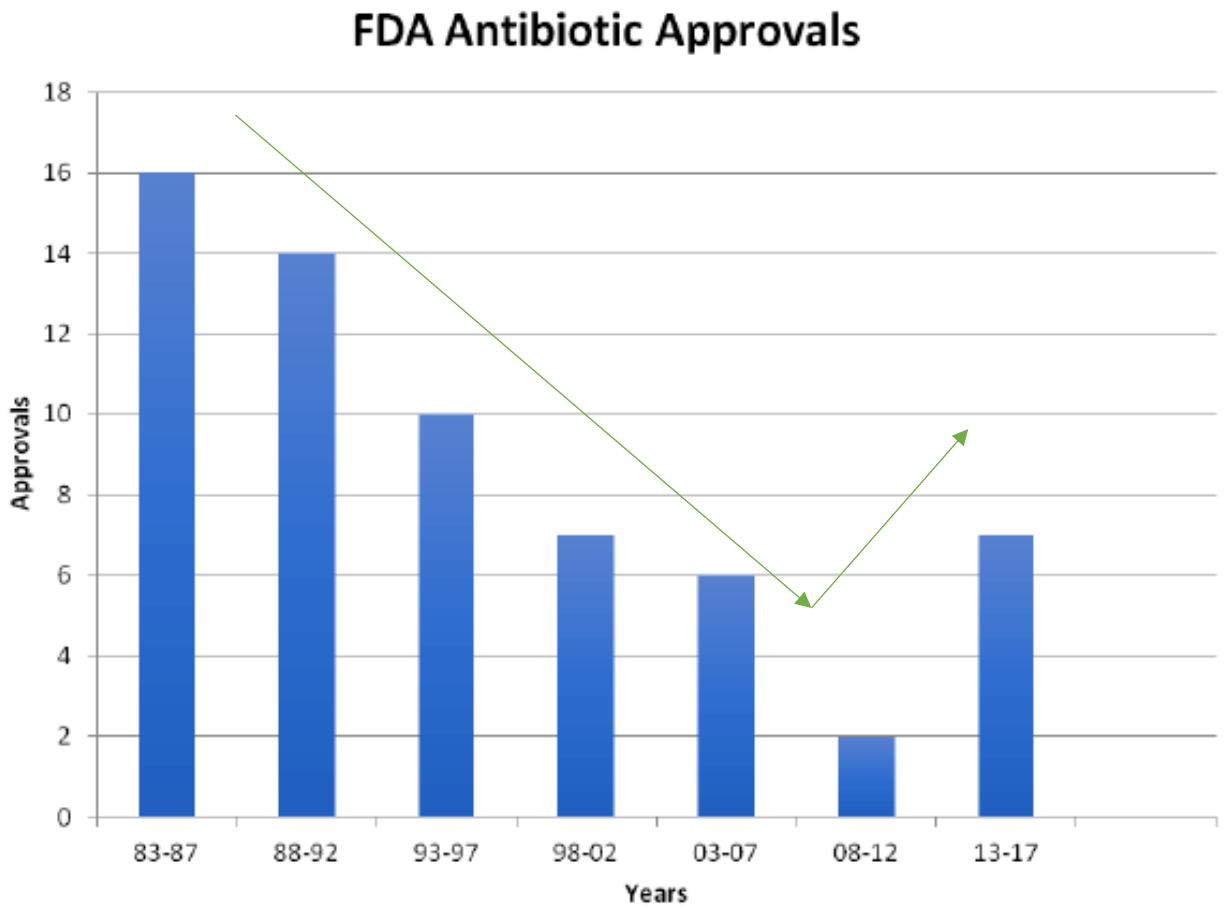
MDR risk factors assessment

Resistance mechanisms identification

New therapeutic options

Dosing optimization

New antimicrobial drugs have been developped to tackle different mechanisms of resistance



1. synthesis of new β-lactam compounds refractory to hydrolysis by these enzymes (eg, cefiderocol)
2. Development of new beta-lactam inhibitors

Talbot CID 2019; doi 10.1093/cid/ciz089

New treatment options based on resistance mechanisms

	Enterobacterales						*P. aeruginosa*								
Resistance mechanisms	**AmpC**	**ESBL**	**CRE Non-CPE**	**KPC**	**NDM VIM**	**OXA-48**	**AmpC**	**Efflux**	**AmpC Efflux OprD-**	**NDM VIM**	**CRAB**	***Steno***	***E. faec***	**MRSA**	***Anas***
Ceftobiprole															
Ceftazidime-avibactam															
Ceftolozane-tazobactam															
Imipenem-relebactam															
Meropenem-vaborbactam															
Aztreonam-avibactam															
Cefiderocol											⚠				

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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]

IDSA Infectious Diseases Society of America

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Carbapenem Resistant ENTEROBACTERALES

	IDSA		ESCMID
	1st line	Alternative	
KPC	Ceftazidime avibactam Meropenem vaborbactam Imipenem relebactam	Cefiderocol	Ceftazidime avibactam Meropenem vaborbactam Imipenem relebactam
Metallo β lactamases	Aztreonam avibactam	Cefiderocol	Cefiderocol Aztreonam avibactam
OXA 48 like carbapenemase	Ceftazidime avibactam	Cefiderocol	Ceftazidime avibactam

CID 2021; 72:169-83. Updated 7th March 2022
CMI 2021; 10.1016/j.cmi.2021.11.025

DTR *Pseudomonas aeruginosa*

IDSA
Infectious Diseases Society of America

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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]

	First line	2nd line
cUTI	Ceftolozane-tazobactam Ceftazidime-avibactam Imipenem-relebactam Cefiderocol	Aminoglycoside
Infections outside cUTI	Ceftolozane-tazobactam Ceftazidime-avibactam Imipenem-relebactam	Cefiderocol

ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

ELSEVIER

CMI CLINICAL MICROBIOLOGY AND INFECTION

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)

Severe infections	Ceftolozane-tazobactam

Tamma et al. CID 2022;75(2):187–212.
Paul et al. CMI 2022; 28: 521-547.

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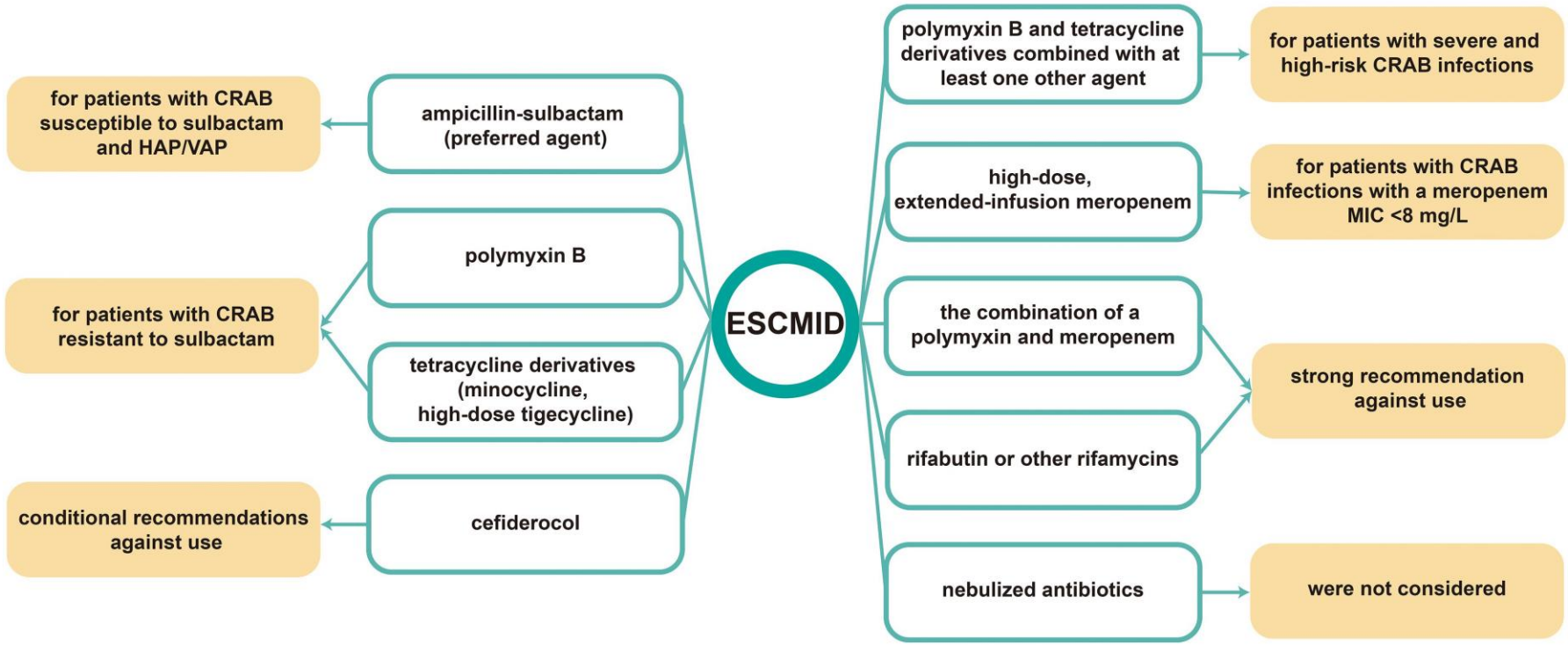
ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Carbapenem Resistant Acinetobacter baumannii



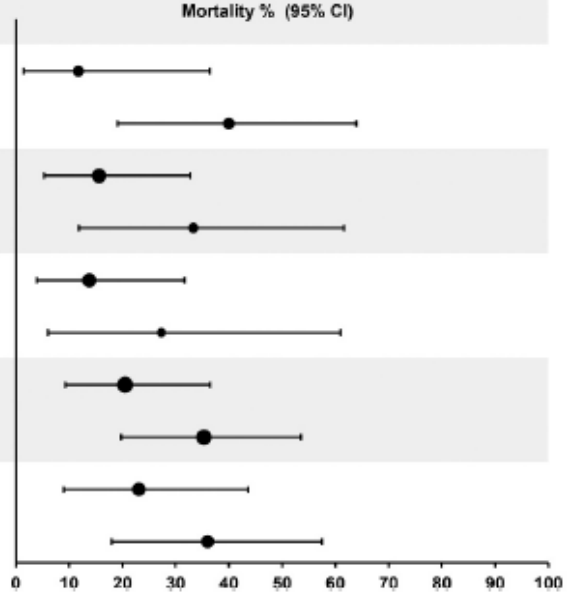
CMI 2021; 10.1016/j.cmi.2021.11.025

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[a], Matteo Bassetti[b], Ricard Ferrer[c], Thierry Naas[d], Yoshihito Niki[e], David L. Paterson[f], Markus Zeitlinger[g] and Roger Echols[h]

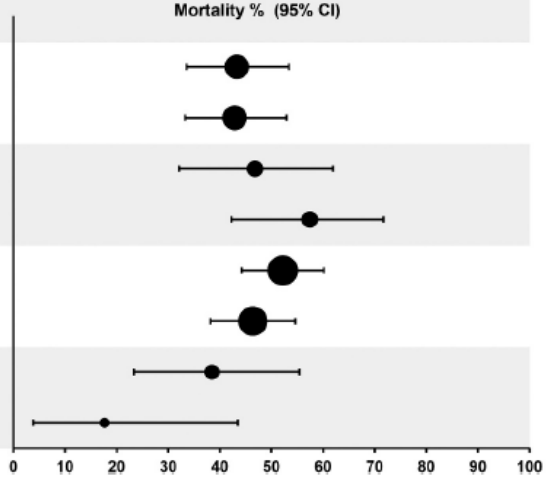
Carbapenem-resistant Enterobacterales

Clinical Trial	Antibiotic	Day 28 ACM % (n/N)
CARE (NCT01970371)[29]	plazomicin	11.8% (2/17)
	colistin	40.0% (8/20)
TANGO II (NCT02168946)[30]	meropenem/vaborbactam	15.6% (5/32)
	BAT	33.3% (5/15)
CREDIBLE-CR (NCT02714595)[31]	cefiderocol	13.8% (4/29)
	BAT	27.3% (3/11)
AIDA (NCT01732250)[32]	colistin + meropenem	20.5% (8/39)
	colistin	35.3% (12/34)
Ji et al.[35]	cefepime + amoxicillin/clavulanic acid	23.1% (6/26)
	tigecycline-based antibiotic therapy	36.0% (9/25)



Carbapenem-resistant Acinetobacter baumannii

Clinical Trial	Antibiotic	Day 28 ACM % (n/N)
Durante-Mangoni (NCT01577862)[33]	colistin + rifampicin	43.3% (45/104)
	colistin	42.9% (45/105)
Sirijatuphat (NCT01297894)[34]	colistin + fosfomycin	46.8% (22/47)
	colistin	57.4% (27/47)
AIDA (NCT01732250)[32]	colistin + meropenem	52.2% (84/161)
	colistin	46.4% (70/151)
CREDIBLE-CR* (NCT02714595)[31]	cefiderocol	38.5% (15/39)
	BAT	17.7% (3/17)



Lodise et al. Exp Rev Infect Ther 2022

Available data of ceftazidime-avibactam in SOT recipients

Efficacy of ceftazidime-avibactam in the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections: Focus on solid organ transplantation recipients

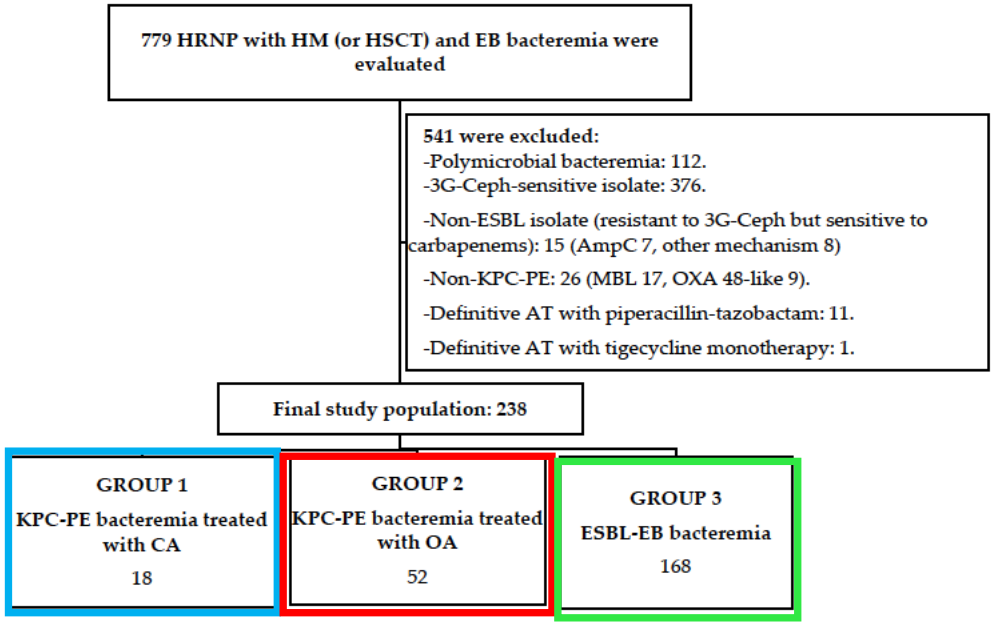
Juan Hu[a,#], Lei Zha[b,#], Yong-Wei Yu[a], Qun Su[a], Xue-Ling Fang[a], Jin-Ru Ji[c], Ping Shen[c], Yun-Bo Chen[c], Xia Zheng[a,*], Yong-Hong Xiao[c,**]

	Patients included in analysis		Adjusted ORs (95% CI)	*P*
	CAZ-AVI	Other regimens		
Solid organ transplantation recipients				
30-day mortality n (%)	7 (23.3)	12 (60.0)	0.19 (0.05,0.69)	0.014
Clinical cure n (%)	27 (90.0)	8 (40.0)	20.2 (4.10,26.7)	< 0.001
90-day mortality n (%)	10 (35.7)	13 (86.7)	0.06 (0.01,0.32)	0.003
Length of ICU stay (median [IQR])	43 (23, 71)	34.5 (22.5, 66.25)	1.25 (-19.6,22.1)	0.905
LOS (median [IQR])	63 (48, 99.5)	45.5 (33.5, 77.25)	22.1 (-9.30,53,5)	0.163
Microbiological clearance*				
Respiratory infection n (%)	9 (56.2)	0 (0.0)	NA	0.012
Intra-abdominal infection n (%)	6 (54.5)	0 (0.0)	NA	0.017
Bacteraemia n (%)	11 (91.7)	5 (38.5)	NA	0.019
Polymicrobial infection			1.22 (0.36-4.06)	0.74

Other regimens:
Polymyxin B combination therapy (45%), Tigecyclin + Polymyxin B (30%)

Hu et al. IJAA 2024; 63: 107152.

Available data of ceftazidime-avibactam in neutropenic patients

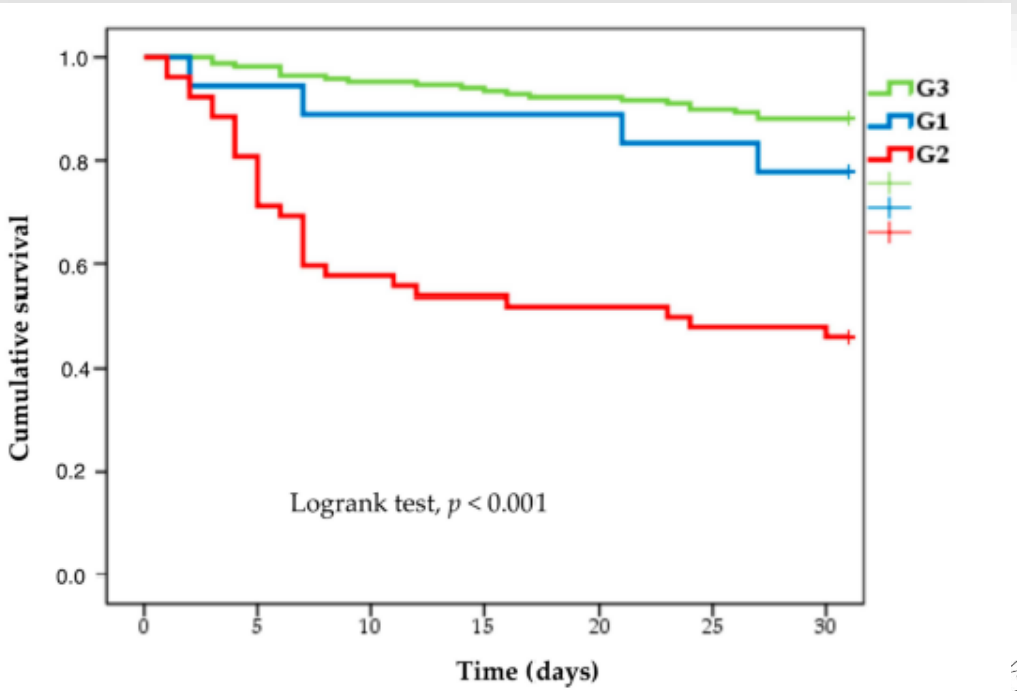


Other antibiotics: carbapenem, tigecyclin, colistin, amikacin

Article

Ceftazidime–Avibactam Improves Outcomes in High-Risk Neutropenic Patients with *Klebsiella pneumoniae* Carbapenemase-Producing Enterobacterales Bacteremia

Fabián Herrera [1,*], Diego Torres [1], Ana Laborde [2], Rosana Jordán [3], Noelia Mañez [4], Lorena Berruezo [5], Sandra Lambert [6], Nadia Suchowiercha [7], Patricia Costantini [8], Andrea Nenna [9], María Laura Pereyra [10], José Benso [11], María Luz González Ibañez [2], María José Eusebio [3], Laura Barcán [4], Nadia Baldoni [5], Lucas Tula [6], Inés Roccia Rossi [7], Martín Luck [8], Vanesa Soto [9], Verónica Fernández [11] and Alberto Ángel Carena [1,†] on behalf of the Argentine Group for the Study of Bacteremia in Cancer and Stem Cell Transplant (ROCAS) Study



Herrera et al. Microorganisms 2024; 12,95.

Available data of ceftolozane/tazobactam in neutropenic patients

Real-Life Use of Ceftolozane/Tazobactam for the Treatment of Bloodstream Infection Due to *Pseudomonas aeruginosa* in Neutropenic Hematologic Patients: a Matched Control Study (ZENITH Study)

Alba Bergas,[a] Adaia Albasanz-Puig,[a,w] Ana Fernández-Cruz,[b,c] Marina Machado,[b] Andrés Novo,[d] David van Duin,[e] Carolina Garcia-Vidal,[f] Morgan Hakki,[g] Isabel Ruiz-Camps,[h] José Luis del Pozo,[i] Chiara Oltolini,[j] Catherine DeVoe,[k] Lubos Drgona,[l] Oriol Gasch,[m] Malgorzata Mikulska,[n] Pilar Martín-Dávila,[o] Maddalena Peghin,[p] Lourdes Vázquez,[q] Júlia Laporte-Amargós,[a] Xavier Durà-Miralles,[a] Natàlia Pallarès,[r] Eva González-Barca,[s] Ana Álvarez-Uría,[b] Pedro Puerta-Alcalde,[f] Juan Aguilar-Company,[h,t] Francisco Carmona-Torre,[i] Teresa Daniela Clerici,[u] Sarah B. Doernberg,[k] Lucía Petrikova,[l] Silvia Capilla,[v] Laura Magnasco,[n] Jesús Fortún,[o] Nadia Castaldo,[p] Jordi Carratalà,[a,w] Carlota Gudiol[a,w,x]

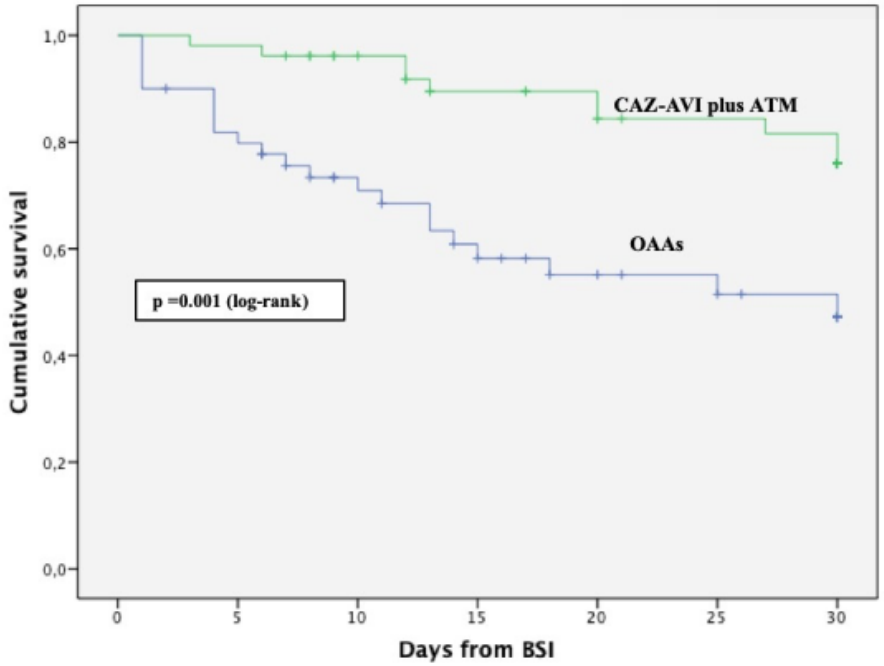
TABLE 6 Univariate and multivariate analysis of factors associated with 30-day case fatality rate

Characteristics[a]	Dead *n* = 53 (%)	Alive *n* = 98 (%)	*P* value	Adjusted OR (95% CI)[a]	*P* value[b]
Female gender	19 (40.4)	28 (59.6)	0.96	0.97 (0.38–2.45)	0.958
Age (yrs) (median, IQR)	53 (18–90)	54.5 (18–79)	0.79	0.98 (0.95–1.00)	0.133
Pneumonia	20 (58.8)	14 (41.2)	0.014	5.45 (1.84–16.13)	**0.002**
Therapy with ceftolozane-tazobactam	10 (22.7)	34 (77.3)	0.004	0.19 (0.07–0.55)	**0.002**
Persistent bloodstream infection	14 (63.6)	8 (36.4)	0.009	5.44 (1.61–18.31)	**0.006**
Infection due to XDR PA	23 (52.3)	21 (47.7)	0.045	1.76 (0.68–4.54)	0.240
Profound neutropenia (<100 cells/mm^3)	41 (48.8)	43 (51.2)	0.009	5.49 (1.96–0.15.36)	**0.001**

Bergas et al. Microbiol Spectr 2022; 10: e0229221.

Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

Marco Falcone,[1] George L. Daikos,[2] Giusy Tiseo,[1] Dimitrios Bassoulis,[2] Cesira Giordano,[3] Valentina Galfo,[1] Alessandro Leonildi,[3] Enrico Tagliaferri,[1] Simona Barnini,[3] Spartaco Sani,[4] Alessio Farcomeni,[5] Lorenzo Ghiadoni,[6] and Francesco Menichetti[1]



Number at risk

CAZ-AVI *plus* ATM	52	51	50	47	45	45	42
OAAs	50	40	36	31	30	29	28

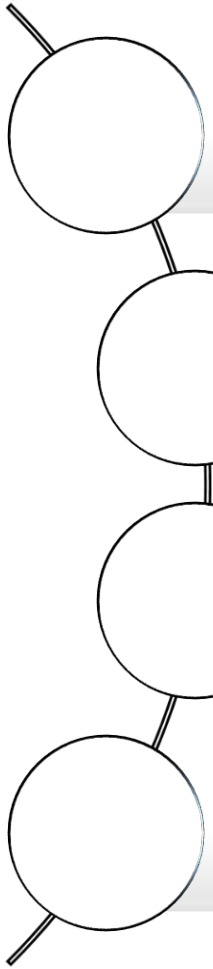
- 102 patients with BSI, 30% immunocompromised
- 80% NDM-producing GNB, 20% VIM-producing GNB
- CAZ-AVI + AZT compared to other antibiotics (COL, FOS, TGC, AZT+FOS)

Table 5. Propensity Score–Adjusted Analysis for Secondary Study Endpoints

CAZ-AVI + ATM	HR (95% CI)	sHR[a] (95% CI)	*P* Value
Clinical failure at day 14	0.30 (.14–.65)	…	.002
Length of hospital stay from BSI onset[a]	…	0.49 (.30–.82)	.007

Falcone et al. CID 2021; 72: 1871-8.

Agenda

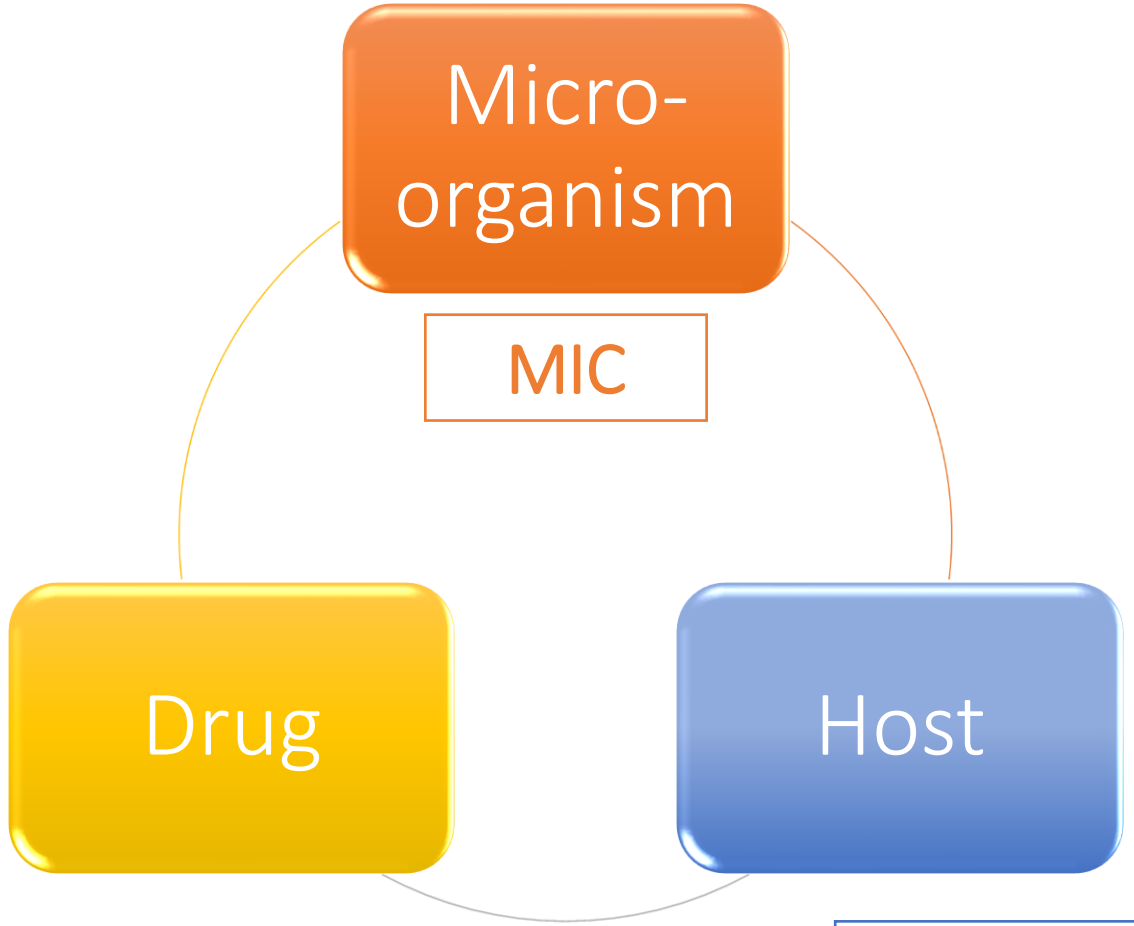


MDR risk factors assessment

Resistance mechanisms identification

New therapeutic options

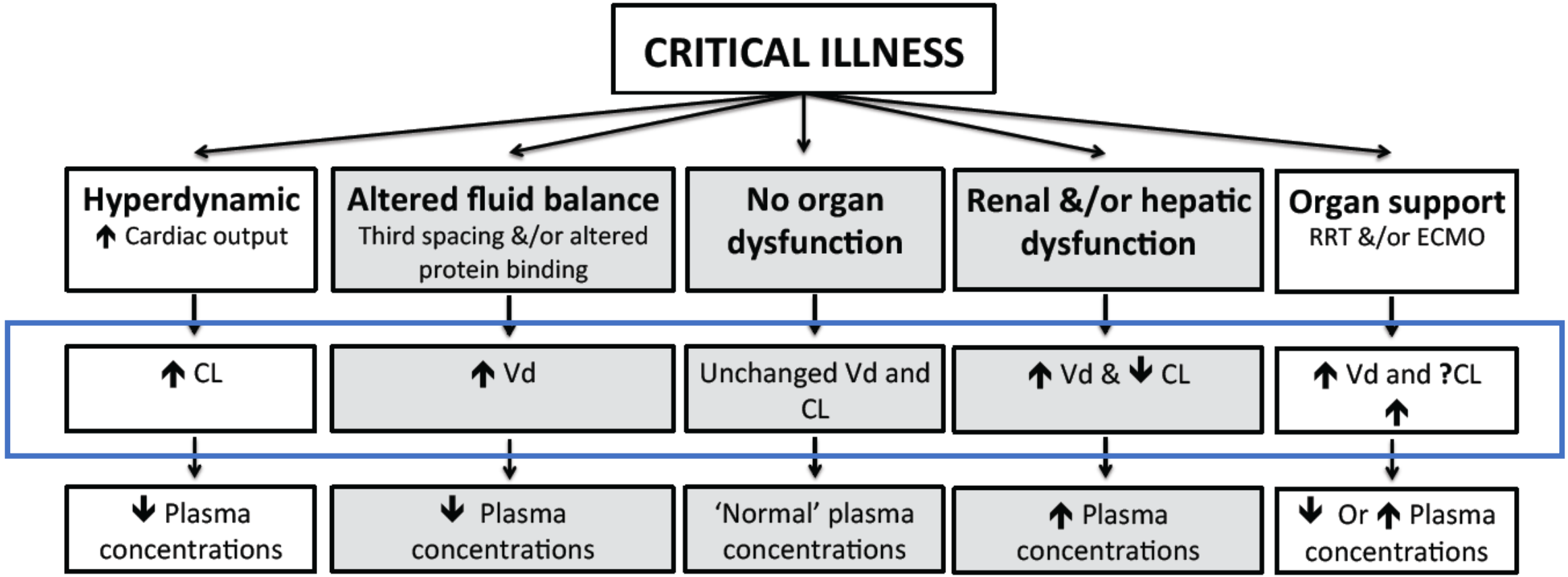
Dosing optimization



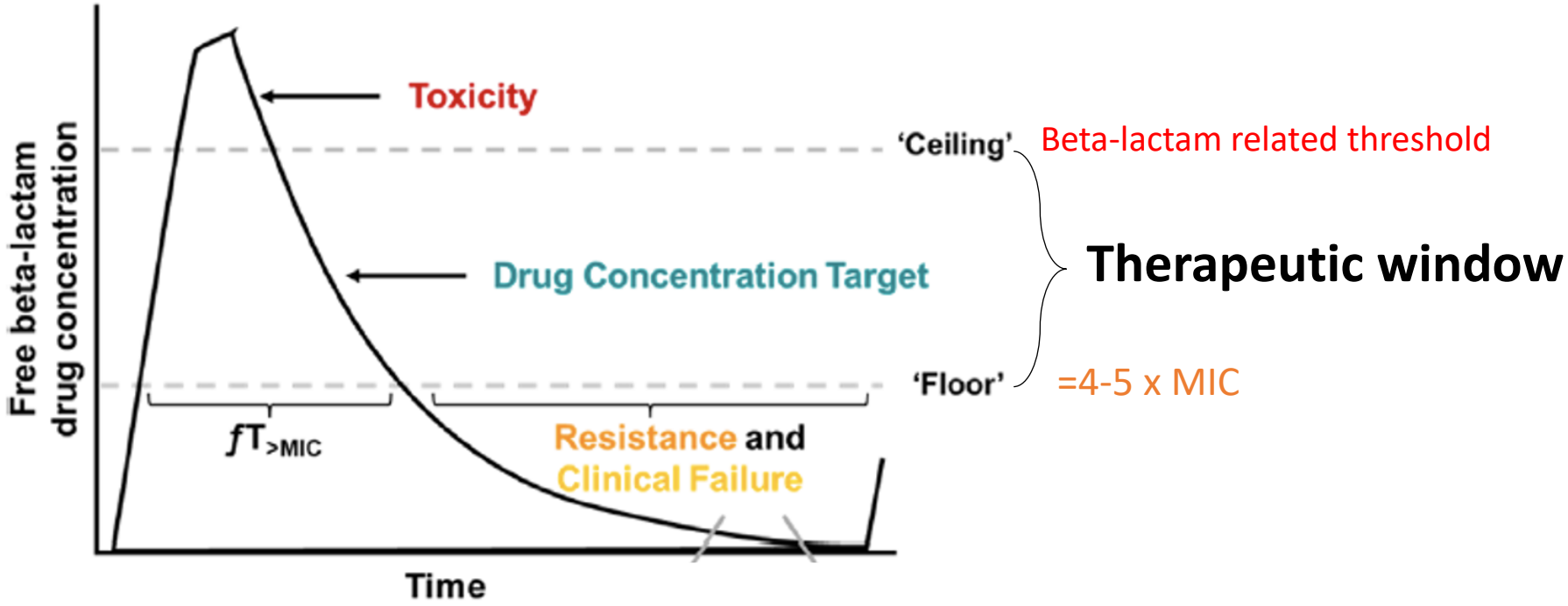
Dosing
Mode of administration
Tissue penetration

Immuno compromised

Pathophysiological alterations in sepsis impact antimicrobial pharmacokinetics



β –lactams PK/PD target: the challenge of high MICs

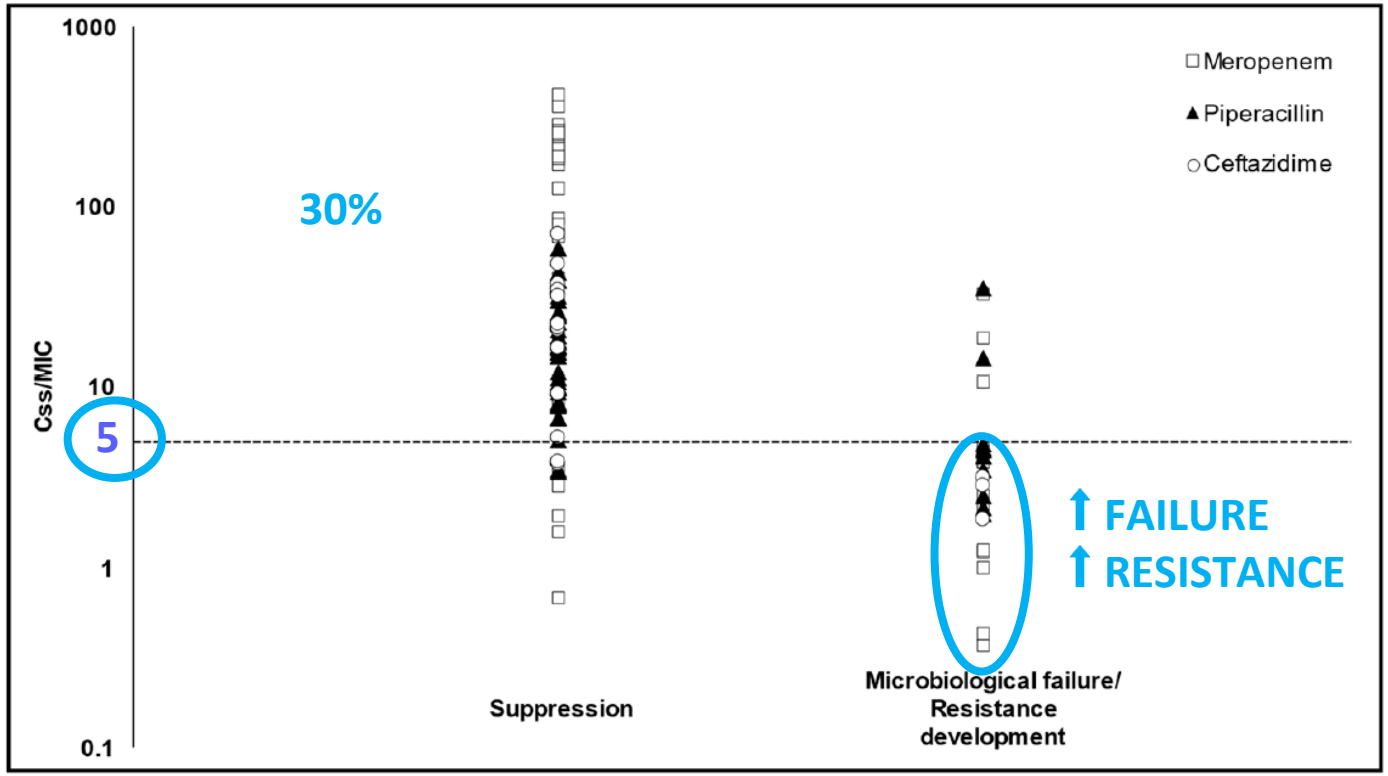


Therapeutic drug monitoring

Crit Care 2019; 23(1):104.
Bergen et al. J Antimicrob Chemother 2016; 71:2509-20.

Css/MIC<5:
↑ risk of treatment failure and emergence of resistance

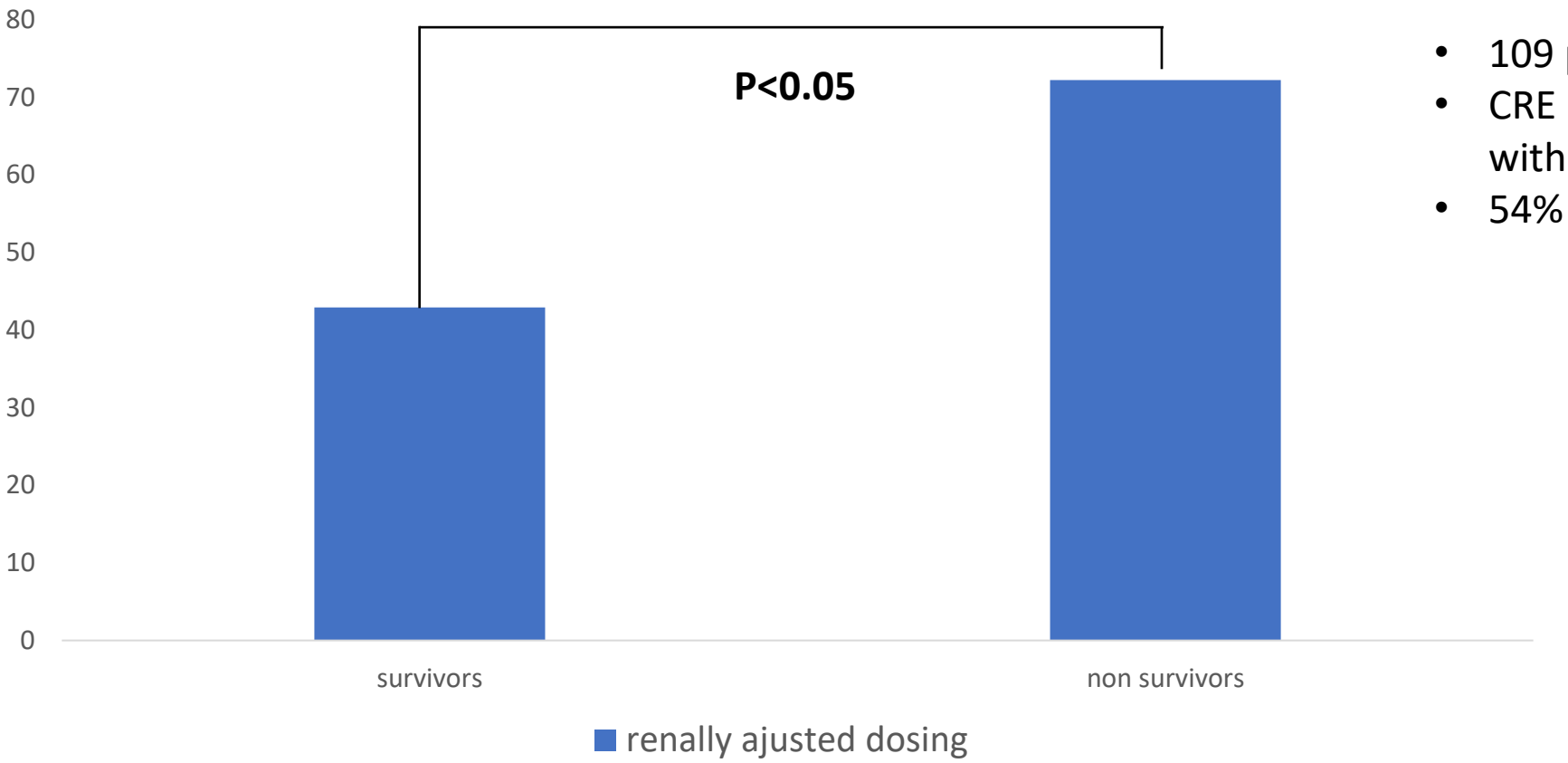
- 116 ICU patients
- GNB infections (50% VAP)
- Beta-lactam concentrations:
  - -Meropenem
  - -Piperacillin
  - -Ceftazidime



Microbiological failure and/or emergence of resistance
x 35
if C_{ss} < 5 X CMI

Gatti et al. Antibiotics 2021; 10:1311.

Risk of underdosing in renally impaired patients with DTR GNB

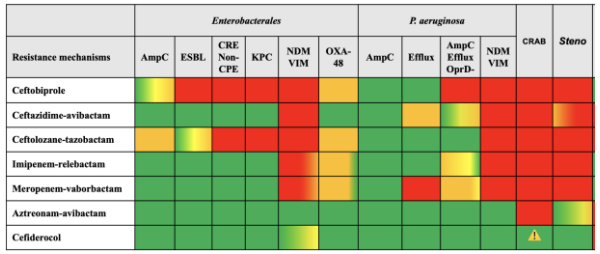


- 109 patients
- CRE infections treated with cefta/avi
- 54% ICU patients

Joregensen et al. Infect Dis Ther 2020; 9:291-304

Personalized approach for choosing antibiotics in MDR infections
Take home messages

OXA-48
MBL
KPC
Non CPE



Risk factors score
Prior colonization

Identify patients at high risk of MDR infections → **Rapid ID of pathogens and resistance mechanisms** → **Selection of appropriate ABx based on resistance mechanisms** → **Dosing optimization**

Genotypic tests
Phenotypic tests




Therapeutic drug monitoring
Prolonged/continuous infusion


THANK YOU
Дякую
Akeva
Köszönöm
Tak
Aitäh
ďakujem
Gracias
Welálin
Cảm ơn anh
Rahmat
Спасибі
Trugéré
Ahéhee
Tualumba
Дзякуй
Takk
Mahalo
Ngiyabonga
Na gode
Falemínderit
Grazzi
Dhanyawaadh
Kiitos
Mulţumesc
Asante
Hvala
Merci
Matur nuwun
Благодаря
Daalụ
Diolch
Grazias
Grazie
Þakka þér
Paldies
Manana
Dank je
Danke
Ačiū
გმადლობ
תודה
Спасибо
Хвала
谢谢
متشكرم
Zikomo
Dankon
Gràcies
Баярлалаа
Misaotra
Tapadh leat
Miigwetch
Dankie
Terima kasih
Tack
Dèkuji
Благодарам
Salamat
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Grazas
Barka
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