Impatto clinico delle nuove linee guida nell'approccio ai germi MDR

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Istituto Nazionale per la Ricerca sul Cancro

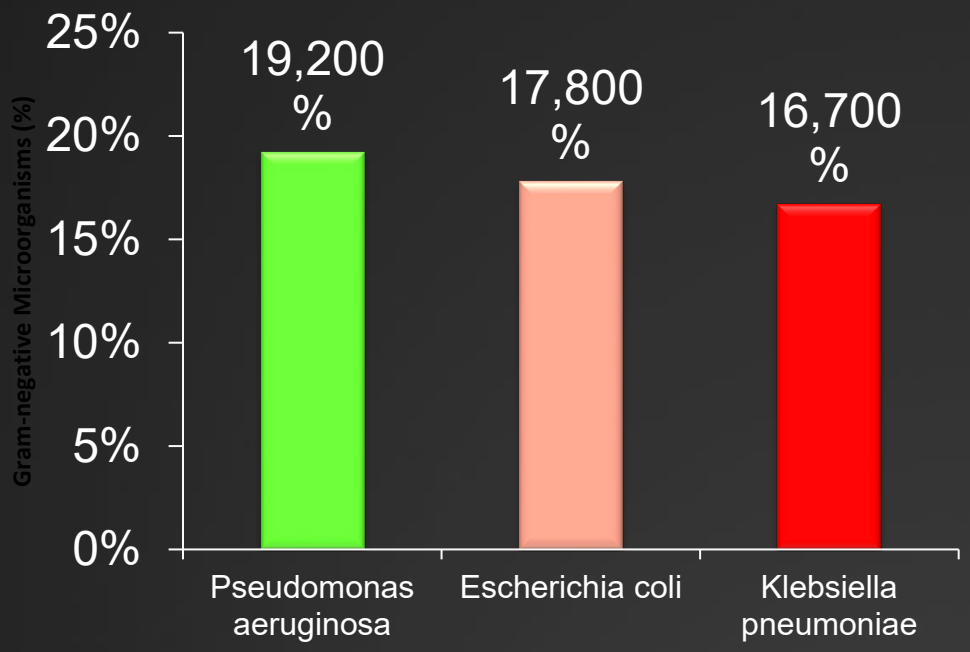
Disclosures
(past 2 years)

- Advisor/consultant/speaker bureau
  - Angelini, Biomerieux, Cidara, Gilead, Menarini, Medscape, Mundipharma, MSD, Pfizer, Shionogi

Gram-negative in critically ill patients: Enterobaterales vs Pseudomonas aeruginosa

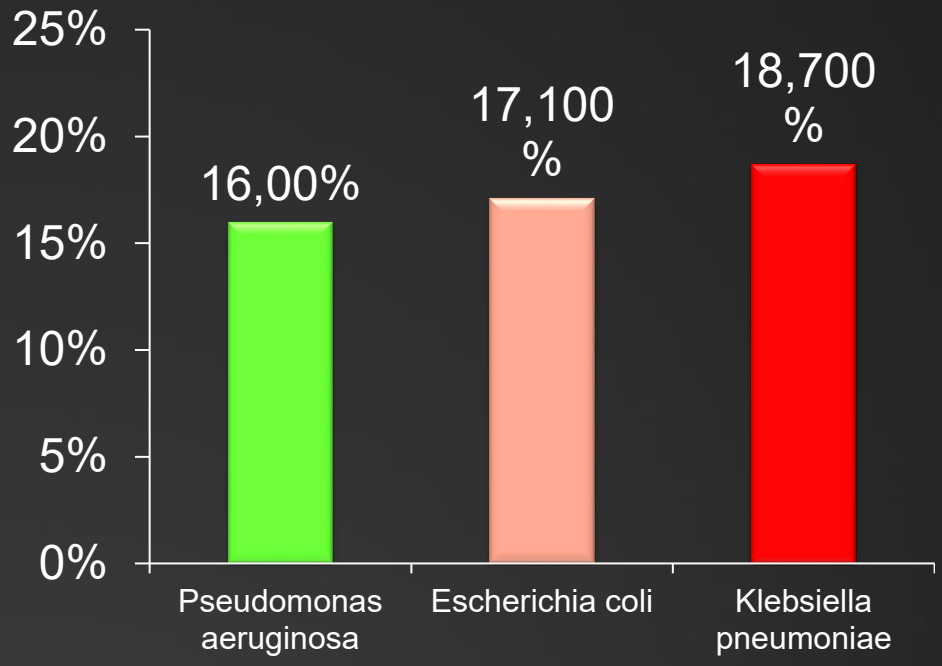
2010

Common Gram-negative Pathogens in the ICU[2]



2020

Common Gram-negative Pathogens in the ICU[1]



1. Vincent et al. JAMA. 2020 Apr 21; 323(15): 1478–1487
2. Data from 71 medical centers in the US during 2012 to 2013. Sader HS et al. IJAA 2015; 46:53-59

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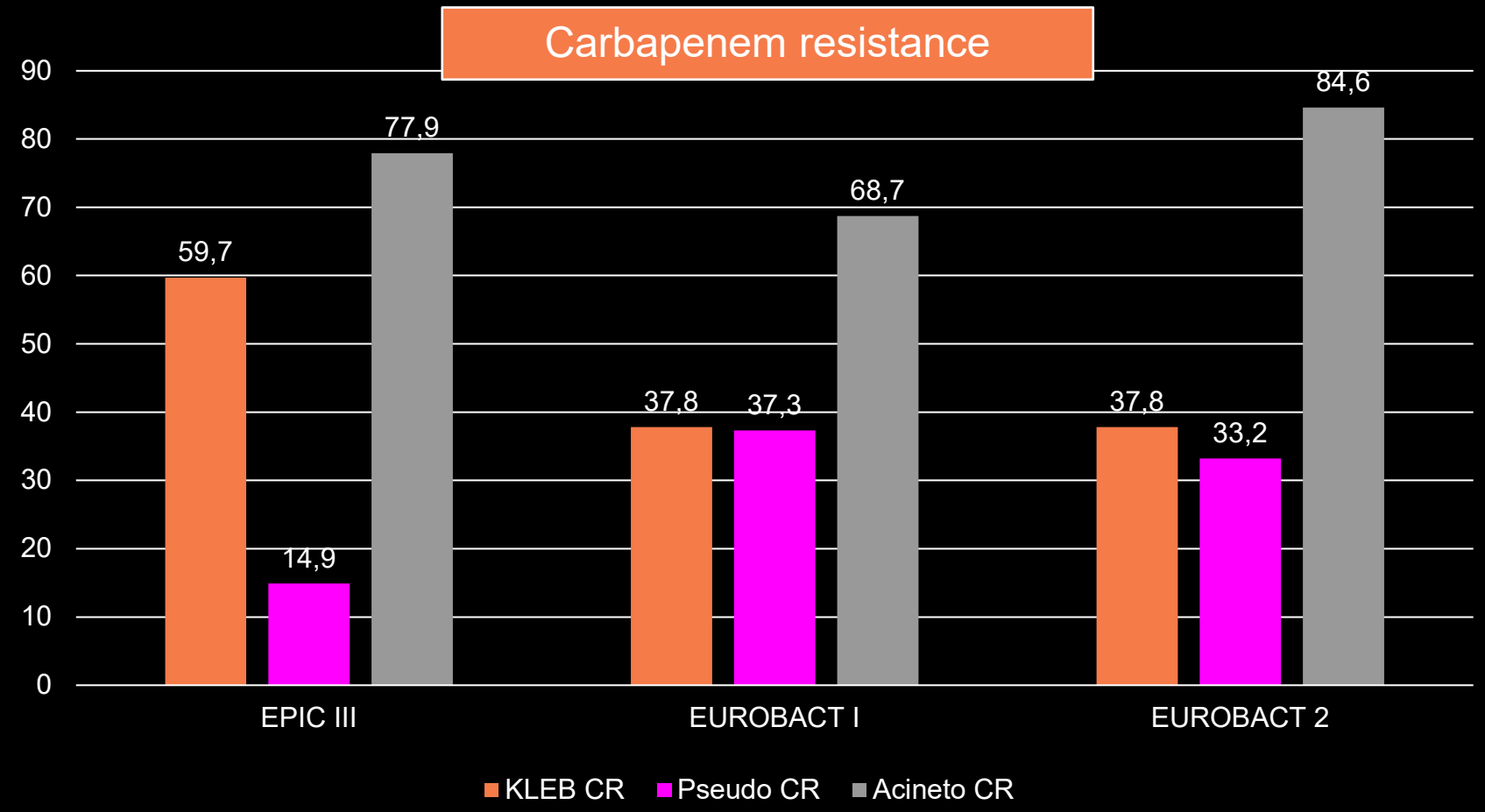
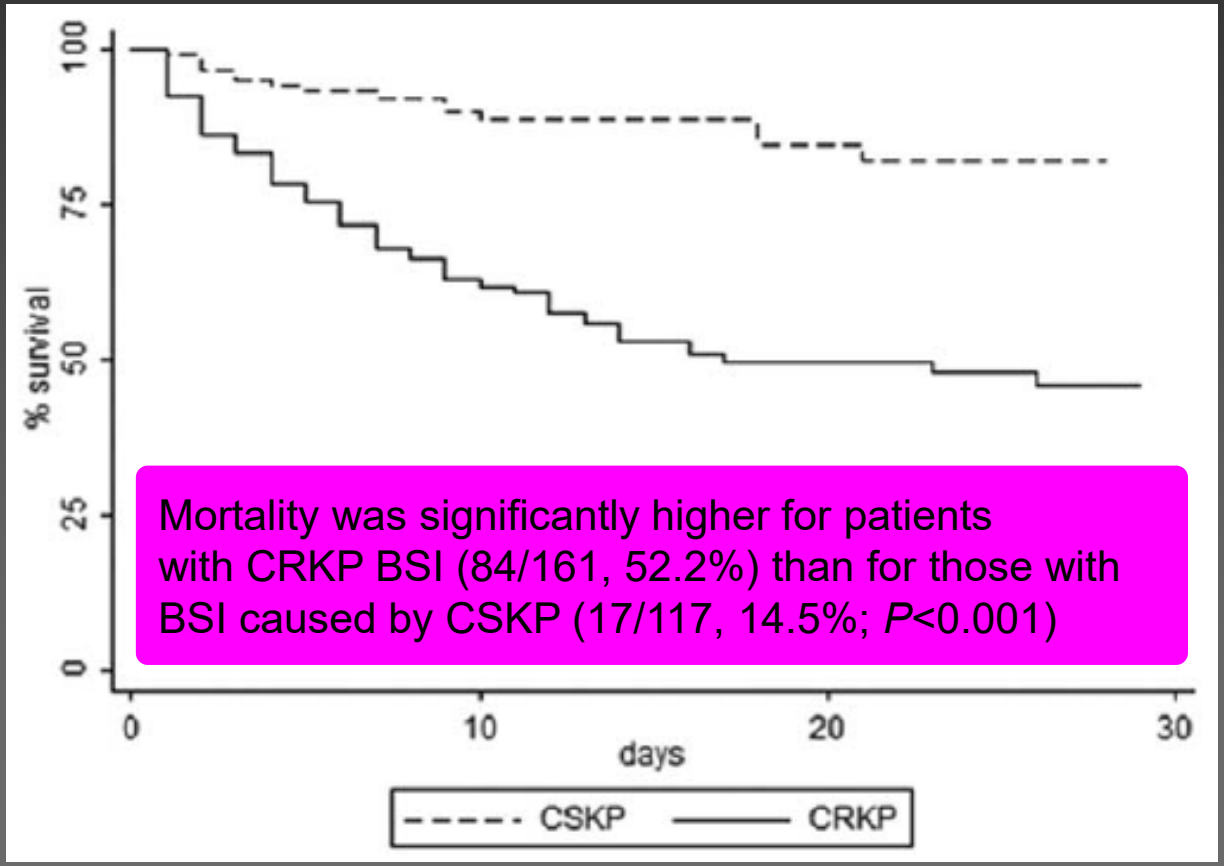
Characteristics of the pathogens in the initial blood culture in EUROBACT-2 and comparison with EUROBACT-1 and EPIC III studies



Vincent et al. JAMA. 2020 Apr 21; 323(15): 1478–1487
Tabah A et al. Intensive Care Med. 2023 Feb 10:1-13.
Tabah A et al. Intensive Care Med. 2012 Dec;38(12):1930-45

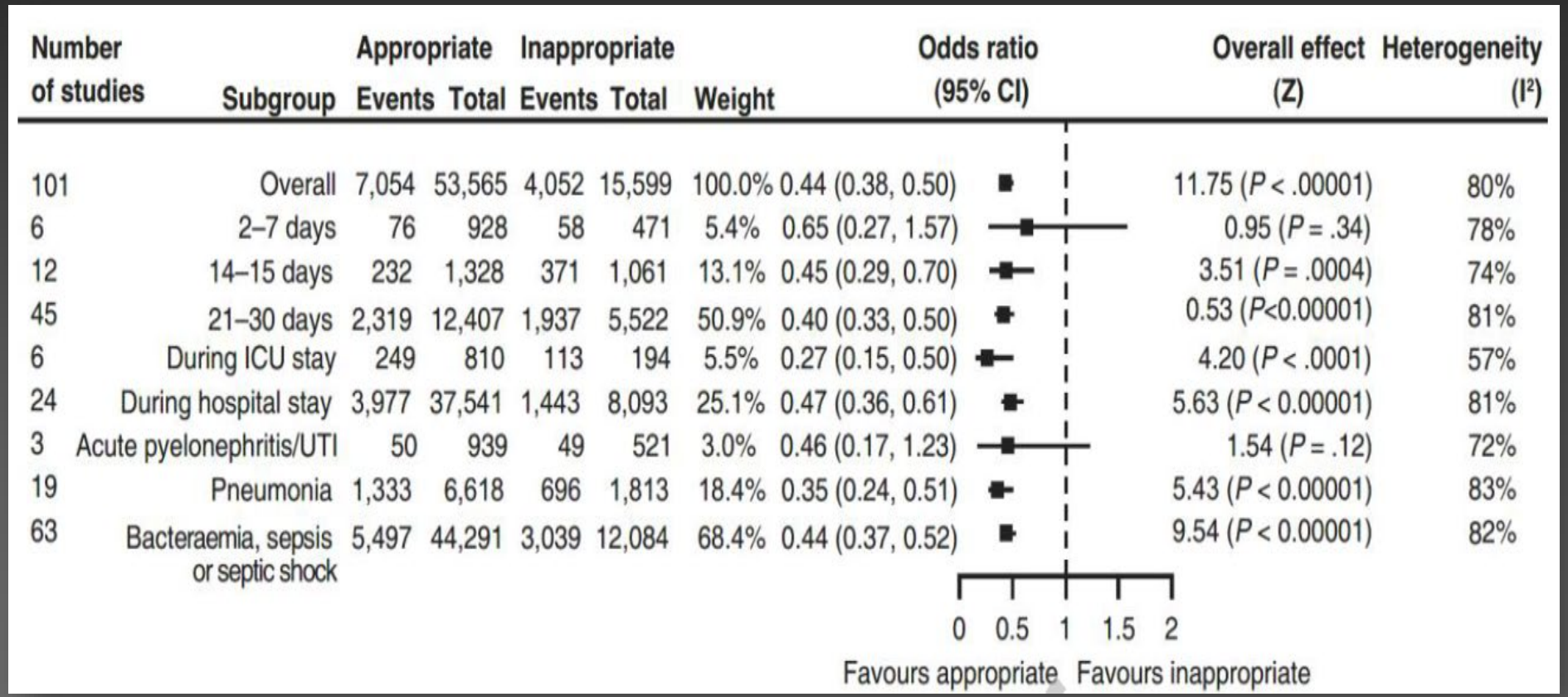
Clinical impact of CRE in hematological patients

Prospective cohort study on KP BSI in 13 Italian hematological units. 161/278 (57.9%) of KP BSI were CR



Trecarichi EM et al. *American J Haematol* 2016

Summary of the effect of appropriate versus inappropriate therapy on mortality



Number of studies	Subgroup	Appropriate Events	Appropriate Total	Inappropriate Events	Inappropriate Total	Weight	Odds ratio (95% CI)	Overall effect (Z)	Heterogeneity (I^2)
101	Overall	7,054	53,565	4,052	15,599	100.0%	0.44 (0.38, 0.50)	11.75 ($P < .00001$)	80%
6	2–7 days	76	928	58	471	5.4%	0.65 (0.27, 1.57)	0.95 ($P = .34$)	78%
12	14–15 days	232	1,328	371	1,061	13.1%	0.45 (0.29, 0.70)	3.51 ($P = .0004$)	74%
45	21–30 days	2,319	12,407	1,937	5,522	50.9%	0.40 (0.33, 0.50)	0.53 ($P<0.00001$)	81%
6	During ICU stay	249	810	113	194	5.5%	0.27 (0.15, 0.50)	4.20 ($P < .0001$)	57%
24	During hospital stay	3,977	37,541	1,443	8,093	25.1%	0.47 (0.36, 0.61)	5.63 ($P < 0.00001$)	81%
3	Acute pyelonephritis/UTI	50	939	49	521	3.0%	0.46 (0.17, 1.23)	1.54 ($P = .12$)	72%
19	Pneumonia	1,333	6,618	696	1,813	18.4%	0.35 (0.24, 0.51)	5.43 ($P < 0.00001$)	83%
63	Bacteraemia, sepsis or septic shock	5,497	44,291	3,039	12,084	68.4%	0.44 (0.37, 0.52)	9.54 ($P < 0.00001$)	82%

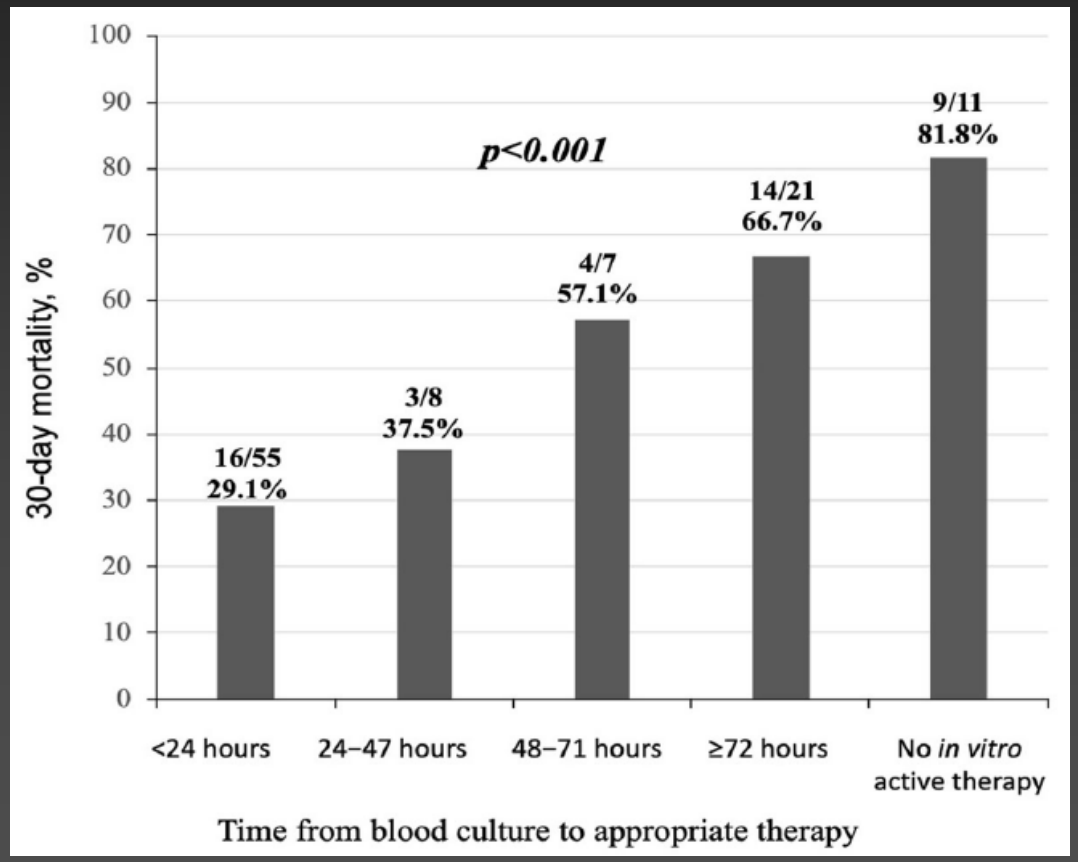
CI, confidence interval; ICU, intensive care unit; UTI, urinary tract infection

Bassetti M, *et al*. *Int J Antimicrob Agents*. 2020:106184.

Klebsiella pneumoniae: Importance of treating it right the first time

102 patients with KPC-Kp bacteraemia hospitalised between January 2015 and December 2018 at two academic centres in Italy

- **Primary outcome**: Relationship between time from blood cultures collection to appropriate antibiotic therapy and 30-day mortality
- **Result:** 30-day mortality was 45%
  - Median time to appropriate antibiotic therapy was shorter in patients who survived (8/5 h [IQR 1–36]) versus those who died (48 h [IQR 5–108], p=0.014)
  - Ceftazidime–avibactam-containing regimens were associated with reduced risk of composite endpoint (30-day mortality OR nephrotoxicity) (HR 0.231 [95% CI: 0.071–0.745], p=0.014) compared to colistin-containing regimens



Falcone M, *et al. Crit Care*. 2020;24(1):29.

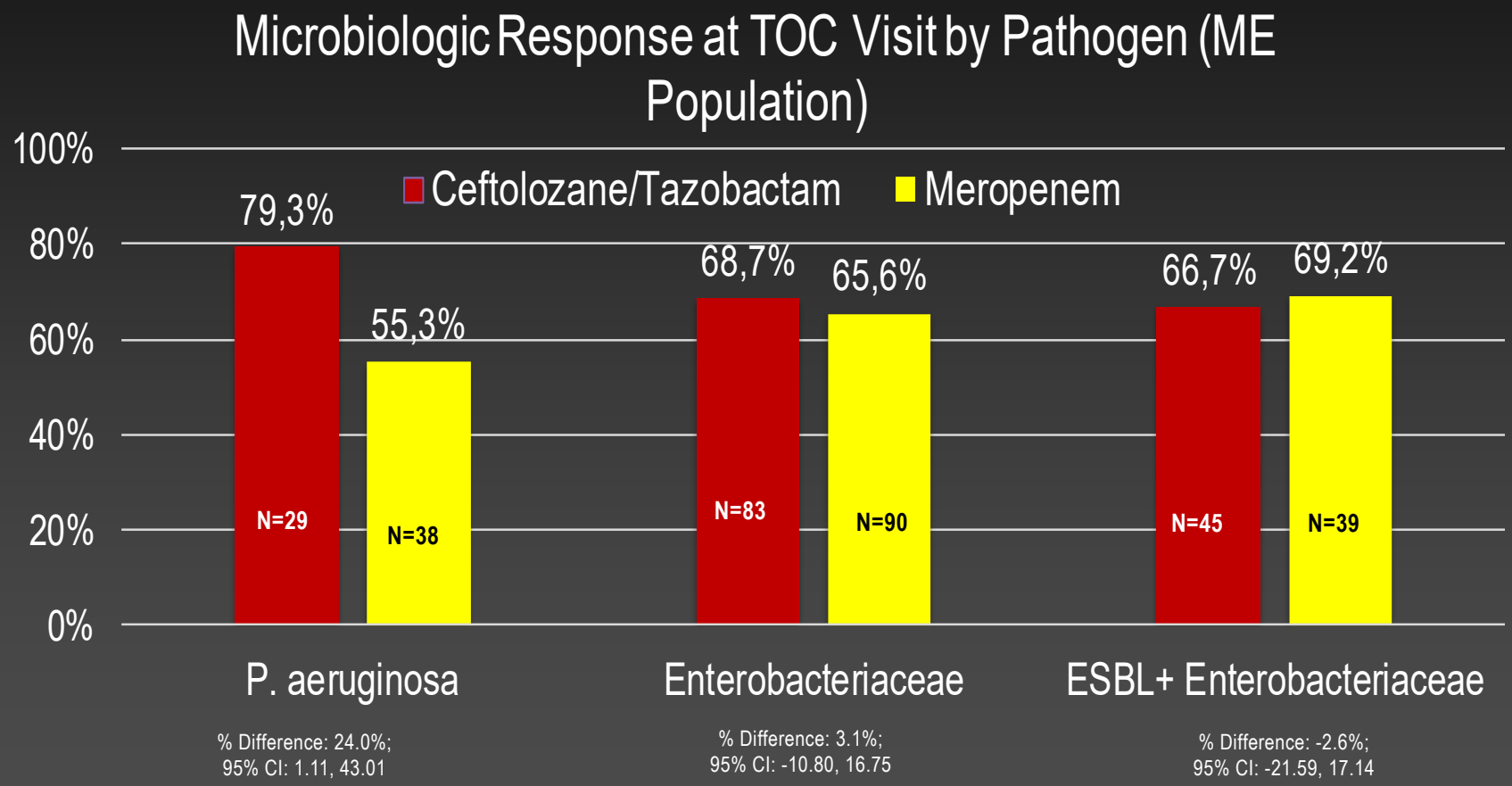
Activity of new agents against Gram-negative pathogens.

Grey shading: variable activity; red shading: non-activity; green shading: activity. KPC: Klebsiella pneumoniae carbapenemases; OXA: OXA-β-lactamases; NDM: New Delhi metallo-β-lactamase.

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	Class B Carbapenemase (*e.g.* NDM)	Class D Carbapenemase (*e.g.* OXA-48)	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Ceftobiprole						
Ceftolozane-tazobactam						
Ceftazidime-avibactam						
Cefiderecol						
Meropenem-vaborbactam						
Imipenem-relebactam						
Aztreonam-avibactam						
Plazomicin						
Eravacycline						

Bassetti M et al. Eur Respir Rev. 2022 Dec 31; 31(166): 220119

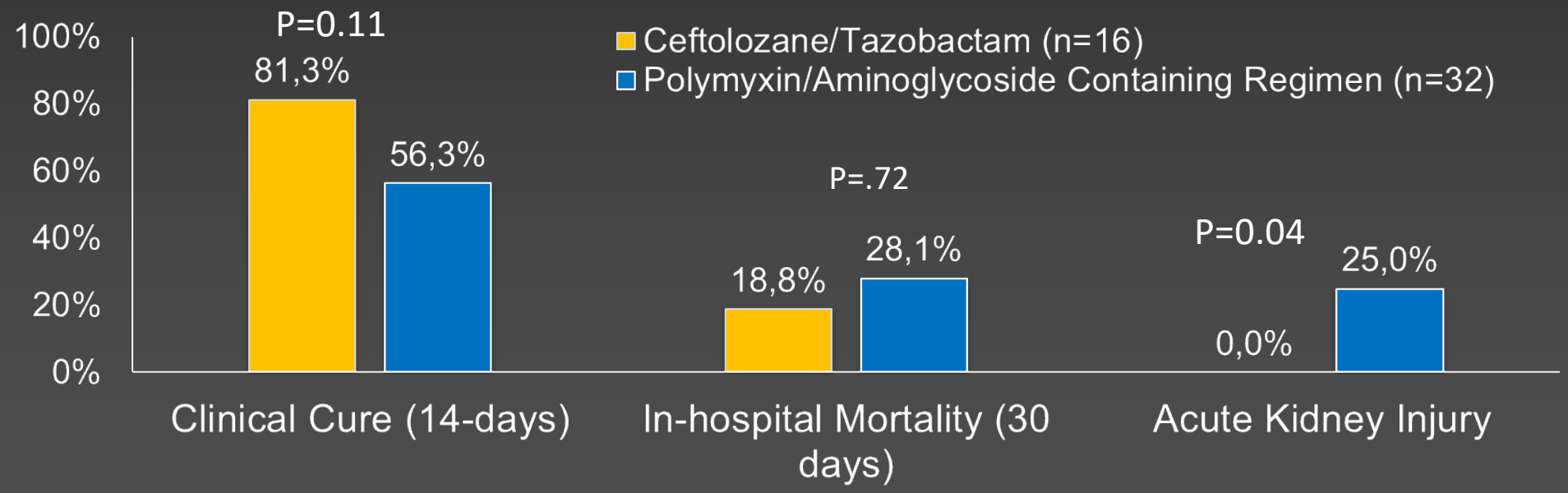
Per-Pathogen Microbiologic Response at Test of Cure (TOC)



Kollef M et al. Lancet Infect Dis. 2019 Sep 25. pii: S1473-3099(19)30403-7

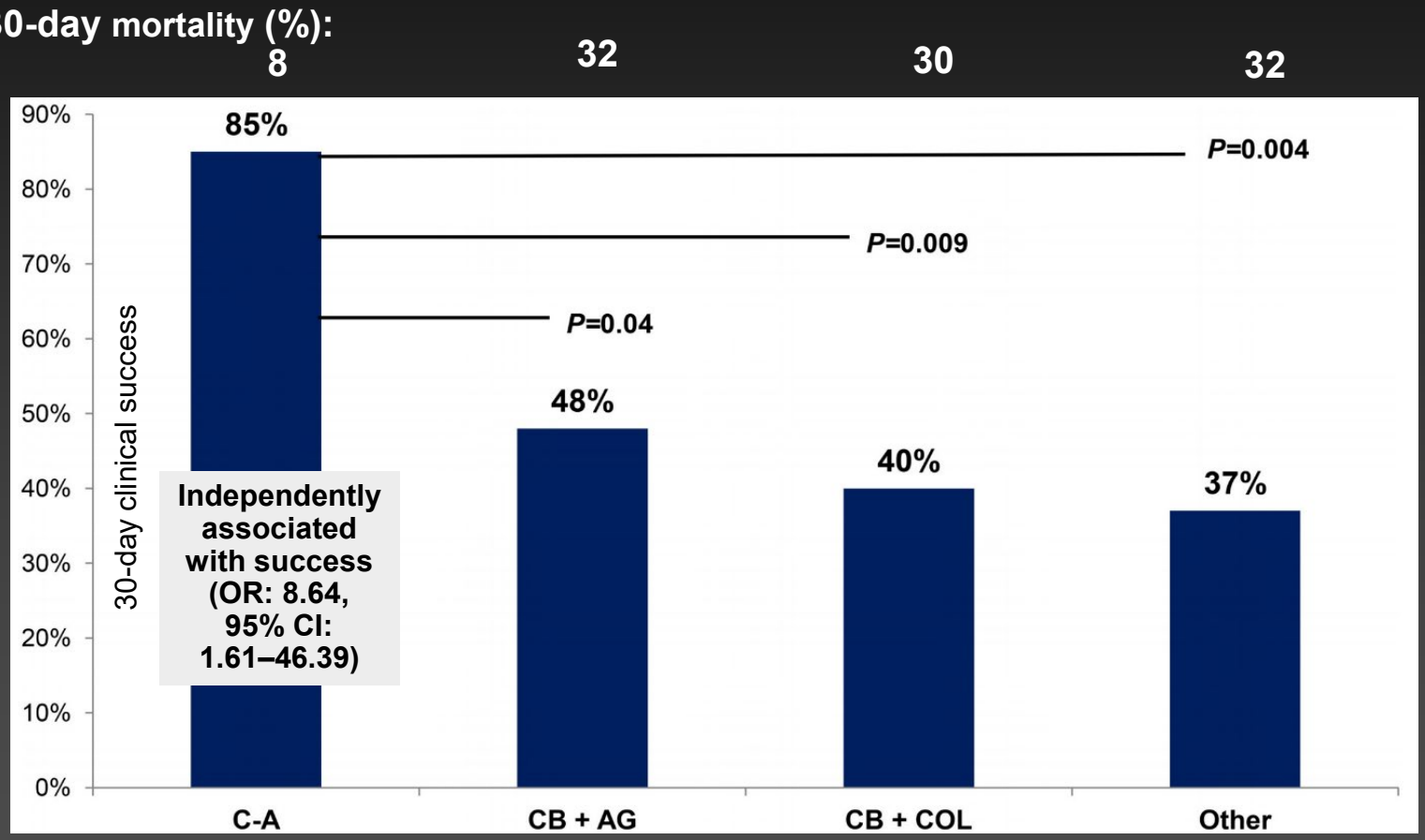
Comparative effectiveness of ceftolozane/tazobactam vs. polymyxin or aminoglycoside containing regimens (Italy)

- 1:2 matched case-control analysis at 9 centers in Italy
  - Patients with nosocomial pneumonia or bloodstream infections due to MDR or XDR P. aeruginosa
  - A trend toward more favorable 14-day clinical cure rates with C/T (81% vs 56%, p=0.11)
  - An increased prevalence of acute kidney injury (25% vs 0%, p=0.04) with colistin/aminoglycoside containing regimens



Vena A et al. Clin Infect Dis 2020

Mortality rate in KPC-producing *K. pneumoniae* bacteraemia experience with CAZ–AVI



N=109

100% resistant to meropenem MIC≥16 mg/L (meropenem dose was not provided)

Secondary bacteremia resulted from abdominal (46%), respiratory tract (13%), urinary tract (13%).

AG, aminoglycoside; CAZ–AVI, ceftazidime-avibactam; CB, carbapenem-based; CI, confidence interval; COL, colistin; KPC, *K. pneumonia* carbapenemase; MIC, minimum inhibitory concentration; OR, odds ratio

Adapted from: Shields R, *et al. Antimicrob Agents Chemother.* 2017;61:e00883–17.

Efficacy and safety of ceftazidime avibactam versus polymyxins in the treatment of carbapenem- resistant Enterobacteriaceae infection

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	polymyxins Events	polymyxins Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2021	5	26	40	103	9.6%	0.50 [0.22, 1.13]
Falcone 2020	3	13	27	61	6.3%	0.52 [0.19, 1.46]
Falcone 2021	10	52	16	27	15.1%	0.32 [0.17, 0.61]
Hakeam 2021	12	32	12	29	15.8%	0.91 [0.49, 1.69]
Ryan 2017	1	13	9	30	1.8%	0.26 [0.04, 1.82]
Satlin 2022	2	21	8	26	3.4%	0.31 [0.07, 1.30]
van Duin 2018	3	38	33	99	5.4%	0.24 [0.08, 0.73]
Zheng 2022	29	82	57	82	41.6%	0.51 [0.37, 0.70]
Zhou 2021	0	4	17	28	1.0%	0.17 [0.01, 2.34]
Total (95% CI)		281		485	100.0%	0.48 [0.37, 0.63]
Total events	65		219			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.85$, $df = 8$ ($P = 0.35$); $I^2 = 10\%$

Test for overall effect: $Z = 5.39$ ($P < 0.00001$)

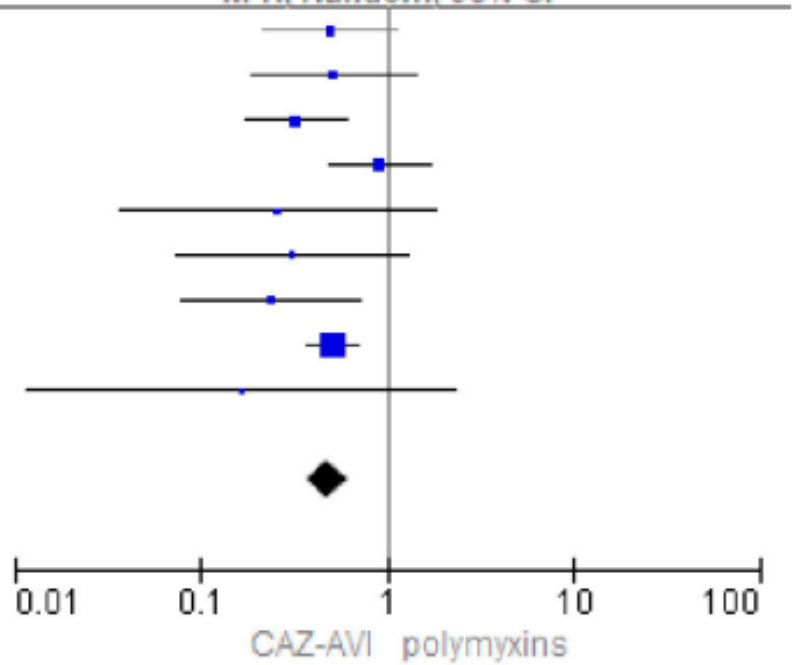


Figure 2 The 30-day mortality of the CAZ-AVI regimens compared with polymyxins regimens. CAZ-AVI, ceftazidime–avibactam.

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Yang P et al. BMJ Open 2023;13:e070491.

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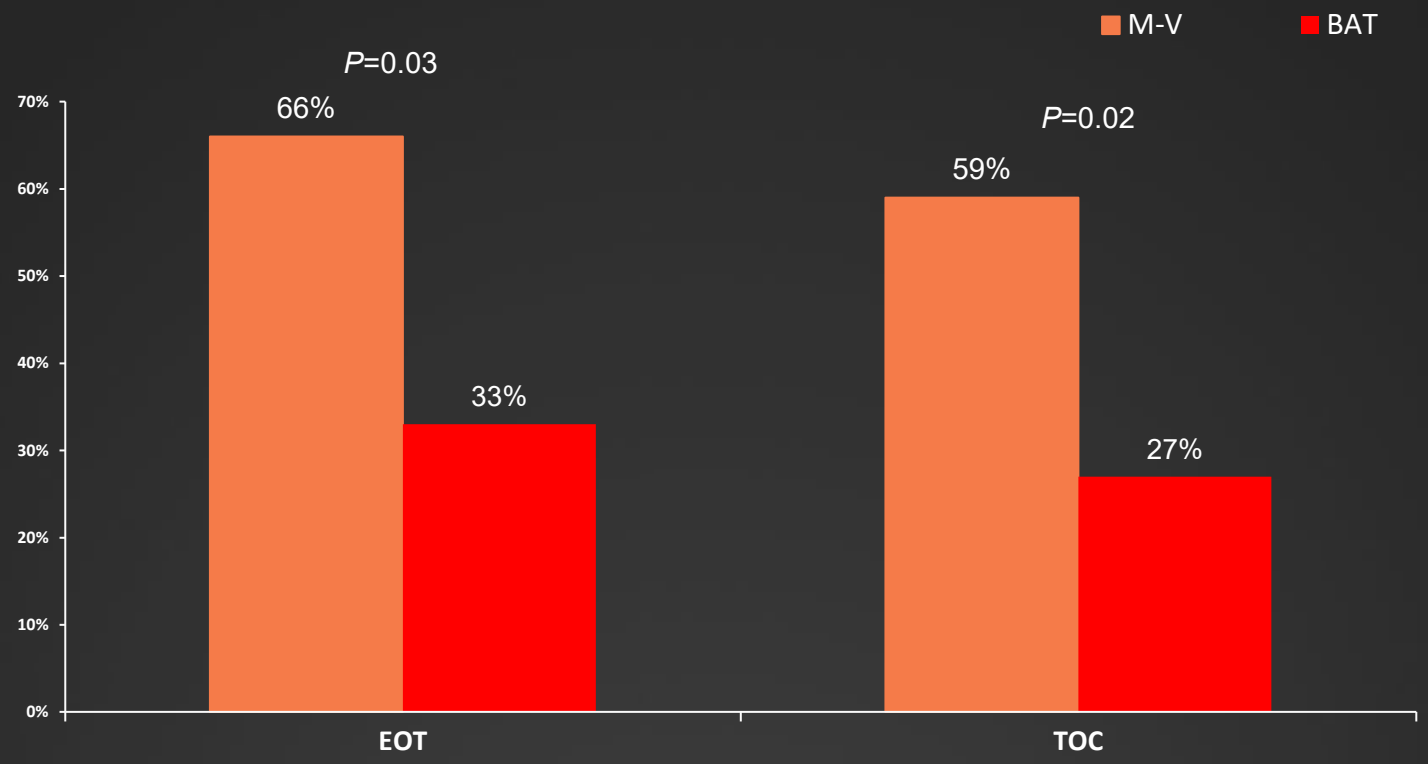
Meropenem-vaborbactam: TANGO II

Meropenem-vaborbactam showed higher clinical cure rates at end of therapy (EOT) and test of cure (TOC)



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Wunderink RG, et al. Infect Dis Ther. 2018;

TANGO II
Day 28 All-Cause Mortality
All Infection Types (mCRE-MITT)

Endpoint/Statistics	MV N=32 n, (%)	Best Available Therapy N=15 n, (%)	Absolute Percent Difference (MV-BAT)	Relative Percent Difference [(MV-BAT)/BAT]
All-Cause Mortality Rate Day 28	5 (15.6)	5 (33.3)	-17.7	-53.2
Subjects Censored*	27 (84.4)	10 (66.7)		
Kaplan-Meier Estimate (95%CI)	15.6 (6.8 to 33.5)	33.3 (15.4 to 62.5)		

*Subjects whose survival status is unknown due to early termination or lost to follow up will be censored at the last day the subject was known to be alive.

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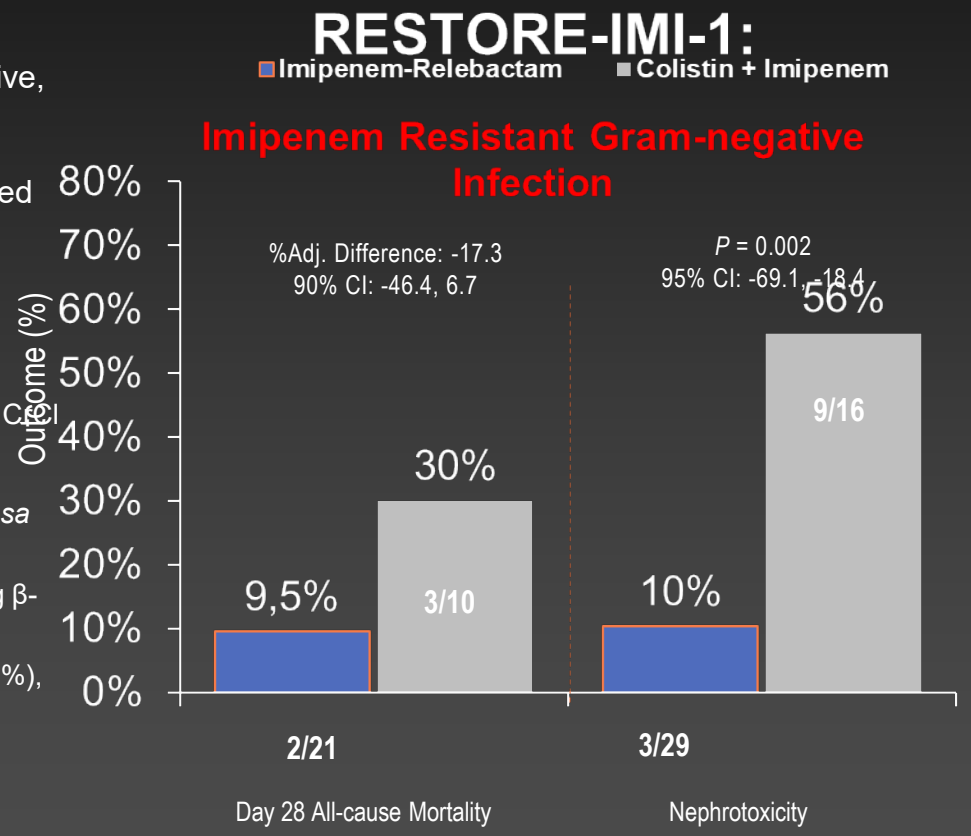
Wunderink RG, et al. Infect Dis Ther. 2018; https://doi.org/10.1007/s40121-018-0214-1

RESTORE-IMI-1: Efficacy & Safety of Imipenem-Relebactam (IMI-REL) in Patients with Imipenem-NS Infections

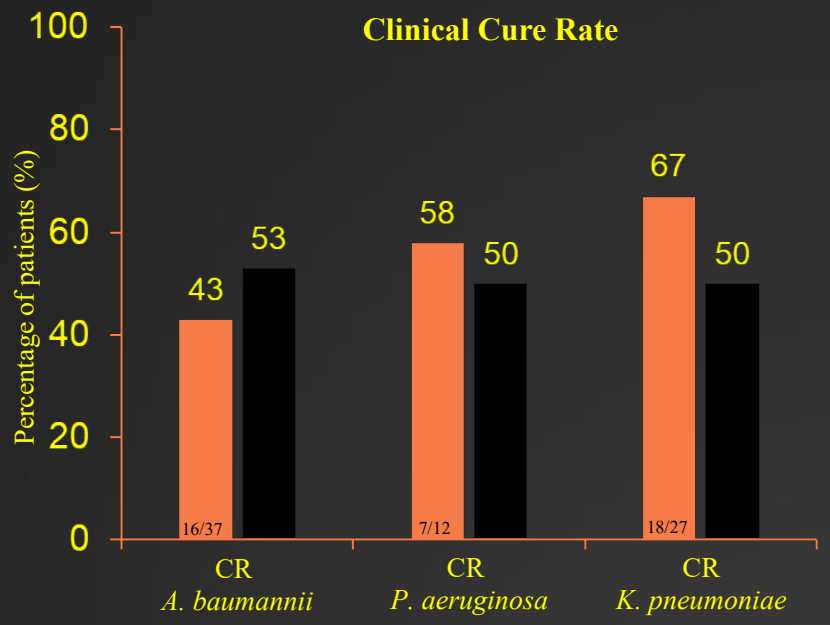
- RESTORE-IMI-1 is the first prospective comparative, randomized, double blind trial of a β-lactam/β-lactamase inhibitor as monotherapy (imipenem/relebactam) compared to dose optimized colistin + imipenem
  - 47 patients were randomized & treated (31 IMI/REL, 16 colistin+IMI), 31 of whom met mMITT criteria (11 HABP/VABP, 16 cUTI, and 4 cIAI)
    - 29% had APACHE-II scores >15, 23% had CrCl <60 mL/min, 35% were ≥65 yrs old.
    - Qualifying baseline pathogens: *P. aeruginosa* (77%), *Klebsiella* spp (16%), and other Enterobacteriaceae (6%), with the following β-lactamases detected: AmpC (84% of all qualifying isolates), ESBLs (39%), KPC (16%), OXA-48 (3%)
  - Efficacy defined by a favorable overall response (survival for HABP/VABP + clinical for cIAI, + clinical/micro for cUTI)

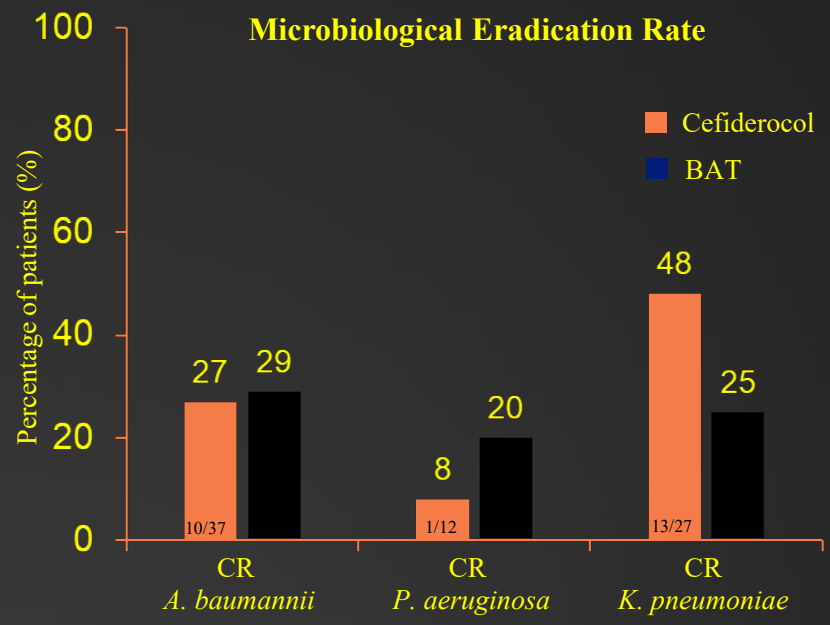


Adjusted difference, based on Miettinen and Numiren method stratified by infection site

Motsch J et al..Clin Infect Dis Clin Infect Dis. 2020;70(9):1799-1808 (RESTORE-IMI-1)

CREDIBLE-CR: similar rates at TOC by baseline pathogen, but higher for cefiderocol in Enterobacterales infection[a]





[a]CR micro-ITT population

BAT, best available therapy; CR, carbapenem resistant; CR Micro-ITT, carbapenem-resistant microbiological intention-to-treat population; TOC, test of cure.

Bassetti M, et al. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30796–9

CREDIBLE-CR: all-cause mortality, Day 28 and End of Study[a]

Timing of death	Cefiderocol (n=101) n (%)	BAT (n=49) n (%)
Up to Day 28	25 (25)	9 (18)
Late: Day 29 to end of study	9 (9)	0 (0)
Overall mortality: end of study	34 (34)	9 (18)

[a]Safety population

BAT, best available therapy.

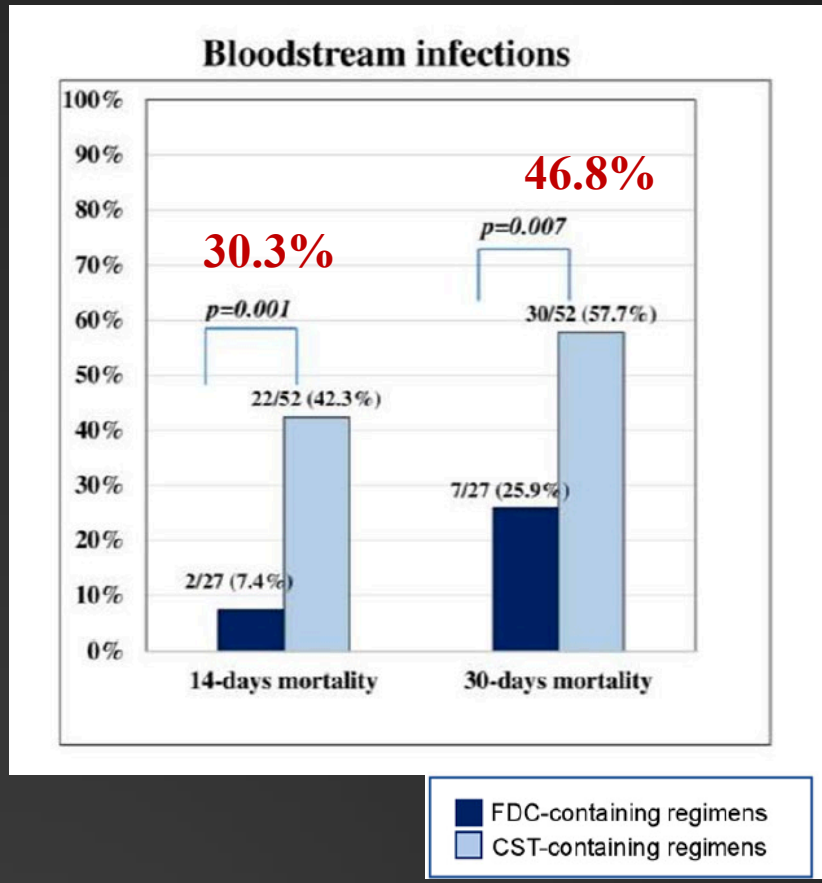
Bassetti M, et al. *Lancet Infect Dis* 2020; Published online October 12, 2020 https://doi.org/10.1016/S1473-3099(20)30796-9

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

- **Study population**
  - 124 patients with *A. baumannii* infections
  - 47 (37.9%) FDC vs 77 (62.1%) CST-containing regimens

- **Risk factors for 30-day mortality**
  - Septic shock
  - SOFA score
  - Age were
  - Cefiderocol therapy (HR 0.44)

- **AEs:** 21.1% COL Vs 2.1%, FDC p<0.01.



Falcone M et al AAC. 2022

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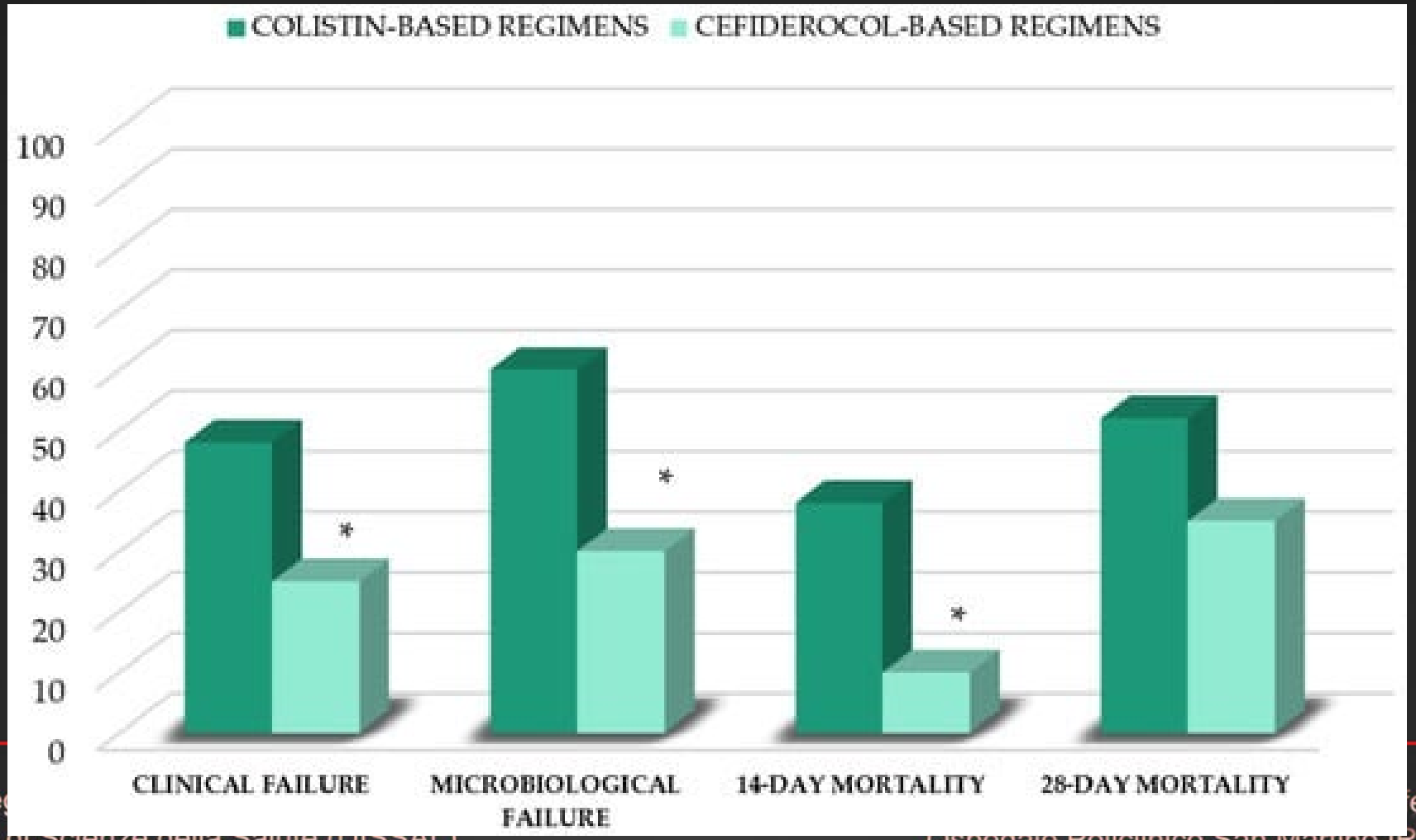
Outcomes of patients stratified by first-line therapy

*** p < 0.05 vs. colistin group.**



Dalfino L et al. *Antibiotics* (Basel) 2023 Jun 14;12(6):1048

Examples of clinical experience of ‘old-style’ vs ‘new-style’ treatment in CRE infections

Study	Treament	Mortality
OLD		
Shields *et al. Antimicrob Agents Chemother* 2017	Ceftazidime/avibactam (monotherapy or combination)	8%
Wunderink *et al. Infect Dis Ther* 2018	Meropenem/vaborbactam	15.6%
Motsch *et al. Clin Infect Dis* 2020	Imipenem/relabactam	9.5%
Bassetti *et al. Lancet Infect Dis* 2021	Cefiderocol	13.8%

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkad262

Journal of Antimicrobial Chemotherapy

Mortality in KPC-producing *Klebsiella pneumoniae* bloodstream infections: a changing landscape

Daniele Roberto Giacobbe [1,2]*, Cristina Marelli [2], Greta Cattardico[1,2], Chiara Fanelli[2,3], Alessio Signori[4], Gabriele Di Meco[2], Vincenzo Di Pilato [5], Malgorzata Mikulska[1,2], Maria Mazzitelli [6], Anna Maria Cattelan[6,7], Carlo Pallotto[8], Daniela Francisci[8], Alessandra Calabresi[9], Andrea Lombardi [10,11], Andrea Gori[11,12], Valerio Del Bono[13], Chiara Aldieri[13], Angela Raffaella Losito[14], Francesca Raffaelli[14], Andrea Cortegiani[15,16], Marta Milazzo[15], Filippo Del Puente[17], Emanuele Pontali[17], Francesco Giuseppe De Rosa [18,19], Silvia Corcione [18], Alessandra Mularoni [20], Giovanna Russelli[20], Mauro Giacomini [21], Flavia Badalucco Ciotta[22], Chiara Oltolini[22], Francesco Saverio Serino[23], Elena Momesso[24], Michele Spinicci[25,26], Lucia Graziani [25], Carlo Torti[27,28], Enrico Maria Trecarichi[27,28], Marco Merli [29], Federico D'Amico[29], Anna Marchese[5,30], Antonio Vena[1,2] and Matteo Bassetti[1,2]† on behalf of the CARBANEW study group

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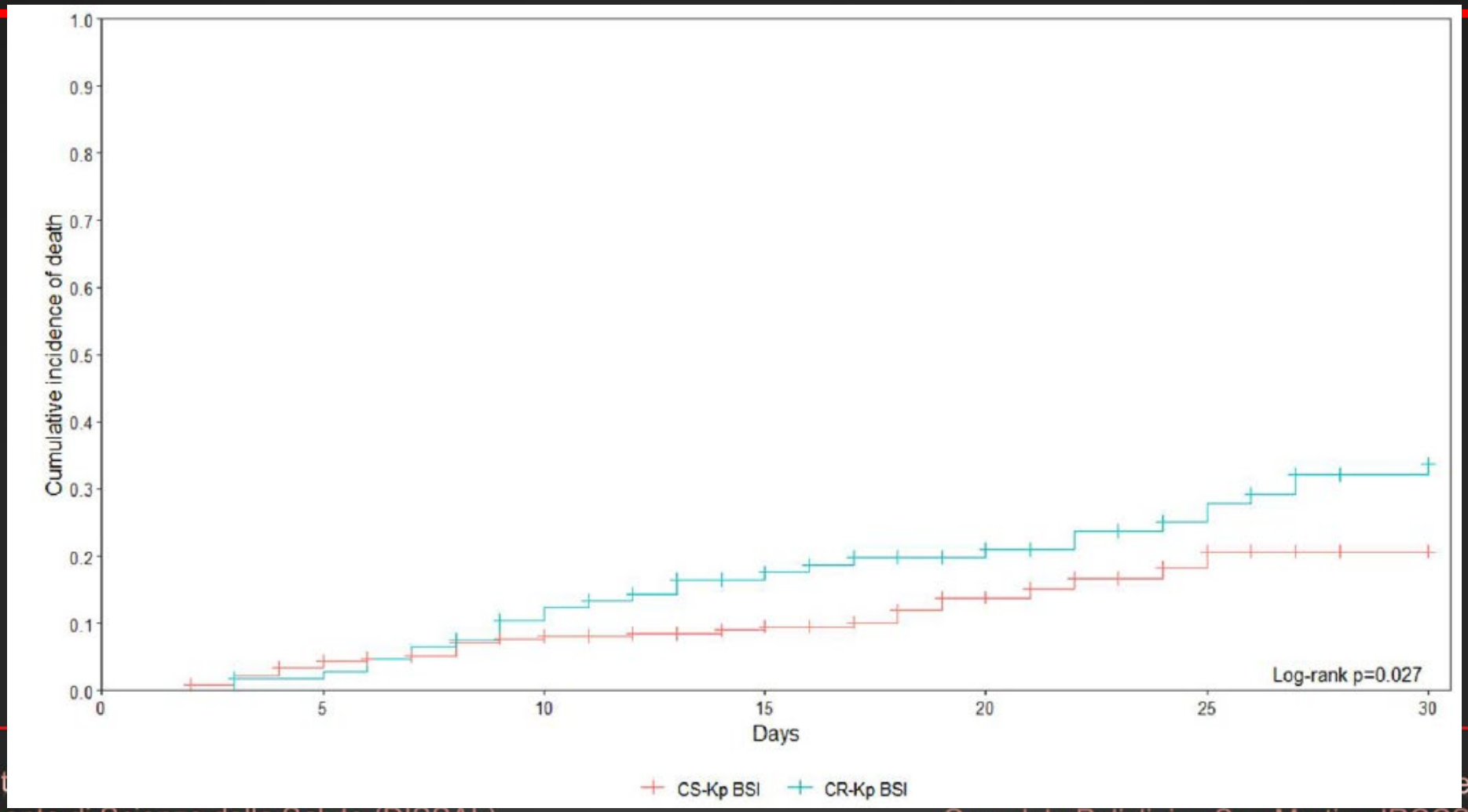
Cumulative mortality up to day 30 in patients with CR-Kp BSI and CS-Kp BSI



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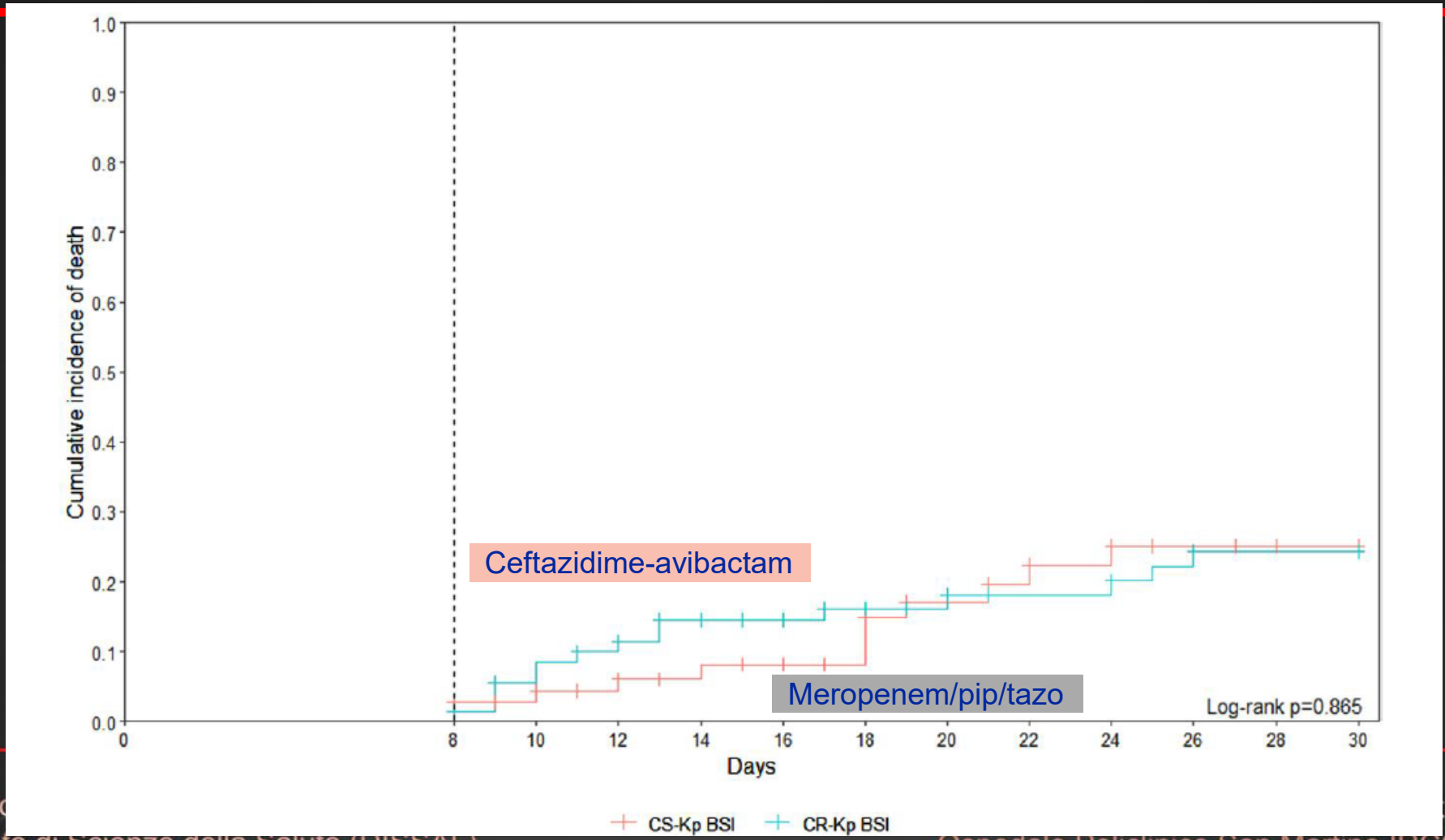
30-day mortality in patients with CR-Kp BSI receiving appropriate therapy with ceftazidime-avibactam (cases) vs patients with CS-Kp BSI receiving appropriate therapy with other agents (controls)



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Contents lists available at ScienceDirect

Clinical Microbiology and Infection

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, §]

CRE- ESCMID

- For patients with severe infections due to CRE, we suggest meropenem-vaborbactam or ceftazidime-avibactam
- For patients with severe infections due to CRE-carrying metallob-lactamases (MBL) and/or resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam, we conditionally recommend treatment with cefiderocol
- For patients with cUTI, we suggest aminoglycosides, including plazomicin, over tigecycline
- We suggest that tigecycline not be used for BSI and HAP/VAP; if necessary, in patients with pneumonia, clinicians may use highdose tigecycline

Paul M et al. Clin Microb Infect 2022; 28:521

CRE- IDSA

- Meropenem-vaborbactam, ceftazidime-avibactam, and imipenemcilastatin-relebactam are preferred treatment options for KPC-producing infections. Cefiderocol is an alternative option.
- Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment options for NDM and other metallo-β-lactamaseproducing infections.
- Ceftazidime-avibactam is the preferred treatment option for OXA-48-likeproducing infections. Cefiderocol is an alternative treatment option.
- **Polymyxin B and colistin are not suggested for the treatment of infections caused by CRE. Colistin can be considered as an alternative agent for uncomplicated CRE cystitis**

Tamma PD et al. Clin Infect Dis 2023; ,428,

CR PA -ESMID

- In patients with severe infections due to DTR-CRPA, we suggest therapy with ceftolozane-tazobactam if active in vitro
- Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam at this time.

Paul M et al. Clin Microb Infect 2022; 28:521

CR PA – IDSA

- For critically ill patients or those with poor source control with P. aeruginosa isolates resistant to carbapenems but susceptible to traditional βlactams, use of a novel β-lactam agent that tests susceptible (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment approach.
- Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenemcilastatin-relebactam are preferred options for the treatment of infections outside of the urinary tract caused by DTR-P. aeruginosa.
- Cefiderocol is an alternative treatment option for infections outside of the urinary tract caused by DTR-P. aeruginosa.

Paul M et al. Clin Microb Infect 2022; 28:521

CR Acinetobacter baumannii

- For patients with CRAB susceptible to sulbactam and HAP/VAP, we suggest ampicillin-sulbactam
- 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.
- We conditionally recommend against cefiderocol for the treatment of infections caused by CRAB

Paul M et al. Clin Microb Infect 2022; 28:521

CR AB – IDSA

- High-dose ampicillin-sulbactam is suggested as a component of combination therapy for CRAB, regardless of whether susceptibility has been demonstrated.
- Cefiderocol should be limited to the treatment of CRAB infections refractory to other antibiotics or in cases where intolerance or resistance 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.

Tamma PD et al. Clin Infect Dis 2023; ,428,

Management of nonfermenting gram-negative infections: a critique of the guidelines

Matteo Bassetti[a,b], *Antonio Vena*[a,b] *and Daniele Roberto Giacobbe*[a,b]

- IDSA and ESCMID approaches should be viewed as complementary and evolving, and should not preclude further revision based on accumulating evidence on the use of novel BL and BL/BLI combinations
- a wise joint consideration of both philosophies could allow to improve adherence to evidence based ESCMID recommendations while at the same time leaving the door opened for the use of alternative novel agents in specific situations

Bassetti M et al. Curr Opin Infect Dis 2023, 36:609–614

RACCOMANDAZIONI AIFA
PER USO OTTIMALE ANTIBIOTICI

Terapia mirata delle infezioni causate da batteri Gram negativi resistenti a multipli antibiotici

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ENTEROBACTERALES RESISTENTI AI CARBAPENEMI

INFEZIONI URINARIE COMPLICATE		Dosaggio	Note
Prima scelta	**Cotrimossazolo**	8-12 mg/kg/die (basato sul trimetoprim) EV/PO diviso q8-12h (dose massima di trimetoprim/die: 960 mg)	
	Amikacina	20 mg/kg/dose d EV per 1^ dose*	Durata massima: 7 giorni
	Gentamicina	7 mg/kg/dose EV per 1^ dose *	
	Meropenem	2 g EV q8h, infuso in 3 ore	Se MIC < 2 mg/l
Seconda scelta	**Ceftazidime-avibactam**	2,5 g EV q8h	
	Meropenem-vaborbactam	4 g EV q8h	
Alternative *se prima e seconda scelta non possibili*	**Cefiderocol**	2 g EV q8h	
	Colistina	Dose da carico 9 mln UI EV seguita da 4,5 mln UI EV q12h	
	Tigeciclina	Dose da carico 100 mg EV, seguita da 50 mg EV q12h	

ENTEROBACTERALES RESISTENTI AI CARBAPENEMI

SEPSI E SHOCK SETTICO, POLMONITI, INFEZIONI ADDOMINALI CON SOURCE CONTROL NON OTTIMALE, INFEZIONI DEL SNC		Dosaggio	Note
Prima scelta	Meropenem	2 g EV q8h, infuso in 3 ore	Se MIC per il meropenem < 2 mg/l
	Ceftazidime-avibactam	2,5 g EV q8h	
	Meropenem-vaborbactam	4 g EV q8h	Non attivo su batterio produttore di OXA-48
Seconda scelta	Amikacina	20 mg/kg/dose EV per 1^ dose*	Infezioni urinarie gravi e solo in combinazione con un altro AUC
	Gentamicina	7 mg/kg/dose EV per 1^ dose*	
	Colistina	Dose da carico 9 mln UI EV seguita da 5,5 mln UI EV q12h	Solo in combinazione con AUC
	Fosfomicina EV	12-24 g EV q8h -q12h	
	Tigeciclina	Dose da carico 100 mg EV, seguita da 50 mg EV q12h	Infezioni addominali gravi e solo in combinazione con un altro AUC
	Meropenem	2 g EV q8h, infuso in 3 ore	Se MIC >2 e ≤ 8 in combinazione con un altro AUC
Alternative *se prima e seconda scelta non possibili*	Cefiderocol	2 g EV q8h	Infezioni urinarie gravi e infezioni polmonari con documentata produzione di metallo-beta-lattamasi
	Ceftazidime-avibactam + aztreonam	Ceftazidime-avibactam: 2,5 g EV q8h + aztreonam: 2 g EV q8h, infuso in 3 ore, possibilmente in contemporanea a ceftazidime-avibactam	Se documentata produzione di metallo-beta-lattamasi

ACINETOBACTER BAUMANNII RESISTENTE AI CARBAPENEMI

SEPSI E SHOCK SETTICO,POLMONITI, INFEZIONI ADDOMINALI CON BONIFICA DEL SITO INFETTIVO NON OTTIMALE, INFEZIONI DEL SNC		Dosaggio	Note
Prima scelta	Ampicillina-sulbactam	9 g EV q8h infuso in 4 ore / 27 g EV q24h in infusione continua	Solo in combinazione con un altro AUC
	Colistina	Dose da carico 9 mln UI EV seguita da 5,5 mln UI EV q12h	
	Tigeciclina	Dose da carico 100 mg EV, seguita da 50 mg EV q12h	
Seconda scelta	Cefiderocol	2 g EV q8h	

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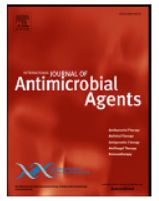

Review

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)

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Italian guidelines for management of MDR bacteria

KPC

Recommendation 5.2:

2.a In patients with infections caused by KPC-producing carbapenem-resistant Enterobacterales (CRE), novel β-lactam agents such as ceftazidime/avibactam and meropenem/vaborbactam should be the first-line treatment options.

2.b Imipenem/relebactam and cefiderocol may also be considered.

2.a	Strength of recommendation:	**STRONG**	Certainty of evidence:	**MODERATE**
2.b	Strength of recommendation:	**CONDITIONAL**	Certainty of evidence:	**LOW**

OXA-48

Recommendation 5.3:

In patients with infections caused by OXA-48-like producing carbapenem-resistant Enterobacterales (CRE), ceftazidime/avibactam should be the first-line treatment option.

Strength of recommendation:	**CONDITIONAL**	Certainty of evidence:	**VERY LOW**

MBL

Recommendation 5.4:

4.a *In patients with infections caused by metallo-β-lactamase (MBL)-producing carbapenem-resistant Enterobacterales (CRE), ceftazidime/avibactam plus aztreonam should be preferred.*

4.b *Cefiderocol may also be considered.*

4.a	Strength of recommendation:	**STRONG**	Certainty of evidence:	**MODERATE**
4.b	Strength of recommendation:	**CONDITIONAL**	Certainty of evidence:	**LOW**

P. aeruginosa DTR

Recommendation 6.1:

In patients with invasive infections caused by Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-PA), based on pre-clinical and clinical data, novel β-lactam agents such as ceftolozane/tazobactam and ceftazidime/avibactam are currently the first-line options for targeted treatment. Imipenem/cilastatin–relebactam and cefiderocol might be potential alternatives, as well as colistin-based therapy.

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

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Teseo GF et al. Int J Antimicrob Agents 60; 2022

RACCOMANDAZIONI PER UNA STRATEGIA EFFICACE CONTRO LA RESISTENZA ANTIMICROBICA

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1. **Metodologia di valutazione dei nuovi antibiotici contro i ceppi batterici resistenti**

Adattare le attuali metodologie per la determinazione del valore degli antibiotici alle caratteristiche di questi farmaci, considerando il loro ruolo salvavita, tenendo presente che questo richiederà una prospettiva più ampia e l'analisi di scenari ed evidenze oltre a quelle necessarie per le attuali richieste di registrazione.

2. **Criteri per il conferimento dello status di farmaco "innovativo" ai nuovi antibiotici contro i ceppi batterici resistenti**

Utilizzare indicatori specifici capaci di misurare efficacemente il grado di innovatività dei nuovi antibiotici, adattando, se necessario, gli attuali elementi di valutazione a supporto della richiesta

3. **Modelli di rimborso ad hoc per i nuovi antibiotici attivi per le resistenze batteriche**

Visto che la stewardship antimicrobica fornisce indicazioni restrittive sull'uso dei nuovi antibiotici nel trattamento delle infezioni causate dai ceppi resistenti per ridurre la probabilità che si sviluppino nuove forme di resistenza, è necessario identificare delle modalità di rimborso[9] che garantiscano agli sviluppatori un ritorno economico tale da aumentare e mantenere nel tempo gli investimenti in ricerca e sviluppo in quest'area.

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2. Formazione degli operatori sanitari

Garantire che i fondi previsti dal PNRR in merito all'avvio di un piano straordinario di formazione sulle infezioni correlate all'assistenza a tutto il personale sanitario e non sanitario degli ospedali e delle cure primarie, siano indirizzati verso programmi specifici sulla stewardship antimicrobica e sul controllo delle infezioni.

3. Team multidisciplinari

Garantire la presenza di un team multidisciplinare (medici specialisti, microbiologi, farmacisti ospedalieri, ecc.) all'interno delle strutture sanitarie con la responsabilità di definire i programmi di stewardship e la loro applicazione.

4. Governo dei nuovi antibiotici

Garantire un accesso tempestivo ai nuovi antibiotici in situazioni di urgenza ed emergenza estendendo la prescrivibilità di questi farmaci "salvavita" ad altri specialisti, con competenze specifiche sull'uso degli antibiotici (intensivisti, ematologi, ecc.), prevededola nell'ambito di progetti di stewardship antimicrobica.

Inoltre, nel contesto di precise raccomandazioni terapeutiche potrebbe essere utile prevedere una finestra di accesso libero e regolamentato che permetta così ai pazienti di ricevere tempestivamente il trattamento necessario nelle prime decisive ore.

5. Integrazione tra stewardship antibiotica e stewardship diagnostica

Sviluppare programmi di stewardship antibiotica fortemente integrata con la stewardship diagnostica nella definizione del Percorso Diagnostico Terapeutico Assistenziale in maniera uniforme a livello nazionale, con il coinvolgimento di tutti gli operatori sanitari ed in particolare della medicina territoriale.

Potenziare, inoltre, l'utilizzo degli strumenti di diagnostica di primo livello (ad es. tampone faringeo per SBEGA, dosaggio PCR, strisce reattive per i test delle urine, otoscopia pneumatica, ecc.) che, nell'ambito delle cure primarie, permette una maggiore precisione diagnostica e una conseguente maggiore appropriatezza prescrittiva.

6. Informazione ai cittadini

Promuovere campagne di comunicazione rivolte alla popolazione sull'uso appropriato e consapevole di antibiotici, puntando ad accrescere il livello di consapevolezza del cittadino.

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