LA TERAPIA DI COMBINAZIONE PRO E CONTRO

Le infezioni da Enterobacterales MDR

Elena Carrara

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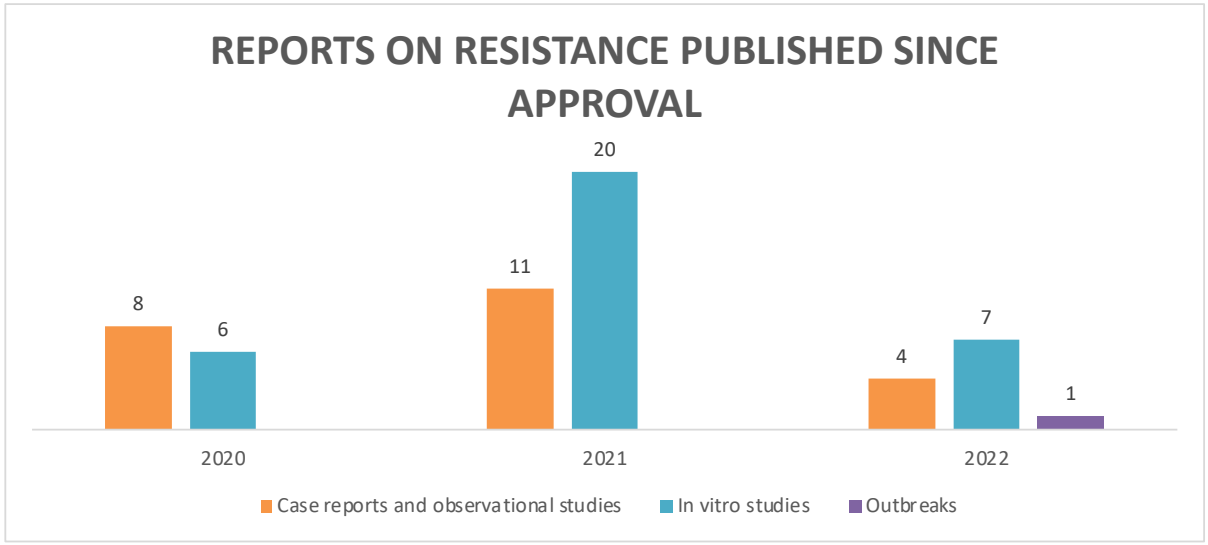
SAVE Stewardship Antibiotica VERONA

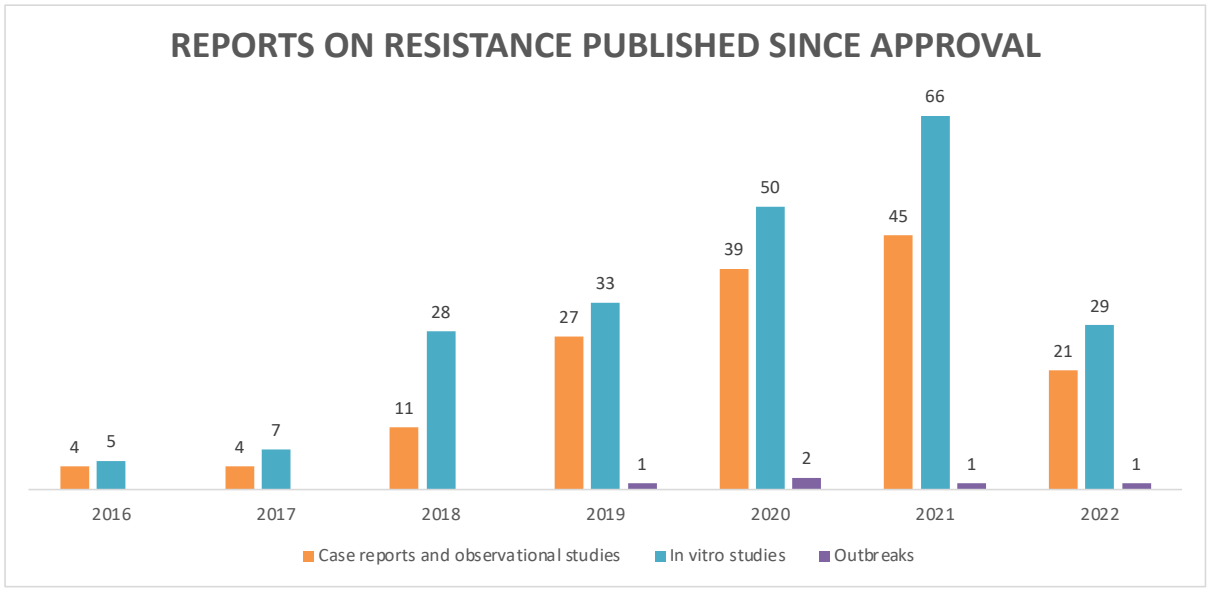
ID-CARE

Emerging resistance to new antibiotics: reports from the literature

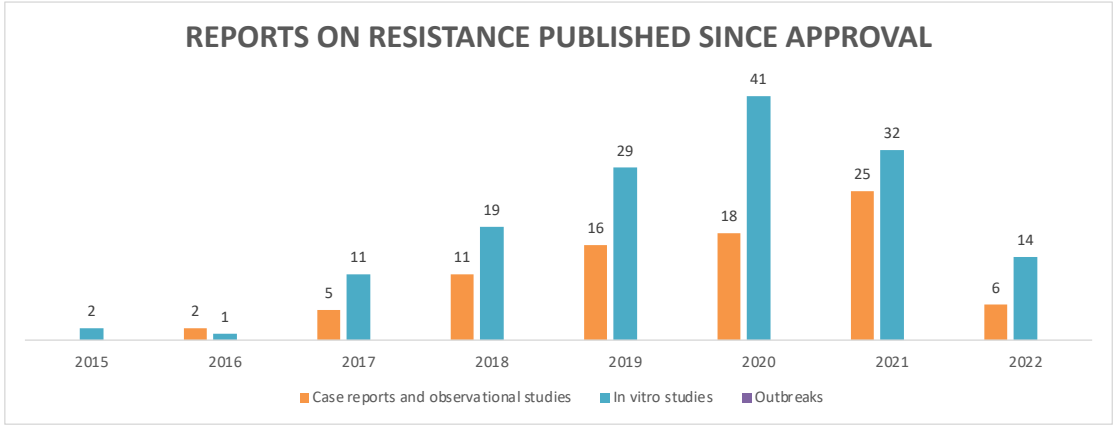
Cefiderocol



Ceftazidime-avibactam



Ceftolozano-tazobactam



https://epi-net.eu

COHERENCE: **CO**mbination t**HER**apy to treat sepsis due to carbapenem-resistant Gram negative bacteria in adult and pediatric population **E**vide**NCE** and common practice

- To comprehensively summarize the **evidence** on the available antibiotic options for the treatment of sepsis sustained by CR- GNB (*Acinetobacter spp*., *P. aeruginosa* and ***Enterobacteriaceae***), including data
  - *in vitro*
  - *[in vivo* (animal)]
  - on humans

- To investigate the **prescription habits and attitudes** of clinicians usually dealing with the treatment of CR-GNB in both pediatric and adult populations from a global perspective

Savoldi, BMC Infect Dis 2021; Carrara, CMI 2021; Scudeller, Int J Antimicr Agents 2021

The prescribers' perspective

36-item questionnaire addressing the following aspects of antibiotic prescribing:

- Diagnostic and therapeutic availability
- **Preferred antibiotic strategies and rationale for selecting combination therapy**

1012 respondents from 95 countries: adjusted by respondent's background, number of cases treated, availability of diagnostics, and income category

	Respondents, *n* (%)
WHO region	
Africa	64 (6·0)
Americas	205 (20·5)
Eastern Mediterranean	116 (11·5)
Europe	444 (44·0)
South East Asia	95 (9·3)
Western Pacific	88 (8·7)
Total	1012 (100)
Patients' age	
Adults	867 (85·6)
Paediatric population	145 (14·3)
Children	110 (10·9)
Neonates	35 (3·5)
Total	1012 (100)
Income category	
High-income countries	512 (50·6)
Upper-middle income countries	296 (29·2)
Lower-middle-income/Low-income countries	204 (20·1)
Total	1012 (100)
Prescribing frequency[a]	
Low-rate prescribers	257 (25·4)
Medium-rate prescribers	416 (41·1)
High-rate prescribers	283 (28·0)
Not specified	56 (5·5)
Total	**1012 (100)**

Carrara & Tacconelli, CMI 2021

The “concept of combination therapy”

✓ According to respondents, ‘combination therapy’ must include antibiotics that retain some degree of in vitro activity (321/783; 42% of respondents) or be synergic (290/783; 38% of respondents).

✓ Twenty per cent of respondents (150/783) conceived ‘combination therapy’ as the simple association of two or more antibiotic compounds, regardless of their potential in vitro activity

Disagreement among respondents clearly reflects the lack of a standardized definition for ‘combination therapy’ also in clinical studies, with the result that there can be a misinterpretation and poor generalizability of study results

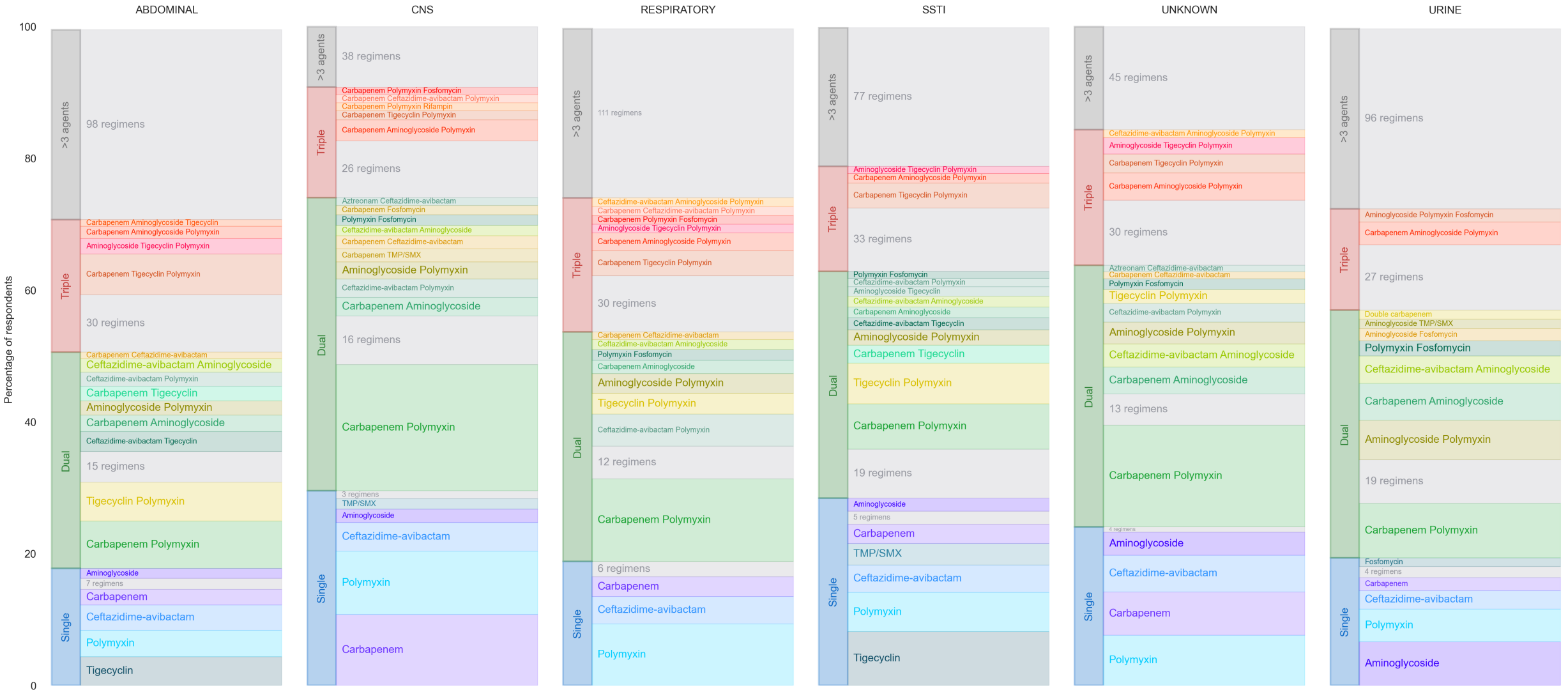
Options	N °
The use of two or more antibiotics (irrespective of their in vitro activity)	150 (19·7)
The use of two or more in vitro active antibiotics	321 (42·1)
The use of two or more antibiotics shown to be synergistic in susceptibility tests	290 (38·0)
I prescribe combination therapy very rarely	2 (0·3)
Total number of respondents: 783	

Respondents' prescription strategies

- **Combination of two antibiotics** (35%-45% of respondents depending on sepsis sources or bacterial species) was the preferred strategy and a carbapenem plus a polymyxin the most prescribed
- The number of regimens ranged **from 40 regimens in CR-Acinetobacter spp. to more than 100 regimens in CR-Enterobacteriales**
- **Single antibiotic therapy** was considered especially for CR-Acinetobacter spp. and CR-Pseudomonas spp. (23%-37% and 26%-35% of respondents, respectively, depending on the sepsis source)
- **Combination of three antibiotics** was regarded as the preferred strategy by a lower number of respondents (15%-20% depending on sepsis sources or pathogen type)

Carrara & Tacconelli, CMI 2021

MORE THAN 100 POSSIBLE COMBINATIONS TO TREAT SEVERE INFECTIONS DUE TO CR-ENTEROBACTERALES



GARDP
Global Antibiotic Research & Development Partnership

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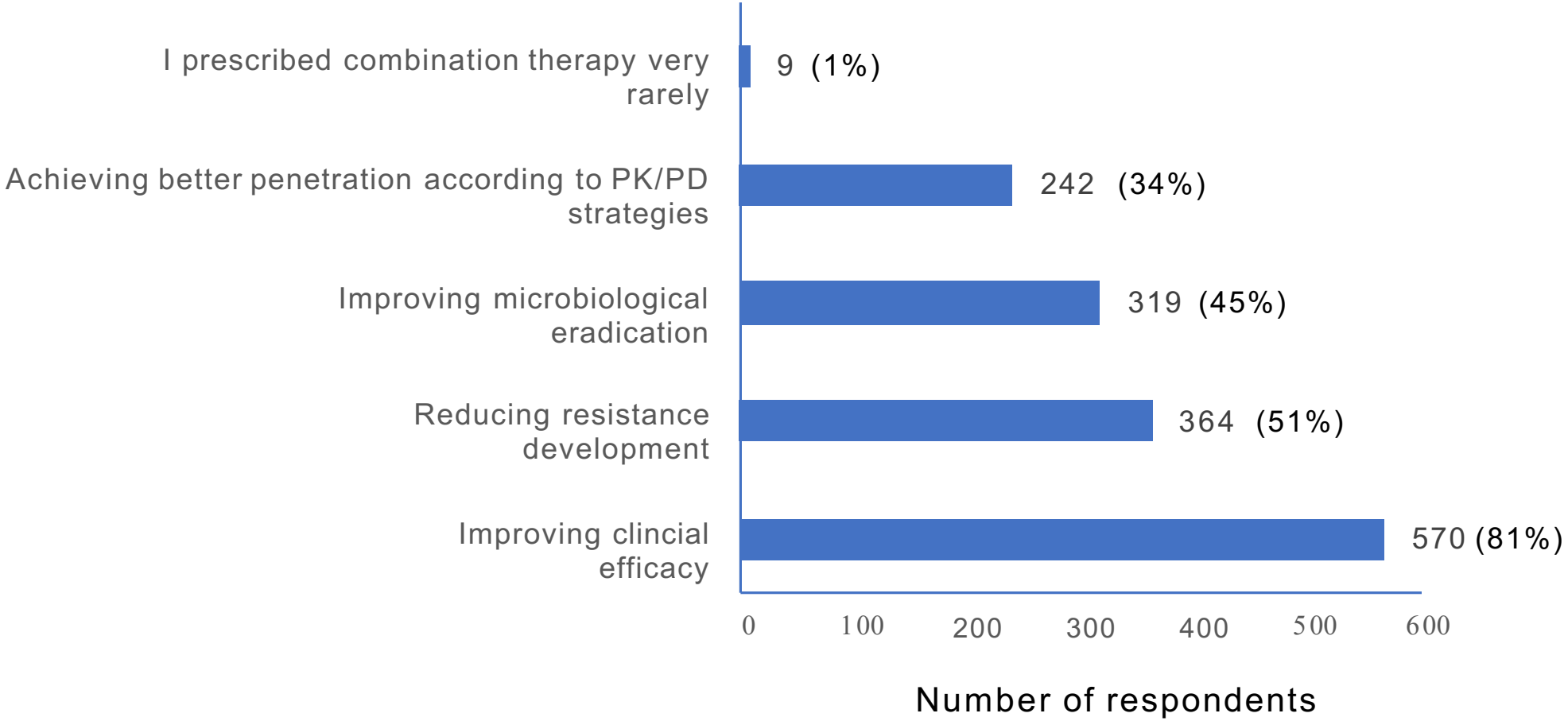
Reasons for prescribing combination therapy



Carrara & Tacconelli, CMI 2021

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Global Antibiotic Research & Development Partnership

The *in vitro* perspective

STUDY DESIGN

Systematic review and Network meta-analysis including pharmacokinetic/pharmacodynamic (PK/PD) time–kill (TK) studies examining the in vitro efficacy of antibiotic combinations against CR-GNB

OUTCOMES

Primary outcome: in vitro synergy *(> 2 log reduction in CFU/ml in bacterial kill/inhibition of combi compared to mono)* -> high: Effect Size ≥ 0.75 / moderate: 0.35 < ES < 0.75 low: ES ≤ 0.35 / absent: ES = 0.

Secondary outcome: bactericidal effect [> 3 log 10 reduction in CFU/mL compared with pre-treatment counts] and **re-growth rate [**≥2 log 10 CFU/mL decrease of the initial colony count followed by an increase of ≥1 log 10 CFU/mL at two subsequent timepoints (12 h and 24 h)].

Scudeller L, Int J Antimicr Agents 2021

Results

- ✓ 108 **combination regimens** from 119 studies were included;
- ✓ The most **frequently** analysed classes were **polymyxins and carbapenems;**
- ✓ Quality assessment was **higher** for PK/PD (65%) compared with TK (53%) studies.

Bacterium/antibiotic combination	TK study	PK/PD study	Total of studies
Acinetobacter baumannii			
Polymyxins + carbapenems	42	7	49
Polymyxins + rifampicin	20	1	21
Carbapenems + rifampicin	14	0	14
Polymyxins + tigecycline	13	2	15
Carbapenems + sulbactam	13	3	16
Total	102	13	115
Klebsiella pneumoniae			
Polymyxins + carbapenems	52	3	55
Double carbapenem	26	1	27
Polymyxins + rifampicin	17	1	18
Polymyxins + fosfomycin	6	5	11
Polymyxins + tigecycline	7	1	8
Total	108	11	119
Pseudomonas aeruginosa			
Carbapenems + aminoglycosides	25	2	27
Carbapenems + fluoroquinolones	22	1	23
Fluoroquinolones + cephalosporins	18	0	18
Polymyxins + carbapenems	8	3	11
Fluoroquinolones + aminoglycosides	10	0	10
Total	83	6	89

Scudeller & Tacconelli, Int J Antimicr Agents 2021

In vitro synergy of antibiotic combinations against K.pneumoniae assessed by PK/PD ans TK studies

Antibiotic regimen	Assay	No. of strains	No. of studies	No. of tests	ES	95% CI	Synergy rate
Ceftazidime/avibactam + amikacin	PK/PD	3	1	1	0.33	0.06–0.79	Low
Ceftazidime/avibactam + aztreonam	PK/PD	1	1	1	1.00	0.21–1.00	High
Colistin + doripenem	PK/PD	1	1	4	0.50	0.00–1.00	Positive trend
Colistin + fosfomycin	PK/PD	8	3	5	0.58	0.28–0.86	Moderate
Polymyxin B + fosfomycin	PK/PD	4	2	4	1.00	0.66–1.00	High
Meropenem + tigecycline	PK/PD	5	1	1	0.40	0.12–0.77	Moderate
Ceftazidime/avibactam + colistin	TK	16	1	1	0.25	0.10–0.49	Low
Colistin + doripenem	TK	62	5	6	0.50	0.28–0.71	Moderate
Colistin + ertapenem	TK	9	1	2	0.38	0.10–0.70	Moderate
Colistin + fosfomycin	TK	2			0.60	0.41–0.78	Moderate
Colistin + gentamicin	TK	26			0.31	0.14–0.50	Low
Colistin + meropenem	TK	9			0.12	0.00–0.46	No synergy
Colistin + meropenem + tigecycline	TK	6			0.00	0.00–0.39	No synergy
Colistin + rifampicin	TK	25			1.00	0.95–1.00	High
Colistin + tigecycline	TK	10			0.42	0.00–0.98	Positive trend
Colistin + tobramycin	TK	4			0.37	0.05–0.76	Moderate
Doripenem + ertapenem	TK	12			0.00	0.00–0.24	No synergy
Doripenem + gentamicin	TK	26	2	2	0.15	0.03–0.32	Low
Imipenem + amikacin	TK	4	1	1	1.00	0.51–1.00	High
Meropenem + amikacin	TK	4	1	1	1.00	0.51–1.00	High
Meropenem + ertapenem	TK	21	1	1	0.43	0.24–0.63	Moderate
Meropenem + gentamicin	TK	13	1	1	0.00	0.00–0.23	No synergy
Meropenem + tigecycline	TK	13	1	1	0.00	0.00–0.23	No synergy
Meropenem + tigecycline + gentamicin	TK	13	1	1	0.00	0.00–0.23	No synergy
Polymyxin B+ doripenem	TK	1	1	4	1.00	0.51–1.00	High
Polymyxin B + imipenem	TK	2	1	3	1.00	0.67–1.00	High
Polymyxin B + meropenem	TK	25	6	50	0.45	0.36–0.53	Moderate

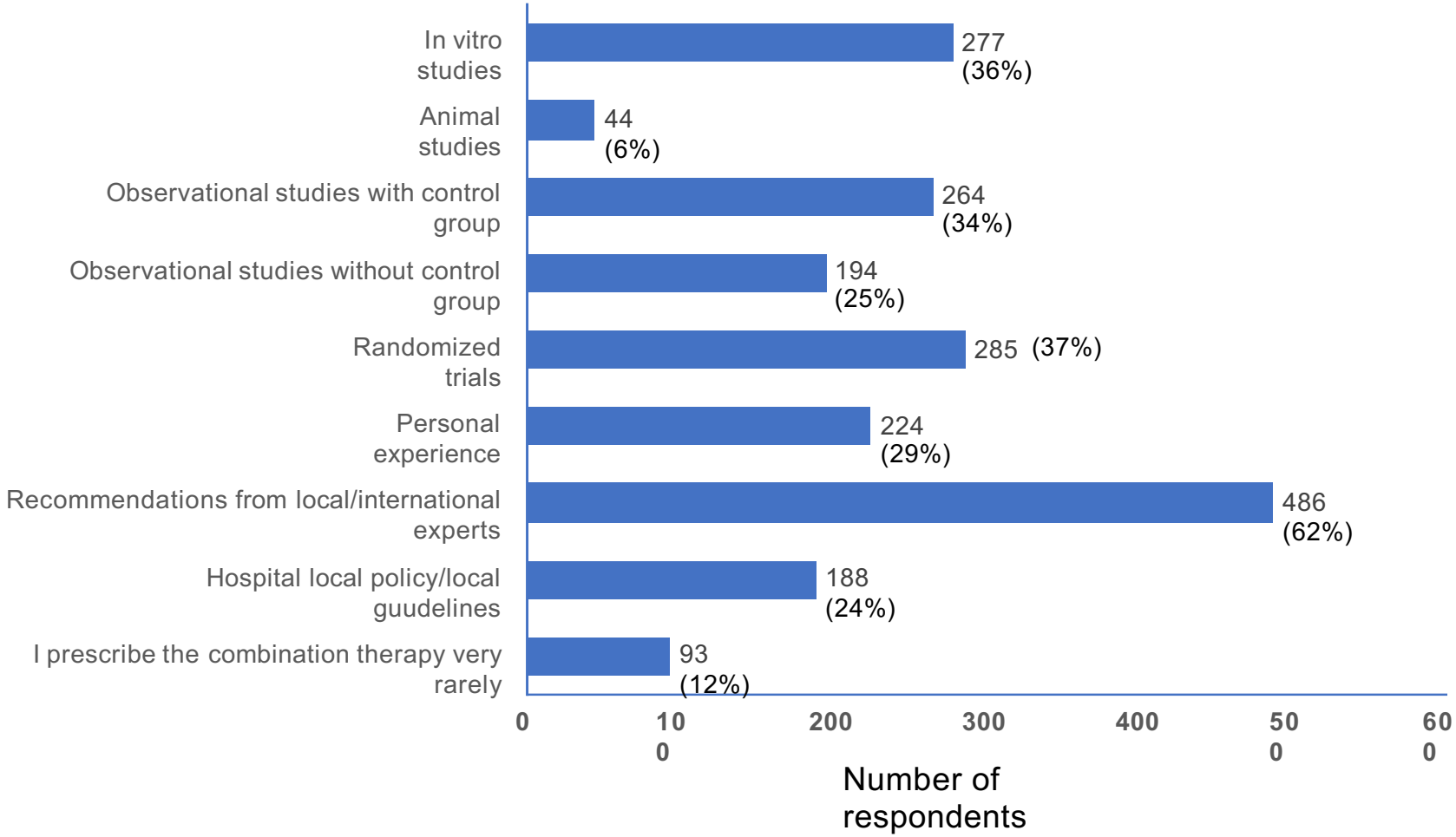
High in vitro SYNERGY for combi vs mono

RE-GROWTH RATE

- ✓ In TK studies, significant difference in re-growth rate ($P < 0.05$) was found between **colistin plus fosfomycin** and monotherapies;
- ✓ Significant differences in re-growth rates ($P < 0.05$) at 24 h were found for **polymyxin B plus meropenem** compared with the combination of polymyxin B plus rifampicin and for **ceftazidime/avibactam compared with colistin alone in TK studies;**
- ✓ Lower re-growth trend at 12 h was shown in PK/PD studies for both **polymyxin B and colistin plus fosfomycin** (SUCRA = 0.8).

Scudeller & Tacconelli, Int J Antimicr Agents 2021

Type of evidence supporting the use of combination therapy



Carrara & Tacconelli, CMI 2021

The clinical perspective
Systematic reviews and meta-analysis

Methods

- Systematic review including observational comparative and non-comparative studies and randomized trials examining any antibiotic option for CR-GNB.
- Studies were included if reporting microbiologically-confirmed infection caused by target microorganism, reporting at least one of the study outcomes, and definitive antibiotic treatment.
- Bayesian network meta-analysis approach was selected for quantitative synthesis to explore feasibility of pooling data on antibiotic regimens

Outcomes

Primary outcomes were 30-day and attributable mortality.

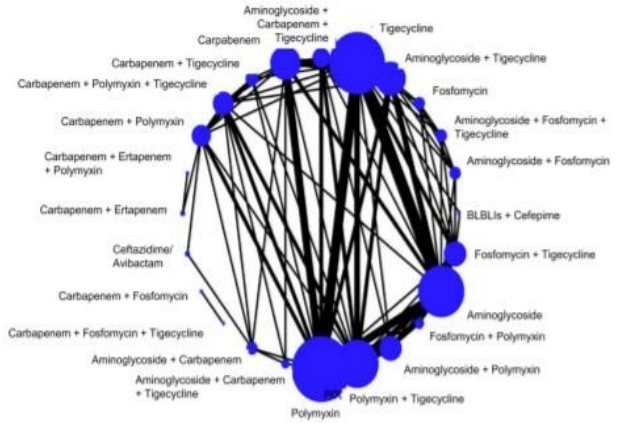
Savoldi & Tacconelli, BMC Infect Dis 2021

Combination therapy to treat severe CRE infections

Patients	All bacteria	Acinetobacter	Enterobacterales	Mixed Gram Negative	Pseudomonas
Undefined	5,863	1,364	2,585	1,806	108
Single-antibiotic regimen					
Meropenem/Vaborbactam	50		50		
Tmp-Smx	12		12		
Tigecycline	416	221	179	16	
Tetracycline	21	21			
Sulbactam	142	142			
Polymyxin	2,383	1,066	252	976	89
Fosfomycin	8		8		
Ceftolozane/Tazobactam	12				12
Ceftazidime/Avibactam	120		107	13	
Cefepime	88				88
Carbapenem	97		97		
Blblis	46				46
Aminoglycoside	174	39	96		39
Dual-antibiotic regimen					
Polymyxin + Tigecycline	210	88	103	19	
Polymyxin + Tetracycline	7			7	
Polymyxin + Sulbactam	153	153			
Polymyxin + Rifampin	246	246			
Fosfomycin + Tigecycline	22		22		
Fosfomycin + Polymyxin	5		5		
Glycopeptide + Polymyxin	71	29		42	
Carbapenem + Tigecycline	48	28	20		
Carbapenem + Sulbactam	180	180			
Carbapenem + Rifampin	20	20			
Carbapenem + Polymyxin	608	388	134	50	36
Carbapenem + Fosfomycin	41		16		25
Carbapenem + Ertapenem	73		73		
Blblis + Polymyxin	27	17			10
Blblis + Cefepime	24		24		
Aminoglycoside + Tigecycline	73	13	60		
Aminoglycoside + Tetracycline	20	20			
Aminoglycoside + Sulbactam	8	8			
Aminoglycoside + Polymyxin	42		42		
Aminoglycoside + Fosfomycin	11		11		
Aminoglycoside + Carbapenem	37		37		
Triple-antibiotic regimen					
Carbapenem + Polymyxin + Tigecycline	33		33		
Carbapenem + Fosfomycin + Polymyxin	24				24
Carbapenem + Fosfomycin + Tigecycline	8		8		
Carbapenem + Ertapenem + Polymyxin	14		14		
Aminoglycoside + Polymyxin + Tigecycline	6		6		
Aminoglycoside + Fosfomycin + Tigecycline	32		32		
Aminoglycoside + Carbapenem + Tigecycline	9		9		
Polymyxin + Rifampin + Tigecycline	19	19			
Carbapenem + Polymyxin + Rifampin	24			24	
Carbapenem + Polymyxin + Tigecycline	15	15			
Carbapenem + Glycopeptide + Polymyxin	4	4			

- ✓ **52 studies (4035 patients)** assessed clinical outcomes in mono vs combi for CR-Enterobacterales;
- ✓ **64% of patients received an unspecified mono or combi treatment.**
- ✓ Among the 'defined regimens' 26 regimens included, 8 were monotherapy, 12 were dual therapy, 6 were triple therapy (1450 patients);
- ✓ The most studied combinations were **carbapenem + polymixin** and **polymixin + tigecycline**.
- ✓ The most studied **monotherapies were polymixin alone or new BL/BLIs**;

- ✓ Heterogeneous and **scattered reporting** of key-clinical and microbiological variables
- ✓ The **NMAs could not be performed** for any of the selected outcome given the presence of too many disconnected components



Savoldi et al. BMC Infectious Diseases (2021)

COMBINATION VS MONOTHERAPY IN CR-GNB INFECTIONS: RISK OF BIAS

Study type	NON-RANDOMIZED (125 studies)	Risk of bias, n (%)		
		CRITICAL	MODERATE	LOW
Domain	Confounding bias	119 (95)	6 (0.5)	0
	Bias in selection of participants	110 (88)	15 (12)	0
	Bias in classification of interventions	107 (86)	18 (14)	0
	Deviation from intended interventions	92 (74)	32 (26)	1 (0.8)
	Missing data	0	15 (12)	110 (88)
	Bias in selection of reported results	0	10 (8)	115 (92)

Confounding (95% of the studies)
Often the analysis is unadjusted due to low sample size or due to the non-homogeneous reporting of relevant variables (i.e., patient severity)

Classification (86% of the studies)
There is no uniform definition of 'combination' (double vs triple, proven *in vitro* activity, potential synergism..)

Selection (88% of the studies)
Treatment might be selected according to patients' conditions (i.e., combination reserved to patients with better chance of survival)

Deviation (74% of the studies)
Antibiotics are often modified during a treatment course with possible 'contamination' between arms

Savoldi et al. BMC Infectious Diseases (2021)

USE OF NOVEL ANTIBIOTICS IN TARGETED TREATMENT

Ceftolozano-tazobactam (+metronidazole)	Meropenem (IAI) Levofloxacin (UTI) Meropenem (NN)	No inferior No inferior No inferior	Solomkin CID 2015 Wagenlehner Lancet 2015 Koleff Lancet Inf Dis 2019
Ceftazidima-avibactam (+ metronidazole)	Meropenem (IAI) Doripenem (UTI) BAT (IAI; UTI; R 3ªGen)	Non inferior Non inferior Non inferior	Mazuski CID 2016 Wagenlehner CID 2016 Carmeli Lancet Inf Dis 2016
Cefiderocol CREDIBLE N59	BAT (NN, UTi, IAI, BSI) Meropenem (NN)	Non inferior Non inferior	Basetti Lancet Inf Dis 2021 Wunderick Lancet Inf Dis 2021
Meropenem-vaborbactam TANGO II N77	BAT (NN, UTI, IAI, BSI)	Non inferior	Wunderick Inf Dis Ther 2018
Imipenem-relebactam	Imipenem (cUTI) Piperacillin/tazobactam (HAP/VAP)	Non inferior	Sims JAC 2017 Titov CID 2020

Pilar R, ECCMID 2022

Cefiderol, cefta-avibactam and imipenem-relebactam vs combination

- **CREDIBLE-CR** trial: 150 patients with proven CR-GNB infections; cefiderocol versus BAT (mostly polymyxin based combination) ++ HAP/VAP and BSI - not powered to conduct specific hypothesis testing. Mortality was higher in the cefiderocol arm at 28 days especially in the CRAB group (24.8% with cefiderocol vs. 18.4%). Clinical and microbiological efficacies of cefiderocol vs. BAT were similar;
- **Retrospective cohorts enrolled a total of 824 patients from three countries (USA, Spain and Italy) and compared ceftazidime-avibactam in combination with other antibiotics vs ceftazidime-avibactam monotherapy, showing no difference in mortality and clinical failure in mixed infections caused by KPC and OXA-48 produce.**
- The **RESTORE IMI-1** reports non-inferior clinical outcomes with imipenem/cilastatin/relebactam versus imipenem/cilastatin plus colistin but is predominantly tested against CR-PA. Effectiveness in non-Pseudomonas organisms remains unclear.

Bassetti, LID 2021; Tumbarello, CID 2019 & 2021; King, AAC 2017; Shields, AAC 2018; De la Calle 2019

In vitro activity of aztreonam-avibactam and comparators against Metallo-β-Lactamase-producing Enterobacterales from ATLAS Global Surveillance Program, 2016-2020

Table 4
Percentage MIC (mg/L) frequency distribution for Enterobacterales collected globally from 2016 to 2020.

Organism/organism group	Antimicrobial	N	Cumulative percentage of isolates at each MIC (mg/L) (absolute count MIC)													
			≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
All Enterobacterales[a]	ATM-AVI	106,686	16.5 (13,687)	47.1 (25,320)	76.9 (24,667)	89.8 (10,689)	**95.4** (**4599**)	97.8 (2029)	98.9 (841)	99.5 (512)	99.8 (288)	99.9 (70)	99.9 (39)	99.9 (9)	99.9 (14)	100.0 (11)	
	ATM		4.6 (3905)	14.4 (8392)	39.9 (21,764)	58.5 (15,906)	64.6 (5250)	66.7 (1821)	68.1 (1175)	69.3 (1050)	70.9 (1364)	73.4 (2153)	77.1 (3131)	83.5 (5472)	89.6 (5210)	**96.0** (**5487**)	100.0 (3402)
MBL-positive Enterobacterales	ATM-AVI	1707	2.6 (42)	8.1 (90)	23.5 (250)	51.5 (456)	77.3 (420)	87.8 (171)	**92.2** (**72**)	95.8 (59)	98.4 (42)	99.4 (16)	99.8 (7)	99.9 (1)	99.9 (0)	100.0 (2)	
	ATM		0.3 (5)	1.0 (11)	2.6 (28)	5.6 (50)	8.5 (49)	10.9 (42)	11.8 (15)	13.4 (26)	14.9 (27)	17.5 (43)	20.7 (54)	27.4 (113)	42.7 (259)	83.6 (694)	**100.0** (**277**)
VIM	ATM-AVI	242	3.8 (9)	15.0 (27)	38.3 (56)	57.1 (45)	74.2 (41)	89.2 (36)	**98.3** (**22**)	100.0 (4)							
	ATM		0.0 (0)	2.1 (5)	6.7 (11)	12.1 (13)	15.8 (9)	19.2 (8)	19.6 (1)	24.2 (11)	28.3 (10)	34.6 (15)	40.8 (15)	48.8 (19)	70.4 (52)	**92.5** (**53**)	100.0 (18)
IMP	ATM-AVI	49	2.1 (1)	6.4 (2)	29.8 (11)	59.6 (14)	85.1 (12)	**93.6** (**4**)	93.6 (0)	100.0 (3)							
	ATM		0.0 (0)	0.0 (0)	8.5 (4)	12.8 (2)	23.4 (5)	25.5 (1)	27.7 (1)	34.0 (3)	40.4 (3)	44.7 (2)	53.2 (4)	61.7 (4)	80.9 (9)	**93.6** (**6**)	100.0 (3)
NDM	ATM-AVI	1421	2.4 (32)	7.0 (62)	20.7 (185)	50.2 (397)	77.6 (368)	87.4 (132)	**91.1** (**50**)	95.0 (52)	98.1 (42)	99.3 (16)	99.8 (7)	99.9 (1)	99.9 (0)	100.0 (2)	
	ATM		0.4 (5)	0.8 (6)	1.7 (13)	4.2 (35)	6.7 (35)	9.1 (34)	10.0 (13)	10.8 (12)	12.1 (17)	13.9 (26)	16.4 (35)	22.8 (90)	36.9 (199)	81.9 (635)	**100.0** (**256**)
NDM-1	ATM-AVI	872	2.9 (24)	8.6 (48)	26.0 (146)	63.7 (317)	87.9 (203)	**96.6** (**73**)	98.2 (14)	99.2 (8)	99.6 (4)	99.8 (1)	100.0 (2)				
	ATM		0.5 (4)	0.9 (4)	2.2 (11)	5.6 (29)	9.2 (31)	11.5 (20)	12.0 (4)	12.9 (8)	14.4 (13)	16.8 (21)	19.4 (22)	25.8 (55)	41.2 (133)	84.1 (370)	**100.0** (**137**)
NDM-5	ATM-AVI	460	1.2 (5)	3.1 (8)	8.3 (22)	21.0 (53)	55.2 (144)	67.1 (50)	75.5 (35)	86.0 (44)	**95.0** (**38**)	98.1 (13)	99.3 (5)	99.5 (1)	99.5 (0)	100.0 (2)	
	ATM		0.2 (1)	0.2 (0)	0.4 (1)	0.7 (1)	1.5 (4)	3.7 (10)	5.7 (9)	6.5 (4)	7.0 (2)	8.0 (5)	10.2 (10)	16.3 (28)	28.0 (54)	77.8 (229)	**100.0** (**102**)
NDM-7	ATM-AVI	59	0.0 (0)	7.0 (4)	26.3 (11)	59.7 (19)	86.0 (15)	**96.5** (**6**)	96.5 (0)	96.5 (0)	96.5 (0)	100.0 (2)					
	ATM			1.7 (1)	3.4 (1)	8.5 (3)	8.5 (0)	13.6 (3)	13.6 (0)	13.6 (0)	17.0 (2)	17.0 (0)	18.7 (1)	25.4 (4)	39.0 (8)	76.3 (22)	**100.0** (**14**)
MBL + KPC[b]	ATM-AVI	51	0.0 (0)	8.0 (4)	26.0 (9)	54.0 (14)	70.0 (8)	86.0 (8)	**100.0** (**7**)								
	ATM		0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	2.0 (0)	2.0 (0)	2.0 (0)	2.0 (0)	6.0 (2)	6.0 (0)	10.0 (2)	16.0 (3)	28.0 (6)	84.0 (28)	**100.0** (**8**)
MBL + OXA-48-like[c]	ATM-AVI	333	0.3 (1)	1.3 (3)	4.6 (10)	20.9 (50)	72.9 (159)	**91.8** (**58**)	94.4 (8)	96.4 (6)	99.4 (9)	99.7 (1)	99.7 (0)	99.7 (0)	99.7 (0)	100.0 (1)	
	ATM		0.0 (0)	0.3 (1)	0.6 (1)	0.9 (1)	1.8 (3)	5.4 (12)	6.3 (3)	6.6 (1)	6.9 (1)	7.8 (3)	8.7 (3)	11.2 (8)	22.3 (37)	75.0 (175)	**100.0** (**83**)

ATM, aztreonam; ATM-AVI, aztreonam/avibactam; MBL, metallo-β-lactamase; N, total number of isolates.
[a] *Escherichia coli, Citrobacter freundii, Citrobacter koseri, Enterobacter asburiae, Enterobacter cloacae, Enterobacter hormaechei, Enterobacter kobei, Enterobacter ludwigii, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Serratia marcescens.*
[b] KPC-2 and KPC-3.
[c] OXA- 162, OXA-181, OXA-232, and OXA-48.
MIC_{90} values are in bold.

Rossolini GM, J Glob Antimicrob Resist 2024

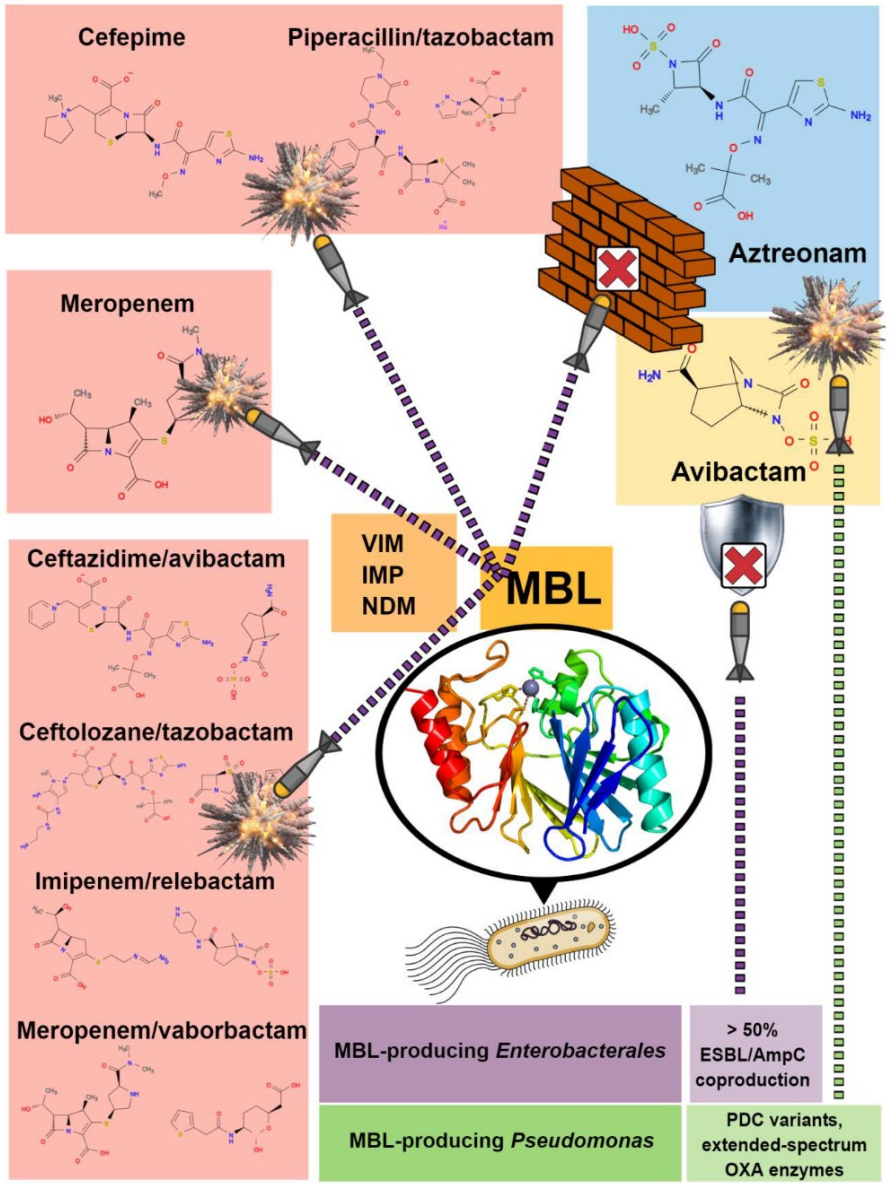


Figure 1. β-lactam antibiotic targets of MBL enzymatic activity.

Mauri C, Antibiotics 2021

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

Table 4. Cox Regression Analysis of Factors Independently Associated With 30-Day Mortality

Factor	HR (95% CI)	*P* Value
Cardiovascular disease	6.62 (2.77–15.78)	<.001
Solid organ transplantation	3.52 (1.42–8.69)	.006
SOFA score (1-point increment)	1.21 (1.1–1.32)	<.001
CAZ-AVI + ATM (vs OAAs)	0.17 (.07–.41)	<.001

Abbreviations: ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; HR, hazard ratio; OAAs, other active antibiotics; SOFA, Sequential Organ Failure Assessment.

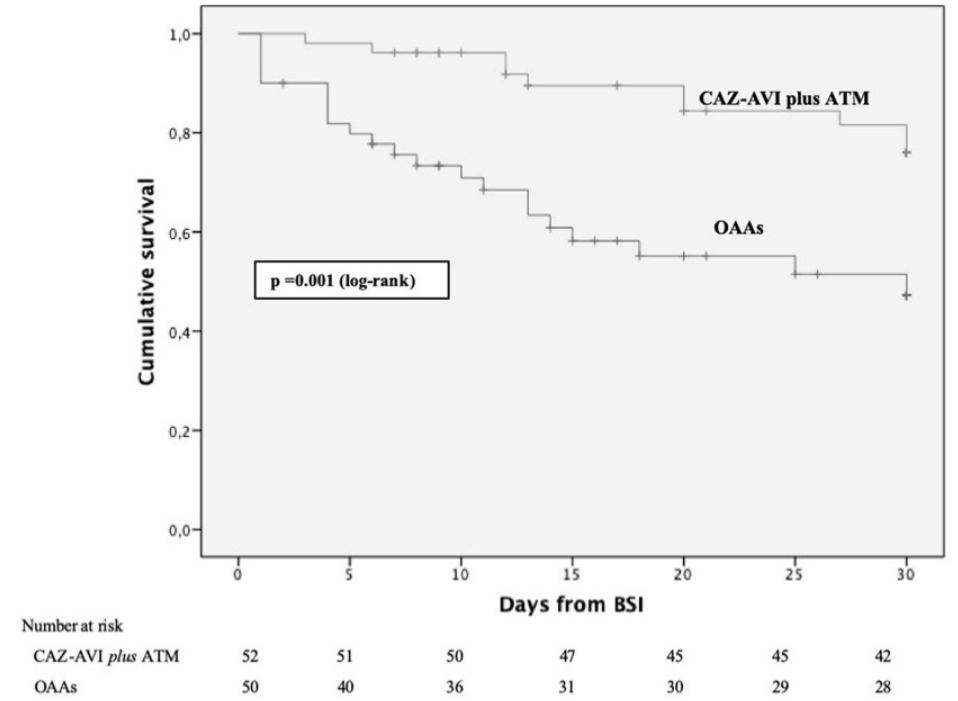
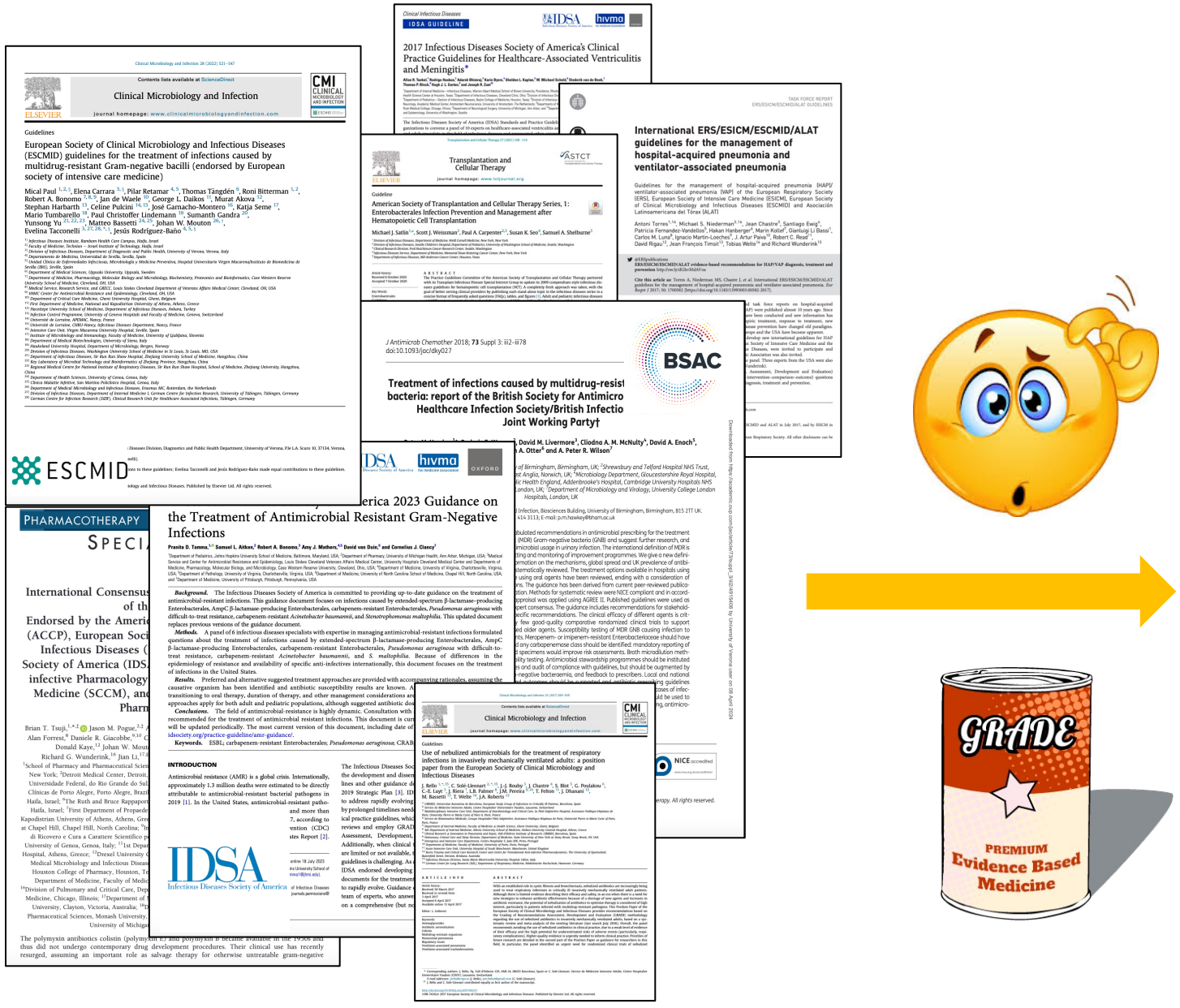


Figure 1. Kaplan-Meier survival curves according to treatment regimen (ceftazidime-avibactam plus aztreonam vs other active antibiotics). Abbreviations: ATM, aztreonam; BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; OAA, other active antibiotics.

Falcone M, CID 2021

TREATMENT OF MICROBIOLOGICALLY DOCUMENTED MDR-GN INFECTIONS



Personal View

How to tailor recommendations on the treatment of multidrug resistant Gram-negative infections at country level integrating antibiotic stewardship principles within the GRADE-ADOLOPMENT framework

Elena Carrara, Paolo Antonio Grossi, Andrea Gori, Lorenza Lambertenghi, Massimo Antonelli, Andrea Lombardi, Filippo Bongiovanni, AIFA-OPERA Working Group, Nicola Magrini, Carlo Manfredi, Stefania Stefani, Mario Tumbarello, Evelina Tacconelli*

Promoting the optimal use of antibiotics through evidence-based recommendations should be regarded as a crucial step in the global fight against antimicrobial resistance. Within this scope, several guidelines and guidance documents for antibiotic therapy have been published in recent years. All documents underline the limitations of existing evidence and remark on the need for tailoring recommendations at the national level, based on local epidemiology, availability of diagnostics and drugs, and antimicrobial stewardship principles. The GRADE-ADOLOPMENT methodology is an evidence-based methodology that allows the adoption, adaptation, and update of existing recommendations to specific settings without performing de novo systematic reviews and grading of the evidence. However, procedures to integrate this evidence with stewardship principles, countries' surveillance data, and capacity in terms of diagnostics and antibiotics' availability have never been defined. This Personal View provides the first example of a country's calibration of international evidence-based guidance documents on treating infections caused by multidrug-resistant bacteria. A panel of experts convened by the Italian Medicine Agency (AIFA) used the GRADE methodology for systematically extracting and evaluating 100 recommendations on the treatment of infections due to multidrug-resistant Gram-negative bacteria from 11 guidance documents and 24 systematic reviews. The ADOLOPMENT procedure was used to calibrate the existing recommendations to the national context, leading to the adoption of 64, the adaptation of 27, and the rejection of nine recommendations. We discuss the technical details of the GRADE-ADOLOPMENT application, the calibration process, and the human resources required to support such an effort. This Personal View also covers the challenges of integrating antibiotic stewardship principles in evidence-based recommendations for treating infections with very limited therapeutic and diagnostic options. The details presented here could support the easy transferability of the methodology to other countries and settings, particularly where the incidence of antibiotic-resistant infections is high.

Introduction

Antimicrobial resistance is one of the last decades' most critical public health emergencies. Multidrug resistant Gram-negative bacteria account for most cases of infections and deaths attributable to antimicrobial resistance in Europe, with Italy being among the most impacted countries.[1,2] With novel antibiotics becoming available over the last few years, evidence-based recommendations to ensure the optimal use of antibiotics and avoid a further increase in antimicrobial resistance, have become essential. In response to this need, several documents have been developed by international institutions and scientific societies to guide clinicians in the difficult task of treating those infections, all with the caveat that recommendations are based on low-quality evidence and need to be tailored to the local context.[3–6] The antimicrobial resistance epidemiology and the availability of resources in terms of diagnostic capacity and antibiotics can widely differ among countries (or even regions within the same country). Therefore, each nation should be able to produce and implement its own recommendations as part of a national antibiotic stewardship strategy. On the other hand, it should be acknowledged that development of recommendations is a complicated process that needs time, training, and dedicated resources. To overcome this challenge, there is a need for an evidence-based methodology that allows the calibration of existing guidance documents to different context in a reliable and cost-effective manner.

Key messages*

- Development and implementation of therapeutic recommendations is a key strategy in improving the appropriateness of antimicrobial prescription at local level.
- Recommendations need to be tailored on local resistance rates and availability of diagnostics and antibiotics, which can differ widely from one country to another.
- The GRADE-ADOLOPMENT methodology, as an evidence-based methodology, allows rapid and efficient adaptation of existing evidence to the local setting.
- The AIFA-OPERA calibration of recommendations for the treatment of multidrug-resistant Gram-negative infections at the country level can be used as a model for other countries calibration and tailoring of existing recommendations.

AIFA=Italian Medicine Agency. AIFA-OPERA=Italian Medicine Agency's Working Group to optimise antibiotic use. *From the experience of the AIFA-OPERA group.

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Carrara, Tacconelli et al. LID 2024

Qualità e forza delle raccomandazioni delle infezioni gravi causate da CRE

ENTEROBACTERALES RESISTENTI AI CARBAPENEMI

Terapia di sepsi e shock settico (indipendetemente dalla fonte di infezione), polmoniti, infezioni addominali nelle quali non si raggiunge una buona bonifica del sito dell´infezione, infezioni del sistema nervoso centrale gravi da Enterobacterales resistenti ai carbapenemi (CRE)

- Nelle infezioni gravi da CRE, si raccomanda l'utilizzo in **prima linea** di **meropenem-vaborbactam o ceftazidime-avibactam** - *raccomandazione debole, qualità delle prove moderata/bassa*.
- Nelle infezioni gravi da CRE, in caso di mancata disponibilità dei nuovi BL-BLIs, si consiglia l'impiego di antibiotici di uso consolidato (inclusa fosfomicina per via endovenosa) in combinazione, selezionando gli agenti in base alla suscettibilità in vitro e alla penetrazione nel sito di infezione - *raccomandazione debole, qualità delle prove moderata.*
- L'utilizzo in routine dei **nuovi BL-BLIs in combinazione non è raccomandato** - *raccomandazione forte, qualità delle prove bassa.*
- L'utilizzo di **un carbapenemico all'interno di una terapia di combinazione** può essere considerato solo in presenza di una **MIC ≤ 8 mg/l, a dosaggio aumentato ed in infusione prolungata** – *raccomandazione debole, qualità delle prove di evidenza bassa.*
- Nelle infezioni da CRE causate da New Delhi Metallo-beta-lactamase (**NDM) o da produttori di altre metallo-beta-lattamasi** in cui sono indicati i nuovi farmaci, si consiglia di utilizzare **ceftazidime- avibactam + aztreonam o cefiderocol** - *raccomandazione debole, qualità delle prove moderata/bassa*.

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

Grazie per l'attenzione

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www.id-care.net

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