KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

XIX. TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI KONGRESİ

28 -31 MART 2018 | GLORIA GOLF RESORT | BELEK / ANTALYA

Therapeutic Options in Colistin Resistant Carbapenem producing Klebsiella Infections

Kolistin Direnci: Tedavi Seçenekleri

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Resistence to Colistin in Gram negatives

- **Polymyxin resistance in Gram-negative bacteria is primarily due to post-translational modification of the lipopolysaccharide (LPS) molecules that form the outer layer of the outer membrane.**

- **In most resistant strains, substituents such as 4-amino-4-deoxy-l-arabinose (l-Ara4N), phosphoethanolamine (pEtN) or galactosamine are enzymatically added to the lipid A or the LPS core; alternatively, the LPS part of the outer membrane may be completely lost in some other isolates.**

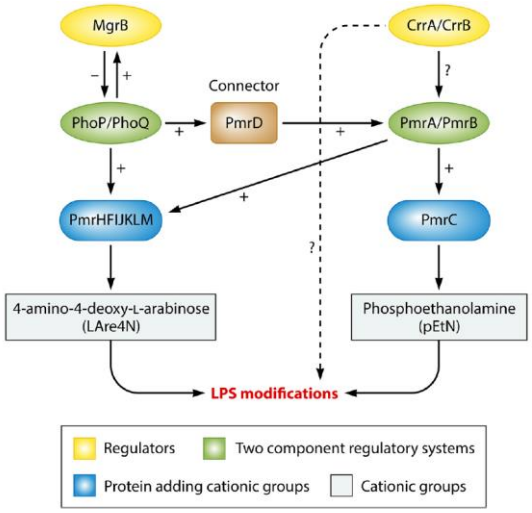
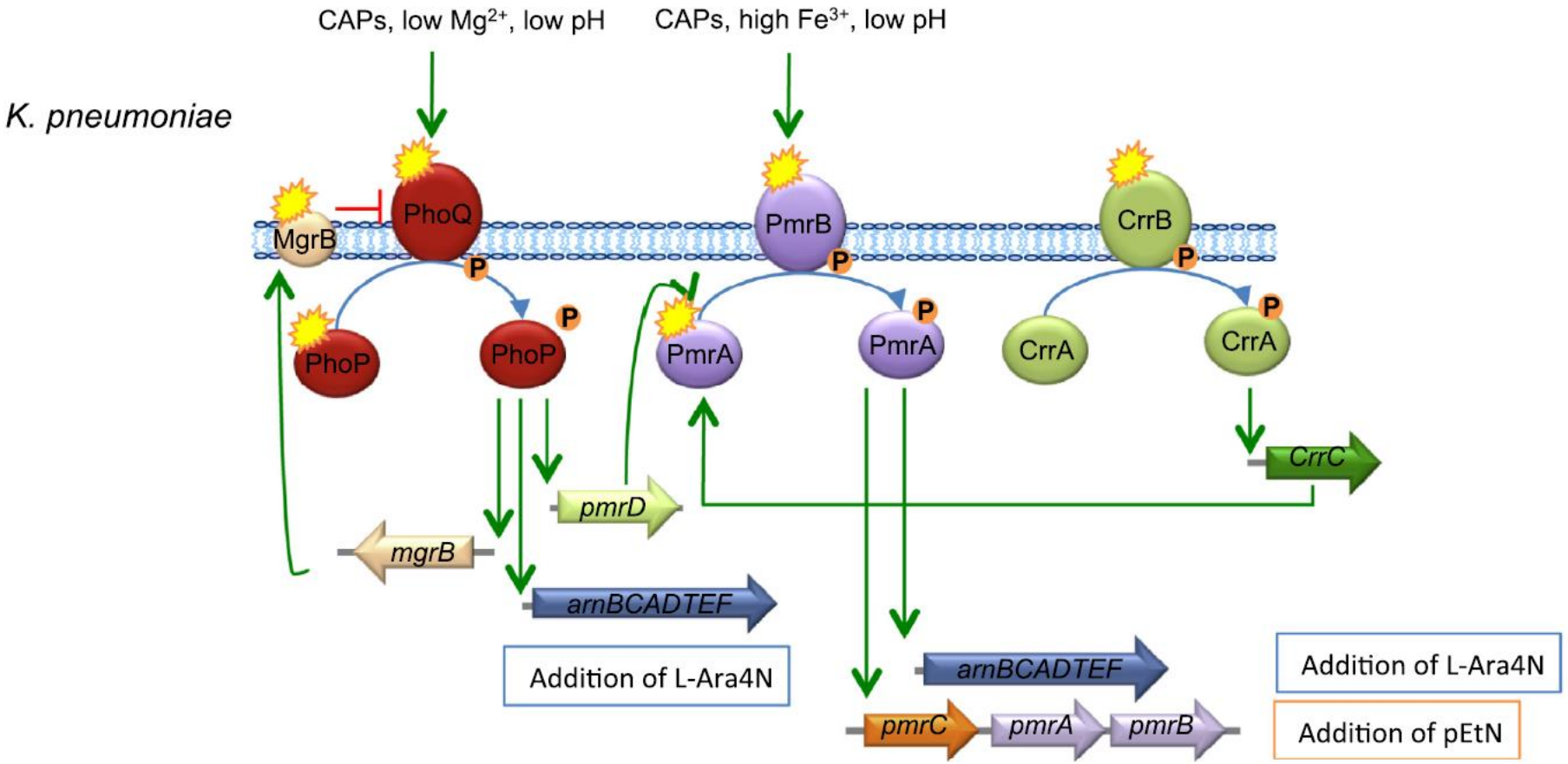


FIG 3 Regulation pathways of LPS modifications in *Klebsiella pneumoniae*.

- **Colistin resistance is predominantly achieved through a reduction of the electrostatic attraction between colistin and the Gram-negative outer membrane**

Trent MS. Biochem Cell Biol 2004;82:71–86.
Ernst RK et al. Microbes Infect 2001;3:1327–34.
Moskowitz SM et al. J Bacteriol 2004;186:575–9.
Pelletier MR et al. Antimicrob Agents Chemother 2013;57:4831–40.
Moffatt JH et al. Antimicrob Agents Chemother 2010;54:4971–7.

Schematic representation of regulation of genes involved in polymyxin resistance in clinical isolates of *Klebsiella pneumoniae*



Jeannot K et al. Int J Antimicrob Agents 2017;49: 526–535

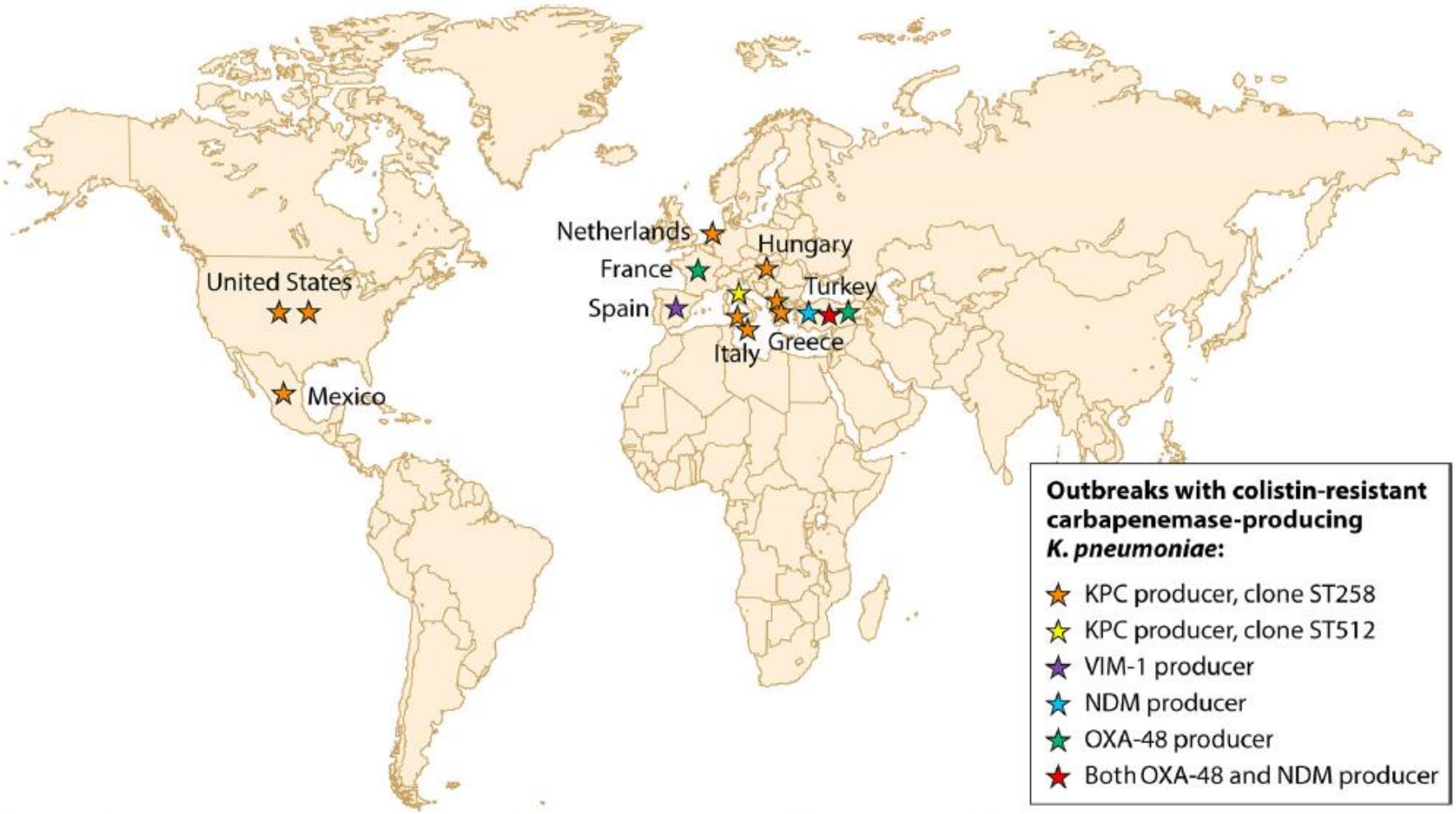


FIG 5 Outbreaks caused by colistin-resistant, carbapenemase-producing *K. pneumoniae* isolates. Each star indicates a single report.

Poirel L et al. Clin Microbiol Rev 2017;30:557-596.

TABLE 3 Chromosomal mutations and amino acid deletions responsible for acquired colistin resistance in *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Escherichia coli*, *Salmonella enterica*, *P. aeruginosa*, and *A. baumannii* isolates

Bacterial group and species	Protein (normal length [aa])	Domain involved (residues)[a,b]	Amino acid change[d]	Reference(s)
Enterobacteriaceae				
K. pneumoniae	PmrA (223)	REC (1–112)	S42N	120
			G53C	105, 120
			G53S	105
		Trans_reg_C (145–216)		
	PmrB (365)	TM (13–35)	ΔR14	118
			L17Q	105
		HAMP (90–142)	L82R	116
			S85R	120
			T140P	120
		HisKA (143–203)	T157P	117–119
			S208N	118
			ΔY209	118
		HATPase_c (250–358)	R256G	117
	PhoP (223)	REC (1–112)	V3F	117
			L26Q	120
			S86L	117
		Trans_reg_C (145–220)	D191Y	81
	PhoQ (488)	PhoQ sensor (10–189)	R16C	105
			L26P	117
			L96P	120
			D150G	117
			S174N	118
		HAMP (195–263)	V258F	117
		HisKA (267–330)		
			L348Q	120
		HATPase_c (375–482)	G385S	120
			D434N	128
	MgrB (47)		K3*	105
			L9*	120
			I13*	120
			A14S	120
			W20R	105
			L24H	130
			V26*	120
			M27K	105
			C28F	120
			C28Y	117, 120, 128, 130
			C28*	105, 120
			Q30*	105, 120
			D31N	120
			Q33*	105
			F35I	120
			G37S	130
			C39Y	105
			N42Y/K43I	105
			I45T	105
			W47R	105
			W47*	105
			*48Y	117
	CrrB (353)		Q10L	128, 137
		TM (12–34)	Y31H	137
		HAMP (81–135)	L94 M	128
		HisKA (136–200)	W140R	137
			N141I	137
			P151S	137
			S195N	137

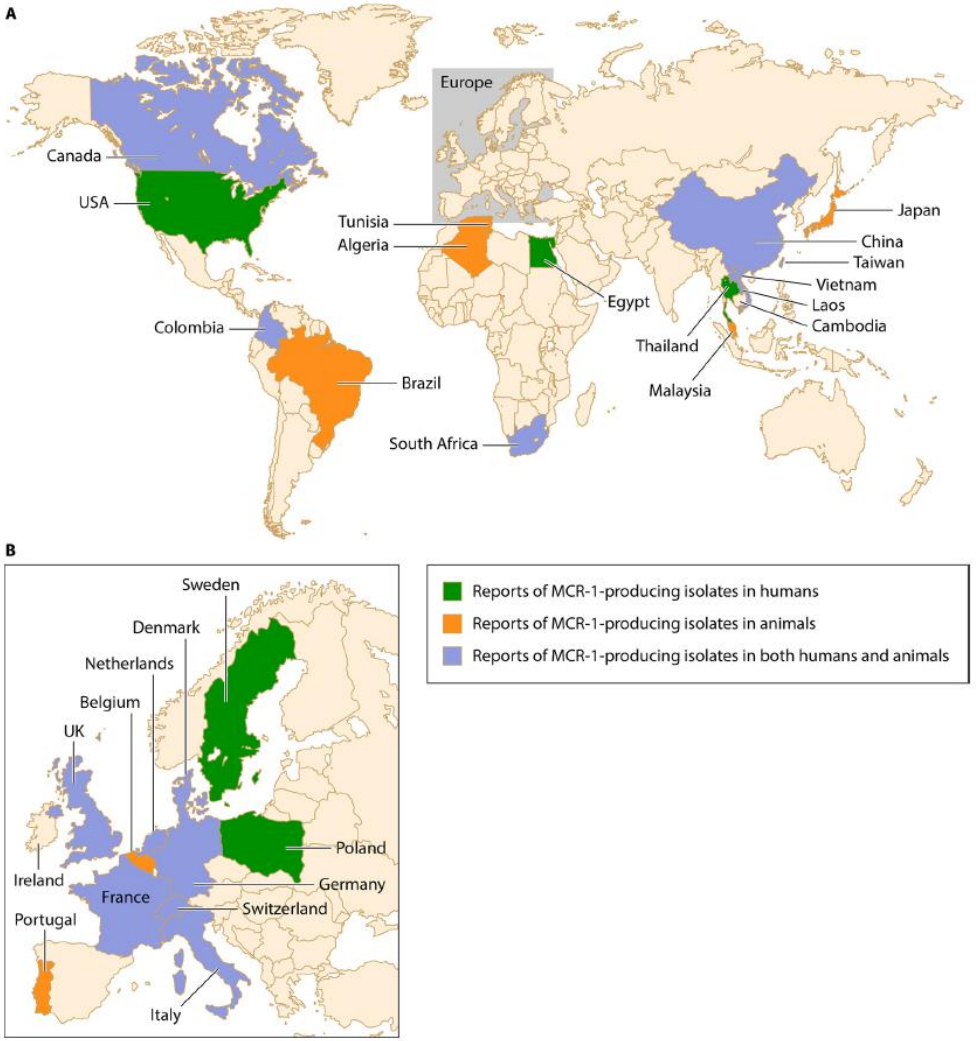


FIG 4 Reports of MCR-1-producing isolates in humans, animals, and both humans and animals.

Poirel L et al. Clin Microbiol Rev 2017; 30:557–596.

Hospital Outbreak of a Colistin-Resistant, NDM-1- and OXA-48-Producing *Klebsiella pneumoniae*: High Mortality from Pandrug Resistance

TABLE 2. CLINICAL CHARACTERISTICS OF THE PATIENTS WHO WERE DETECTED AS POSITIVE FOR CARBAPENEM-RESISTANT *KLEBSIELLA PNEUMONIAE* THROUGHOUT THE OUTBREAK PERIOD

Patient	*Age/sex*	*Comorbidity and infection*	*ICU*	*Clinical sample*	*CR/COLr*	*Carbapenemase*	*PFGE type*	*Treatment*	*Outcome*
A	74/M	Malignancy Colon resection Pneumonia	AR-ICU	Empyema	+/+	OXA-48 NDM-1	I	MEM/Col	Died
B	21/M	CNS Ca Pneumonia Sepsis	AR-ICU	Blood	+/+	OXA-48 NDM-1	I	MEM/Col	Died
C	0/M	CNS surgery Meningitides	NB-ICU	CSF	+/–	NDM-1	II	MEM/Col	Survived
D	30/M	Trauma Sepsis	AR-ICU	Blood	+/+	OXA-48 NDM-1	I	MEM/Col	Died
E	28/M	Suicides Sepsis Pneumonia	AR-ICU	Blood Tracheal aspirate	+/+ +/+	OXA-48 NDM-1 OXA-48 NDM-1	I I	MEM/Col	Died
F	84/M	COPD Pneumonia	AR-ICU	Tracheal aspirate	+/+	OXA-48 NDM-1	I	(–)	Died
G	0/F	Asphyxia Bacteremia	NB-ICU	Blood	+/–	(–)	III	FEP/Col	Died
H	0/M	Congenital urinary anomalies —	NB-ICU	Urine	+/+	OXA-48 NDM-1	I	—	Survived

Guducluogu H et al. Microb Drug Resist. 2017 Dec 21

Impact of the ST101 clone on fatality among patients with colistin-resistant *Klebsiella pneumoniae* infection

115 pts→ mortality 72%

Table 3. Predictors of 30 day mortality among patients infected with ColR-Kp

	Univariate analysis			Adjusted analysis[a]		
	OR	CI	*P*	OR	CI	*P*
Female	0.7	0.3–1.54	0.341	–	–	–
ICU stay	6.6	1.85–29.97	0.001	7.4	2.23–29.61	0.002
Bacteraemia	0.9	0.4–2.1	0.848	–	–	–
More than two comorbidities	0.5	0.22–1.29	0.145	–	–	–
VAP	2.3	0.99–5.33	0.038	1.6	0.71–3.86	0.249
Prior colistin use within the last 3 months	0.6	0.27–1.41	0.252	–	–	–
Carbapenem resistance	2.2	0.35–15.53	0.43	–	–	–
NDM-1	0.9	0.32–2.69	>0.999	–	–	–
OXA-48	1.4	0.48–3.9	0.628	–	–	–
ST101	3.2	1.36–7.52	0.004	3.4	1.46–8.15	0.005

Can F et al. J Antimicrob Chemother. 2018 Feb 3.

Colistin susceptible K. pneumoniae

B.A.L. per germi comuni

	Numerose colonie di K. pneumoniae
Antibiogramma	
Criteri EUCAST	
Materiale	Broncolavaggio
Organismo	Klebsiella pneumoniae
Carica batterica	Sviluppo di numerose colonie

ANTIBIOTICI	MIC - Sensibilità
Amikacina	Resistente Mic: >16
Amoxicillina/A.CLAV.	Resistente Mic: >32/2
Ampicillina	Resistente Mic: >8
Cefepime	Resistente Mic: >8
Cefotaxime	Resistente Mic: >4
Ceftazidime	Resistente Mic: >8
Cefuroxime	Resistente Mic: >8
Ciprofloxacina	Resistente Mic: >1
Colistina	In corso
Ertapenem	Resistente Mic: >1
Fosfomicina	Sensibile Mic: 32
Gentamicina	Intermedio Mic: 4
Imipenem	Resistente Mic: >8
Levofloxacina	Resistente Mic: >2
Meropenem	Resistente Mic: >8
Piperacillina	Resistente Mic: >16
Piperacillina/tazobactam	Resistente Mic: >16/4
Tigeciclina	In corso
Tobramicina	Resistente Mic: >4
Trimetoprim/Sulfam.	Resistente Mic: >4/76
Markers	Beta-lattamasi a spettro esteso
	Potenziale produttore di carbapenemasi

ANTIBIOTICI	MIC - Sensibilità
Colistina	0,06 Sensibile (Microdiluizione in brodo)
Tigeciclina	1 Sensibile (E-Test)
Commento	Ripetizioni del 13/03/18
Test fenotipico conferma CRE	ceppo produttore di carbapenemasi
Disco diffusione con EDTA e PBA	di tipo KPC (serinobetalattamasi)

COL susceptibility confirmed by broth microdiluition

Colistin resistant K. pneumoniae

Antibiogramma	
Criteri EUCAST	
Materiale	T. rettale
Organismo	Klebsiella pneumoniae
Carica batterica	Sviluppo di numerose colonie

ANTIBIOTICI	MIC - Sensibilità
Amikacina	Resistente Mic: >16
Amoxicillina/A.CLAV.	Resistente Mic: >32/2
Ampicillina	Resistente Mic: >8
Cefepime	Resistente Mic: >8
Cefotaxime	Resistente Mic: >4
Ceftazidime	Resistente Mic: >8
Cefuroxime	Resistente Mic: >8
Ciprofloxacina	Resistente Mic: >1
Colistina	Resistente Mic: >4
Ertapenem	Resistente Mic: >1
Fosfomicina	Sensibile Mic: 32
Gentamicina	Intermedio Mic: 4
Imipenem	Resistente Mic: >8
Levofloxacina	Resistente Mic: >2
Meropenem	Resistente Mic: >8
Piperacillina	Resistente Mic: >16
Piperacillina/tazobactam	Resistente Mic: >16/4
Tobramicina	Resistente Mic: >4
Trimetoprim/Sulfam.	Resistente Mic: >4/76
Markers	Beta-lattamasi a spettro esteso
	Potenziale produttore di carbapenemasi

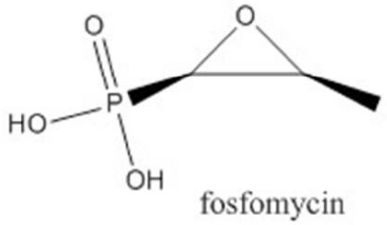
MULTA CORDA UNA CAUSA

Istituto di Ricovero e Cura a Carattere Scientifico

LAZZARO SPALLANZANI

Colistin-resistant *Klebsiella pneumoniae.* Which treatment?

Fosfomycin



fosfomycin

- Cell wall active antibiotic, with a structural simplicity and low molecular weight
- Penetration into the cell wall achieved through transport systems utilized by alpha-glycerol-phospate and glucose-6-phosphate→ block the formation of N-acetylmuramic acid→bactericidal (Gram+, Gram-)
- Urinary infections→ fosfomycin tromethamine (>50% bioavability after oral administration)
- Systemic infections→ IV formulation (4 gm every 6 hours and more).
- Resistance is rare in E coli (chromosome encoding transport systems→GlpT and UhpT)

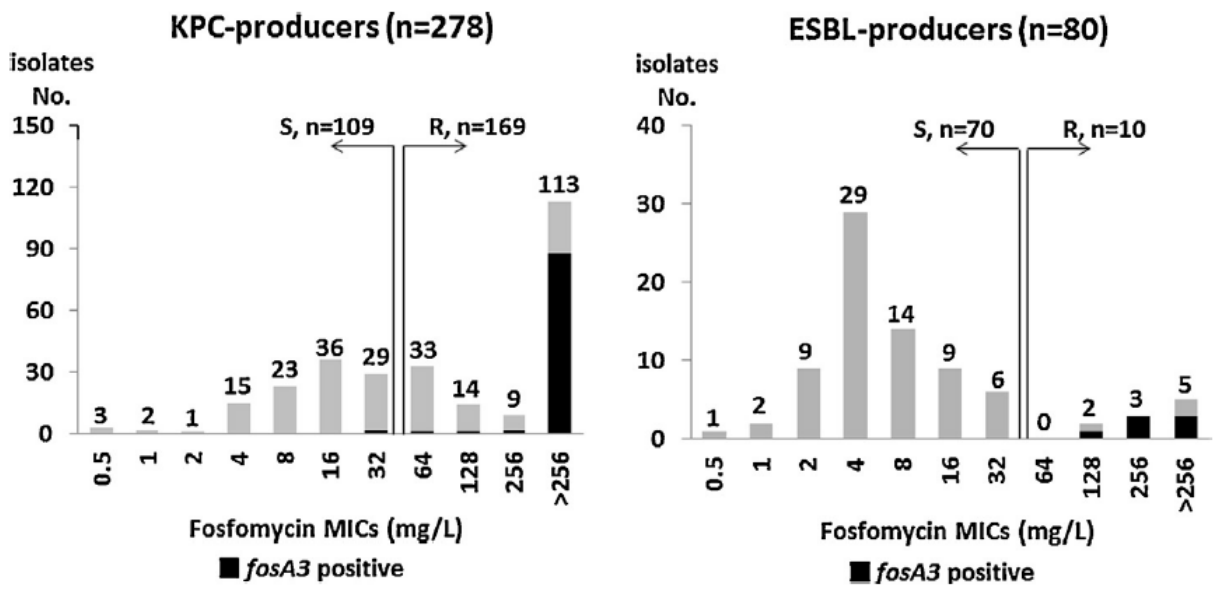
Fosfomycin resistance in Klebsiella and Enterobacter sp.

- **In clinical isolates up to 20% (Akova M et al. Clin Microb Infect 2012; 18:439-48)**

- **Resistance is also mediated through plasmids that code for fosfomycin-inactivating enzymes (fosA).**

Monotherapy with Fosfomycin may select resistance

Y. Jiang et al. / International Journal of Antimicrobial Agents 45 (2015) 66–70



Tigecycline

TABLE 1. Distribution of carbapenemase-producing *Enterobacteriaceae* isolates according to carbapenemase type and medical center location

Organism (no. of strains)	Carbapenemase	Medical center		Tigecycline MIC range (μg/ml)
		No.	Location (no. of strains)	
K. pneumoniae (53)	KPC-2/3	4	New York, NY (37)	0.25–4
	KPC-2	1	Mineola, NY (6)	1–2
	VIM-1	1	Athens, Greece (10)	0.12–1
K. oxytoca (7)	KPC-2	2	Little Rock, AK (3)	0.25–0.5
	KPC-2/3	1	New York, NY (3)	0.12–1
	KPC-3	1	Charlottesville, VA (1)	0.5
C. freundii (9)	KPC-2/3	2	New York, NY (7)	0.25–2
	KPC-2	1	Mineola, NY (1)	1
	KPC-3	1	Wilmington, DE (1)	0.12
E. cloacae (22)	KPC-2/3	2	New York, NY (3)	0.12–0.5
	KPC-2	1	Charlottesville, VA (3)	0.5
	NMC-A	1	New York, NY (1)	0.12
	IMP-1	1	Istanbul, Turkey (10)	0.25–0.5
		1		
		1		
	VIM-1	1		
		1		
E. gergoviae (1)	KPC-3	1		
E. hormaechei (1)	KPC-2	1		
S. marcescens(7)	KPC-2/3	2		
	SME-1	1		
		1		
		1		
		1		
E. coli (4)	KPC-2/3	2		
		1		

Castanheira M et al. Antimicrob Agents Chemother 2008; 52: 570-3

Table 3. Area under the concentration–time data and penetration ratio[a]

Tissue or body fluid group	Site AUC_{0-24} (mg·h/L or mg·h/kg)[b]	Serum AUC_{0-24} (mg·h/L)	AUC_{0-24} ratio (site:serum)
Bile	2815/1787	5.24/4.86	537/368
Gall bladder	119.99/65.96	5.24/4.86	23/14
Colon	17.30/9.83	6.58/5.46	2.6/1.8
Lung	9.19/8.02	4.48/3.99	2.0/2.0
Bone	2.05/1.26	4.95/4.49	0.41/0.28
Synovial fluid	1.68/1.58	5.35/4.86	0.31/0.32
CSF	0.460/0.426	4.18/3.59	0.11/0.12

Rodvold KA et al. J Antimicrob Chemother 2006; 58: 1221–1229

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Gonzalez-Padilla M et al. J Antimicrob Chemother 2015; 70: 905–913

retrospective cohort study on 50 patients with severe infection caused by carbapenem-resistant and colistin-resistant K. pneumoniae

Type of infection	
pneumonia	24 (48.0)
purulent tracheobronchitis	4 (8.0)
urinary tract infection	10 (20.0)
surgical wound infection	4 (8.0)
intra-abdominal infection	1 (2.0)
infection of skin and soft tissue	1 (2.0)
endocarditis	1 (2.0)
primary or catheter-related bacteraemia	4 (8.0)
infection of the CNS	1 (2.0)

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

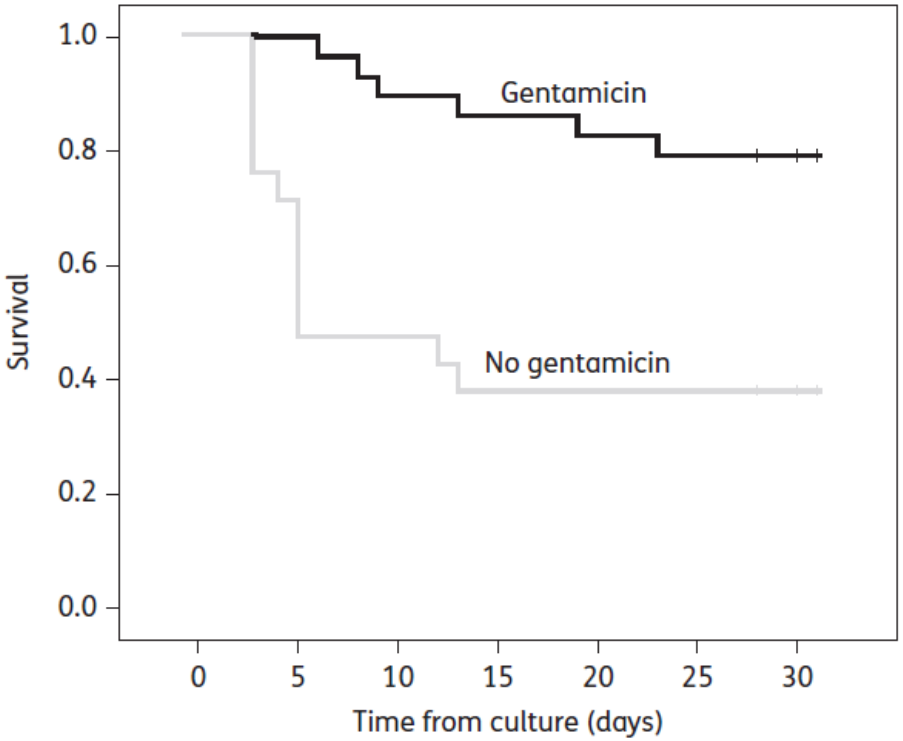
Gonzalez-Padilla M et al. J Antimicrob Chemother 2015; 70: 905–913

Table 2. Antibiotics used in 50 patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae*

	Number (%) of patients					
	optimal	mortality	suboptimal	mortality	total	mortality
Empirical treatment	6 (8.0)	2 (33.3)	44 (92.0)	17 (38.6)	50	19 (38.0)
tigecycline	4 (66.6)	2 (50.0)	0	0	4 (8.0)	2 (50.0)
tigecycline + gentamicin	2 (33.3)	0	0	0	2 (4.0)	0
fosfomycin	0	0	1 (2.2)	0	1 (2.0)	0
meropenem	0	0	18 (40.9)	8 (44.4)	18 (36.0)	8 (44.4)
piperacillin/tazobactam	0	0	7 (15.9)	0	7 (14.0)	0
amoxicillin/clavulanic acid	0	0	2 (4.5)	0	2 (4.0)	0
others	0	0	16 (36.4)	9 (56.2)	16 (32.0)	9 (56.2)
Targeted treatment	37 (74.0)	9 (24.3)	13 (26.0)	10 (76.9)	50	19 (38.0)
monotherapy	16 (43.2)	4 (25.0)	6 (46.2)	5 (83.3)	22 (44.0)	9 (40.9)
tigecycline	8 (21.6)	3 (37.5)	1 (7.7)	0	9 (18.0)	3 (33.0)
high-dose tigecycline	3 (8.1)	0	0	0	3 (6.0)	0
gentamicin	8 (21.6)	1 (12.5)	0	0	8 (16.0)	1 (12.5)
meropenem	0	0	5 (38.5)	5 (100)	5 (10.0)	5 (100)
combination therapy	21 (56.7)	5 (23.8)	7 (53.8)	5 (71.4)	28 (56.0)	10 (35.7)
tigecycline + gentamicin	21 (56.7)	5 (23.8)	0	0	21 (42.0)	5 (23.8)
high-dose tigecycline	7 (18.9)	1 (14.3)	0	0	7 (14.0)	1 (14.3)
meropenem + fosfomycin	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
tigecycline + colistin	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
high-dose tigecycline	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
meropenem + colistin ± fosfomycin	0	0	5 (38.5)	3 (60.0)	5 (10.0)	3 (60.0)

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Gonzalez-Padilla M et al. J Antimicrob Chemother 2015; 70: 905–913



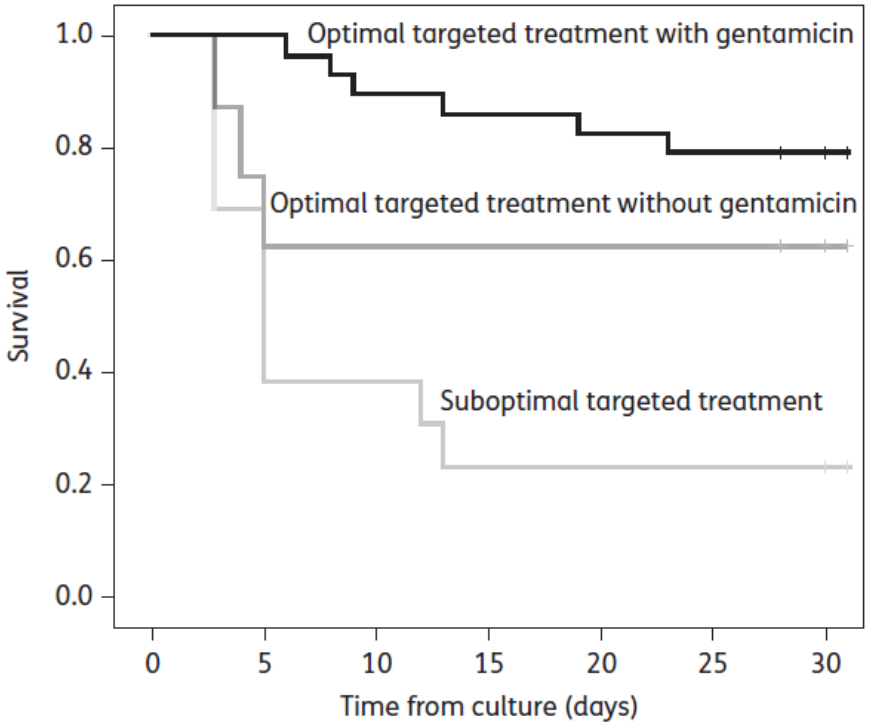


Figure 1. Kaplan–Meier curves showing the impact of targeted treatment with gentamicin on survival at 30 days in patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae* (log-rank test 11.9, $P=0.001$).

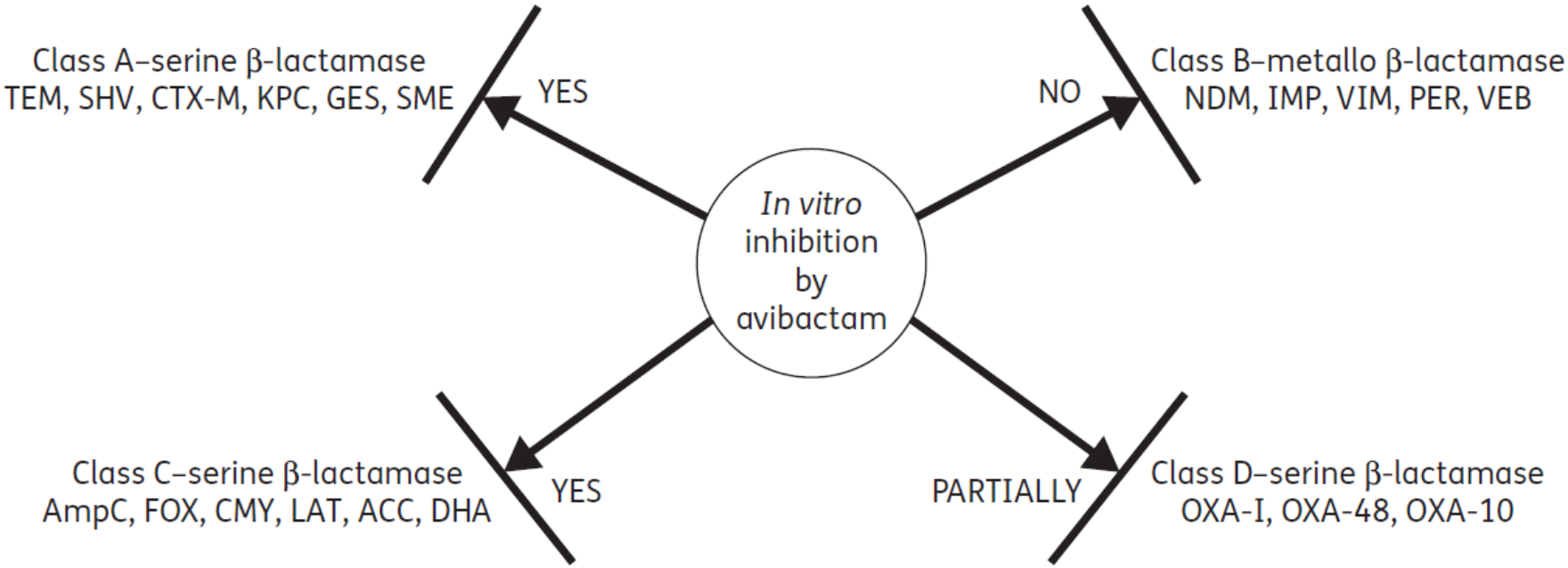
Novel antimicrobial agents against CRE

- **Avibactam is a non-β-lactam β-lactamase inhibitor that is active against known Ambler class A and C β-lactamases with activity against some Ambler class D enzymes as well.**

- ***In vitro*, avibactam inhibits the activity of Ambler class A (including ESBL and KPC), class C (*i.e.* AmpC), and some class D (including OXA-48) enzymes.**

- **It is not active against MBLs (*e.g.* NDM, VIM, IMP) due to the absence of the active-site serine residue in these enzymes.**

Lee CS et al. Infect Chemother 2014; 46:149-64



Activity of avibactam against different classes of β-lactamases.

Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing *Klebsiella pneumoniae*

Aurélie Jayol[1–4], Patrice Nordmann[1–3,5], Laurent Poirel[1–3]* and Véronique Dubois[4,6]

J Antimicrob Chemother 2018; **73**: 542–544

- **A collection of 63 K pneumoniae, all resistant to colistin (MICs of colistin ranging from 8 to>128 mg/L), recovered from clinical samples in France, Colombia and Turkey were tested.**
- **Aim: to determine the *in vitro* activity of ceftazidime/avibactam, alone (for A [KPC] and D [Oxa48 et der] carbapenemase producers) or in combination with aztreonam (for class B [MBL] carbapenemase producers) against Colistin-resistant and carbapenemase-producing K. pneumoniae**

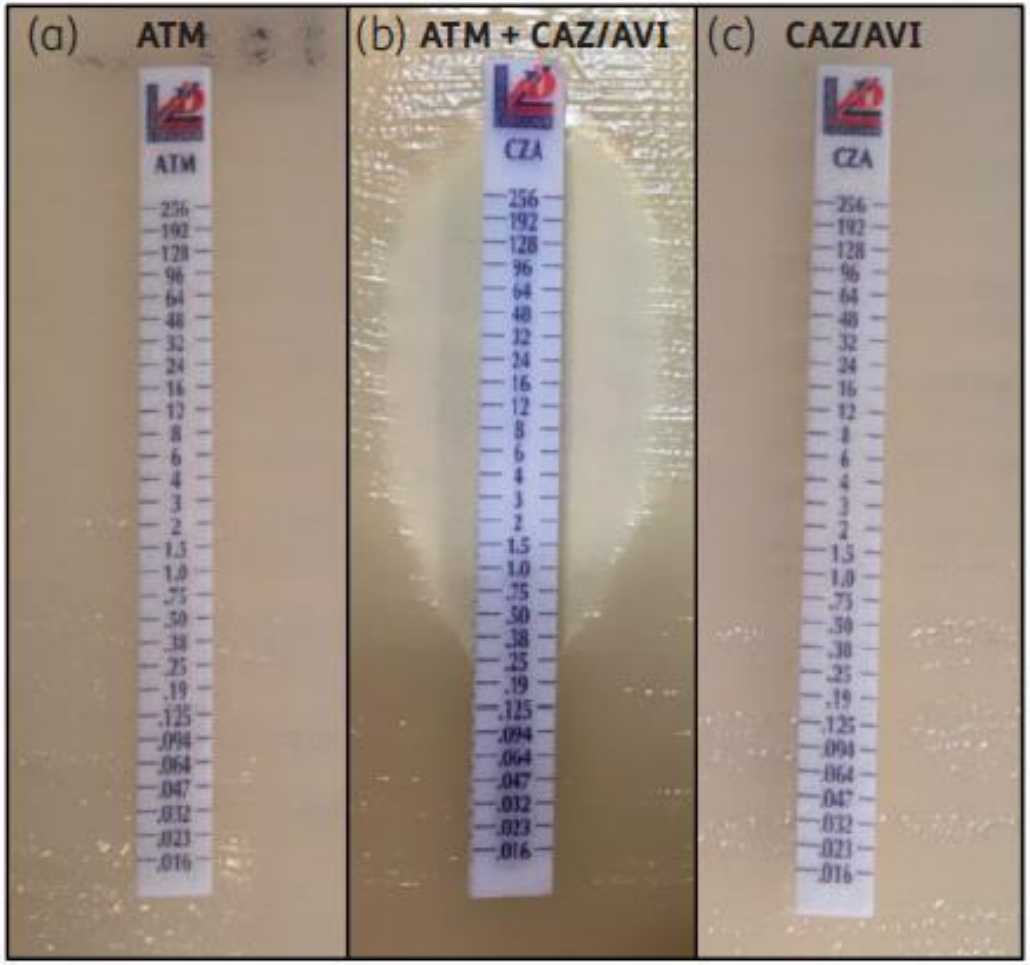


Figure 1. Example of synergistic combination of ceftazidime/avibactam (CAZ/AVI) and aztreonam (ATM) for an NDM + ESBL-producing *K. pneumoniae*. Susceptibility testing of ATM alone (a), combination of CAZ/AVI with ATM (b) and CAZ/AVI alone (c). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

The synergy of the combination of ceftazidime/avibactam with aztreonam against NDM producers could be explained by the neutralization of the ESBL activity by avibactam allowing a restoration to aztreonam.

Plazomicin activity against polymyxin-resistant Enterobacteriaceae, including MCR-1-producing isolates

- **Plazomicin (plazomicin sulphate, ACHN-490) is a novel semisynthetic aminoglycoside derived from sisomicin.**
- **Plazomicin is insensitive to classical aminoglycoside-modifying enzymes such as acetyl-, phosphoryl- and nucleotidyl-transferases.**
- **Plazomicin is active against clinical isolates possessing a broad range of resistance mechanisms, including ESBLs, carbapenemases and fluoroquinolone target site mutations.**
- **This novel antibiotic has the potential to address an unmet medical need for patients with serious MDR Enterobacteriaceae infections, including those caused by carbapenem- and colistin-resistant isolates.**

Denervaud-Tendon V et al. J Antimicrob Chemother 2017; 72: 2787-91

Plazomicin activity against polymyxin-resistant Enterobacteriaceae, including MCR-1-producing isolates

- **Susceptibility to plazomicin and comparators was tested by broth microdilution for a collection of 95 colistin-resistant enterobacterial isolates collected from 29 hospitals in eight countries.**

- **Forty-two isolates (Klebsiella pneumoniae and Klebsiella oxytoca) possessed chromosomally encoded resistance mechanisms to colistin, 21 isolates (Escherichia coli and Salmonella enterica) expressed the mcr-1 gene, 8 isolates (Serratia, Proteus, Morganella and Hafnia) were intrinsically resistant to colistin and 24 isolates (K. pneumoniae, E. coli and Enterobacter spp.) had undefined, non-mcr-1 mechanisms.**

Denervaud-Tendon V et al. J Antimicrob Chemother 2017; 72: 2787-91

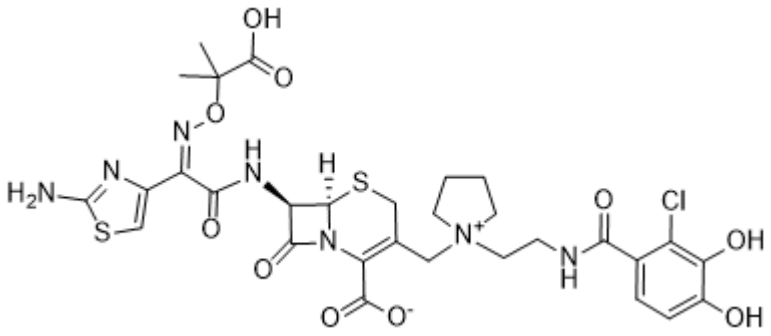
Plazomicin activity against polymyxin-resistant Enterobacteriaceae, including MCR-1-producing isolates

- **Plazomicin inhibited 89.5% and 93.7% of the colistin-resistant enterobacterial isolates at 2 and 4mg/L, respectively.**
- **MICs of plazomicin were 2mg/L for all of the mcr-1 positive isolates and 4mg/L for all the intrinsic colistin-resistant Enterobacteriaceae.**
- **Non-susceptibility to currently marketed aminoglycosides was common: amikacin, 16.8%; gentamicin, 47.4%; and tobramycin, 63.2%.**
- **Plazomicin was the most potent aminoglycoside tested with an MIC90 of 4mg/L, compared with 32,>64 and 64mg/L for amikacin, gentamicin and tobramycin, respectively.**

Denervaud-Tendon V et al. J Antimicrob Chemother 2017; 72: 2787-91

Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens

- **Cefiderocol (CFDC) is a novel parenteral siderophore cephalosporin also known as S-649266.**
- **It possesses a unique mechanism for penetrating efficiently into Gram-negative pathogens.**
- **It uses a “Trojan horse” strategy by binding free iron and is then actively transported into bacterial cells across the outer membrane of Gram-negative bacteria by way of the iron-transport system**



Dobias J et al. Eur J Clin Microbiol Infect Dis 2017; 36:2319–2327

Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens

Evaluation of the antimicrobial activity of cefiderocol against a panel of 753 multidrug-resistant bacterial isolates from human clinical sources with characterized antibiotic resistance mechanisms.

Table 1 Bacterial strains tested in this study

Genus (species)	Number of tested isolates	Characterized resistance
Klebsiella pneumoniae (298)		
	101	KPC (-2/3/11)
	89	OXA (-48/162/163/181/204/232)[a]
	18	NDM[b] (-1/4)
	20	VIM (-1/4/19), IMP (-1/4/8)
	25	CTX-M (-3/15)
	45	Colistin R

Dobias J et al. Eur J Clin Microbiol Infect Dis 2017; 36:2319–2327

Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens

- **Colistin-resistant strains had high susceptibility to cefiderocol (≤0.5/≤2) and some activity for ceftolozane–tazobactam in the case of E. coli (0.25/>64), ceftazidime–avibactam (0.5/>64), amikacin (≤4/16), and tigecycline (≤1/≤1).**

- **Except for cefiderocol and tigecycline, the MIC90 values were close to or above the upper limit of the concentration range of the tested antibiotics for the Enterobacteriaceae being resistant to colistin.**

Dobias J et al. Eur J Clin Microbiol Infect Dis 2017; 36:2319–2327

Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

TABLE 1 Antibiotic susceptibility comparison by Vitek 2, broth microdilution, and Etest methods against 4 *K. pneumoniae* isolates[a]

Isolate no. (day of hospitalization)	Specimen	Antibiotic	MIC (mg/liter)[b]		
			Vitek 2	Etest	BMD
1 (48)	Endotracheal aspirate	IPM	≥16	>32	32
		MEM	≥16	>32	64
		ERTA	≥8	>32	256
		DOR	n.t	n.t	64
		AK	≥64	48	32
		COL	≥16	2	32
		FOSFO	≥128	32	64
		TGC	≥8	0.38	0.5
2 (48)	Blood	IPM	≥16	>32	32
		MEM	≥16	>32	64
		ERTA	≥8	>32	512
		DOR	n.t	n.t	32
		AK	≥64	48	32
		COL	≥16	4	16
		FOSFO	≥128	64	128
		TGC	≥8	1	0.5
3 (53)	Blood	IPM	≥16	>32	32
		MEM	≥16	>32	64
		ERTA	≥8	>32	64
		DOR	n.t	n.t	64
		AK	≥64	48	32
		COL	≥16	6	16
		FOSFO	≥128	32	64
		TGC	≥8	0.38	0.5
4 (59)	Blood	IPM	≥16	>32	32
		MEM	≥16	>32	64
		ERTA	≥8	>32	512
		DOR	n.t	n.t	64
		AK	≥64	64	32
		COL	≥16	4	16
		FOSFO	≥128	32	64
		TGC	≥8	0.75	0.5

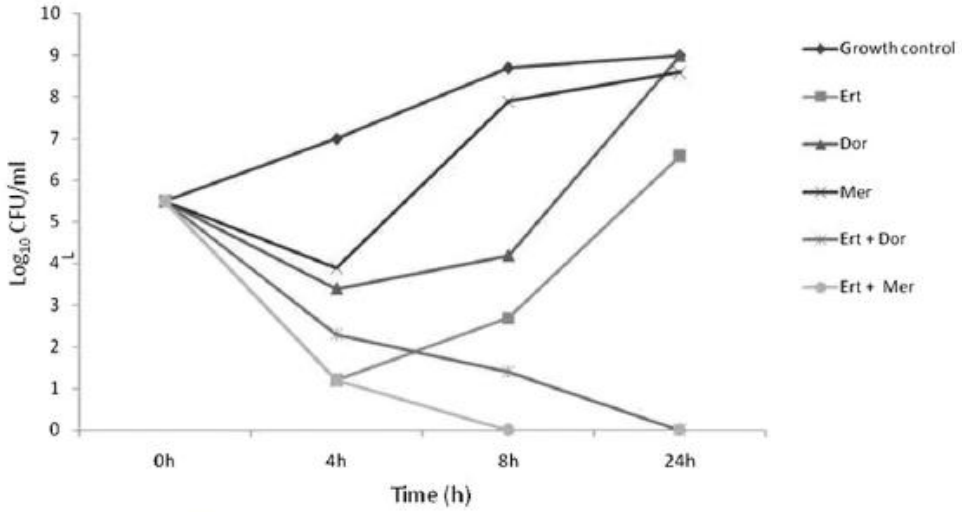


FIG 1 Time-kill curves for *K. pneumoniae* with ertapenem (Ert) at 1 × MIC (512 mg/liter), doripenem (Dor) at 1 × MIC (64 mg/liter), meropenem (Mer) at 1 × MIC (64 mg/liter), and the combinations of ertapenem plus doripenem at 1 × MIC and ertapenem plus meropenem at 1 × MIC.

Ceccarelli G et al. Antimicrob Agents Chemother 2013; 57: 2900-1

Should Colistin always be avoided for C-R K pneumoniae?

The Combination of Doripenem and Colistin Is Bactericidal and Synergistic against Colistin-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae*

TABLE 4 AUCs for two-drug combinations after 24 h of incubation

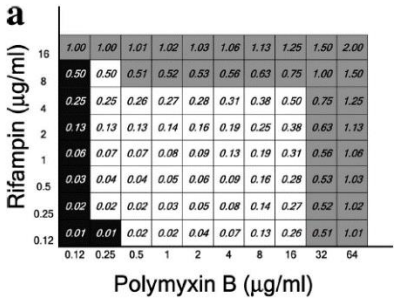
	AUC[a]					
	Colistin			Doripenem		
Isolate	Plus doripenem	Plus gentamicin	Plus doxycycline	Plus gentamicin	Plus doxycycline	Gentamicin plus doxycycline
1	62.34	88.02	NA	209.5	NA	106.6
18	69.6	103.9	NA	81.7	NA	134.2
82	74.8	57.4	141.0	62.8	150.6	52.9
124	47.8	37.46	132.5	NA	128.2	NA
133	87.9	110.2	NA	176.5	168.5	206.0
136	84.8	121.4	138.5	202.9	213.6	143.4
141	59.4	29.1	99.9	22.4	156.7	50.8
145	81.5	139.0	157.4	NA	195.3	NA
167	33.9	NA	51.0	207.6	207.4	220.1
180	118.3	132.4	146.7	155.4	138.7	203.7
182	112.3	137.0	135.5	183.8	164.8	168.2
183	82.1	10.0	132.1	15.9	107.5	26.4
Median (range)	78.2 (33.9–118.3)	103.9 (10.0–139.0)	135.5 (51.0–157.4)	165.9 (15.9–209.5)	160.8 (107.5–213.6)	138.8 (26.4–220.1)

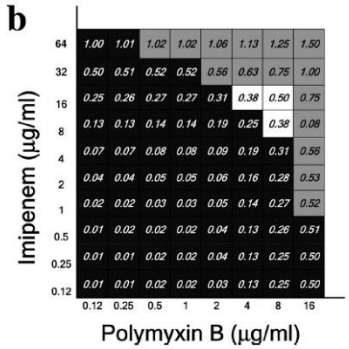
[a] NA, not applicable; area under the curve was not calculated for antagonistic combinations.

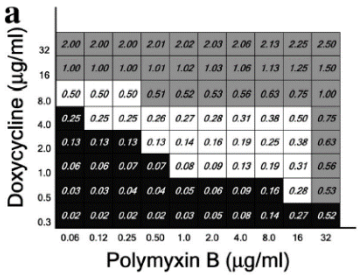
Doripenem plus colistin was synergistic against 60% (6/10) or 67% (4/6) of isolates that were resistant to colistin (MICs, 4 to 64 ug/ml) or resistant to all agents, respectively

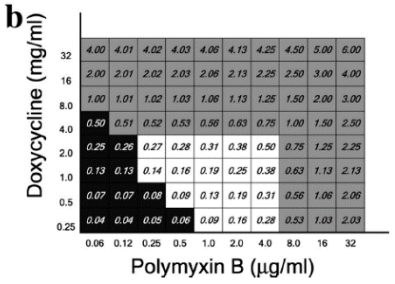
Jernigan MG et al. Antimicrob Agents Chemother 2012;56:3395-8

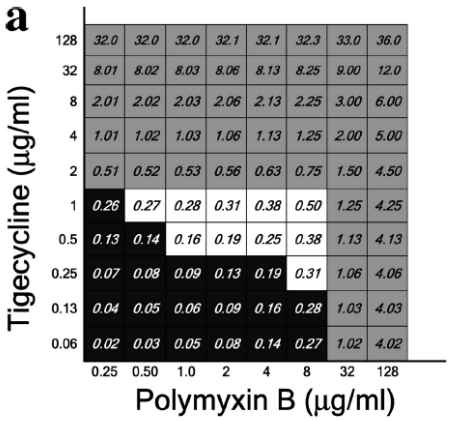
In Vitro Evaluation of Antibiotic Synergy for Polymyxin B-Resistant Carbapenemase-Producing *Klebsiella pneumoniae*[▽]

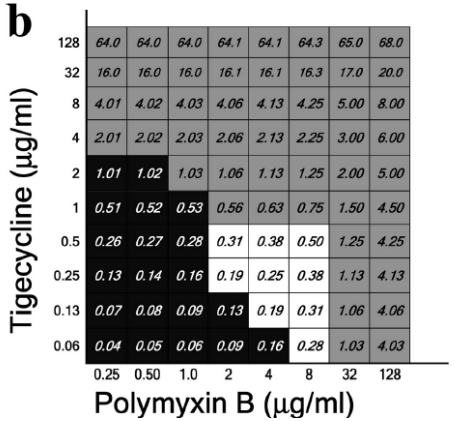


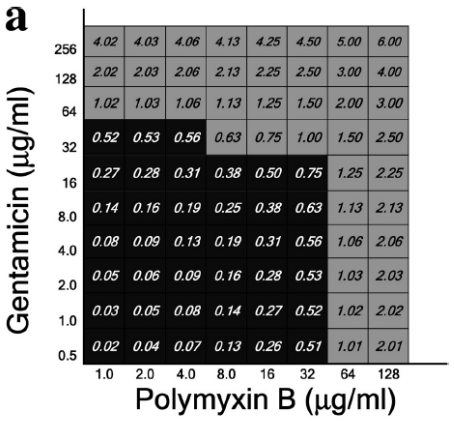


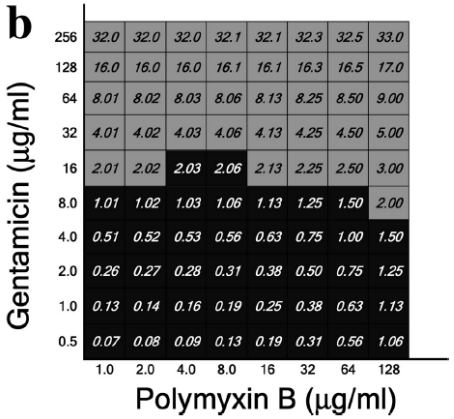












Synergy when rifampin, doxycycline and tygecycline were added for polymixin B resistant CRE

Elemam A et al. J Clin Microbiol 2010;48:3558-62

Overcoming *mcr-1* mediated colistin resistance with colistin in combination with other antibiotics

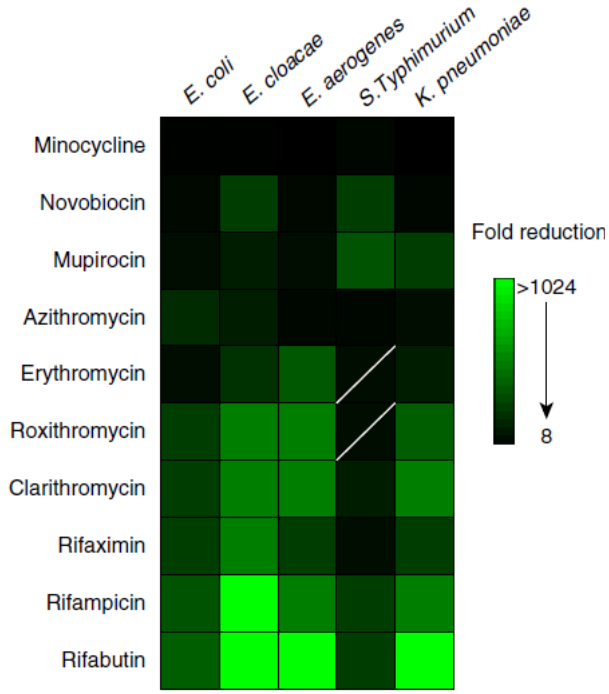
Craig R. MacNair[1], Jonathan M. Stokes[1], Lindsey A. Carfrae[1], Aline A. Fiebig-Comyn[1], Brian K. Coombes[1], Michael R. Mulvey[2] & Eric D. Brown[1]

NATURE COMMUNICATIONS | (2018)9:458

- **mcr-1 confers resistance to colistin-induced lysis and bacterial cell death, but provides minimal protection from the ability of colistin to disrupt the Gram-negative outer membrane.**

- **For colistin-resistant strains of Enterobacteriaceae expressing plasmid-borne mcr-1, clinically relevant concentrations of colistin potentiate the action of antibiotics that, by themselves, are not active against Gram negative bacteria.**

- **Several antibiotics, in combination with colistin, display growth-inhibition at levels below their corresponding clinical breakpoints.**



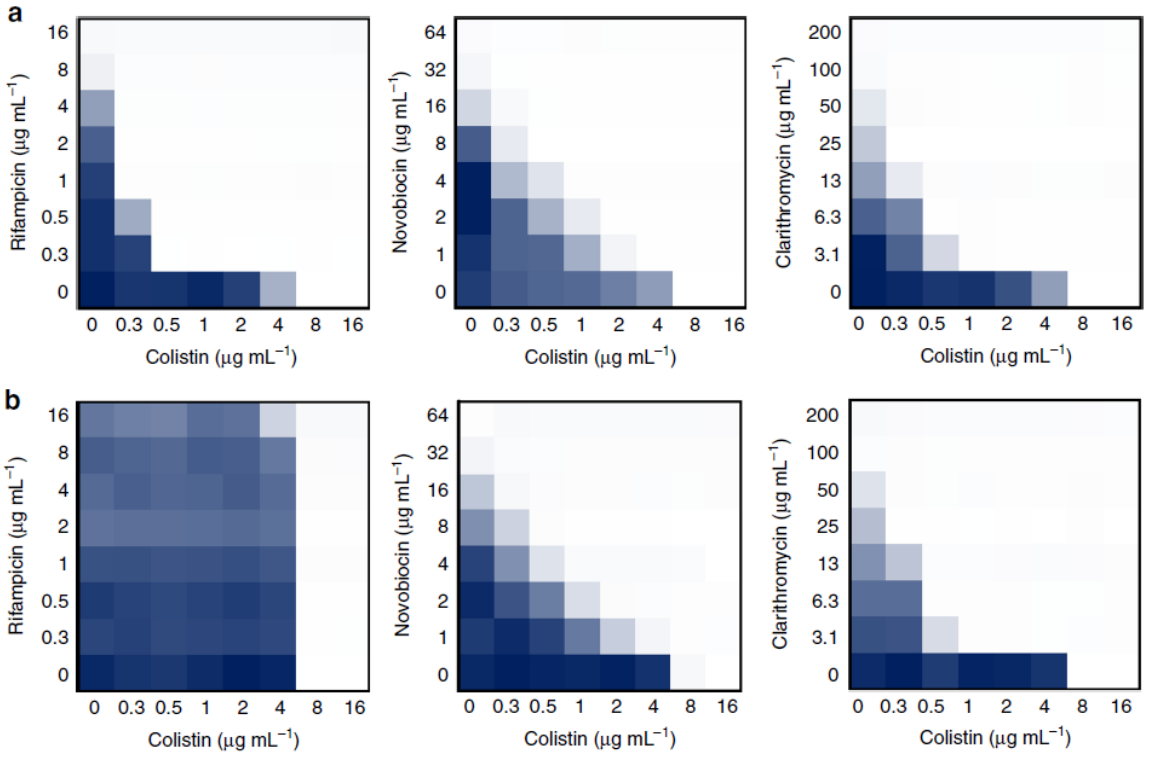
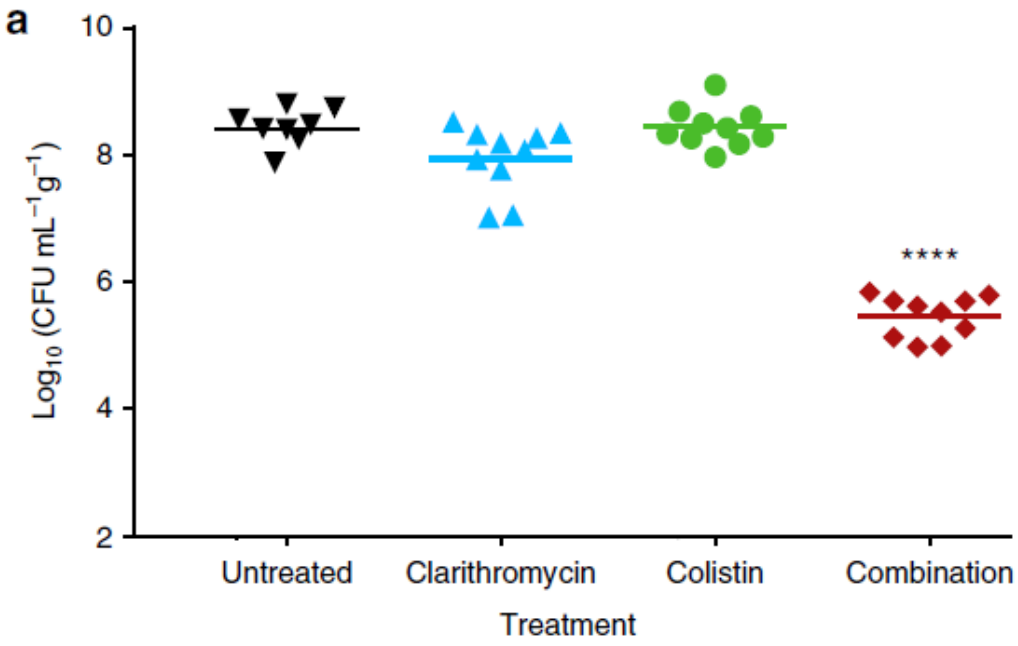
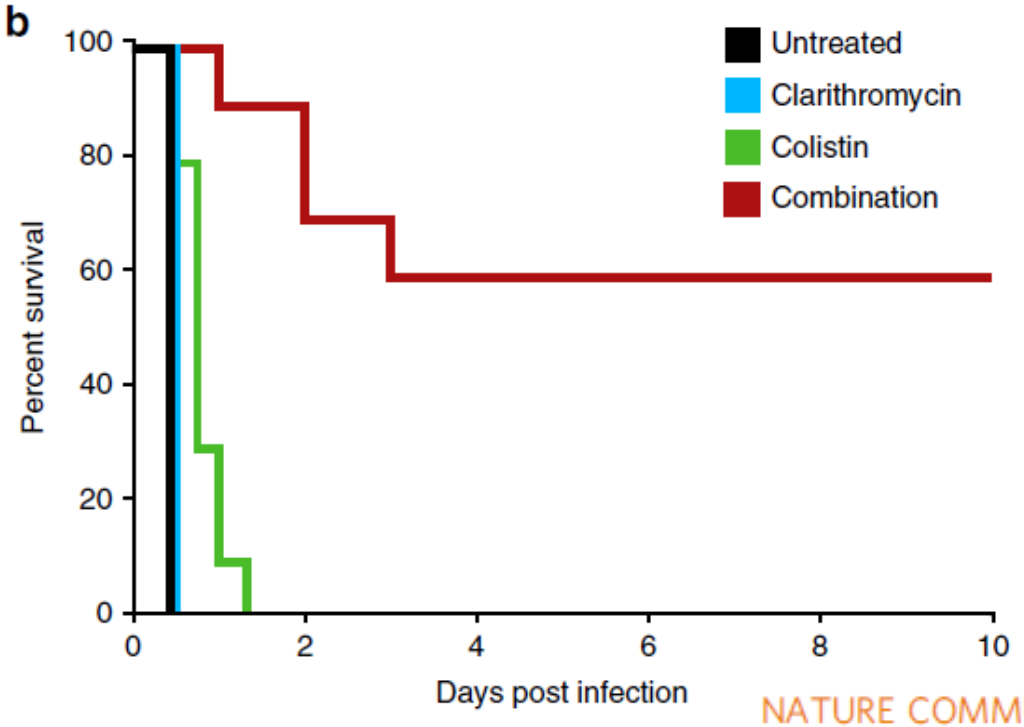


Fig. 1 Colistin potentiates antibiotics conventionally used against Gram-positive bacteria in Enterobacteriaceae expressing *mcr-1*. Heat map showing the mean fold reduction of MIC in the presence of 2 μg mL^{-1} colistin for strains transformed with pGDP2:*mcr-1*. Antibiotics listed were potentiated ≥ 8-fold across all lab generated Enterobacteriaceae strains. A lack of potentiation below clinical breakpoint is indicated by a diagonal white line. Data are representative of two biological replicates


a
10
8
6
4
2
Log10 (CFU mL−1 g−1)
****
Untreated
Clarithromycin
Colistin
Combination
Treatment


b
100
80
60
40
20
0
Percent survival
Untreated
Clarithromycin
Colistin
Combination
0
2
4
6
8
10
Days post infection

New therapy from old drugs: Synergistic bactericidal activity of sulfadiazine with colistin against colistin-resistant bacteria, including plasmid mediated colistin-resistant *mcr-1* isolates

A collection of 55 COL-resistant and -susceptible bacteria from different origins (Laos, Thailand and France) were used

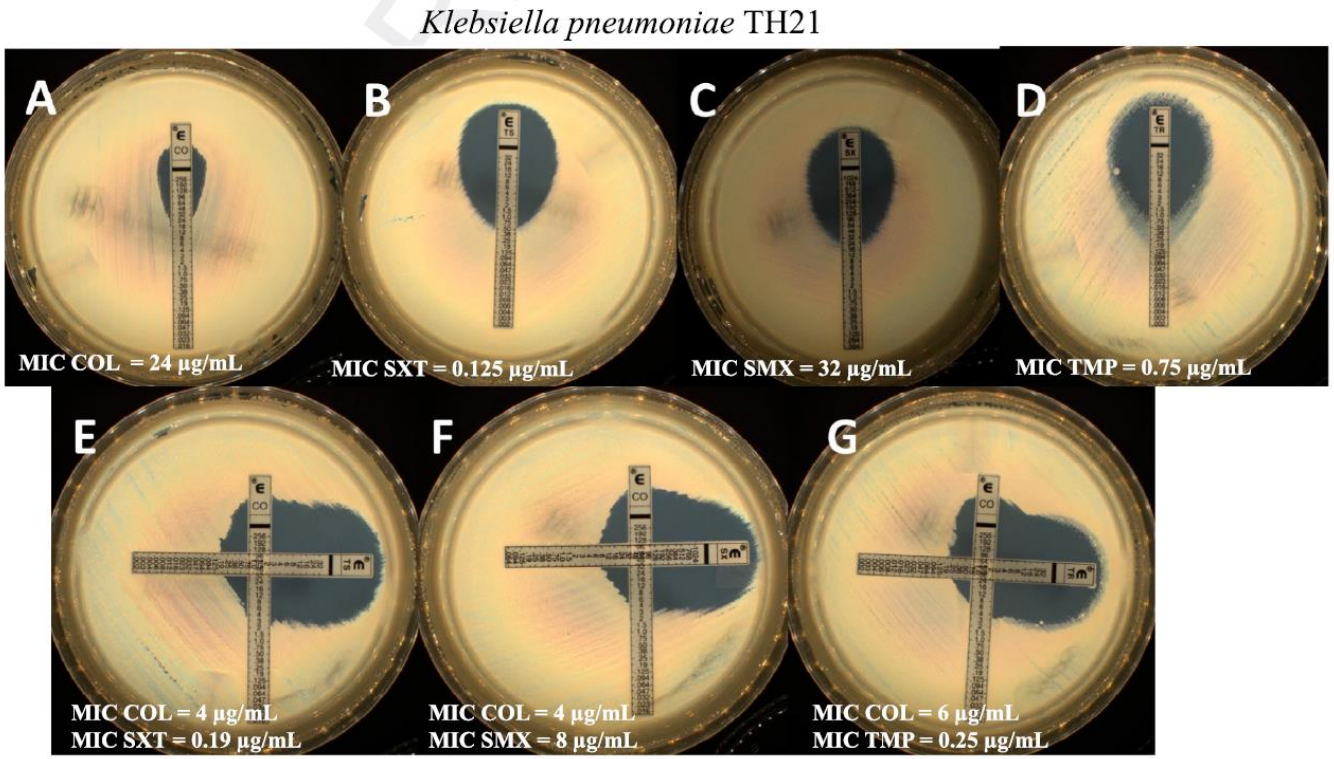


Fig. 1. Etest results for *Klebsiella pneumoniae* TH21 strain. (A–D) Minimum inhibitory concentration (MIC) results of COL (A), SXT (B), SMX (C) and TMP (D); and (E–G) Etest cross method for COL + SXT (E), COL + SMX (F) and COL + TMP (G). COL, colistin; SXT, trimethoprim/sulfamethoxazole; SMX, sulfamethoxazole; TMP, trimethoprim.

Okdah L et al. Int J Antimicrob Agents. 2018 Feb 5

New therapy from old drugs: Synergistic bactericidal activity of sulfadiazine with colistin against colistin-resistant bacteria, including plasmid mediated colistin-resistant *mcr-1* isolates

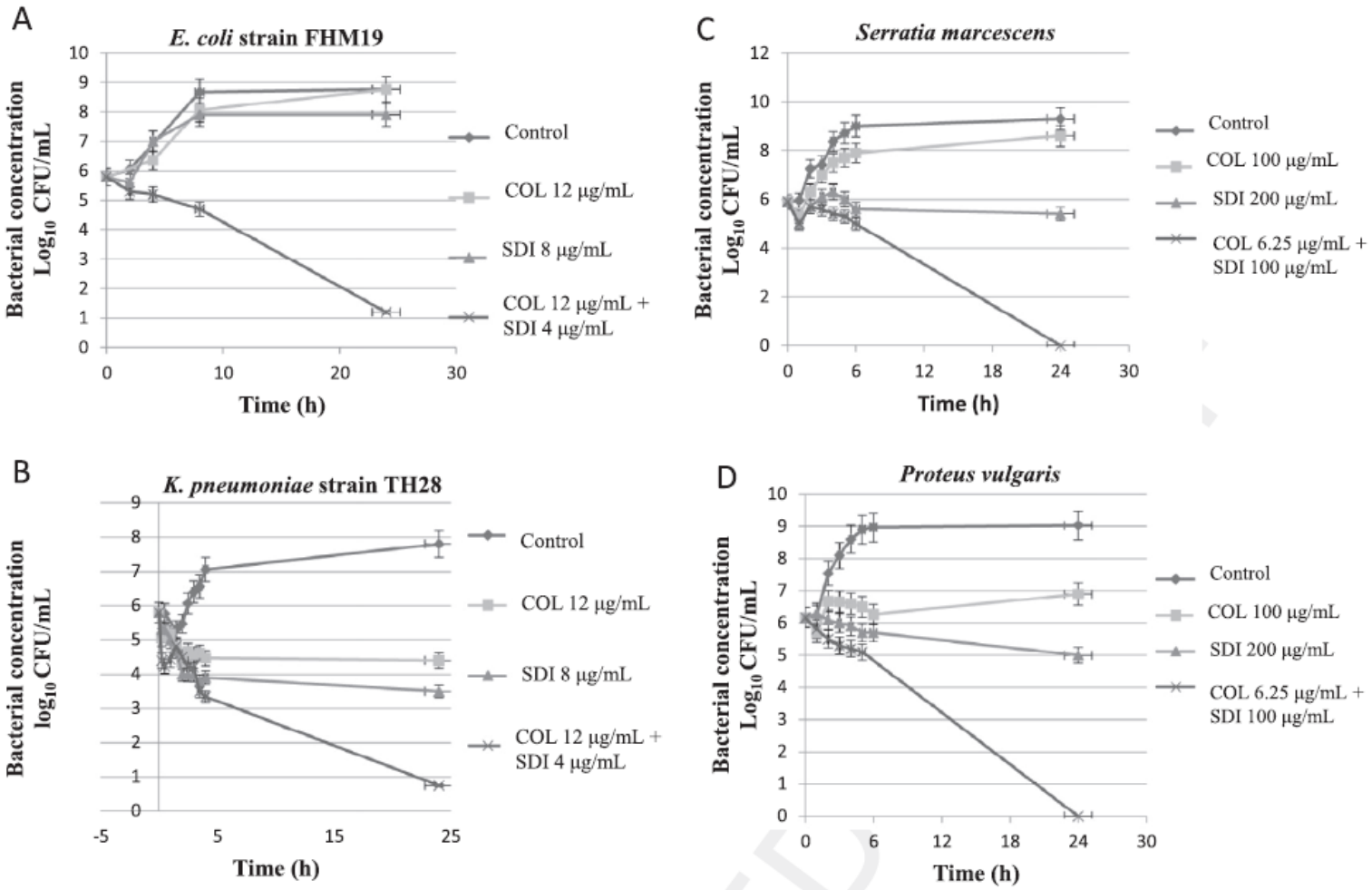


Fig. 4. Time–kill assays conducted with colistin (COL), sulfadiazine (SDI) and the combination of COL + SDI in (A) *Escherichia coli* strain FHM19, (B) *Klebsiella pneumoniae* strain TH28, (C) *Serratia marcescens* and (D) *Proteus vulgaris*.

Okdah L et al. Int J Antimicrob Agents. 2018 Feb 5

New therapy from old drugs: Synergistic bactericidal activity of sulfadiazine with colistin against colistin-resistant bacteria, including plasmid mediated colistin-resistant *mcr-1* isolates

Review of in vitro studies of colistin/sulfonamide combinations

Date	Combination	Strain	Origin	Colistin resistance	Method(s) used	Type of activity
1958	Polymyxin B + sulfonamide	*Proteus* sp.				
1963	Colistin(E) + sulfafurazole	*Proteus* sp.	Isolate	Resistant	Disk diffusion Nutrient broth	Bactericidal action
1970	Polymyxin B + sulfadiazine	*Serratia marcescens*	Clinical isolates	Resistant	Agar pre-treated plate + disk Broth culture	Lethal action
1970	Colistin sulphomethate sodium(E) + sulfamethoxazole and trimethoprim	164 Gram-negative bacilli	Clinical isolates	-*Proteus:* resistant -143 excluding *Proteus* were colistin-resistant	Agar pre-treated plate + disc(2) Replica plate	Bactericidal
1973	Polymyxin + sulfadiazine	*Proteus mirabilis* *Staphylococcus aureus*	ATCC Clinical isolates	-2 colistin-resistant -L-form colistin-susceptible	Culture on TSB Agar pre-treated Plate + disk	-*Proteus*: bactericidal -*S. aureus*: bacteriostatic
1974	Polymyxin B + sulfamethoxazole and trimethoprim	Gram-negative bacilli	Clinical isolates: *Klebsiella pneumoniae*, *Serratia*, *Providencia*, *Proteus*, *Pseudomonas*	-28/52 colistin-resistant	Chequerboard	-Synergy -*Proteus*, *Providencia*: bactericidal
1974	Colistin(E) + sulfamethoxazole and trimethoprim	*Pseudomonas maltophilia*, *Pseudomonas cepacia*	Clinical isolates	Colistin resistant	Agar pre-treated plate	Synergy
1976	Polymyxin E + sulfamethoxazole and trimethoprim	*S. marcescens*	Clinical isolates	Colistin resistant	Chequerboard Time–kill curves	Bactericidal
1993	Ciprofloxacin, polymyxin E, sulfadiazine and p-aminobenzoic acid	*Pseudomonas aeruginosa* *S. aureus*	NCTC	6/12 colistin-resistant	Chequerboard Time–kill curves	Killing
2002	Colistin(E), rifampicin, trimethoprim sulfamethoxazole	*Stenotrophomonas maltophilia*	Clinical isolates		Time–kill curves	Killing re-growth
2012	Colistin sulfate(E) + sulfamethoxazole and trimethoprim, vancomycin	*Acinetobacter baumannii* *P. aeruginosa* *K. pneumoniae*	Clinical isolates = 3 ATCC strains and their mutants		Chequerboard Time–kill curves	Bactericidal at 0.5 MIC

TSP, trypticase soy broth.

Okdah L et al. Int J Antimicrob Agents. 2018 Feb 5

Take home messages

- **Colistin-resistant CR-Enterobacteraceae infections is challenging**
- **Treatment options are limited. They should take into account the medication itself, patophysiology, site of infection and PK/PD profile**
- **Scant data are available on mono vs combo therapy**
- **Combo therapy includes tige+aminoglicoside, fosfo+aminoglicoside+tige, etc..**
- **New options: avibactam, plazomicin, siderophors**
- **For mcr1 strains colistin can be included in the combination therapy**
- **Old drugs should not be ruled out (sulfadiazine, macrolides)**