Colistin in the treatment of infections by carbapenemase producing bacteria

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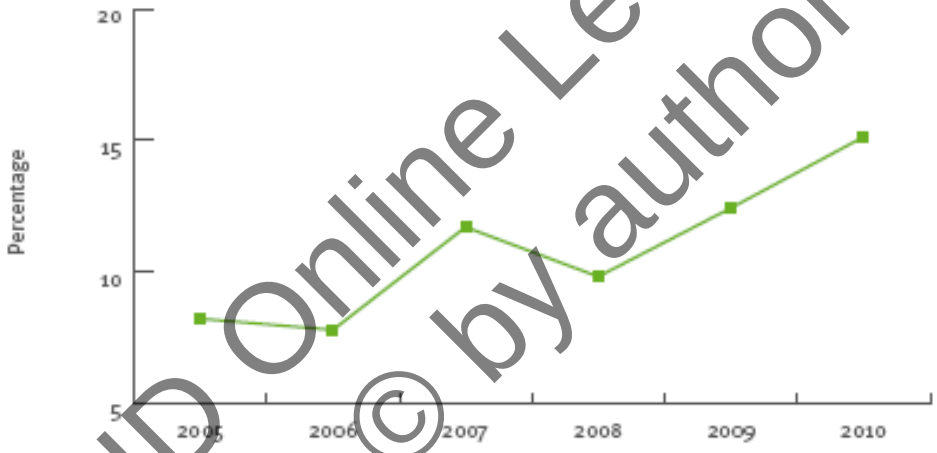
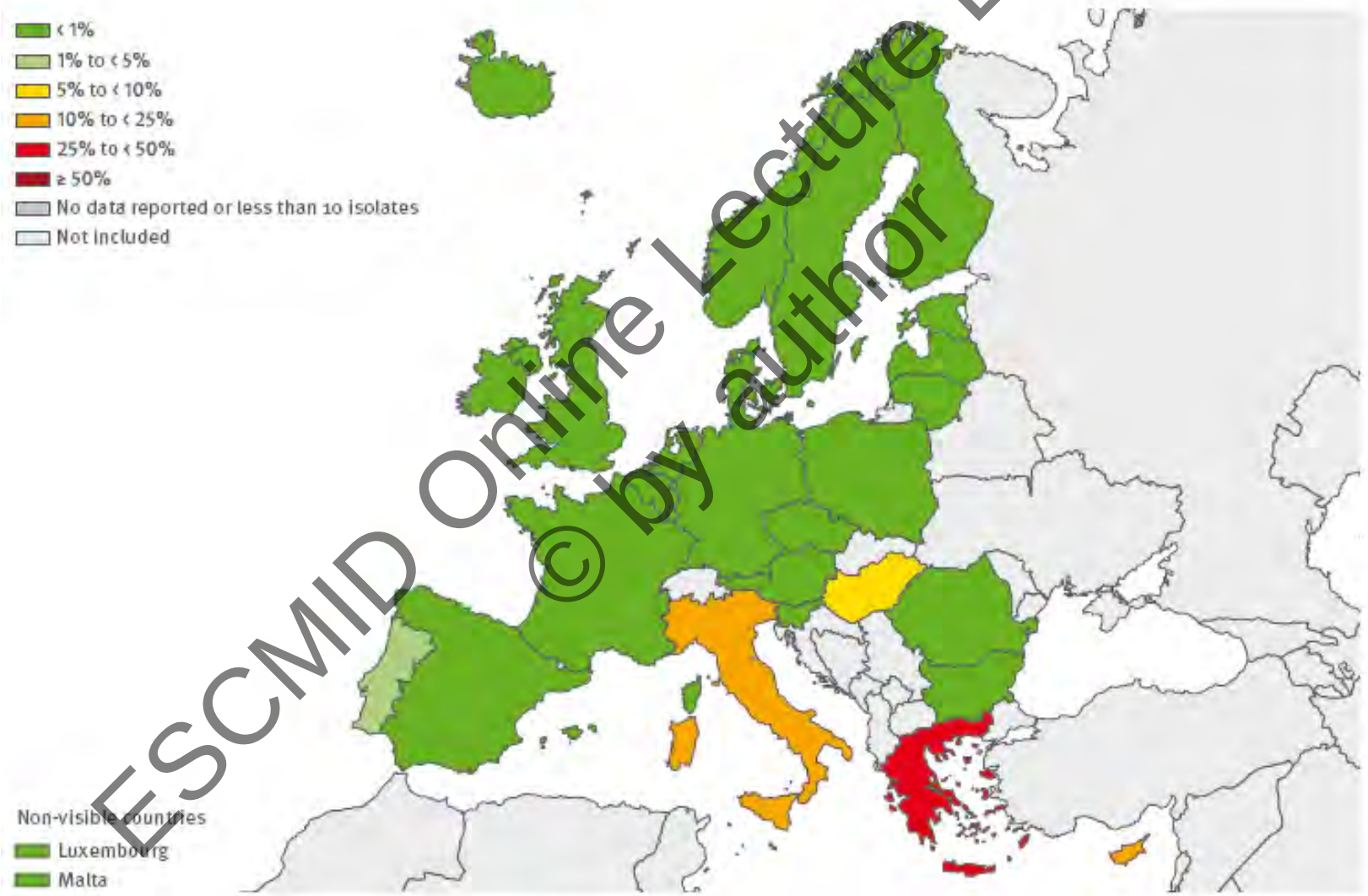
Carbapenemase-Producing Gram-negative Microorganisms: Detection, Epidemiology and Therapeutic Challenges.
ESCMID PostGraduate Education Course, Athens 1st-2nd December 2012.

Trend of carbapenem resistance in *Klebsiella pneumoniae* in Europe



EARS-Net 2010

Carbapenem resistant *Klebsiella pneumoniae* in Europe - 2010



EARSS-Net 2010

Carbapenem resistance in *Pseudomonas aeruginosa* - 2010

What remains against carbapenem-resistant Enterobacteriaceae?

International Journal of Antimicrobial Agents 37 (2011) 415–419

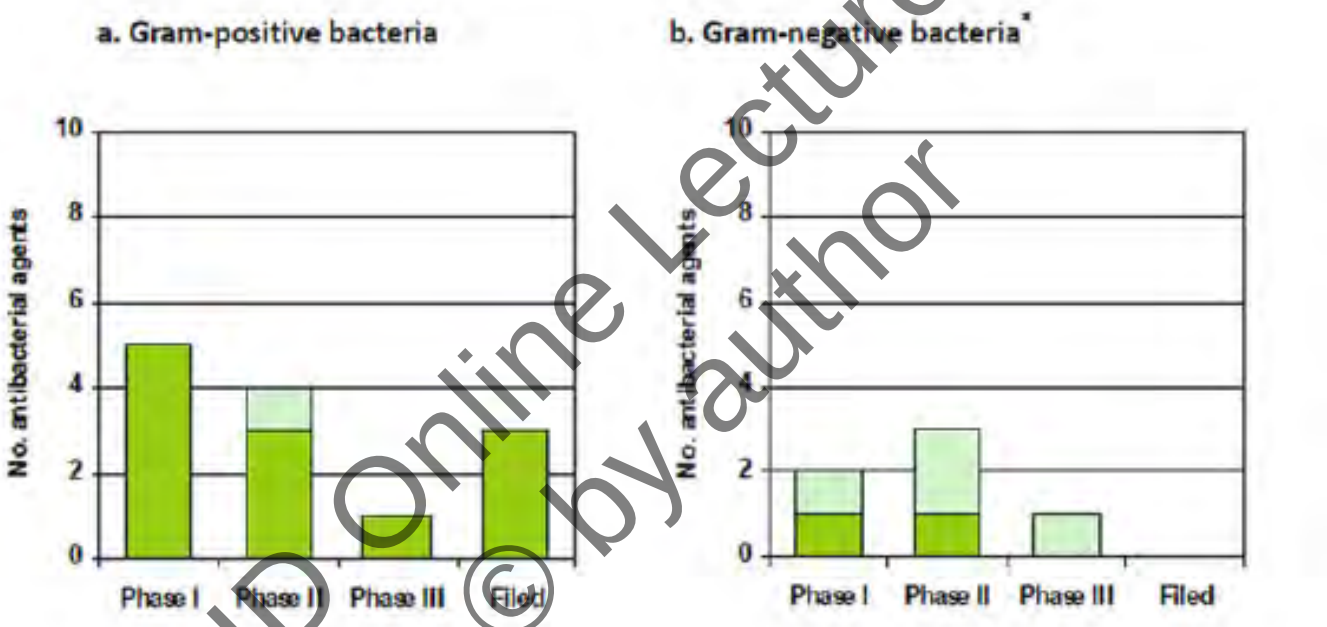
Antibiotic/species	No. isolates with indicated MIC (mg/L):												
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Colistin													
Klebsiella spp.				36[r]	13	1			1	2			
Enterobacter spp./*C. freundii*				16[r]	3	1		1					
E. coli				6[r]	1								
Fosfomycin													
Klebsiella spp.						2[r]	2	7	5	9	10	7	10
Enterobacter spp./*C. freundii*						2[r]	3	3	4	4	3	1	
E. coli						5[r]	1	1					
Tigecycline													
Klebsiella spp.				6	15	22	9						
Enterobacter spp./*C. freundii*				1	9	5	3	2					
E. coli			1	3	3								

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%	64; 128	0%	32; 128	0%
Meropenem	32; 32	3%	32; >32	3%	>32; >32	3%
Piperacillin-tazobactam	>64; >64	0%	>64; >64	0%	>64; >64	0%
Cefotaxime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Ceftazidime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Cefpirome	>64; >64	0%	>64; >64	0%	>64; >64	0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	8%	>8; >8	8%	>8; >8	8%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
Amikacin	>64; >64	0%	>64; >64	0%	>64; >64	0%
Minocycline	16; >32	0%	32; >32	0%	8; 16	0%
Tigecycline	1; 4	64%	4; 8	56%	1; 2	67%
Colistin	0.5; 8	89%†	1; 32	94%†	1; 2	100%†

Lancet Infect Dis. 3099 (10) 70143-2

Novel antimicrobials against Gram (-)

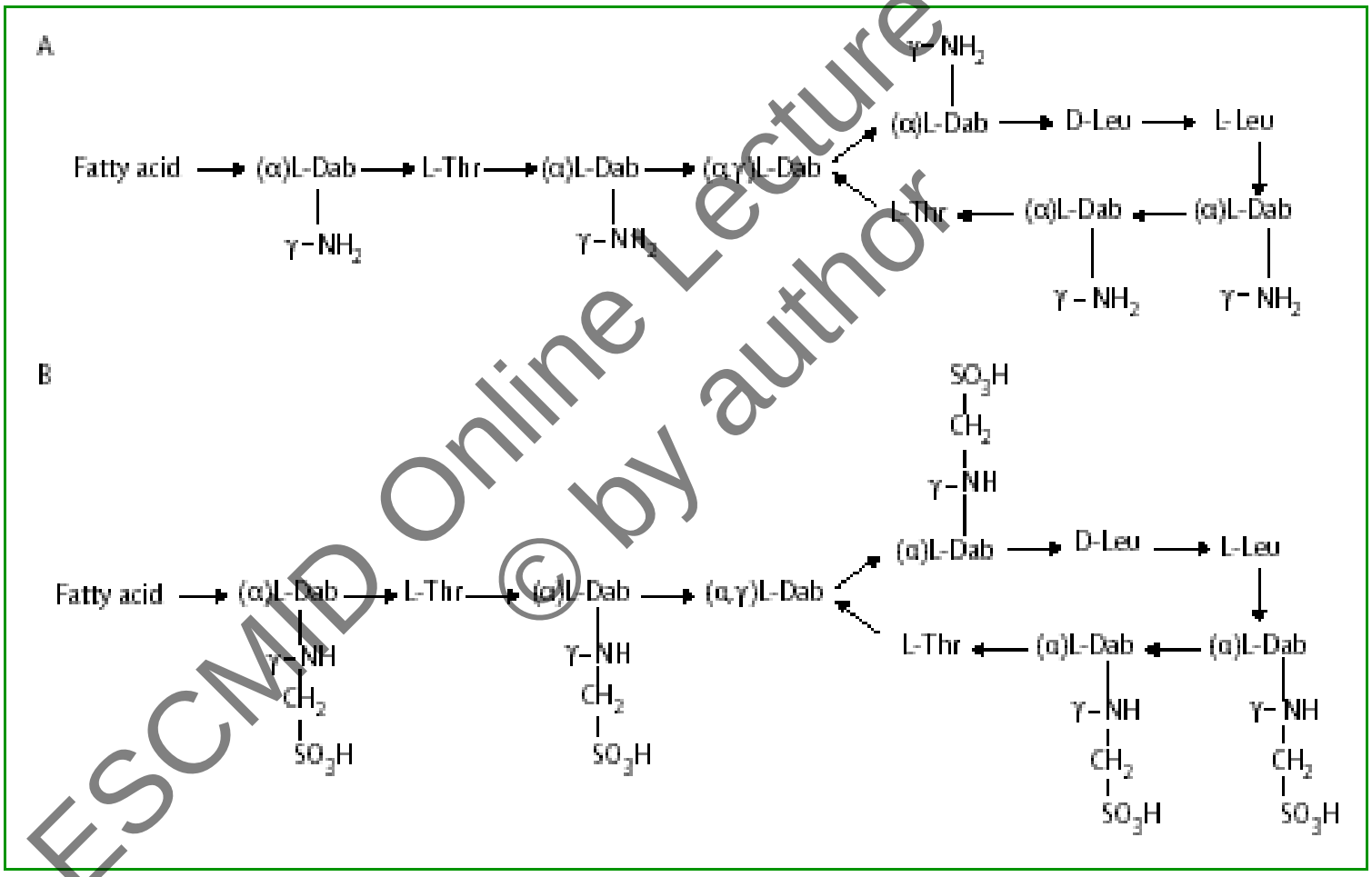


Resurgence of colistin

Pharmacology - History

- Polymyxin lipopeptide
- Polymyxin E
- Isolated in 1950 from *Bacillus colistinus*
- Mixture of various forms
- Main forms: Colistin A and B
- Available in two pharmaceutical forms
  - Colistin sulfate: Local use
  - Colistimethate sodium – CMS
    - Less toxic
    - Parenteral use

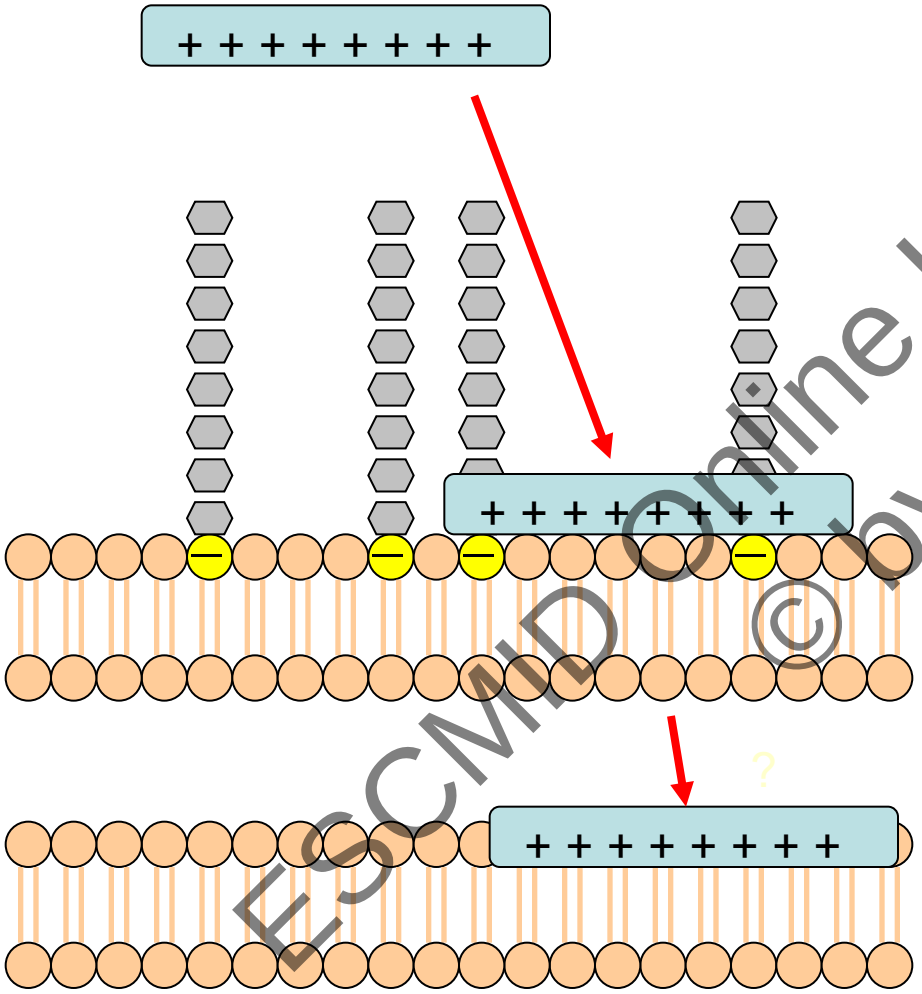
Structure of colistin (A) and Colistimethate Sodium (B)



Mode of Action

- Attachment of colistin to LPS of Gram-negative outer membrane
- Displacement of Ca and Mg ions that stabilize the outer membrane
- Increased permeability
- Antiendotoxic activity

Mode of Action



Colistin

Polysaccharide O

Outer Membrane

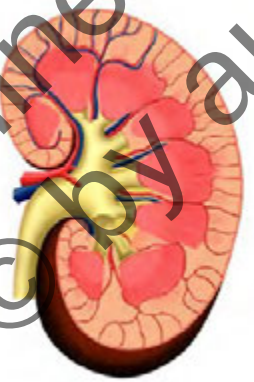
Periplasmic space

Inner membrane

Non-enzymatic hydrolysis

CMS
(Inactive Prodrug)

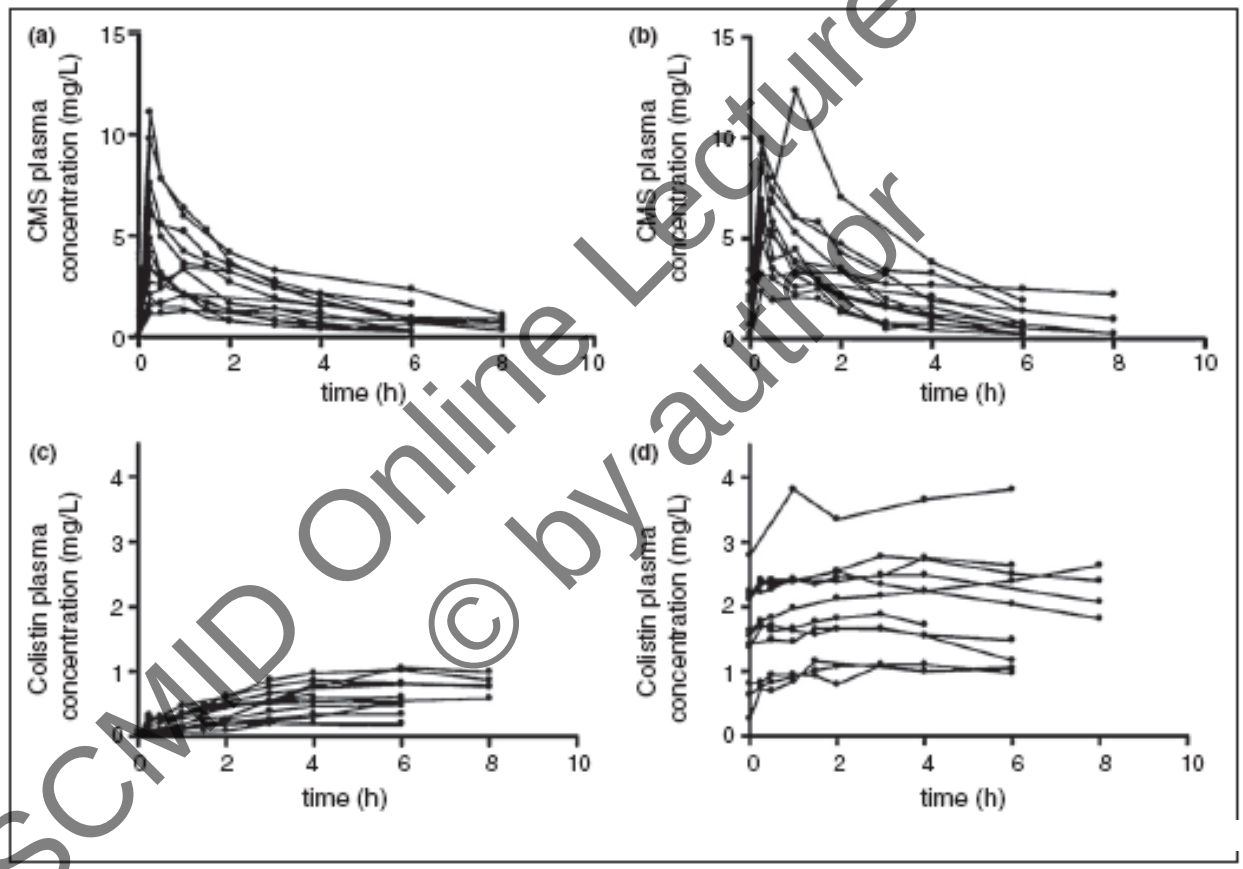
Colistin



Chemical degradation

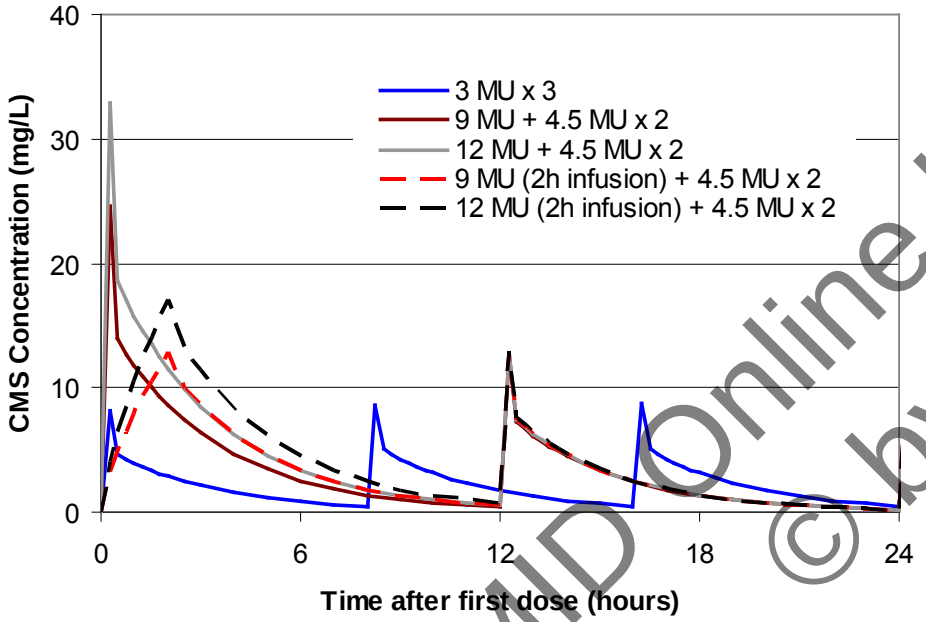
Bergen PJ et al. *AAC* 2006

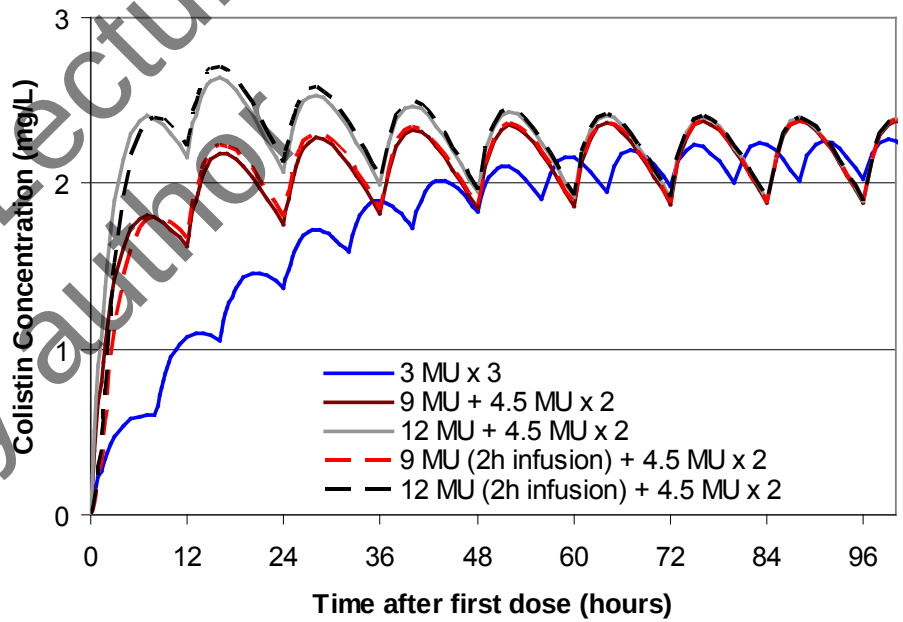
Colistin PK in critically ill patients



Plachouras D. *Antimicrob Agents Chemother* 2009

Dosage regimen simulation

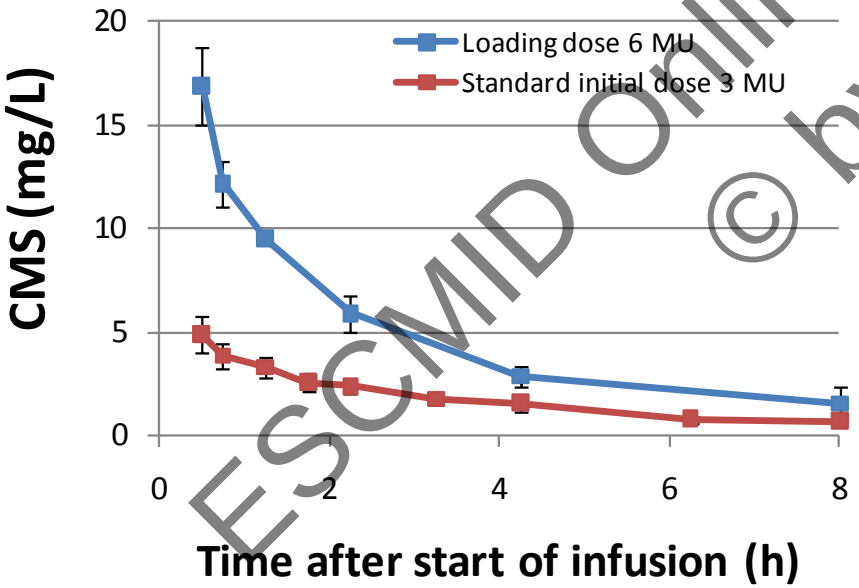


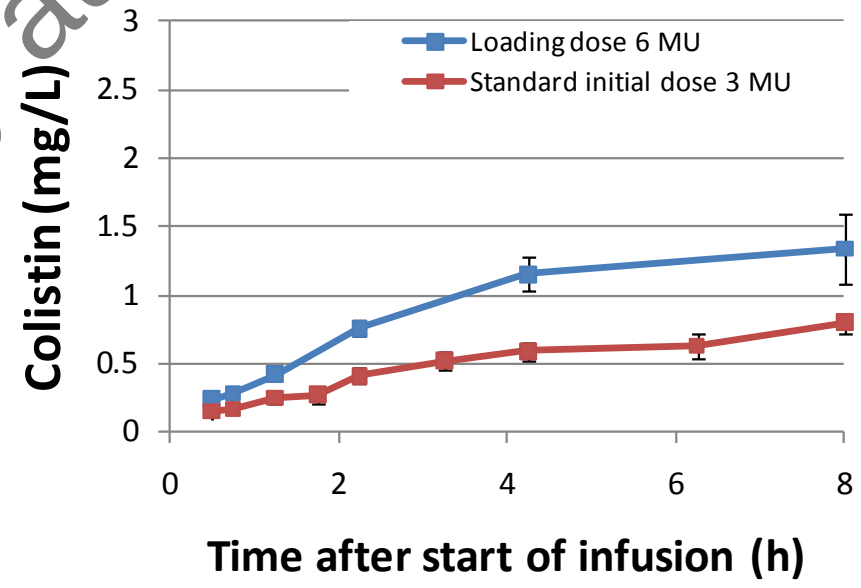


Plachouras D et al. Antimicrob Agents Chemother. 2009 Aug;53(8):3430-6

Colistin Pharmacokinetics after Administration of a Loading Dose of Colistin Methanesulphonate (CMS)

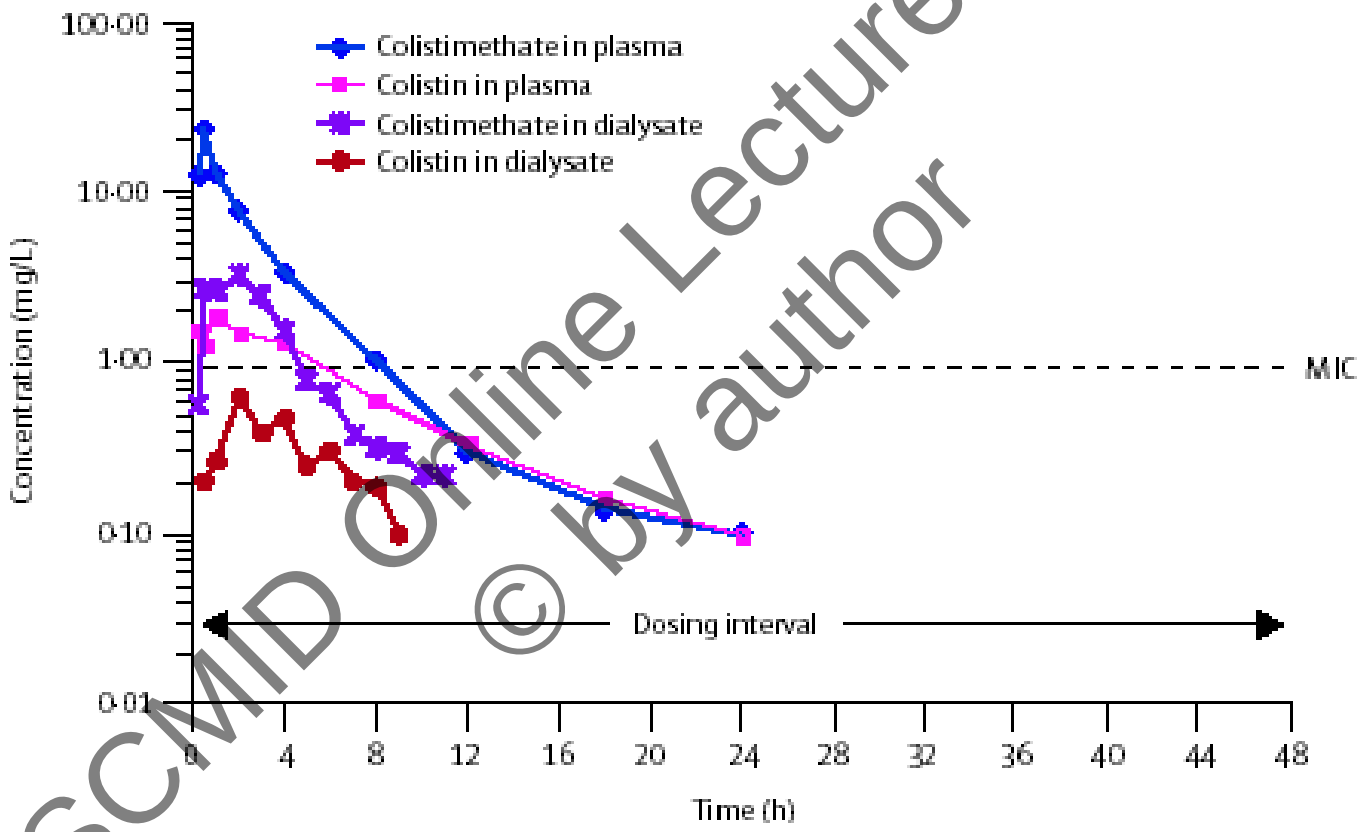
n=10 (6 males, 4 females)
Age (mean (range)) : 55.4 (32-88) years
APACHE II score (mean (range)) :15.4 (7-24)
Observed plasma concentrations :
Cmax after loading dose (mean (SEM)):
CMS : 16.9 (1.83) mg/L
Colistin: 1.43 (0.25) mg/L



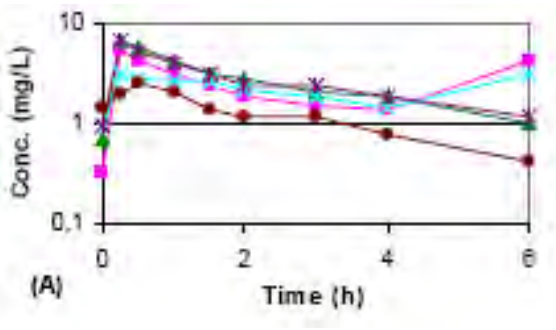


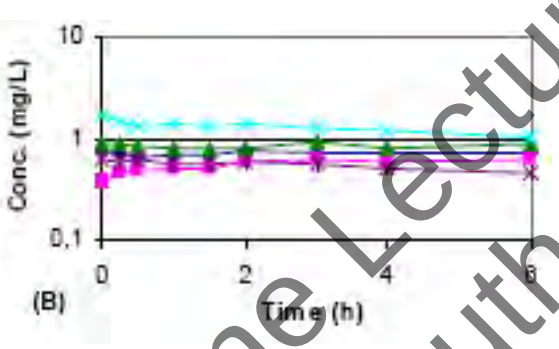
Mohamed AF, Karaiskos I et al. Submitted

Pharmacokinetics in Continuous Veno-venous Hemodiafiltration (CVVHDF)



Colistin pharmacokinetics in patients on continuous veno-venous hemodiafiltration (CVVHDF)





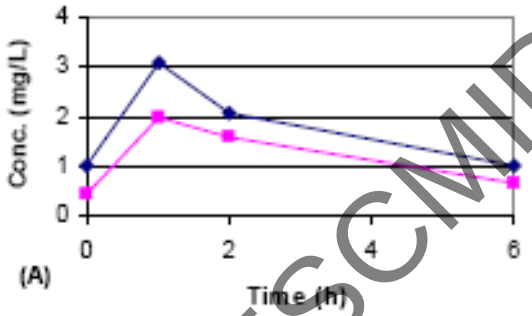
Serum CMS (A) and colistin (B) concentrations

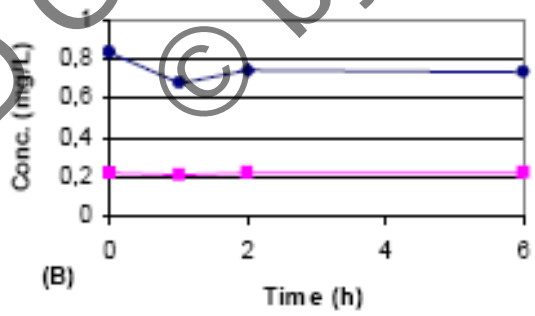
5 patients

2 mIU tid iv

Cmax : 0.92 mg/L

Extraction: 68%





CMS (A) and colistin (B) concentration before and after filter

	CMS	Colistin
C_{max} (mg/L)	4.93 (2.01)	0.92 (0.46)
C_{min} (mg/L)	1.08 (0.40)	-
$T_{½}$ (terminal, h)	3.29 (0.62)	-
Extraction (%)	30 (13)	68 (8)
CL_{bHDF} (L/h)	2.45 (1.26)	5.5 (1.10)

Karvanen M. ECCMID 2009

Journal of Antimicrobial Chemotherapy (2008) 62, 1311–1318
doi:10.1093/jac/dkn425
Advance Access publication 15 October 2008

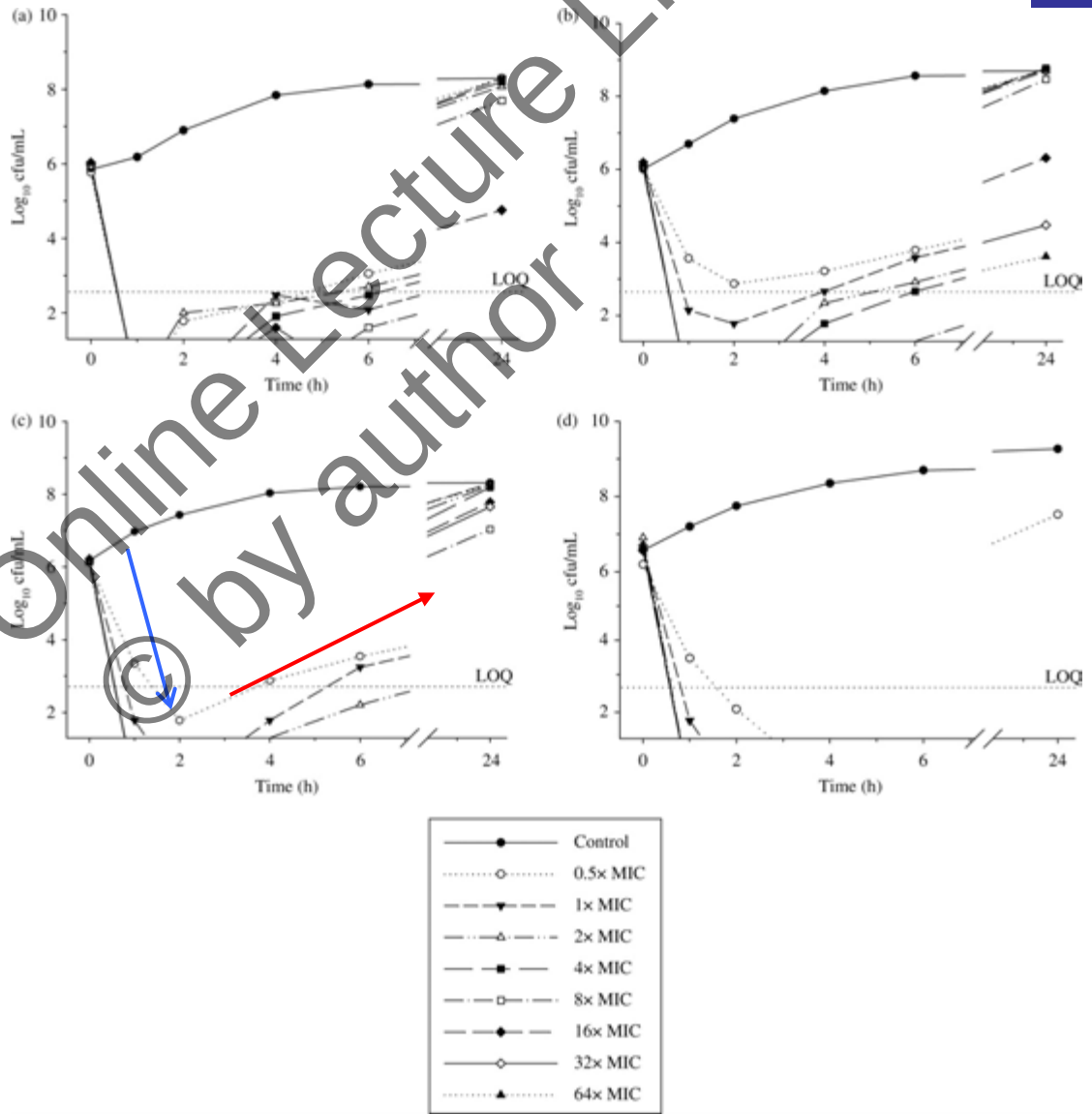
JAC

In vitro pharmacodynamics of colistin against multidrug-resistant *Klebsiella pneumoniae*

- Concentration dependent
- Bactericidal

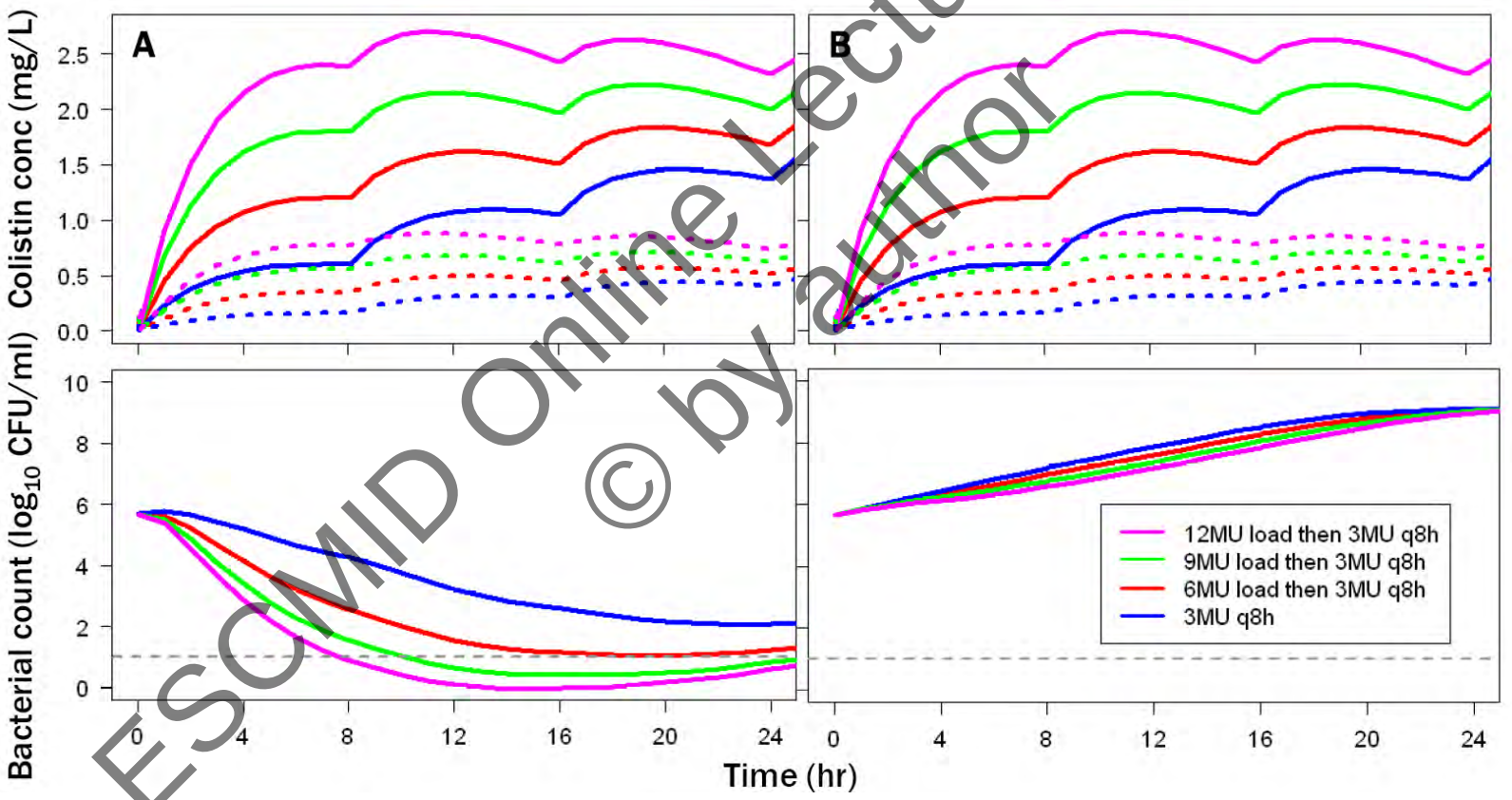
But

- Emergence of resistance
- ? Heteroresistance



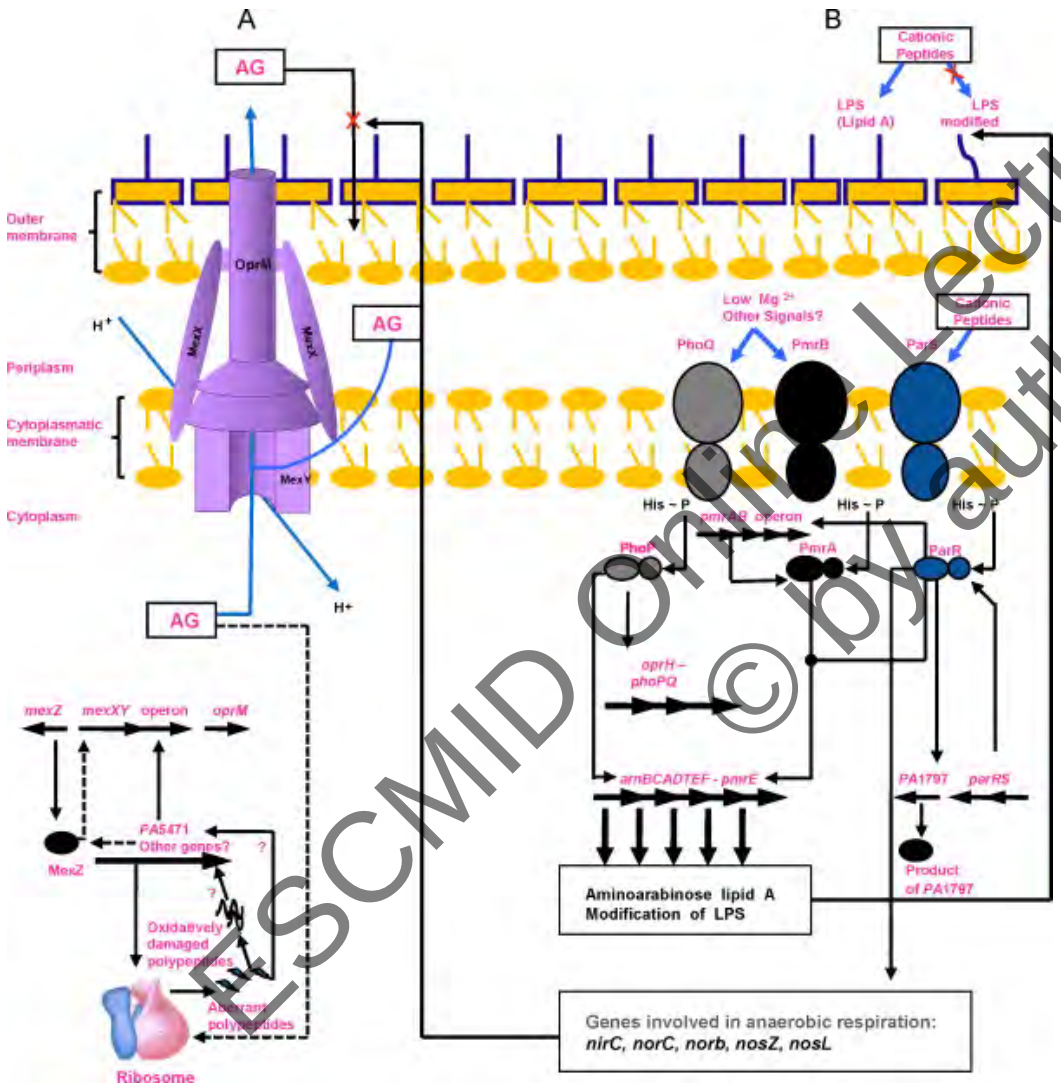
Colistin pharmacodynamics

Modelling of bacterial killing by various dosing regimens



Mohamed AF, Karaiskos I et al. Submitted

Adaptive resistance



Skiada A. *Int J Antimicrob Agents* 2011

Antimicrobial spectrum

- Gram negative bacteria
  - Enterobacteriaceae → *E. coli, K. pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumanii*
- Excluding
  - *Proteus, Providencia, Morganella, Serratia*

MIC breakpoints

- Colistin sulfate
- CLSI: ≤ 2 mg/L
- EUCAST: < 4 mg/L
- E-test
  - Especially when disk inhibition zone 12-13 mm
    - » Galani I et al. Int J Antimicrob Agents 2008

Resistance

- Modification of negative LPS charge -> reduced binding of colistin (*pmrA-pmrB*)
- 18 strains colistin resistant *Klebsiella pneumoniae*
  - » Antoniadou A. JAC 2007
- 33 strains *Klebsiella pneumoniae*, 6 *Acinetobacter baumanii* και 2 *Pseudomonas aeruginosa*
  - » Matthaiou DK et al. Crit Care Med 2008
- Risk factor: duration of colistin treatment > 13 days
  - » Mentzelopoulos SD. Intensive Care Med 2007
- heteroresistance in *Acinetobacter*
  - » Li J et al. AAC 2006

Colistin resistance

Retrospective cohort study of emergence of colistin resistance incl. 150 patients

	Colonization, No (%)	Infection				All-cause mortality, No (%)
		VAP	BSI	Other	Total	
CR pathogen						
Klebsiella pneumoniae	30 (20)	1	5	1	7 (23)	6 (86)
Pseudomonas aeruginosa	2 (1)				0	0
Acinetobacter baumanii	4 (3)				0	0
Enterobacter aerogenes	3 (2)			1	1 (33)	1 (100)
Escherichia coli	2 (1)				0	0
CIR pathogens						
Serratia marcescens	16 (13)		3		3 (18)	2 (67)
Providencia stuartii	8 (5)				1 (13)	1
Proteus mirabilis	23 (15)	2	3		5 (22)	2 (40)
Morganella morganii	16 (11)		3		3 (19)	3 (100)

	Colonized by CRKP	Not colonized by CRKP	Univariate analysis	Multivariate analysis	Odds ratio
Age, median (range)	68 (22–86)	72 (14–89)	NS		
Gender (female/male)	11/19	54/66	NS		
APACHE II score, median (IQR)	19.5 (11.75)	18.0 (10)	NS		
Colistin treatment (%)	27 (90)	67 (56)	<0.001	<0.001	5.2
Carbapenem treatment (%)	23 (77)	81 (68)	NS		
Piperacillin/tazobactam treatment (%)	16 (53)	77 (64)	NS		
Median length of stay in ICU, days (IQR)	65 (61)	26 (32)	<0.001	NS	
Median duration of colistin treatment, days (IQR)	20.0 (17)	14.5 (23)	0.048		

All cases of infection by CIR pathogens occurred in patients having received colistin (p 0.003, OR 1.7)

Kontopidou F. *Clin Microbiol Infect* 2011

J Antimicrob Chemother 2011
doi:10.1093/jac/dkr007
Advance Access publication 25 January 2011

Heteroresistance in Enterobacteriaceae

Colistin heteroresistance in carbapenemase-producing *Klebsiella pneumoniae*

Georgios Meletis[1]*, Egki Tzampaz[1], Effrosyni Sianou[1], Ioannis Tzavaras[2] and Danai Sofianou[1]

[1]*Department of Clinical Microbiology, Hippokration General Hospital, Thessaloniki, Greece;* [2]*3rd Army Veterinary Hospital, Thessaloniki, Greece*

Strain	Colistin treatment	Carbapenemase type	Broth MIC (mg/L)	Highest concentration of growth in PAPs (mg/L)	Proportion of resistant subpopulations	Resistant colonies MIC before daily passages onto colistin-free medium (mg/L)	Resistant colonies MIC after 2 week daily passages onto colistin-free medium (mg/L)	Susceptibility	PFGE group
1	yes	VIM-1	2	8	4.4×10^{-7}	16	16	heteroresistant	A
2	yes	VIM-1	2	8	8×10^{-7}	16	16	heteroresistant	
9	no	VIM-1	1	8	4.1×10^{-7}	64	32	heteroresistant	
3	yes	KPC	2	8	2.6×10^{-6}	32	32	heteroresistant	B
6	yes	KPC	1	8	1.7×10^{-5}	32	16	heteroresistant	
12	no	KPC	1	8	1.5×10^{-5}	64	64	heteroresistant	
17	no	KPC	1	8	1.2×10^{-6}	16	16	heteroresistant	
18	no	KPC	1	8	2×10^{-6}	32	16	heteroresistant	
19	no	KPC	1	8	3.6×10^{-7}	16	16	heteroresistant	
8	yes	KPC	1	8	3.5×10^{-5}	4	1	heteroresistant	
5	yes	KPC	4	8	NA	NA	NA	resistant	C
7	yes	KPC	4	8	NA	NA	NA	resistant	
13	no	VIM-1	4	8	NA	NA	NA	resistant	
10	no	VIM-1	2	8	3.2×10^{-7}	32	32	heteroresistant	D
20	no	VIM-1	2	8	4.2×10^{-7}	16	16	heteroresistant	
4	yes	KPC	4	8	NA	NA	NA	resistant	E
11	no	KPC	0.5	0.5	NA	NA	NA	susceptible	ND
14	no	KPC	0.5	0.5	NA	NA	NA	susceptible	
15	no	KPC	0.5	0.5	NA	NA	NA	susceptible	
16	no	VIM-1	0.5	0.5	NA	NA	NA	susceptible	

Dosage

- 80 mg CMS = 1 million IU
- Intravenous
  - 1-2 mIU tid (UK) or 4-6 mg/kg in three divided doses
  - 6.5-13 mg/kg in three doses - USA (max 800 mg)
  - 2-3 IU tid (480-720 mg) in Greece
  - Adjustment in renal failure
- Intrathecal / Intraventricular
  - 125.000 – 250.000 IU/day
- Inhalational (Tadim)
  - 1-2 mIU tid/qid
- Other routes: i.m. (?)

Colistin dosage recommendation

Patient category	Dose (mIU) to target of Css,avg 2 mg/L
	Loading dose
All patients	**BW** (kg) / 7.5** (max 10)
	Maintenance dose
Not on renal replacement	**(Cl_{Cr}/10)+2** in 2-3 doses 1st dose 24 h after loading dose
Intermittent hemodialysis	**2** (in two doses) +30% on the day of hemodialysis after session
Continuous renal replacement	**12** In 2-3 doses

* 1million IU of CMS ~ 30mg of CBA ~ 80 mg of CMS

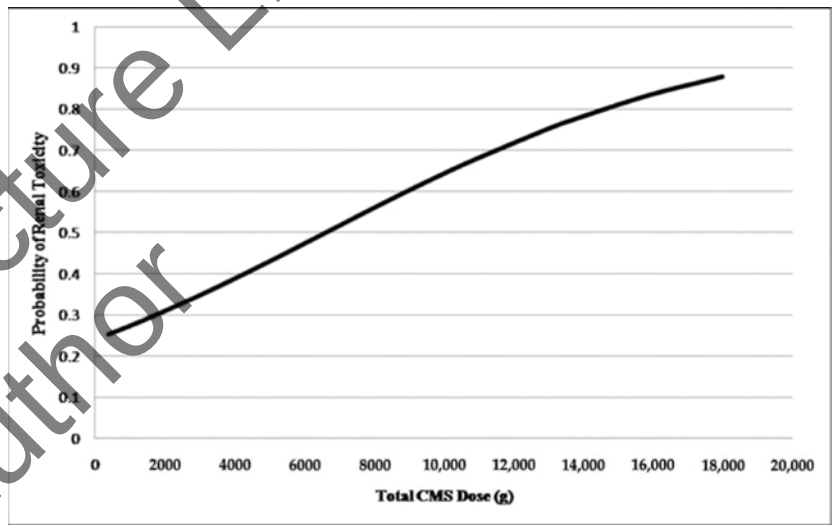
**Lower of ideal or actual body weight in kg

Garonzik SM et al. AAC 2011 (modified)

Is Colistin Safe?

Nephrotoxicity

- Wide range of reported toxicity: 0-39%
- Less than previously thought



Category	Criteria
Risk (R)	Increased creatinine level × 1.5 or GFR decrease >25%
Injury (I)	Increased creatinine level × 2 or GFR decrease >50%
Failure (F)	Increased creatinine level × 3, GFR decrease >75%, or creatinine level >4 mg/dL
Loss (L)	Persistent acute renal failure or complete loss of function for >4 weeks
ESKD (E)	ESKD for >3 months

NOTE. ESKD, end-stage kidney disease; GFR, glomerular filtration rate.

	No. (%) of patients fulfilling criterion				
Criterion	At last CMS dose (n = 66)	At peak creatinine level during CMS treatment (n = 66)	1 week after last CMS dose (n = 59)	1 month after last CMS dose (n = 50)	3 months after last CMS dose (n = 26)
No injury	39 (59)	36 (54)	36 (61)	35 (70)	23 (88)
Risk (R)	14 (21)	13 (20)	11 (19)	14 (28)	3 (12)
Injury (I)	9 (14)	10 (15)	10 (17)	1 (2)	0 (0)
Failure (F)	4 (6)	7 (11)	2 (3)	0 (0)	0 (0)
Loss (L)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ESKD (E)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

NOTE. CMS, colistimethate sodium; ESKD, end-stage kidney disease.

Hartzell JD, *Clin Infect Dis* 2009

J Antimicrob Chemother. 2011 Nov 28. [Epub ahead of print]

Ascorbic acid protects against the nephrotoxicity and apoptosis caused by colistin and affects its pharmacokinetics.

Yousef JM, Chen G, Hill PA, Nation RL, Li J.

Other adverse effects

- Neurotoxicity
  - Dose dependent
  - Neuromuscular blockade
  - Paresthesias (face, tongue, limbs)
  - Confusion, seizures
- Hypersensitivity reactions
- Bronchospasm
  - Inhalational treatment

Rare to non-existent

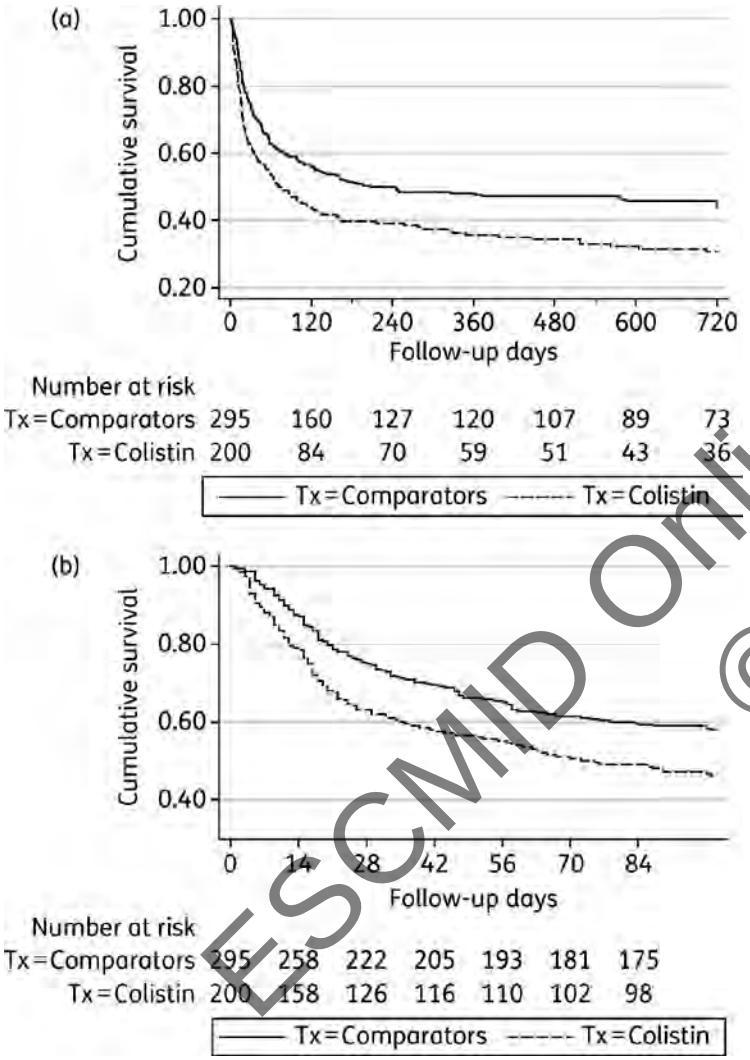
Spapen H. *Ann Intensive Care* 2011

Is Colistin effective?

Colistin efficacy studies

	Number	Pathogens (%)	Study Design	Combination	Efficacy (%)	Daily Dose
Pintado V. J Inf 2008	**60**	Acinetobacter 50 Pseudomonas 23 Klebsiella 13	Retrospective cohort	87	72	2-4 mIU
Kasiakou SK. AAC 2005	50	Acinetobacter 52 Pseudomonas 43 Klebsiella 4	Retrospective cohort	92	67	3 mIU
Reina R. Int Care Med 2005	**55**	Acinetobacter 65 Pseudomonas 35	Prospective cohort	Unavailable	15 (on day 6)	4.5 mIU
Levin AS. Clin Infect Dis 1998	60	Acinetobacter 65 Pseudomonas 35	Uncontrolled observational	Unavailable	58 25 in LRTI	2 mIU
Michalopoulos AS. Clin Microbiol Infect 2005	**43**	Acinetobacter 19 Pseudomonas 81	Retrospective case series	74	74	9 mIU
Markou N. Crit Care 2003	26	Acinetobacter 23 Pseudomonas 77	Uncontrolled observational	100	73	9 mIU

Is colistin effective?



J Antimicrob Chemother 2010; **65**: 1019–1027
doi:10.1093/jac/dkq069 Advance publication 18 March 2010

Journal of Antimicrobial Chemotherapy

Effectiveness and safety of colistin: prospective comparative cohort study

Mical Paul[1,2*], Jihad Bishara[1,2], Ariela Levcovich[1,2], Michal Chowers[2,3], Elad Goldberg[1,2], Pierre Singer[2,4], Shaul Lev[2,4], Perla Leon[5], Maria Raskin[1,2], Dafna Yahav[2,6] and Leonard Leibovici[2,6]

Prospective cohort study

495 patients Israel

OR 1.99 bacteremic patients

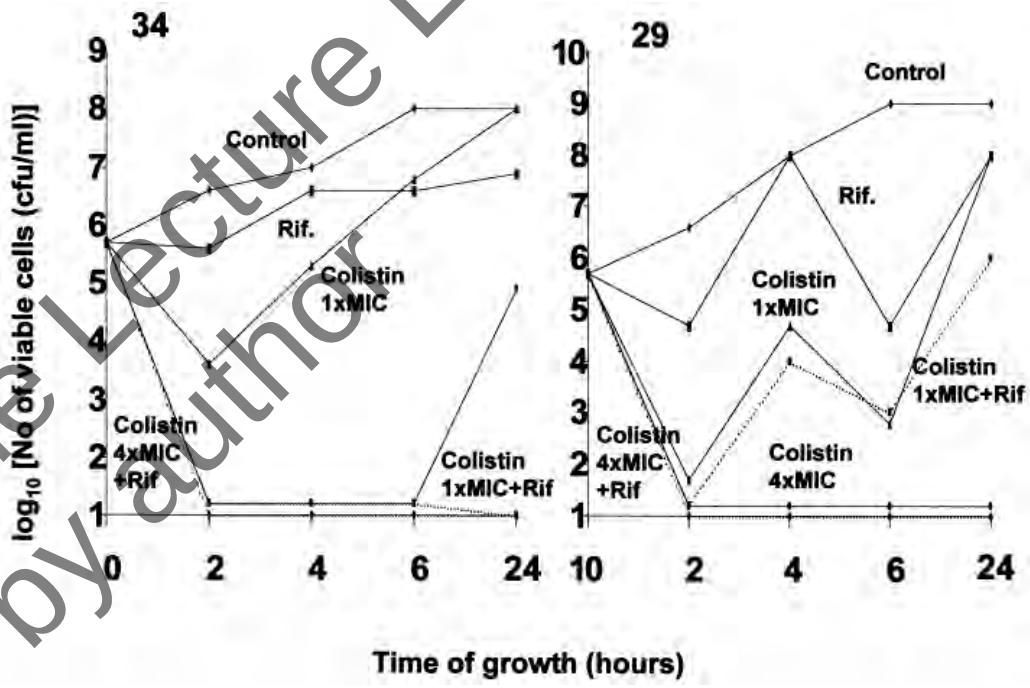
(More) Unresolved Issues

Synergy

- Colistin + Rifampin / carbapenem
  - In vitro
  - Animal models
  - Clinical studies effectiveness

    (No RCT):

    65-76%



Petrosillo N. Clin Microbiol Infect 2008

Giamarellos-Bourboulis EJ. Diagn Microbiol Infect Dis 2001

Bassetti M et al. JAC2008

Inhaled colistin

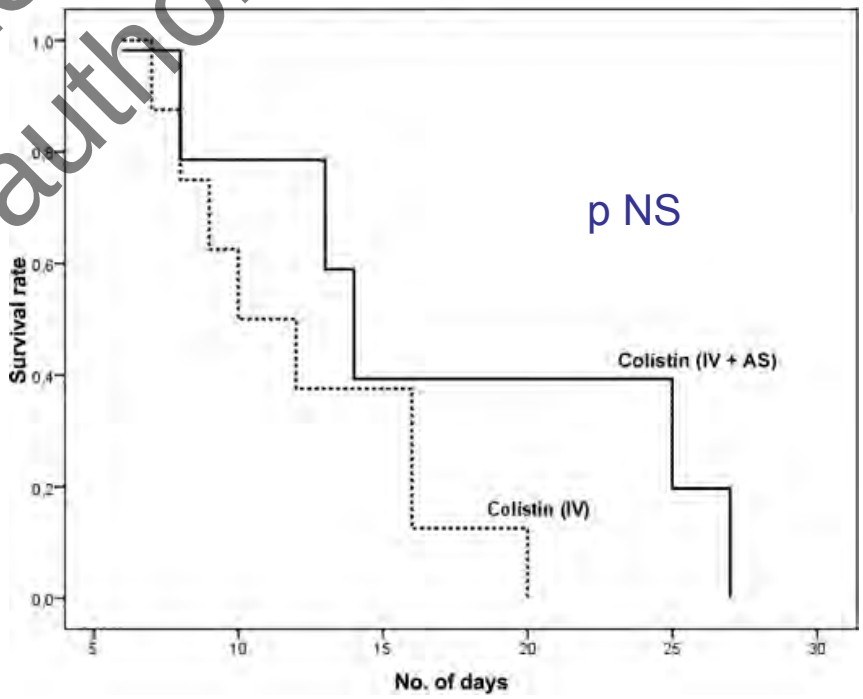
Controlled clinical trial of iv colistin vs iv + inh colistin in VAP

43 pts in each group

Outcome	No. (%) of patients: IV colistin group (n = 43)	AS-IV colistin group (n = 43)	P
Clinical outcome			
Clinical cure	14 (32.5)	23 (54)	.05
Clinical improvement	12 (28)	9 (21)	.451
Clinical failure	14 (32.5)	7 (16)	.126
Recurrence	3 (7)	4 (9)	>.99
Bacteriological outcome[a]			
Eradication	17 (50)	19 (45)	.679
Persistent	12 (35)	10 (24)	.272
Recurrence	2 (6)	5 (12)	.450
Colonization	3 (9)	8 (19)	.208
Mortality			
All-cause	18 (42)	10 (23)	.066
VAP-related	11 (26)	7 (16)	.289
Adverse events			
Nephrotoxicity	8 (19)	8 (19)	>.99
Neurotoxicity	0	0	

NOTE. AS, aerosolized; IV, intravenous; VAP, ventilator-associated pneumonia

[a] Bacteriological outcome was evaluated in 34 patients in the IV colistin group and in 42 patients in the AS-IV colistin group.



p NS

Kofterides DP. *Clin Infect Dis* 2010

Pitfalls of colistin studies

- No prospective, randomized, controlled clinical trials
- Colistin monotherapy is understudied
- Most published studies focused on *Pseudomonas* and *Acinetobacter*
- Diagnostic inaccuracy in VAP affects assessment of treatment efficacy
- Treatment efficacy and toxicity difficult to assess due to multiple confounding factors in critically ill patients

Future challenges

- Dosage optimization (loading dose, optimum interval)
- Prospective randomized, controlled clinical trials

Thank you!