Colistin: pharmacokinetics/pharmacodynamics: an update

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all slides are available there

click on "Advanced Courses"

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

With the support of *Wallonie-Bruxelles-International*

Contents of the presentation

- colistin : a reminder
- antimicrobial activity
- pharmacokinetics/pharmacodynamics
- toxicodynamics
- current use and perspectives

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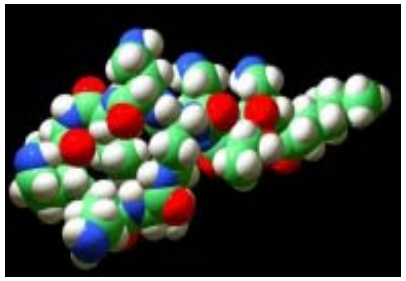
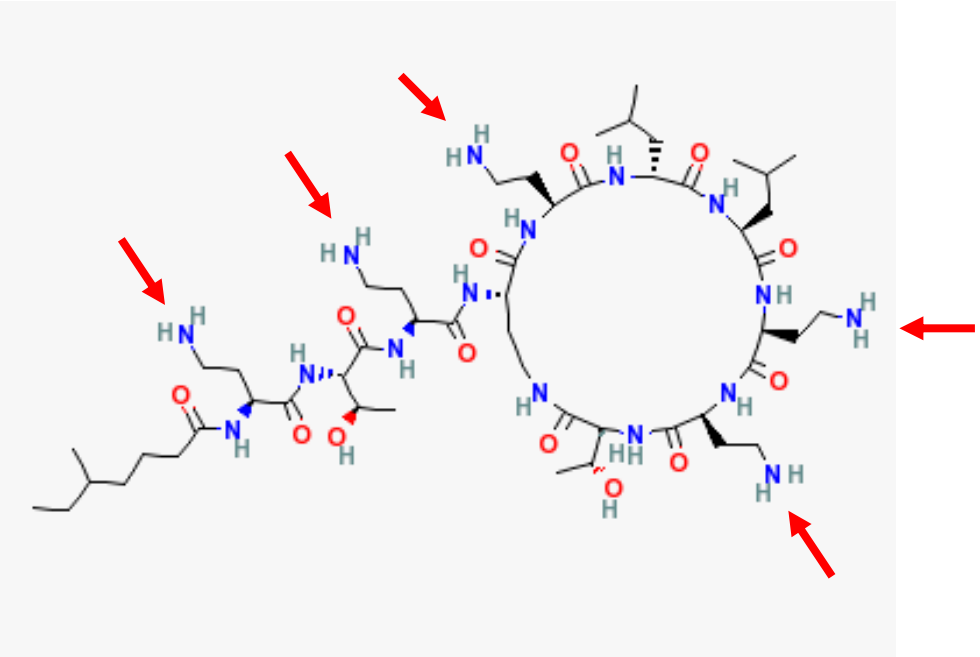


Credit: DR TIM EVANS/SCIENCE PHOTO LIBRARY

or

?

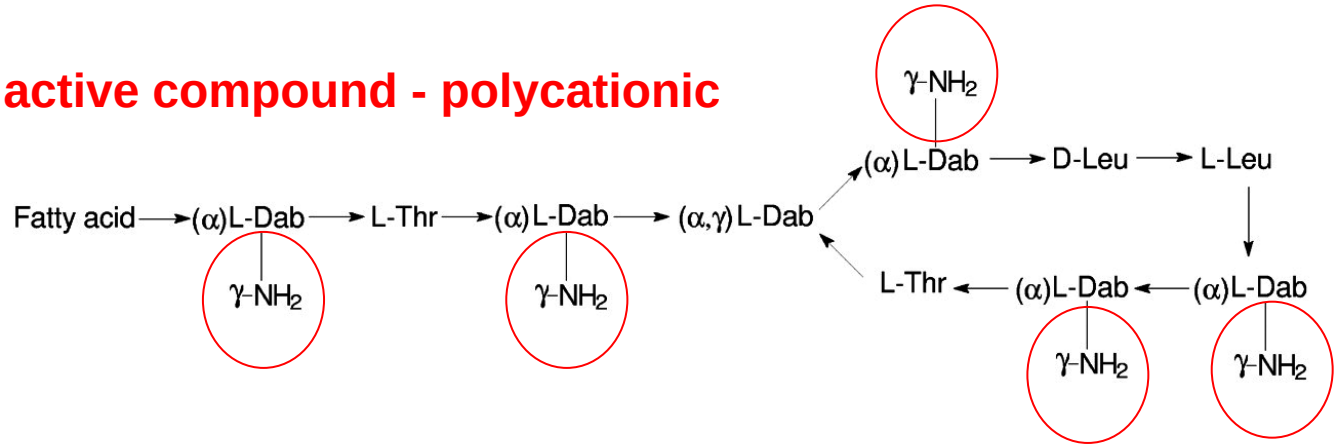
What is (exactly) colistin in its active form ?



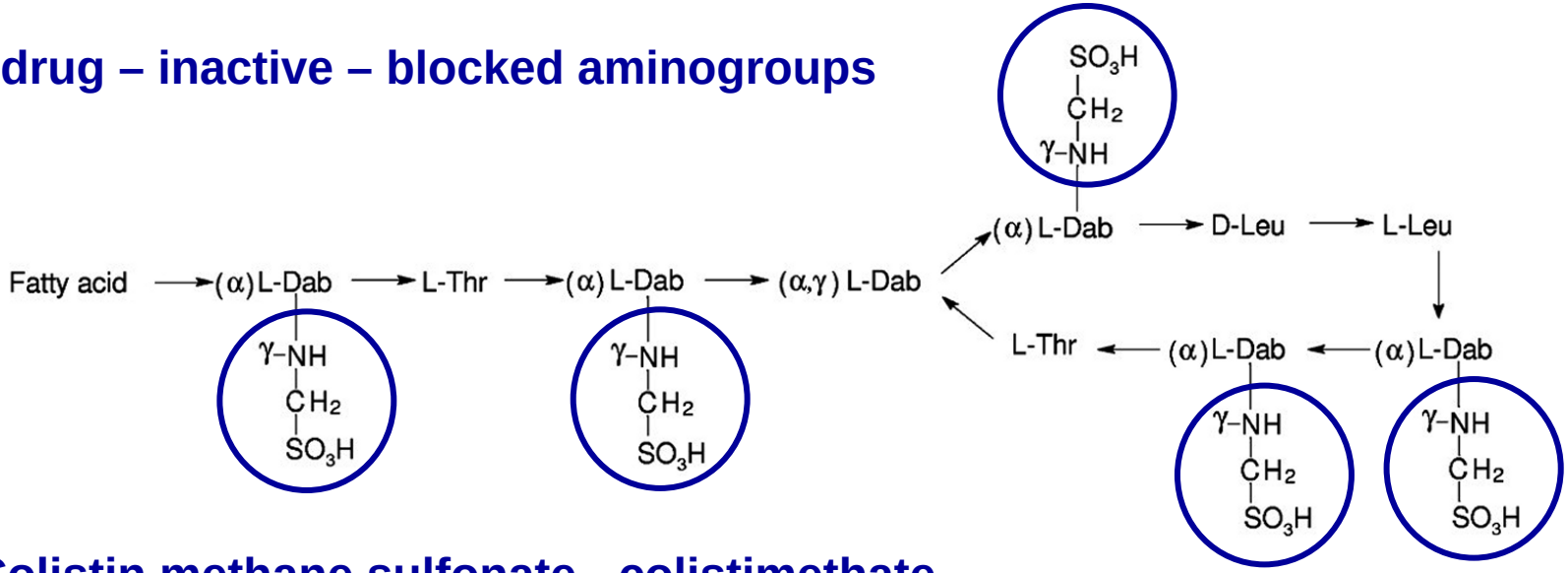
- A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain
- which **interacts with the lipopolysaccharide (LPS)** of the outer membrane of Gram-negative bacteria, triggering a "self-promoted uptake" process
- and **displaces Ca^{++} and Mg^{++}**, which further destabilizes microbial outer membranes and helps conferring more specificity towards procaryotic cells

Colistin and its prodrug

active compound - polycationic



Prodrug – inactive – blocked aminogroups

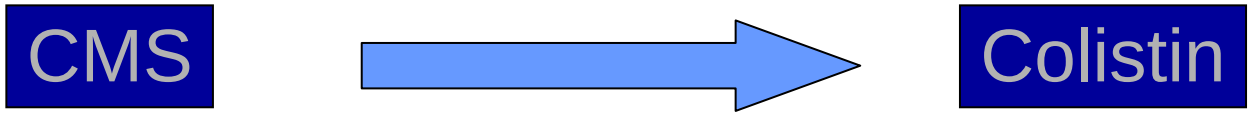


Colistin methane sulfonate - colistimethate

must be hydrolyzed to act -- has a lesser toxicity and a faster elimination -- conversion is spontaneous in aqueous media … and complicates PK studies

Li et *al.* AAC 2003; 47:1364-1370 – Bergen *et al.* AAC 2006; 1953-1958

Colistin : conversion from the prodrug



Occurs in vitro and in vivo in aqueous media

- critical for activity
- need for specific assay and careful sample handling (PK/PD studies)
- colistin sulfate should be used for in vitro susceptibility testing

Colistin: mg and units …

International units (IU)

1 Mio IU =80 mg CMS = 30 mg CBA
2 Mio IU = 160 mg CMS = 60 mg CBA
3 Mio IU = 240 mg CMS = 90 mg CBA

Common daily dose: 9 Mio IU (270 mg CBA)

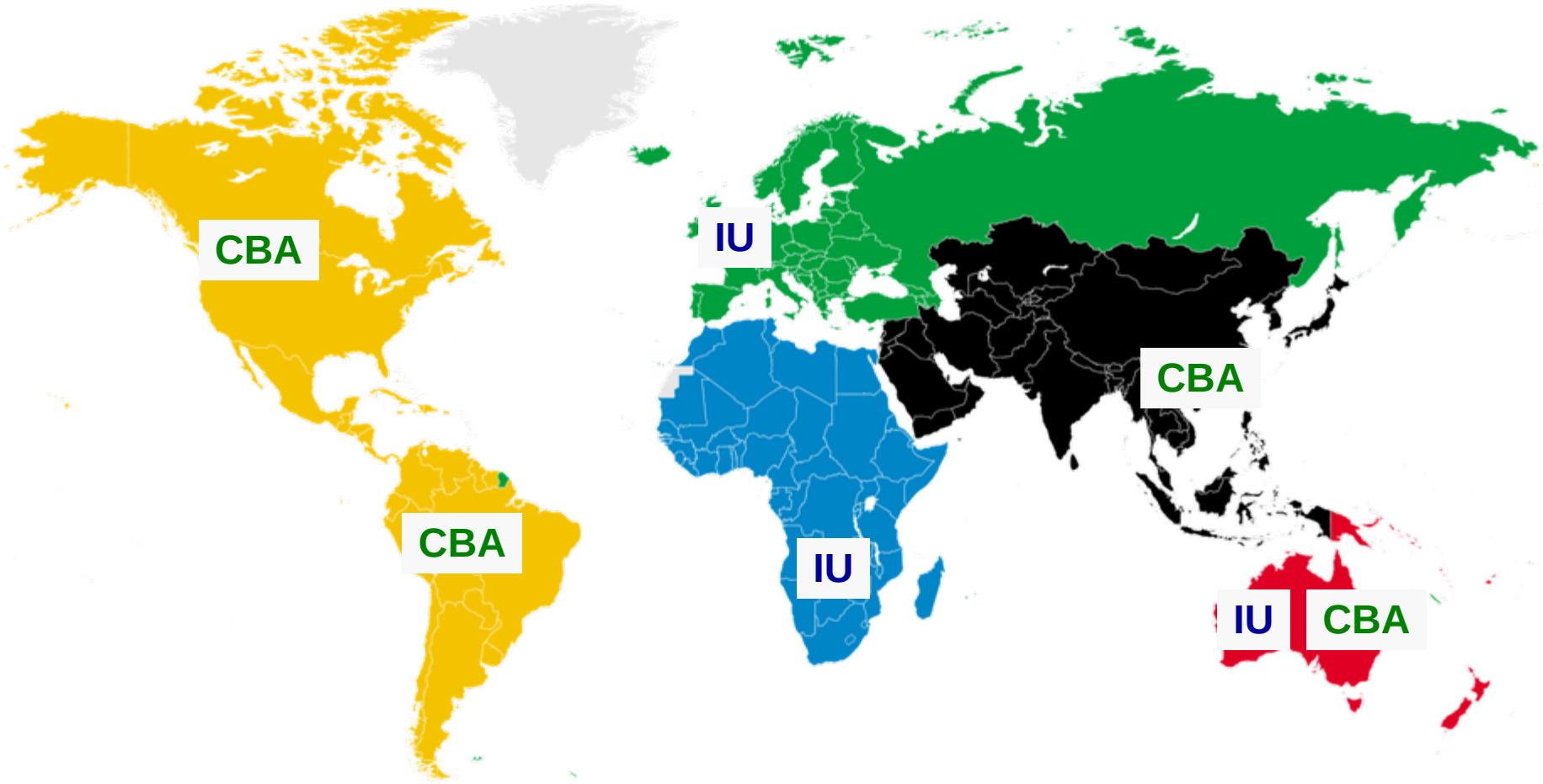
~

Colistin base activity (CBA)

240 mg CBA = 400 mg CMS
2 Mio IU = 160 mg CMS = 60 mg CBA
3 Mio IU = 240 mg CMS = 90 mg CBA

Common daily dose: 5 mg/kg/day (300 mg CBA = 10 Mio IU)

Colistin around the world



Colistin: mg and units : what about Vietnam ?

Thông tin liên quan Colistimethate for Injection Thông tin tóm tắt — Mục lục từ viết tắt

Nhà sản xuất	Ben Venue Laboratories
Nhà phân phối	Viet Phap
Thành phần	Colistin.
Chỉ định	NK cấp/mạn tính (không do Proteus/Neisseria). Khởi đầu điều trị NK nặng. Điều trị/phòng ngừa NK.
Liều dùng	***Người lớn, trẻ em*** *Tiêm IM/IV:* 2.5-5 mg/kg/ngày chia thành 2-4 liều nhỏ, suy thận: giảm liều hoặc tăng khoảng cách các liều. *Tiêm trực tiếp ngắt quãng:* tiêm chậm ½ liều mỗi ngày trong 3-5 phút mỗi 12 giờ. *Tiêm truyền liên tục:* tiêm chậm ½ tổng liều mỗi ngày trong 3-5 phút. Tối đa 5 mg/kg/ngày.
Chống chỉ định	Tiền sử mẫn cảm với thành phần thuốc.
Thận Trọng	Bệnh nhân đang nguy cơ suy thận, lái xe/vận hành máy móc, có thai/nuôi con bú, lớn tuổi, trẻ em.
Phản ứng có hại	Rối loạn tiêu hóa, nhói đầu chi và lưỡi, nói nhịu, lơ mơ, hoa mắt chóng mặt, dị cảm, ngứa toàn thân, mề đay, ban, sốt, tăng BUN, tăng creatinine, giảm thanh thải creatinine, ngừng thở và khó thở, độc thận, giảm bài niệu. Xem mẫu Thông báo các phản ứng phụ.
Tương tác thuốc	Aminoglycoside, polymyxin, thuốc giãn cơ, sodium cephalothin.
Phân loại MIMS	Các loại kháng sinh khác (Other Antibiotics)
Phân loại ATC	J01XB01 - colistin ; Belongs to the class of polymyxins. Used in the systemic treatment of infections.

Trình bày/Đóng gói

Dạng bào chế	Đóng gói
Colistimethate for Injection Bột pha tiêm 150 mg	1's 12's

Colistin base activity (CBA)

240 mg CBA = 400 mg CMS
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Common daily dose: 5 mg/kg/day (300 mg CBA = 10 Mio IU)

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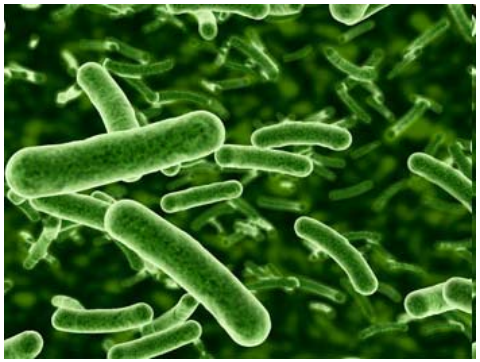
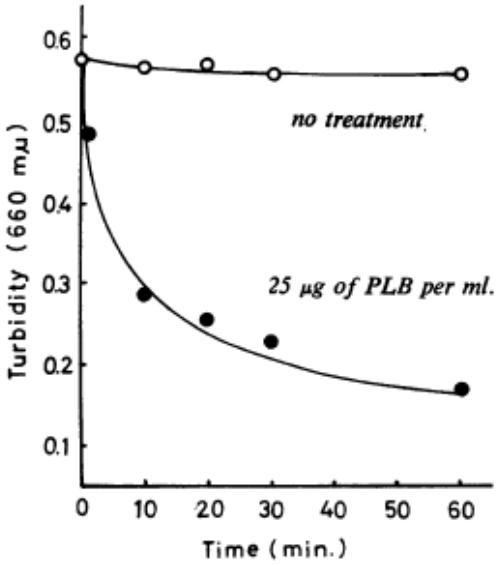
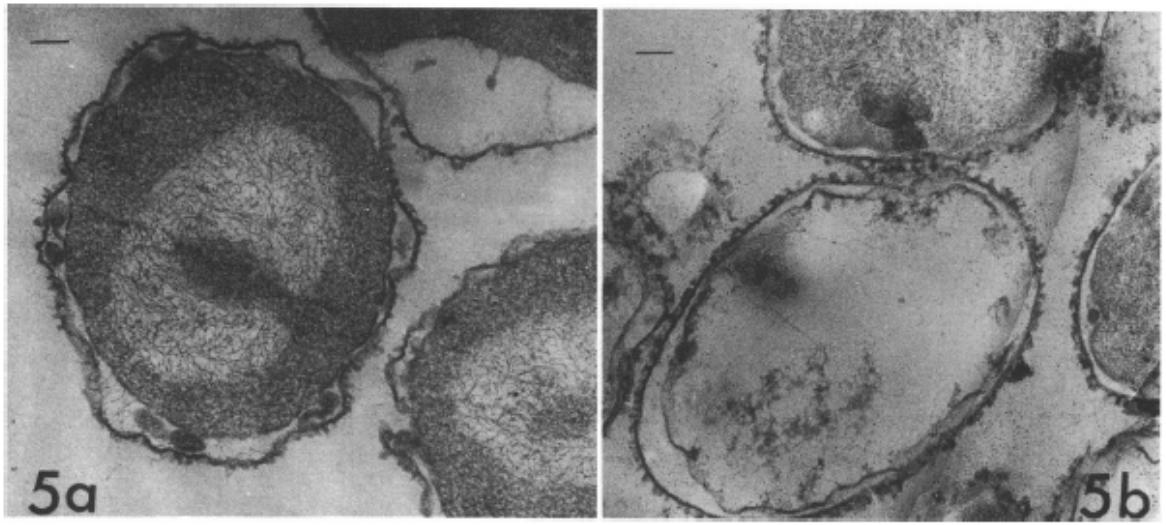


The absence of new antibiotics has led to a growing reliance on older, more toxic drugs such as colistin, but resistance to these is already arising. ChiroACCESS Mini-review, 27 April 2011; http://www.chiroaccess.com

Colistin Microbiology: lysis of bacteria



Lysis of the spheroplast of E. coli B



Koike et al. J. Bacteriol. 1969; 97:448-452

Colistin microbiology

- About 10 x more active against Gram-negative than Gram-positive bacteria
  - inactive against *Burkholderia cepacia*, *Serratia*, *Proteus, Bacteroides fragilis* … and most Gram-negative cocci [inherent resistance];
  - synergism with most antibiotics (increase in their penetration
- Bactericidal 
- Marked inoculum effect 
- Loss of susceptibility of pre-exposed bacteria 
- MIC values highly dependent upon technique used 
  - poor diffusion through agar
  - microdilution is preferred but influence by the inoculum, sticking on plastic)

Issues in testing susceptibility to colistin

- CMS is a prodrug → test colistin sulfate
- Colistin is a mixture of colistin A and B
  - USP standard: colistin B
  - Sigma reagent colistin A
- Activity depends on calcium concentration
- Colistin sticks to plastic ..
  - Do not add any detergent to avoid adsorption, this effect is taken into account since MIC have been determined in plastic plates fro PK/PD measures
- Colistin in agar: do not use, as calcium content not optimally controlled in MHagar; poor diffusion

Do all the methods tell you the same thing ?

TABLE 1 Summary of colistin susceptibility test methods used in phase I and phase II of the study

Test[a]	Method reference	Description	Test medium[b] (manufacturer)	Inoculum[c]	Study phase
AD	CLSI M07 (12)	In-house prepared AD plates	MHA (BBL)	0.5 McFarland suspension diluted in sterile saline to obtain 10^4 CFU/spot	II
BMD	CLSI M07 (12)	In-house prepared BMD panels in untreated polystyrene microplates	CAMHB (Difco)	0.5 McFarland suspension diluted in sterile water to obtain 3×10^5 to 5×10^5 CFU/ml	II
BMD-T	Modification of CLSI M07 (12)	In-house prepared BMD panels in untreated polystyrene microplates	CAMHB (Difco)	0.5 McFarland suspension diluted in sterile water + 0.02% polysorbate 80 to obtain 3×10^5 to 5×10^5 CFU/ml; final polysorbate 80 concn, 0.002%	I & II
TDS	CLSI M07 (12)	In-house prepared tube dilution in borosilicate tubes washed with Micro-90	CAMHB (Difco)	0.5 McFarland suspension diluted in CAMHB to obtain 3×10^5 to 5×10^5 CFU/ml	I
Etest	bioMérieux package insert	Agar gradient diffusion	MHA (BBL); MHA (Remel); MHA (Hardy)	0.5 McFarland suspension	I
TREK GNXF Sensititre panels	TREK package insert	Dried MIC panel	Sensititre cation-adjusted Mueller-Hinton broth with TES buffer	0.5 McFarland suspension diluted in deionized water to obtain 3×10^5 to 5×10^5 CFU/ml	II

[a] AD, agar dilution; BMD, broth microdilution; BMD-T, broth microdilution with 0.002% polysorbate 80; TDS, broth macrotube dilution.

[b] MHA, Mueller-Hinton agar; CAMHB, cation-adjusted Mueller-Hinton broth; TES, *N*-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid.

[c] The initial suspension of the organism was prepared in normal saline for all testing, with the exception of TREK GNXF, for which the suspension was prepared in deionized water.

Do all the methods tell you the same thing ?

		Phase I (n = 107)			Phase II (n = 50)			
Isolate no.[a]	Organism	BMD-T	TDS	Etest	BMD-T	BMD	AD	TREK
1*	*A. baumannii*	4	4	1[b]	0.5	8[c]	0.5	1
2	*A. baumannii*	8	16	1.5[b]	>8	>8	>16	>4
3	*A. baumannii*	>8	8	2[b]	>8	>8	8	4
4	*A. baumannii*	8	>16	3	>8	>8	>16	>4
5	*A. baumannii*	>8	16	0.5[b]	ND[d]	ND	ND	ND
6	*A. baumannii*	>8	16	3	ND	ND	ND	ND
7	*A. baumannii*	>8	16	12	ND	ND	ND	ND
7A	*A. baumannii*	2	4[c]	2	2	4[c]	2	1

In vitro evaluation of colistin susceptibility is fraught with complications, due in part to the inherent cationic properties of colistin. In addition, no reference method has been defined against which to compare the results of colistin susceptibility testing. This study systematically evaluated the available methods for colistin MIC testing in two phases. In phase I, colistin MICs were determined in 107 fresh clinical isolates of multidrug-resistant (MDR) Gram-negative bacilli (GNB) by broth microdilution with polysorbate 80 (BMD-T), broth macrodilution (TDS), and the Etest. In phase II, 50 of these isolates, 10 of which were colistin resistant, were tested in parallel using BMD-T, TDS, agar dilution, broth microdilution without polysorbate 80 (BMD), and the TREK Gram-negative extra MIC format (GNXF) Sensititre. The Etest was also performed on these 50 isolates using Mueller-Hinton agar (MHA) from three different manufacturers. Colistin MIC results obtained from the five methods were compared to the MIC results obtained using BMD-T, the method that enables the highest nominal concentration of colistin in the test medium. Essential agreement ranged from 34% (BMD) to 83% (TDS), whereas categorical agreement was >90% for all methods except for BMD, which was 88%. Very major errors (VMEs) (i.e., false susceptibility) for the Etest were found in 47 to 53% of the resistant isolates, depending on the manufacturer of the MHA that was used. In contrast, VMEs were found for 10% (n = 1) of the resistant isolates by BMD and 0% of the isolates by the TDS, agar dilution, and Sensititre methods. Based on these data, we urge clinical laboratories to be aware of the variable results that can occur when using different methods for colistin MIC testing and, in particular, to use caution with the Etest.

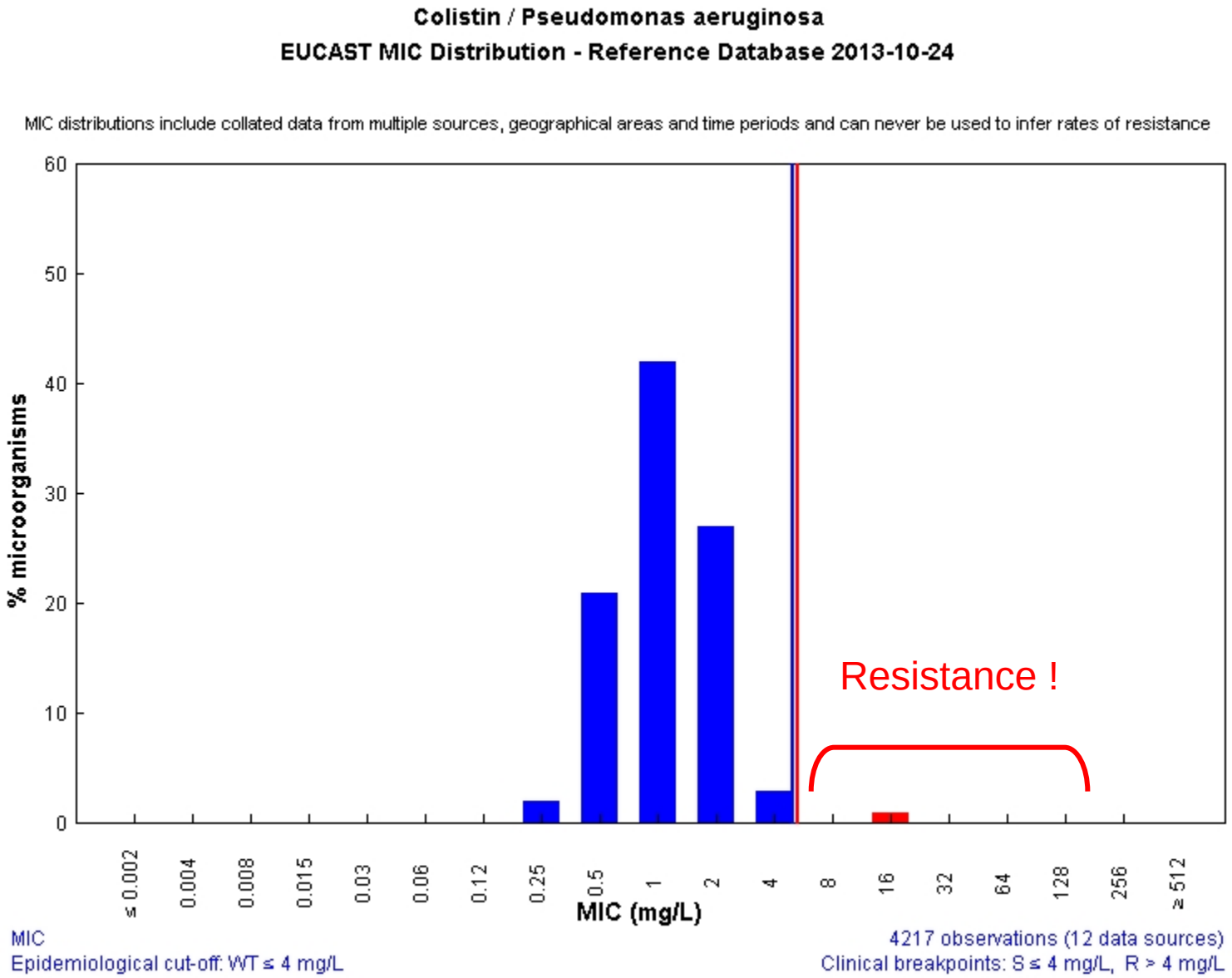
Hindler et al, J Clin Microbiol, 2013 Jun;51(6):1678-84.

Current EUCAST and CLSI breakpoints

species	EUCAST		CLSI	
	S ≤	R >	S ≤	≥ R
Enterobacteriaceae	2	2	2	8
Acinetobacter	2	2	2	4
Pseudomonas	4	4	2	8

PK/PD validation still in process…suggest to use epidemiological cut-off

Two typical EUCAST MIC distributions for colistin



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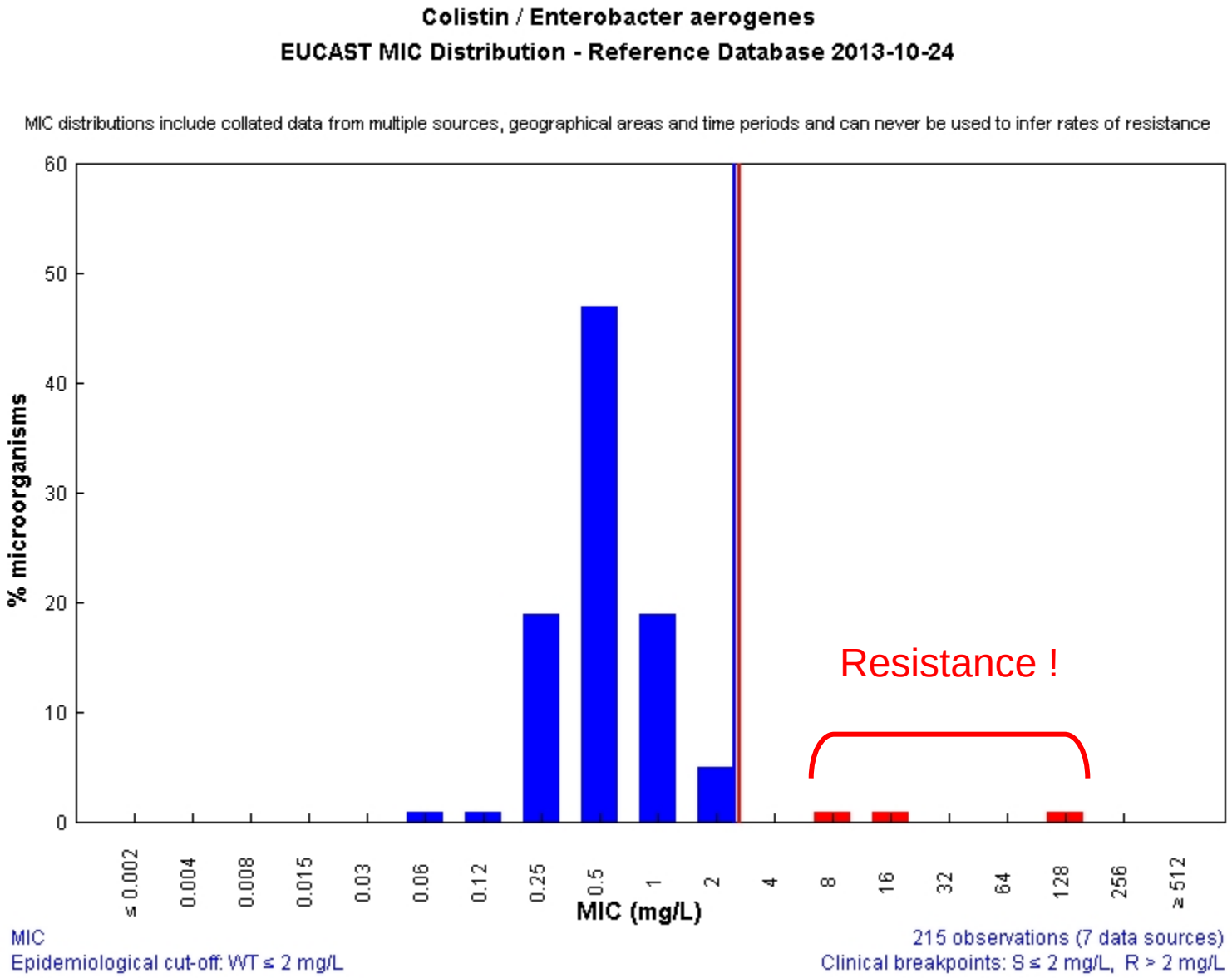

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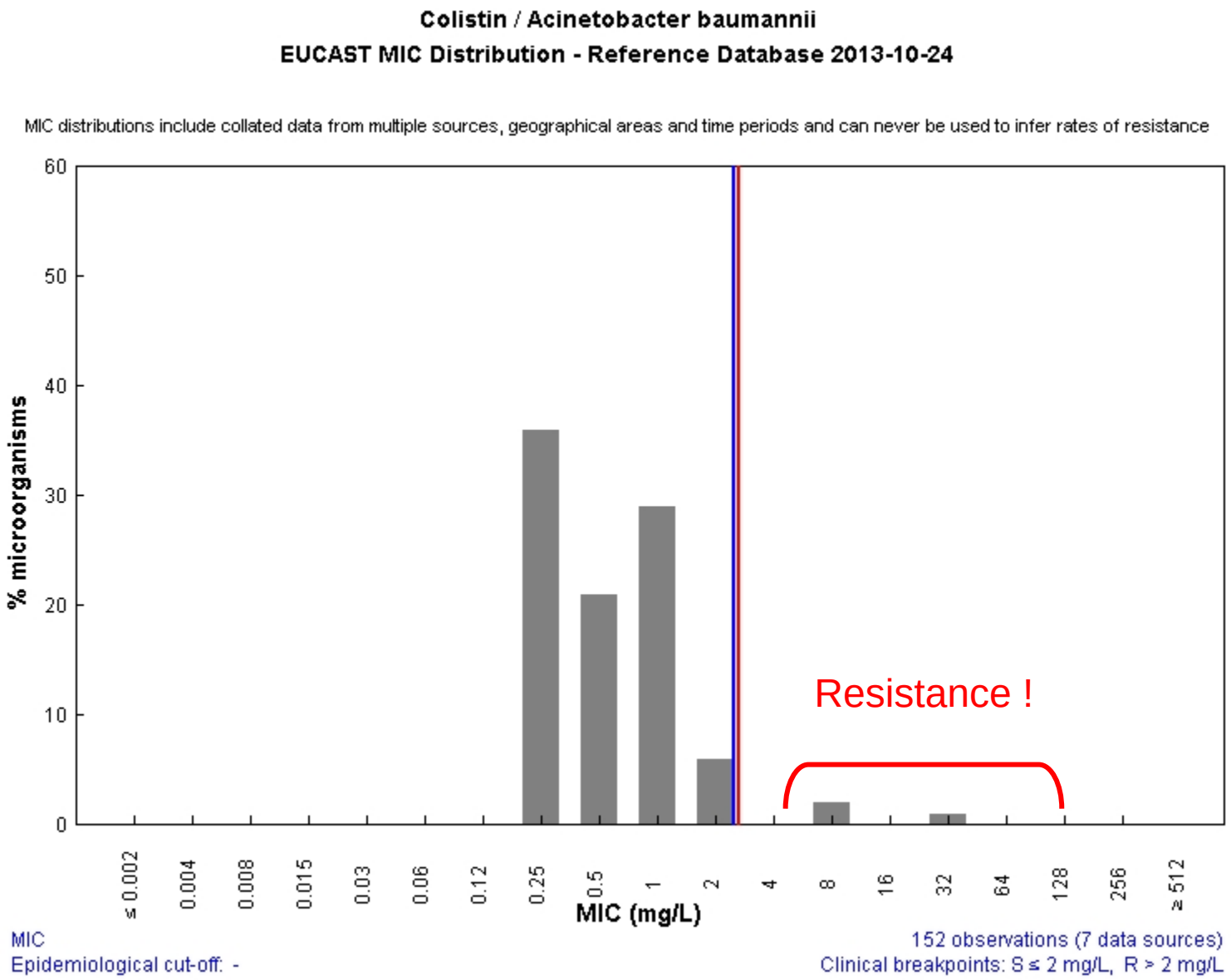

Susceptibility to colistin in Asia

Key antimicrobial resistance patterns for the 12 monitored nations in the APAC RRS region

(26 sites; 5,053 strains)	ESBL (%)		CARB-R (%)[a]		
Nation (no. of sites/no. of strains)	*E. coli*	*Klebsiella* spp.	*Klebsiella* spp.	*P. aeruginosa*	COL/TIG[b]
Australia (6/1,136)	12	15	0	16	0/2
Hong Kong (1/237)	46	23	0	17	0/0
India (5/915)	78	64	25	32	0/2
Indonesia (1/175)[f]	71	64	0	8	0/0
Japan (4/398)[c]					
South Korea (2/462)	37	40	0	43	0/6
Malaysia (1/239)	36	45	0	24	0/4
New Zealand (2/477)	11	10	0	6	0/0
Philippines (1/195)[f]	47[d]	55[d]	5[d]	50	0/5
Singapore (1/251)	21	32	0	22	0/4
Taiwan (1/137)	91	75	10	0	10/0
Thailand (2/431)[f]	55	50	5	30	6/0
All (26/5,053)	60	47	9	26	1/2

Mendes *et al*, AAC (2013) 57: 5721–5726

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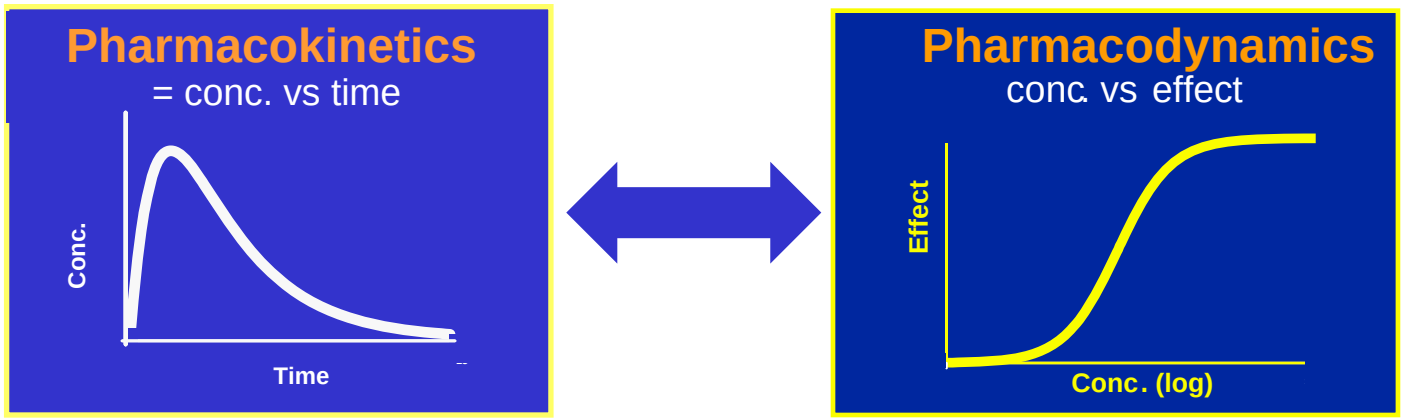


Colistin disposition

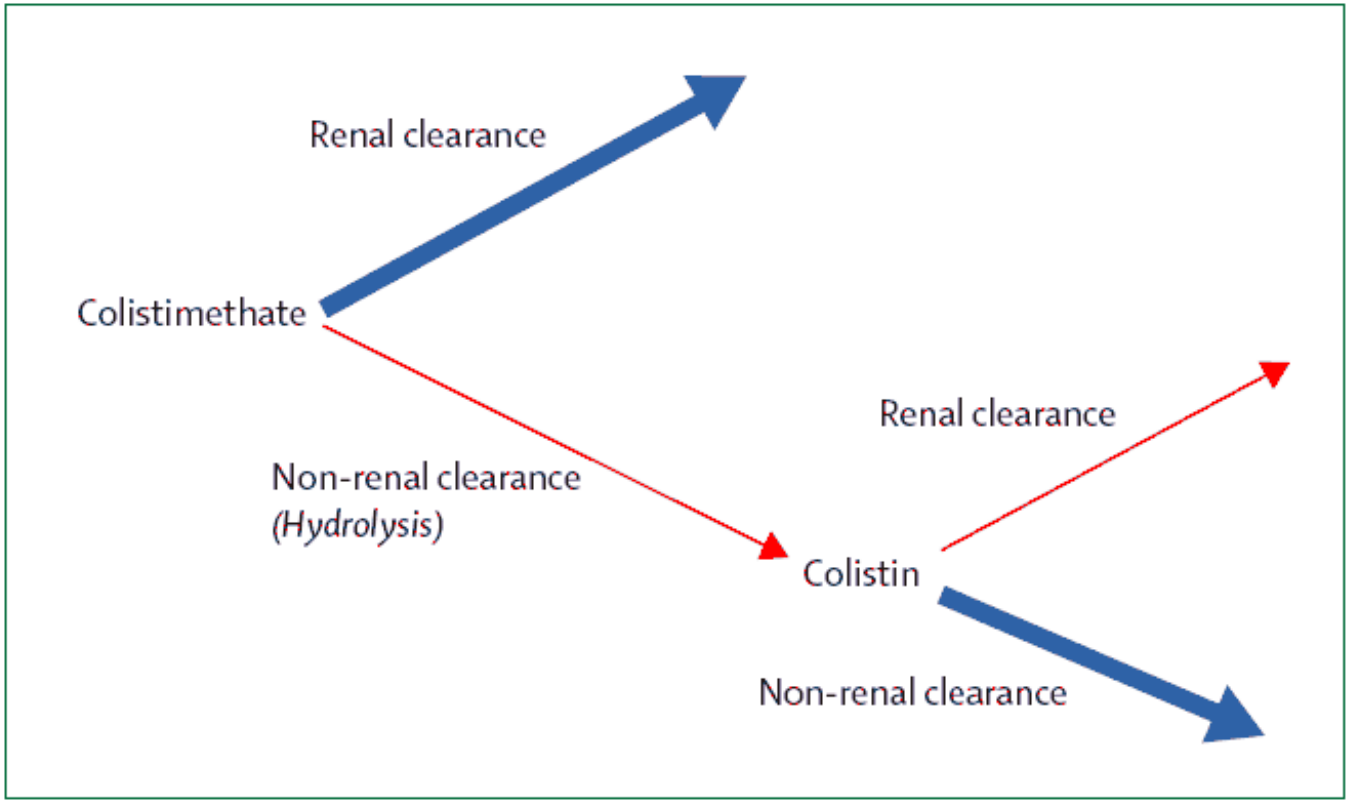
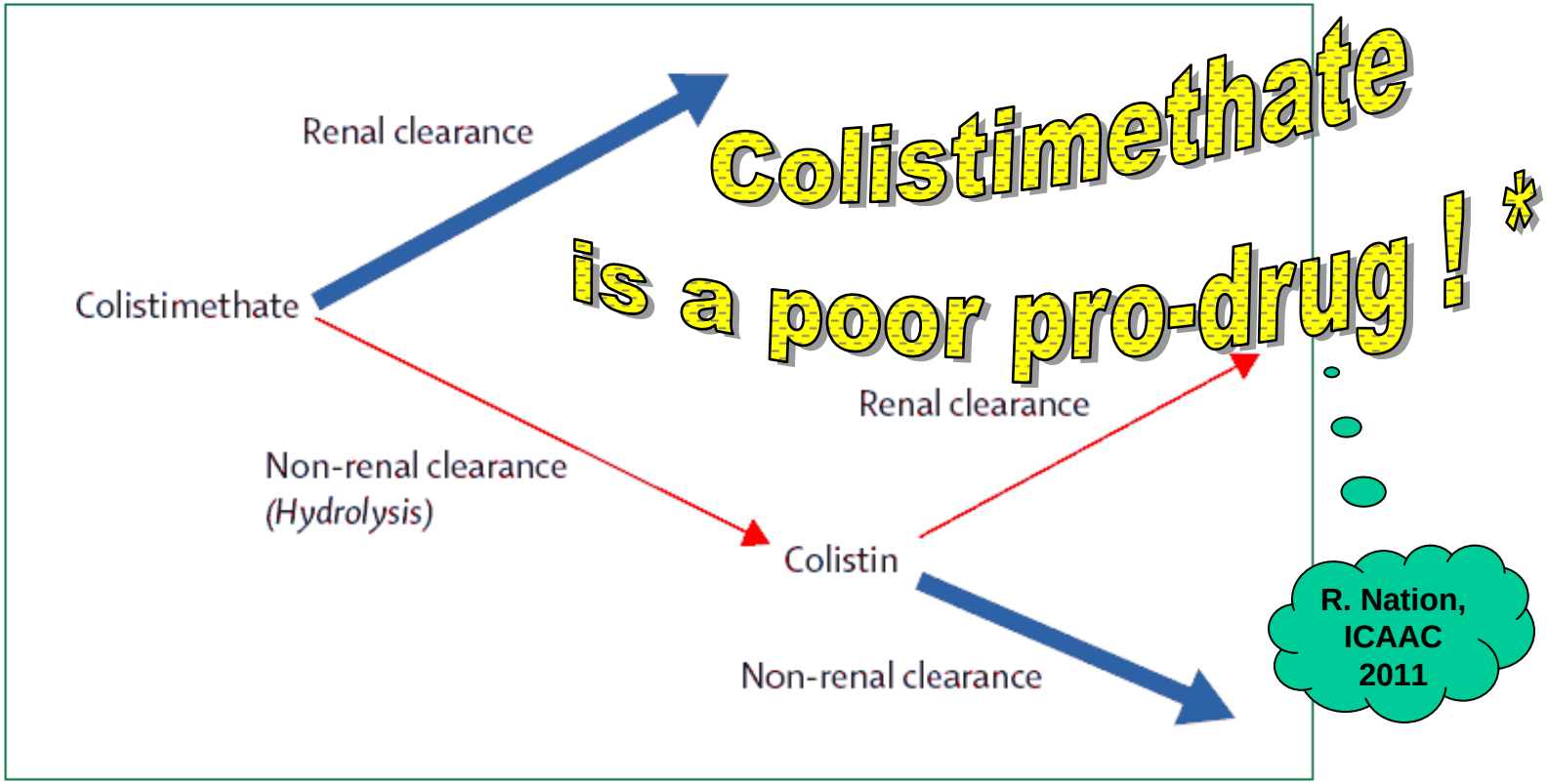


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Li et al. Lancet Infect. Dis. 2006; 6:589-601

Colistin disposition



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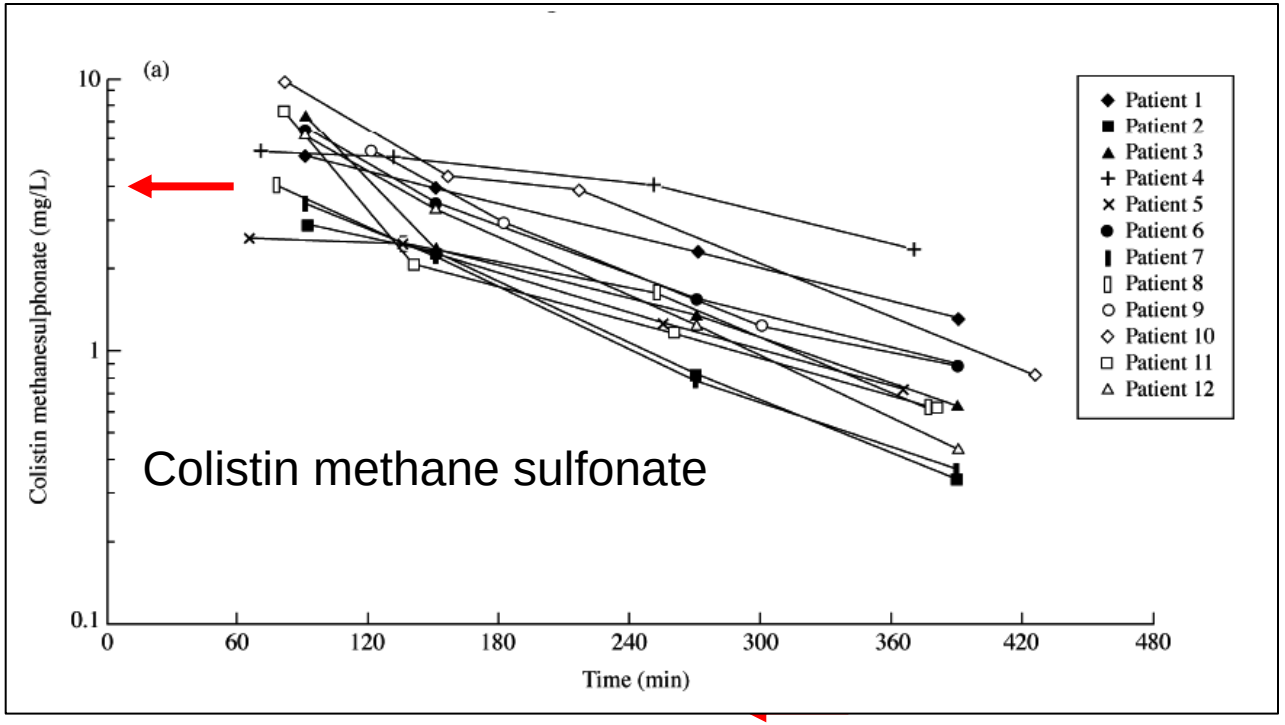
Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate



Patients with
160 mg TID
~ 2 x 10^6 Units)
for > 2 days

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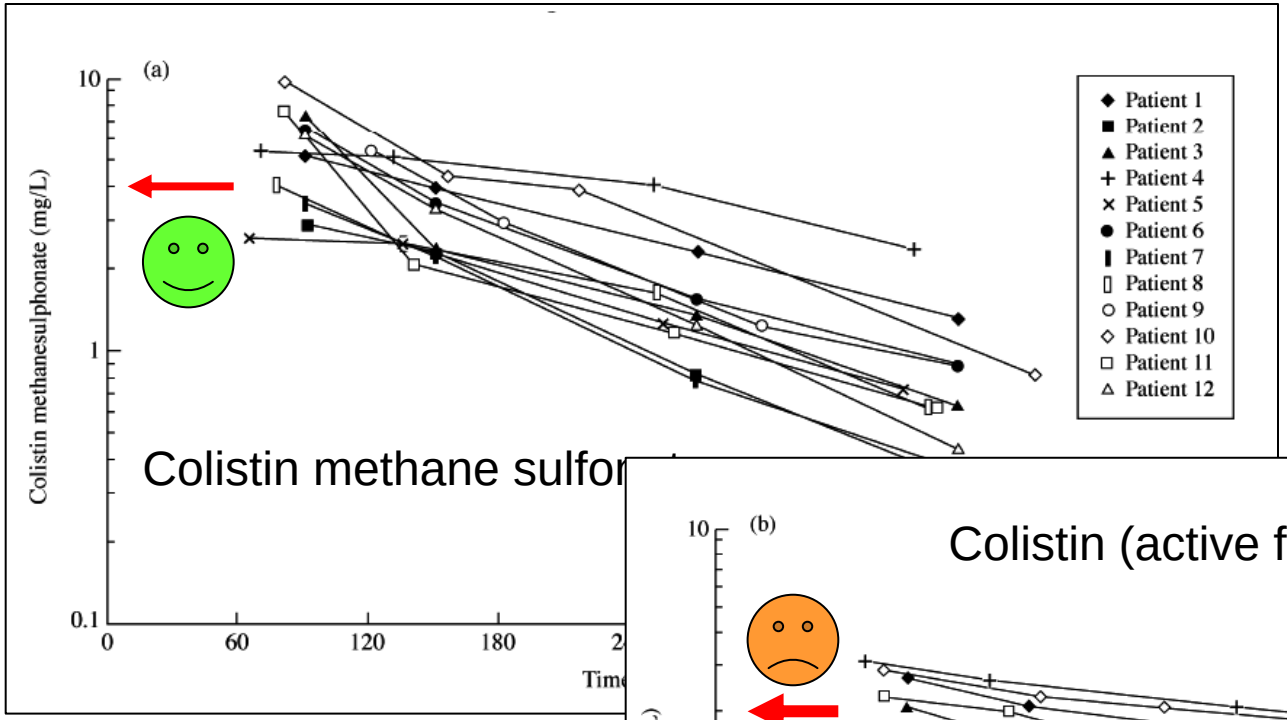

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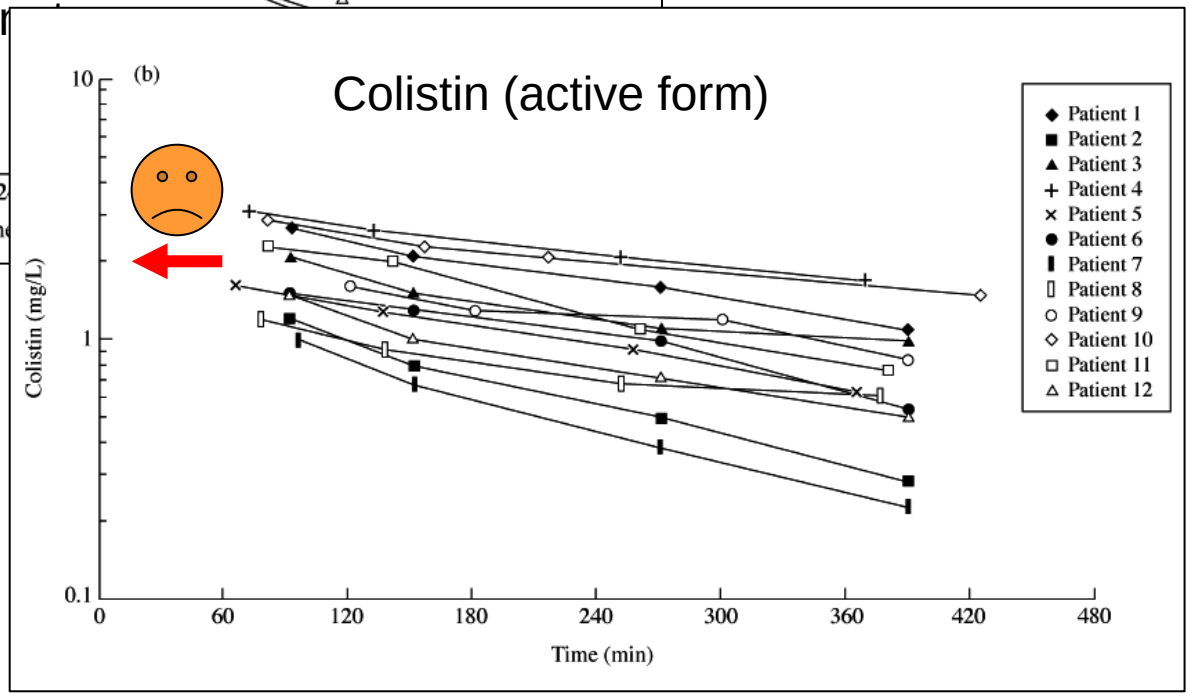


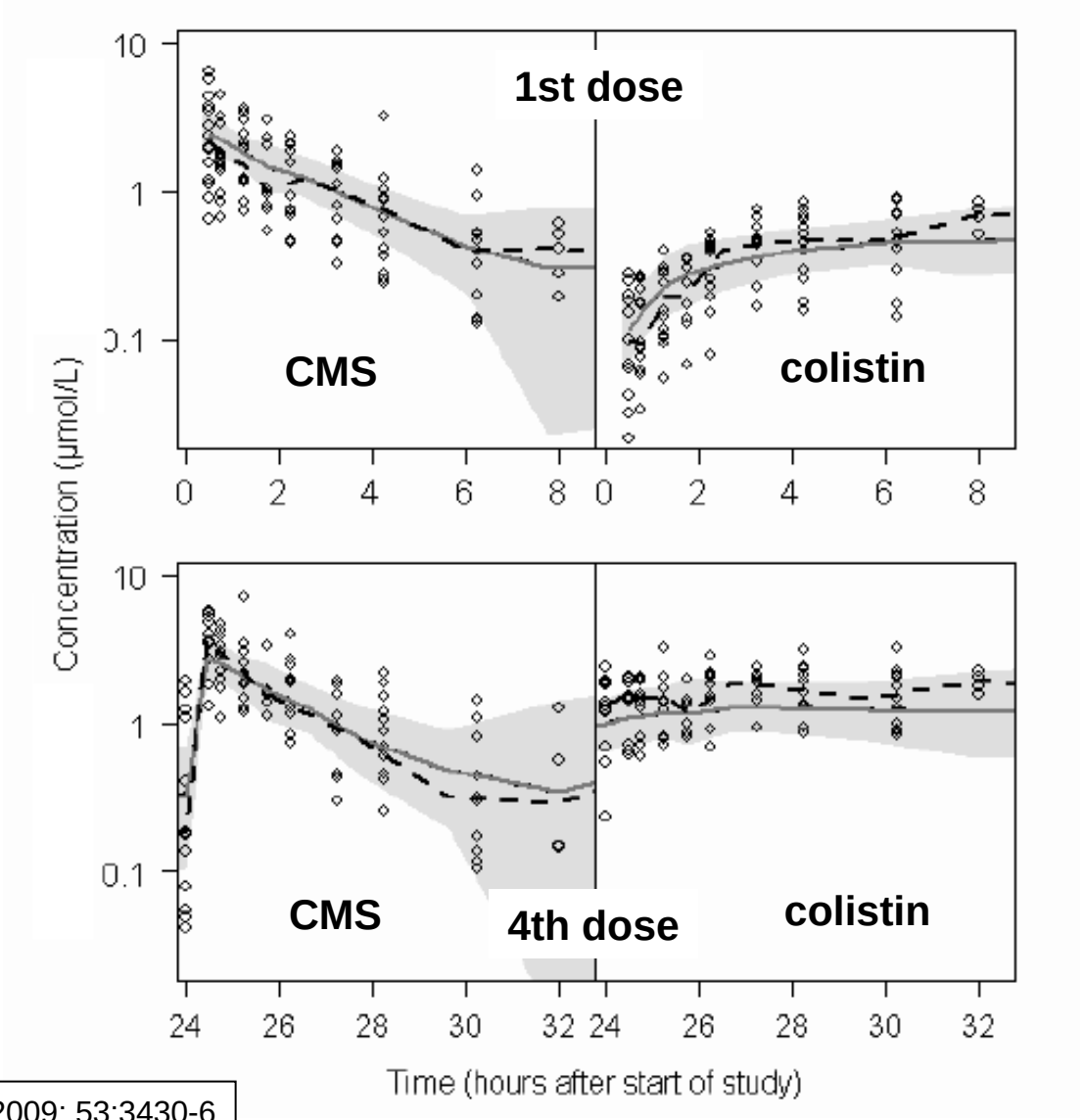
Population pharmacokinetics of colistin in critically-ill patients

Dosage (colistine methane sulfonate [CMS]): 240 mg (3 x 10^6 U) every 8h

CMS
- $t_{1/2}$ ~ 2.3 h,

Colistin:
- $t_{1/2}$ ~ 14.4 h.
- Cmax (pred.)
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.

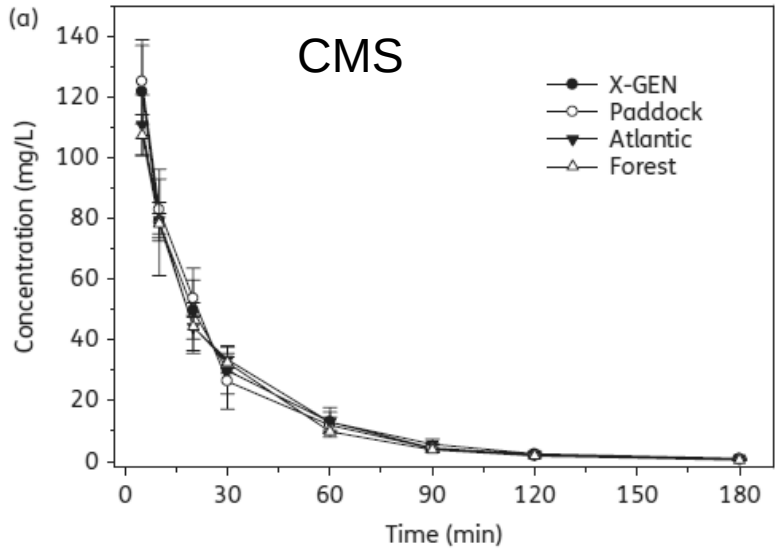
Conclusions: Colistin long half-life and insufficient plasma concentrations before steady state suggest the necessity of a loading dose …

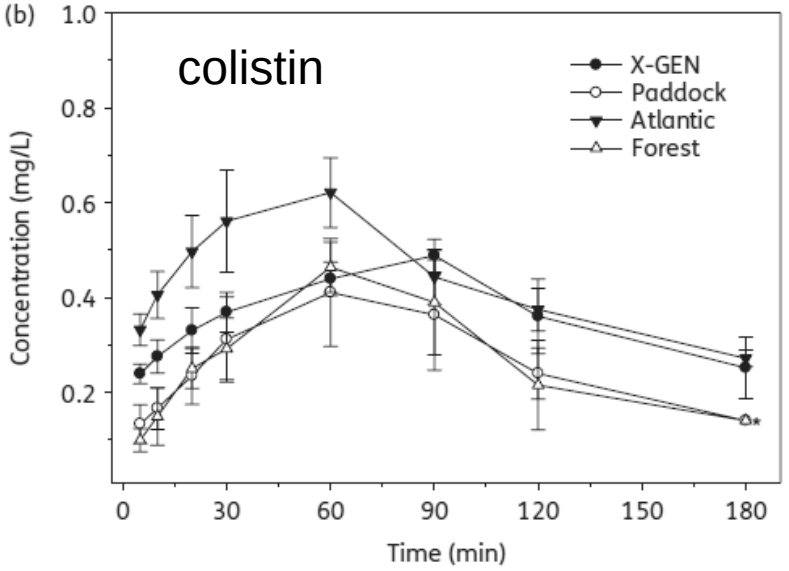


Plachouras et al. Antimicrob Agents Chemother. 2009; 53:3430-6

Colistin regeneration depends on the brand!

Comparison of PK profile in rats for 4 brands





Pharmacokinetic parameters of CMS and formed colistin in rats ($n=4$)

Parameters	X-GEN (USA)	Paddock (USA)	Atlantic (Thailand)	Forest (UK)
Formed colistin				
$t_{1/2}$ (min)[a]	108.0 ± 57.2	68.9 ± 12.0	107.2 ± 13.5	45.3 ± 10.0
C_{max} (mg/L)	0.49 ± 0.035	0.44 ± 0.10	0.62 ± 0.075	0.47 ± 0.053
$AUC_{0-180min}$ (mg·min/L)	65.4 ± 6.81	40.5 ± 10.6	77.8 ± 9.54	42.4 ± 12.0
ratio of $AUC_{0-180min}$ of colistin to CMS (%)[b]	2.73 ± 0.41	1.68 ± 0.35	3.29 ± 0.43	1.98 ± 0.58

He et al, JAC (2013) 68: 2311-17

Colistin pharmacokinetics : current clinical data

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01733-10

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients[▽]

S. M. Garonzik,[1]† J. Li,[2]† V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[2] F. P. Silveira,[6]‡ A. Forrest,[1]‡ and R. L. Nation[2]*‡

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Received 13 December 2010/Returned for modification 13 March 2011/Accepted 28 April 2011

- **open-label population PK study (2 centers in US; 1 in Thailand)**
- **105 patients (February 2009 - July 2010)**
- **12 with HD, 4 with CRRT (3 CVV hemodialysis; 1 CVV hemofiltration)**
- **physician-selected doses: 75 to 410 mg/day colistin base (2.2 to 12.5 x 10^6 U)/day**
- **dosage intervals: 8 to 24 h,**

Population pharmacokinetics of CMS and colistin in normal, HD, and CCRT patients

CMS

formed colistin

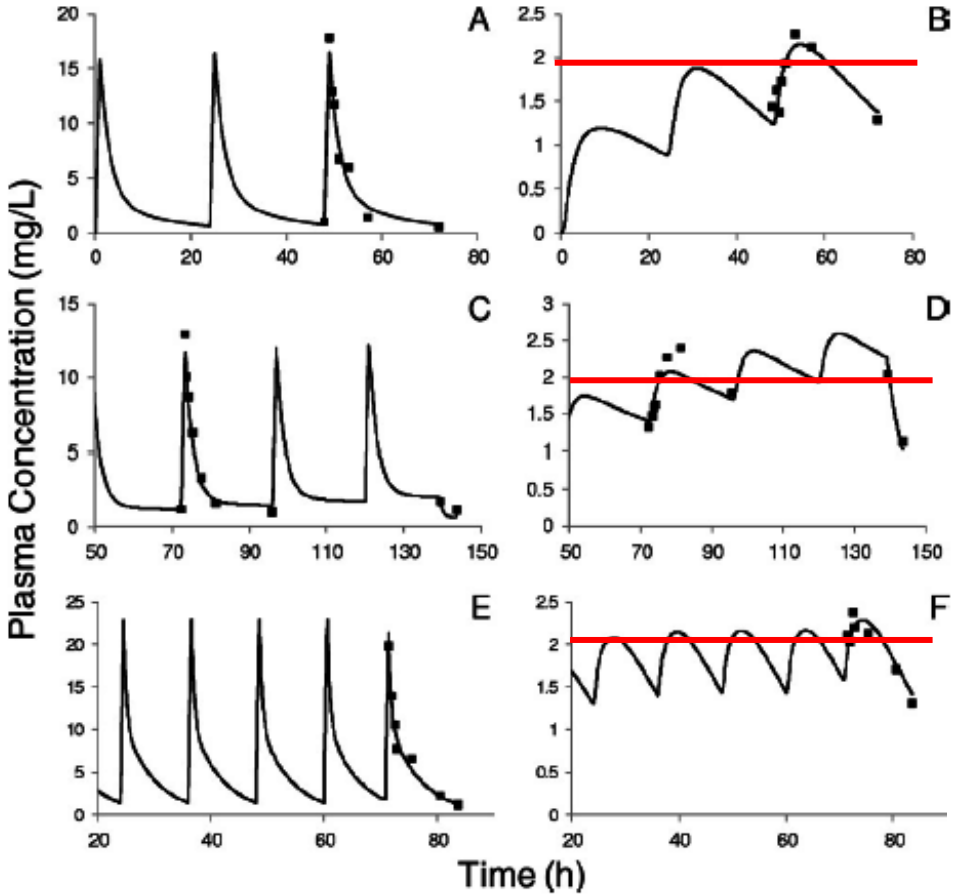

FIG. 3. Representative individual population PK model fits of CMS (A, C, and E) or formed colistin (B, D, and F) in critically ill patients. Panels A and B are representative of a subject not on renal replacement, C and D are representative of a subject on HD, and E and F are representative of a subject on CRRT.

Current dosing recommendations (*): 1 of 3

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.

a **Expressed as mg of colistin base (**) activity (CBA) for various categories of critically ill patients. The suggested maintenance daily dose would commence 24 h after administration of a CMS loading dose.**

Example: To target a colistin Css,avg of 2.5 mg/liter, a 55-kg patient with a CrCL of 40 ml/min/1.73 m^2 would receive a loading dose of 275 mg CBA (***) followed in 24 h by commencement of a maintenance regimen of 225 mg CBA/day in 2 to 3 equally divided doses.

b **Colistin Css,avg target is expressed in mg/liter. This target should be based on MIC, site, and severity of infection.**

c **Use the lower of ideal or actual body weight, expressed in kg. At this time, we suggest caution in the use of a loading dose greater than 300 mg CBA**

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* after Garonzik et al. Antimicrob. Agents Chemother. (2011) 55:3284-3294

** 33 mg colistin base = 80 mg colistimethate = 1 x 10^6 U

*** 275 mg CBA for loading dose = 8.3 x 10^6 U

Current dosing recommendations (*): 2 of 3

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.

d **Based upon the population PK analysis for 101 critically ill patients not on continuous renal replacement therapy. Colistin Css,avg target expressed in mg/L.**

Creatinine clearance (CrCL) expressed in ml/min/1.73 m^2. Although the Jelliffe equation was used to estimate CrCL in this study, other means (e.g., Cockcroft and Gault equation) may be used to estimate CrCL which would then be normalized to a body surface area of 1.73 m^2.

in patients with CrCL values 70 ml/min/1.73 m^2 or when targeting a "high" colistin Css,avg, both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.

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* after Garonzik et al. Antimicrob. Agents Chemother. (2011) 55:3284-3294

** 33 mg colistin base = 80 mg colistimethate = 1 x 10^6 U

*** 275 mg CBA for loading dose = 8.3 x 10^6 U

Current dosing recommendations (*): 3 of 3

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Maintenance dose	Receiving intermittent hemodialysis	Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target[b] = 30 mg[e]. Supplemental dose of CBA on a HD day[f]: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
	Receiving continuous renal replacement	Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.[g] Doses may be given every 8-12 h.

***e* Based upon use of equation 10 and setting CrCL to zero.**

***f* Supplemental dose of CMS to achieve a similar colistin Css,avg on a HD day as occurs on a non-HD day. It is assumed that the hemodialysis session occurs toward the end of a CMS dosage interval.**

***g* Based on the population PK analysis for 4 critically ill patients receiving continuous renal replacement therapy.**

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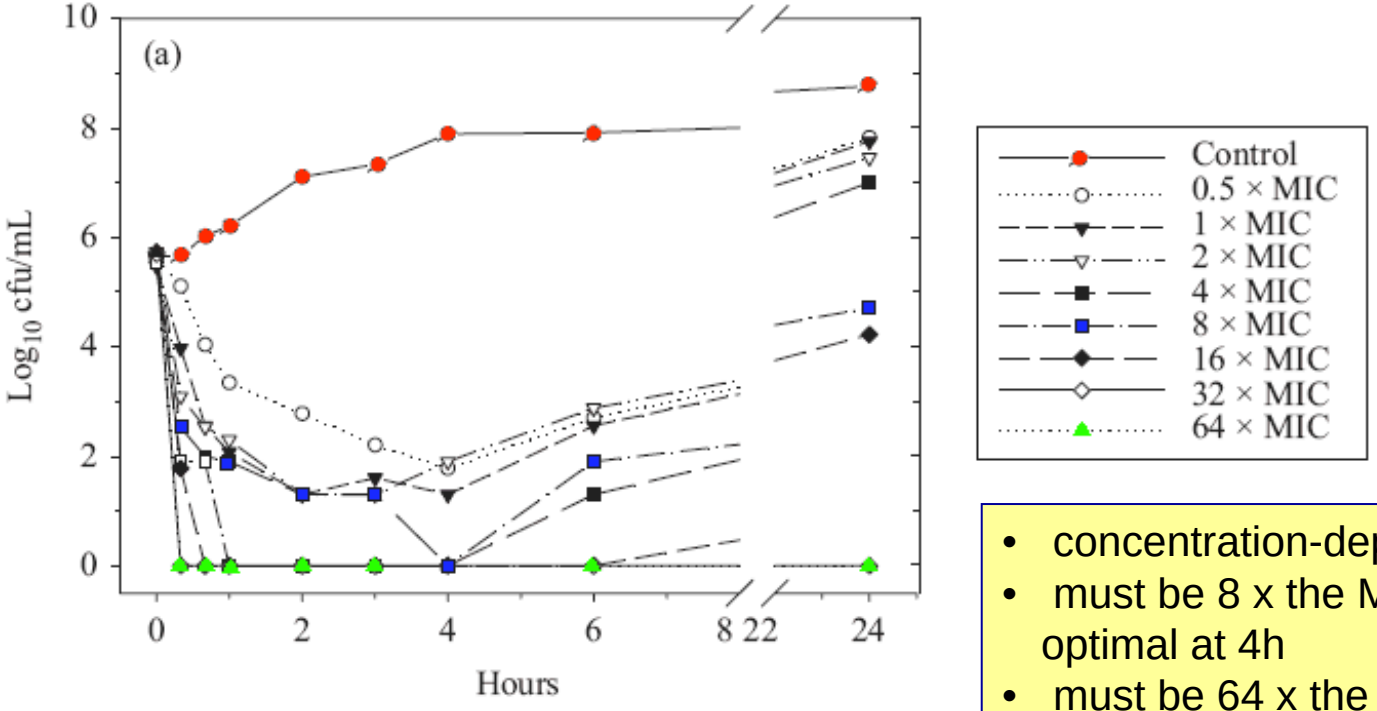
* after Garonzik et al. Antimicrob. Agents Chemother. (2011) 55:3284-3294

** 33 mg colistine base = 80 mg colistimethate = 1 x 10^6 U

*** 275 mg CBA for loading dose = 8.3 x 10^6 U

Colistin pharmacodynamics in vitro

Time kill curves against *A. baumanii*



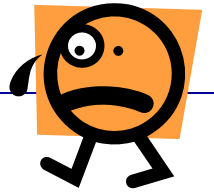
- concentration-dependence
- must be 8 x the MIC to become optimal at 4h
- must be 64 x the MIC to avoid regrowth
- modest post-antibiotic effect (see data in paper)

Conclusions: **These findings suggest that monotherapy with colistin methanesulphonate, the parenteral form of colistin, and long dosage intervals (e.g. 24 h) may be problematic for treatment of infections caused by colistin heteroresistant *A. baumannii*.**

Owen et al. JAC 2007; 59:473-477

Colistin pharmacodynamics in vitro

In conclusion, the present study demonstrated initial rapid bacterial killing by colistin against susceptible *K. pneumoniae*. However, the concerning findings were a high frequency of colistin heteroresistance, the substantial regrowth within 24 h that occurred even at colistin concentrations up to 64× MIC and no significant colistin PAE. These findings suggest the potential risk that monotherapy with CMS and extended-interval dosage regimens may promote colistin resistance in multidrug-resistant *K. pneumoniae*.

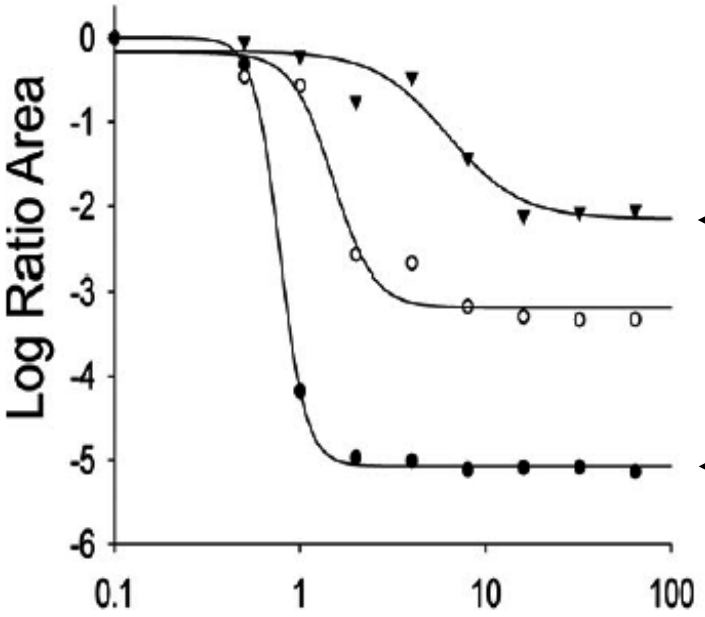


Poudyal et al. JAC 2008; 62:1311-1318

Colistin and inoculum effect

A)

Inoculum	E_0	Emax	EC_{50}	H
10^6 CFU/mL	-0.003	5.07	0.777	6.10
10^8 CFU/mL	-0.173	3.01	1.49	3.95
10^9 CFU/mL	-0.156	1.99	6.22	2.20



high inoculum (~ *in vivo*

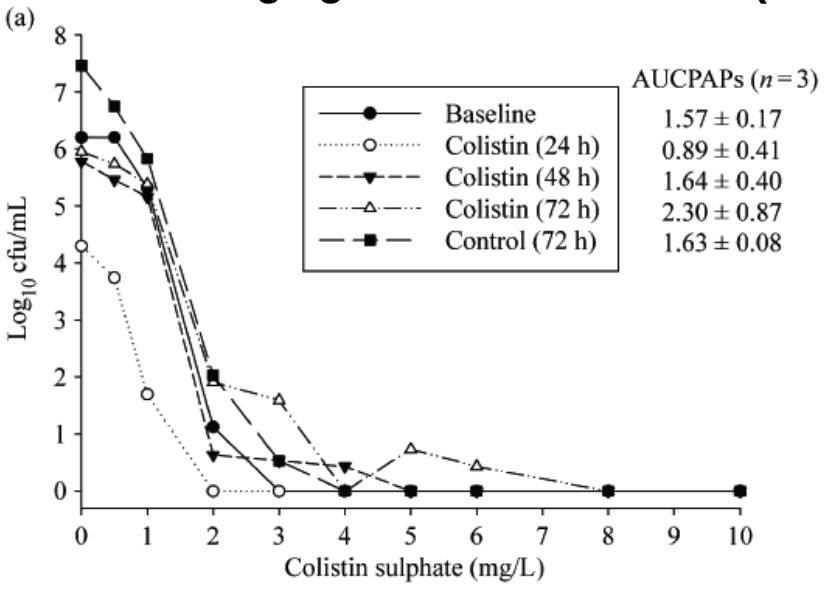
low inoculum (~ *in vitro* testing)

The extent and rate of killing of *P. aeruginosa* by colistin were markedly decreased at high CFUo compared to those at low CFUo.
Bulita et al. Antimicrob. Agents Chemother. (2010) 54:2051-2062

Colistin pharmacodynamics and resistance

Population analysis of *P. aeruginosa* after exposure to colistin modeling:

5 mg/kg divided in 3 admin. (TID)



5 mg/kg in one admin (qD)

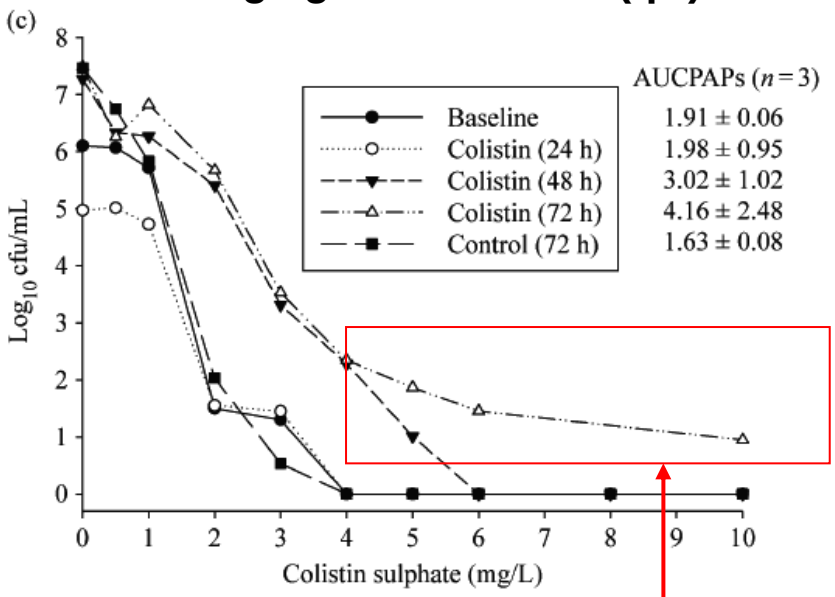


Figure 2. PAPs of ATCC 27853 in the *in vitro* PK/PD model: (a) 8 hourly (c) 24 hourly dosing.

less-susceptible organisms

Bergen et al. JAC 2008; 61:636-642

***Conclusions*: No difference in overall bacterial kill was observed when the recommended maximum daily dose was administered at 8, 12 or 24 h intervals. However, the 8 hourly regimen appeared most effective at minimizing emergence of resistance.**

Colistin pharmacodynamics in vitro: conclusions

These recent elegant studies confirm what early investigators had already observed, namely that colistin

- Displays a **high and fast bactericidal effect** (named today: concentration-dependent antibiotic)

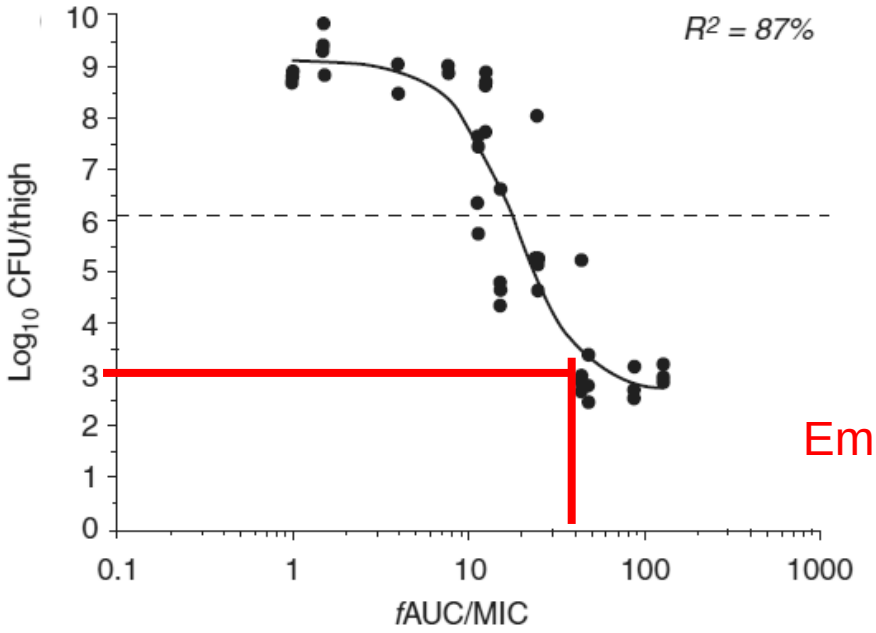
  ➔ **A loading dose to reach quickly max. bactericidal effect is essential**

- But that its activity **vanishes after even transient exposure** (named today: **heteroresistance** and/or **persistence of less susceptible** isolates, or **adaptative resistance**)

  ➔ colistin needs to be **administered several times a day to avoid regrowth**

Colistin pharmacodynamics in vivo

Tigh infection model - Pseudomonas

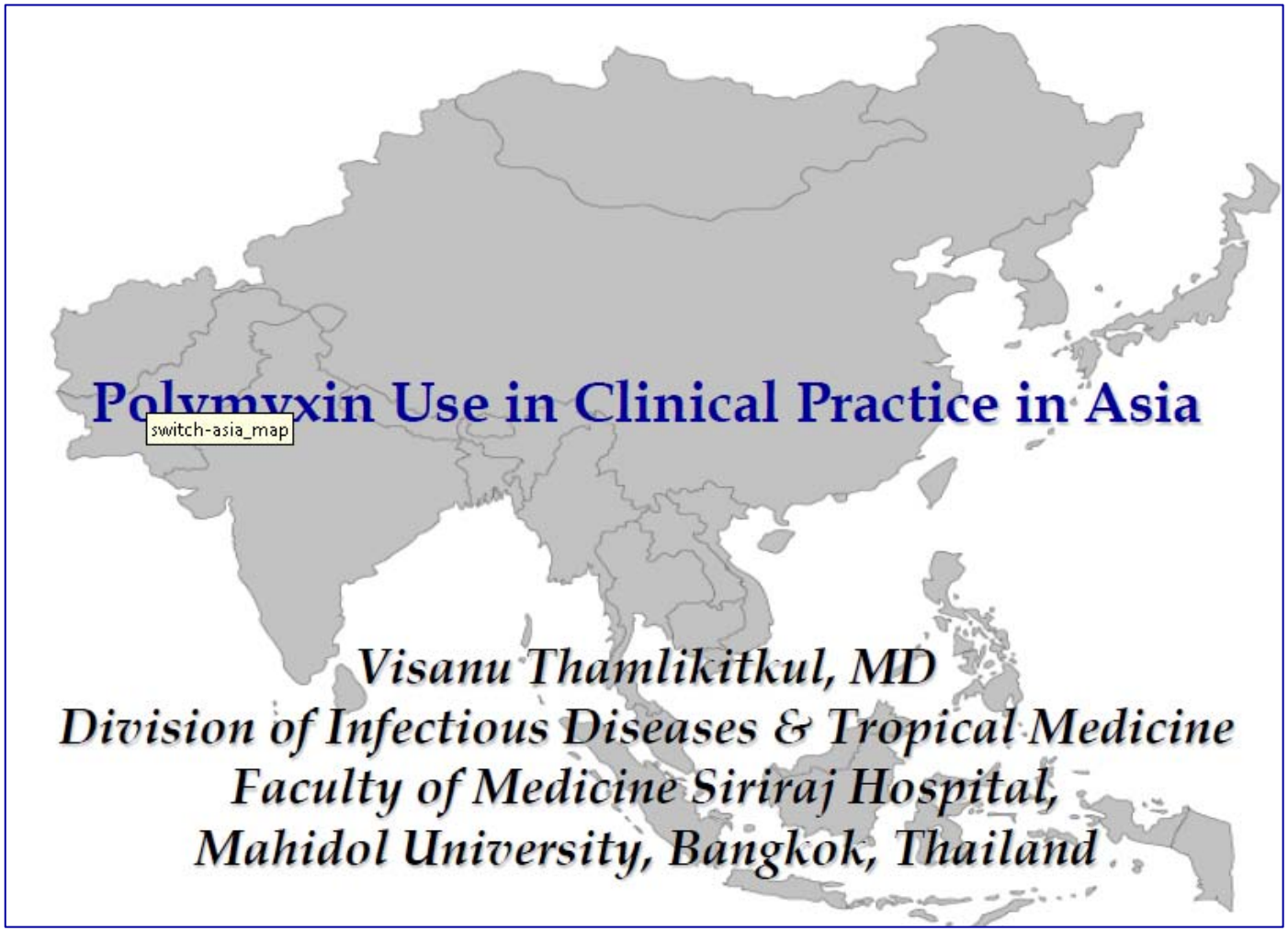


Emax at fAUC/MIC = 40

Activity is depending on the free AUC → optimize the daily dose

Bergen et al, Cur.Op. Pharmacol. (2011), 11:464–469

An application in humans: Asian study in Thailand



First International Conference on polymyxins, Prato, Italy, 2013

An application in humans: Asian study in Thailand

Polymyxin Use in Thailand

- PK study in 103 Thai patients
- Colistin dosing regimens were computed from PK data

✓ Colistin MIC Distribution XDR non-fermenters from 103 Thai Patients : MIC_{50} = 0.5, MIC_{90} = 1

✓ PK/PD Targets : Cmax ~ 2.5 and AUC/MIC ~ 50

An application in humans: Asian study in Thailand

CMS Dosing (Colistin Base Activity) before 2011

- **Manufacture's Recommendation**

✓ Sr. Cr 0.7 - 1.2 100 - 150 mg q 12 h (5mg/kg/d)
✓ Sr. Cr 1.3 - 1.5 75 - 115 mg q 12 h (2.5-3.8mg/kg/d)
✓ Sr. Cr 1.6 - 2.5 100 - 150 mg q 24 h (2.5mg/kg/d)
✓ Sr. Cr 2.6 - 4 100 - 150 mg q 36 h (1.5mg/kg/d)

- **The Sanford Guide to Antimicrobial Therapy**

✓ Cr. Clearance* > 50 ml/min 160 mg q 12 h
✓ Cr. Clearance* 10 - 50 ml/min 160 mg q 24 h
✓ Cr. Clearance* < 10 ml/min 160 mg q 36 h

**Cockcroft & Gaulf equation*

- Empiric Therapy 30%
- Combination Therapy 70%
- Median Duration Colistin 10 days

An application in humans: Asian study in Thailand

Suggested Colistin Dosing Regimens since March 2011

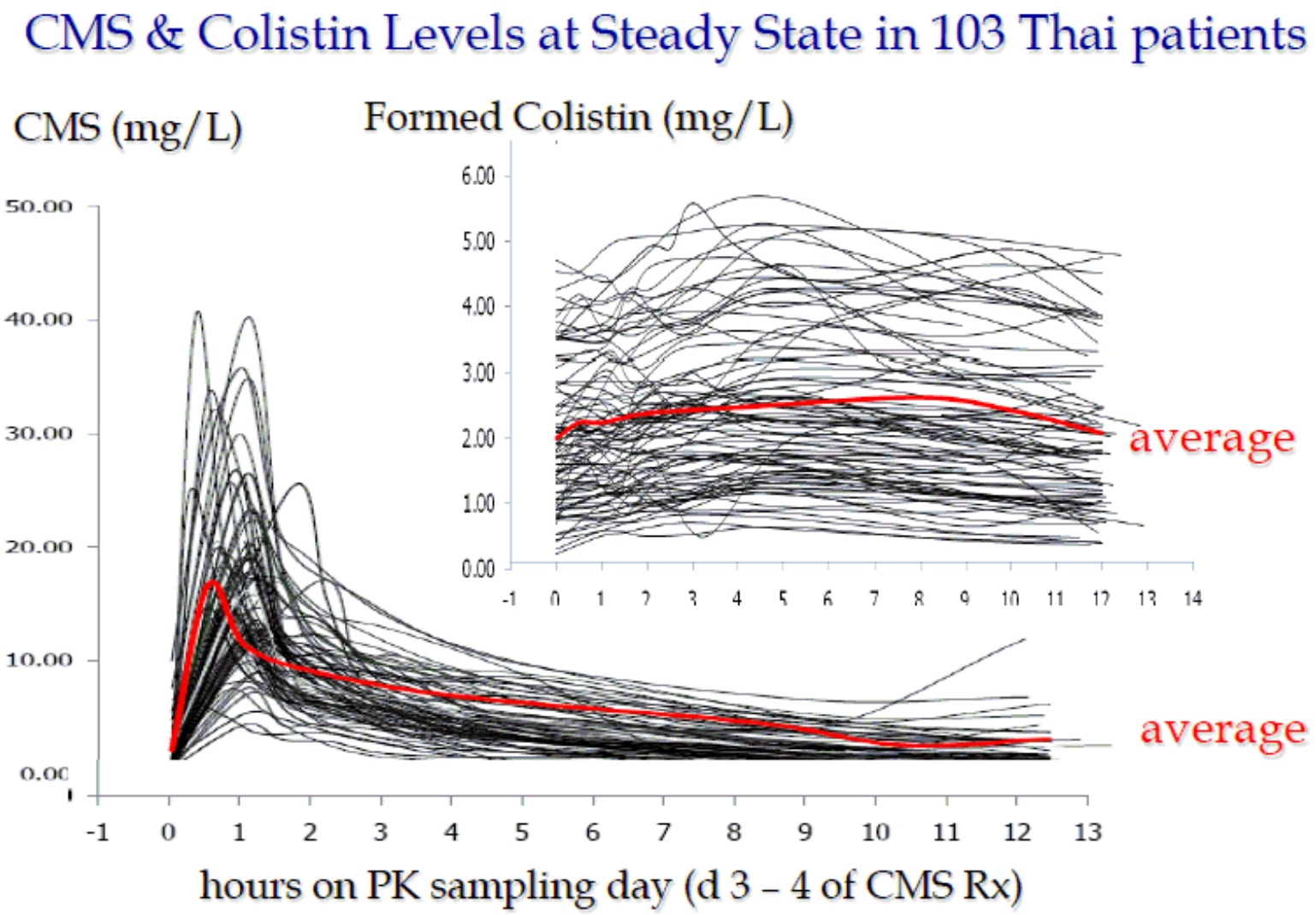
No-RRT

Cr. Clearance* (ml/min)	Loading Dose (mg)	Maintenance Dose (mg)
> 50	300	150 q 12 h or 100 q 8 h
41 – 50	300	150 q 12 h or 75-100 q 8 h
31 – 40	300	75 - 100 q 12 h
21 – 30	300	75 q 12 h or 150 q 24 h
11 – 20	300	100 q 24 h
≤ 10	150	75 q 24 h

**Cockcroft & Gaulf equation*

Acute RRT	150	100 q 24 h

An application in humans: Asian study in Thailand



An application in humans: Asian study in Thailand

Effectiveness of Suggested Dosing Regimens

	Probability of Target Attainment (PTA) for GNB with										CFR (%)	
	MIC=0.25		MIC=0.5		MIC=1		MIC=2		MIC=4			
	D1	SS	D1	SS	D1	SS	D1	SS	D1	SS	D1	SS
SD	0.99	1.00	0.95	0.96	0.70	0.86	0.21	0.40	0.03	0.18	76	85
AD	0.88	0.99	0.58	0.89	0.10	0.46	0.01	0.09	0	0	34	64
MD	0.96	0.98	0.73	0.90	0.41	0.69	0.03	0.22	0	0.01	54	74
GD	0.95	0.99	0.72	0.93	0.32	0.59	0.10	0.17	0	0	59	71

CFR = Cumulative Fraction of Response
D1 = Day 1 SS = Steady State
SD = Suggested Dosing AD = Actual Dosing
MD = Manufacture Dosing GD = Sanford Guide Dosing

An application in humans: Asian study in Thailand

Effectiveness of Suggested Dosing Regimens

	Probability of Target Attainment (PTA) for GNB with 3% / 48% / 86% / 38% / 8% / 4%										CFR (%)	
	MIC=0.25		MIC=0.5		MIC=1		MIC=2		MIC=4			
	D1	SS	D1	SS	D1	SS	D1	SS	D1	SS	D1	SS
SD	0.99	1.00	0.95	0.96	0.70	0.86	0.21	0.40	0.03	0.18	76	85
AD	0.88	0.99	0.58	0.89	0.10	0.46	0.01	0.09	0	0	34	64
MD	0.96	0.98	0.73	0.90	0.41	0.69	0.03	0.22	0	0.01	54	74
GD	0.95	0.99	0.72	0.93	0.32	0.59	0.10	0.17	0	0	59	71

CFR = Cumulative Fraction of Response
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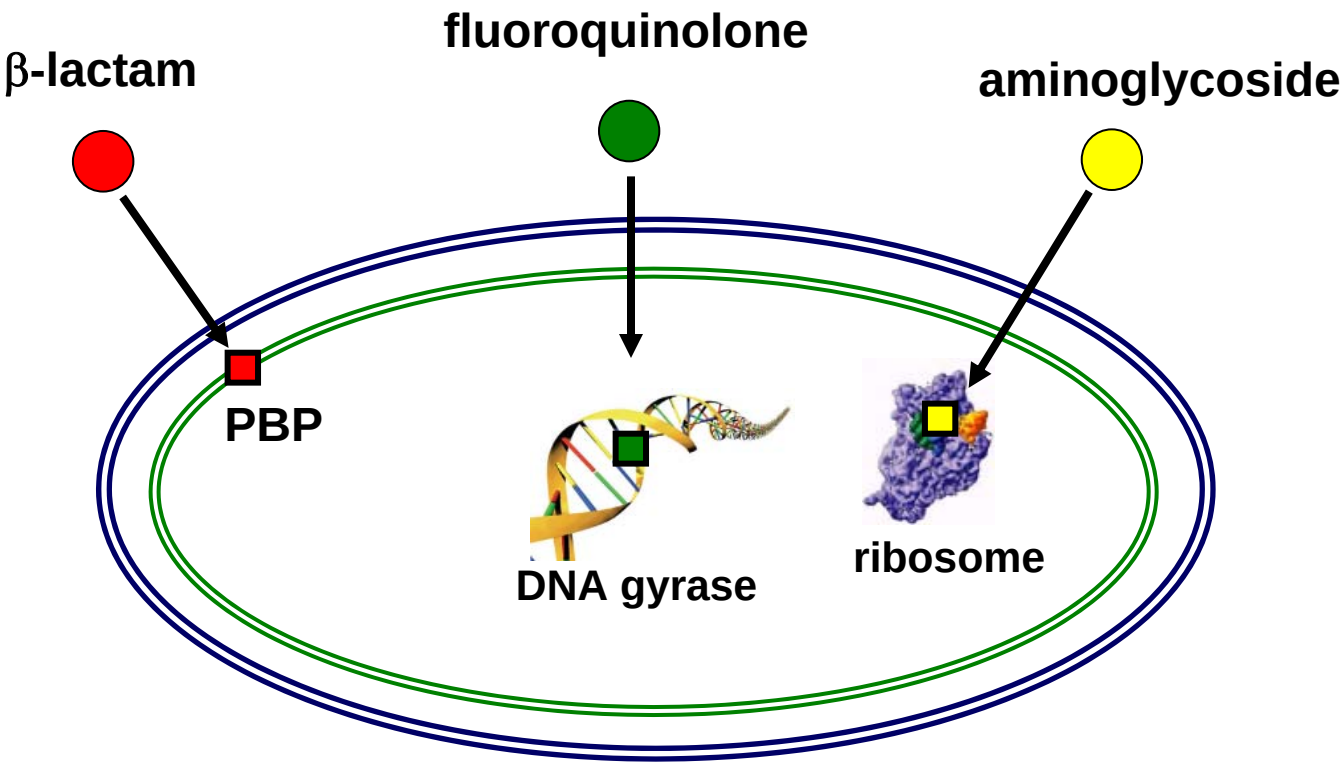
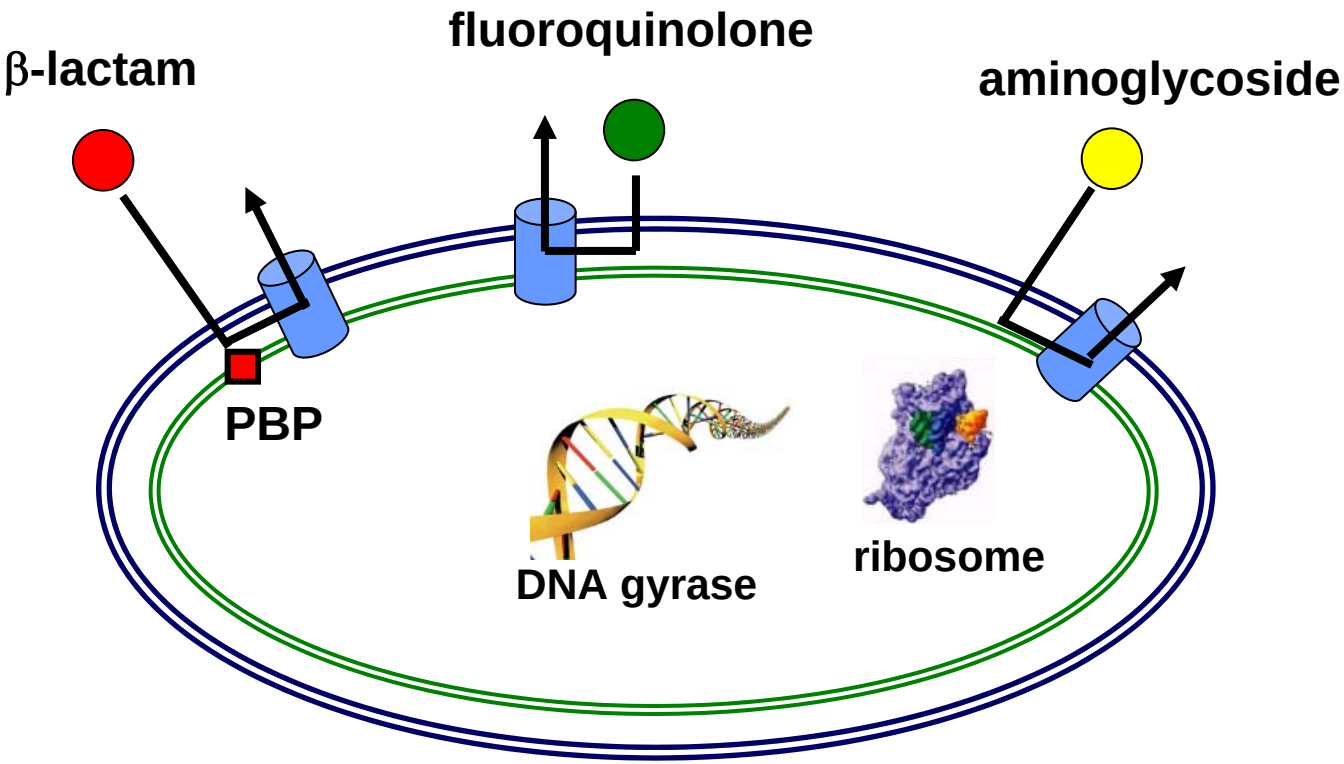
Colistin synergy: the rationale (1 of 3)



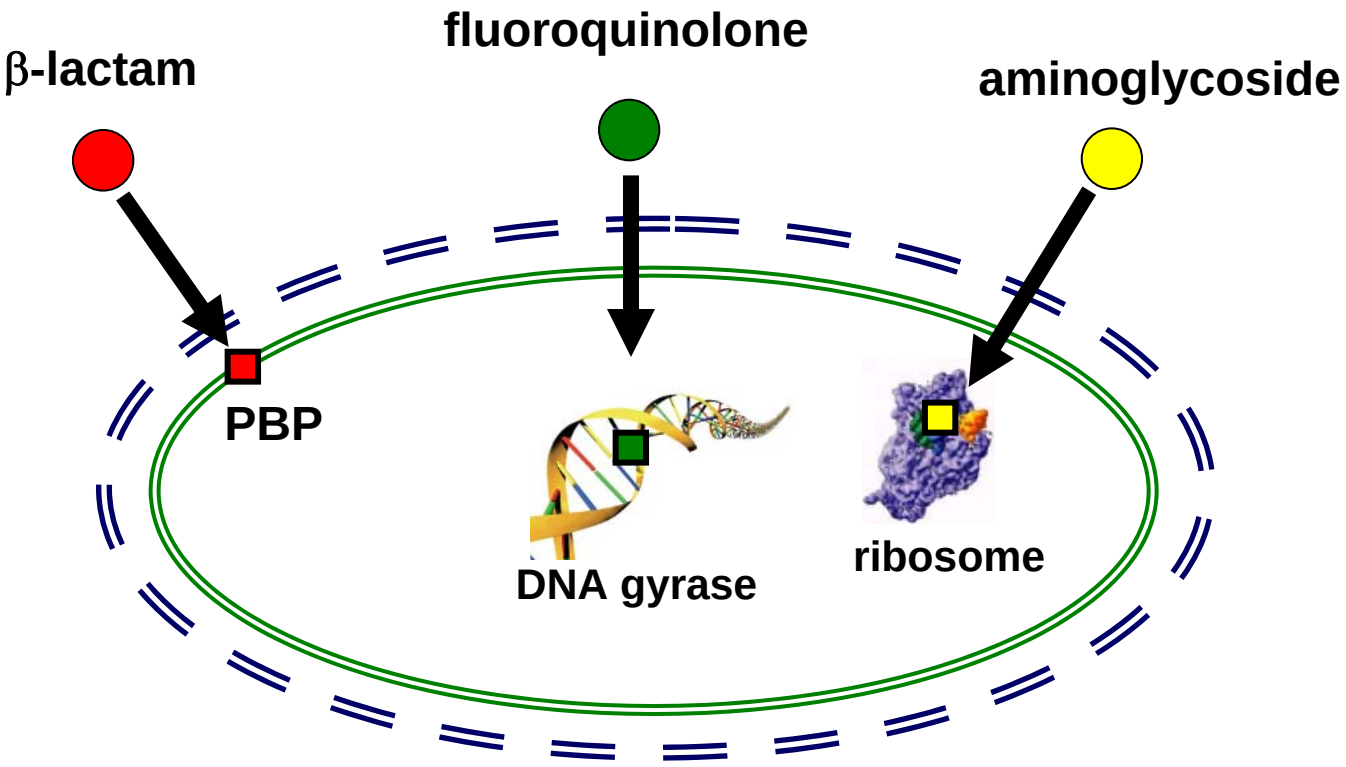
- Gram-negative bacteria have two membanes (OM and IM)
- Antibiotic targets are most often located in the IM or intracellularly
- Most antibiotics must at least pass across the OM to reach their target, which may represent a limiting step

Colistin synergy: the rationale (2 of 3)



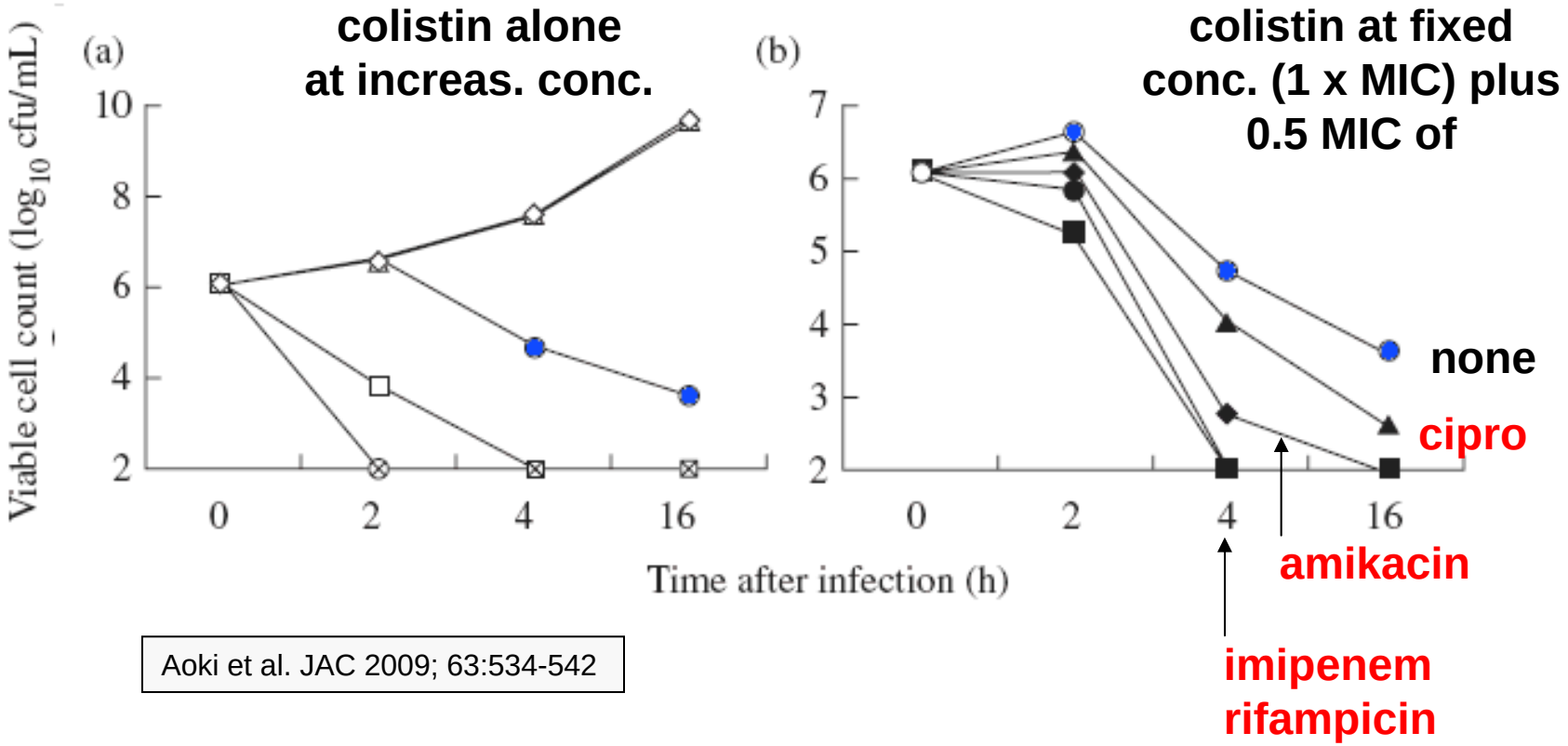
- **Gram-negative bacteria have also efflux systems defeating the passage of drugs across the OM and explaining the low activity of many antibiotics (intrinsic resistance) and the so-called "adaptative" resistance (aminglycosides)**

Colistin synergy: the rationale (3 of 3)



- **Disrupting the OM (as colistin does) will facilitate access of the other antibiotics to their targets**
- **This may apply EVEN to antibiotics for which the bateria are resistant (if due to OM impermeability/efflux phenomenon)**

Colistin synergy *in vitro* and *P. aeruginosa*



Aoki et al. JAC 2009; 63:534-542

Souli et al. AAC 2009; 2133-2135:

- Synergy / Improved activity if susceptible to both agents or to colistin only
- **Antagonism frequent if colistin-insensitive**

Is it used in the clinics ?

Survey performed in 2011 (284 respondents from 56 different countries)

Response to what drugs are used for combination therapy with colistin.

	Frequency (%)		
	Never	Uncommon	Common
Carbapenem	24.5	31.7	43.8
Gentamicin	41.3	38.8	20.0
Tigecycline	47.4	34.2	18.4
Rifampicin	51.9	29.8	18.3
Piperacillin/tazobactam	49.3	35.5	15.2
Fluoroquinolone	52.8	39.6	7.7
Fosfomycin	81.5	12.0	6.5
Minocycline	81.1	14.5	4.4
Other[a]	64.3	23.1	12.6

[a] Other includes cephalosporins, trimethoprim/sulfamethoxazole, glycopeptide, linezolid and doxycycline.

Wertheim et al, Journal of Global Antimicrobial Resistance (Epub)

Is it used in the clinics ?

Ongoing clinical trials are evaluating the interest of combinations in practice

Example: NIH-10065:
colistin/placebo vs colistin/imipenem for MDR Gram-negative bacilli

- HAP/VAP, bloodstream infections
- primary outcome: mortality at day 28
- secondary outcomes: bacterial eradication & toxicity

→ **objectives**
- efficacy of the combination ?
- risk of resistance ?
- relationship between plasma level, microbiological eradication and toxicity
- relationship between in vitro synergism and clinical outcomes ?

Contents of the presentation

- colistin : a reminder
- antimicrobial activity
- pharmacokinetics/pharmacodynamics
- toxicodynamics
- current use and perspectives

??

Colistin gross toxicology

- Colistin methanesulfonate is about 50 to 100 X less toxic in LD_{50} evaluations than colistine sulfate
- Renal toxicity (polymyxin B << other polymyxins)
  - Up to 20 % of patients in early trials
  - Occurs after 4 days of treatment
  - Acute tubular necrosis (can progress after drug discontinuation)
  - Related to overdosage (obese ! Oliguric renal failure if if doses higher than recommended are used)
- Neurotoxicity:
  - Giddiness, numbness, paresthesia, peripheral neuropathy
  - Confusion, coma, psychosis at large doses
  - Neuromuscular blockade (paralysis) related to doses but other contributing factors

Colistin nephrotoxicokinetic is complex…

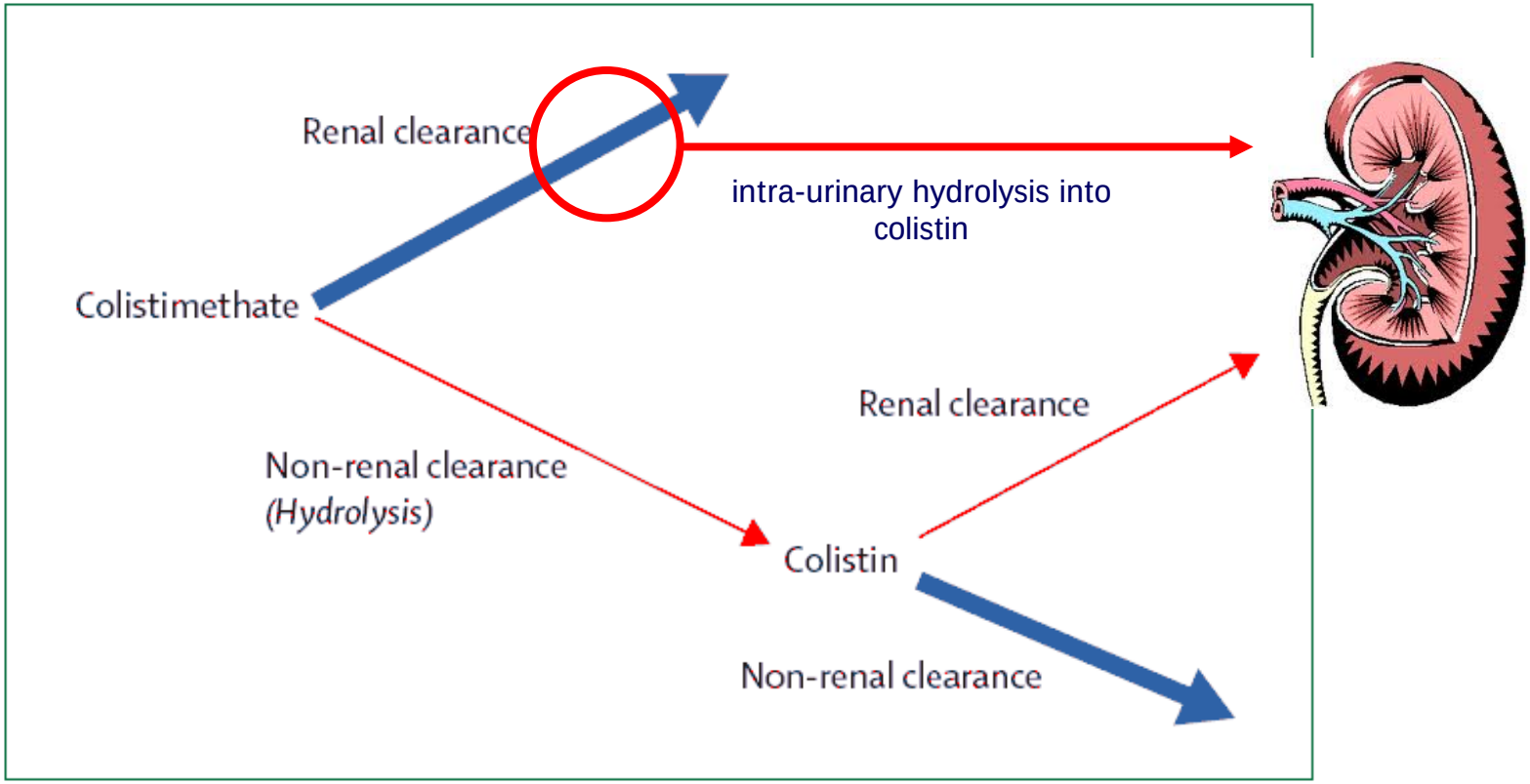
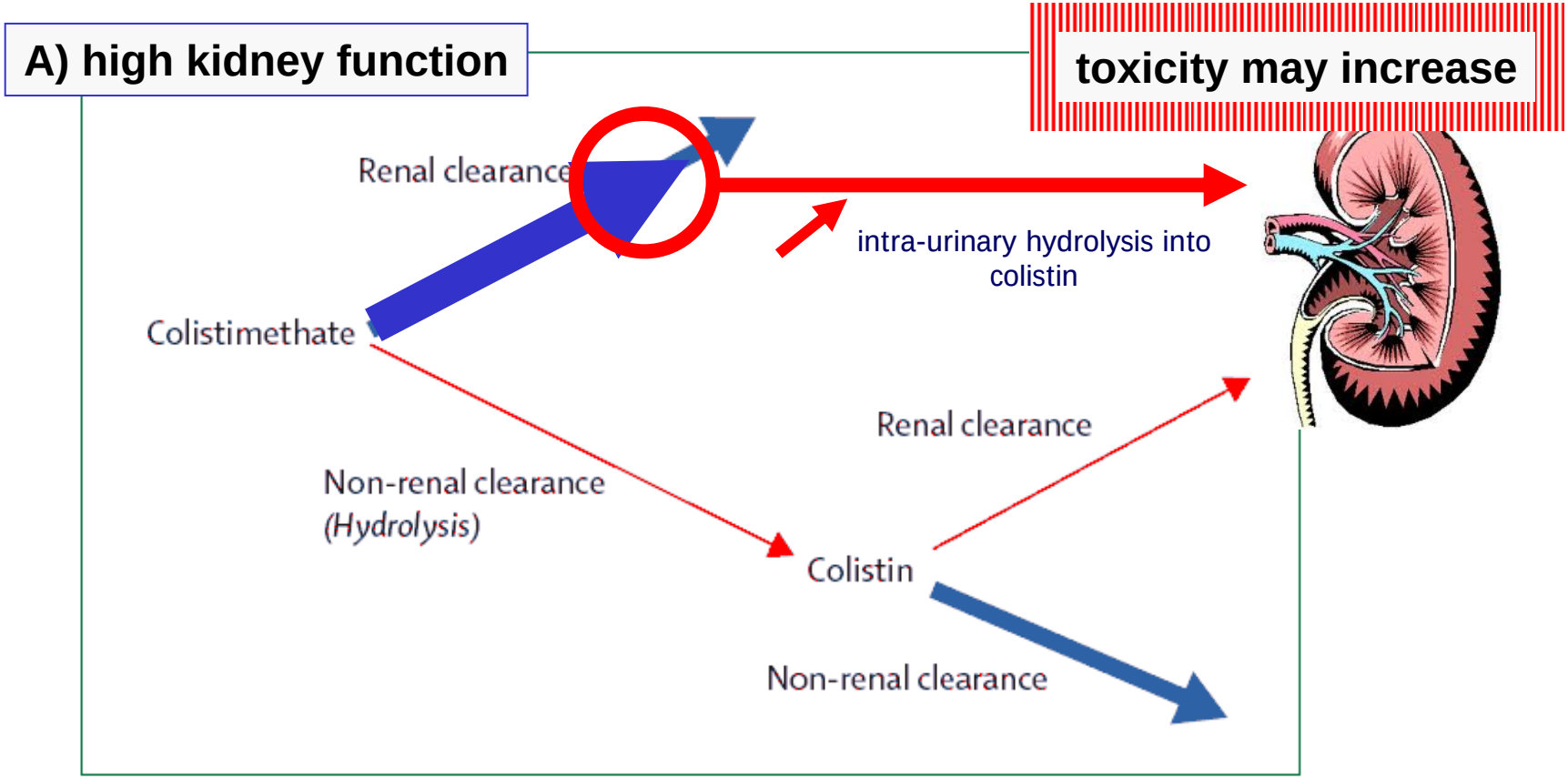


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Li et al. Lancet Infect. Dis. 2006; 6:589-601 (modified)

Colistin nephrotoxicokinetic is complex…



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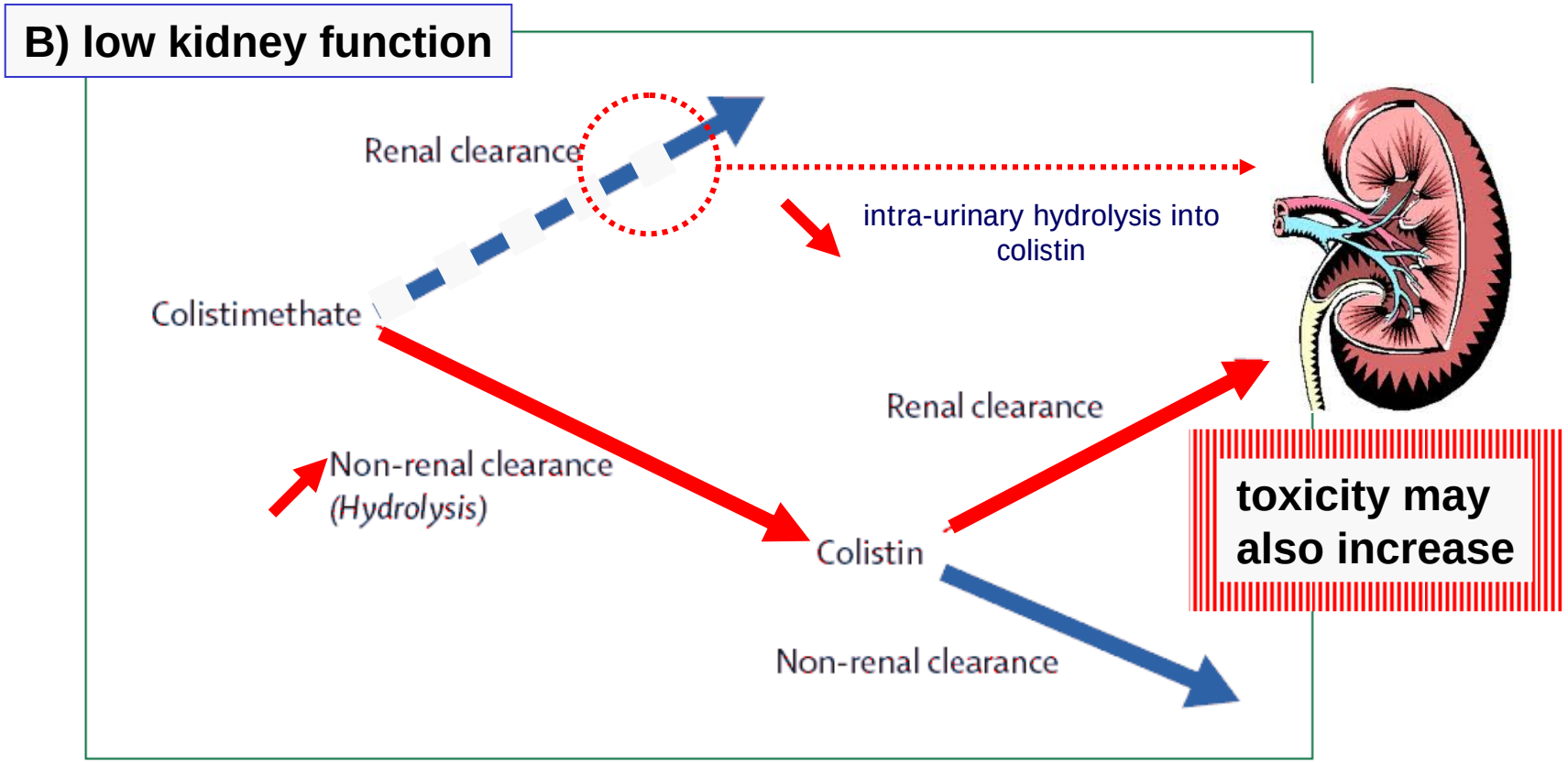

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Colistin nephrotoxicity

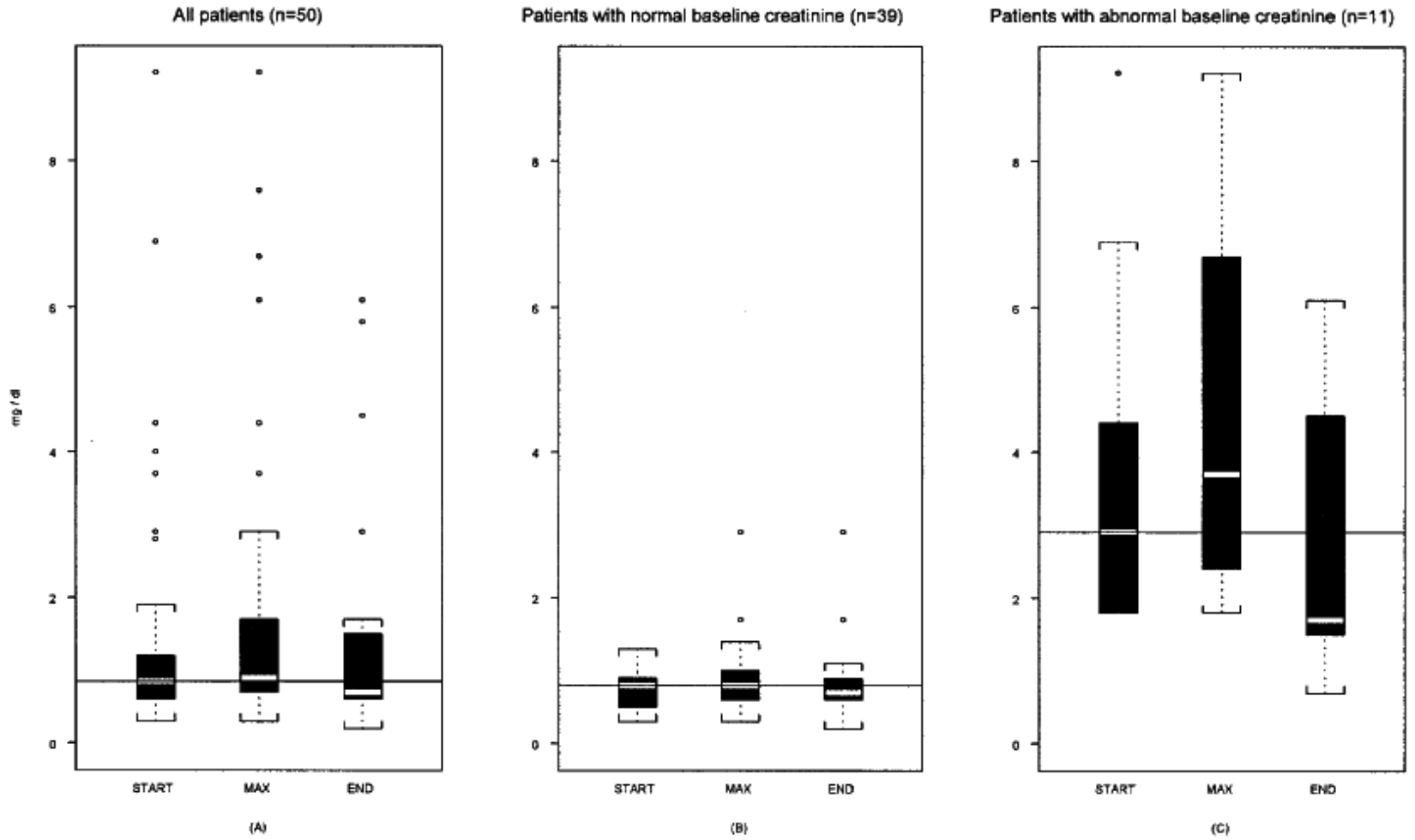


FIG. 1. The distribution of serum creatinine levels on the first day of colistin treatment (START), at the peak value (MAX), and at the end of colistin treatment (END) in all studied patients (A), in the group of patients with normal baseline creatinine values (B), and in the group of patients with abnormal baseline creatinine values (C). The horizontal lines within the boxes represent the median creatinine baseline value at the first day of colistin treatment.

Kasiakou *et al*. AAC 2005; 49:3136-3146

Contents of the presentation

- colistin : a reminder
- antimicrobial activity
- pharmacokinetics/pharmacodynamics
- toxicodynamics
- current use and perspectives

Meta-analysis of 13 published studies

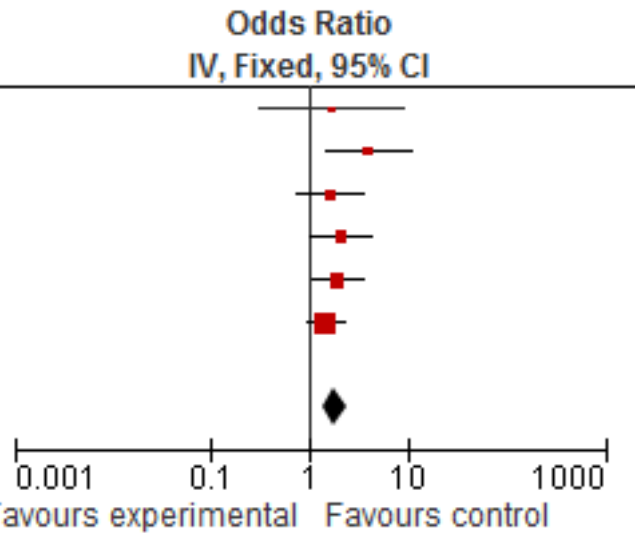
[by Mical Paul; Tel Aviv University, Israël]

IV colistin vs comparators - mortality in sepsis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Betrosian 2008 J Infect	0.512824	0.857296	2.8%	1.67 [0.31, 8.96]
Rigatto 2013 Infection	1.360977	0.51843	7.6%	3.90 [1.41, 10.77]
Kallel 2007 Int CM	0.4796	0.4027	12.6%	1.62 [0.73, 3.56]
Oliveira 2008 (polyB) JAC	0.7275	0.3561	16.1%	2.07 [1.03, 4.16]
Kvitko 2011 (polyB) JAC	0.6471	0.3017	22.4%	1.91 [1.06, 3.45]
Paul 2011 JAC	0.3646	0.23	38.6%	1.44 [0.92, 2.26]
Total (95% CI)			**100.0%**	**1.79 [1.35, 2.36]**

Heterogeneity: $Chi^2 = 3.44$, $df = 5$ ($P = 0.63$); $I^2 = 0\%$

Test for overall effect: $Z = 4.06$ ($P < 0.0001$)



Adjusted OR 1.79 (95% CI 1.35-2.36)

First International Conference on polymyxins, Prato, Italy, 2013

Meta-analysis of 13 published studies

[by Mical Paul; Tel Aviv University, Israël]

IV colistin vs comparators – mortality in pneumonia

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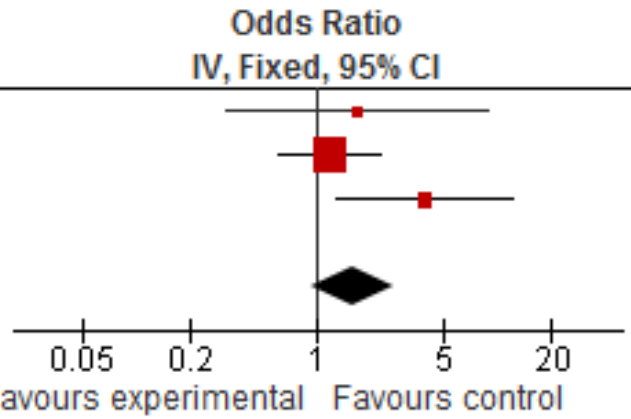
Paul 2011 JAC	0.165514	0.328477	67.7%	1.18 [0.62, 2.25]
Rigatto 2013 Infection	1.376244	0.571904	22.3%	3.96 [1.29, 12.15]
Total (95% CI)			**100.0%**	**1.60 [0.94, 2.72]**

Heterogeneity: Chi² = 3.37, df = 2 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.74 (P = 0.08)



Adjusted OR 1.60 (95% CI 0.94-2.72)

Meta-analysis of 13 published studies

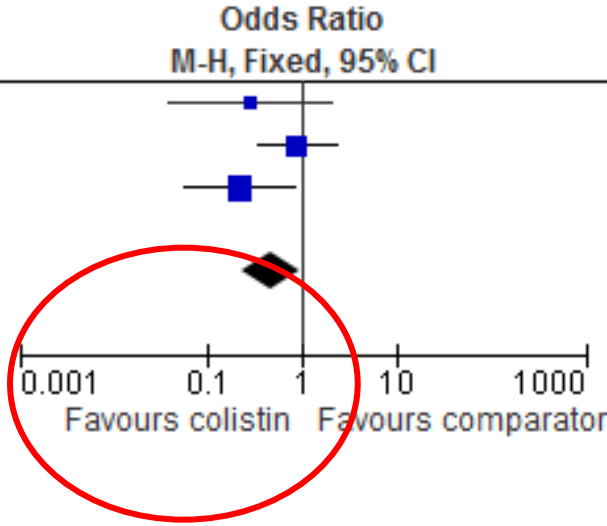
[by Mical Paul; Tel Aviv University, Israël]

IV colistin vs inappropriate antibiotics - mortality

Study or Subgroup	Colistin Events	Colistin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Qureshi 2012 AAC	5	14	4	6	15.6%	0.28 [0.04, 2.09]
Lim 2011 J Korean med	11	31	15	39	37.3%	0.88 [0.33, 2.34]
Koomanachai 2007 Int J	36	78	12	15	47.1%	0.21 [0.06, 0.82]
Total (95% CI)		**123**		**60**	**100.0%**	**0.47 [0.23, 0.96]**
Total events	52		31			

Heterogeneity: Chi² = 3.15, df = 2 (P = 0.21); I² = 37%

Test for overall effect: Z = 2.07 (P = 0.04)

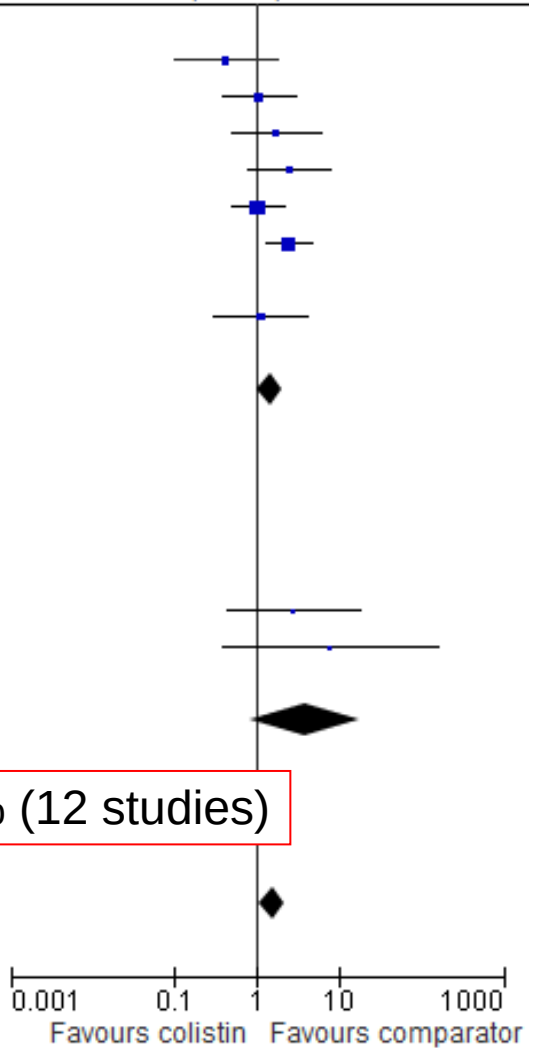


OR 0.47 (95% CI 0.23-0.96)

Meta-analysis of 13 published studies

[by Mical Paul; Tel Aviv University, Israël]

Study or Subgroup	Colistin Events	Colistin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Non-matched						
Garnacho-Montero 2003 CID	5	21	6	14	10.6%	0.42 [0.10, 1.79]
Hachem 2007 AAC	7	31	14	64	13.6%	1.04 [0.37, 2.92]
Kvitko 2011 (polyB) JAC	5	45	6	88	6.9%	1.71 [0.49, 5.94]
Lim 2011 J Korean med	10	20	10	35	7.0%	2.50 [0.80, 7.84]
Oliveira 2008 (polyB) JAC	18	69	21	81	27.5%	1.01 [0.49, 2.10]
Paul 2011 JAC	26	168	17	244	22.6%	2.44 [1.28, 4.67]
Reina 2005 Int CM	0	55	0	130		Not estimable
Rigatto 2013 Infection	9	45	4	22	8.3%	1.13 [0.30, 4.16]
Rios 2007 Eur Resp	0	31	0	20		Not estimable
Subtotal (95% CI)		**485**		**698**	**96.4%**	**1.45 [1.02, 2.07]**
Total events	80		78			
Heterogeneity: Chi² = 7.74, df = 6 (P = 0.26); I² = 23%						
Test for overall effect: Z = 2.06 (P = 0.04)						
1.4.2 Matched						
Betrosian 2008 J Infect	5	15	2	13	2.7%	2.75 [0.43, 17.49]
Durakovic 2011 Intern Med	3	26	0	26	0.8%	7.89 [0.39, 160.91]
Kallel 2007 Int CM	0	60	0	60		Not estimable
Subtotal (95% CI)		**101**		**99**	**3.6%**	**3.95 [0.84, 18.48]**
Total events	8		2			
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**586**		**797**	**100.0%**	**1.54 [1.09, 2.18]**
Total events	88		80			
Heterogeneity: Chi² = 9.33, df = 8 (P = 0.31); I² = 14%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: Chi² = 1.53, df = 1 (P = 0.22), I² = 34.8%						



Overall toxicity: 15 % (12 studies)

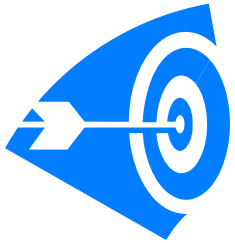
Ongoing clinical trials

- Efficacy: vs carbapenems
- Combinations: with carbapenems
  rifampin
  fosfomycin
- Inhalation: IV vs IV+ inhalation for VAP/HAP
- Prevention of toxicity by ascorbic acid

If colistin had to be submitted for registration today …

A few problems…

- Pharmaceutical aspects:
  - uncertainties about the composition and strengths of the medicinal product offerings
- Microbiology:
  - High risk of failures by loss of bacterial susceptibility (regrowth and development of resistance)
- Preclinical safety:
  - Uncertain and incomplete animal safety testing
- Preclinical assessment of efficacy:
  - Incomplete and often unconvincing pharmacokinetics/pharmacodynamic parameters
- Clinical safety:
  - Uncertainties about the true human nephrotoxic potential and definite risk of emergence of resistance
- Clinical effectiveness:
  - incomplete clinical development



if colistin is you last option …

- A repeated dosage of 3 Mio IU = 240 mg CMS = 90 mg CBA) every 8h is probably the best option …
- A loading dose (6-9 Mio IU = 480-720 mg CMS = 160-240 mg CBA) is essential
- Never use it in monotherapy … (meropenem, doripenem, … even if non-susceptible)
- Test for susceptibility on a repeated fashion …
- Monitor the renal function and adjust by decreasing the dose and prolonging the interval …
- Remember that this is a last resource drug which should be put back on the shelf as soon as possible… and should not have left in the first place !

Disclosures and slides availability

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- the Belgian Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Research grant from Bophar Pharmaceuticals B.V., importer of colistimethate in Belgium (from Forest Pharmaceuticals UK])

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