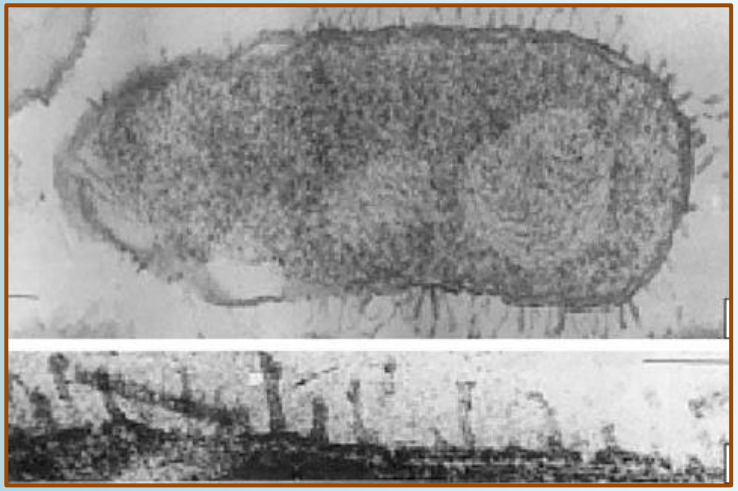
Use of Colistin



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NVMM/VIZ/BVIKM/SBIMC Fall Meeting
17/11/2017

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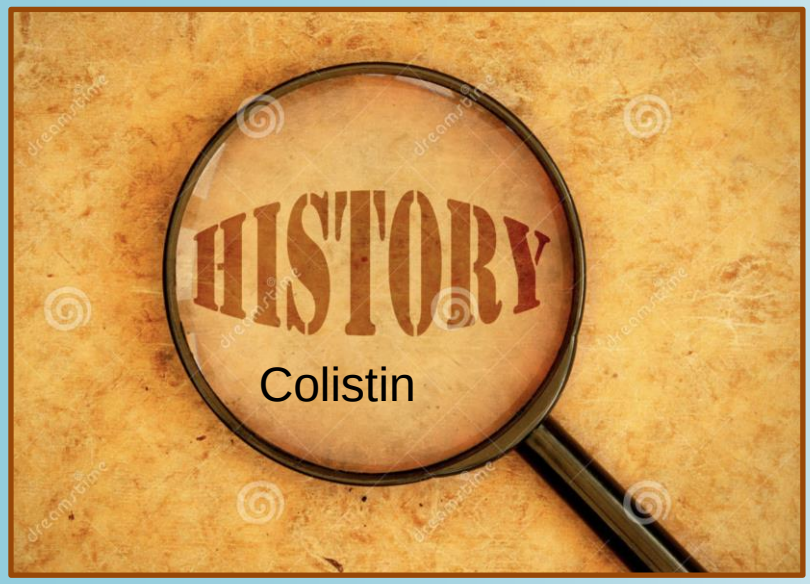
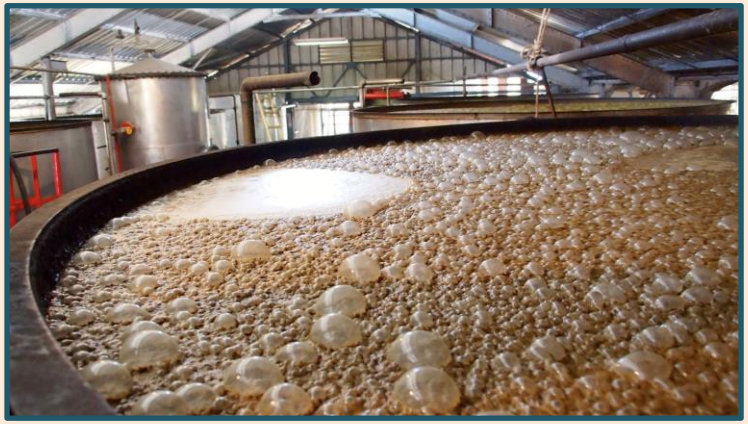
Disclosure

(potential) conflict of interest	None
For this meeting possibly relevant relationships with companies	Company names: None
• Sponsoring or research funding • Fee or other (financial) compensation • Shareholder • Other relationship, namely …	•None •None •None •None

Introduction



- Discovered in 1949
- Obtained from the *Bacillus polymyxa* subspecies *colistinus* by fermentation



- Was abandoned in the 1970s because:
  - Toxic++++++
  - Development of more effective antimicrobial agents

Introduction

- And in the 1990s,……

03/10/2008 11:10 - Lavage broncho-alvéolaire	
Examen direct	
Type	Prélèvement de bonne qualité (< 1% de cellules épithéliales)
Polynucléaires	(3+)
Hématies	Rares
Macrophages	(3+)
Lymphocytes	Rares
Cel. bronchiques	Rares
Flore	Présence de
Bacilles gram négatif	(3+)
Culture aérobie	
>100.000 CFU/ml	
Culture aérobie	1. Pseudomonas aeruginosa . Présence de carbapénémase
	1
Pipéra. +Tazobactam	R
Ceftazidime	R
Céfépime	R
Aztreonam	R
Imipénem	R
Méropénem	R
Gentamicine	R
Amikacine	I
Tobramycine	R
Ciprofloxacine	R
Colistine	S

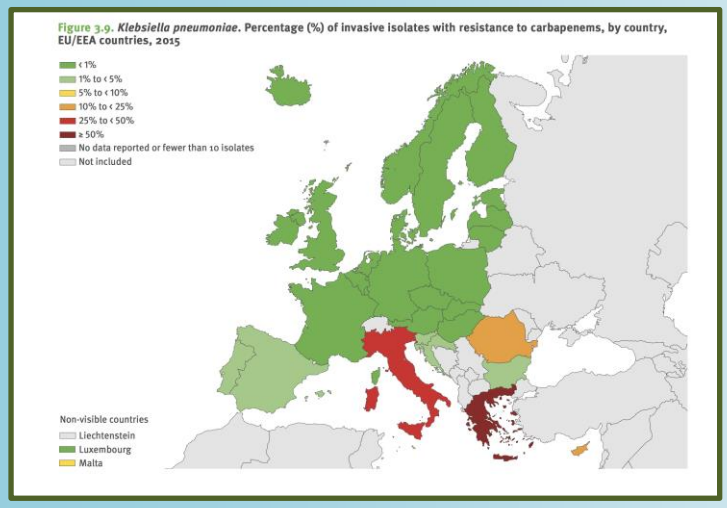
β-lactams

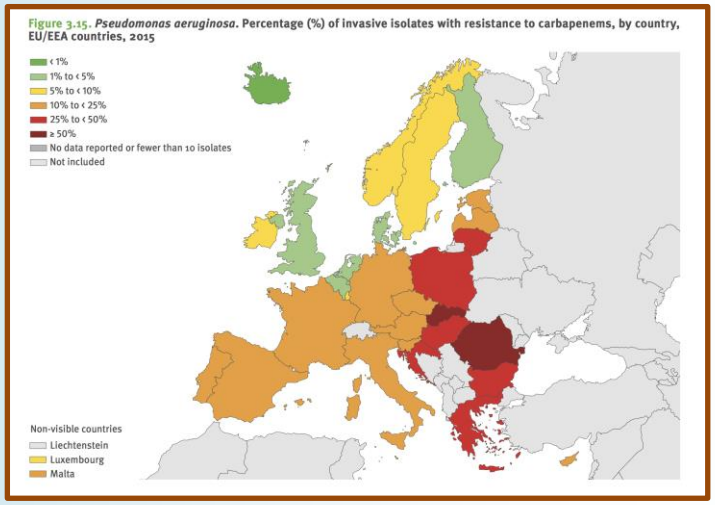
Aminoglycosides

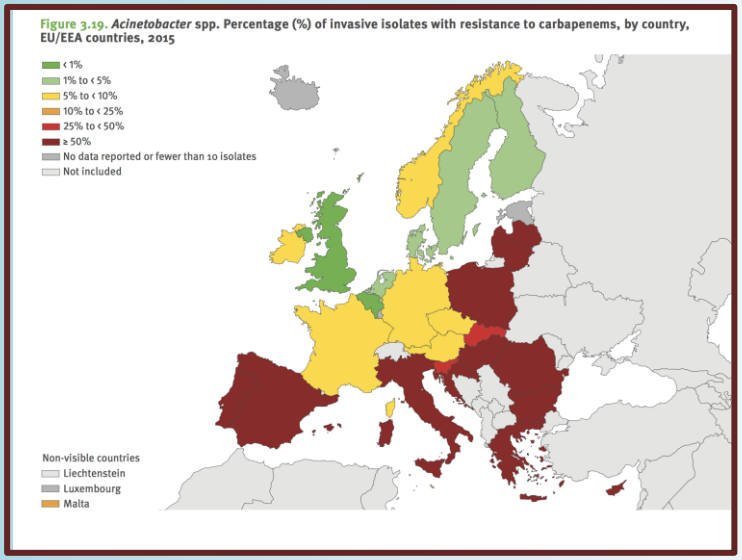
Quinolones

Colistin was once again used!

Bacteria resistant to carbapenems in Europe







Indication for use of Colistin!

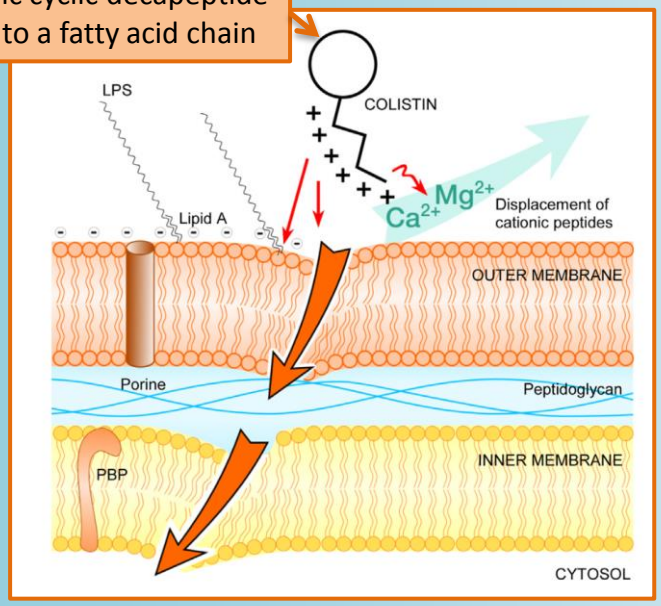
Antimicrobial Surveillance in Europe 2015
accessed at https://ecdc.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015

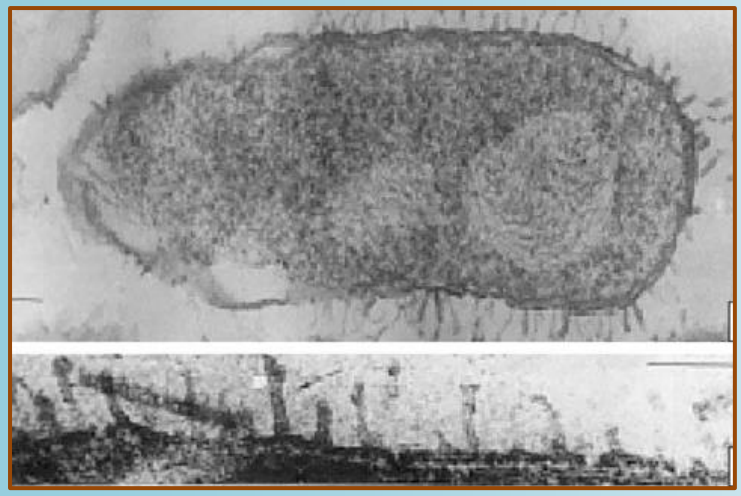
Plan

- Structure and Mechanism of action
- Spectrum of activity
- PK of Colistin
- Adverse events: nephrotoxicity
- Optimized treatment regimens
  - Loading dose
  - Intrathecal therapy
  - Aerosol therapy
  - Therapeutic drug monitoring
- Conclusions
  - Resistance to Colistin and clinical implications

Structure and mechanism of action

Cationic cyclic decapeptide linked to a fatty acid chain





Displaces Ca^{2+} and Mg^{2+} from outer cell of Gram-negative bacteria

↓

Binds with anionic LPS molecules

↓

Δ permeability of cell envelope

↓

Cell leakage→ CELL DEATH!

Acts as a detergent by disrupting cell membranes!

1. Martis et al. J Infection. 2014; 69:1-12.
2. Newton et al. Bacteriol Rev. 1956; 20: 14-27

Spectrum of activity

Only Gram-negative aerobic bacteria (GNB)!

- **Active against:**
  - *E. coli*
  - *Pseudomonas sp*
  - *Klebsiella sp*
  - *Enterobacter sp*
  - *Salmonella sp*
  - *Shigella sp*

- Not active against (due to intrinsic R):
  - *Proteus sp*
  - *Serratia sp*
  - *Burkholderia sp*
  - *Providencia sp*
  - *Morganella morganii*
  - *Edwardisella sp*

Current susceptibility breakpoints

MIC testing: ISO-20776 standard broth microdilution (BMD) method

Species	EUCAST	
	S ≤	R >
Enterobacteriaceae	2	2
Acinetobacter	2	2
Pseudomonas	2	2

Target $Colistin_{SS}$ concentrations: ≥ 2 mg/L

1. European Committee on Antimicrobial susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 7.1, 2017.
2. EUCAST. 2016. Recommendations for MIC determination of Colistin as recommended by the joint CLSI-EUCAST Polymyxin Breakpoints W group.

PK/PD properties

Colistimethate (CMS)

- Must be hydrolyzed to be active
- Conversion is spontaneous in aqueus solutions → complicates PK studies
- Half-life: short (~ 2.3h)
- Less toxic than colistin

Colistin

- Rapid bactericidal effect
- Protein binding: ~50%
- PK/PD index for efficacy: fAUC/MIC
  - Ratio of 12 =2 log bacterial kill for C_{SS} of 1 mg/L
- VD: small (~ 0.5 ± 0.06 L/kg)
- Half-life: long (~ 14.4 h)
- Elimination rate depends on renal function
- Considerable inter and intra-individual variability
  - Loading dose 9 MIU: 0.95 to 5.1 mg/L
  - Steady state: 0.68 to 8.72 mg/L

1. Mohamed et al. Antimicrob Agents chemother. 2012; 56: 4241-9
2. Couet W et al. CMI. 2011; 18: 30-39.

PK of Colistin

CMS= product of fermentation → each batch of the drug contains a mixture of CMS derivatives

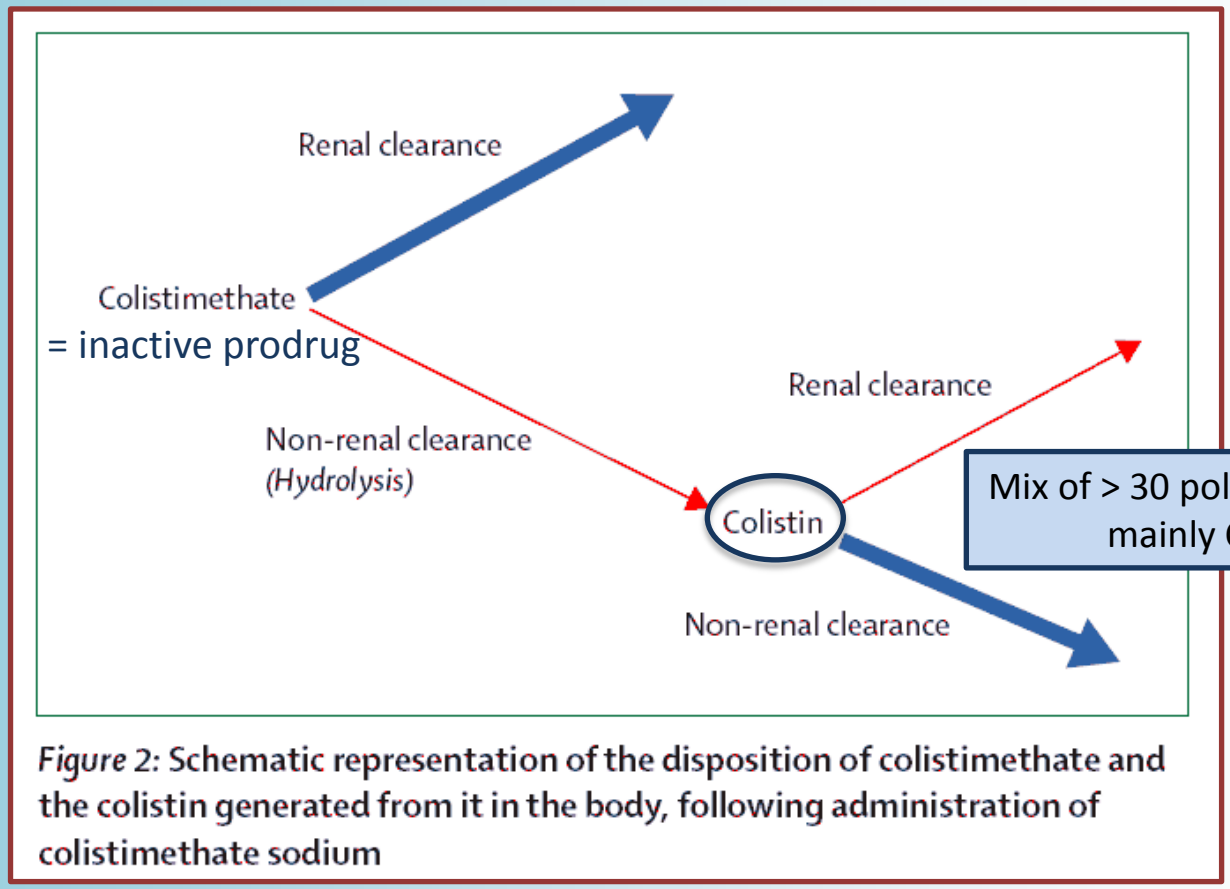


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Mix of > 30 polymyxin compounds, mainly Colistin A + B

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

PK of Colistin: Impact of renal function on elimination

If renal clearance is augmented

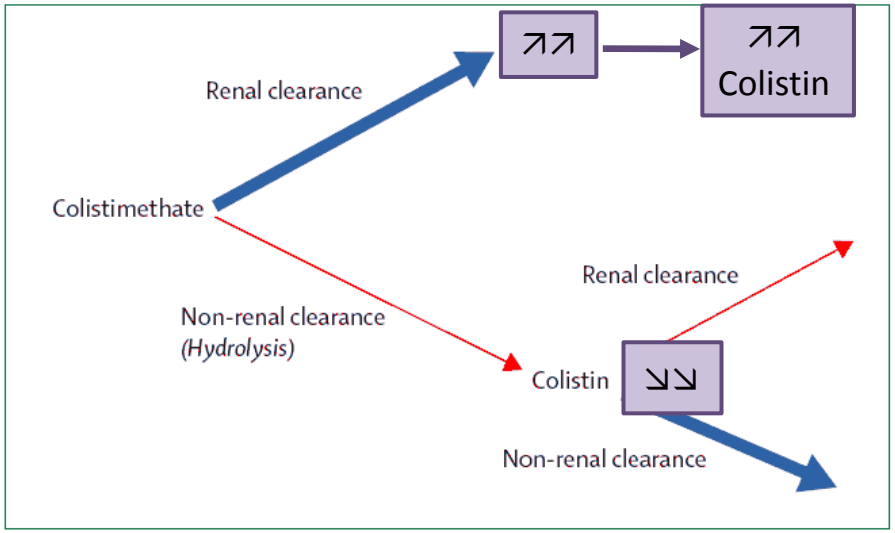


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

If renal function is impaired

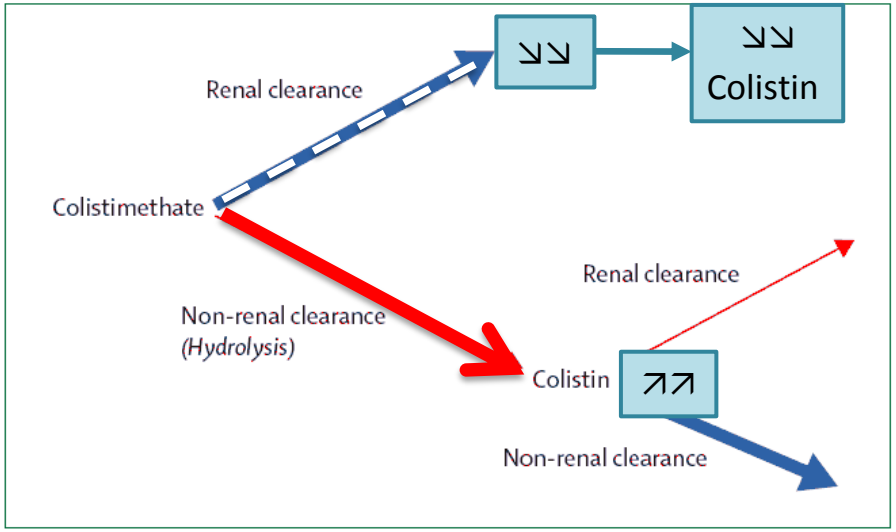


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

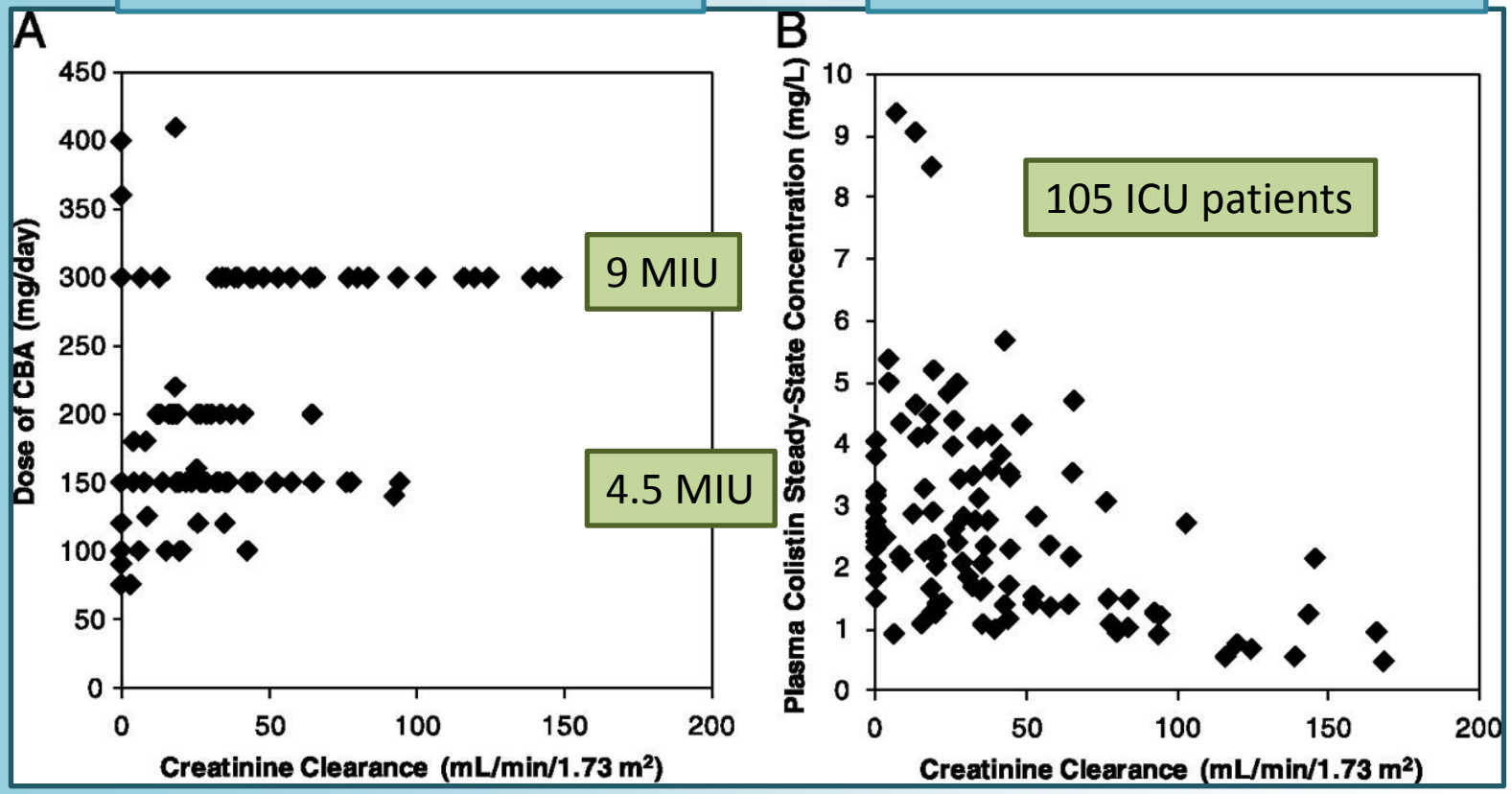
↘ dose of CMS!

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

Colistin dose needs to be adjusted to renal function

Physicians selected daiy dose of colistin base activity (CBS)

Resultant average steady-state plasma colistin concentrations in function of CrCL

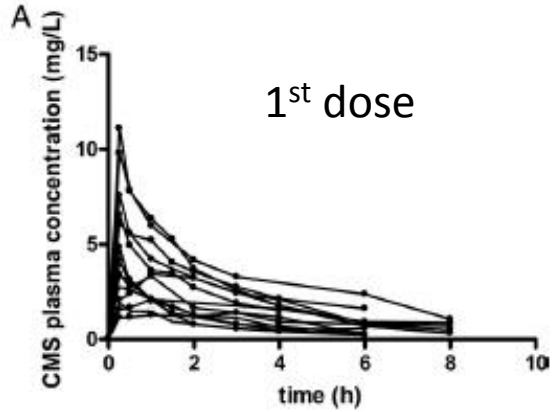


Garonzik et al. Antimicrob Agents Chemother. 2011; 55:3284-94.

PK of CMS: need for a loading dose?

CMS

1st dose



Colistin 3 MIU x 3:day IV

Colistin

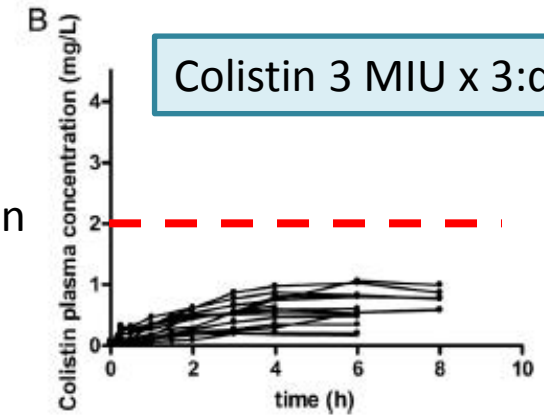
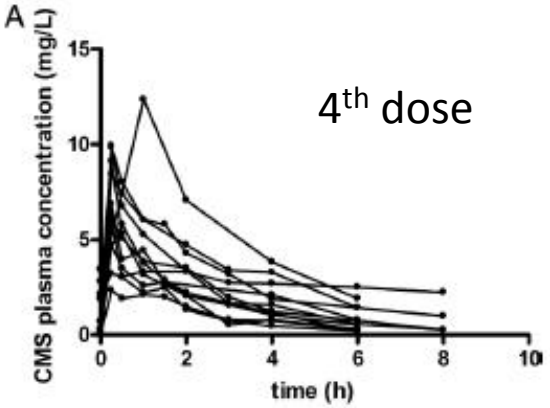


FIG. 1. Observed individual concentrations of CMS (A) and colistin (B) in plasma after the administration of the first dose of CMS. Data for patients 14, 15, 17, and 18 (Table 1) were not available after the first dose.

CMS

4th dose



Colistin

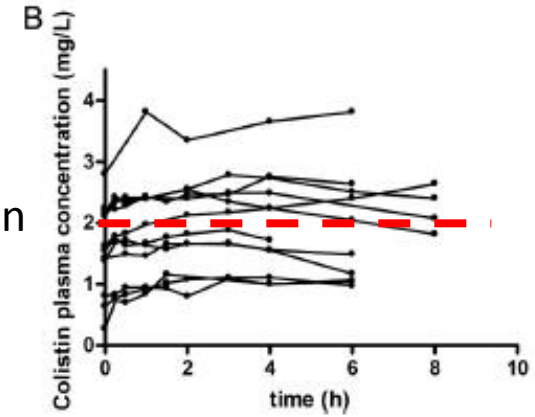


FIG. 2. Observed individual concentrations of CMS (A) and colistin (B) in plasma after the administration of the fourth dose of CMS. Data for patients 4, 14, 15, 16, 17, and 18 (Table 1) were not available after the fourth dose.

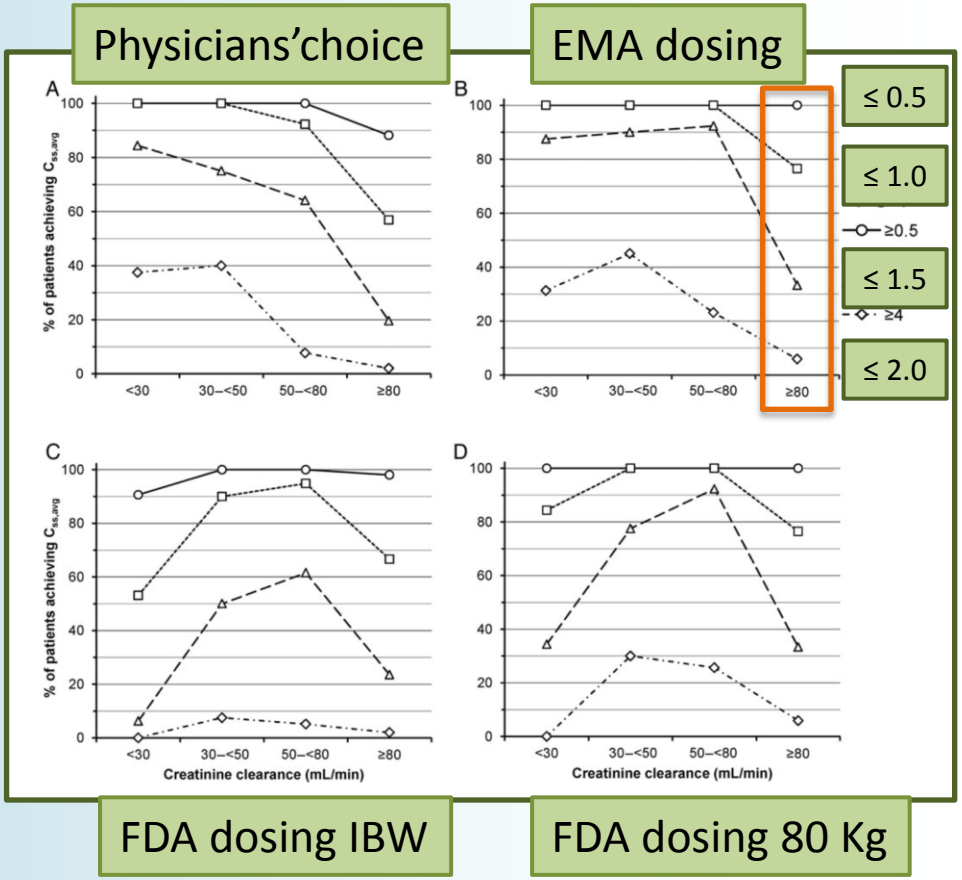
Plachouras D et al. Antimicrob Agents Chemother. 2009; 53(8): 3430-6.

Dosage regimens

- 1 MIU CMS = 30 mg of colistin base activity (CBA)

Table 2. European Medicines Agency– and US Food and Drug Administration–Approved Daily Maintenance Dose Suggestions Evaluated

EMA (MIU)	Creatinine Clearance (mL/min)	European Medicines Agency Daily Dose Evaluated[a]	US Food and Drug Administration Daily Doses Evaluated[b]: Patient Body Weight Approach	US Food and Drug Administration Daily Doses Evaluated[b]: Uniform Weight of 80 kg Approach
9 MIU	≥80	360 mg CBA[c]	5 mg/kg CBA	360 mg CBA
9 MIU	50 to <80	300 mg CBA	3.8 mg/kg CBA	304 mg CBA
7.5 MIU	30 to <50	250 mg CBA	2.5 mg/kg CBA	200 mg CBA
5.5 MIU	10 to <30	183 mg CBA	1 mg/kg CBA	80 mg CBA
3.5 MIU	<10	117 mg CBA	1 mg/kg CBA[e]	80 mg CBA[e]



Nation et al. CID: 2016; 62: 552-8.

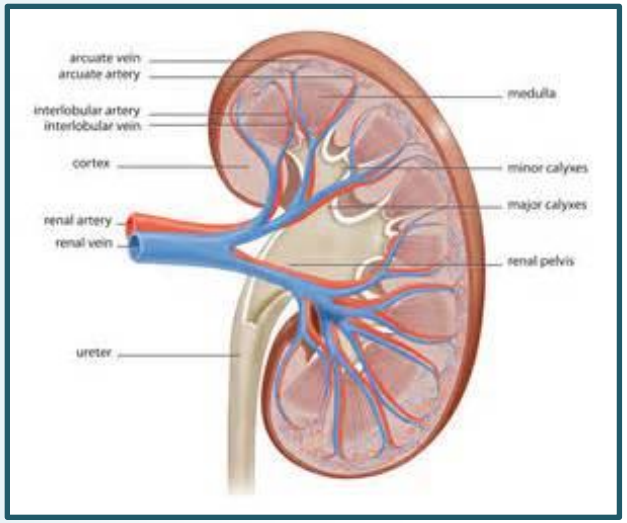
Adverse effects: Nephrotoxicity

- Mechanism:
  - accumulation of colistin in renal tubular cells
  - Δ morphology of mitochondria, loss of cytoplasmic membrane potential → apoptosis

- Rates: 6-55 %
  - Limited number of patients included in studies
  - Variability in severity of the underlying illness
  - Dose of Colistin administered
  - Definition of nephrotoxicity (AKIN, RIFLE,..)

- Mild-to-moderate

- Reversible in most cases



1. Spapen H et al. Ann Intensive Care. 2011; 1:14.
2. Dickstein et al. BMJ Open. 2016; 6: e009956.

Risk factors for nephrotoxicity

- Other concommitant nephrotoxic agents
- Age
- Weight and/or BMI
- Co-morbidities: Charlson Index
- Severity of baseline illness
- Dose of Colistin
- Duration of treatment
- Colistin $C_{SS,avg} > 2.5$ mg/L
- Minimum colistin plasma concentration ≥ 2.2 mg/L (odds ratio= 4.6 on day 7)

1. Dalfino L et al. Clin Infect Dis. 2015; 61: 1771-7.
2. Sorli L et al. BMC Infect Dis. 201313: 380.
3. Forrest A et al. 54th ICAAC 2014; Washington DC.
4. Pogue JM et al. Intl J Antimicrob Agents. 2016: 622-26.

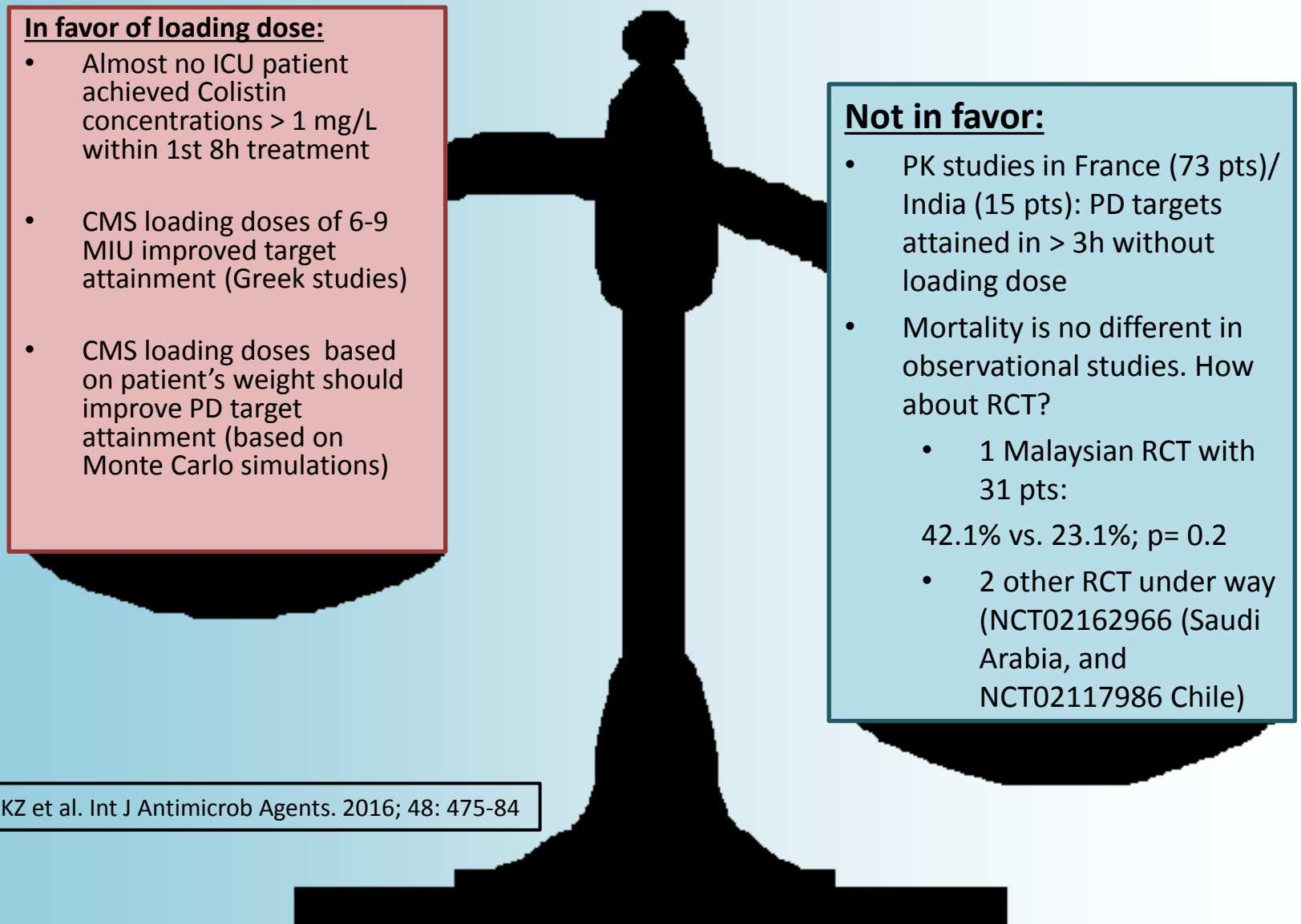
Optimized administration of Colistin

When treating infections due to XDR/MDR GNB, using Colistin:

- Mortality rates: 8-62%
- Treatment failure: 15-75%

1. Vardakas KZ et al. Int J Antimicrob Agents. 2017; 49: 233-38.
2. Vardakas KZ et al. Int J Antimicrob Agents. 2016; 48: 475-84.

Loading dose of Colistin



In favor of loading dose:

- Almost no ICU patient achieved Colistin concentrations > 1 mg/L within 1st 8h treatment
- CMS loading doses of 6-9 MIU improved target attainment (Greek studies)
- CMS loading doses based on patient's weight should improve PD target attainment (based on Monte Carlo simulations)

Not in favor:

- PK studies in France (73 pts)/ India (15 pts): PD targets attained in > 3h without loading dose
- Mortality is no different in observational studies. How about RCT?
  - 1 Malaysian RCT with 31 pts:

  42.1% vs. 23.1%; p= 0.2
  - 2 other RCT under way (NCT02162966 (Saudi Arabia, and NCT02117986 Chile)

Vardakas KZ et al. Int J Antimicrob Agents. 2016; 48: 475-84

Loading dose of Colistin

- What dose?
  - EMA « standard dose »:

    9 MIU CMS

  - Adjustable to body weight?
    - But max dose of 9 MIU → inadequate for obese patients!

Patients with actual body weight of 60 kg: loading dose of 9 MIU!!

  - FDA: no loading dose

Vardakas KZ et al. Int J Antimicrob Agents. 2016; 48: 475-84

Loading dose of Colistin

- When to administer next dose?
  - EMA does not specify when maintenance doses should be started[1]
  - 24h after loading dose, for safety concerns[2]?

    But, colistin concentrations after the first 8-12h may be insufficient to facilitate bacterial killing!
  - At next dosing interval (i.e. 8h or 12h later)?

    Bacterial killing is increased in a PK/PD model[3]

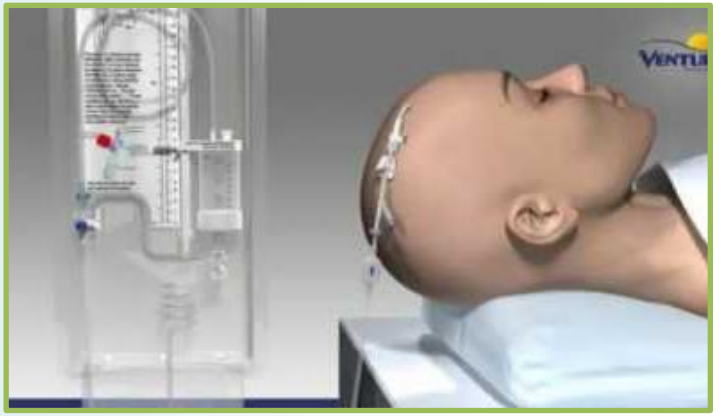
1. EMA completes review of polymyxin-based medicines. 2014
2. Garonzik et al. 2011. Antimicrob Agents Chemother; 55: 3284-94.
3. Mohamed AF et al. J Antimicrob Chemother. 2014; 69: 1350-61.

Intrathecal therapy: clinical context

- Hospital related ventriculitis/meningitis due to GNB:
  - Head trauma
  - Post neurosurgery
  - External ventricular deviation (EVD)

PK of Colistin in CSF

- Penetration of CMS and colistin into CSF is poor:
  - ratio CSF/serum concentration of colistin: 0.051-0.057

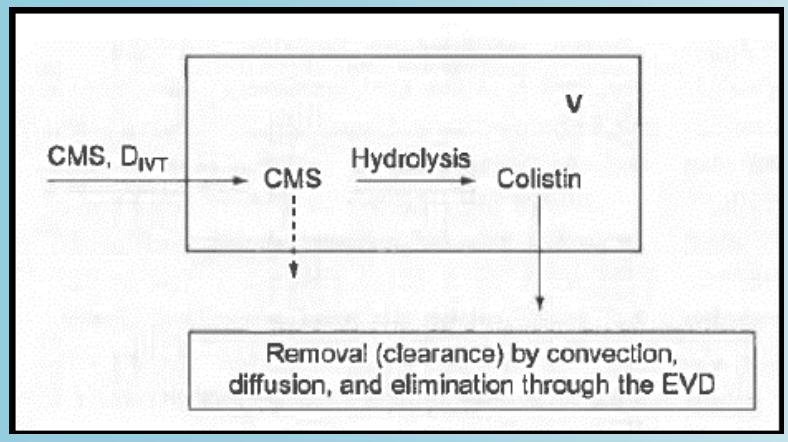


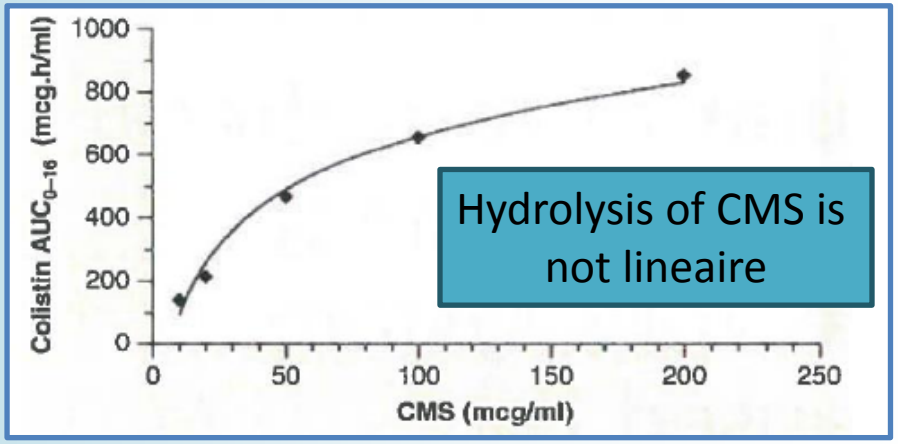
Systemic Colistin results in inadequate CSF concentrations to treat infections due to MDR GNB!

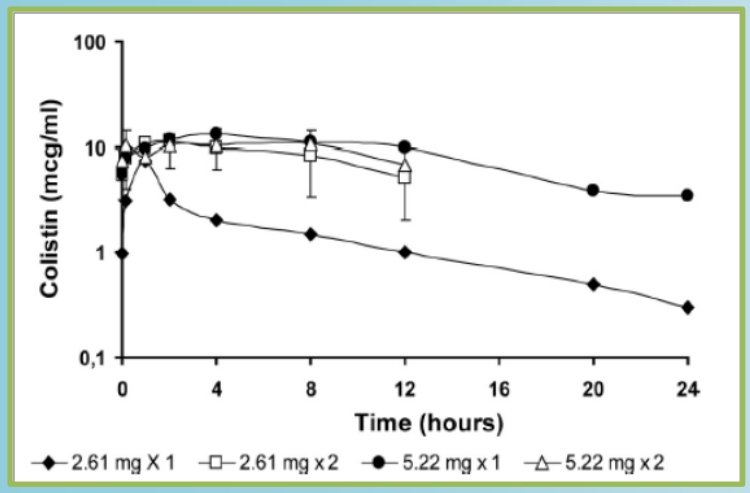
- Intrathecal colistin?

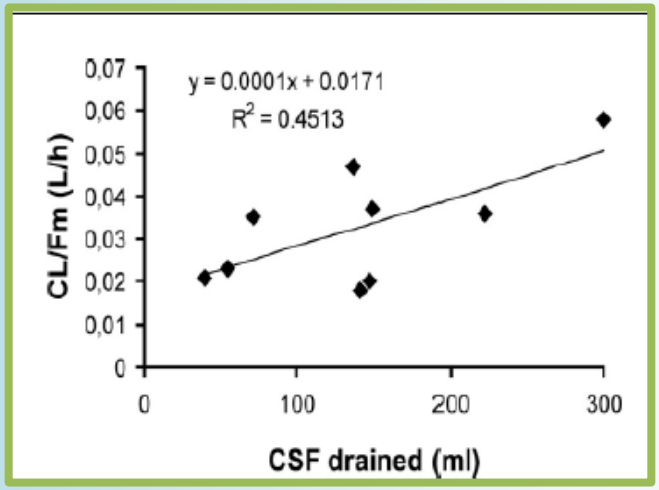
1. Markantonis et al. *Antimicrob Agents Chemother*. 2009: 53(11): 4907-4910
2. Antachopoulos C et al. *Antimicrob Agents Chemother.* 2010: 54(9): 3985-3987.
3. Imberti R et al. *Antimicrob Agents Chemother*. 2012. 56: 4416-21.

PK of Intrathecal Colistin









Significant correlation between drained CSF and CL of Colistin

Colistin CL: 10%/H

1. Imberti R et al. *Antimicrob Agents Chemother.* 2012. 56: 4416-21.
2. Imberti R et al. *Expert Rev Anti Infect Ther*. 2014. 12(4): 471-8.

Clinical data concerning the intrathecal/ventricular administration of colistin

Dose?

- > 60,000 IU/day → CSF concentrations of colistin ≥ 2 mg/L
- 125,000 IU/day + IV(3 MIU TID)→ CSF concentration < 2 mg/L

Pathogens	Number of infections treated	Median dose of Colistin IT/ventricular	Clinical success
Acinetobacter spp.	107	125.000 IU	90%
Pseudomonas spp.	12	125.000 IU	83%
Klebsiella spp.	15	62.500- 250.000 IU	79%

1. Karaiskos I et al. Int J Antimicrob Agents. 2013. 41: 499-508.
2. Bargiacchi O et al. Infection. 2014. 42: 801-9.
3. Remes F et al. J Neurosurg. 2014. 119: 1596-602.
4. Karagoz G et al. Int J Antimicrob Agents. 2014. 43:93-94.
5. Ziaka M et al. Antimicrob Agents chemother. 2013. 57: 1938-40.
6. Nevrekar S et al. Ann Pharmac. 2014. 48: 274-8.
7. Fotakopoulos G et al. Acta Neurochir. 2016; 158: 603-10.
8. De Bonis P et al. European J Neuro. 2015; 1: 68-75.

Clinical data concerning intrathecal/ventricular administration of colistin

- Colistin intrathecal/intraventricular ± IV vs. Colistin IV:
  - Better survival
  - Shorter hospital stays
  - Higher CSF concentrations of Colistin

- Adverse effects: rare
  - Chemical ventriculitis/ meningitis
  - Seizures
  - Cauda equina syndrome

EMA Recommendations: 125.000 IU/ day in IT (dilution in 3-4 mL NaCl) + 1h clamping of the EVD[4]

1. Fotakopoulos G et al. Acta Neurochir. 2016; 158; 603-10.
2. De Bonis et al. Eur J Neurol. 2015; 31: 68-75.
3. Karaiskos I et al. Int J Antimicrob Agents. 2013. 41: 499-508.
4. EMA. 2014

Aerosols of Colistin

- Rationale:
  - Colistin penetrates poorly into pulmonary parenchyma
  - Aerosolized Colistin:
    - Achieves high drug concentrations in the respiratory tract
    - Avoids systemic effects
    - Has successfully prevented pulmonary exacerbation and lung deterioration in patients with CF colonized with *Ps. aeruginosa*

Ratjen. et al. *J Antimicrob Chemother*. 2006. 57: 306-11.

Aerosols of Colistin

- Parameters that may affect effectiveness of inhaled Colistin:
  - Generators/ delivery circuit of colistin aerosol
    - droplet size
    - Extent of particle disposition
    - Residual volume
  - Patient's clinical status
    - Level of consciousness
    - Mechanically ventilated
    - Not mechanically ventilated: Inhalation techniques

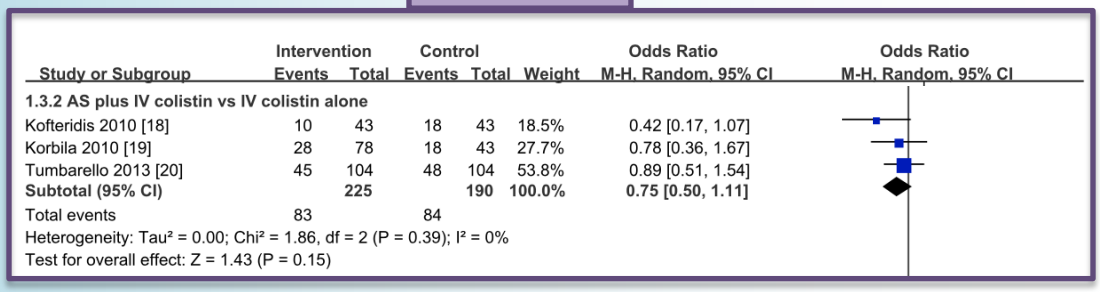
Important variations in delivered dose of AB in function of the nebulizor used!!!!

Aerosols of Colistin: clinical data?

Table 2
Nephrotoxicity and outcomes in the IV and nebulizer groups.

Variable	IV group N = 44	Nebulizer group N = 51	p-Value
Nephrotoxicity	26/43 (60.5%)	8/51 (15.7%)	<0.0001[a]
Risk	10/43 (22.7%)	4/51 (7.8%)	
Injury	8/43 (18.2%)	3/51 (5.9%)	
Failure	8/43 (18.2%)	1/51 (2.0%)	
None	17/43 (39.5%)	43/51 (84.3%)	
Microbiological outcomes			0.921
Eradication	26/40 (65.0%)	33/50 (66.0%)	
Persistence	8/40 (20.0%)	1/50 (2.0%)	
Recurrence	6/40 (15.0%)	16/50 (32.0%)	
Clinical outcomes			0.719
Cure	4 (9.1%)	5 (9.8%)	
Improvement	31 (70.5%)	34 (66.7%)	
Failure	9 (20.5%)	12 (23.5%)	
Infectious mortality	6 (13.6%)	10 (19.6%)	0.438

Mortality



Aerosol Colistin Monotherapy: systematic review and meta-analysis:

- Mortality: 33.8% (95% CI: 24.6%-43.6%
- Clinical success: 65.9% (53.3-77.5%)
- Microbiologicla success: 71.3% (57.6-83.2%)

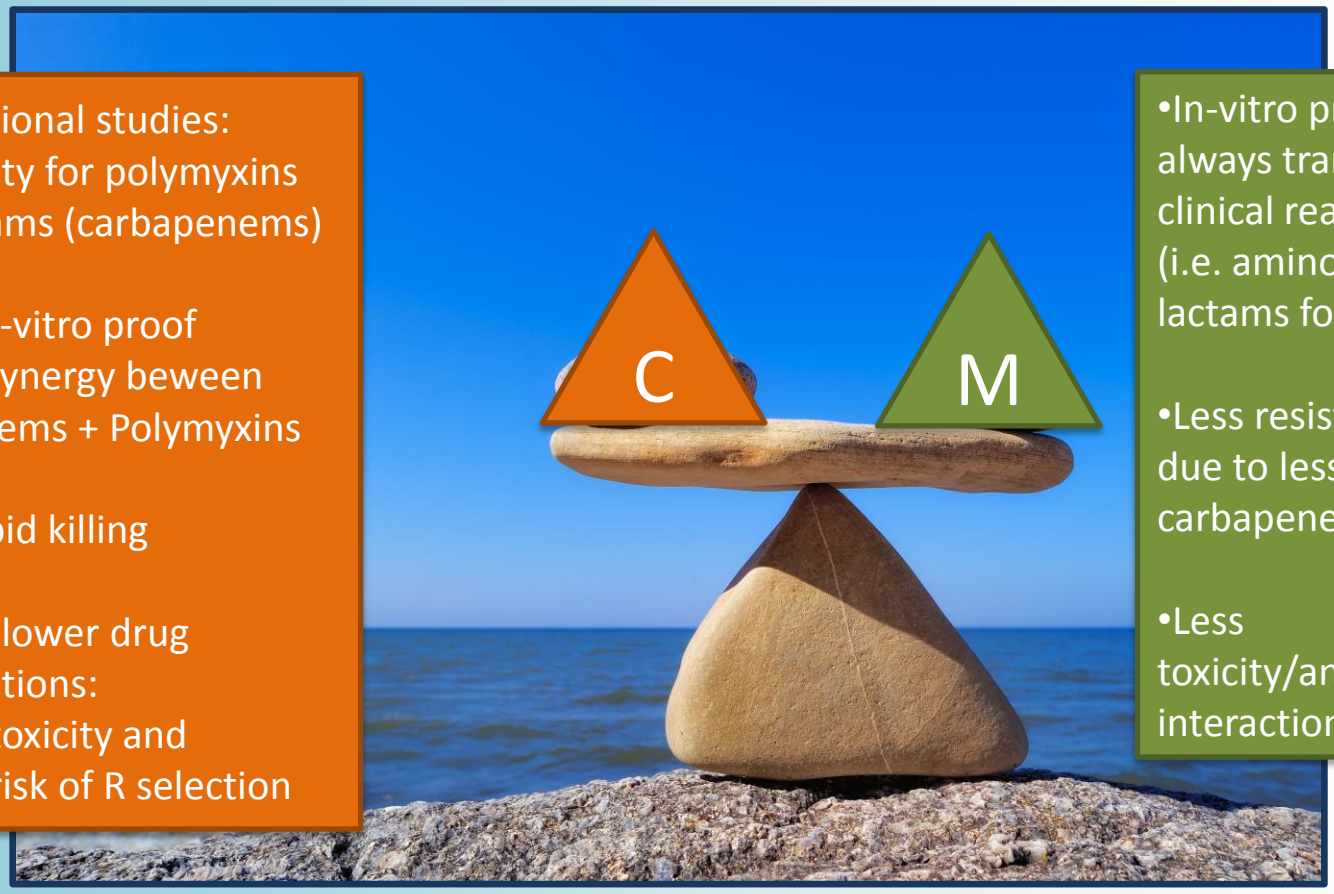
Great variations in the mean dose of aerosols of Colistin

→ optimal dose still to be established!

1. Jang JY et al. J Crit Care. 2017; 40: 251-56.
2. Gu WJ et al. Int J Antimicrob Agents. 2014; 44: 477-85.
3. Vardakas KZ et al. Int J Antimicrob Agents. 2017, http://dx.doi.org/doi: 10.1016/J.ijantimicag.2017.05.016.

Combination or Monotherapy?

- Observational studies: ↗ mortality for polymyxins vs. β-lactams (carbapenems)
- Strong in-vitro proof showing synergy beween Carbapenems + Polymyxins
- More rapid killing
- Killing at lower drug concentrations:
  - ↘ toxicity and
  - ↘ risk of R selection



- In-vitro proof does not always translate into clinical reality (i.e. aminoglycosides + β-lactams for sepsis
- Less resistance selection due to less widespread carbapenem usage
- Less toxicity/antagonistic interactions between AB

→ 2 RCT on going (AIDA/ NIH): Meropenem + Colistin vs. Colistin

1. Dickstein et al. BMJ Open. 2016; 6:e009956

Primary endpoint: to show superiority of Colistin–Meropenem to Colistin monotherapy in treatment of patients infected with CR GN

Secondary endpoint: to obtain improved Pop-PK models for Colistin

Multicentre, open-label, 1:1 superiority randomised conntrolled trial:

- Greece
- Israel
- Italy

Proven infections due to carbapenem non-susceptible and colistin susceptible GNB:

- HAP
- VAP
- Urosepsis
- Bloodstream (any source)

AIDA

360 patients

Colistin: 9 MUI loading dose, then 4.5 MIU x 2/d (10 days)

Colistin + Meropenem 2g x 3/d (10 days)

+ 2 TDM during study

<u>Endpoint (Day 14): treatment success</u>

1. Patient alive
2. TA systolique > 90 mmHg without vasopressor treatment
3. SOFA: stable or improved
4. If HAP/VAP: PaO2/Fi02 stable or improved
5. If bloodstream infection: fever, and negative blood cultures

NIH-funded RCT

- Blood stream infections and/or pneumonia due to XDR Gram-negative bacteria

- Multicentric, randomized, controlled, double blinded study:
  - USA
  - Thailand
  - Taiwan
  - Israel

Meropenem + Colistin 14 days

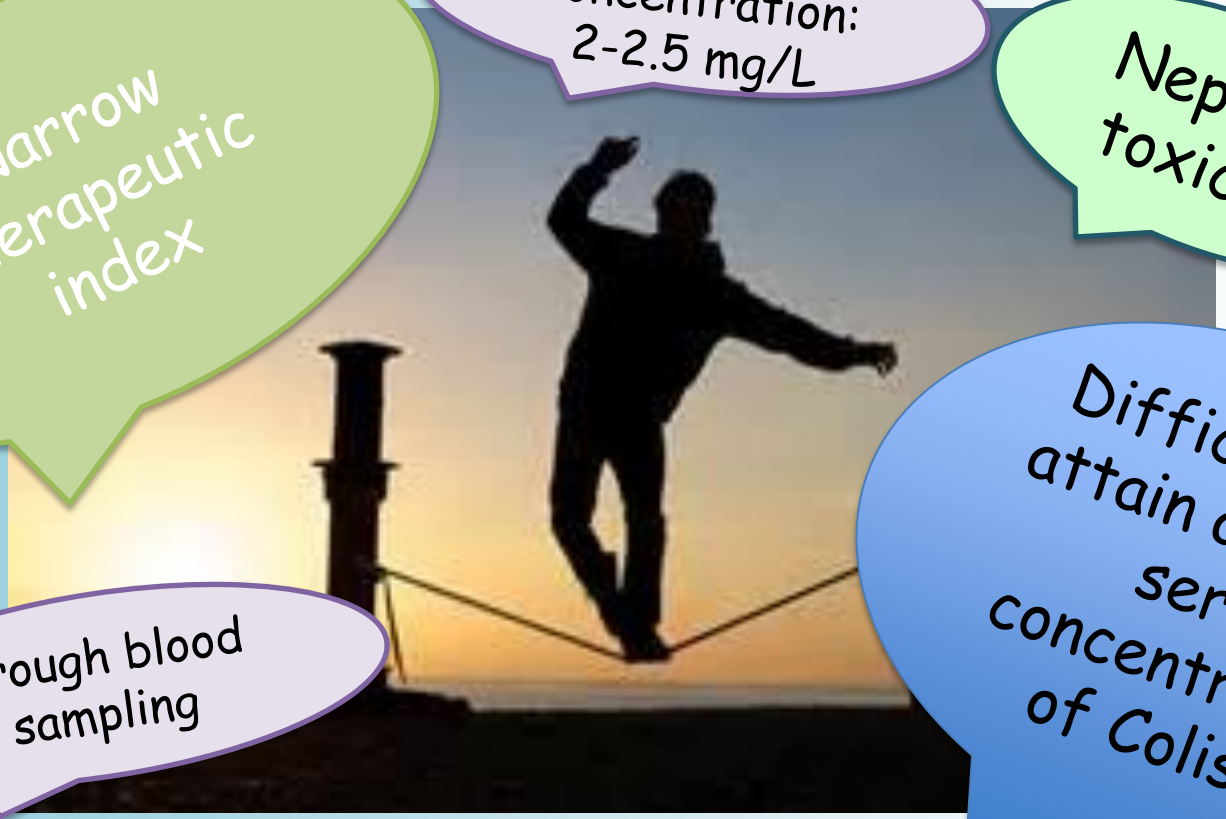
vs.

Colistin 14 days

- Number of patients to include: 444

- Endpoint: mortality

Therapeutic drug monitoring



Narrow therapeutic index

Target concentration: 2-2.5 mg/L

Nephro-toxicity

Difficulties to attain adequate serum concentrations of Colistin

Trough blood sampling

Couet W. et al. *Clin Microbiol Infect*. 2012. 18(1): 30-9.

Conclusions

We begin to see the light at the end of the tunnel!

- We know a lot more today on Polymyxin E than when we began to revive this old AB in the ‘90s
- However, administering an optimal dosage regimen remains difficult
  - < very narrow therapeutic index of colistin!
- Current clinical data has many limitations!

Conclusions

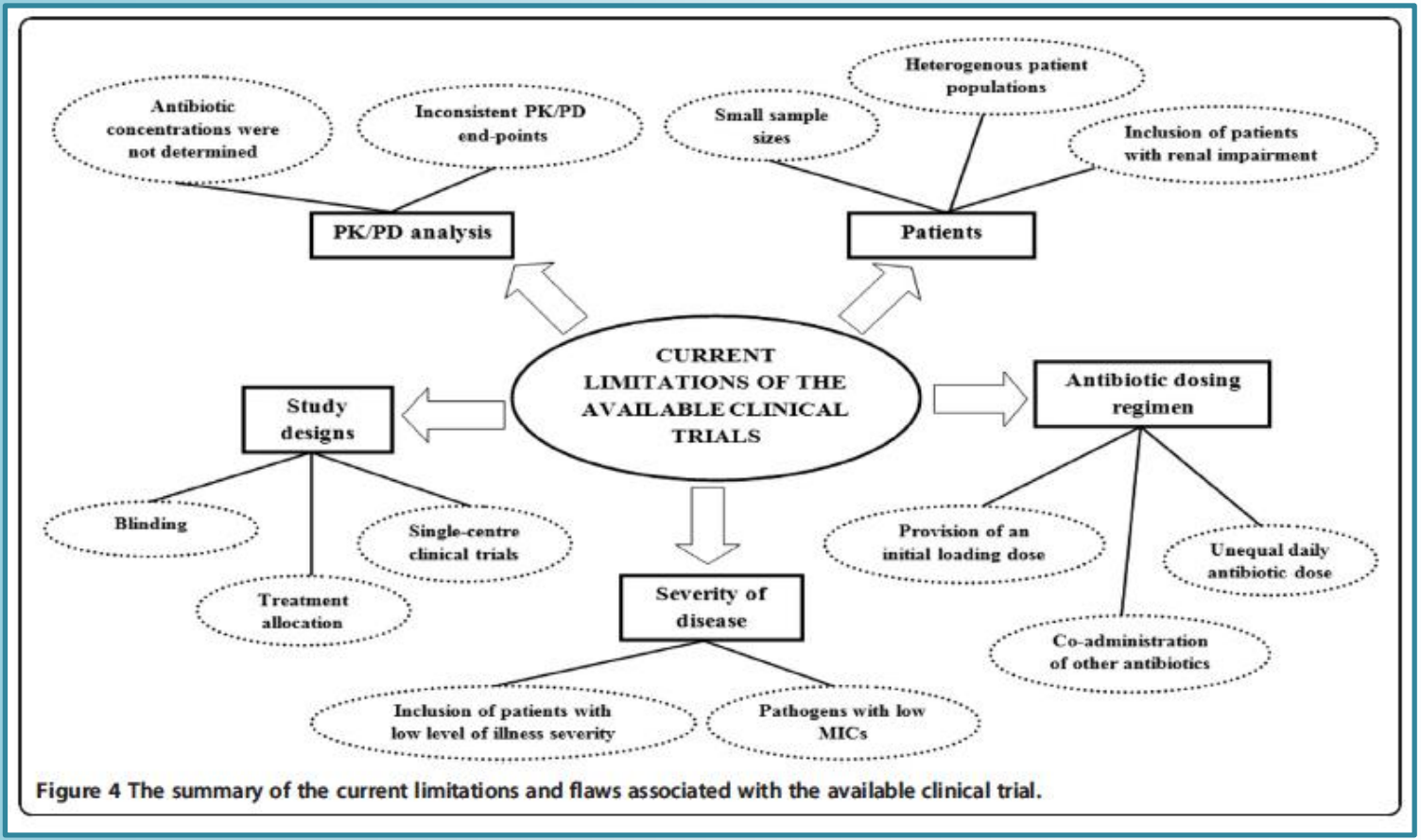


Figure 4 The summary of the current limitations and flaws associated with the available clinical trial.

But, RCT are ongoing……maybe we will have answers to some of our questions…… unless we have no more use of Colistin!!!!

Abdul-aziz et al. Annals of Intensive Care. 2012; 2:37

Colistin resistance

- Mechanisms for colistin resistance: **chromosomal mutations or adaptive mechanisms**
  - modification of genes involved in lipopolysaccharide biosynthesis →changes in the outer membrane of the bacteria → reduced affinity for polymyxins.
  - Presence of an efflux pump

- These resistance genes: not transmissible between bacteria → not so widely disseminated

- Risk factors for Colistin resistance [1-4]
  - Neutropenia
  - Lengthy hospitalisation
  - Previous treatment with colistin

1. Matthaiou et al. Crit Care Med. 2008. 306: 807-811.
2. Papadimitriou-Olivergis M et al. Infection. 2014. 42: 883-890.
3. Kontopidiou F et al. Clin Microbiol Infect. 2011. 17: E9-E11.
4. Giacobbe DR et al. Clin Microb Infect. 2015

Colistin R strains in Europe

Journal of Antimicrobial Chemotherapy (2007) **59**, 786–790
doi:10.1093/jac/dkl562
Advance Access publication 16 February 2007

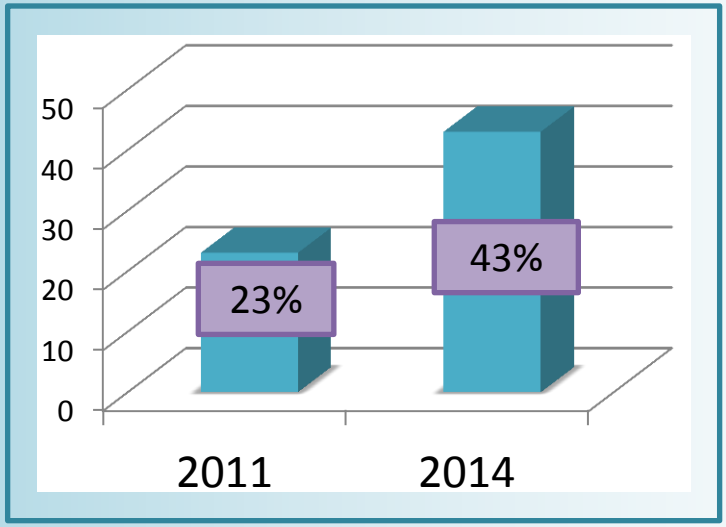
JAC

Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multiclonal cluster

Anastasia Antoniadou[1]*, Flora Kontopidou[1], Garifalia Poulakou[1], Evangelos Koratzanis[1], Irene Galani[1], Evangelos Papadomichelakis[2], Petros Kopterides[2], Maria Souli[1], Apostolos Armaganidis[2] and Helen Giamarellou[1]

[1]*Fourth Department of Internal Medicine, Athens University Medical School, University General Hospital 'ATTIKON', Athens, Greece;* [2]*Second Department of Intensive Care, Athens University Medical School, University General Hospital 'ATTIKON', Athens, Greece*

Currently, 25% of *Kl. pneumoniae* KPC are Colistin R!



Kl pneumoniae KPC R to Colisitn

1. Maltezou et al. J Global Antimicrob Res.2014.2:11-16.
2. Monaco and al. Euro Surveill.2014: 19(42)

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

- The **plasmid** bearing the colistin resistance mechanism was readily passed between *Escherichia coli* strains, including strains with known epidemic potential, such as ST131.

Illustration of *E. coli* bacteria. *E. coli* bacteria carrying the *mcr*-1 gene was found in a urine sample from a patient in Pennsylvania in May 2016.

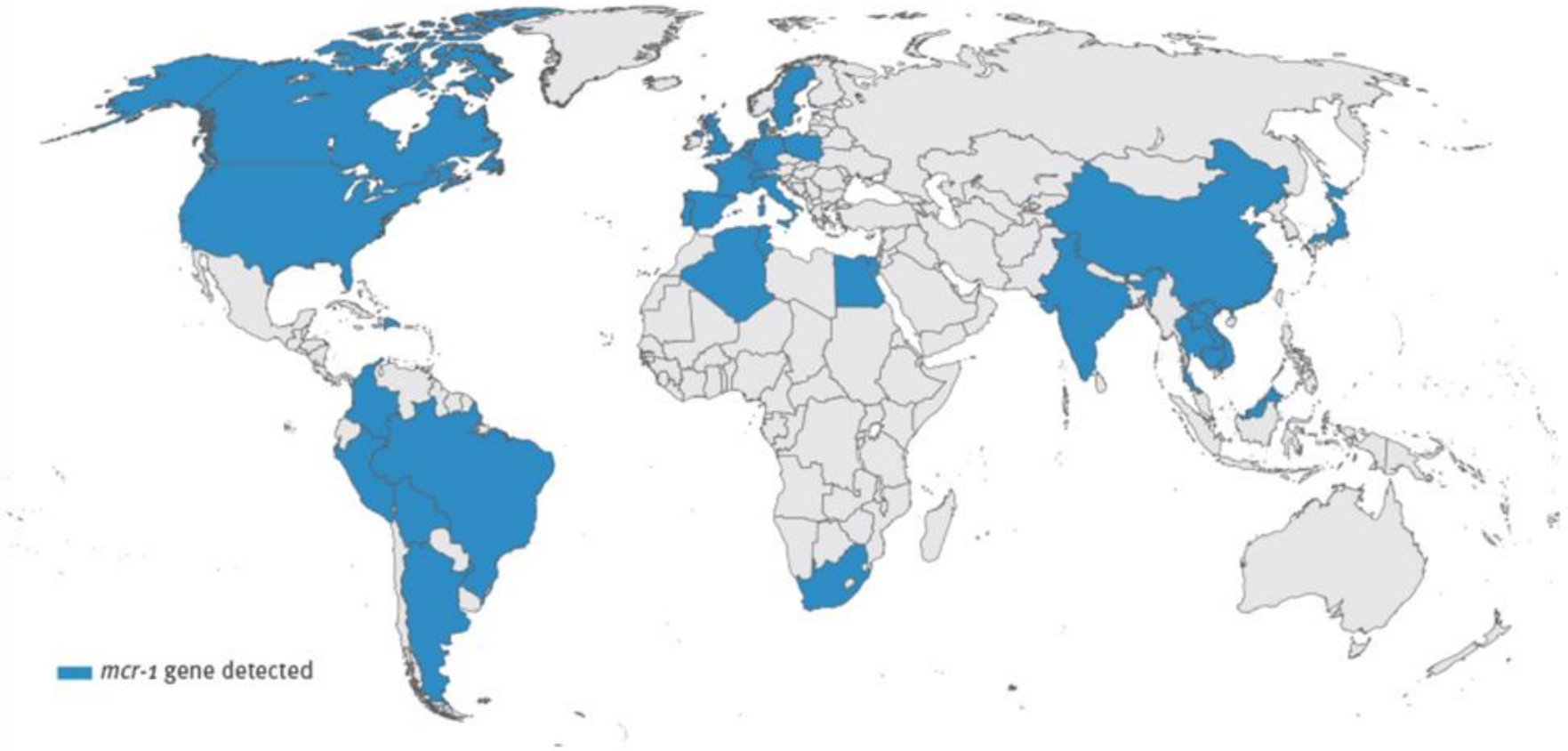
- The plasmid also passed to strains of:
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*

- The plasmids are quite stable → even in the absence of selection pressure by colistin, the plasmids persist

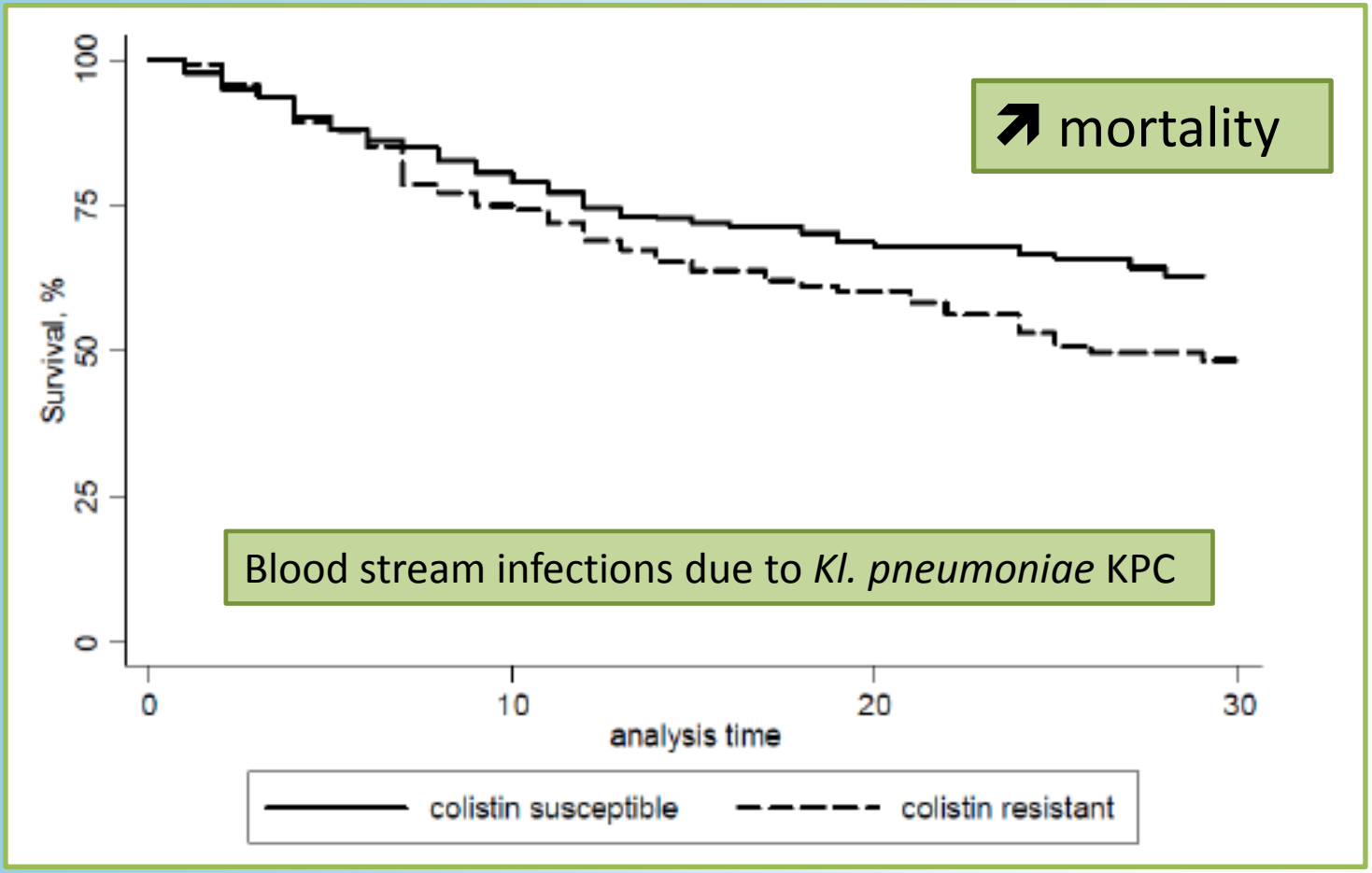
The Lancet Infectious Diseases. 2016; 16(2): 161-168

Figure 4

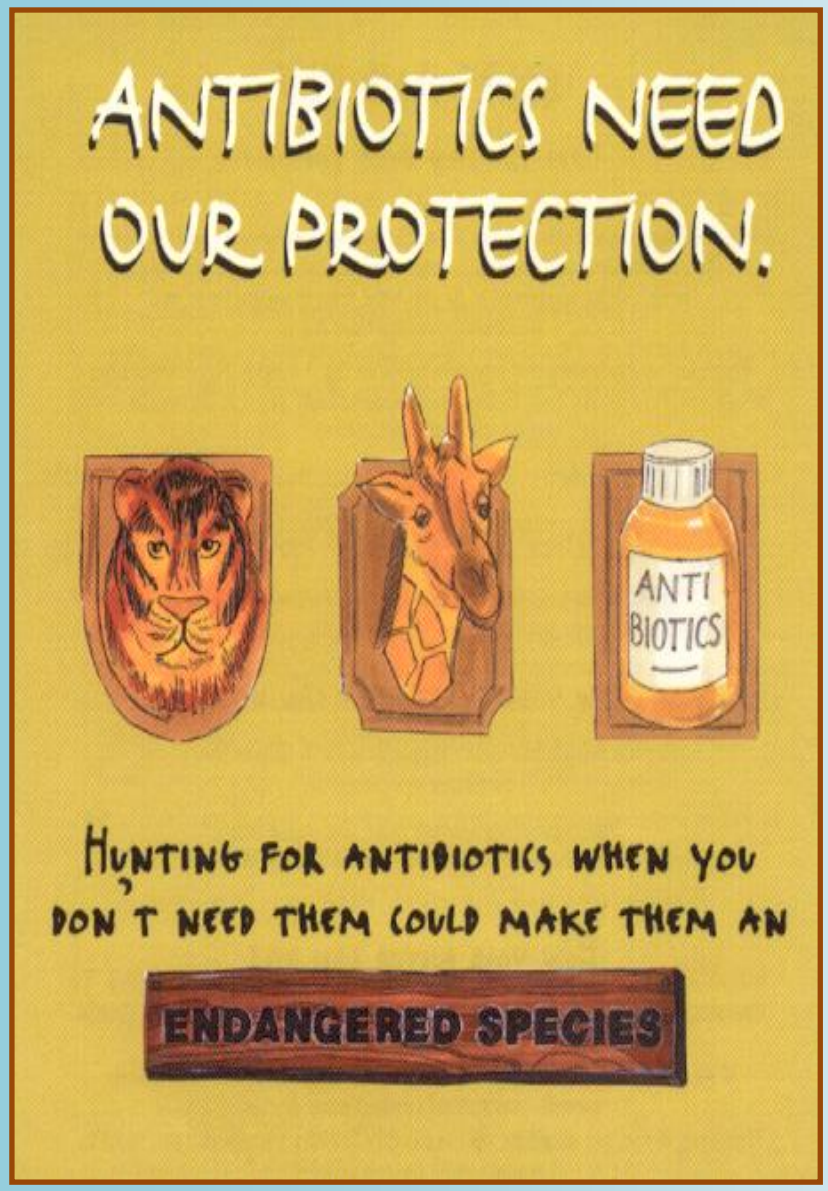
Countries (n = 32)* reporting presence of *mcr-1* in samples of animal, environmental or human origin (data collected till 27 June 2016)

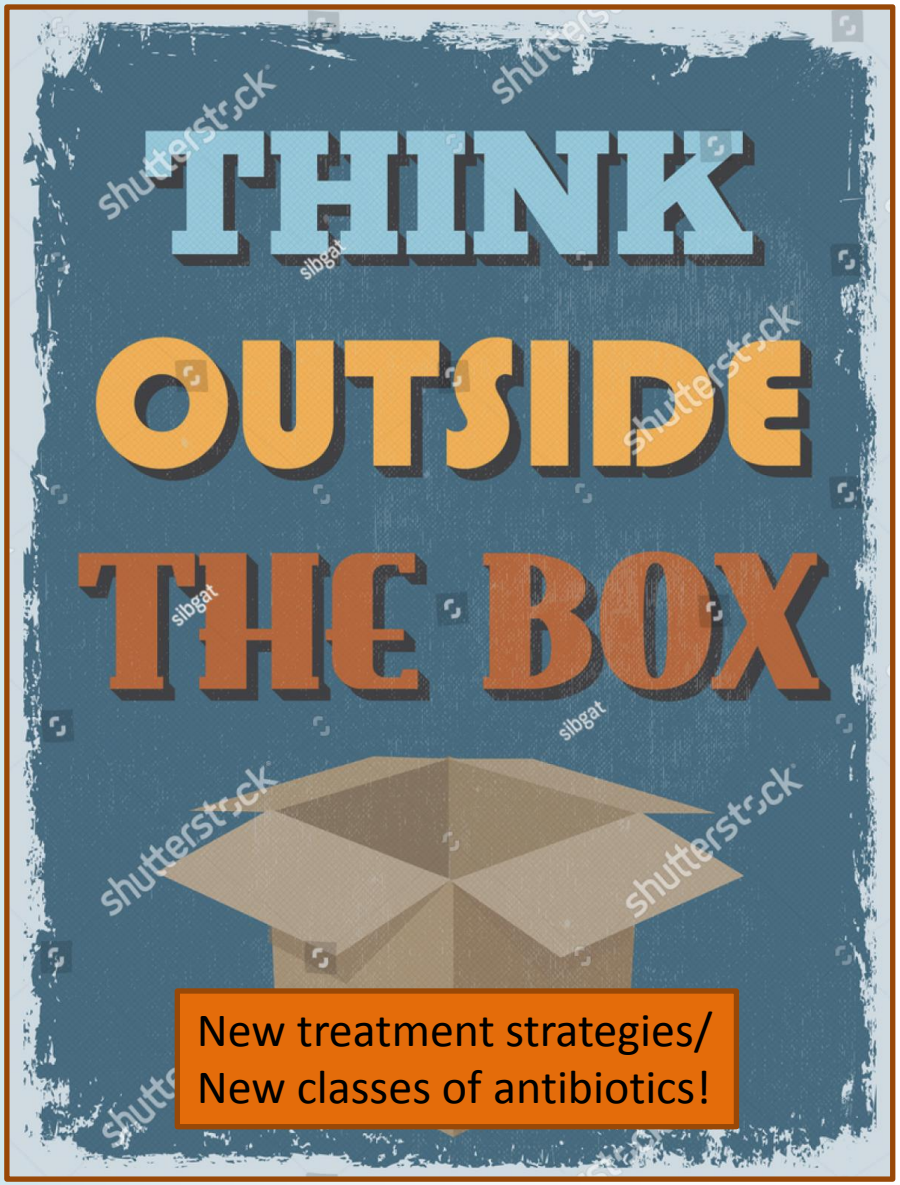


Clinical implications of infections due to pathogens resistant to Colistin



Giacobbe et al. Clin Microb Infect. 2015


ANTIBIOTICS NEED OUR PROTECTION.
ANTI BIOTICS
HUNTING FOR ANTIBIOTICS WHEN YOU DON T NEED THEM COULD MAKE THEM AN
ENDANGERED SPECIES


THINK OUTSIDE THE BOX
New treatment strategies/
New classes of antibiotics!

If you want to learn more…

3rd International Conference on Polymyxins

Wednesday - Thursday, April 25-26, 2018
7:30 am - 1:00 pm

Hospital Universitario 12 de Octubre
Avenida de Córdoba s/n, 28041
Madrid, Spain
Phone: 91-390-80-00

Register Online | Register by Mail or Fax

Course Overview

The University of Michigan and the University of Buffalo are excited to announce the 3rd International Conference on Polymyxins, April 25-26, 2018, at the Hospital Universitario 12 de Octubre in beautiful Madrid, Spain.

This opinion-leader conference will feature cutting-edge presentations by world leaders in research and clinical use of polymyxins, and regulatory and funding agency representatives. Each symposium session will provide opportunity for discussion and input from the audience.

Topics will include:

- Setting the Scence: Polymyxins in an Age of New Antibiotics
- Walking the Tightrope between Efficiancy and Toxicity
- Young Investigator Session: Oral Presentations for Polymyxin New and Upcoming Research
- Polymyxin Combinations:Thinking out of the Box and Clinical Use of Combinations
- The Road Ahead: Optimizing Clinical Use, Advances and Challenges

RDV in Madrid, 25-26 April, 2018