22nd ECCMID London, United Kingdom 31 March – 3 April 2012

Educational Workshop

EW12: Colistin use in clinical practice

Arranged with AIDA (FP7 project: „Preserving old antibiotics for the future")

Convenors: **Mical Paul (Petah-Tiqva, IL)**
Johan W. Mouton (Nijmegen, NL)

Faculty: **Johan W. Mouton (Nijmegen, NL)**
William Couet (Poitiers, FR)
Mical Paul (Petah-Tiqva, IL)
Yehuda Carmeli (Tel Aviv, IL) – no presentation submitted

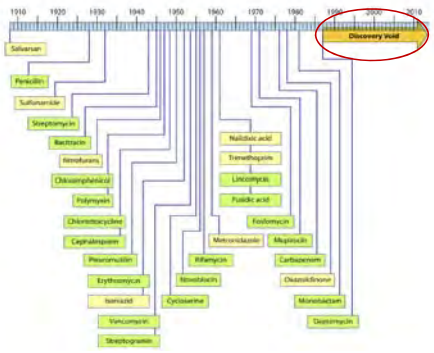
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Nijmegen Institute for Infection, Inflammation & Immunity

Optimizing Use of Old Antibiotics
The PK/PD perspective

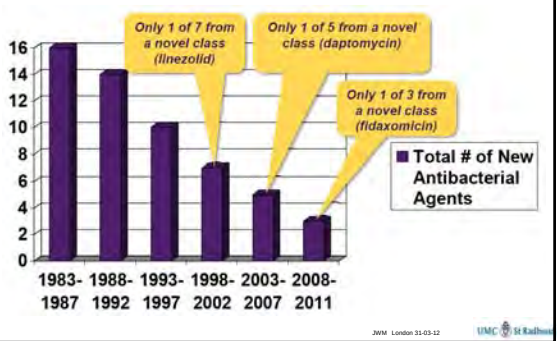
Johan W. Mouton MD PhD FIDSA

Discovery void



CMR, Jan. 2011, p. 71–109

Steady decline in the No. of FDA approvals



What is in the pipeline?

New antibacterial drugs in clinical development

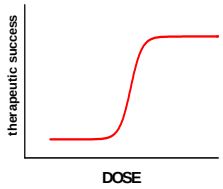
Compound name	Chemical class	Target	Dev. stage	Main indication	Route	Developing company
BC-3205	Pleuromutilin	Ribosome	Phase 1	–	Oral	Nabriva
BC-7013	Pleuromutilin	Ribosome	Phase 1	–	Topical	Nabriva
CG400549	Triclosan	FabI	Phase 1	–	iv	Crystal Genomics
AF-1252	New lead	FabI	Phase 1	–	iv	Affinium
FAB-001	Triclosan	FabI	Phase 1	–	iv	FAB Pharma
Delafloxacin	Fluoroquinolone	DNA gyrase	Phase 2	cSSSI/CAP	iv/oral	Rib-X
TP-434	Tetracycline	Ribosome	Phase 2	cIAI	iv/oral	Tetraphase
BC-3781	Pleuromutilin	Ribosome	Phase 2	cSSSI	iv/oral	Nabriva
Solithromycin	Ketolide	Ribosome	Phase 2	CAP	iv/oral	Cempra
ACHN-490	Aminoglycoside	Ribosome	Phase 2	UTI/AP	iv	Achaogen
CB-183,315	Lipopeptide	Membrane	Phase 2	CDAD	Oral	Cubist
Ramoplanin	Lipoglycodepsipeptide	Cell wall	Phase 2	CDAD	Oral	Nanotherapeutics
GSK-1322322	New lead	PDF	Phase 2	cSSSI	iv	GSK
JNJ-Q2	Fluoroquinolone	DNA gyrase	Phase 2/3	CAP/abSSSI	iv/oral	Furiex
Nemonoxacin	Quinolone	DNA gyrase	Phase 2/3	CAP/DFI	Oral	TaiGen/Warner
Oritavancin	Glycopeptides	Cell wall	Phase 3	abSSSI	iv	The Medicine Co
Dalbavancin	Glycopeptides	Cell wall	Phase 3	abSSSI	iv	Durata
Torezolid	Oxazolidinone	Ribosome	Phase 3	SSSI	iv/oral	Trius
Radezolid	Oxazolidinone	Ribosome	Phase 3	SSSI/CAP	iv/oral	Rib-X
Amadacycline	Tetracycline	Ribosome	Phase 3	cSSSI/CAP	iv/oral	Paratek
Cethromycin	Ketolide	Ribosome	Phase 3	CAP	Oral	Advanced Life Sciences

Current Opinion in Microbiology 2011, 14:564–569

- Drugs developed 30 or more years ago have not undergone the rigorous development and regulatory scrutiny to which are new agents subject
- Often the “label” is not updated as new information becomes available
  - the prescriber, as an occasional user, may be relying on obsolete information to make treatment or dosing decisions

Colistin (methanesulfonate)

Dosing should be such that the level of antmicrobial activity is associated with a high likelihood of therapeutic success.



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Dose Finding and Breakpoints- The Past

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Efficacy of the drug

Potency of a drug
(MIC)

Exposure to the bug
In vivo
(PK)

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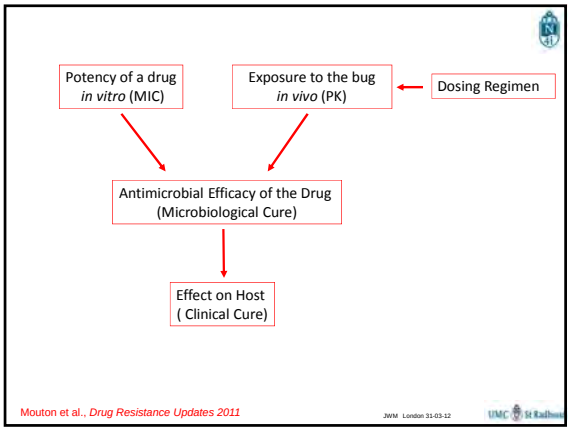
Potency of a drug
in vitro (MIC)
Exposure to the bug
in vivo (PK)
Dosing Regimen
Antimicrobial Efficacy of the Drug
(Microbiological Cure)
Effect on Host
(Clinical Cure)
Mouton et al., *Drug Resistance Updates 2011*
JWM London 31-03-12
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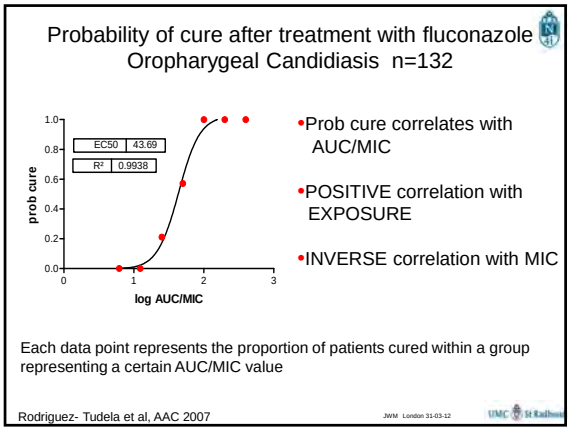
Probability of cure after treatment with fluconazole
Oropharygeal Candidiasis n=132
prob cure
log AUC/MIC
EC50 43.69
R² 0.9938
•Prob cure correlates with AUC/MIC
•POSITIVE correlation with EXPOSURE
•INVERSE correlation with MIC
Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value
Rodriguez- Tudela et al, AAC 2007
JWM London 31-03-12
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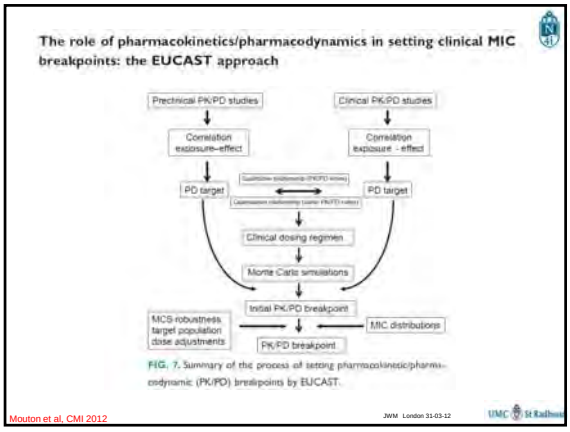
The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach
Preclinical PK/PD studies
Clinical PK/PD studies
Correlation exposure–effect
Correlation exposure - effect
PD target
PD target
Clinical dosing regimen
Monte Carlo simulations
Initial PK/PD breakpoint
MCS-robustness target population dose adjustments
MIC distributions
PK/PD breakpoint
FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.
Mouton et al, CMI 2012
JWM London 31-03-12
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Old antibiotics.....

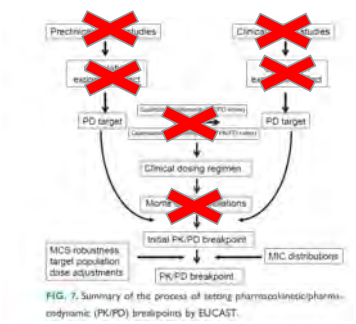


FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.

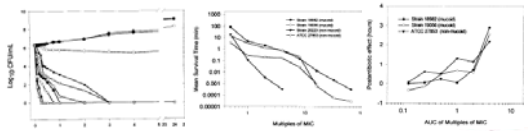
Mouton et al, CMI 2012

What do we know of colistin?

Colistin
In vitro pharmacodynamics

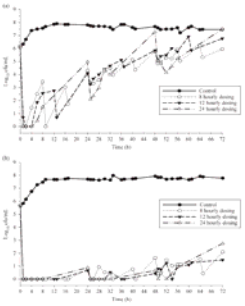
- Killing pattern: concentration-dependent
- Post-antibiotic effect: modest at best

- PRODRUG!



Li et al., AAC 2001; 45:781-5

Colistin
In vitro pharmacodynamics - IVIM

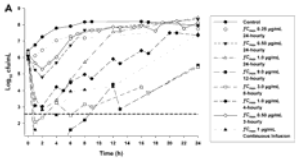


- 2 pseudomonas strains
- Dosing q8, q12 and q24

Bergen, JAC 2008

JWM London 31-03-12

Colistin
In vitro pharmacodynamics - IVIM



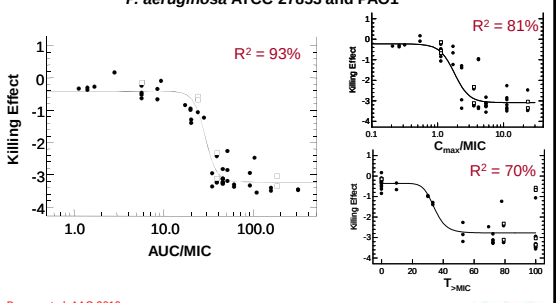
- 3 pseudomonas strains
- Dosing CI, q8, q12 and q24

Bergen, AAC 2010

JWM London 31-03-12

Colistin pharmacodynamics

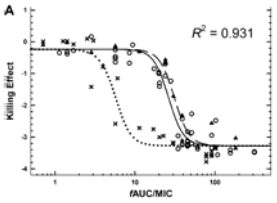
***P. aeruginosa* ATCC 27853 and PAO1**



Bergen et al. AAC 2010

JWM London 31-03-12

Colistin
In vitro pharmacodynamics - IVIM



- 3 pseudomonas strains
- Dosing CI, q8, q12 and q24

Bergen, AAC 2010

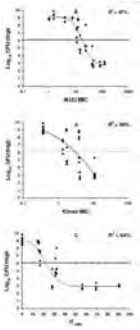
Colistin
In vitro pharmacodynamics - IVIM

TABLE 3. Median target values from 1,000 bootstrap replicates of colistin fAUC/MIC for 1- and 2-$\log_{10}$ reductions in the area under the CFU/ml curve relative to growth control and for 90% (EI_{90}) of maximal effect

Killing effect	Median target values (90% nonparametric confidence intervals)		
	ATCC 27853	PAO1	19056 muc
1-$\log_{10}$ reduction	22.6 (19.9–25.7)	27.1 (23.6–29.9)	5.04 (3.93–10.5)
2-$\log_{10}$ reduction	30.4 (27.2–33.0)	35.7 (32.6–41.7)	6.81 (5.21–14.3)
EI_{90}	42.0 (35.3–52.1)	49.3 (40.8–68.5)	9.78 (6.71–20.3)

Bergen, AAC 2010

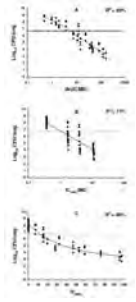
In vivo pharmacodynamics – thigh mice



- Dose fractionation study
- AUC/MIC correlates best with outcome

Dudhani et al, aac 2010

In vivo pharmacodynamics – lung mice



- Dose fractionation study
- AUC/MIC correlates best with outcome

Dudhani et al, aac 2010

In vivo pharmacodynamics –mice pseudomonas

Kill effect	ATCC 27853	PAO1	19066
Thigh infection			
Static effect	17.3	14.4	8.34
1-$\log_{10}$ kill	22.7	22.8	15.6
2-$\log_{10}$ kill	31.2	36.1	27.6
3-$\log_{10}$ kill	55.1	66.7	53.3
Lung infection			
Static effect	6.43	5.42	4.07
1-$\log_{10}$ kill	15.6	16.7	12.2
2-$\log_{10}$ kill	37.9	45.9	36.9
3-$\log_{10}$ kill	105	135	141

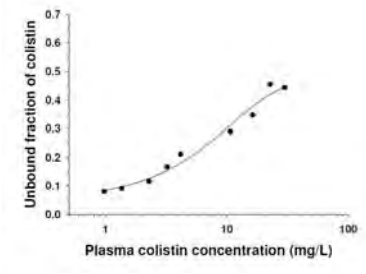
Dudhani et al, aac 2010

In vivo pharmacodynamics –mice acinetobacter

	*f*AUC/MIC		
Kill effect	ATCC 19606	248-01-C.248[a]	N-16870.213[a]
Thigh infection model			
Static effect	1.89	6.75	7.41
1 $\log_{10}$ kill	6.98	13.6	11.9
2 $\log_{10}$ kill	43.0	24.7	17.5
Lung infection model			
Static effect	1.57	6.08	6.52
1 $\log_{10}$ kill	8.18	12.9	42.1
2 $\log_{10}$ kill	95.0	22.5	[b]

Dudhani et al, jac 2010

Colistin
Protein binding in Mice



Dudhani et al, aac 2010

Colistin
Animal model toxicodynamics

Toxicity is dose-related and also regimen related

- Doses mimicking once-daily dosing give <u>more severe</u> lesions more frequent dosing

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2008, p. 1159–1161 Vol. 52, No. 3
0066-4804/08/$08.00+0 doi:10.1128/AAC.01019-07

Subacute Toxicity of Colistin Methanesulfonate in Rats: Comparison of Various Intravenous Dosage Regimens[▽]

Stephanie J. Wallace,[1] Jian Li,[1] Roger L. Nation,[1]* Craig R. Rayner,[1]† David Taylor,[2] Deborah Middleton,[3] Robert W. Milne,[4] Kingsley Coulthard,[4,5] and John D. Turnidge[5]

The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

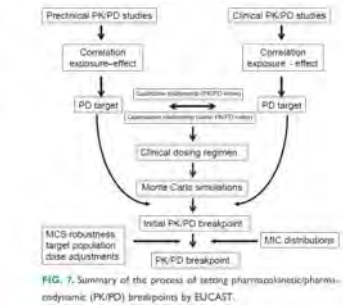
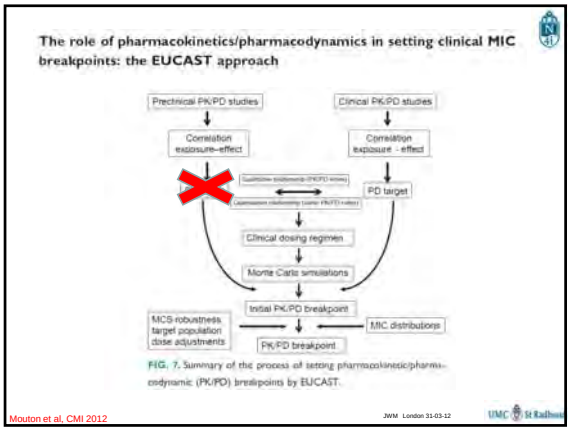
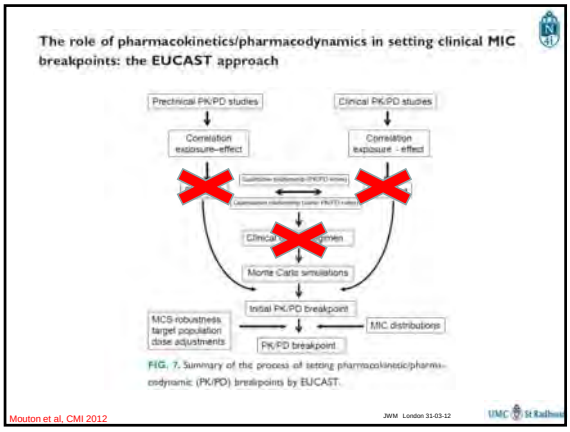


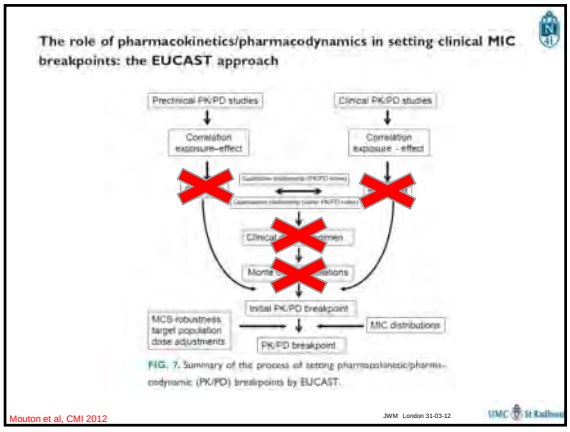
FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.

Mouton et al, CMI 2012

Mouton - Optimizing Use of Old Antibiotics: The PK/PD perspective







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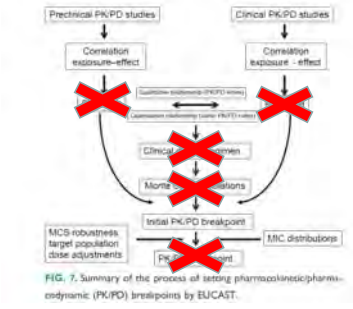

FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.

Mouton et al, CMI 2012

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Nijmegen Institute for Infection, Inflammation & Immunity

Acknowledgements:

This work was financially supported by:

AIDA *the EU-project AIDA (grant Health-F3-2011-278348)*

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UMC St Radboud

Université de Poitiers

Instituts thématiques Inserm

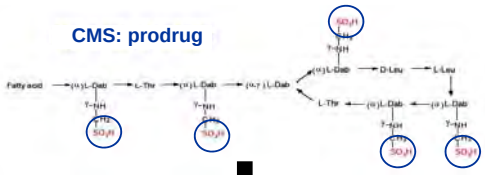
Colistin PK/PD: lessons from recent studies

William Couet, PharmD, PhD

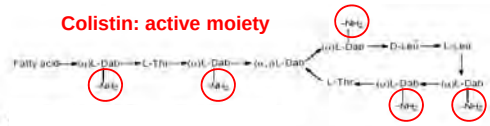
CHU de Poitiers

Colistin: an old antibiotic

CMS: prodrug



Colistin: active moiety



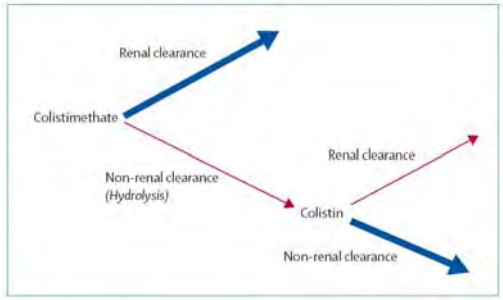
THE LANCET Infectious Diseases

Review

Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections

http://infection.thelancet.com Vol 6 September 2006

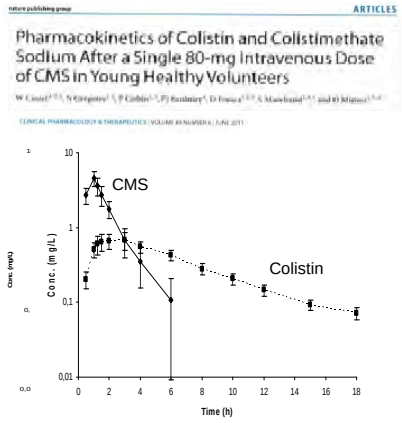
CMS and colistin pharmacokinetics
(from Li et al., Lancet Inf Dis, 2006)

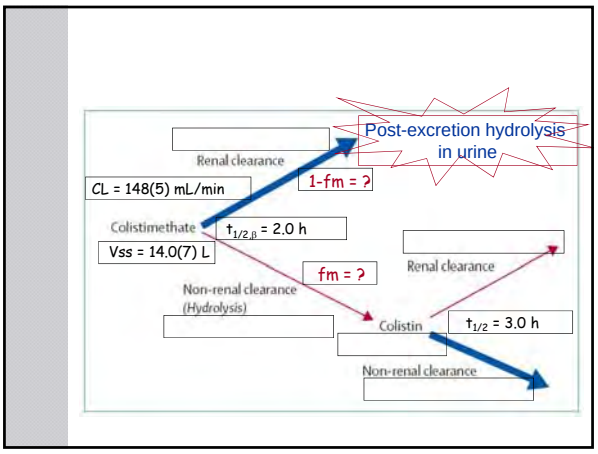


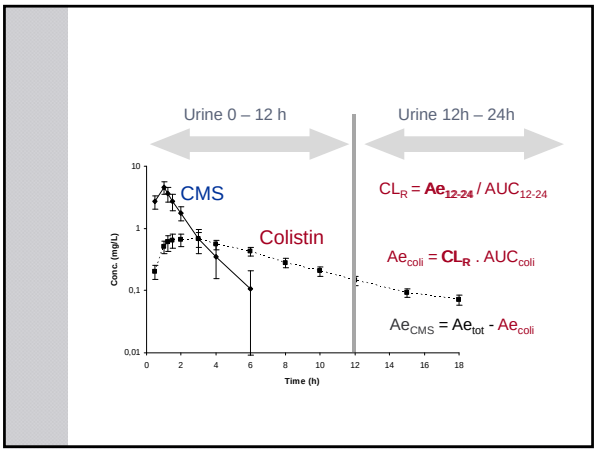
Colistin assay

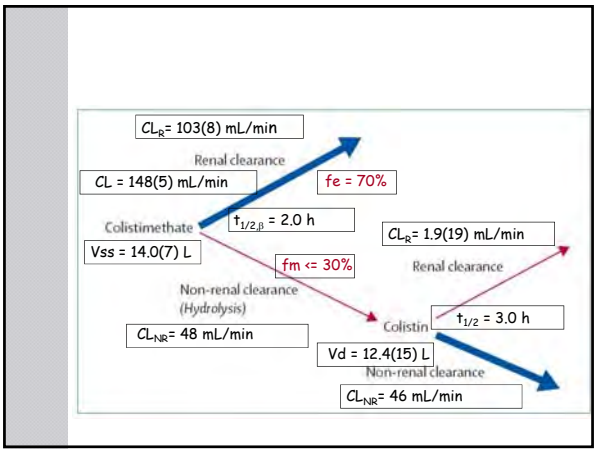
From bioassay…

… to HPLC and LC-MS/MS assay




Post-excretion hydrolysis in urine
Renal clearance
CL = 148(5) mL/min
1-fm = ?
Colistimethate
$t_{1/2,\beta}$ = 2.0 h
Vss = 14.0(7) L
fm = ?
Renal clearance
Non-renal clearance
(Hydrolysis)
Colistin
$t_{1/2}$ = 3.0 h
Non-renal clearance

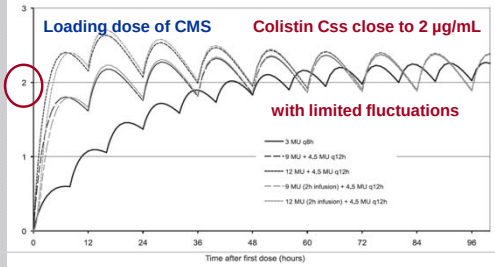

Urine 0 – 12 h
Urine 12h – 24h
CMS
Colistin
Conc. (mg/L)
Time (h)
$CL_R = Ae_{12\text{-}24} / AUC_{12\text{-}24}$
$Ae_{coli} = CL_R . AUC_{coli}$
$Ae_{CMS} = Ae_{tot} - Ae_{coli}$


CL_R= 103(8) mL/min
Renal clearance
CL = 148(5) mL/min
fe = 70%
Colistimethate
$t_{1/2,\beta}$ = 2.0 h
Vss = 14.0(7) L
CL_R= 1.9(19) mL/min
fm <= 30%
Renal clearance
Non-renal clearance
(Hydrolysis)
CL_{NR}= 48 mL/min
Colistin
$t_{1/2}$ = 3.0 h
Vd = 12.4(15) L
Non-renal clearance
CL_{NR}= 46 mL/min

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3430–3436 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.01361-08

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria[▽]†

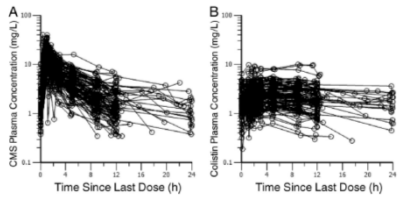
D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]



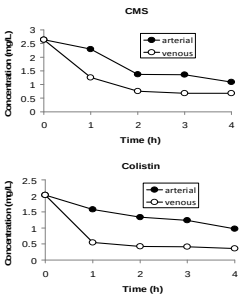
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01753-10

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]*‡



… including patients under hemodialysis



(Marchand S., et al., J Antimicrob Chemother. 2010)

CL_{creat} was the major PK factor in the maintenance dosing algorithm

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.
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 m², every 12 h, 10-70 ml/min/1.73 m² every 12 (or 8) h, and >70 ml/min/1.73 m² every 12 (or 8) h. See important caveat in footnote d.
	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.

[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 $C_{ss,avg}$ of 2.5 mg/liter, a 55-kg patient with a CrCL of 40 ml/min/1.73 m² 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 $C_{ss,avg}$ 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 (see the text for more details).
[d] Based upon the population PK analysis for 101 critically ill patients not on continuous renal replacement therapy. Colistin $C_{ss,avg}$ target expressed in mg/L. Creatinine clearance (CrCL) expressed in ml/min/1.73 m². 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 m². See text for caveat regarding use of the algorithm in patients with CrCL values > 70 ml/min/1.73 m² or when targeting a "high" colistin $C_{ss,avg}$, both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.
[e] Based upon use of equation 10 and setting CrCL to zero.
[f] Supplemental dose of CMS to achieve a similar colistin $C_{ss,avg}$ 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.

But 3 parameters govern colistin Css

REVIEW

Colistin pharmacokinetics: the fog is lifting

Clin Microbiol Infect

W. Couet[1], N. Grégoire[1], S. Marchand[1] and O. Mimoz[1,2]

1) Inserm ERI-23, CHU, Service de Toxicologie et Pharmacocinétique, UFR Médecine-Pharmacie, Université de Poitiers and 2) Intensive Care Unit, University Hospital of Poitiers, Poitiers, France

Colistin concentrations at steady-state

Rate of formation = Rate of elimination

$$\frac{fm \cdot Dose}{\tau} = CL_{coli} \cdot C_{SS}$$

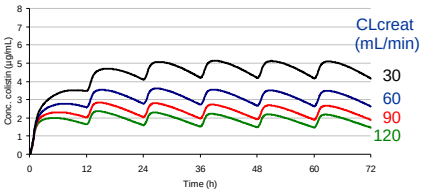
$$C_{SS} = \frac{CL_{NR}}{CL_R + CL_{NR}} \cdot \frac{Dose}{\tau \cdot CL_{coli}}$$

GFR — Limited impact on Css — Uncontrolled

Effect of CMS renal clearance on colistin Css

($CL_{R,CMS}$ = 0.85 CLcreat)

9 MIU loading dose + 4.5 MIU / 12h



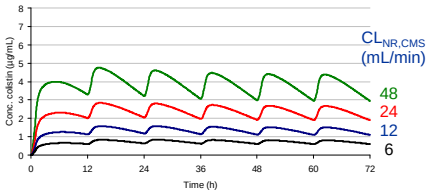
$CL_{CMS,R}$: Real impact but easy to predict

How to reduce maintenance dose when GFR decreases ?

$CL_{CMS,NR}$ = 24 mL/min CLcoli = 35 mL/min

Effect of CMS non-renal clearance on colistin Css

9 MIU loading dose + 4.5 MIU / 12h

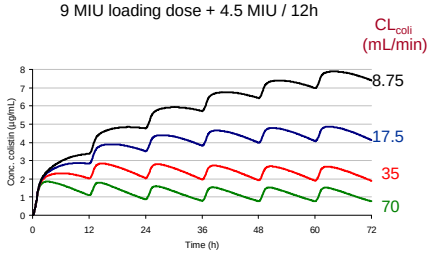


$CL_{CMS,NR}$: Probably of moderate impact

$CL_{CMS,R}$ = 90 mL/min CLcoli = 35 mL/min

Effect of Colistin clearance on colistin Css

9 MIU loading dose + 4.5 MIU / 12h



CL_{coli}: Important impact and difficult to predict

$CL_{CMS,R}$ = 90 mL/min $CL_{CMS,NR}$ = 35 mL/min

Time for individualized dosing regimen?

CASE REPORT Journal of Infection (2011)

Convulsions and apnoea in a patient infected with New Delhi metallo-β-lactamase-1 *Escherichia coli* treated with colistin

Herbert D. Spapen [a,*], Patrick M. Honore [a], Nicolas Gregoire [b], Patrice Gobin [b], Jouke de Regt [a], Geert A. Martens [c], Denis Pierard [a], William Couet [b]

24 mL/min

3 MIU / 8h

$$C_{SS} = \frac{CL_{NR}}{CL_R + CL_{NR}} \cdot \frac{Dose}{\tau \cdot CL_{coli}}$$

Expected: 3.4 µg/mL

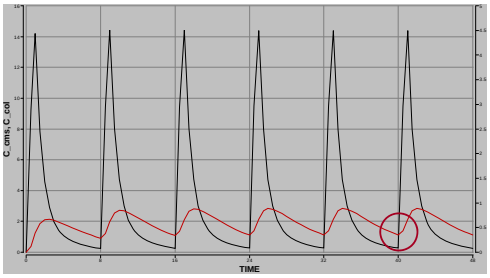
42 mL/min

Initial guess: 35 mL/min

Observed: 8.1 µg/mL

Revised: 15 mL/mn

What would be the best sampling time ?

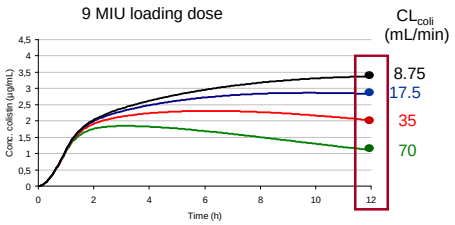


At « trough » when CMS concentrations are the lowest

What would be the best strategy ?

And after loading dose…

… when bayesain procedures become available

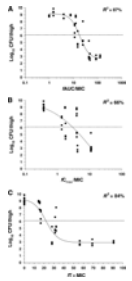


$CL_{CMS,R}$ = 90 mL/min

$CL_{CMS,NR}$ = 35 mL/min

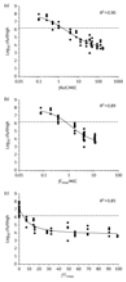
What would be the optimal concentrations ?

fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic



Pseudomonas aeruginosa

Antimicrob Agents Chemother. 2010 54(3):1117-24.



Acinetobacter baumannii

J Antimicrob Chemother. 2010 65(9):1984-90.

Murine thigh and lung infection models

MONASH University

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- Nicolas Grégoire
- Patrice Gobin
- Sandrine Marchand
- Olivier Mimoz

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Handouts

Efficacy, use and dosing of colistin: what have contemporary studies taught us?

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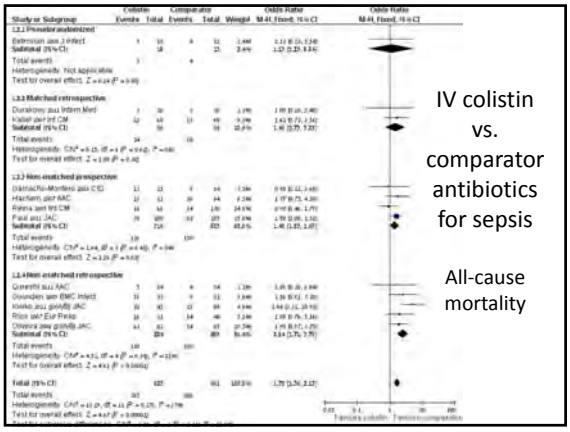
Israel

RABIN MEDICAL CENTER
BEILINSON • HASHARON

TEL AVIV UNIVERSITY
Sackler Faculty of Medicine

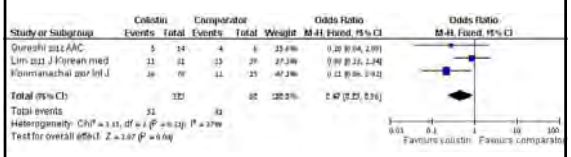
Infectious Diseases University Research Center



IV colistin vs. comparator antibiotics for sepsis

All-cause mortality

Colistin vs. inappropriate antibiotics
All-cause mortality



Dosing and clinical outcomes univariate

- Retrospective cohort study, 2000-2007, Henry Dunant Hospital, Athens, Greece
- Overall 258 patients, 222 (86%) hospitalised in the ICU

In-hospital mortality (%)	3 MIU	6 MIU	9 MIU
All	38.6%	27.8%	21.7%
Normal RF	34.3%	27.6%	19.5%

Falagas et al. Int J Antimicrob Agents 2010

Dosing and clinical outcomes multivariate

- Retrospective cohort study, 2000-2007, Henry Dunant Hospital, Athens, Greece
- Overall 258 patients, 222 (86%) hospitalised in the ICU

Multivariable analysis, in-hospital mortality	aOR (95% CI
Higher daily colistin dose	1.22 (1.05-1.42)
Cure of infection	9 (3.6-23.1)
Higher APACHE II score	0.89 (0.84–0.95)
Rise in creatinine	0.21 (0.1–0.45)
Haematological disease	0.23 (0.08–0.66)

Falagas et al. Int J Antimicrob Agents 2010

Hieronymus Bosch. Allegory of Gluttony and Lust. 1490-1500

Falagas and Karageorgopoulos Lancet 2010

Colistin-carbapenem combination therapy

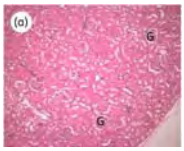
- Data from two retrospective cohorts
- Carbapenem-resistant bacteria

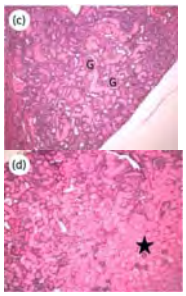
	Location, bacteria	Outcome	Colistin monotherapy	Combination therapy
Falagas 2010 [1]	Greece, mostly *A. baumannii*	Failure	2/20 (10%)	14/84 (16.7%)
		Mortality	Not significant	
Qureshi 2012 [2]	US, KPC-producing *K. pneumoniae*	Mortality	4/7 (57%)	1/5 (20%)
Total			**27**	**89**

[1] Falagas et al. Int J Antimicrob Agents 2010; [2] Qureshi et al. Antimicrob Agents Chemother 2012

Colistin-related nephrotoxicity Mechanism

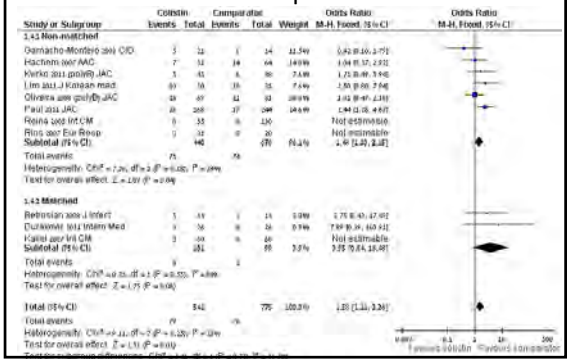
- Increased membrane permeability, cell swelling and lysis (bladder)
- Oxidative stress





Yousef et al. J Antimicrob Chemother 2012

Nephrotoxicity for colistin vs. comparators in sepsis



"Interesting" risk factors for nephrotoxicity

- Obesity (BMI ≥31.5 kg/m^2) [1]
- Dosing of ≥5.0 mg/kg CBA per day of ideal body weight (adjusted OR 15-23) and dosing ≥3.0 mg/kg (adjusted OR 3) [2]
- Duration of therapy/ total cumulative dose [3]
- Male sex [4]

[1] Gauthier et al. Antimicrob Agents Chemother 2012; [2] Pogue et al. Clin Infect Dis 2011, ; [2] Rattanaumpawan J Infect 2011; [3] Hartzell et al. Clin Infect Dis 2009; [4] Kwon et al. Int J Antimicrob Agents 2010

Protection from colistin-induced nephrotoxicitiy

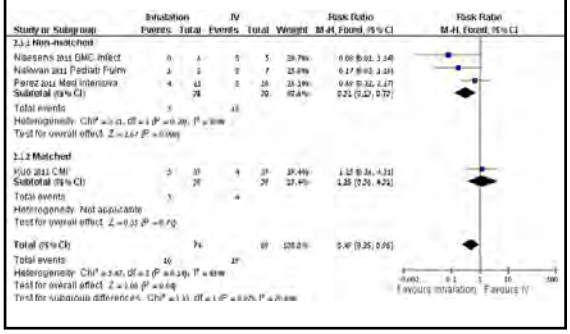
- Avoidance of concomitant nephrotoxic agents (including IV contrast material) [1]

In-vivo studies:

- Ascorbic acid [2]
- N-acetylcysteine [3]
- Melatonin [4]

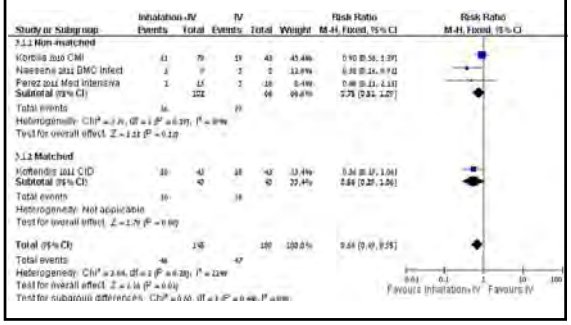
[1] Doshi et al. Pharmacotherapy 2011; [2] Yousef et al. J Antimicrob Chemother 2012; [3] Ozyilmaz et al. Intensive Care Med 2011; [4] Yousef et al. J Antimicrob Chemother 2011

Colistin inhalation vs. IV colistin
all-cause mortality



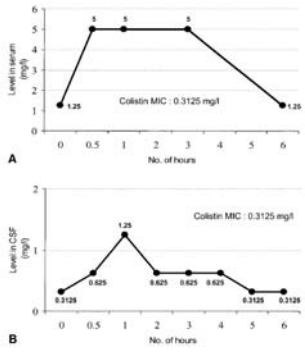
Paul - Efficacy, use and dosing of colistin: what have contemporary studies taught us?

IV + inhalation colistin vs. IV colistin
all-cause mortality



Intrathecal/ ventricular colistin

- Main indication: post neurosurgical *A. baumannii* meningitis with/ without shunt
- Q1: Penetration of intravenous colistin
- Q2: comparative effectiveness of IV and IT treatment
- Q3: Safety/ efficacy of intrathecal/ ventricular colistin



Colistin penetration to CSF

Jiménez-Mejías et al. Eur J Clin Microbiol Infect Dis 2002

Study	CMS dose mg (MIU) /kg/day	Serum µg/ml	CSF µg/ml	CSF/ serum	Serum µg/ml	CSF µg/ml	CSF/ serum
Adults [1]	30-60 min. after IV dose			Before next IV dose			
1 *	8.3 (0.1)	1.55	0.083	5.4%			
2 *	10.1 (0.13)	1.92	0.099	5.2%			
3 *	4.4 (0.05)	0.82	0.043	5.3%			
4	8.3 (0.1)	1.55	0.083	5.4%	0.82	0.042	5.1%
5	2 (0.02)	1.53	0.088	5.7%	0.87	0.048	5.5%
Children [2]							
1	4.8 (0.06)	0.29	0.06	19.3%	0.19	0.05	25.2%
1	10.4 (0.13)	1.46	0.05	3.4%	0.52	0.06	11.1%
1 **	16 (0.2)	1.33	0.46	34.8%	0.73	0.50	67.7%
2 *	16 (0.2	1.60	0.11	7.2%	0.97	0.15	16.1%
3	18 (0.23)	2.20	0.07	3.2%	2.29	0.07	3%

* Meningitis ** meningitis with inflammation. [1] Markantonis et al. AAC 2009; [2] Antachopoulos et al. AAC 2010

IV vs. IV + intrathecal colistin

- Two tertiary university hospitals in Madrid
- All cases of adult neurosurgical *A. baumannii* meningitis

	N patients	N deaths (%)
IV beta-lactam +/- IV aminoglycoside*	29	11 (37.9%)
IV carbapenem + IT aminoglycoside	9	2 (22.2%)
IV colistin + IT colistin	8	0 (0%)

* Mostly carbapenems (24) or ampicillin-sulbactam (4) monotherapy. Combination with IV aminoglycoside in 2 cases.

Rodriguez Guardado et al. J Antimicrob Chemother 2008

Intrathecal/ intraventricular colistin

- Case series and literature review [1,2]
- Concomitant IV antibiotics usually

	Intrathecal N=15	Intraventricular N=24
Death	2	5
Relapse	1	1
Chemical meningitis	2	1
Other neurological toxicity	1/8	1

- In a systematic review of case reports on all IT/IV polymyxins, cure in 51/64 (80%) and major toxicitiy in 17/60 (28%) [3]

[1] Cascio et al. Int J Infect Dis; [2] Khawcharoenporn et al. Clin Microbiol Infect 2010; [3] Falagas et al. Int J Antimicrob Agents

The Future: registered RCTs

- Colistin vs. colistin+imipenem for treatment of documented carbapenem-resistant bacteremia or VAP (2 trials, AIDA, NIH)
- Colistin vs. meropenem as empirical treatment for VAP with suspicion of multi-resistant Gram-negative bacteria (MAGIC BULLET)
- Colistin vs. colistin+fosfomycin for *A. baumannii* infections
- Colistin vs. colistin+rifampin for *A. baumannii* or P. *aeruginosa* infections
- IV vs. nebulized+IV colistin for VAP/ HAP (2 trials)
- Colistin vs. colistin+ascorbic acid for prevention of colistin-associated nephrotoxicity