

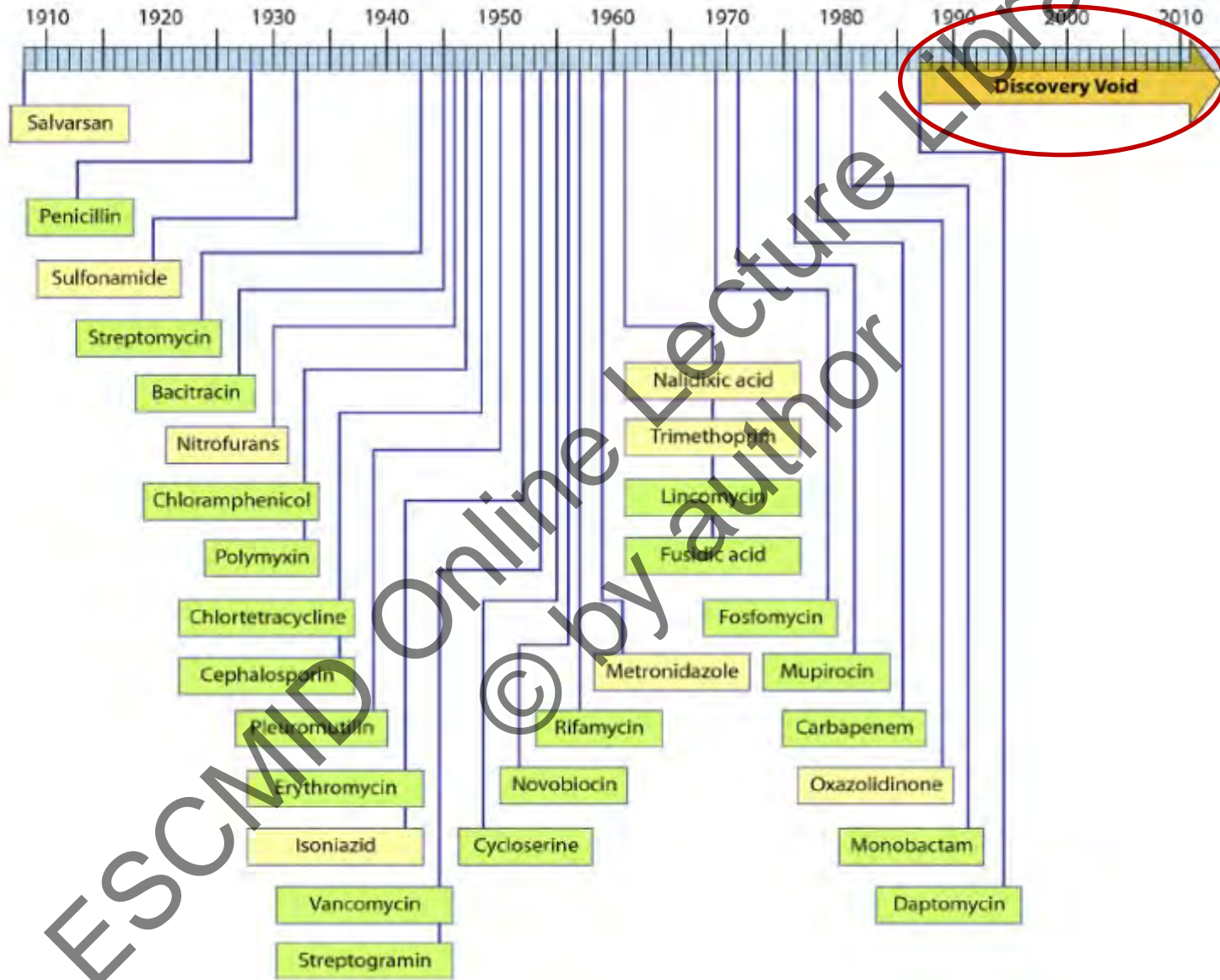


Optimizing Use of Old Antibiotics The PK/PD perspective

Johan W. Mouton MD PhD FIDSA

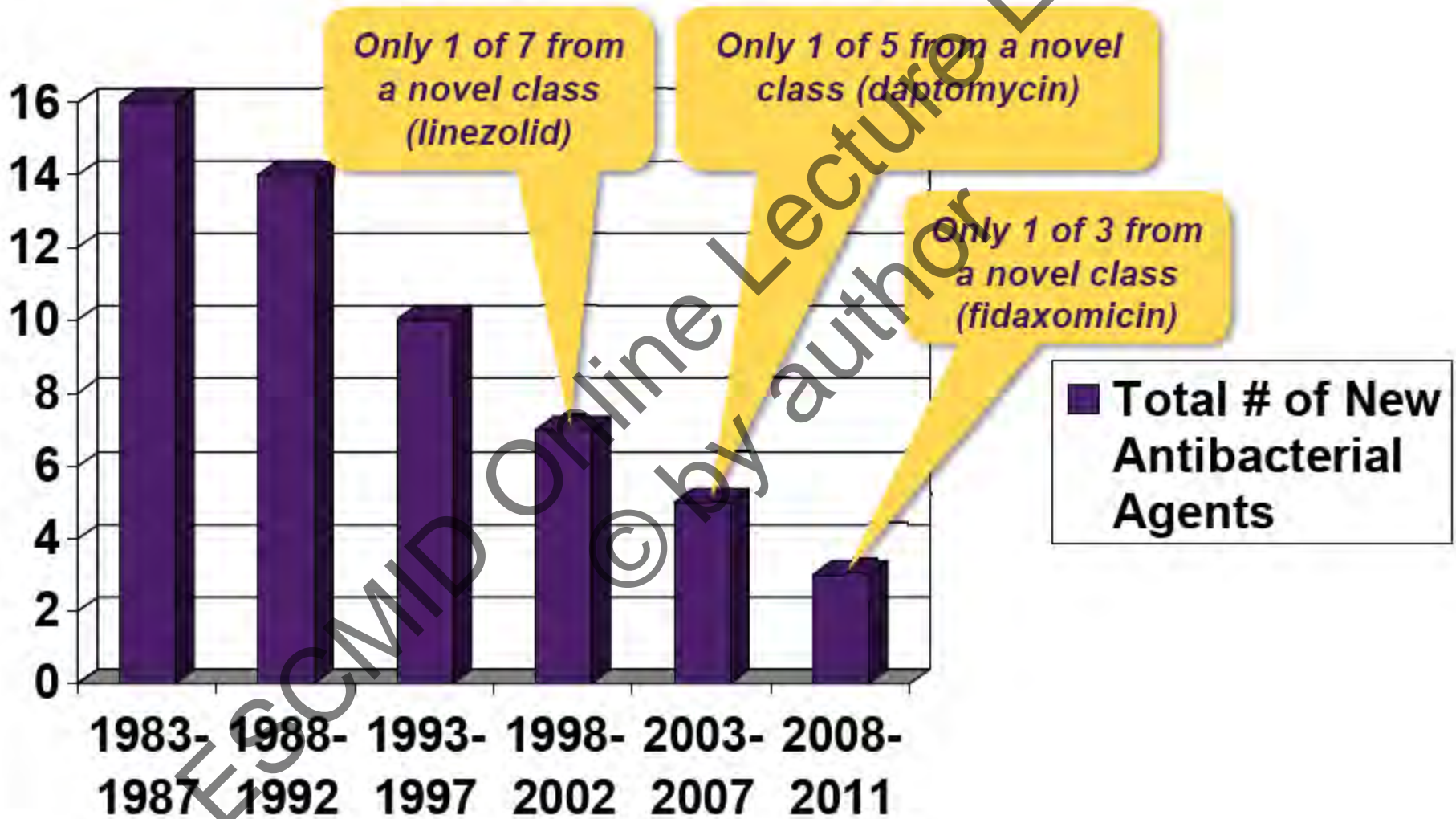
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Discovery void



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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	oAI	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	Lipoglycopeptide	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

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- 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)



NDC 42023-107-01
Coly-Mycin® M Parenteral
(Colistimethate for Injection, USP)
150 mg Colistin base activity
1 Vial

JHP
PHARMACEUTICALS

Rx only
For Intramuscular and Intravenous Use

For full prescribing information and directions on reconstitution, see package insert. Store between 20°-25° C (68°-77° F). (See USP controlled room temperature.)
Mfg. & Dist. by:
JHP Pharmaceuticals, LLC
Rochester, MI 48307

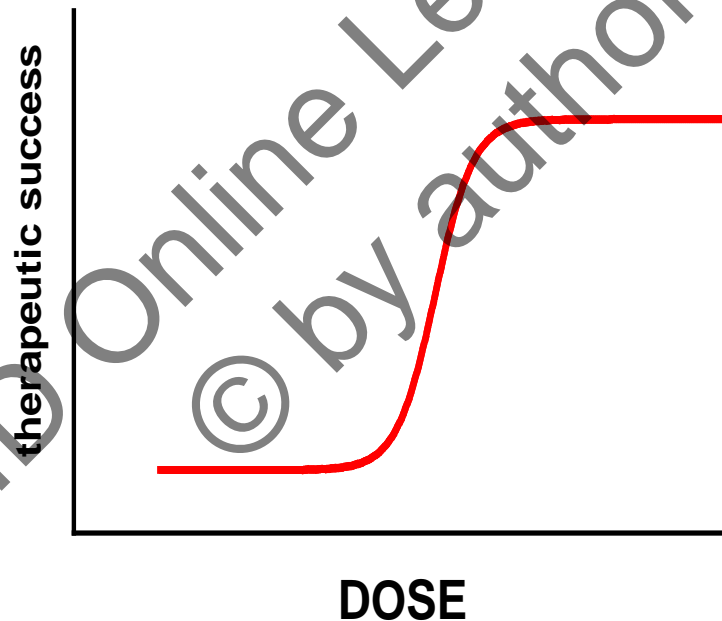


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Dosing should be such that the level of antimicrobial activity is associated with a high likelihood of therapeutic success.





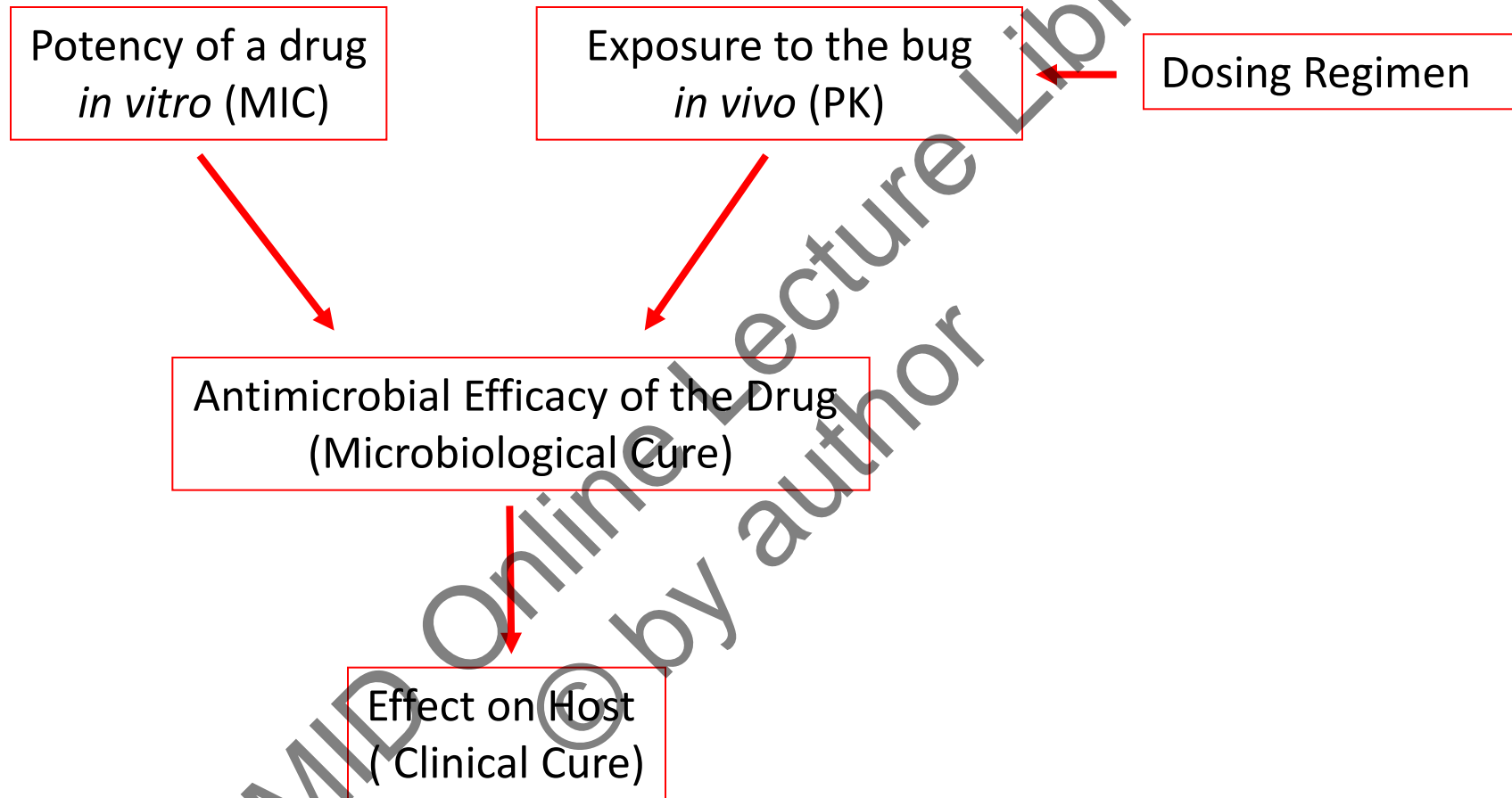
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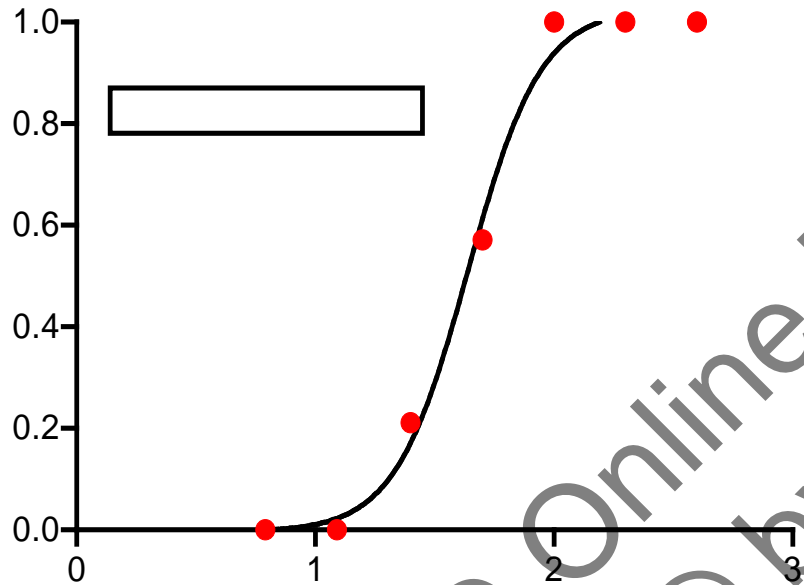
Efficacy of the drug



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Probability of cure after treatment with fluconazole Oropharyngeal Candidiasis n=132



- 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

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

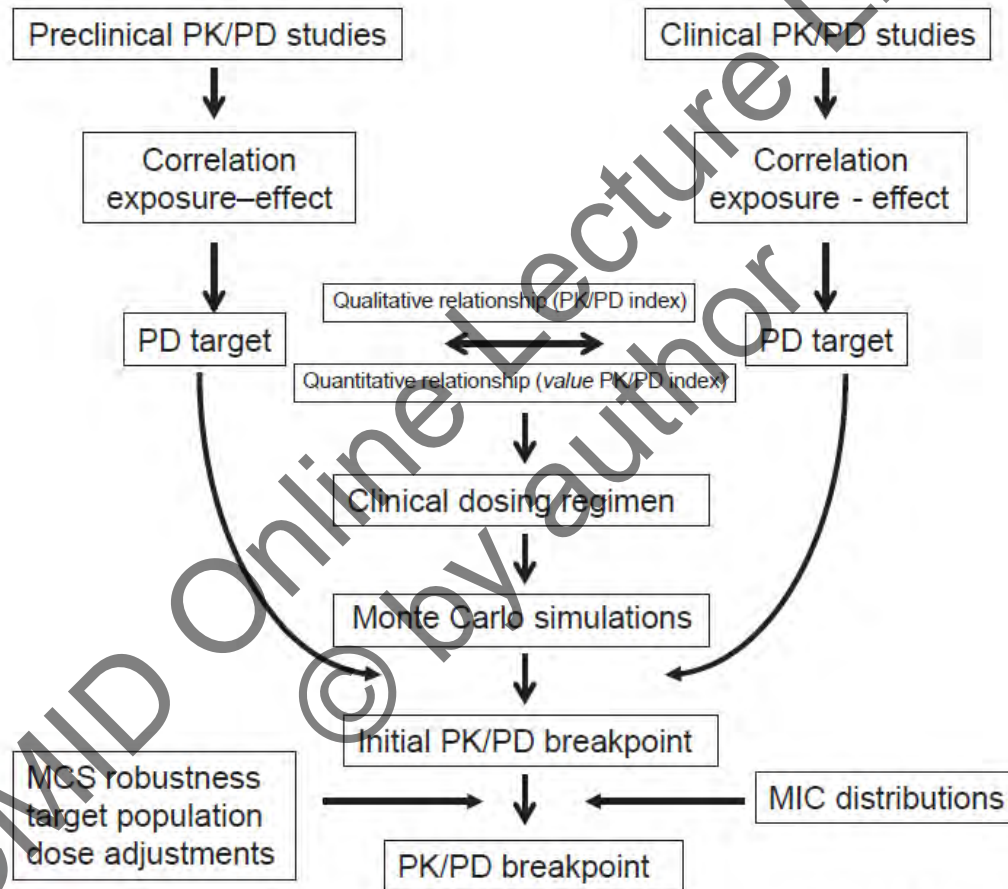


FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.

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Old antibiotics.....

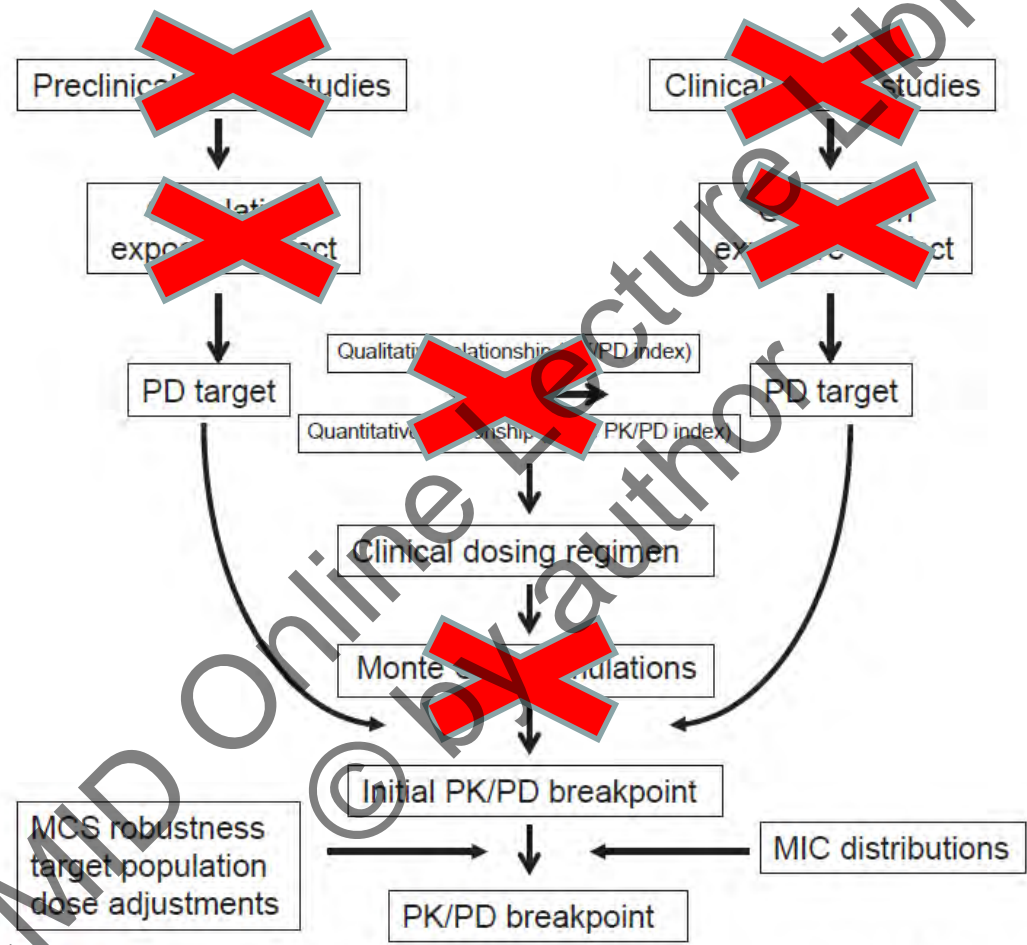


FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.

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What do we know of colistin?

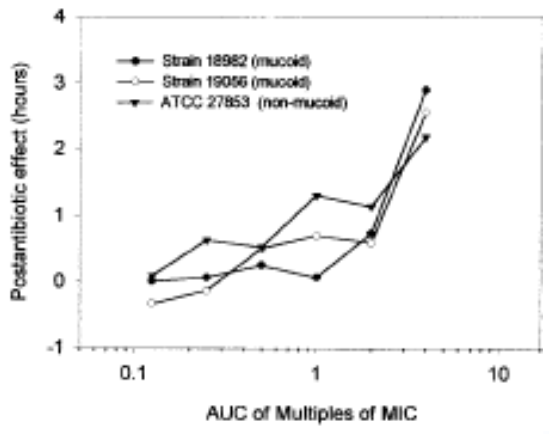
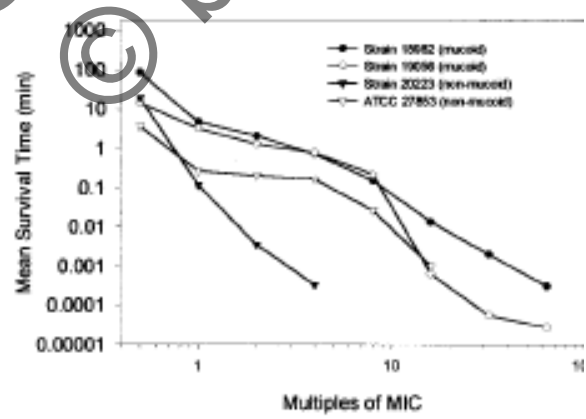
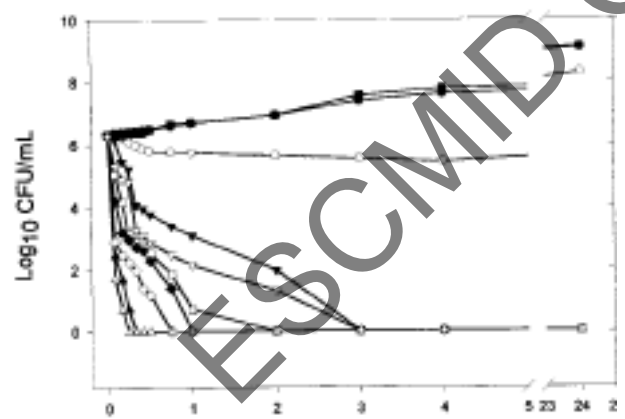
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Colistin

In vitro pharmacodynamics

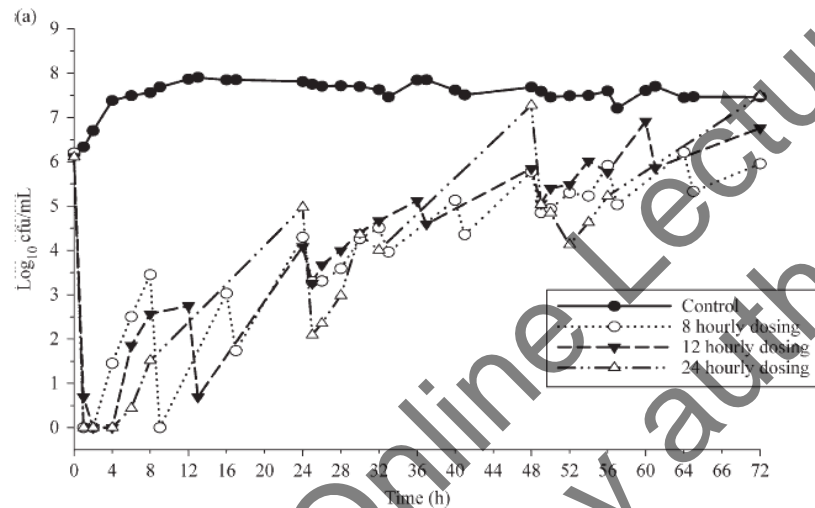
- **Killing pattern:** concentration-dependent
- **Post-antibiotic effect:** modest at best
- **PRODRUG!**



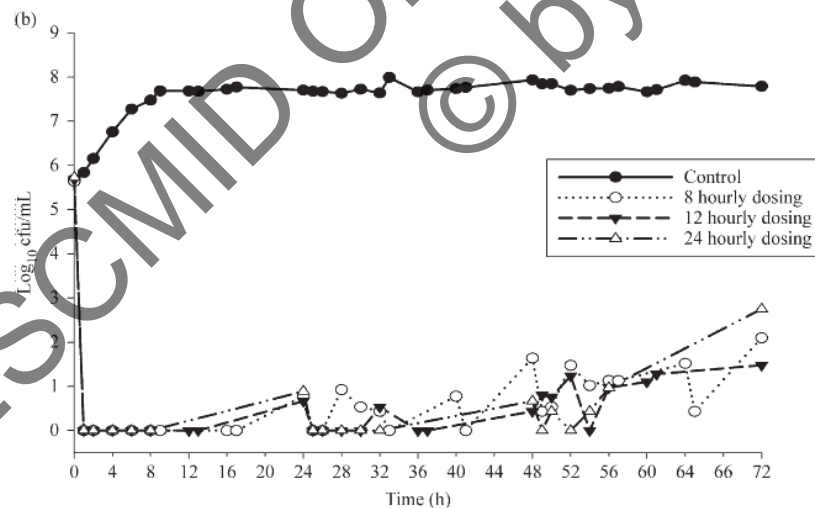


Colistin

In vitro pharmacodynamics - IVIM



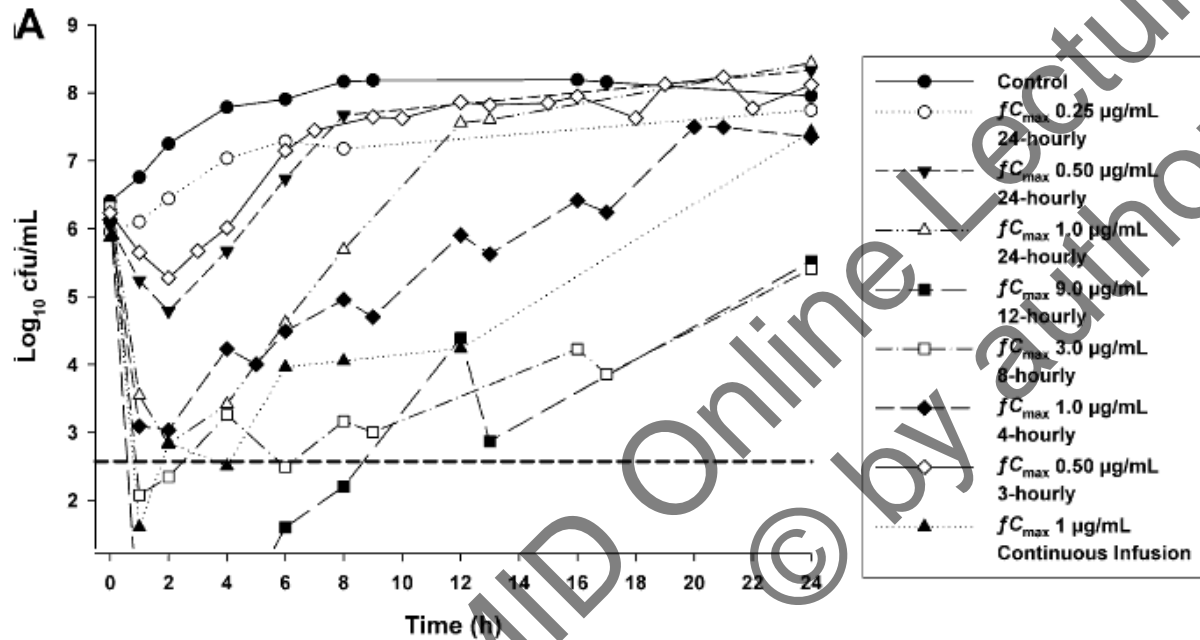
- 2 pseudomonas strains
- Dosing q8, q12 and q24





Colistin

In vitro pharmacodynamics - IVIM

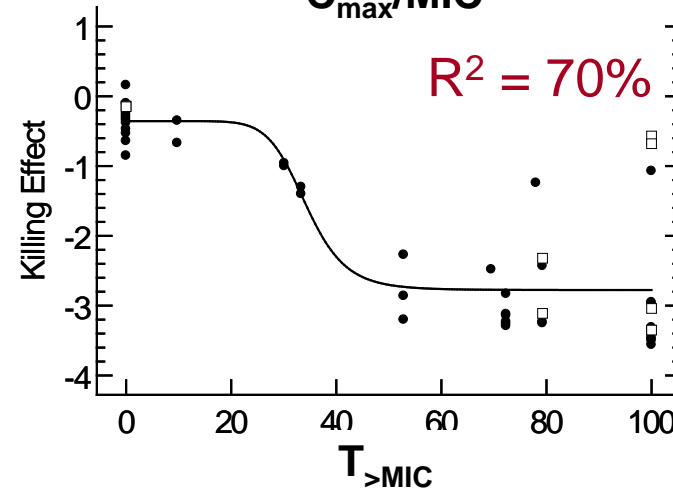
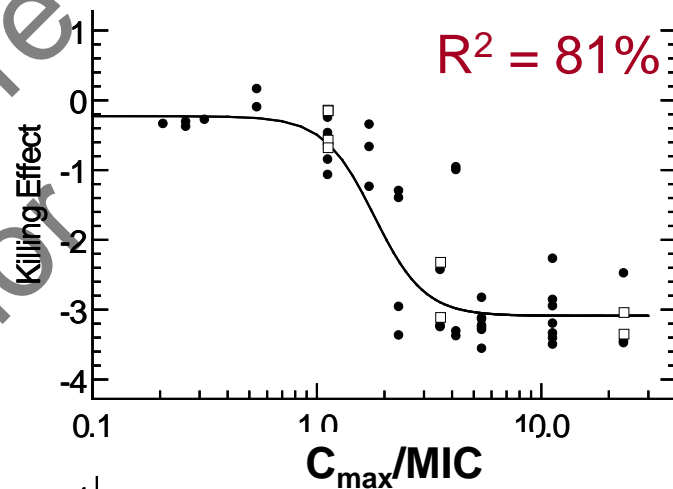
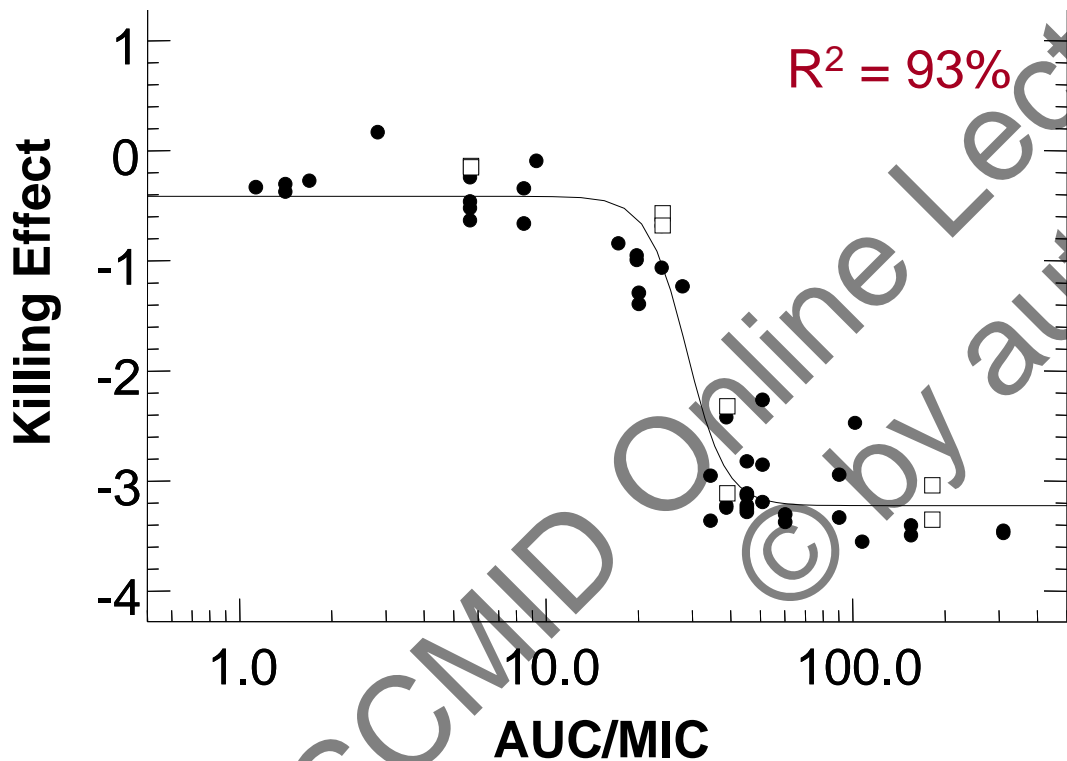


- 3 pseudomonas strains
- Dosing CI, q8, q12 and q24

Colistin pharmacodynamics



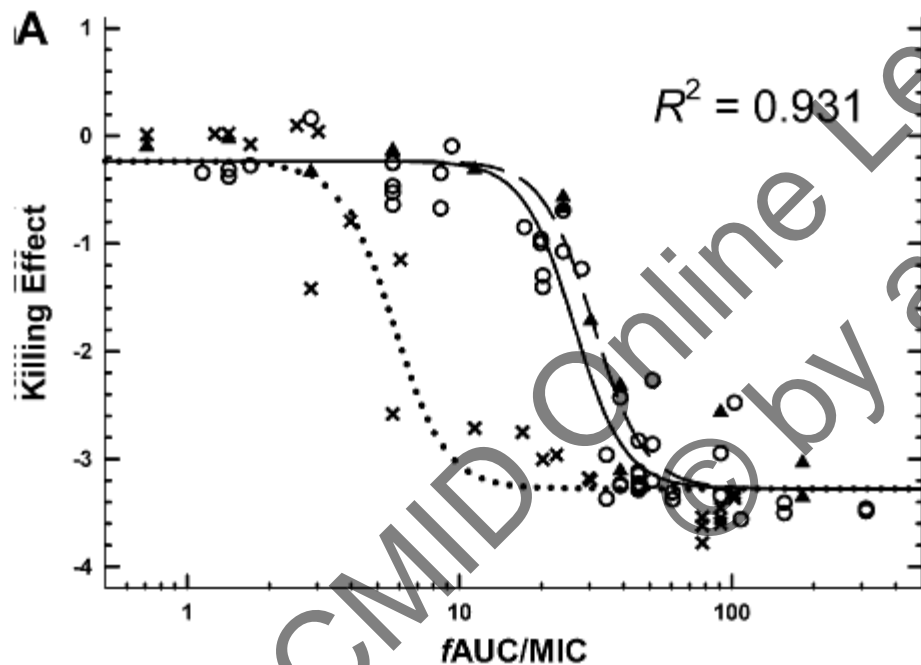
P. aeruginosa ATCC 27853 and PAO1





Colistin

In vitro pharmacodynamics - IVIM



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



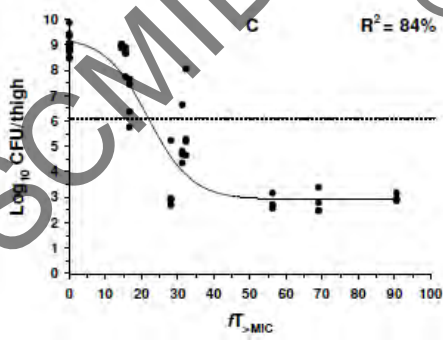
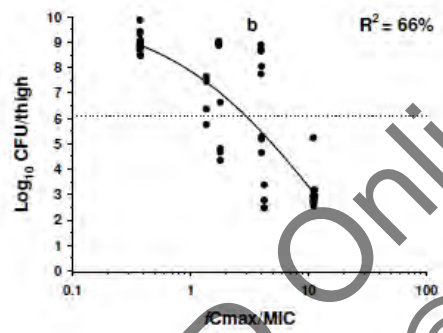
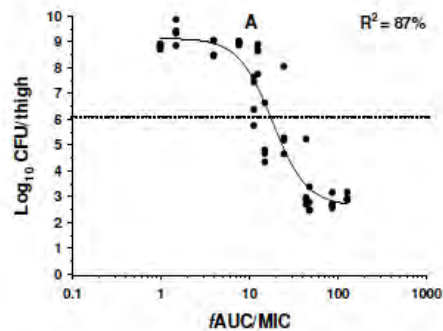
Colistin

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)

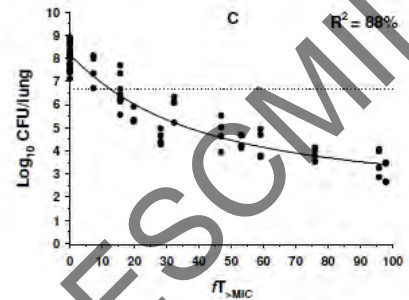
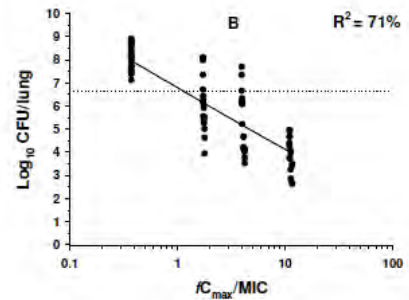
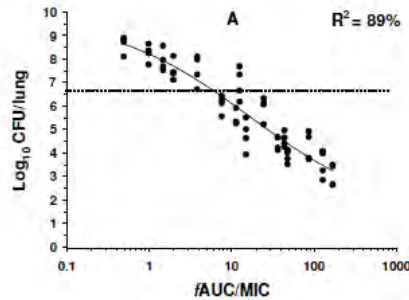
In vivo pharmacodynamics – thigh mice



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

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In vivo pharmacodynamics – lung mice



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

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In vivo pharmacodynamics – mice pseudomonas

Kill effect	ATCC 27853	PAO1	19056
<i>Thigh infection</i>			
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
<i>Lung infection</i>			
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

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In vivo pharmacodynamics – mice acinetobacter

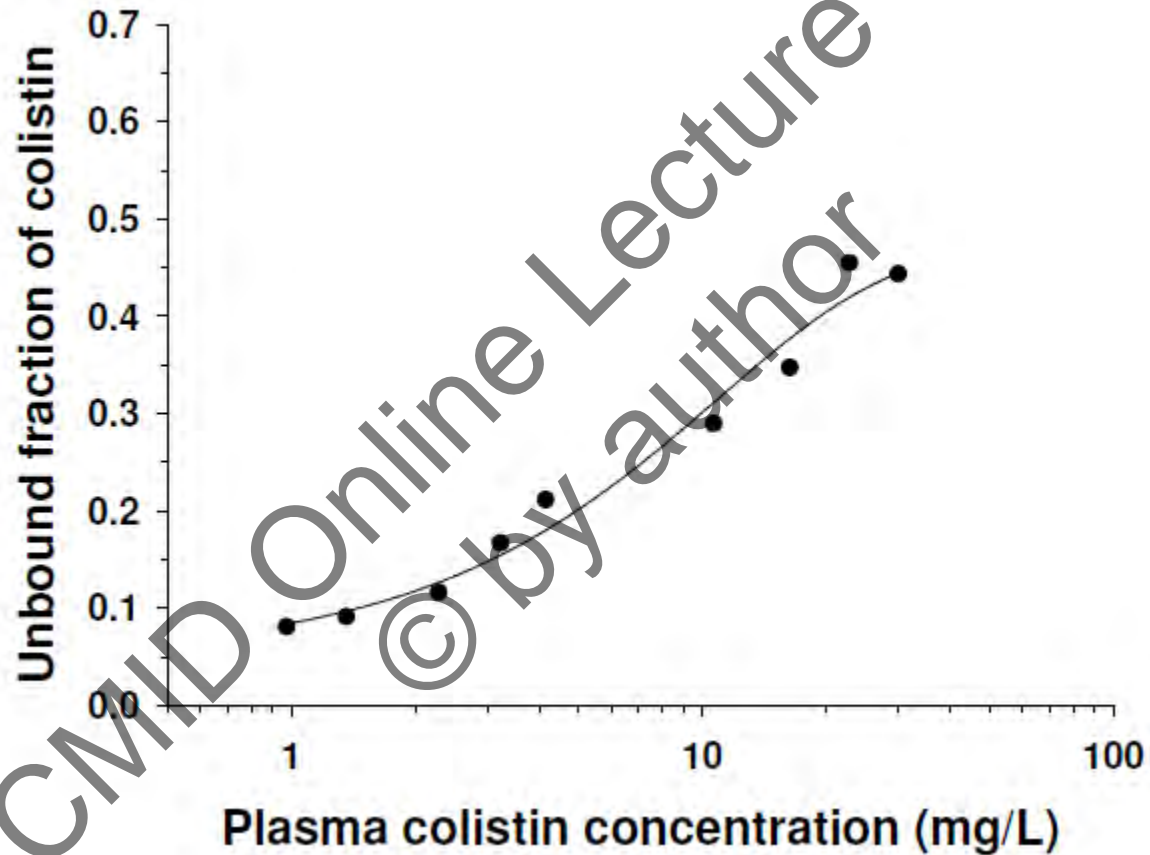
Kill effect	fAUG/MIC		
	ATCC 19606	248-01-C.248 ^a	N-16870.213 ^a
Thigh infection model			
Static effect	1.89	6.75	7.41
1 log ₁₀ kill	6.98	13.6	11.9
2 log ₁₀ kill	43.0	24.7	17.5
Lung infection model			
Static effect	1.57	6.08	6.52
1 log ₁₀ kill	8.18	12.9	42.1
2 log ₁₀ kill	95.0	22.5	^b

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Colistin

Protein binding in Mice



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Colistin

Animal model toxicodynamics

Toxicity is dose-related and also regimen related

- Doses mimicking once-daily dosing give more severe lesions more frequent dosing

ANTHROPOL. AGENTS AND CHEMOTHERAPY, May 2008, p. 1159-1161

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Subacute Toxicity of Colistin Methanesulfonate in Rats: Comparison of Various Intravenous Dosage Regimens⁷

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. Turnidge⁶

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

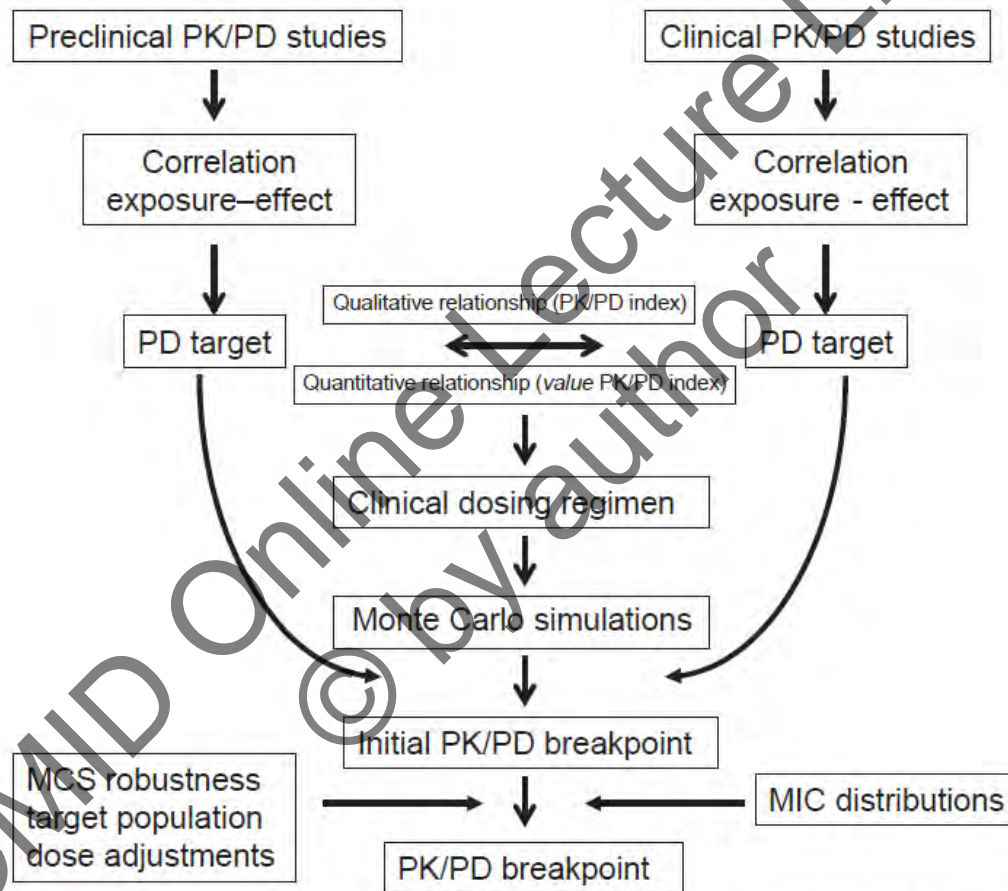


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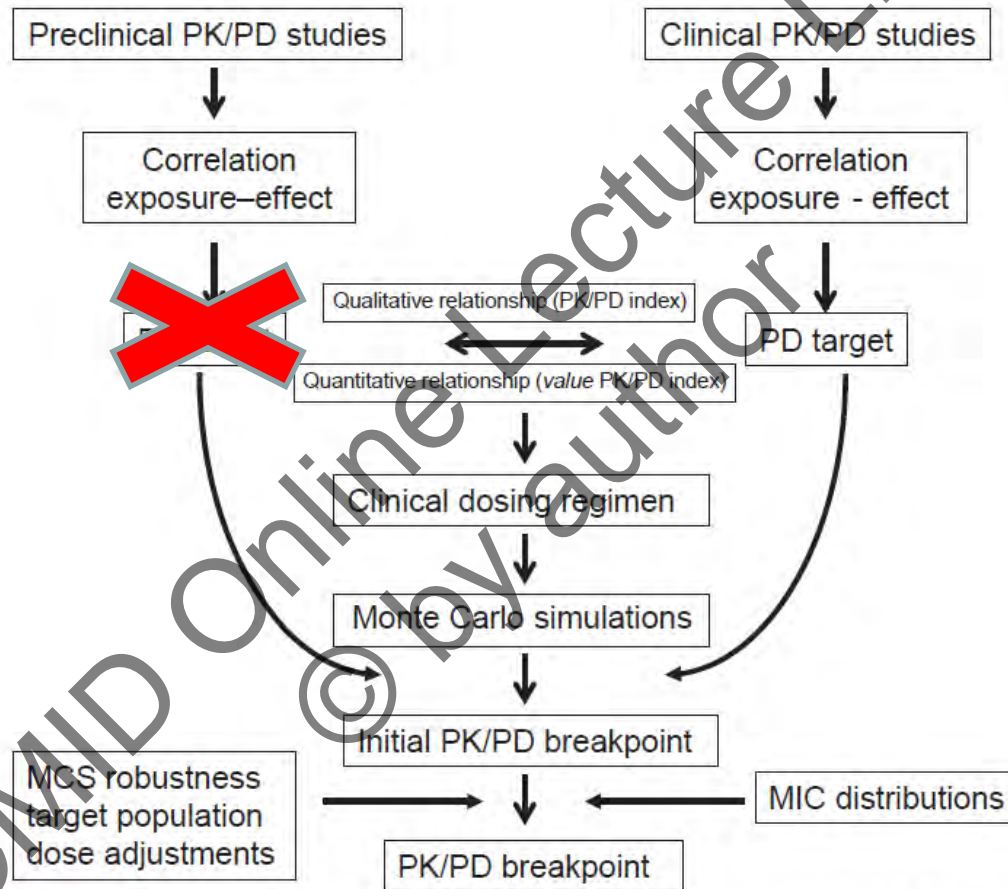


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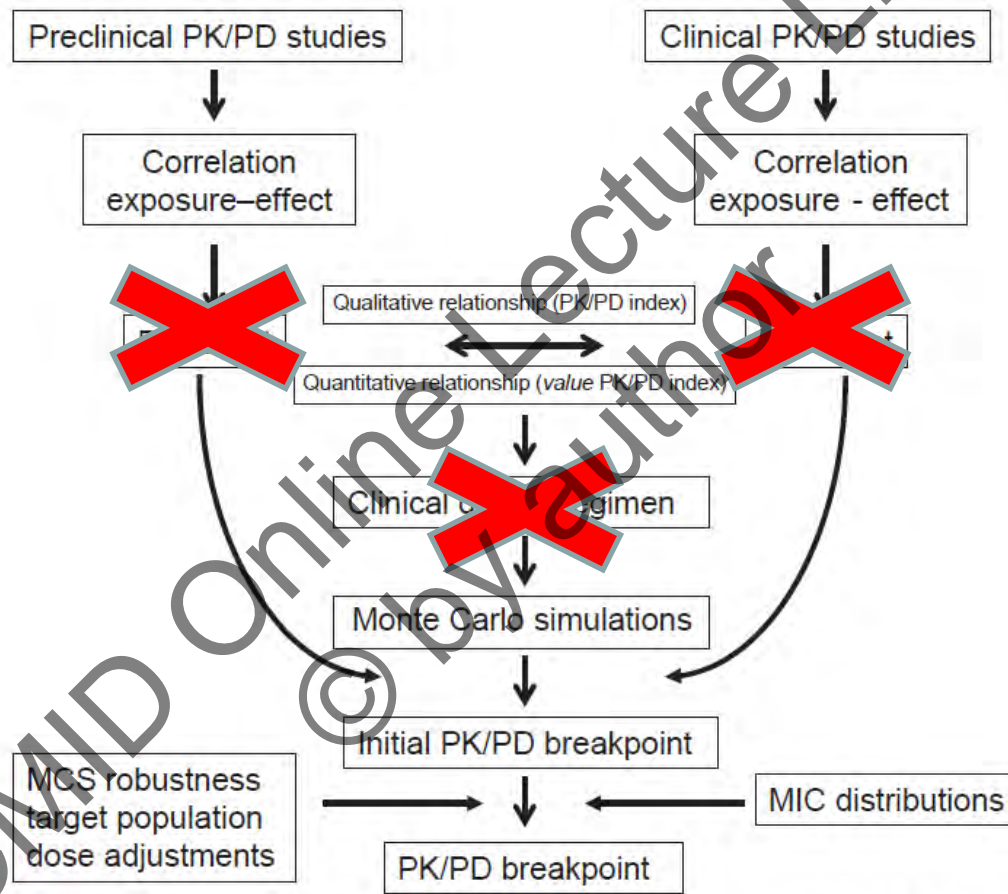


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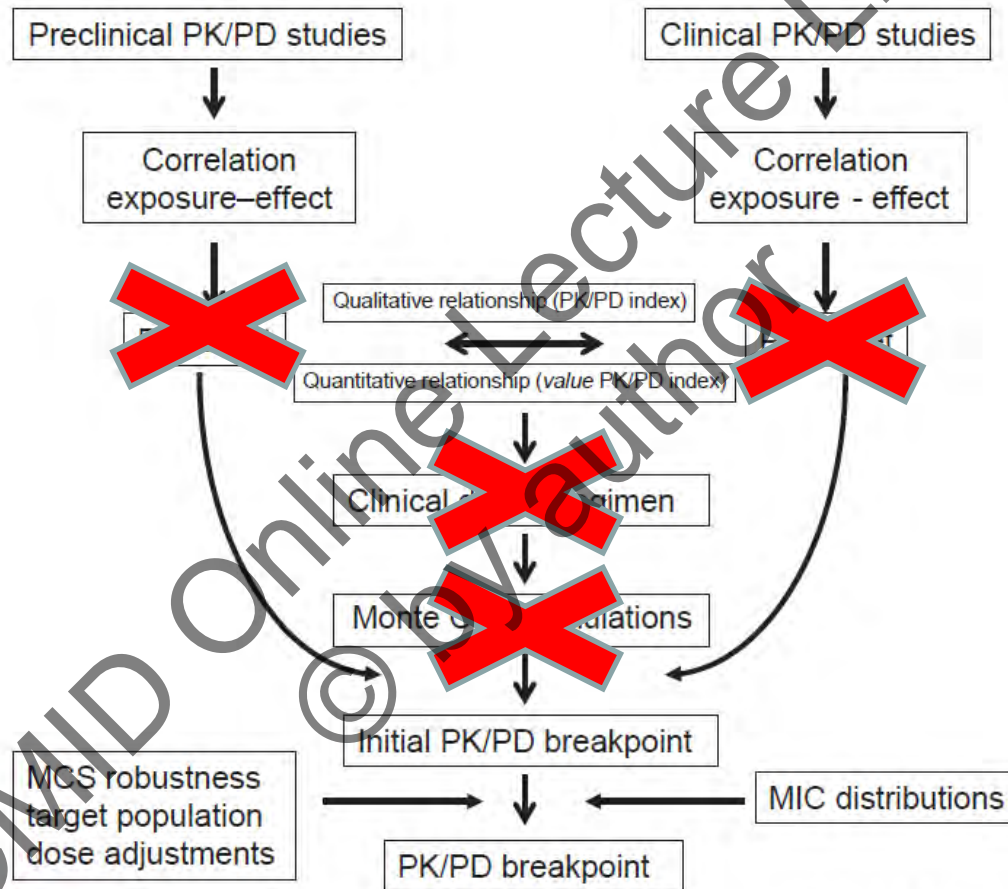


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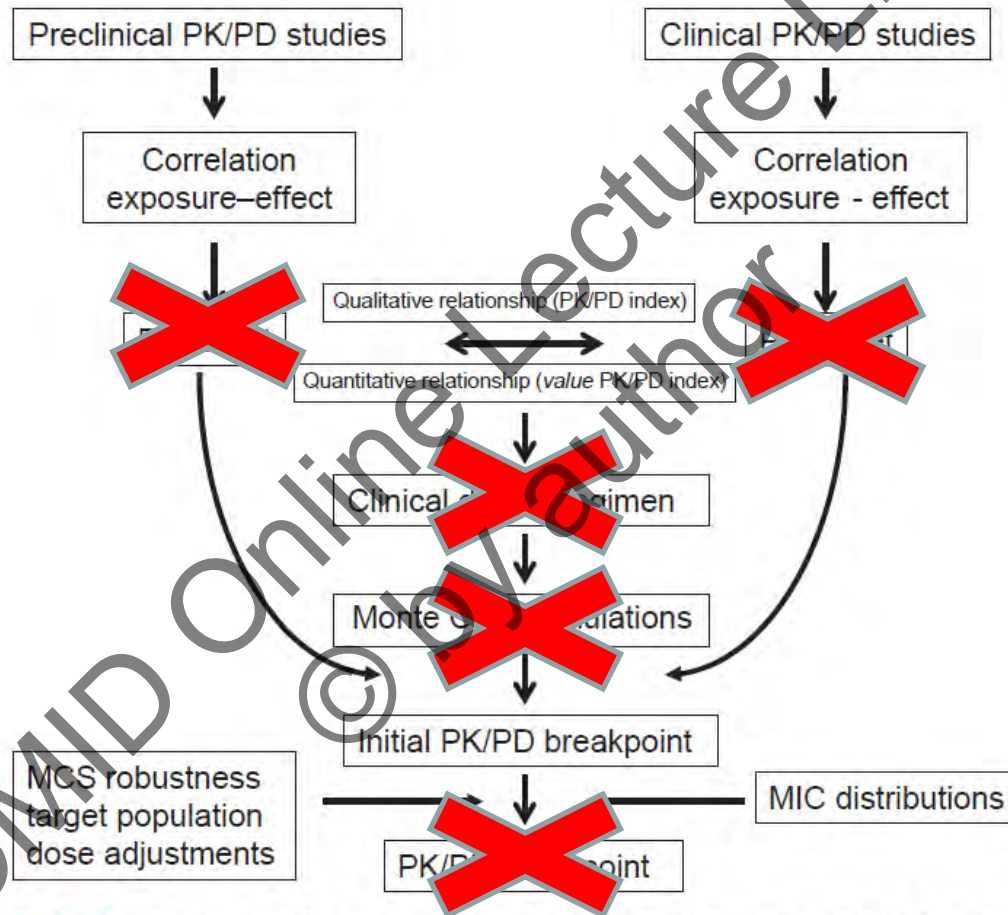


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