Improving dosing regimens to minimise resistance

Alasdair MacGowan
Professor of Antimicrobial Therapeutics
Bristol Centre for Antimicrobial Research & Evaluation (BCARE)
University of Bristol & North Bristol NHS Trust (NBT)
Southmead Hospital
Bristol
UK

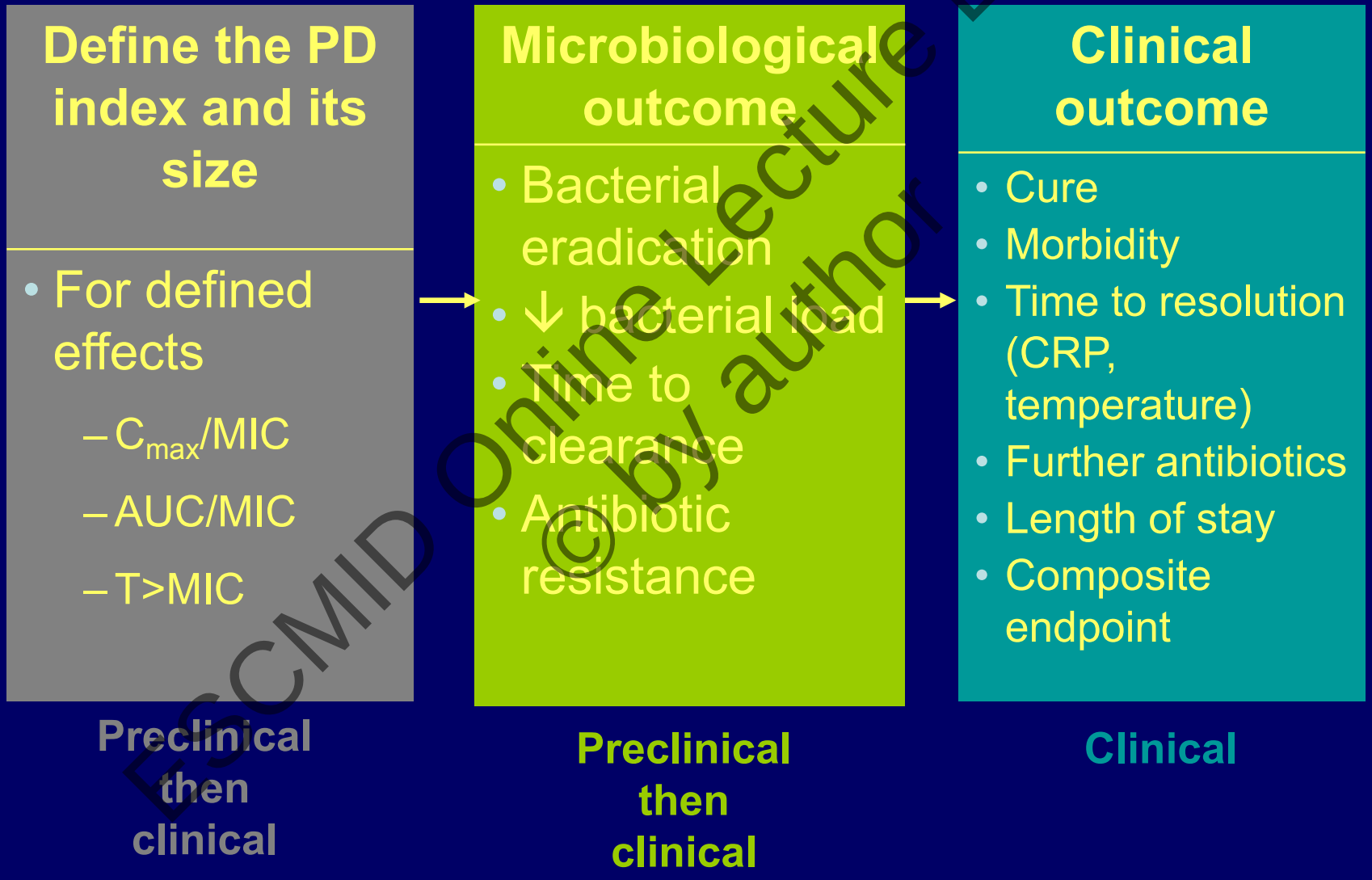
Tel: +44 (0) 117 323 5651/2
e-mail: alasdair.macgowan@nbt.nhs.uk

Antimicrobial Stewardship Lead for NBT

Topics

- the existing pharmacokinetic-pharmacodynamic (PK-PD) paradigm for determining dosing
- how pre clinical models can be used to determine risks of resistance with dosing regimens
- clinical limitations and extrapolations

The PK/PD paradigm



Defining the pharmacodynamic index and its size: pre-clinical models

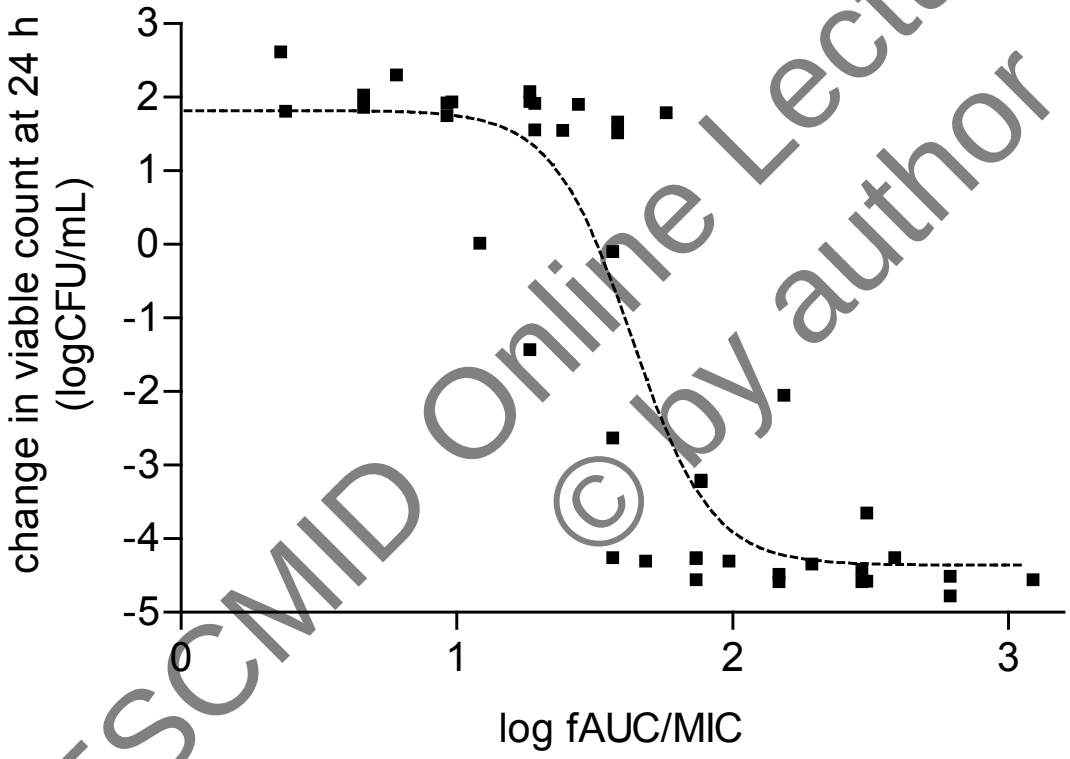
- Animal (*in vivo*) models:
  - Neutropenic thigh infection: mice
  - Pneumonia: mice, rats, rabbits
  - Endocarditis: rabbits
  - Meningitis: rabbits, mice
  - Urosepsis: mice
  - Other
- *In vitro* models:
  - Dilutional (with and without filter membranes)
  - Dialysis (hollow fibre models)
  - Intracellular infection
  - Foreign body
  - Other

Defining (confirming) the pharmacodynamic index and its size: Clinical Trials

- Usually nested studies within commercial registration RCTs
- Use population PK to establish individual patient drug exposures (i.e. AUC 218mg/L.h) combine with MIC of patient pathogen (i.e. MIC 0.5mg/L) to develop an individual PD index size (i.e. AUC/MIC=436)
- Relate AUC/MIC to microbiological outcome (or speed of resolution) using logistic regression or CART analysis
- Limited by insufficient numbers (often failures), most studies under powered by factor of 2-5, unclear if CART is the correct analytical tool, optimum study size unknown but probably >200

Case Study on anti-bacterial effect: daptomycin Exposure-response relationship in a preclinical *in vitro* PK model: setting the pharmacodynamic target

Relationship between daptomycin fAUC/MIC ratio and antibacterial effect for *S.aureus*



Bowker KE et al. J Antimicrob Chemother 2009;64:1044-1051

Defining the pharmacodynamic index size for daptomycin and *S.aureus*

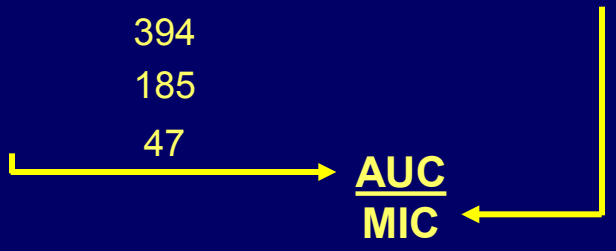
Model	Total drug AUC/MIC for 24hr bacteriostatic effect	Average (95% C1)
In vitro dilutional	656, 432, 286, 788, 423, 181	372 (182-561)*
Murine thigh	388, 537, 420, 409	
Murine thigh	120, 360, 272	358 (237-480)

*Corrected for protein binding

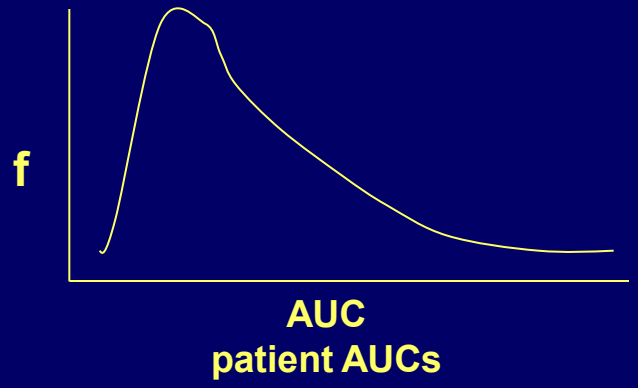
Louie et al, 2001; Dandekar et al, 2003; Safdar et al, 2004; Bowker et al, 2009

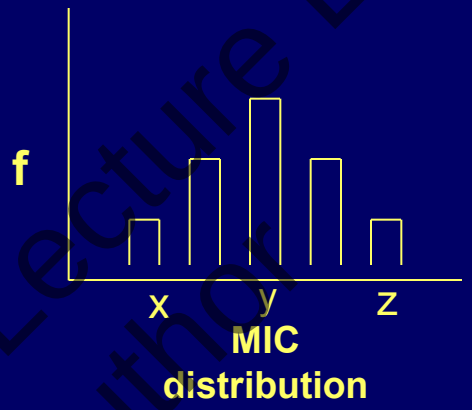
Monte Carlo simulation: a method of creating distributions of observations

Daptomycin (4 mg/kg)	AUC distributions, mg/l*h		MIC, µg/ml	
	Healthy	Infected	Value	Frequency
0–99.9	0	0		
100–199.9	0	6		
200–299.9	7	30	≤0.03	1
300–399.9	23	16	0.06	706
400–499.9	25	19	0.12	8032
500–599.9	20	4	0.25	18,216
600–699.9	2	3	0.5	8413
700–799.9	1	4	1	597
800–899.9	1	3	2	11
>900	0	1	≥4	0
n	79	86		35,976
Mean	442	394		
SD	110	185		
%CV	25	47		

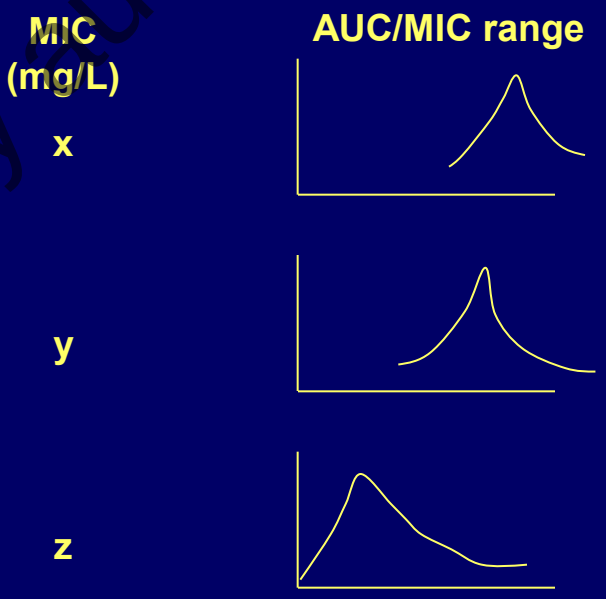


Integrating the pharmacodynamic index size, MIC and drug exposure : Monte Carlo simulation



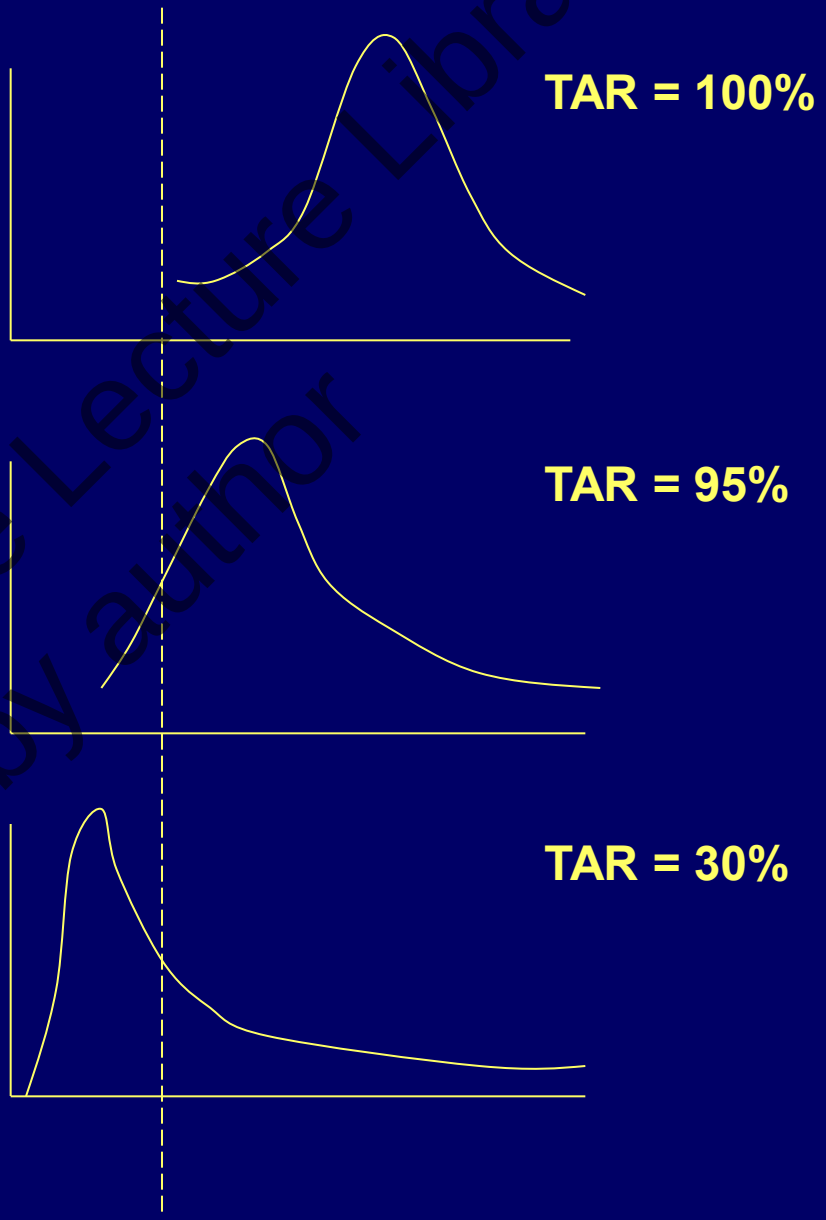


model expected MIC distributions to produce an AUC/MIC range for each MIC



overlay the
AUC/MIC target

PD
Breakpoint
(TAR ≥90%)



Modelling target attainment rates for daptomycin by Monte Carlo simulation, stratified by MIC/AUC/MIC target based on data from in vitro and animal models

Dose	4mg/kg/d		6mg/kg/d		8mg/kg/d	
MIC (mg/L)	Healthy volunteers	Infected patients	Healthy volunteers	Simulated* infected patients	Healthy volunteers	Simulated* infected patients
0.25	100	100	100	100	100	100
0.5	100	95.1	100	99.7	100	100
1	77.6	49.4	100	90.3	100	98.5
2	3.1	9.4	97.2	39.7	100	71.6
4	0	0	2.2	3.4	43.3	16.9
8	0	0	0	0	0	0

Target attainment rate ≥90% suggest the pharmacodynamic breakpoint

*** Inflated variance in US terminology**

Dosing to suppress emergence of resistance: what the pre clinical models tell us

Factors associated with risk of emergence of resistance:-

- **species (*P.aeruginosa*, *S.aureus*, >*S.pneumoniae*)**
- **drug exposure**
- **time of drug exposure**
- **fractionation of exposure (B-lactams)**

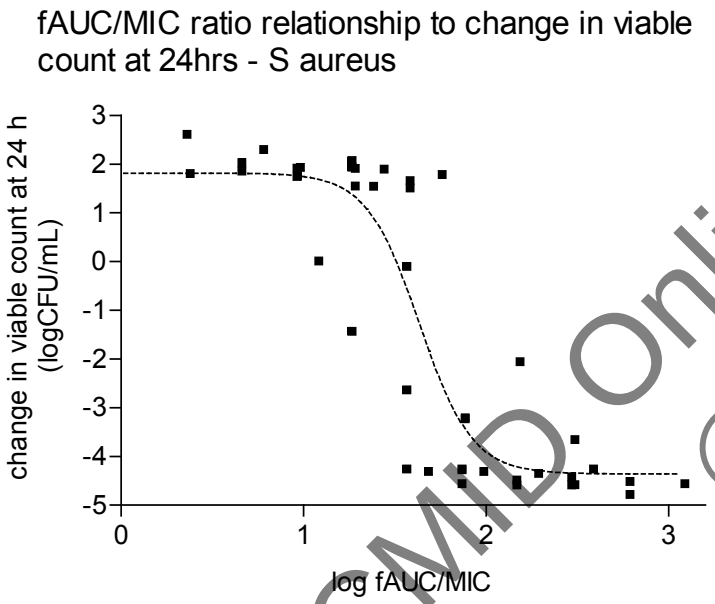
Impact of exposure: the inverse "U" relationship: moxifloxacin and *P.aeruginosa*

Moxifloxacin $fAUC_{72}/MIC$	index of resistance: change in population profile
0	34 ± 7
320 Experiment 1	95
320 Experiment 2	88 ± 13
322	84 ± 1
644	99 ± 2
1280 Experiment 1	23 ± 29
1280 Experiment 2	28 ± 14

MacGowan et al, 2003

Impact of drug exposure

Daptomycin and *S.aureus*: fAUC/MIC relationship to antibacterial effect and changes in population profile

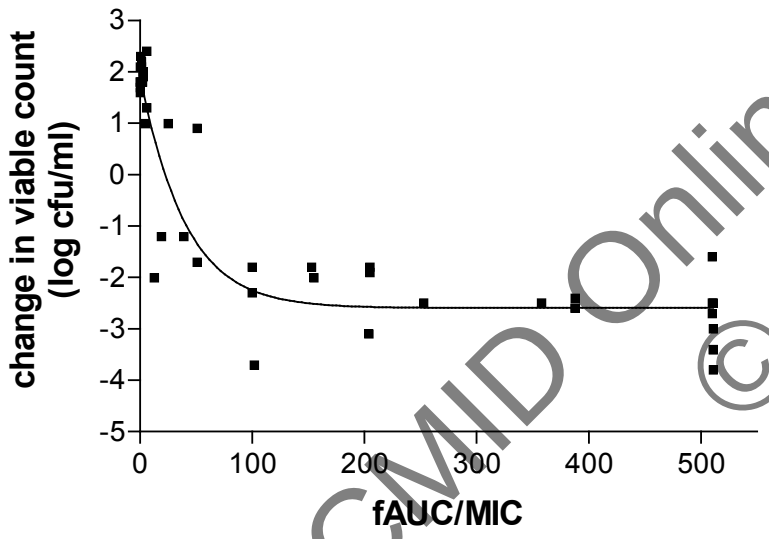


fAUC/MIC	number of experiments	% experiments with growth on MICx4 plates	bacterial count on MICx4 plates
0.5-10	11	73(8)	4.3 ± 1.3
10-30	5	60(3)	3.9 ± 0.8
30-40	3	67(2)	3.6
>40	6	17(1)	4.7

Bowker et al, 2009; JAC 64: 1044-1051

Impact of drug exposure

Telavancin and *S.aureus*: fAUC/MIC relationship to antibacterial effect and changes in population profile

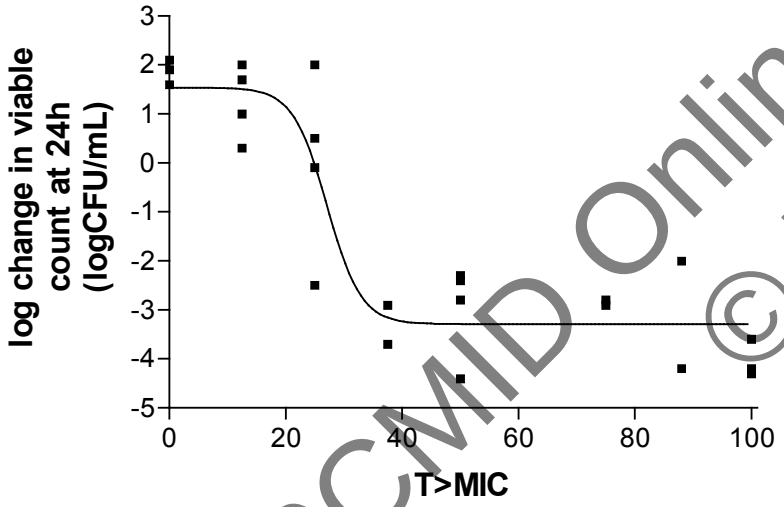


fAUC/MIC	number of experiments	% experiments with growth on MICx2 plates	bacterial count on MICx2 plates
1-3	8	100(8)	5.6 ± 1.9
3-10	3	100(8)	4.7 ± 0.6
10-50	8	50(4)	4.3 ± 1.1
50-175	7	29(2)	4.2
175-400	7	14(1)	2.1
>400	5	0	<2

Bowker et al, 2009; ICAAC Abst A-1271

Impact of drug exposure

Doripenem and *P.aeruginosa*: fT>MIC relationship to antibacterial effect and changes in population profile



fT>MIC %	number of experiments	% experiments with growth on MICx2 plates	bacterial count on MICx2 plates
12.5-25	8	75(6)	7.1 ± 0.9
>25-50	6	17(1)	3.9
>50-75	6	17(1)	3.0
>75	5	0	<2
		% experiments with growth on MICx4 plates	bacterial count on MICx4 plates
12.5-25	8	38(3)	6.2 ± 1.1
>25-50	6	0	<2
>50-75	6	0	<2
>75	5	0	<2

Impact of time

doripenem 500mg 8hrly free drug simulations against *P.aeruginosa* MIC 0.25mg/L (fT>MIC 88%)

		viable count at dori MIC multiple			
		0	x1	x2	x4
time	0	6.2 ± 0.1	<2	<2	<2
time	24	3.1 ± 1.3	<2	<2	<2
	48	4.7 ± 1.8	<2	<2	<2
	72	5.0 ± 1.8	<2	<2	<2
	96	6.2 ± 1.7	4.2 ± 2.4	2.9 ± 1.0	<2

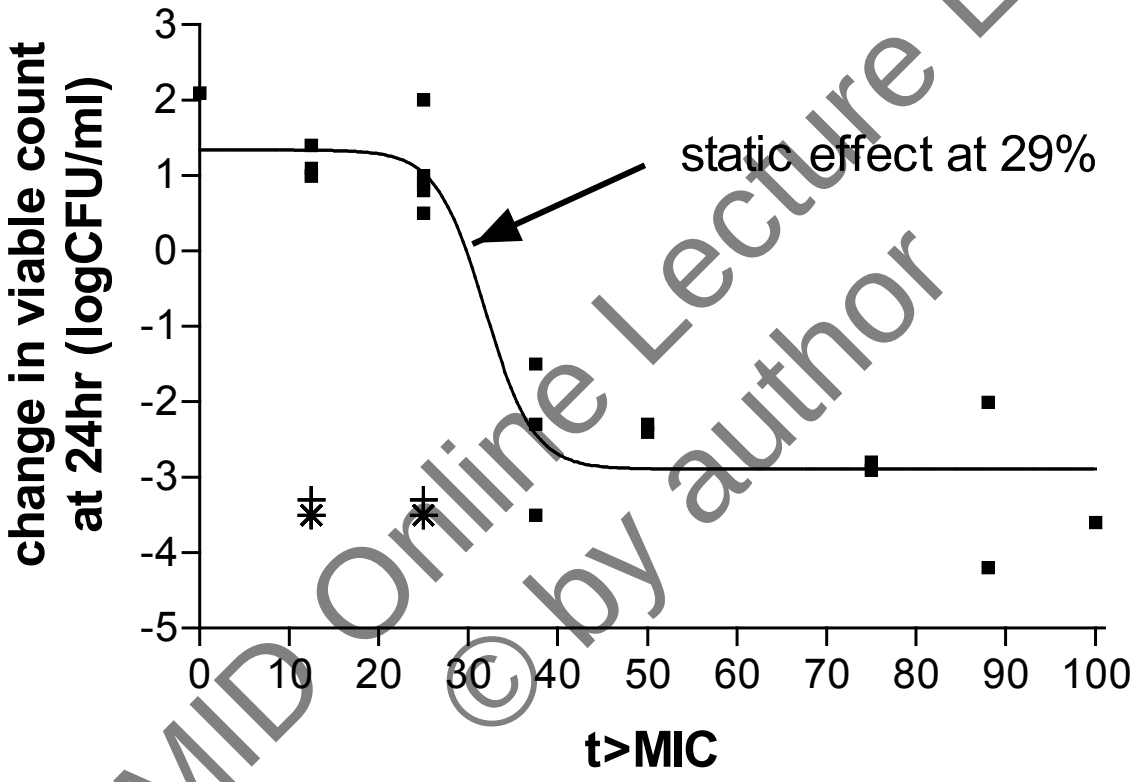
Impact of time and exposure

Changes in population profiles of MRSA strains exposed to 5 days dosing of razupenem: 1g 12 hrly simulations

		growth on MICx2 recovery media (log CFU/ml)		
strain		**MRSA 36895**	**MRSA 27706**	**MRSA 33820**
MIC (mg/L)		**0.38**	**1.5**	**3.0**
	fT>MIC	**75%**	**64%**	**44%**
pre exposure	**(time 0)**	**<2**	**<2**	**<2**
post exposure	**+24h**	**<2**	**<2**	**<2**
	+48h	**<2**	**<2**	**<2**
	+72h	**<2**	**<2**	**4.1 ± 0.7**
	+96h	**<2**	**<2**	**4.3 ± 0.6**
	+120h	**<2**	**3.0^{+}**	**5.2 ± 0.1**

average of 2 of 4 experiments

P aeruginosa strain 38475 - relationship between T>MIC and antibacterial effect and emergence of resistance



▪ change in viable count at 24hr

✳ growth on MICX4 at 24hrs

\+ growth on MICX8 at 48hrs

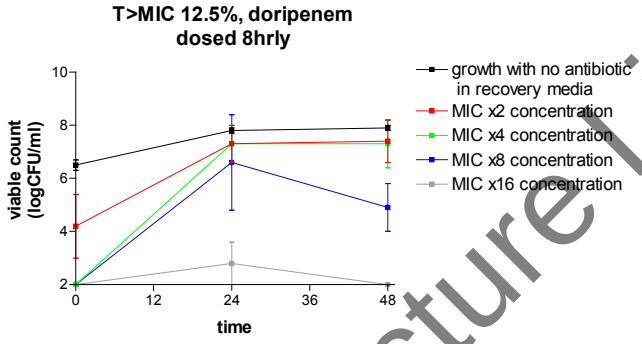
Impact of fT>MIC fractionation

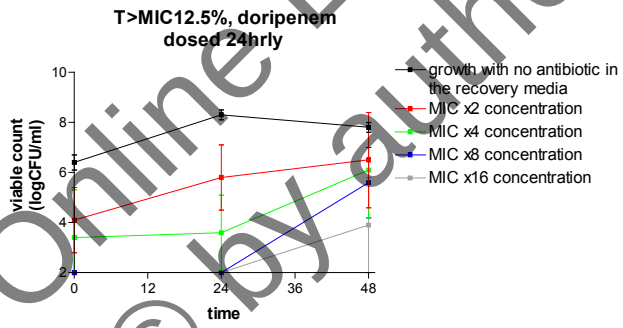
P.aeruginosa doripenem MIC 0.25mg/L

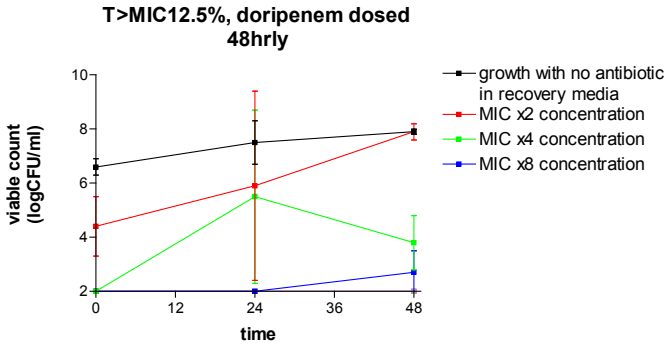
Doripenem administered to give T>MIC of 12.5%, 25% or 37.5% as

6 exposures (8 hrly dosing over 48h)
2 exposures (24 hrly dosing over 48h)
1 exposure (48 hrly dosing)

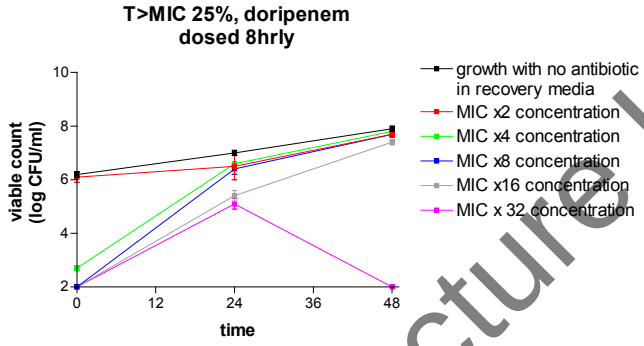
Impact of dose fractionation: fT>MIC 12.5%

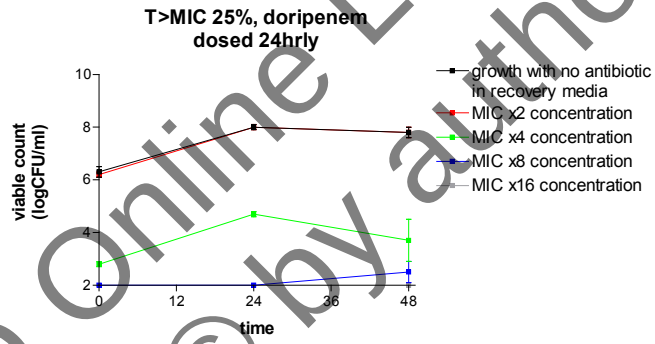


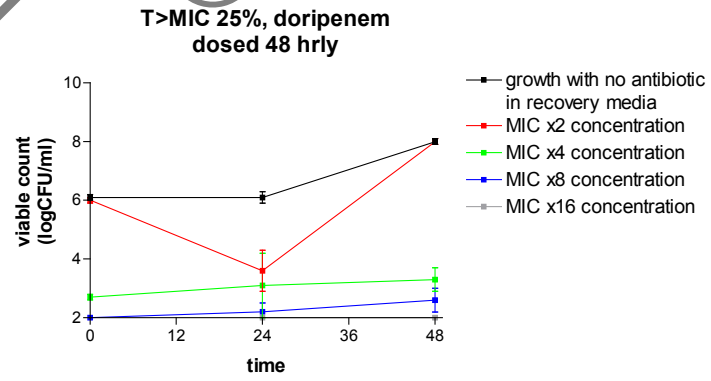




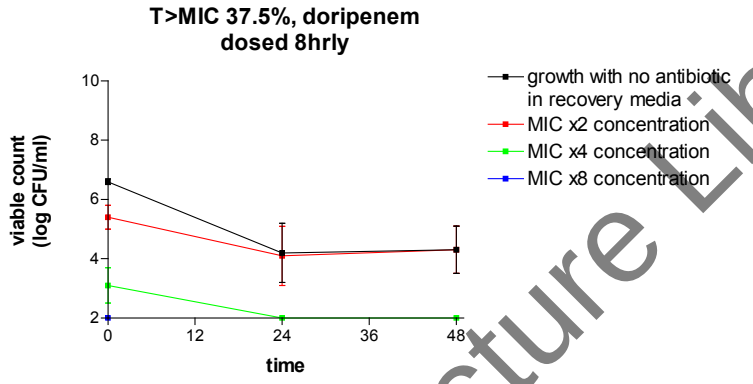
Impact of dose fractionation: fT>MIC 25%, 24h static effect

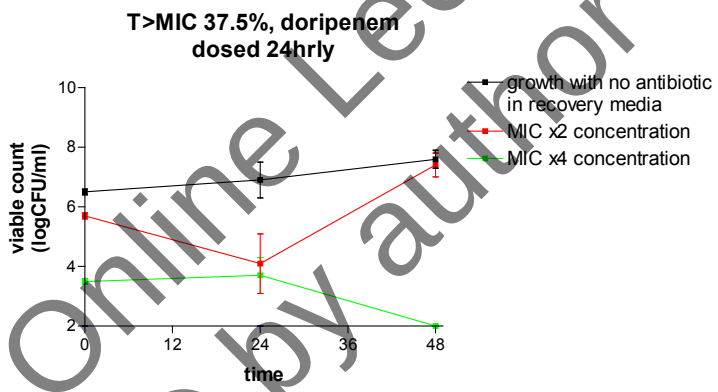


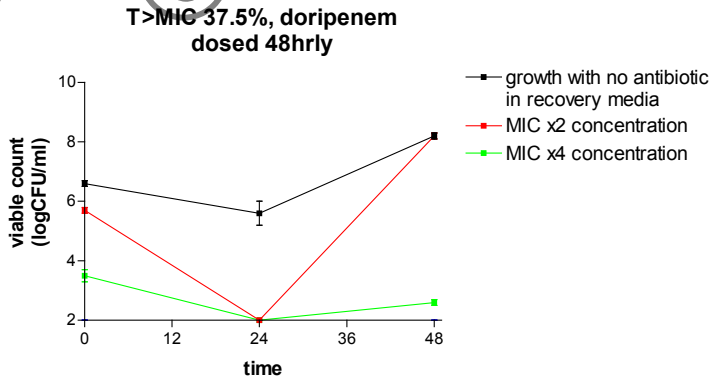




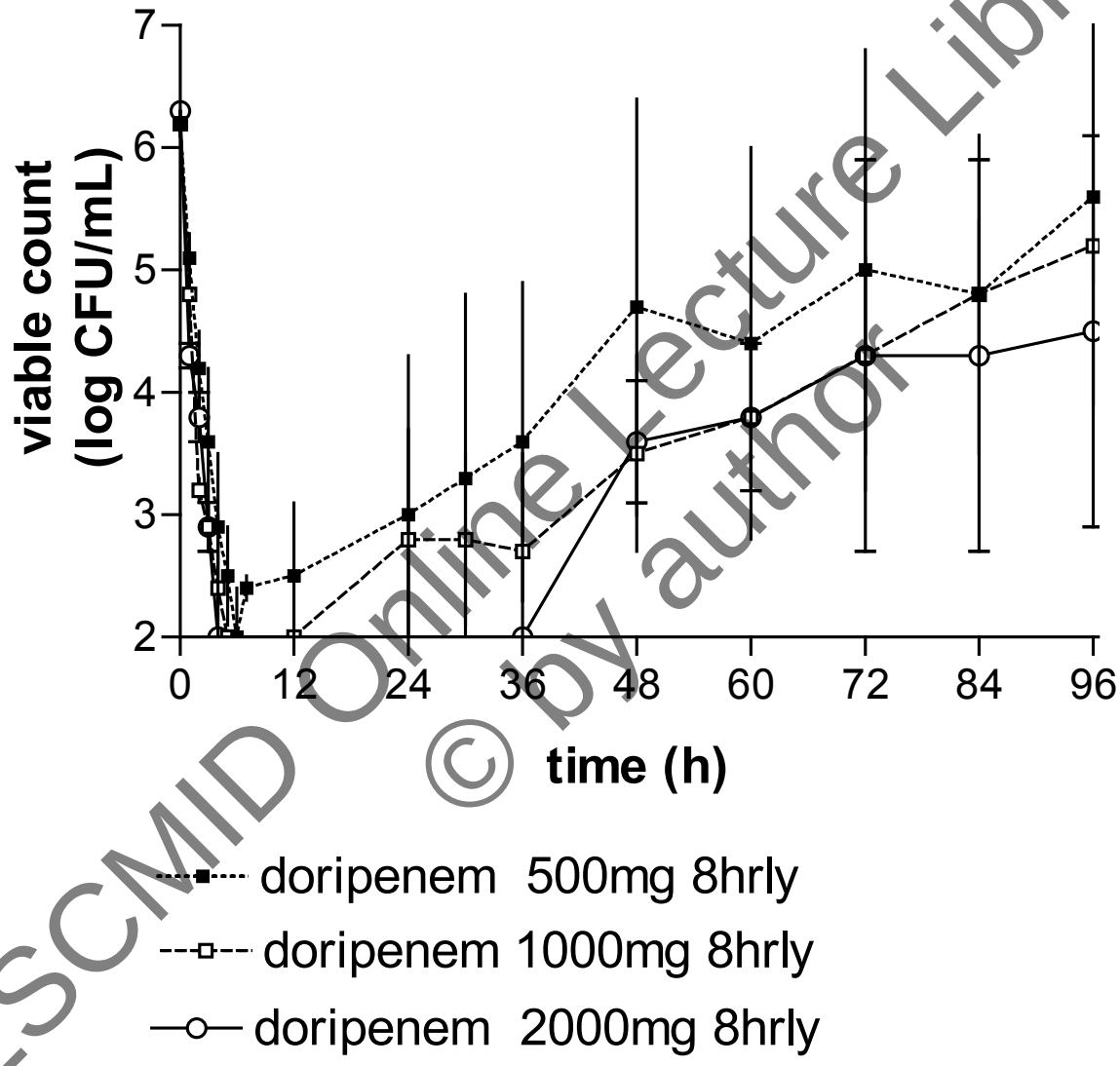
Impact of dose fractionation: fT>MIC 37.5%, 24h -2 log drop







Dose escalation: sometimes you cannot give enough drug
Doripenem: dose escalation in *P.aeruginosa*



Limitations

- optimising dosing can only prevent emergence of resistance in pathogens at the site of infection
  - not pathogens on body surfaces
  - not pathogens in the environment
- pre clinical ~ clinical correlates are not yet strong for emergence of resistance
- little data on impact of dosing on gene transfer compared to up regulation efflux pumps or target site mutation
- sometimes not enough of a single drug can be given to prevent resistance

Extrapolations to clinical practice: implications for stewardship

- high dose therapy preferable to low dose ⇒
  ?maximum tolerated doses for all indications
- short course therapy preferable to long course ⇒
  - ?5 days for CAP, HAP, ?VAP
  - ?3 days for complicated UTI
  - ?7 days for pyleonephritis
  - ?5 day community acquired peritonitis
- beware of treating susceptible pathogens with MICs close to the breakpoint
- combination therapy may prevent emergence of resistance – but no clinical data and ?effect on adverse events ⇒ clinical trials required
- pharmacodynamic-optimisation via individual patient optimisation may have role in preventing resistance, i.e. continuous infusion B-lactams or Therapeutic Drug Monitoring