Cutting-edge issues in translational pharmacodynamics and personalised antimicrobial therapy

Combination therapy to prevent emergence of resistance

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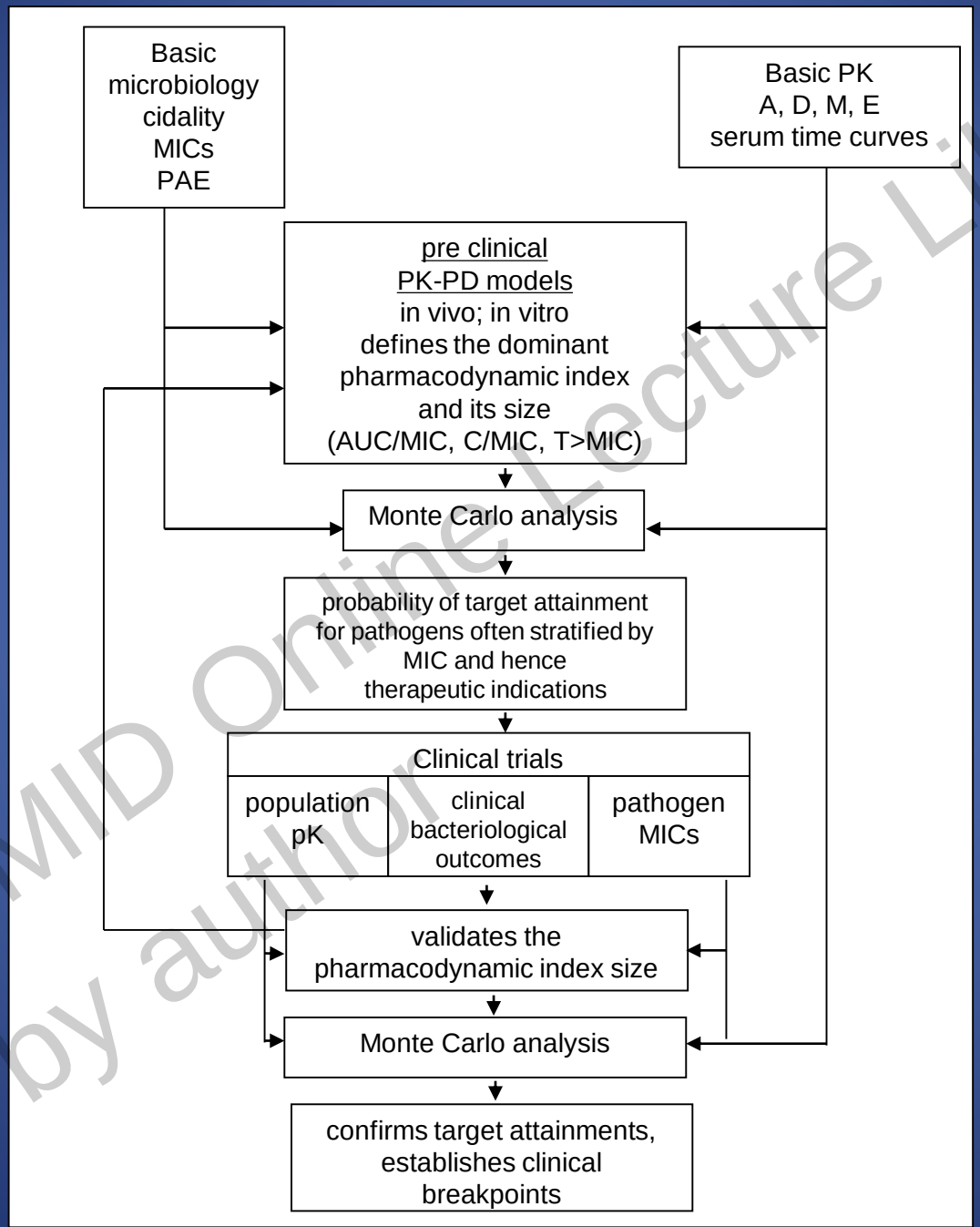
Topics:-

- Brief overview of the present pharmacodynamic paradigm for bacterial clearance
- Pre-clinical data on factors associated with risks of emergence of resistance in target pathogens
- Why combination therapy?
- Clinical correlates and future directions

The Pharmacokinetic-Pharmacodynamic paradigm to predict bacterial inhibition/killing



Pre-clinical data on emergence of resistance

Impact of species: *S.pneumoniae* compared to *P.aeruginosa*

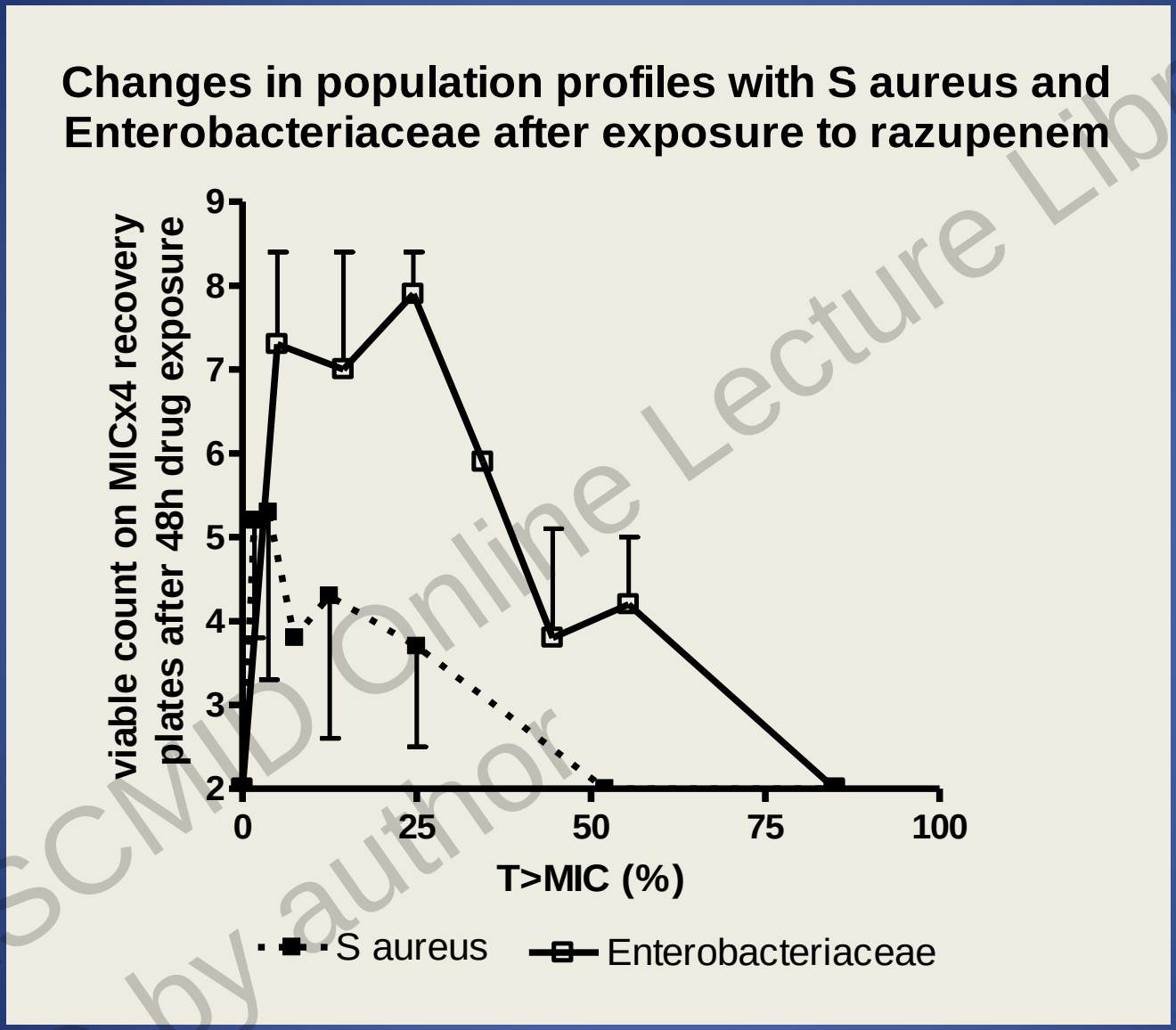
moxifloxacin at fAUC/MIC ratios of 107 and 428

species	fAUC / MIC	AUC-PAP at time - 0	24	48	72
S.pneumoniae	107	3.0 ± 0.1	1.1 ± 1.1	<1	<1
P.aeruginosa	107	13.7 ± 7.1	32.2 ± 15.4	74.7 ± 18.3	87.7 ± 12.9
S.pneumoniae	428	3.0 ± 2.2	1.2 ± 2.1	1.1 ± 1.4	4.4 ± 8.8
P.aeruginosa	428	30.7 ± 8.3	23.1 ± 7.8	15.9 ± 6.7	28.0 ± 14.2

P.aeruginosa **more heterogenous initial population profile, more rapid emergence of resistance**

MacGowan et al, 2003; AAC 47: 1088-95

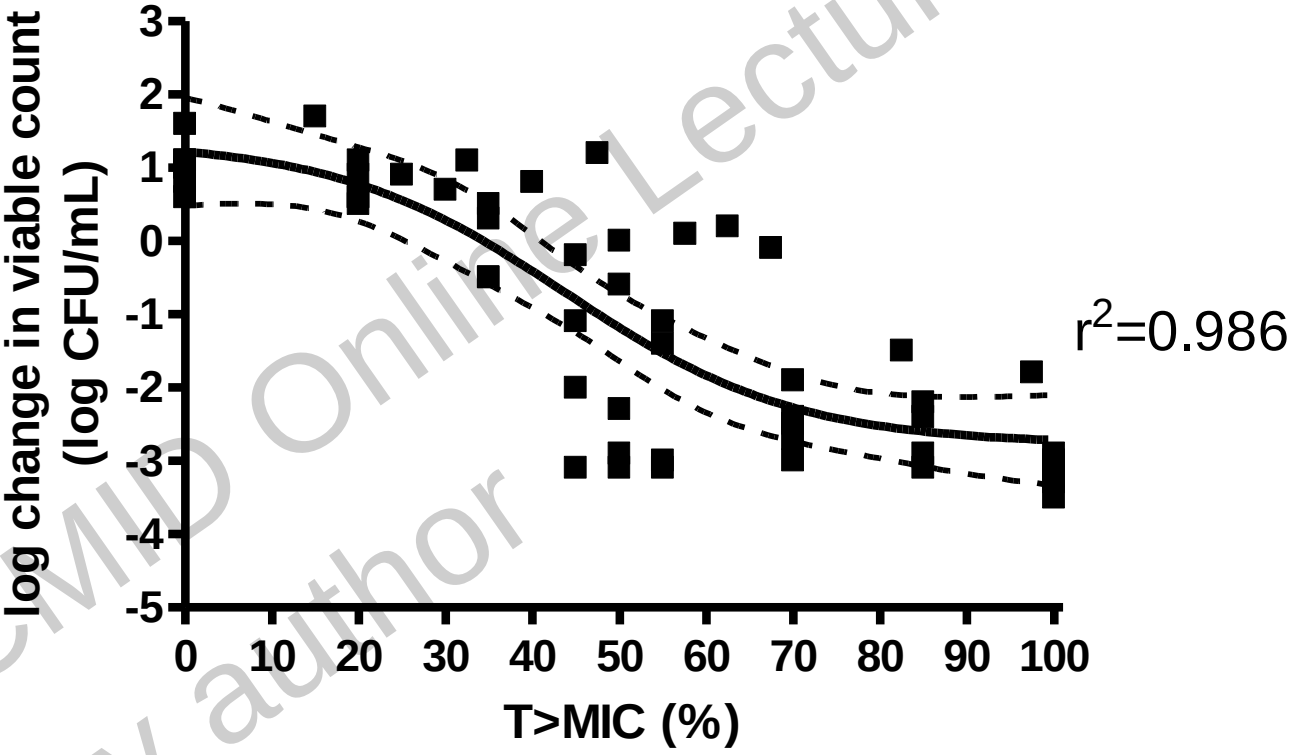
Impact of species: S.aureus and Enterobacteriaceae



T>MIC for -1 log drop S.aureus 12.5% ± 6; Enterobacteriaceae 42.5% ± 8

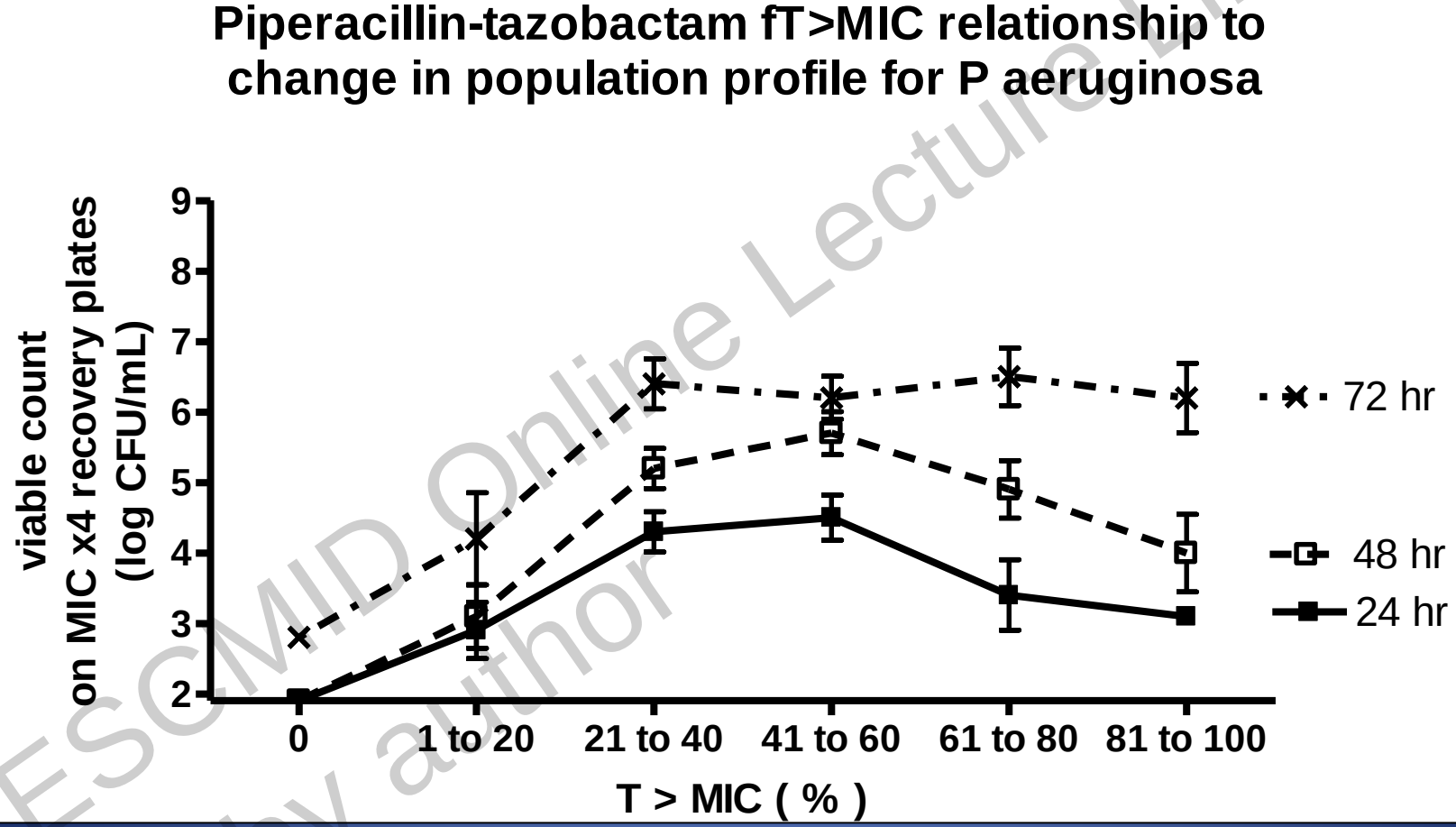
Impact of amount of drug exposure

Piperacillin-tazobactam fT>MIC relationship to antibacterial effect at 24 h for P aeruginosa



Bowker et al, 2012

The inverse U relationship between antibiotic exposure and resistance

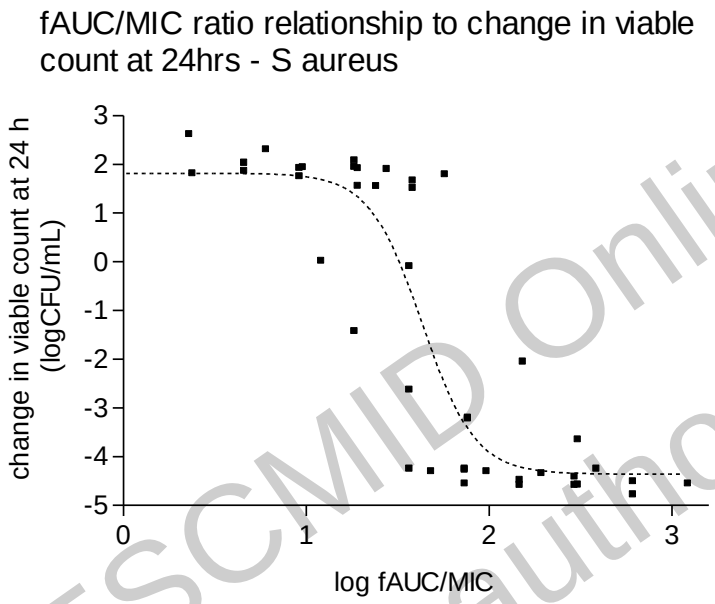


T>MIC for static effect 40-50% at 24h

Bowker et al, 2012

Impact of the amount of drug exposure with a fixed time

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

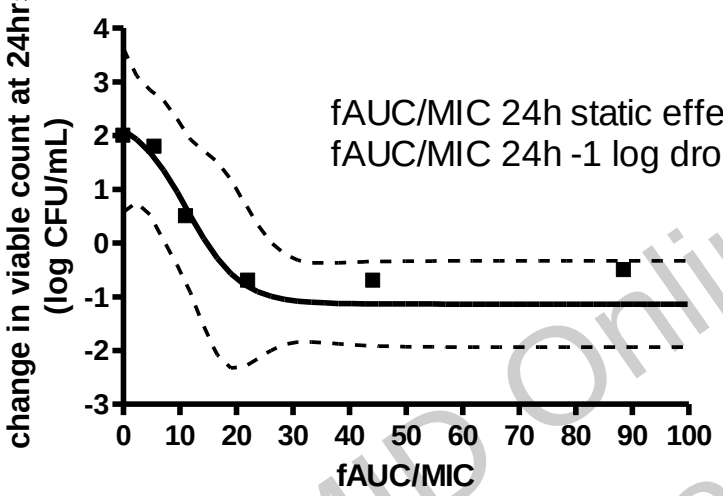


fAUC/MIC	number of experiments	% experiments with growth on MICx4 plates	bacterial count on MICx4 plates
0.5-10	11	73(8)	4.3 ± 1.3
10-30	5	60(3)	3.9 ± 0.8
30-40	3	67(2)	3.6
>40	6	17(1)	4.7

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

Impact of amount of drug exposure

fAUC/MIC minocycline relationship to antibacterial effect for Acinetobacter spp



Risk of emergence of resistance at 72h stratified by fAUC/MIC ratio

fAUC/MIC	Growth on MIC x 4 plates		Growth on MIC x 8 plates	
	Number of experiments	Mean count	Number of experiments	Mean count
1-5	1/3	3.6	1/3	3.2
>5-10	2/3	7.2	2/3	5.5
>10-15	2/3	7.6	0/3	-
>15-20	0/3	-	0/3	-
>20	0/3	-	0/3	-

Noel et al, 2014

Impact of antibiotic exposure on bacterial kill and risk of emergence of resistance

Agent	Pathogen	Pharmacodynamic Index (PDI)	Size of PDI for		
			24h static effect	24h -1 log drop oin count	Maximum amplification of resistant population
Razupenem	MRSA	T>MIC	5±1.5	13±6	2.5-10
Daptomycin	MRSA	AUC/MIC	37±16	41±18	30-40
Telavancin	MS/RSA	AUC/MIC	43±38	50±40	1-10
Ceftaroline	MS/RSA	T>MIC	27±10	31±12	15-40
Minocycline	MRSA	AUC/MIC	12±7	22±12	No resistance
Razupenem	Enterobacteriaceae	T>MIC	34±18	42±8	30-39
Ceftaroline	E.coli	T>MIC	35±6	37±7	20-40
	K.pneumoniae	T>MIC	36±8	44±9	1-30
Amikacin	K.pneumoniae	AUC/MIC	36±18	58±20	10-20
Doripenem	P.aeruginosa	T>MIC	25±11	30±11	12.5-25
Ceftolozane-tazobactam	P.aeruginosa	T>MIC	25±3	26±4	10-30
Amikacin	P.aeruginosa	AUC/MIC	51±15	70±14	1-20
Piperacillin-tazobactam	P.aeruginosa	T>MIC	39±8	51±13	20-60
Doripenem	A.baumanii	T>MIC	20±11	25±10	12.5-25
Minocycline	A.baumanii	AUC/MIC	16±3	23±4	5-15
Telavancin	Enterococcus sp	AUC/MIC	15±8	40±30	3-10

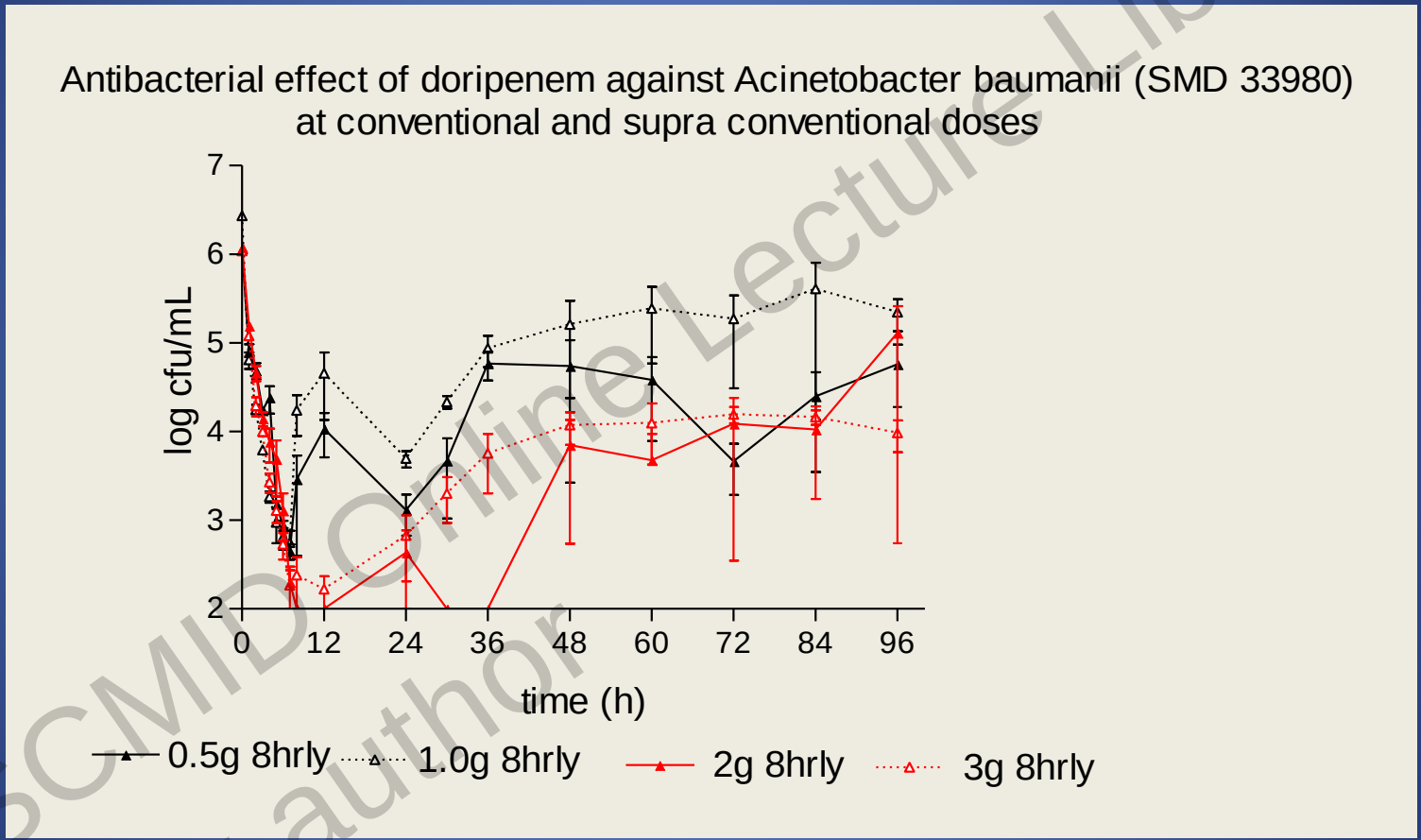
Impact of time – optimised dosing

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

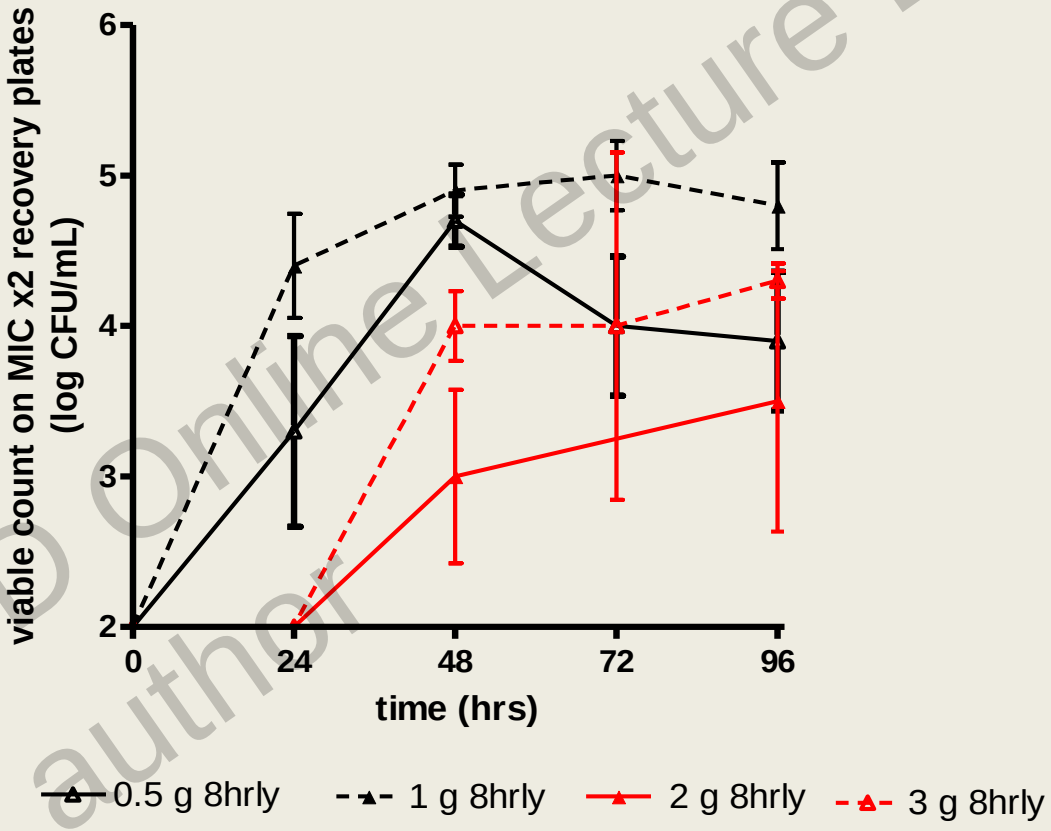
Bowker et al, 2012

Suppressing resistance: increasing exposure



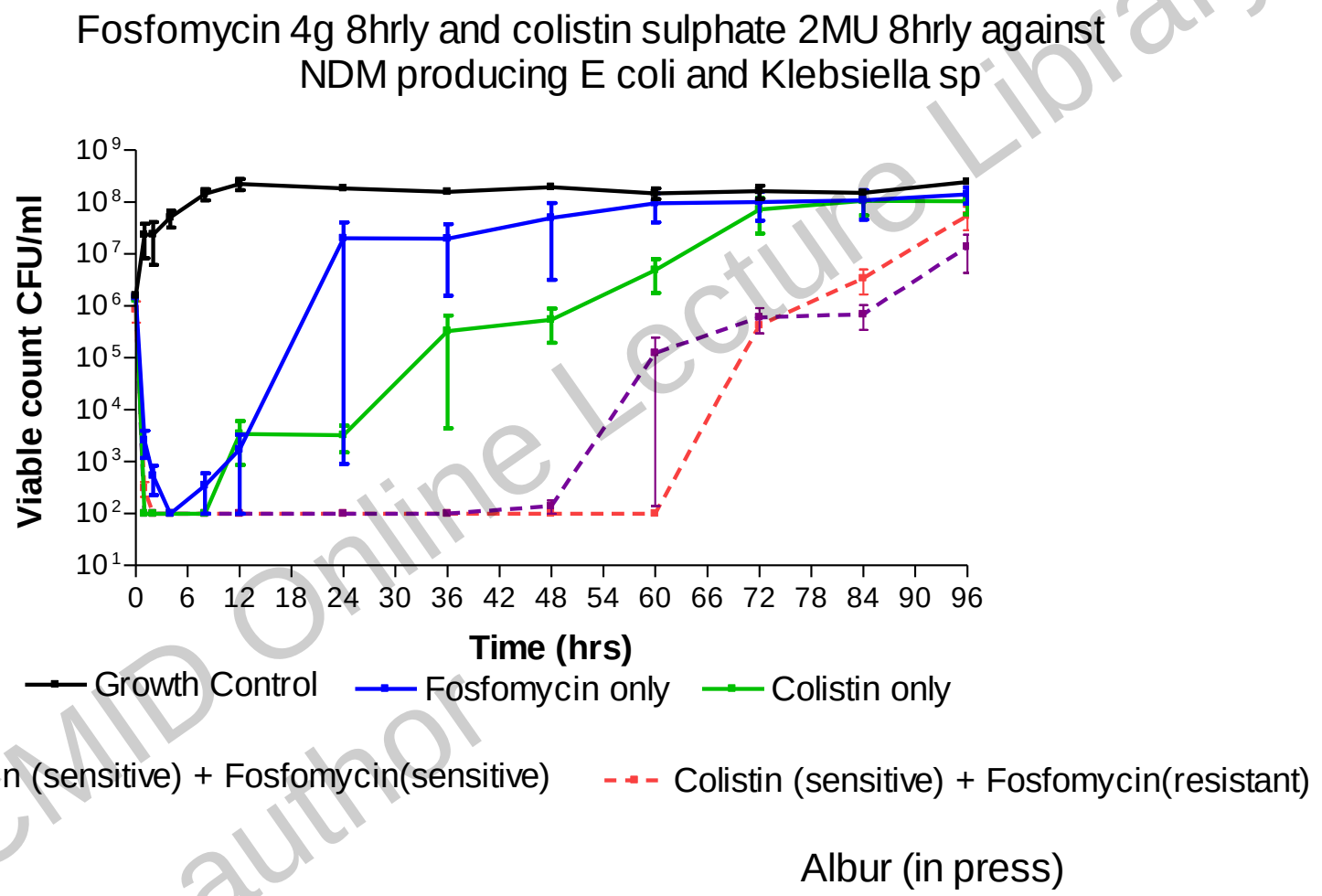
Supressing resistance: increasing exposure

Changes in population profiles of Acinetobacter baumanii (SMD 33890) after exposure to doripenem dose simulations of 0.5g, 1g, 2g and 3g 8hrly



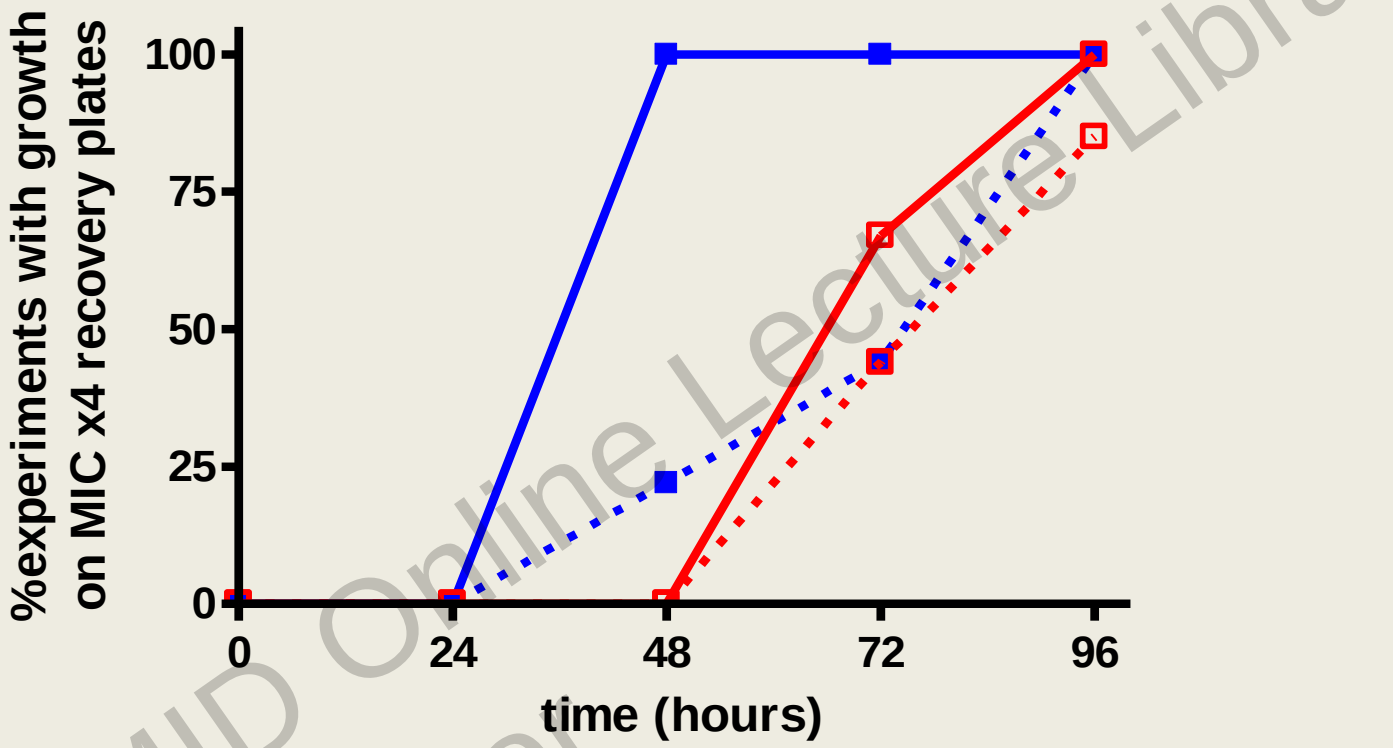
Also see Tam et al, 2008, Aminoglycosides and *P.aeruginosa*; *A.baumanni* (Cmax/MIC 30/12hrly to suppress resistance

Suppressing resistance: combinations

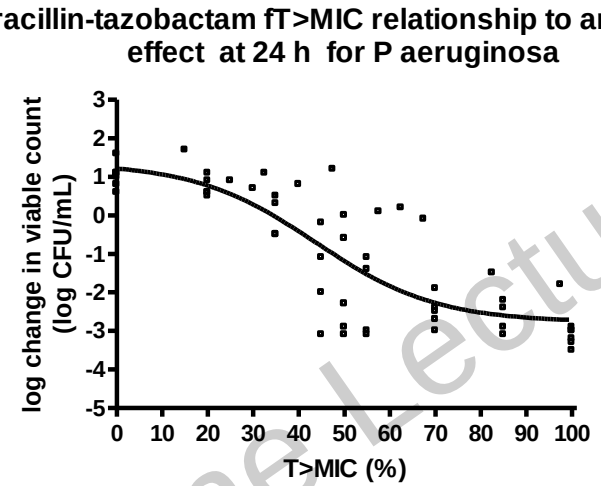


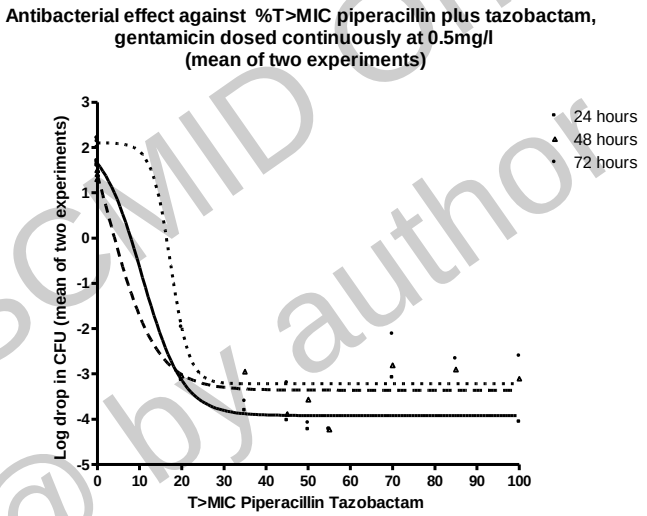
Albur (in press)

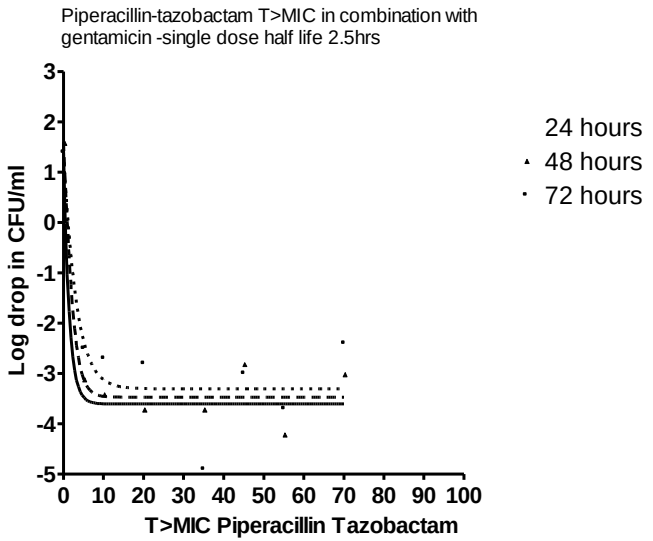
Supressing resistance: combinations



Suppressing resistance: combinations (Cochrane, personal communication)







Supressing resistance: combinations – mechanisms of resistance

- Chequerboard time-kill studies
- Wild type and MexAB hyper-producing mutants of P.aeruginosa
  MexAB only pumps meropenem
- Tobramycin and meropenem
- Resistance emergence greater to meropenem than tobramycin

	AUC (log CFU/ml mg/L)	
	Wild type	**MexAB mutant**
Meropenem resistance with		
O mg/L	7.7 ± 1.7	57.6 ± 6.4
0.25 mg/L tobramycin	2.2 ± 0.2	28.7 ± 5.5
0.5 mg/L	0.3 ± 0.5	7.1 ± 2.2
Trobramycin resistance with		
0 mg/L	17.9 ± 2	20.8 ± 3.2 NS
0.5 mg/L meropenem	5.6 ± 0.7	18.5 ± 2.2
1 mg/L	2.2 ± 0.7	17.3 ± 1.9
2 mg/L	0.7 ± 1.2	10.8 ± 2.6

Drusano et al, 2009

Clinical correlates: monotherapy (1)

Guillernot et al, 1998

Observational prospective study of carriage of penicillin resistant S.pneumoniae in children; low dose, >5 days therapy associated with increased risk of carriage.

Thomas et al, 1998

Pooled data from four LRTI studies. 107 patients, 128 pathogens, 5 drugs. 25% isolates developed resistance on therapy. AUC/MIC related to emergence of resistance. >80% AUC/MIC <100. 0-10% AUC/MIC >100

AUC/MIC	% resistance
0-15 (n=8)	75
50-100 (n=9)	88.9
100-250 (n=21)	14.3
250-500 (n=16)	6.3
≥500 (n=60)	8.3

Clinical correlates (2)

Schrag et al, 2001

RCT of amoxicillin 90mg/kg/day for 5d vs 400mg/kg for 10d for children with RTI.

Carriage of penicillin resistant S.pneumoniae 24% with high dose, short course, 32% with low dose.

Pre-clinical study conclusions

Risk of emergence of resistance in target pathogens related to:-

- species treated (P.aeruginosa>Enterobacteriaceae, >S.aureus, >S.pneumoniae)
  → different dose strategies for different species

- Time of exposure (longer>shorter)
  → keep durations as short as possible

- Drug exposure related to risk in inverse U relationship
  → extreme care when treating strains close to existing breakpoints
  → move to more bactericidal target for breakpoint setting

- Inoculum (high>low)
  → different dosing for high load infection (pneumonia), low load infection (cSSTI)

- Combinations suppress resistance
  → use of combination therapy – reduces emergence of resistance

Is there under dosing?
Piperacillin-tazobactam concentrations in ICU patients with Gram-negative pulmonary infection receiving 4.5g TDS or QDS

Patient	Piperacillin concentration (mg/L)		Tazobactam concentration (mg/L)		Pathogen	MIC (mg/L)	Optimised for T>MIC 100%
	pre	post	pre	post			
1	2.2	46.2	0.7	1.3	E.coli	24	No
2	163.4	324.3	37.3	40.4	Enterobacter	≤8	Yes
3	97.8	205.8	3.3	3.4	Coliform	6	Yes
4	<1	24.6	3.0	11.8	E.coli	2	No
					Klebsiella	3	
5	14.0	56.6	6.5	7.9	P.aeruginosa	6	Yes
6	1.5	28.8	0.9	1.4	A.baumannii	1.5	Yes
7	29.1	153.8	2.4	4.0	P.aeruginosa	8	Yes
8	8.6	89.5	0.9	5.3	P.aeruginosa	3	Yes
9	<1	28.1	2.1	13.8	E.coli	1.0	No
					S.aureus	0.75	
Mean ± SD	35.4 ± 57.1	106.4 ± 103.0	6.3 ± 11.7	9.9 ± 12.2			Yes = 6 No = 3

Limitations for combination therapy to suppress resistance

- some (?most) resistance acquired by gene transfer (i.e. B.lactamases)
- relevance of serum concentrations to what is probably a mucosal or extracorporeal phenomenon
- not always clear what the mechanism of changes in population analysis profiles are and their reversibility
- few clinical correlates as yet
- impact of WBC absent from *in vitro* models

Impact of neutrophils on pathogen clearance

- Kill rate of A.baumanni and P.aeruginosa increased with increasing neutrophil count to near maximum of >1000 cells/mm^3
- Total bacterial burden of A.baumanni and P.aeruginosa increase with declining neutrophil count
- Neutrophil response appears saturable; burden of $<10^6$ CFU/q P.aeruginosa resulted in reduced bioburdens over 24h
- Hypothesis: if bioburden kept below critical value then granulocyte redirected clearance can occur

- Guo et al, 2011; Drusano et al, 2011

However – trends are towards

- High dose, short duration therapy:
  - With > combinations
    (especially high bacterial load and some pathogens)

    > front loading regimens
- Increased TDM in critical care environments to optimise effect and minimise resistance
- Clear need for well designed and conducted clinical trials to test pre-clinical hypothesis on prevention of resistance

○ Increased antibacterial effect	○ Increased adverse effects
○ Decreased risk of resistance	○ Increased cost
	○ Increased risk of resistance