Pharmacodynamics in Clinical Breakpoint Setting

Use of pre-clinical data

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Question:

What is the purpose of a clinical breakpoint?

What is a clinical breakpoint?

a numerical value which result in bacteria being categorised as susceptible, intermediate or resistant to an anti infective

EUCAST Definitions

Clinically susceptible(s)

- a micro-organism is defined as susceptible by a level of activity associated with a high likelihood of therapeutic success

- a micro-organism is categorised as susceptible by applying the appropriate breakpoint in a defined phenotypic test system

- this breakpoint may be altered with legitimate changes in circumstances

How can PK-PD help?

The PK/PD paradigm

PD index size
Cmax/MIC
AUC/MIC
T>MIC

→

microbiological outcome

- bacterial eradication
- ↓ bacterial load
- time to clearance
- antibacterial resistance

→

Clinical outcome

- cure
- mortality
- time to resolution (CRP, Temp, WBC)
- further antibiotics
- length of stay

PD Index

- Pharmacokinetic component (Cmax; AUC; Kel etc.)
- Susceptibility component (MIC)

Hence, if you can define PD index target, can define MIC breakpoint

For example: drug X

AUC/MIC PD index target = ≥64

AUC_{24} drug X = 32mg/L.h

MIC breakpoint ≤0.5mg/L

Topics:

- Pharmacodynamic factors in clinical breakpoint setting
- Factors in determining PD index targets
- Conclusions

Pharmacodynamic factors in breakpoint setting

- doses and modes of administration
- identifying the dominant PD index
- defining the size of the PD index in pre clinical models for translational to clinical practice
- defining the size of the PD index in clinical studies
- healthy volunteer and patient based pharmacokinetics
- (Monte Carlo) simulation to define MIC specific target attainment rates

Other factors in clinical breakpoint setting?

- Clinical data (trials)
- Microbiological data (MIC distributions, mechanisms of resistance)
- Patterns of use and clinical practice (old agents only)
- Expert opinion

Dosing – for example iv penicillins across the EU

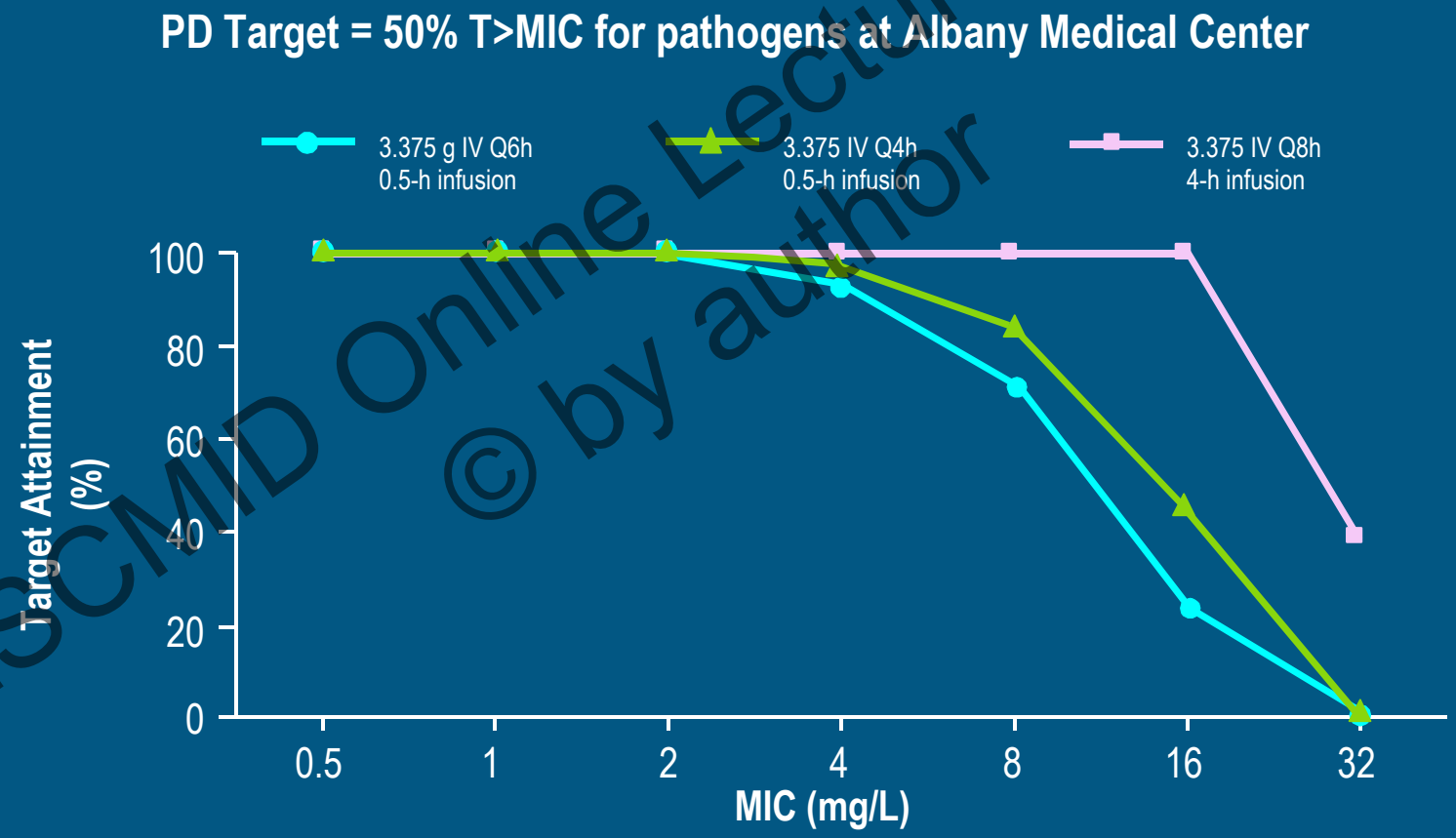
Country	Dosing regimen		MIC breakpoint to achieve A >90% target attainment rate with a T>MIC of		
			30%	40%	50%
Benzyl penicillin					
UK	2.4g	6hrly	2	1	0.25
UK	1.2g	6hrly	1	0.5	0.12
The Netherlands	0.6g	4hrly	1	0.5	0.25
Sweden	1.0g	8hrly	0.25	0.12	≤ 0.12
amoxicillin					
-	2g	8hrly	8	8	4
-	1g	8hrly	4	4	2
-	1g	6hrly	8	4	4
-	0.5g	8hrly	2	1	1

If assume T>MIC of 40% required then for S. pneumoniae non meningitis breakpoints

penicillin	0.12-1mg/L
amoxicillin	1-8mg/L

Dosing: Prolonged or continuous infusion B.lactams

Pharmacodynamic Profiling of Piperacillin-Tazobactam by Monte Carlo Simulation



Lodise TP et al. *CID*. 2007;44:357-363.

Question:

What proportion of E.coli and P.aeruginosa in your country/hospital have MICs of 8 or 16mg/L?

Factors which impact on the size of the pharmacodynamic index for antibacterial effect in pre-clinical studies

- bacterial species
- drug class (carbapenem, penicillin cephalosporin and T>MIC)
- B.lactam-B.lactamase inhibitors or other combinations
- choice of end point (stasis, kill, resistance, duration)
- total or free drug
- resistance mechanism
- inoculum density
- mutational frequency of bacteria/population profile
- host immunity (neutropenia, antibodies)
- other treatment modalities (human) 2nd agents, surgery, immunomodulation

Impact of bacterial species:

Gram-positive vs Gram-negative
Minocycline and MRSA or Acinetobacter baumannii

	fAUC/MIC for 24h		
	Static effect	-1 log drop	-2 log drop
S.aureus (n=5)	12.3 ± 6.8	22.5 ± 11.8	>200 (n=3)
Acinetobacter (n=3)	16.4 ± 2.6	23.3 ± 3.7	>100

Bowker et al, 2013, 2014

Impact of bacterial species: ceftaroline

		T>MIC % for 24hr			
Species	n	static effect	-1 log drop	-2 log drop	-3 log drop
S.aureus					
MSSA	4	27±10	31±12	28±6	33±9
MRSA	4	22±9	25±7	27±6	32±8
E.coli	4	35±6	37±7	38±8	40±10
K.pneumoniae	5	36±8	44±9	52±13	85±15
Citrobacter sp	2	47	49	52	54
Serratia sp	1	65	66	70	>100

Noel et al, 2012, Bowker et al 2013

Resistance mechanism

Impact of ESBL production on T>MIC for cephalosporins

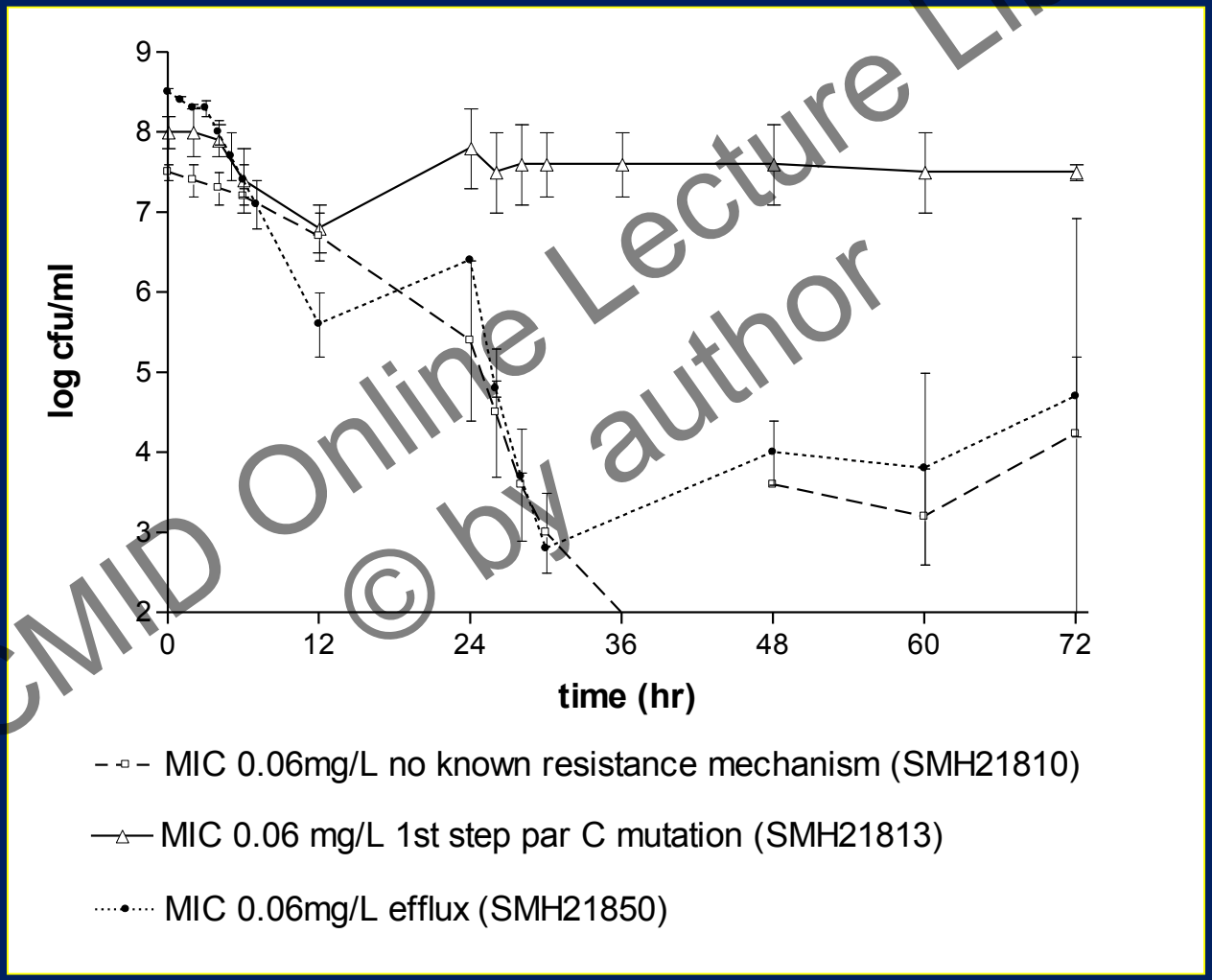
neutropenic animal thigh model.

drugs: cefotaxime, ceftriaxone, ceftazidime, cefepime
βlactamases: TEM-3, TEM-7, TEM-10, TEM-12, TEM-26
SHV2, SHV4, SHV5, SHV7, CXT-M

	T>MIC (%) for			
	static effect	-1 log drop	-2 log drop	-3 log drop
ESBL +	20-40	30-60	40-80	>80
ESBL -	30-50	30-60	40-80	>50

Craig et al

Effect of resistance mechanisms on the antibacterial effect of gemifloxacin with strains of S.pneumoniae with the same MIC (0.06mg/L)



MacGowan & Bowker, 2005; Bowker et al, 2010

Inoculum density

Vancomycin AUC/MIC and UK MRSA 15 and 16

antibacterial effect log drop at 24h	initial inoculum 10^6 CFU/ml		10^8 CFU/ml	
	dose g/d	free drug AUC/MIC	dose g/d	free drug AUC/MIC
static	0.05	17	-	-
-1 $\log_{10}$	0.1	33	0.67	213
-2 $\log_{10}$	0.4	127	0.9	294
-3 $\log_{10}$	0.95	303	>4	>1274
-4 $\log_{10}$	>4	>1274	>4	>1274

MacGowan et al, 2008

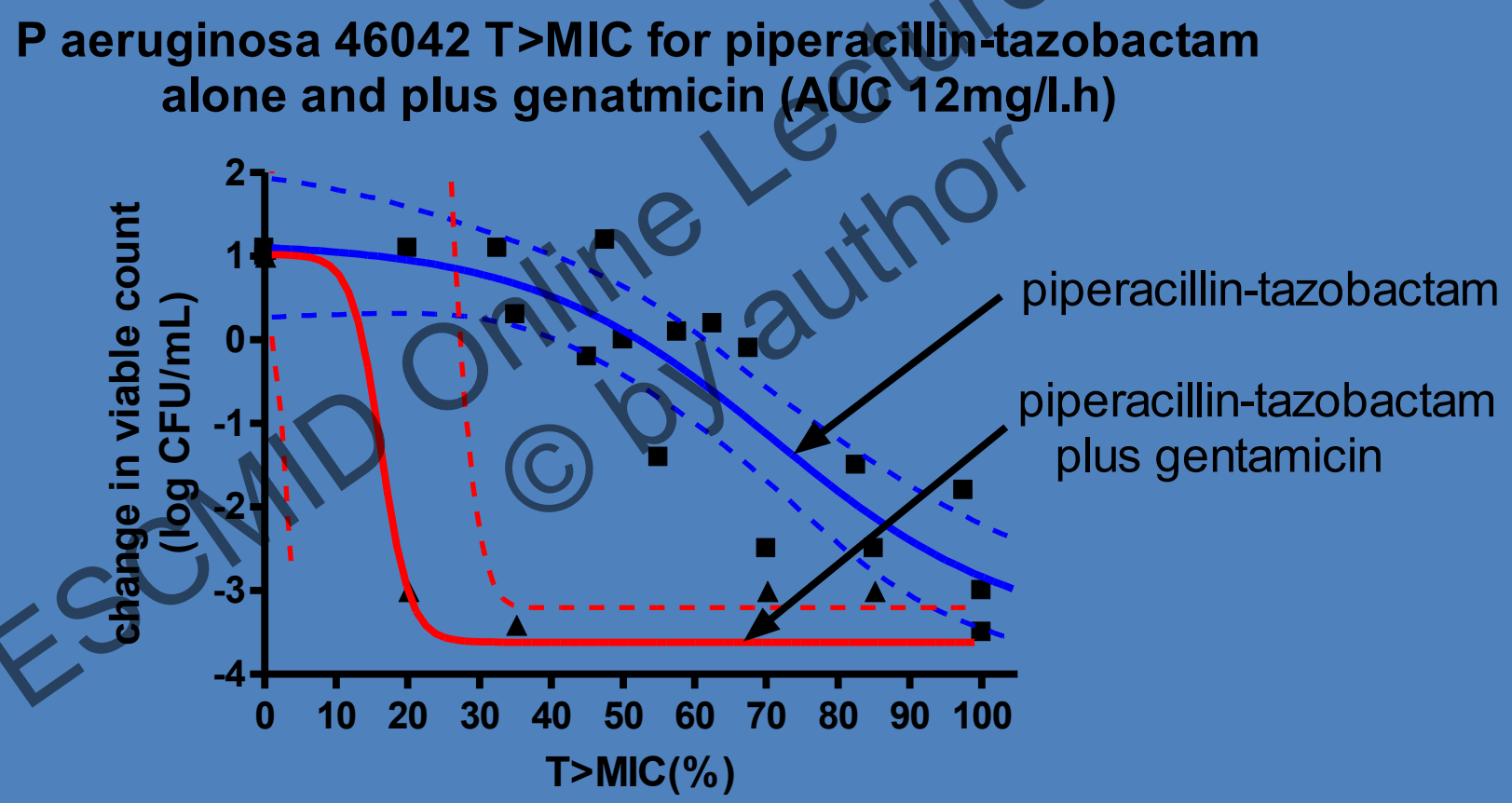
B.lactams-B.lactamase Inhibitors - ceftolozane-tazobactam

Strain	Method of testing	fT>MIC% at 24h for			
		Static effect	-1 log drop	-2 log drop	-3 log drop
E.coli 10909	TOL	21.5	25.2	28.5	32.8
Amp^R	TOL+TAZ (2/1)	23.5	25.5	28.2	30.5
E.coli 47204	TOL+TAZ (2/1)	81.9	93.1	>100	>100
(ESBL producer)	TOL+TAZ (4mg/L CI)	26.2	34.2	43.6	63.8
	TOL+TAZ (500mg 8hrly)	21.4	30.1	40.1	58.5

Noel et al, 2013

Impact of combination antimicrobial chemotherapy

Piperacillin-tazobactam – dose ranging for fT>MIC 0-100%, plus gentamicin 12mg/L.h



Cochrane, unpublished

Host immune status

- neutropenia increases the size of the pK/pD index
- pharmacodynamic parameter with or without immunoprotection *S.pneumoniae* MIC 2-4mg/L, mouse model; hyperimmune sera

	minimal dose to produce 100% survivors (mg/kg)	T>MIC % dose interval
amoxicillin	25	26
amoxicillin + hyperimmune sera	3.1	3

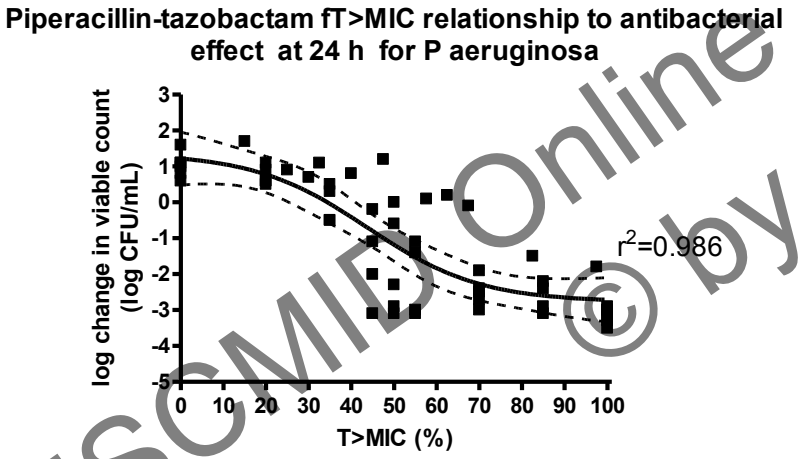
Casal et al, 2002
Yuste et al, 2002

Question:

What is the size of the pharmacodynamic index (Cmax/MIC, T>MIC, AUC/MIC) to be used in translational modelling?

Which Antibacterial effect endpoint size?

Piperacillin-tazobactam vs P.aeruginosa



	T>MIC%
24hr static	39.1 ± 8.8
24hr -1 log drop	51.1 ± 13.4
24hr -2 log drop	62.9 ± 17.7
24hr -3 log drop	>100

Variability in the pharmacodynamic index: impact of strain (1)

species (n)	agent	pD index	static effect	% CV
S.pneumoniae (n=8)	linezolid	AUC/MIC	49 ± 31	62
S.aureus (n=4)	linezolid	AUC/MIC	83 ± 57	68
S.pneumoniae (n=9)	XRP 2868	AUC/MIC	32 ± 16	50
S.aureus (n=4)	XRP 2868	AUC/MIC	14 ± 10	71
S.pneumoniae (n=9)	gatifloxacin	AUC/MIC	52 ± 10	39
S.aureus (n=4)	gatifloxacin	AUC/MIC	36 ± 9	25
S.pneumoniae (n=9)	daptomycin	AUC/MIC	166 ± 51	32
S.aureus (n=4)	daptomycin	AUC/MIC	438 ± 67	16
S.pneumoniae (n=4)	ceftaroline	T>MIC	39 ± 9	23
S.aureus (n=3)	ceftaroline	T>MIC	26 ± 8	31
S.aureus (n=5)	moxifloxacin	AUC/MIC	33 ± 11	33
S.aureus (n=5)	tomopenem	T>MIC	8 ± 5	62
S.aureus (n=5)	telavancin	AUC/MIC	43 ± 38	88
S.aureus (n=5)	razupenem	T>MIC	5.0 ± 1.4	28
S.aureus (n=6)	daptomycin	AUC/MIC	37 ± 17	46
S.aureus (n=8)	ceftaroline	T>MIC	25 ± 10	40
P.aeruginosa (n-3)	doripenem	(T>MIC)	25 ± 10	40
A.baumannii (n=3)	doripenem	(T>MIC)	20 ± 11	55
A.baumanii (n=3)	minocycline	AUC/MIC	16.4 ± 2.6	16
P.aeruginosa	ceftolozane+ tazobactam	T>MIC	24.9 ± 3.0	12
E.coli	aztreonam	T>MIC	47.3 ± 13.7	18

Andes et al, 2002; Andes & Craig, 2003; Andes and Craig, 2006; Safdar et al, 2004; Noel et al, 2007; Noel et al, 2007; MacGowan et al, 2008; Bowker et al, 2009; Bowker et al, 2013; Bowker et al, 2014; Noel et al, 2014; Bowker et al, 2015

Variability in the pharmacodynamic index size (impact of strain)

Proteus mirabilis and ceftaroline

		T>MIC % for 24h		
Strain		Static effect	-1 log drop	-2 log drop
45967		27	29	31
45416		45	46	46
45322	Exp 1	<5	<5	<5
	Exp 2	11.4	12.8	14.1
45266	Exp 1	73	74	74
	Exp 2	>75	>75	>75

Noel et al, 2013

Target attainments against *S.aureus* for moxifloxacin-meaned data compared to use of target distribution: coping with PDI variation (2)

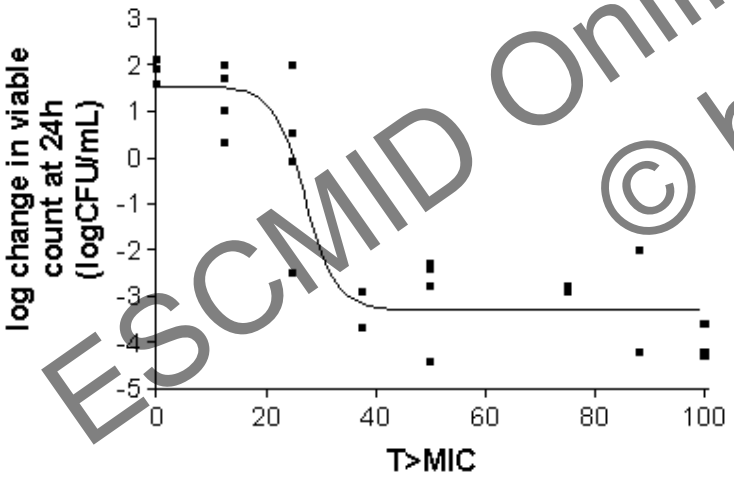
MIC (mg/L)	mean target	target using normal distribution
0.06	100	100
0.12	100	100
0.25	100	100
0.5	96	79
1	15	5
2	0	0

MacGowan et al, 2009

Pharmacokinetic/Pharmacodynamic evaluation problems

- insufficient data to determine the dominant PD index (i.e. chloramphenicol, co-trimoxazole, fusidic acid, rifampicin, fosfomycin, nitrofurantoin, trimethoprim)
- insufficient data to determine the size of the PD index across different species
- insufficient strains tested to determine the size of the PD index for a given species
- lack of clarity as to whether using a bactericidal/static PD index end point
- inappropriate pharmacokinetic data available – lack of information with older agents, lack of patient data with new agents

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

Bowker et al, 2012

Conclusions

Pharmacodynamics of breakpoint setting depends on:-

- **Robust pharmacodynamic index target for relevant pathogens**
- **Human pharmacokinetic data in relevant populations (including protein binding)**
- **Mathematic modelling of target attainment rates by MIC**
- **Confirmation of pharmacodynamic index targets from clinical trials**

Finally:-

- **Pharmacodynamics is only part of breakpoint setting**