

**Breakpoint evolution or the need
for continuous revision**

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Evolution and continuous revision:

Clarifications on breakpoint setting

breakpoint setting is –

- more “intelligent design” than “Darwinian evolution”
- continuous critical evaluation of factors in breakpoint setting and data available with a readiness to change clinical breakpoints, not “continuous revolution” (Mao Zedong)

Which breakpoints can change?

Clinical breakpoints: classify micro organisms based on clinical therapeutic outcome ($S \leq x \text{ mg/L}$; $I > x, \leq y \text{ mg/L}$; $R > y \text{ mg/L}$)

Epidemiological cut-off values: define micro organisms on statistical grounds or absence of a resistance mechanism

$WT \leq Z \text{ mg/L}$; non WT $> Z \text{ mg/L}$

therefore

epidemiological cut-offs are unchanging – clinical breakpoints are subject to revision

(www.srga.org/Eucastwt/eucastdefinitions.htm)

Relevant factors in setting clinical breakpoints in Europe

- national factors regarding dose, formulations (oral/iv), existing clinical indications and uses
- MIC distributions of relevant target pathogens
- dose-effect relationships from in vitro, in vivo and human studies
- mathematical modelling processes, such as Monte Carlo techniques
- clinical data relating susceptibility/MIC to outcome
- clinical breakpoints are tested against MIC distributions to ensure reproducible categorisation on routine laboratory testing

(www.srga.org/Eucastwt/bpsetting.htm)

Factors which drive change –

- clinical data RCTs, other prospective and retrospective data collection and analysis
i.e. vancomycin and *S.aureus*
- mechanisms of resistance i.e. ESBL or carbapenemase production
- pharmacokinetics/dynamics dose change, mode administration, emergence of resistance, methodological issues
i.e. daptomycin or prolonged infusion Bactams

Factors which inhibit change –

- **concerns about the quality of scientific/medical data**
 - **clinical relevance of pre clinical data**
 - **questionable value of some clinical data, i.e. case reports, retrospective case series, single centre studies**
- **lack of clarity about the required threshold for change in terms of cost benefit**
- **regulatory and other “process” issues, i.e. France vs United Kingdom
i.e. automated systems vs disc methods**

Clinical studies relating MIC and outcome

- levofloxacin for blood stream infection due to Gram negative organisms (DeFife et al, 2009)
- fluoroquinolones and *Salmonella typhi* (Crump et al, 2008)
- piperacillin/tazobactam and *P.aeruginosa* blood stream infection (Tam et al, 2007)
- cefepime and blood stream infection due to Gram negative organisms (Bhat et al, 2007)
- vancomycin and *S.aureus* infection (Fridkin et al, 2003; Sakoulas et al, 2004; Charles et al, 2004; Hidayat et al, 2006; Soriano et al, 2008; Price et al, 2009)

MIC and outcome (1) – levofloxacin

DeFife et al, 2009

- retrospective, single centre, cohort study of patients with Gram negative BIS (*E.coli* 53%; *Klebsiella* 28%; *P.aeruginosa* (15%))

	value for patients (n=275) related to			
	MIC ≤0.25mg/L (n=56)	MIC 0.5mg/L (n=201)	MIC ≥1-2mg/L (n=18)	
mortality	8 (12.5%)	26 (11.5%)	3 (14.3%)	p=0.91
length of stay post culture (d)	7.3	7.9	16.4	p=0.02
duration infection (d)	1.0	1.2	2.1	p=<0.00 1

No difference in all cause mortality but increased length of stay
CLSI clinical bp S_≤2mg/L; EUCAST S_≤1mg/L

MIC and outcome (2) – piperacillin/tazobactam

Tam et al, 2007

retrospective, single centre, cohort study of BSI due to *P.aeruginosa*

P/T	MIC	32 or 64 mg/L (n=7)	85.7% (6/7) dead at 30d
P/T	MIC	≤16mg/L (n=10)	20% (2/10) dead at 30d

CLSI clinical bp for *P.aeruginosa* S_≤64mg/L;
EUCAST S_≤16mg/L

MIC and outcome (3)

Vancomycin MIC and outcome in *S.aureus* infection – mainly MRSA

study design	findings	possible breakpoint	reference
prospective multi centre case control study – mixed infections recruited by CDC across USA	MIC ≥ 4 mg/L (n=21) mortality 63%; MIC ≤ 2 mg/L (n=42) mortality 21% OR 12.7 (3.4-48.0)	≤ 2 mg/L	Fridkin et al, 2003
retrospective multi centre cohort study, mixed infections from previous studies of vancomycin	MIC 1-2mg/L (n=21) “success” 9.5%; MIC ≤ 0.5 mg/L (n=9) “success” 55.6%	≤ 0.5 mg/L	Sakoulas et al, 2004

MIC and outcome (3) continued

Vancomycin MIC and outcome in *S.aureus* infection – mainly MRSA

study design	findings	possible breakpoint	reference
retrospective single centre cohort study in BSI	MIC 2-4mg/L AUC/PAP >0.9 (n=5); MIC 0.5-2mg/L AUC/PAP <0.9 (n=48) similar mortality but longer bacteraemia and fever days	<2mg/L	Charles et al, 2004
prospective single centre cohort study mainly pneumonia ± BSI	MIC ≥2mg/L or <2mg/L (n=95) compared mortality similar 24% vs 10% MIC predicted end of treatment response	<2mg/L	Hidayat et al, 2006

MIC and outcome (3) continued

Vancomycin MIC and outcome in *S.aureus* infection – mainly MRSA

study design	findings	possible breakpoint	reference
retrospective single centre cohort study in BSI	MIC 2mg/L (n=92); MIC 1.5mg/L (n=213); MIC 1mg/L (n=109) all case mortality similar MIC 2mg/L associated with mortality after adjustment for shock	≤1.5mg/L	Soriano et al, 2008
retrospective single centre cohort studies in BSI mainly BSI	MIC <1mg/L (n=11); MIC 1-1.49mg/L (n=14) MIC 1.5-2.0mg/L (n=20) MIC 2mg/L associated with improved survival		Price et al, 2009

Vancomycin MIC distribution for *S.aureus* (EUCAST)

MIC (mg/L)	number
≤ 0.12	70 (<0.1%)
0.25	607 (0.7%)
0.5	13,393 (15.6%)
1.0	63,332 (73.7%)
2.0	8,263 (9.6%)
4.0	217 (0.3%)
8.0	3 (<0.1%)
≥ 8.0	3 (<0.1%)
	85,888

VS, hVISA and VISA – all defined by AUC-PAP

	% strains MIC (mg/L)				
	0.5	1	2	4	8
VS (n=106)	10%	86%	4%	-	-
hVISA (n=57)	-	2%	80%	18%	-
VISA (n=20)	-	-	-	55%	45%

Wootton et al, 2005

- Conclusion** :
- wild type population defined by MIC ≤ 2 mg/L
 - clinical evidence that strains with MICs > 2 mg/L poorer clinical response
 - hence proposal to reduce bp but not cut into wild type

Mechanisms of resistance

- if mechanism acts to increase MIC and that determines outcome (i.e. ESBL), clinical breakpoint will detect clinically significant resistance
- if mechanism acts to increase the MIC but not to a degree where clinical resistance occurs then WT cut-off help to identify presence of a mechanism
- the likely significance of a resistance mechanism can be established in pre clinical models (ESBLs, KPC, VIM, etc.) augmented by clinical data

Pharmacokinetics/pharmacodynamics

- changes in dose or mode of administration
 - dose escalation (i.e. levofloxacin, daptomycin, temocillin)
 - prolonged infusion/continuous infusion, i.e. piperacillin/tazobactam; meropenem; doripenem
- dosing to prevent emergence of resistance
- methodological issues
 - modelling variability in pharmacodynamic target (i.e. moxifloxacin)
 - understanding protein binding
 - impact of pK from infected patients compared to healthy volunteers

Increasing doses (1) - Temocillin

Fraction of the time (%) during which the median serum concentrations remain above a given MIC (% fT > MIC) after 2g temocillin 12 hrly or 8 hrly: MCS from pK data of De Jongh et al, 2007

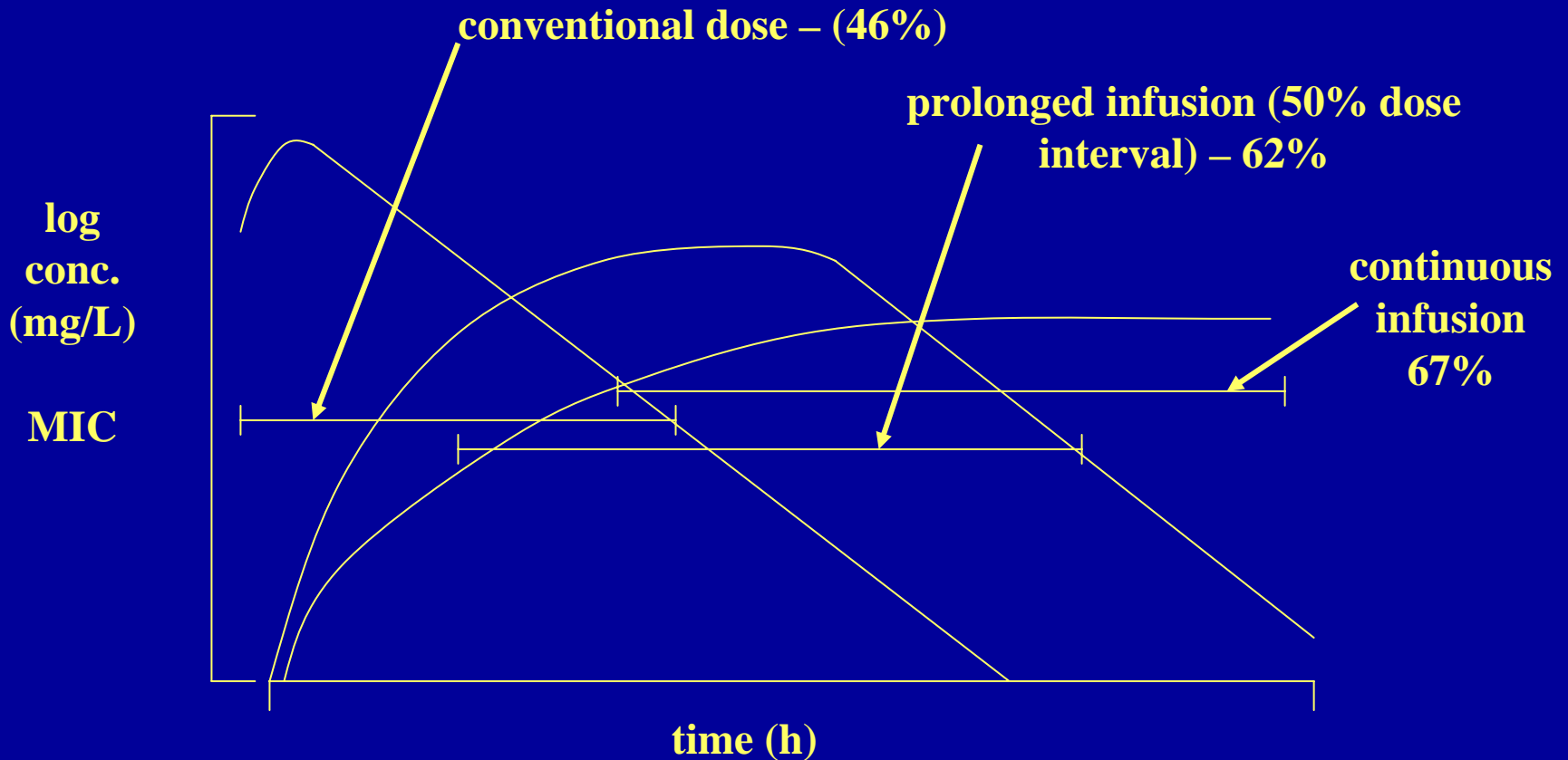
MIC (mg/L)	fT > MIC %	
	12 hrly	8 hrly
0.5	100	100
1.0	100	100
2.0	100	100
4.0	100	100
8.0	80	100
16.0	45	80
32.0	10	27
64.0	0	0

Increasing doses (2) - Daptomycin

Total drug AUC/MIC for daptomycin at 4mg/kg; 6mg/kg; 8mg/kg: MCS on pK data from healthy volunteers (MD) using EUCAST mean AUC/MIC target of 350

	dose (mg/kg/d)		
	4	6	8
0.25	100	100	100
0.50	100	100	100
1.0	99	100	100
2.0	1	43	97
4.0	0	0	2
8.0	0	0	0

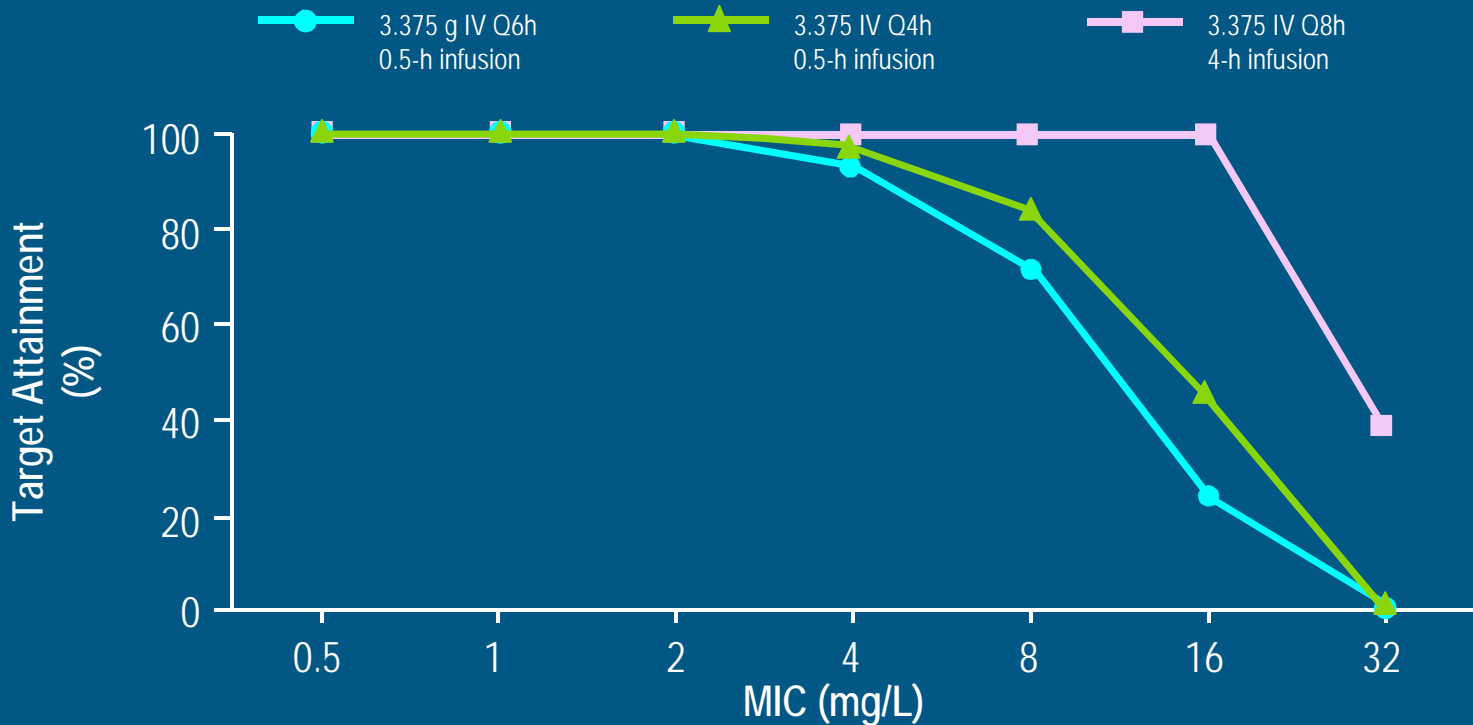
Prolonged infusion/continuous infusion



but: at high MICs $T > MIC$ low despite dosing
: at low MICs $T > MIC$ high, whatever dosing

Pharmacodynamic Profiling of Piperacillin-Tazobactam by Monte Carlo Simulation

PD Target = 50% T>MIC for pathogens at Albany Medical Center



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

For piperacillin/tazobactam

What are the MIC distributions?

(www.bsacsurv.org; UK bacteraemia isolates 2001-05)

MIC (mg/L)	% of distribution with each MIC							
	E coli (n=1216)	P. aeruginosa (n=927)	Serratia (n=315)	Acinetobacter (n=1721)				
≤ 0.5	6.5	1.5	5.7	53.5				
1	14.2	1.2	21.6	5.2				
2	40.8	11.0	29.5	6.4				
4	25.4	50.5	10.8	11.6				
8	9.3	17.7	7.3	4.1				
16	4.6	10.0	5.1	4.1				
32	2.2	4.3	11.4	3.5				
≥ 64	2.7	3.8	8.5	11.7				
	} 13.9		} 27.7		} 12.4		} 8.2	

EUCAST bp

Enterobacteriaceae

≤8mg/L

P.aeruginosa

≤16mg/L

Impact of continuous infusion (CI) versus intermittent infusion (II) with non-concentration dependant antibacterials

Kasiakou et al, Drugs 65, 2499-511, 2005

Systematic review of RCT to evaluated PK and PD of CI vs II (Jan 1950-Jan 2005)

Found 17 RCTs

C_{max} higher in II than CI

C_{max} 5.5 (1.9 – 11.2) x higher C_{ss} CI

C_{ss} (CI 5.8 (1.2 – 15.6) x higher C_{MIN} II

3/6 studies reported longer T>MIC

“data suggested that CI antibacterials with time dependent killing seems superior to II dosing from a PD view at least when treating bacteria with high MICs for the studied drugs”

**Four recent clinical trials of extended duration/
continuous infusions Blactams**

Lau et al, 2006, AAC 50, 3556 – 3563

piperacillin/tazobactam

**Continuous vs intermittent infusion in complicated intra abdominal
infection (CIAI)**

Lodise et al, 2007 CID, 44, 357-363

piperacillin/tazobactam

extended (4h) vs intermittent infusion in *P.aeruginosa* infection

Roberts et al, 2007, JAC, 59, 285-291

ceftriaxone

continuous vs intermittent infusion in ICU sepsis

Lorente et al 2009, IJAA, 33, 464-468

piperacillin/tazobactam

continuous vs intermittent infusion in VAP

Lorente et al, 2009

Piperacillin-tazobactam 4.5g 6 hrly – mainly *P.aeruginosa*

	continuous infusion (n=37)	intermittent infusion (n=46)
cure of VAP n (%)	22 (89%)	26 (56%)
MIC 4mg/L	18 (90%)	19 (76%)
MIC 8mg/L	8 (89%)	6 (40%)
MIC 16mg/L	7 (88%)	1 (17%)

Emergence of resistance (1)

Razupenem (PZ601): antibacterial effect and emergence of resistance in MRSA

fT>MIC (%)	log change in viable count at 24h	number of simulations	growth on MIC x 2 plates	
			number of simulations (%)	log CFU/ml
0.5 - 2.5	0.9 ± 0.3	6	5 (83%)	4.3 ± 0.8
>2.5 - 5	0.2 ± 0.3	6	5 (83%)	4.8 ± 0.8
>5 - 10	-0.7 ± 0.6	5	3 (60%)	4.1 ± 0.6
>10 - 15	-1.5 ± 0.9	6	2 (33%)	3.4
>15 - 35	-2.5 ± 0.7	7	3 (43%)	3.2 ± 0.2
>35 - 70	-3.3 ± 0.6	9	0	<2
>70	-3.5 ± 0.5	6	0	<2

fT>MIC 24 hr static effect $5 \pm 1.4\%$, -1 log reduction $12.5 \pm 5.8\%$

Bowker (unpublished)

Emergence of resistance (2)

Doripenem: antibacterial effect and emergence of resistance in *P.aeruginosa*

fT>MIC (%)	log change in viable count at 24h	number of simulations	growth on MIC x 2 plates	
			number of simulations (%)	log CFU/ml
12.5	1.1 ± 0.7	4	4 (100)	7.0 ± 1.0
25 – 37.5	-0.8 ± 1.3	6	2 (33)	7.5
50 – 75	-3.7 ± 0.7	6	2 (33)	2.9
87 – 100	-3.7 ± 0.6	5	1 (20)	3.0

fT>MIC 24 hr static effect 25 ± 11%, -1 log reduction 30 ± 11%

Bowker et al (unpublished)

Emergence of resistance (3)

Daptomycin: antibacterial effect and emergence of resistance in MRSA

<u>fAUC</u> MIC	log change in viable count at 24h	total number of simulations	growth on MIC x 4 plate	
			number of simulations (%)	log CFU/ml
0.5 – 10	+18	11	8 (73)	4.3 ± 1.3
>10 – 30	+1.2	5	3 (60)	3.9 ± 0.8
>30 – 40	-0.4	3	2 (67)	3.6
>40	-2.8	6	1 (17)	4.7

fAUC/MIC 24 hr static effect 37 ± 16 ; -1 log reduction 41 ± 18

Bowker et al (in press)

Methodology (1)

Understanding bacterial strain to strain variation in the pharmacodynamic index target size moxifloxacin and *S.aureus*

	strain MIC (mg/L)	fAUC/MIC for antibacterial effect at 24h -		
		Static effect	-1 log drop	-2 log drop
36633	0.03	54	62	71
37099	0.03	42	49	57
37312	0.03	19	23	26
37390	0.045	12	15	19
37503	0.047	20	30	46
38002	0.047	17	19	21
38004	0.094	9	20	42
37276	0.7	30	44	65
36742	1.0	20	21	23
36945	2.0	43	53	89
mean		26	33	46
SD		15	17	24
95% CI		16-37	21-45	29-63
single estimate from pooled data		19	27	39

Methodology (2)

Attainment rates (%) for target AUC/MICs

MIC (mg/L)	non-parametric distribution of target	single point estimate
0.03	100	100
0.06	100	100
0.12	100	100
0.25	99	100
0.5	81	99
1.0	47	68
2.0	10	1
4.0	<1	0

EUCAST bp for moxifloxacin vs *S.aureus* $S \leq 0.5\text{mg/L}$

Conclusions: pressures to change clinical breakpoints (1)

- **changes in clinical practice
doses, modes of administration (i.e. daptomycin,
continuous, prolonged infusion Bactams, inhaled
Bactams or aminoglycosides)**
- **emergent clinical data relating drug exposure, bacterial
susceptibility to outcome (i.e. vancomycin and MRSA,
various agents and GNBs)**
- **worries about detection of resistance mechanisms**
 - **epidemiology: wild type cut-offs**
 - **clinical outcome: clinical breakpoints**

Conclusions: pressures to change clinical breakpoints (2)

- **development of methods used to determine clinical breakpoints (i.e. which pK; protein binding; patient pK at steady state: which targets: which target attainment rates - >90, >95, >99%**
- **changes in views on what breakpoints are for**
 - **clinical breakpoints to help predict outcome**
 - **wild type cut-offs to help detect resistance mechanisms**
 - **?breakpoints to help prevent emergence of resistance**