ESCMID Conference on Fighting Infections due to MDR Gram positives

Schedules and administration routes

Alasdair MacGowan
Professor of Clinical Microbiology & Antimicrobial Therapeutics
Bristol Centre for Antimicrobial Research & Evaluation
North Bristol NHS Trust & University of Bristol
Bristol
UK

Definitions

Dosing schedule:

dose size, dose frequency, mode of administration (bolus, prolonged, or continuous infusion, slow release)

Route of administration:

po, iv, topical, inhaled, etc.

Topics:

- dose size issues with anti Gram positive agents (vancomycin, teicoplanin, daptomycin)
- modes of administration (prolonged infusion Blactams, continuous infusion vancomycin, linezolid)
- dosing and adverse events (vancomycin, linezolid, daptomycin, tigecycline)
- pre clinical pharmacodynamic factors which may impact on dosing in the future

Schedules

Dose size issues: vancomycin

- in response to MIC shift and new outcome data

(a) Maintain troughs ≥ 15mg/L?

- no advantage in terms of efficacy

(Jeffres et al, 2006)
(Hidayat et al, 2006)

- increased risk of nephrotoxicity (with aminoglycoside, amphotericin use, long duration)

(Hidayat et al, 2006)

Dose size issues: vancomycin

(b) Give high dose vancomycin (≥ 4g/day)?

- increased nephrotoxicity compared to standard dose or linezolid (35% vs 11% vancomycin doses)

troughs	≥ 4g/day	18.4 ± 7.9mg/L
	< 4g/day	9.1 ± 4.5mg/L

Lodise et al, 2008

Relationship of serum AUC_{24}/MIC to outcome for vancomycin

S.aureus **infection treated with vancomycin (n=54)**

AUC_{24}/MIC		
	<400	80% persistence at 10d
	>400	50% persistence at 10d
		0% at 20d

Moise & Schentag

Simulations to determine vancomycin efficacy

Gatta Garcia et al, 2007

46 patients in ICU, one compartment model

CL 0.86mL/min/kg; V_D 1.7L/kg % CV 128

vancomycin dose (g/day)	% probability of AUC/MIC ≥ 400
1	43
2	78
3	89
4	95
5	99

used EUCAST MIC distribution: median MIC 1mg/L

suggests vancomycin ≥ 4g/day required for "sensitive" *S.aureus*

Dose size issues: teicoplanin

- in right side IE (mainly *S.aureus*) pre dose 10-16mg/L, peak >40mg/L improves outcome

  Leport et al, 1989

- IE dose to *S.aureus* (mainly right sided) pre dose <20mg/L 6/10 failed, pre dose >20mg 1/11 failed

  Wilson et al, 1994

- heterogenous group patient (n=58) mainly staphylococcal infection Cmax, Cmin related to outcome

  MacGowan et al, 1996

Dose size issues: teicoplanin

- *S.aureus* bacteraemia (n=92), line infection excluded

	cured	failed
age (yrs)	49 ± 20	61 ± 18
daily dose (mg)	388 ± 146	287 ± 78
dose (mg/kg)	5.9 ± 2.0	4.7 ± 1.8
combination therapy	42%	36%
MIC_{50} (range, mg/L)	0.5 (0.03-2)	0.25 (0.03-0.5)
average trough (range)	7.8 ± 4.8 (0-22.2)	4.4 ± 2.0 (1.5-7.6)

trough level >10mg/L gives >90% cure up to 85 yrs of age

Harding et al, 2000

Dose size issues: new agents

linezolid	**600mg 12 hrly:**	**all indications (limited by toxicity?)**
daptomycin	**4mg/kg 24 hr:**	**skin & skin structure**
	6mg/kg 24 hr:	**right sided IE ± bacteraemia**
tigecycline	**100/50mg load**	**50/25mg day (limited by toxicity?)**

Modes of administration – continuous infusion vancomycin

- equivalent clinical effect to intermittent injection (Wysocki et al, 2001; Vuagnat et al, 2004)
- no more toxic than conventional therapy (Vuagnat et al, 2004; Wysocki et al, 2001; Filippo et al, 1998)
- fewer drug assays, fewer dose adjustments, more levels within therapeutic range, reduced costs (Wysocki et al, 2001; Grof et al, 2007; Vuagnat et al, 2004)

Modes of administration – once a day vancomycin

2g 24hr similar outcomes to 1g 12hr in study of hospitalised patients treated with vancomycin (n=103).

No differences in outcome or adverse events.

Cohen et al, 2002

Modes of administration – prolonged infusion Blactams – for example, ceftobiprole

From Phase III studies of complicated skin and skin structure infection

T>MIC	Failure Rate		
<30%	32%	(7/22)	failed
≥30%	9%	(27/290)	failed
<50%	29%	(7/24)	failed
≥50%	9%	(27/290)	failed

2 patients had T>MIC values 30-50%

Kimko et al, 2007

Ceftobiprole 500mg 8hrly by 0.5h and 2hr infusion – target attainment rates

	T>MIC ≥ 30%		T>MIC ≥ 50%	
infusion time (h)	0.5	2.0	0.5	2.0
MIC (mg/L)				
0.25	0.99	0.99	0.98	0.99
0.5	0.99	0.99	0.98	0.99
1	0.98	0.99	0.95	0.98
2	0.97	0.99	0.88	0.94
4	0.88	0.99	0.71	0.80
8	0.58	0.99	0.35	0.43

Lodise et al, 2007

Dosing and adverse events

Linezolid and thrombocytopenia

platelet count reduction related to AUC, and duration of therapy

Forest et al, 2000

Daptomycin and CPK rises

in animals, TDS dosing worse than OD
in humans, C_{MIN} threshold of 25.7mg/L

		risk CPK rise		
		at 7 days	at 14 days	overall
C_{MIN}	≥25.7mg/L	0.14	0.50	0.43
	<25.7mg/L	0.01	0.06	0.03

Oleson et al, 2000
Bhavnani et al, 2006

Tigecycline and nausea & vomiting

AUC (mg/L.h)	risk of nausua & vomiting (%)
<3.2	3.8 (n=53)
3.2-6.5	17.4 (n=253)
>6.5	27.4 (n=106)

Rubino et al, 2007

vancomycin and nephrotoxicity

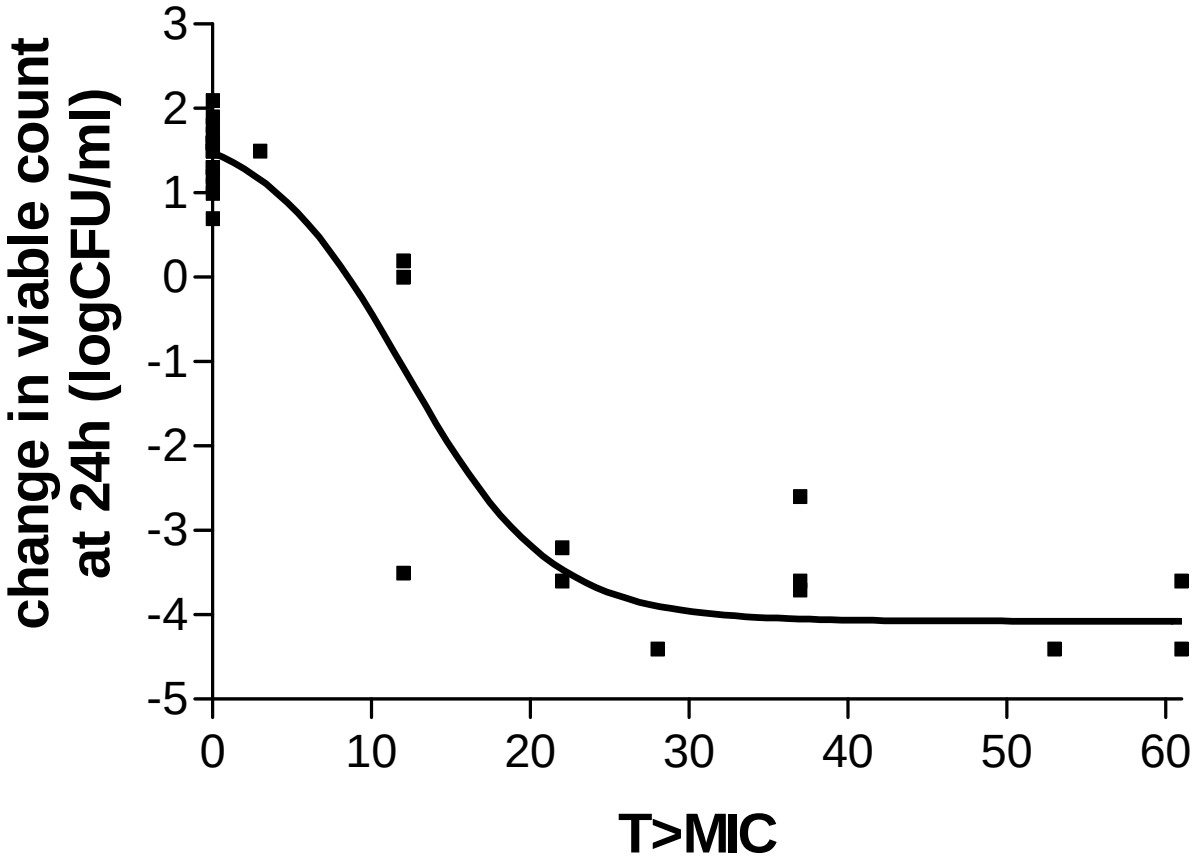
teicoplanin and thrombocytopenia

Pre clinical pharmacodynamic factors which may impact on dosing -

- **bactericidal or bacteriostatic antibacterial effects**
- **variability in the pharmacodynamic index (AUC/MIC, T>MIC) at strain level**
- **impact of inoculum on pharmacodynamic target and target attainment rates**
- **protein binding – realities**
- **preventing emergence of resistance in *S.aureus***

Bactericidal or static effects

Tomopenem T>MIC relatioship to antibacterial effect on S aureus - data from all strains



Variability in the pharmacodynamic index

Relationship between fAUC/MIC and antibacterial effect for moxifloxacin again *S.aureus*

in vitro pK model

	strain					mean ± SD	all strains
	0.03	0.73	0.7	1.0	2.0		
AUC/MIC for							
static effect	38	49	31	19	28	33 ± 11	27
-1 log drop	62	65	47	20	38	46 ± 18	39
-2 log drop	100	83	68	22	60	67 ± 29	60
-3 log drop	182	102	100	25	-	102 ± 64	102
r^2 sigmoid	0.996	0.9816	0.9354	0.999	0.999		0.859

Variability in the pharmacodynamic index

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

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, in press

Coping with variability

Target attainments against *S.aureus* for 4mg/kg daptomycin – single point analysis

MIC (mg/L)	% target attainment with an AUC/MIC of		
	372 (-one SD)	438 (mean)	503 (+one SD)
≥2	0	0	0
1	97	77	43
0.5	100	100	100
≤0.25	100	100	100

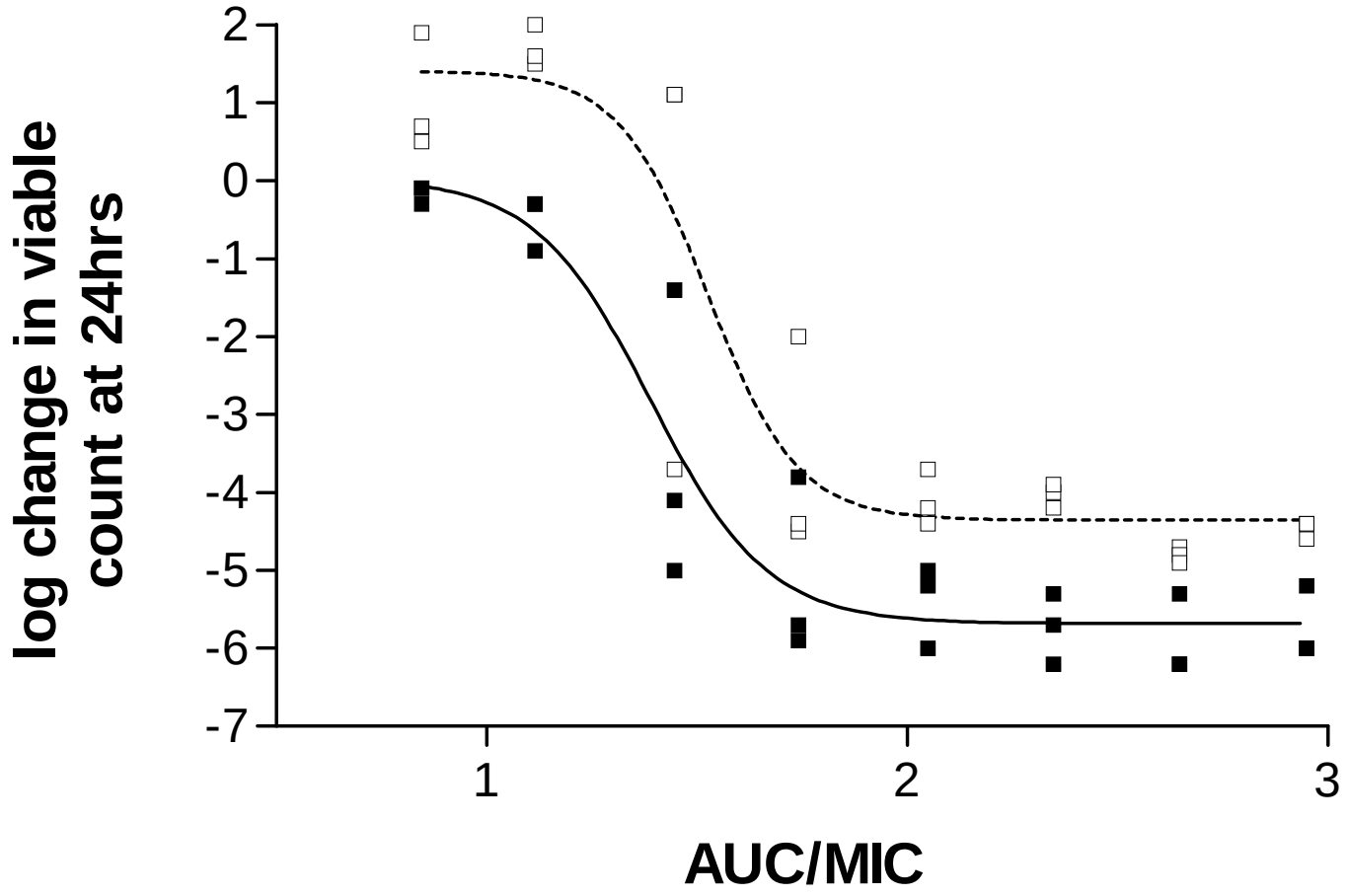
MacGowan, EUCAST Technical Note, 2006

Modelling variability

Target attainment rates for moxifloxacin against *S.aureus*; single estimate versus normal based target distribution

MIC (mg/L)	normal-based distribution	single estimate
0.06	100	100
0.12	100	100
0.25	100	100
0.5	79	96
1	5	15
2	0	0

Figure 1 Relationship of AUC/MIC to change in viable count at 24h for an intial inoculum of 10^6 and 10^8 cfu/ml



Impact of inoculum – tomopenem and MRSA

in vitro pK model

	inoculum	
	10^6 CFU/ml	10^8 CFU/ml
T>MIC% for		
static effect	8 ± 5	-
-1 log drop	12 ± 8	6 ± 5
-2 log drop	16 ± 9	13 ± 18
-3 log drop	21 ± 13	21 ± 26
-4 log drop	32 ± 18	30 ± 33

MacGowan et al, 2008

Impact of inoculum – vancomycin and MRSA

in vitro pK model

	inoculum	
	10^6 CFU/ml	10^8 CFU/ml
fAUC/MIC for		
static effect	17	-
-1 log drop	33	213
-2 log drop	127	293
-3 log drop	303	>1275
-4 log drop	>1275	>1275

MacGowan et al, 2008

Vancomycin target attainment rates for -1 log, -2 log, -3 log reduction in CFU/ml using total drug AUC/MIC magnitudes with initial inocula of 10^6 and 10^8 CFU/ml

	% target attainment rate					
	10^6 inoculum			10^8 inoculum		
antibacterial	log drop			log drop		
effect	-1	-2	-3	-1	-2	-3
vancomycin MIC (mg/L)						
0.25	100	100	100	100	100	0
0.5	100	100	77	97	80	0
1.0	100	93	15	48	18	0
2.0	100	31	2	7	2	0
4.0	90	3	0	0	0	0
8.0	27	2	0	0	0	0
16.0	2	0	0	0	0	0

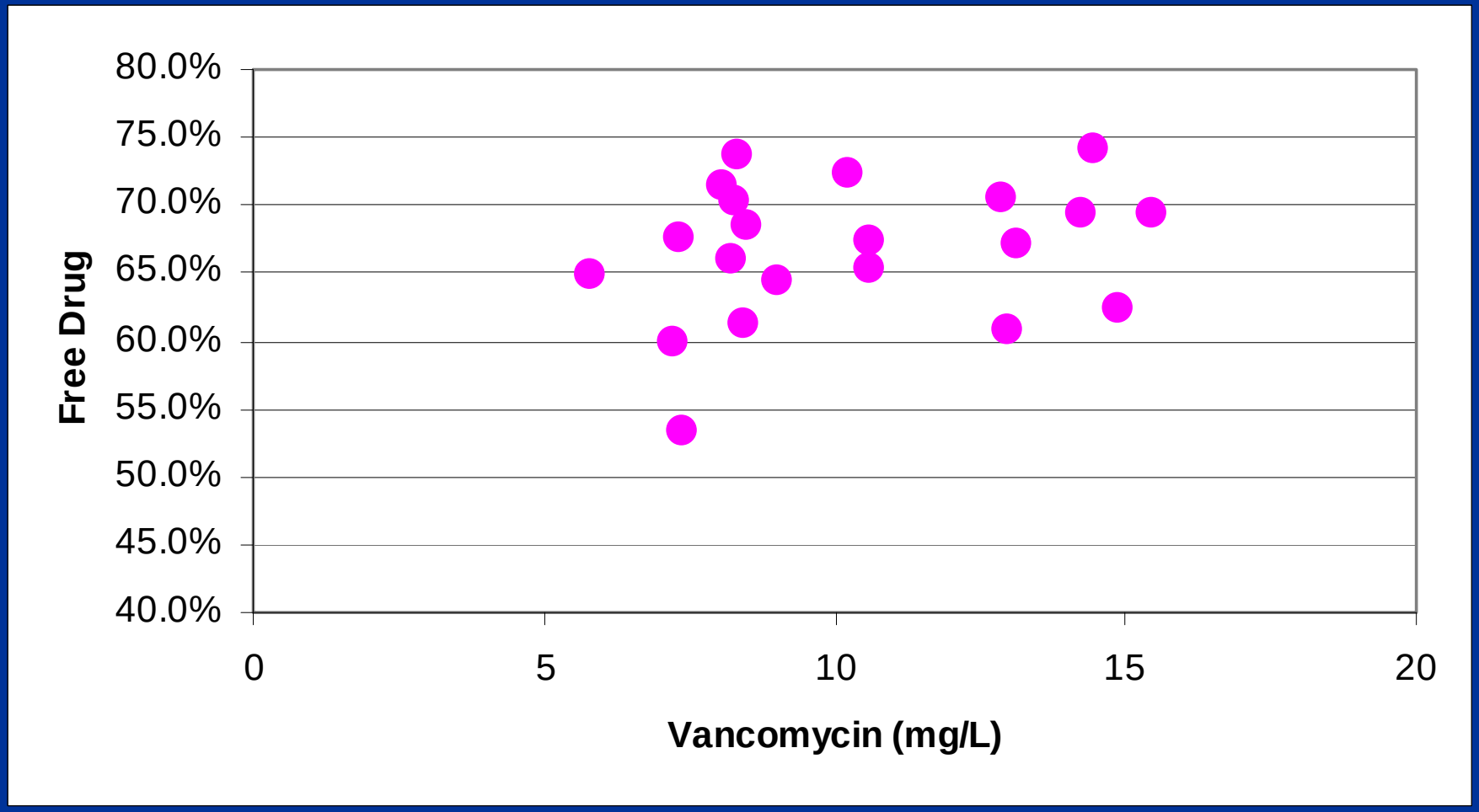
MacGowan et al, 2008

Pharmacokinetic variability – protein binding

Daptomycin

creative clearance	renal support	daptomycin free fraction
≥ 30ml/min	None	0.08
<30ml/min	Haemodialysis	0.124 (+55%)
	CAPD	0.141(+76%)

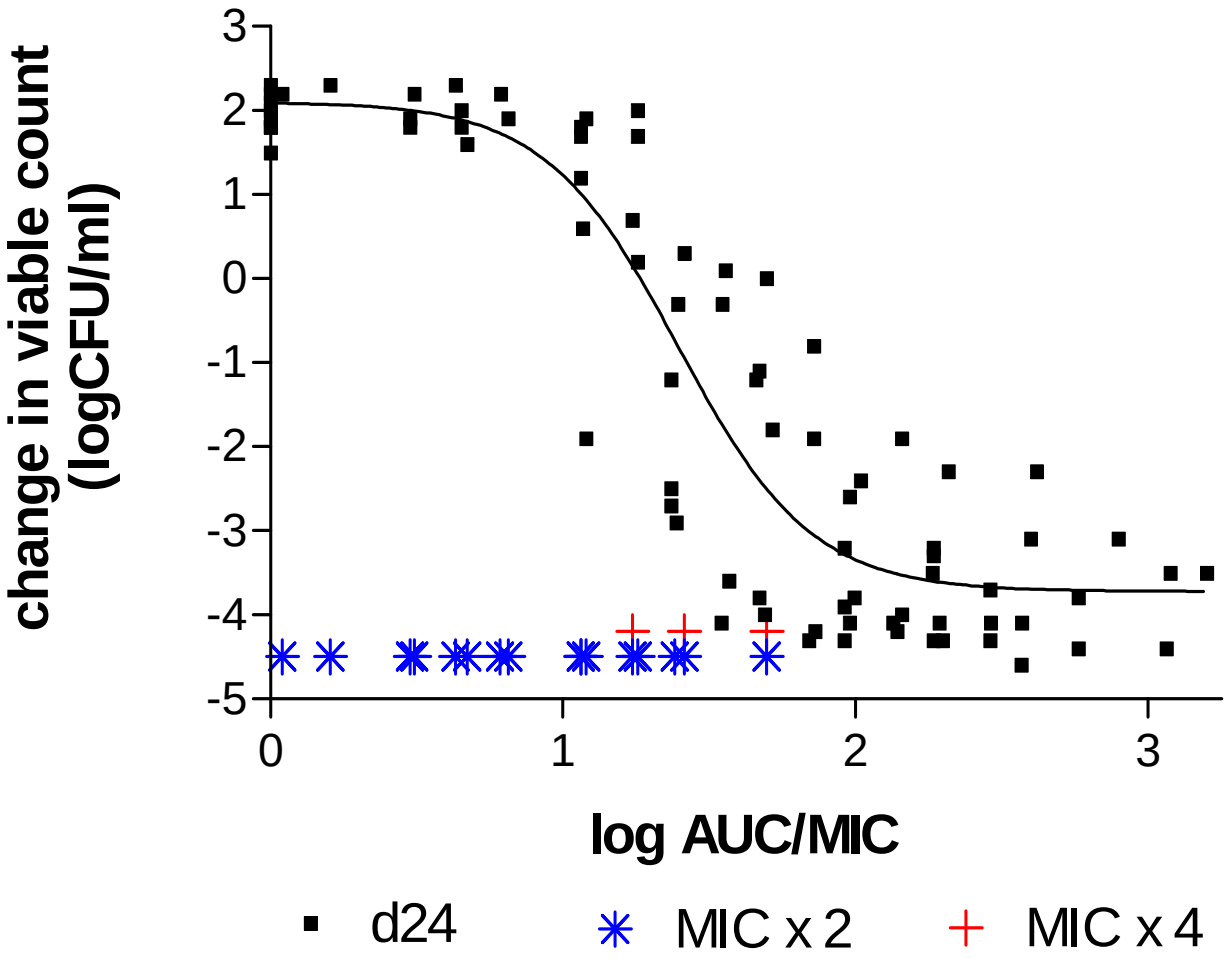
Vancomycin Protein Binding In Patients With Serious Staphylococcal Sepsis



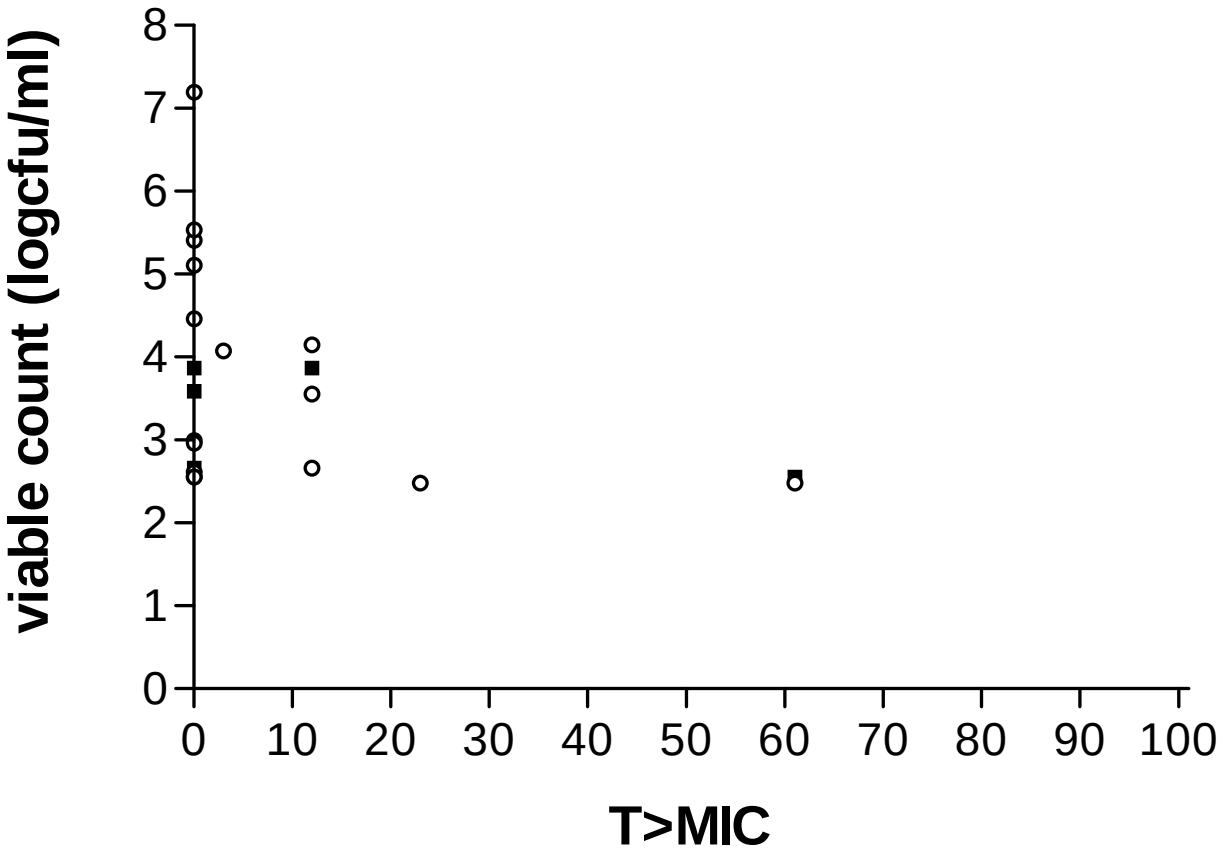
N = 21
Mean free drug = 66.7% (95% CI: 64.5-69.9%)

Prevention of resistance

Relationship between moxifloxacin AUC/MIC and antibacterial effect and emergence of resistance for S aureus

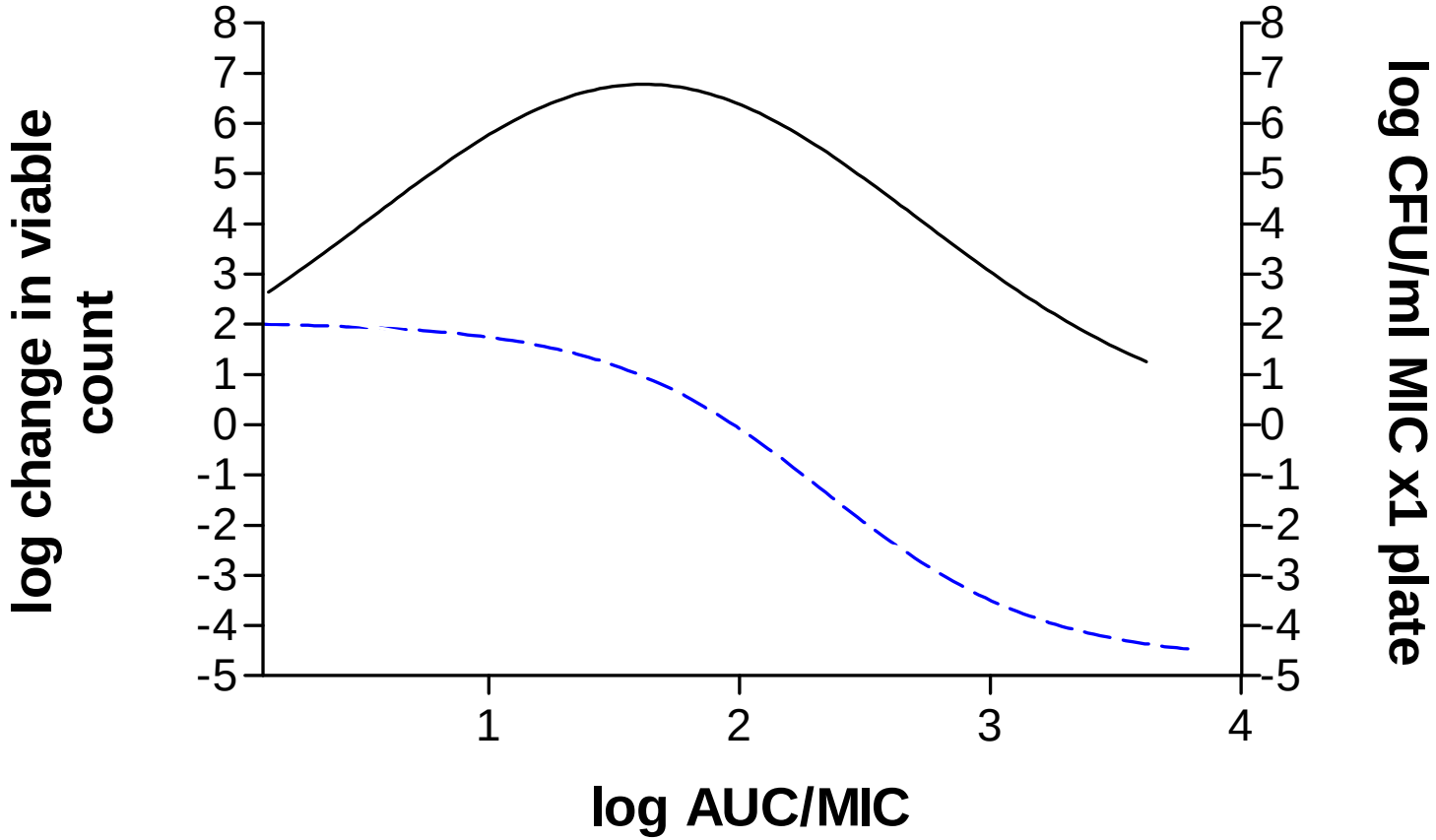


Emergence of resistance to tomopenem in S aureus



- ∘ viable count MIC x2 plate
- ▪ viable count MIC x4 plate

Dalbavancin antbacterial effect and emergence of resistance



Pharmacodynamic index size and emergence of resistance

	size of pD index				
	static effect	log drop -1	log drop -2	log drop -3	growth on MIC x 4 plates
moxifloxacin (AUC/MIC)	19	27	39	69	4-50
dalbavancin (AUC/MIC)	100	182	331	676	18-120
telavancin (AUC/MIC)	26	53	101	-	1-150
tomopenem (T>MIC)	8	12	16	21	1-12

Is a static to -1 log drop target suitable?

MacGowan, Bowker & Noel, unpublished

Conclusions: Schedules and administration

- dose size, frequency of dosing, and mode of administration impact on efficacy and toxicity for Gram positive agents
- pre clinical models continue to pose questions about the factors which impact on bacteriological outcomes in man
- in particular, dosing to prevent emergence of resistance as well as maximise efficacy may impact on which species are regarded as susceptible to some agents; clinical breakpoints will be lower