GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

23rd August 2016

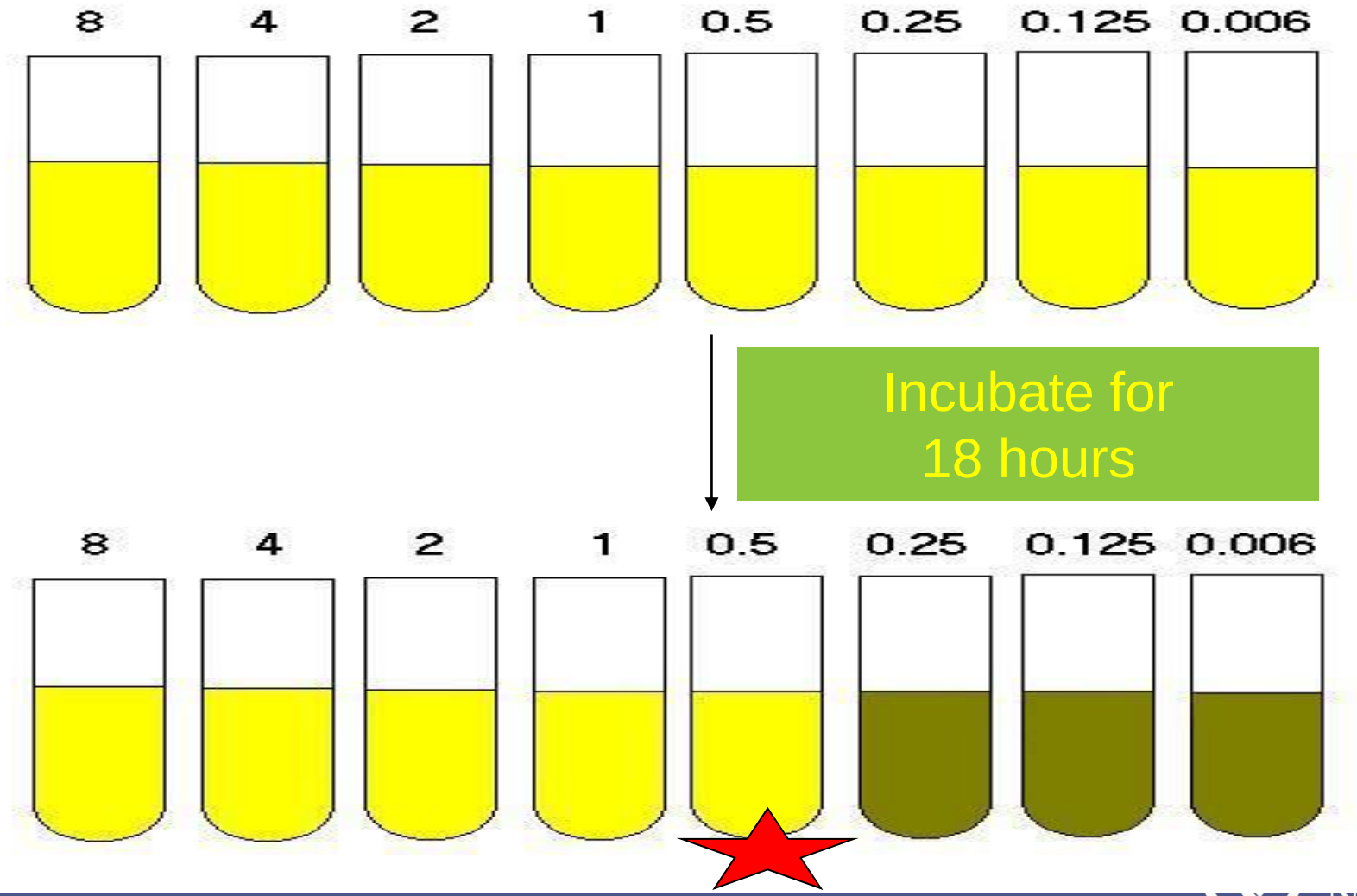
Setting Clinical Breakpoints/ECOFFS

Robin A Howe

- An *E. coli* is grown from blood cultures
  - Cefuroxime MIC 2mg/L
  - Zone around CXM 30ug disc 27mm

- Is it sensitive?

MIC (minimum inhibitory concentration)– the gold standard for susceptibility testing



Definitions of antimicrobial susceptibility and resistance in relation to clinical breakpoints

- **Clinically Susceptible (S)**
  - –a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success

- **Clinically Intermediate (I)**
  - –a micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect

- **Clinically Resistant (R)**
  - –a micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.

Micro-organism SIR is defined by applying the appropriate breakpoint in a defined phenotypic test system

Cefuroxime

3. Breakpoints prior[1] to harmonisation (mg/L) S≤ / R>							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI[2]
General breakpoint							
		4/32	4/16	2/8	1/4	8/8	
Species specific breakpoints:							
Enterobacteriaceae	8/8	8/32			0.5/8	0.5/1	8/32
Pseudomonas spp.							
Acinetobacter spp.	8/8						
Staphylococcus spp.	1/1				2/8	Cefoxitin	8/32
Streptococcus spp.	1/1					0.12/2	
Streptococcus pneumoniae	1/1	0.5/2			0.5/4	0.12/0.25	0.5/1

Setting Breakpoints

- BP will be something to do with
  - The amount of drug available in the body
  - Free drug
  - Whether the drug is active in the body

Breakpoint = (C_{max}f/te)s

C_{max}=peak blood concentration

F = protein binding factor
- <70% = 1
- 70-90% = 0.5
- >90% = 0.2

T = half-life factor
- <1 hour = 2
- 1-3 hours = 1
- >3 hours = 0.5

e = factor by which C_{max} should exceed MIC (usually 4)

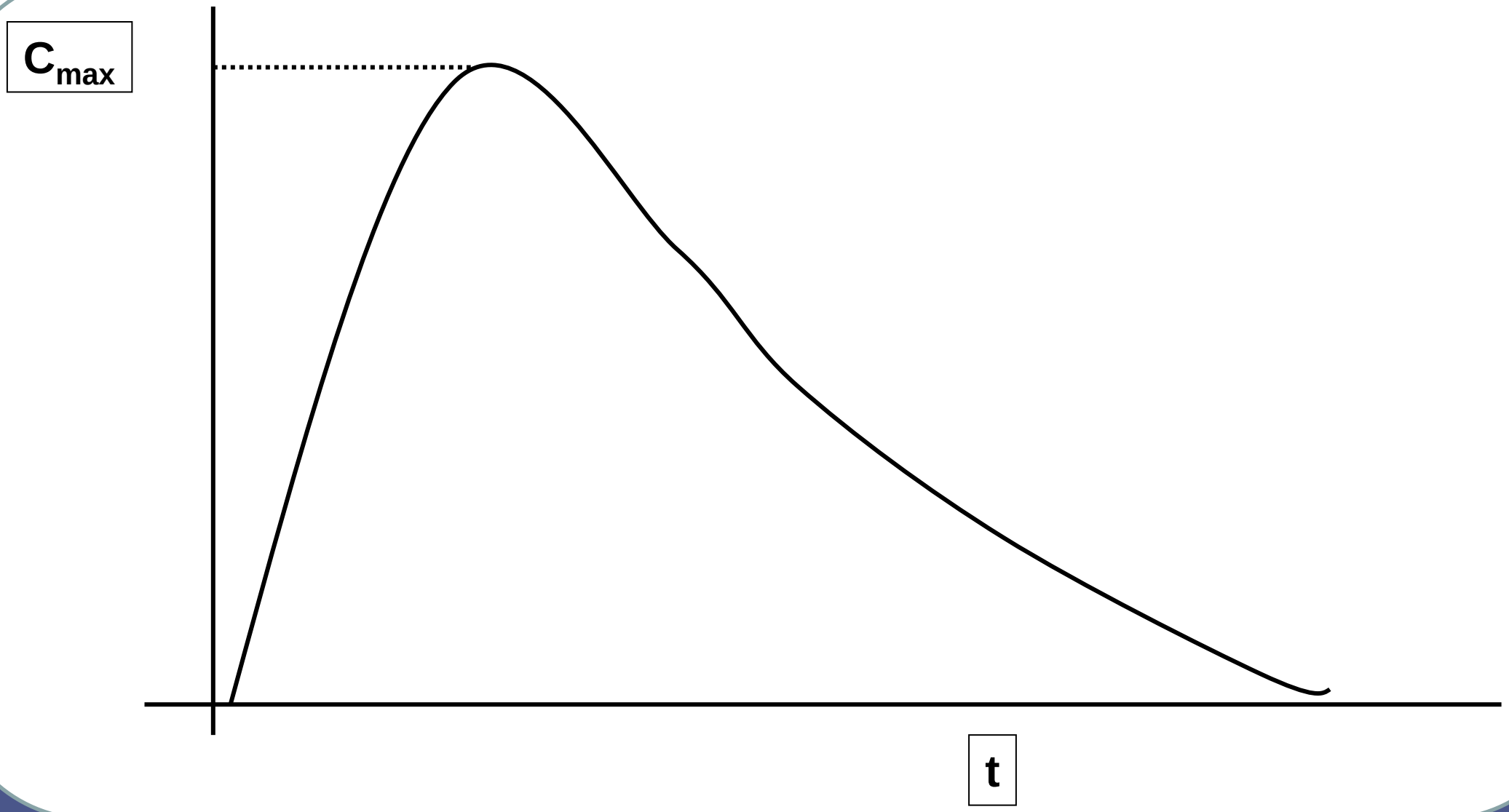
s = factor to allow for maximal reproducibility

Pharmacodynamics

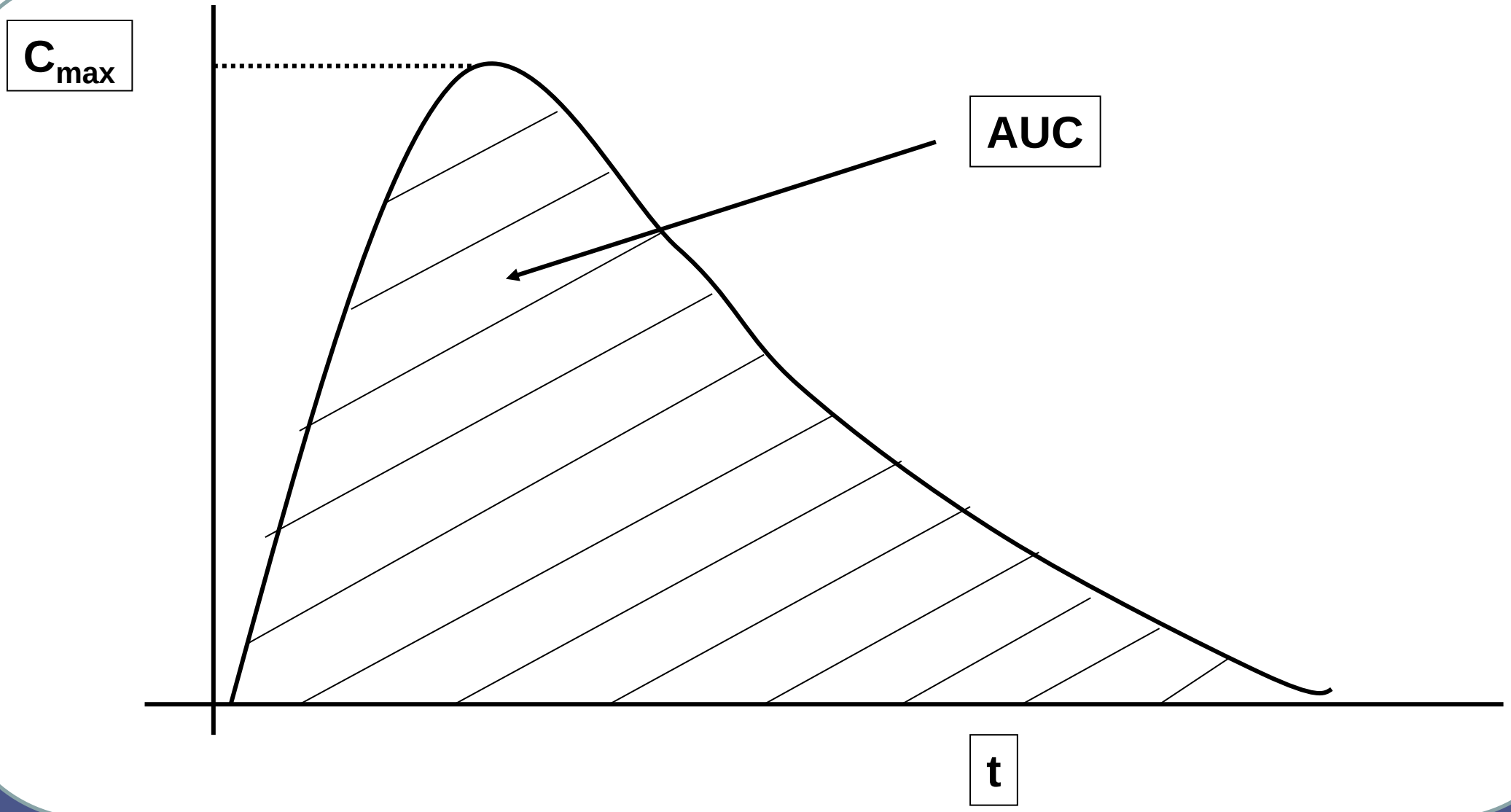
- **pharmacokinetics (pK)**
  study of changing drug concentrations over time

- **pharmacodynamics (pD)**
  study of the impact of drug concentration on effect

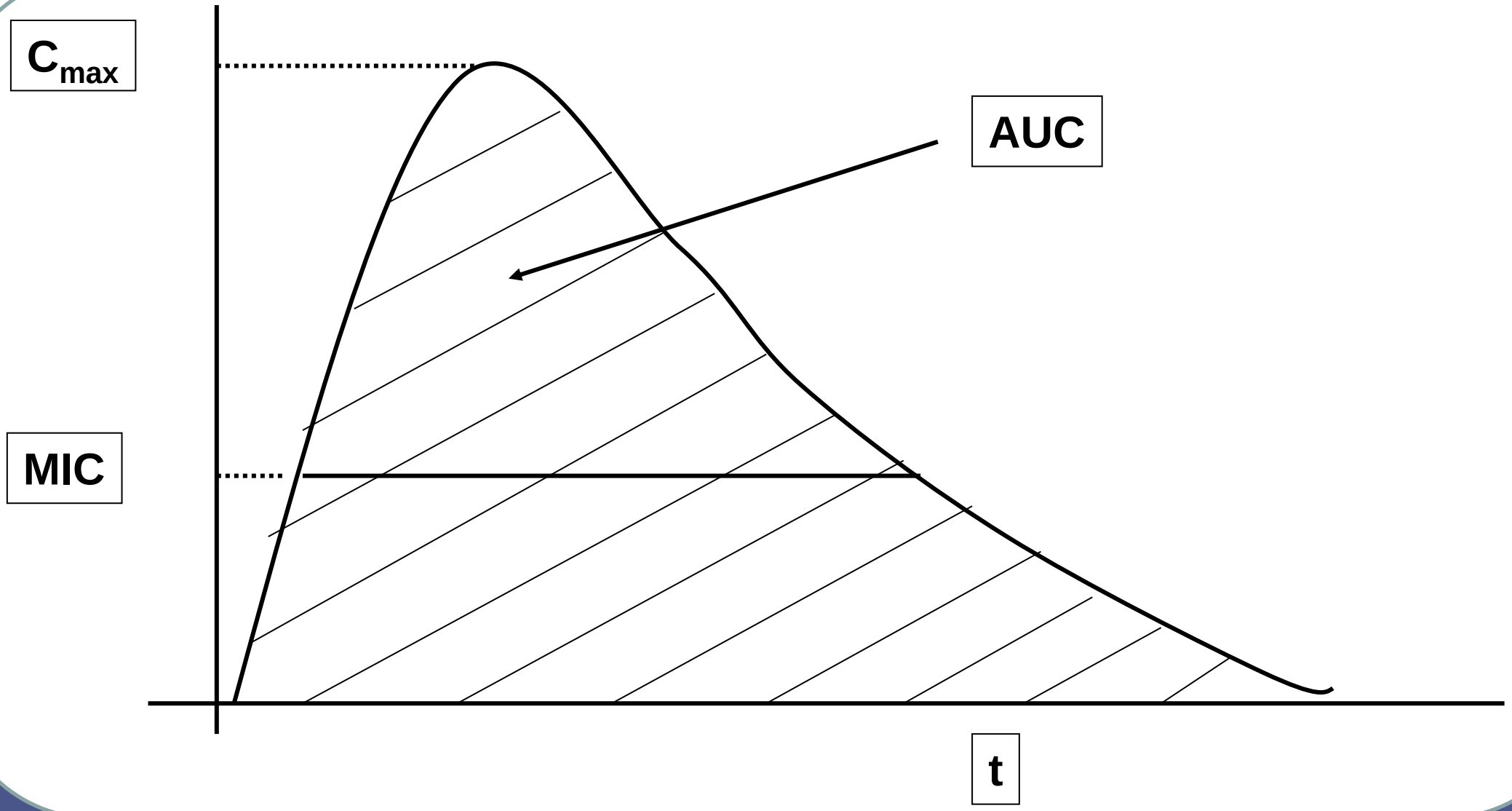
Pharmacodynamic parameters



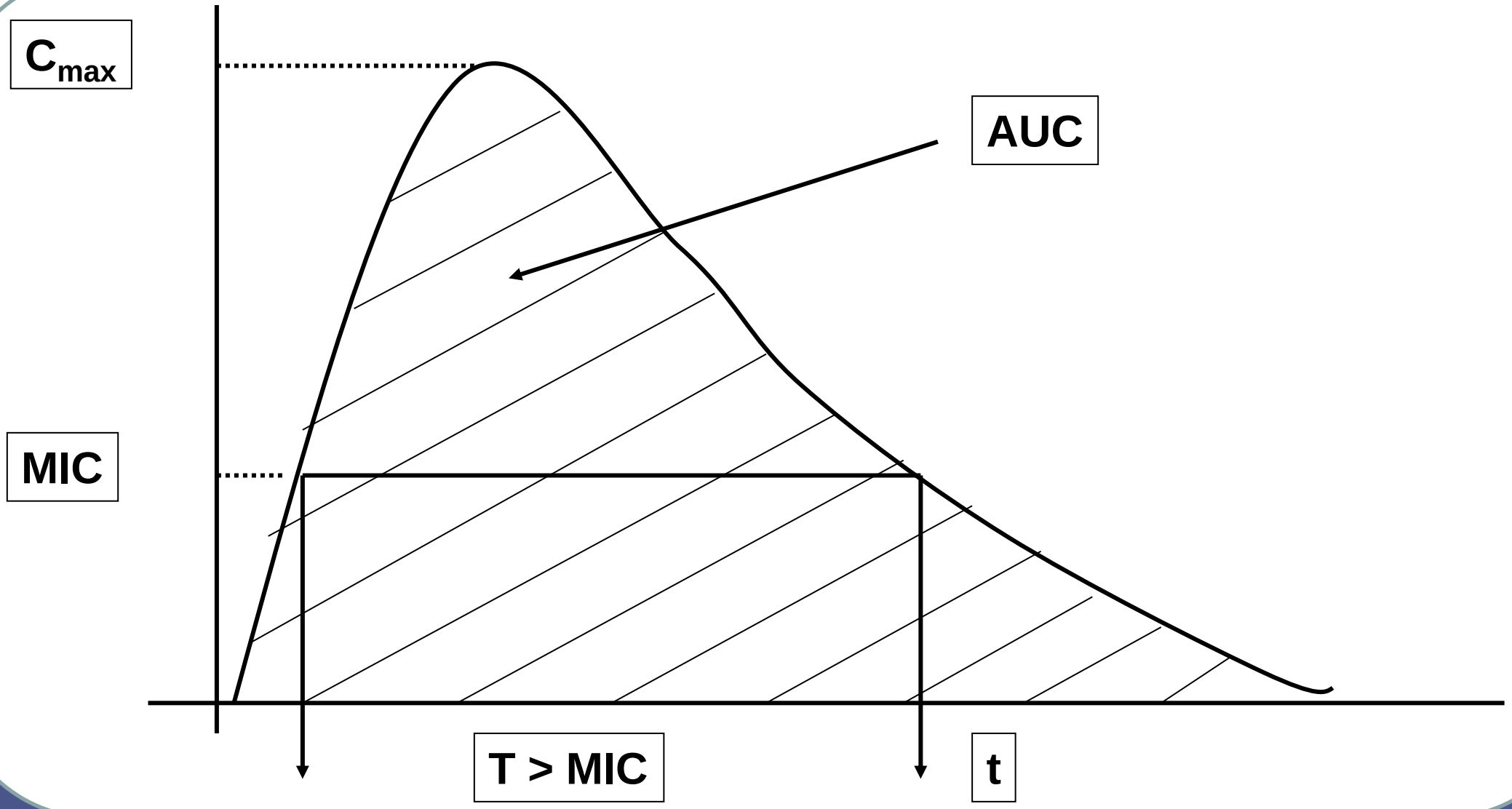
Pharmacodynamic parameters



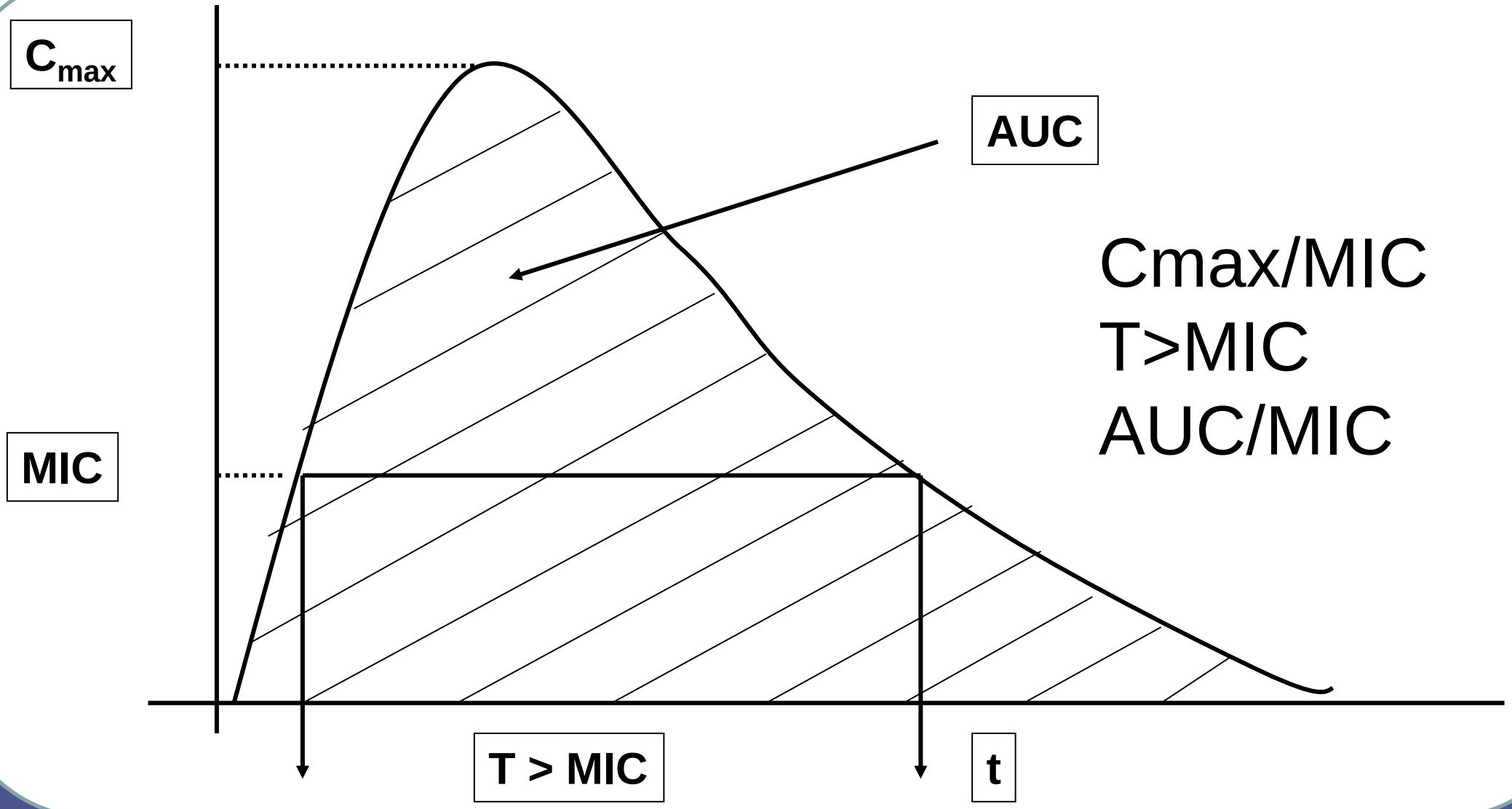
Pharmacodynamic parameters



Pharmacodynamic parameters

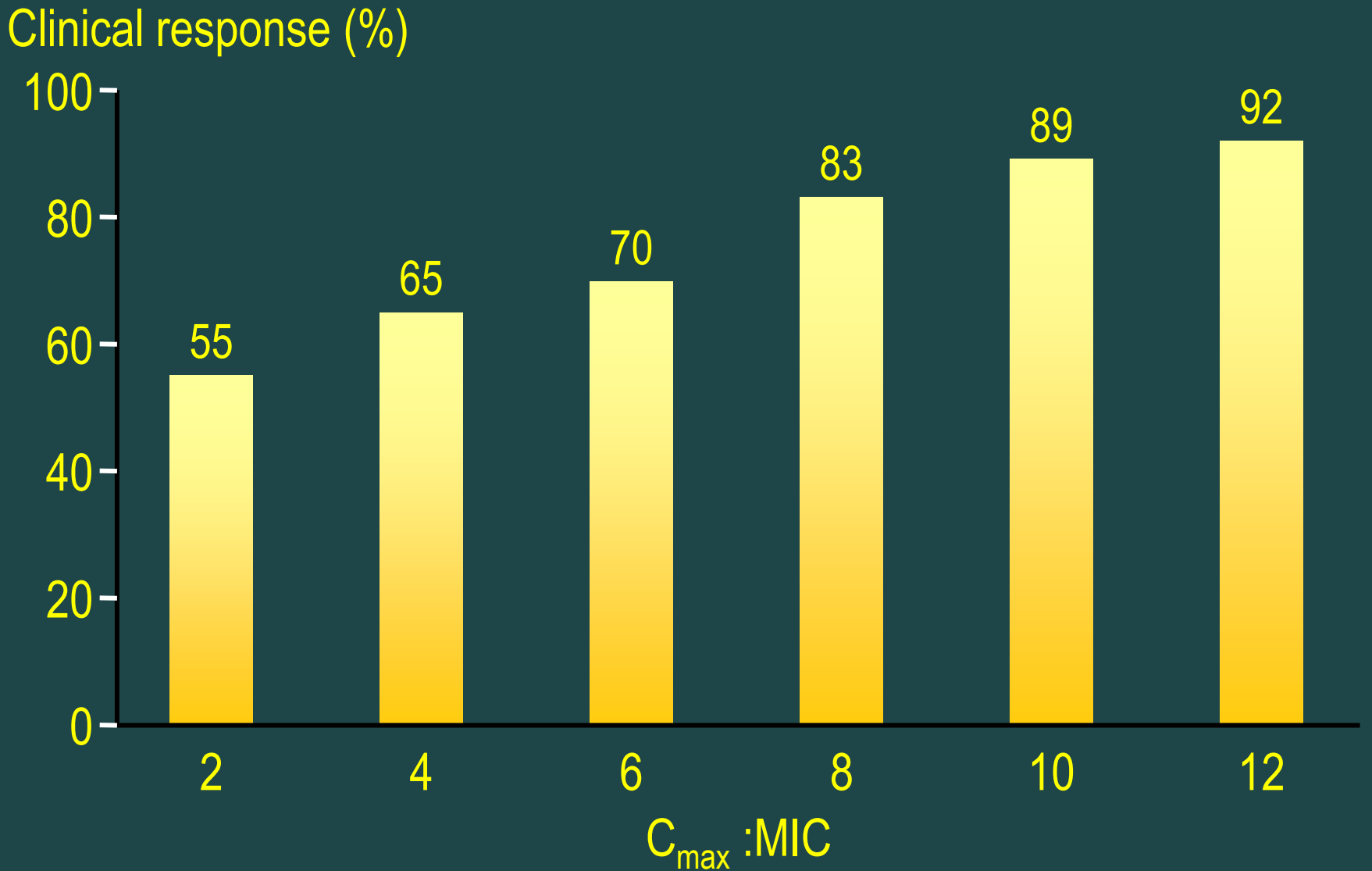


Pharmacodynamic parameters



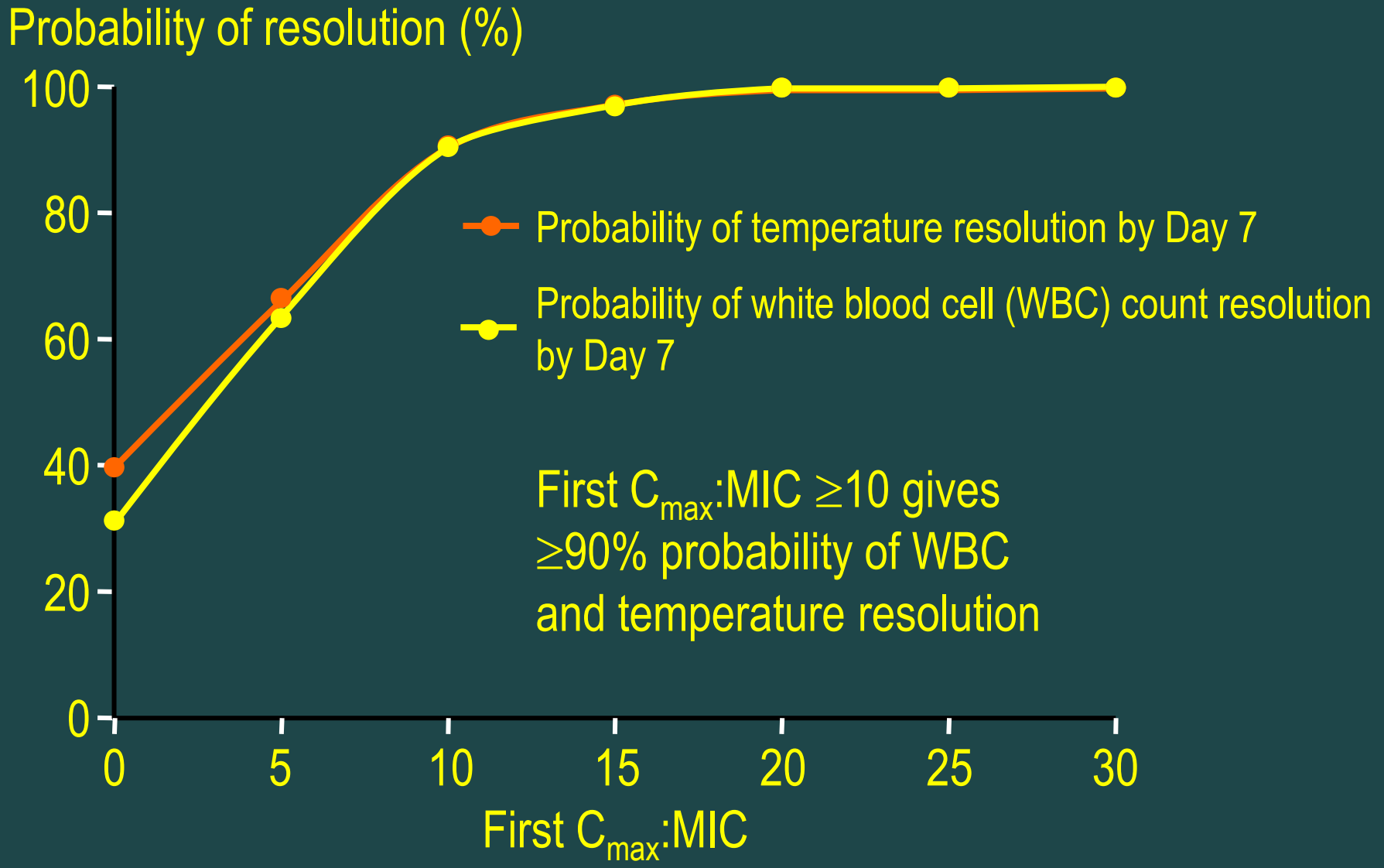
Cmax/MIC
T>MIC
AUC/MIC

Aminoglycosides: relationship between C_{max}:MIC ratio and clinical response



Moore et al. J Infect Dis 1987;155:93–99

Optimising aminoglycoside therapy for nosocomial pneumonia (n=78)



Kashuba et al. Antimicrob Agents Chemother 1999;43:623–629

PD parameter for ciprofloxacin

- Forrest *et al.* 1993
  - 74 patients with pneumonia treated with iv ciprofloxacin on ICU
    - 25 *P. aeruginosa*
    - 36 GNB
    - 11 *S. aureus*
  - by univariate analysis
    - MIC $\geq$0.5 mg/L
    - C_{max}/MIC $\leq$4
    - AUC/MIC $\leq$125

} Worse for Outcome

PD parameter for ciprofloxacin

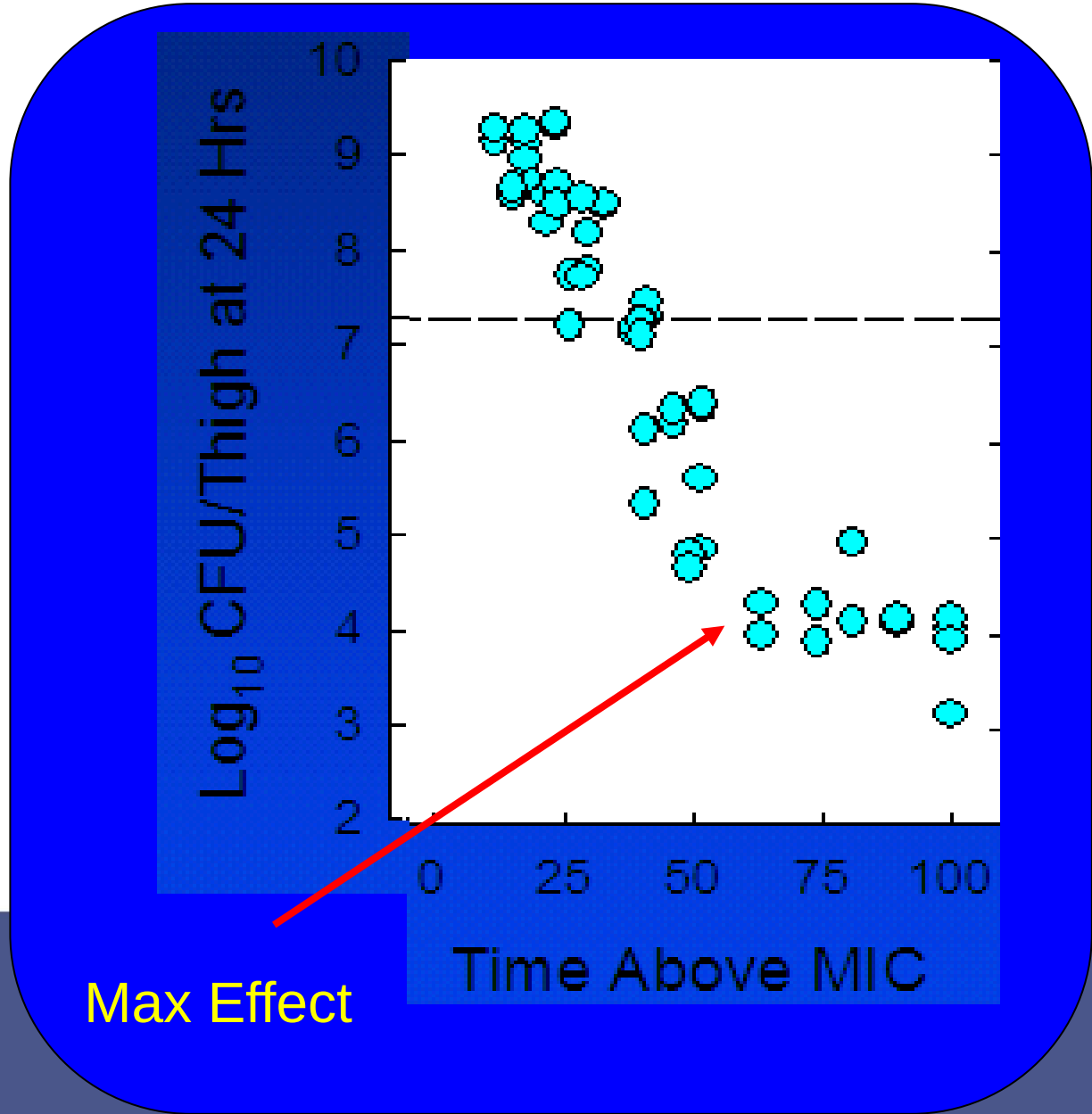
Forrest *et al.* 1993 (continued)

Multivariate analysis: AUC/MIC ≥124

AUC/MIC	microbiological cure		clinical cure	
	n	%	n	%
≤62.5	2	22	9	44
62.5-125	3	22	10	40
125-250	13	81	16	88
250-500	6	86	7	71
>500	18	82	22	77

T>MIC for beta-lactams

- Clear relationship between T>MIC and effect for beta-lactams



Courtesy: J Mouton

PK/PD examples

Antimicrobial class	Dominant PD parameter	Magnitude of dominant PD parameter
Beta-lactams	T>MIC	>40-60%
Aminoglycosides	Cmax/MIC	>10
Fluoroquinolones	AUC/MIC	>125 for Gram neg >33 for Gram pos

Setting Breakpoints

1. Most common dosing regimens
4. Pharmacokinetic data
5. Pharmacodynamic data, PD Targets
6. Monte Carlo Simulations, PTA
7. Clinical and other data
8. Pk/Pd and WT distributions

Cefuroxime dosing across Europe

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	0.75g x 3	0.75g x 3	0.75g x 3	1.5g x 3	0.75-1.5g x 3	0.75-1.5g x 3
Maximum dose schedule	1.5g x 3	1.5g x 3	1.5g x 3	1.5g x 3	1.5g x 3	1.5g x 3
Available formulations[1]	iv	iv	iv	iv	iv	iv

Cefuroxime

4. Pharmacokinetics

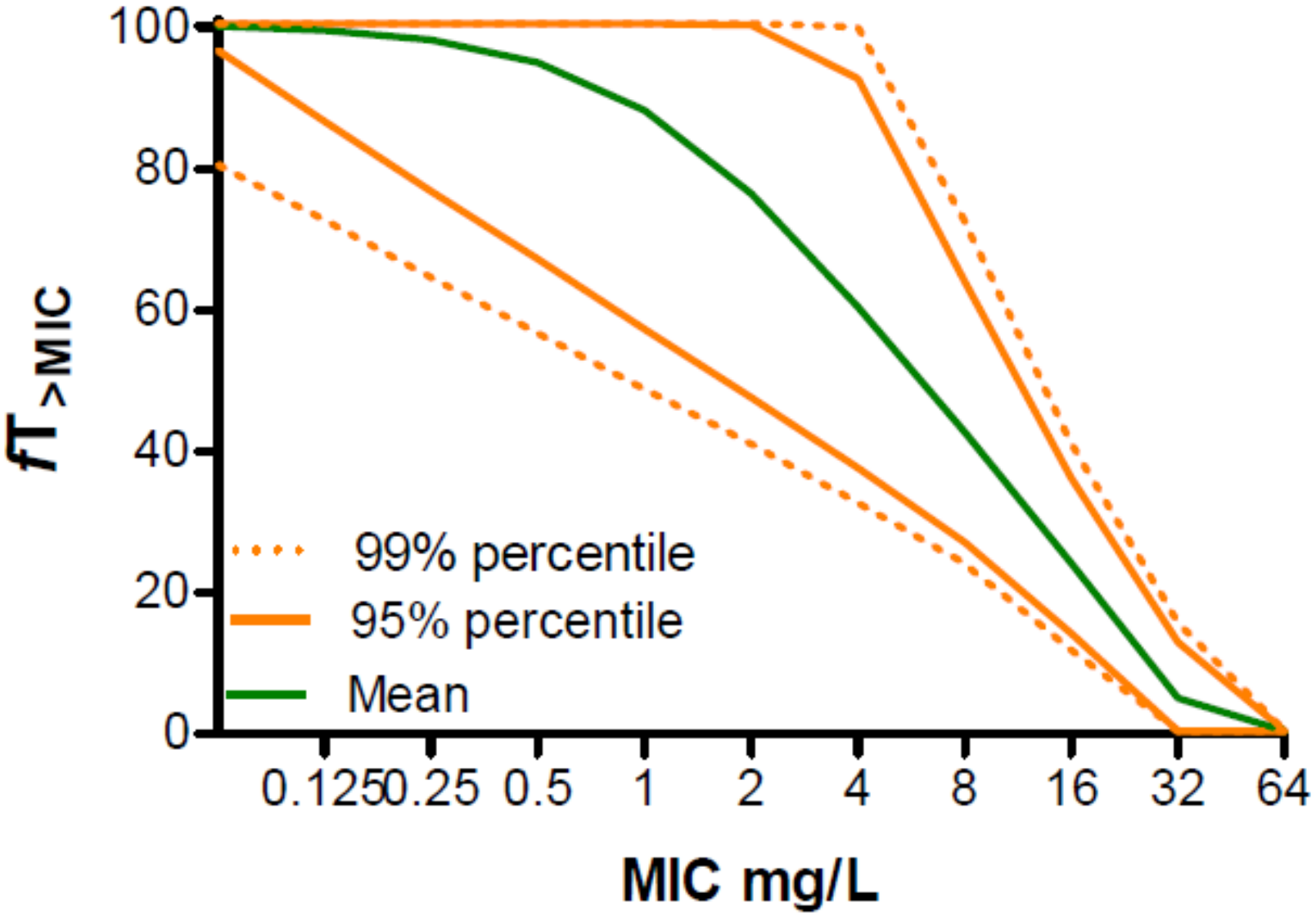
Dosage (mg)	750 x 3 iv	1500 x 3 iv
Cmax (mg/L)	75	200
Cmin (mg/L)		
Total body clearance (L/h)		
T ½ (h), mean (range)	1.1-1.4	1-1.4
AUC24h (mg.h/L)		
Fraction unbound (%)	60-70	60-70
Volume of distribution (L/kG)		

Cefuroxime

5. Pharmacodynamics

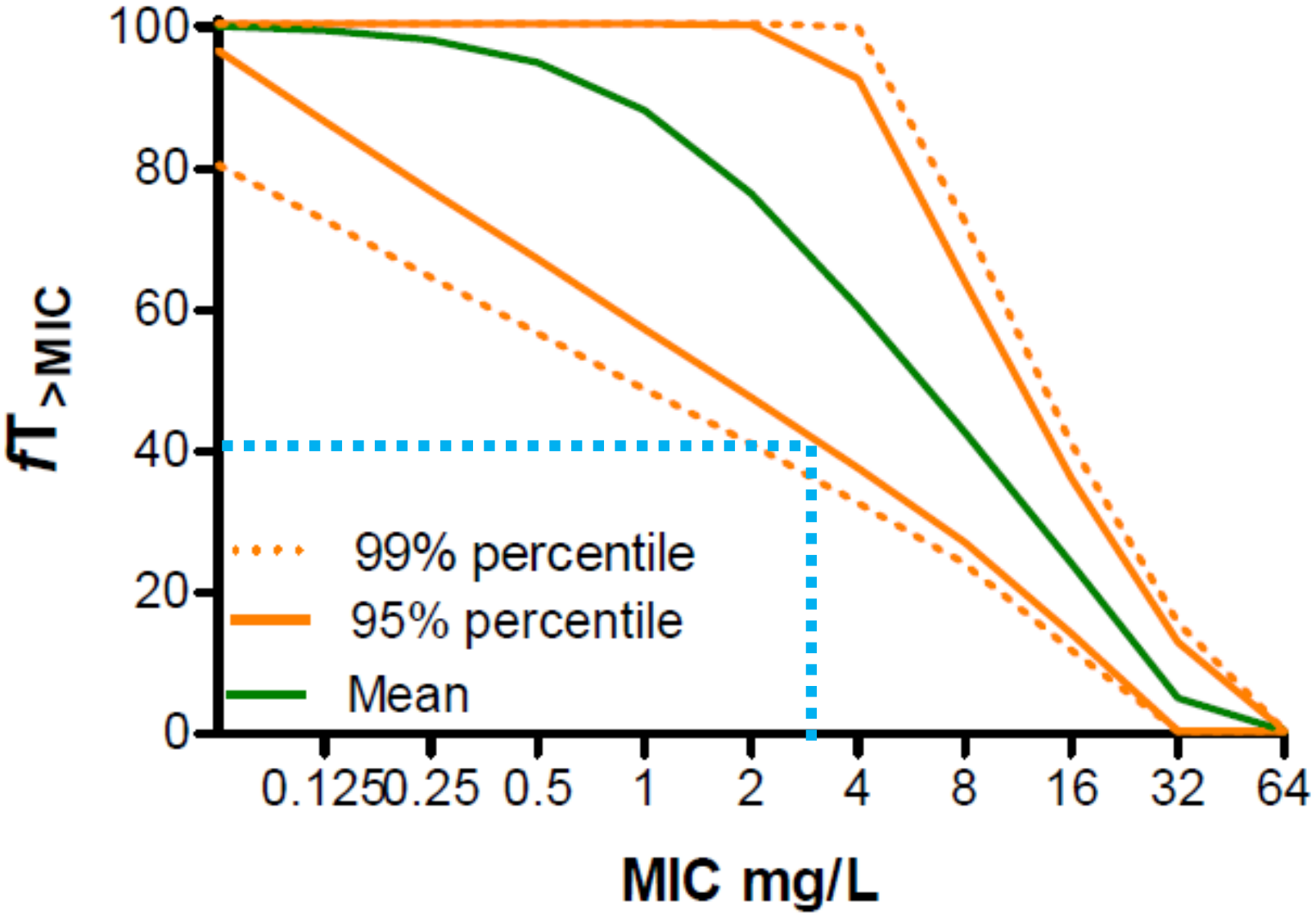
	Enterobacteriaceae	*Streptococcus pneumoniae*	*Staphylococcus aureus*
%*f*T>MIC for bacteriostasis	35-40	35-40	20-30
%*f*T>MIC for 2 log reduction			
%*f*T>MIC from clinical data			
Comments	• %fT>MIC is the dominant pharmacodynamic index. • Values based on general characteristics of cephalosporins.		

Monte Carlo simulation – probability of target attainment



750 mg
TDS

Monte Carlo simulation – probability of target attainment



Target of 40% T>MIC

PD BP 2-4 mg/L

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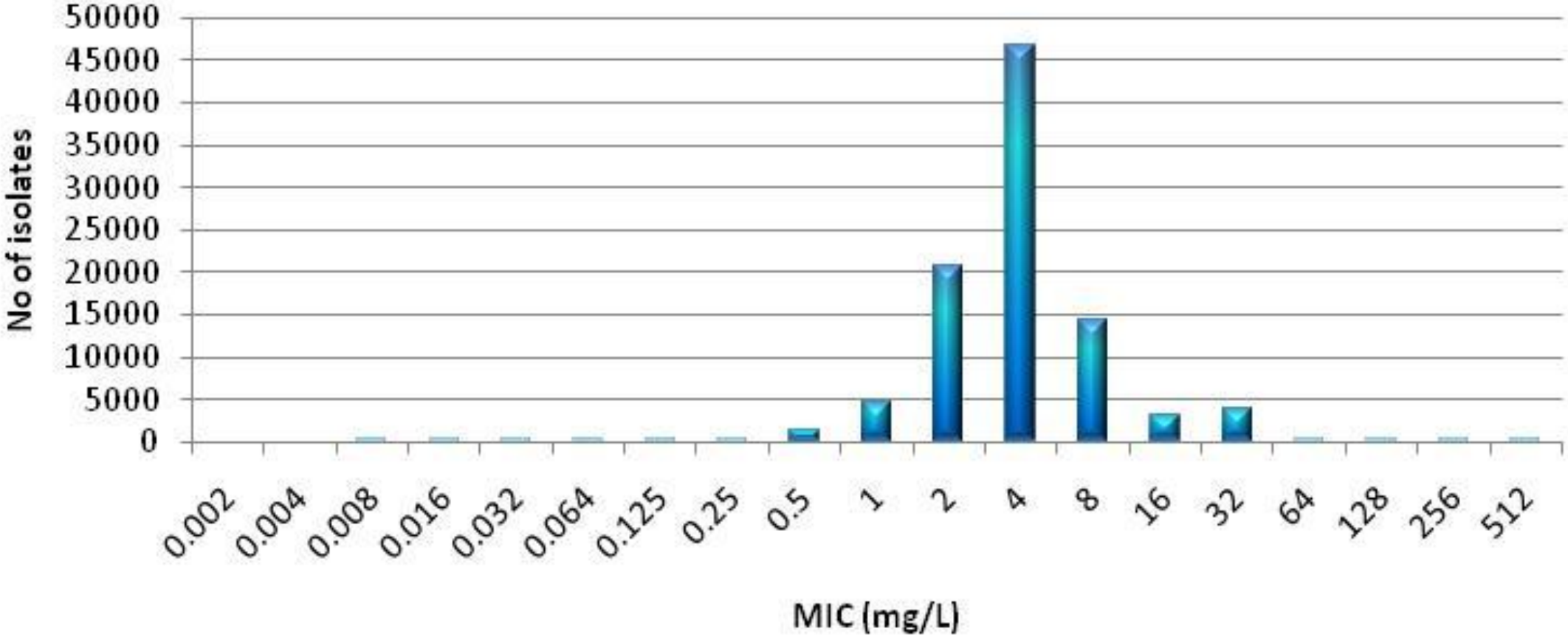
Clinical data

- Clinical trials have shown the efficacy of cefuroxime for
  - complicated UTI with or without septicaemia
  - community acquired pneumonia
  - complicated skin and soft tissue infections

Cefuroxime MIC distribution for *E. coli*



Cefuroxime

- PD BP 4 mg/L for 750 mg TDS
- For Enterobacteriaceae
  - S ≤8 mg/L / R >8 mg/L
  - S/I breakpoint increased from 4 to 8 mg/L to avoid splitting the wild type MIC distribution
  - BPs relate to high dose therapy (1.5 g x 3)

Usually single BP for each AB/organism. But ...

Table 6. MIC and zone diameter breakpoints for Enterobacteriaceae (including *Salmonella* and *Shigella* spp.)

	MIC breakpoint (mg/L)				Interpretation of zone diameters (mm)			
Aminoglycosides								
Amikacin	16	16	8	30	15	16-18	19	*Salmonella* spp. should be reported resistant to these agents, irrespective of susceptibility testing result, as they are inactive against *Salmonella* spp. *in vivo*. Individual aminoglycoside agents must be tested; susceptibility to other aminoglycosides cannot be inferred from the gentamicin result and *vice versa*.
Gentamicin	4	4	2	10	16	17-19	20	
Tobramycin	4	4	2	10	17	18-20	21	
Penicillins								
Amoxicillin	8	-	8	10	14	-	15	Species that have chromosomal penicillinases (*Klebsiella* spp.) or those that typically have inducible AmpC enzymes (e.g. *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp.) are intrinsically resistant to ampicillin/amoxicillin.
Ampicillin	8	-	8	10	14	-	15	
Co-amoxiclav Systemic	8	-	8	20/10	20	-	21	Species that typically have inducible AmpC enzymes (e.g. *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp.) are intrinsically resistant to co-amoxiclav. Zone diameter based on a 2:1 ratio of amoxicillin: clavulanate are currently under review to establish correlation with an MIC breakpoint with a fixed concentration of clavulanate.
Co-amoxiclav UTI[1-5]	32	-	32	20/10	12	-	13	

Usually single BP for each AB/organism. But ...

Table 11. MIC and zone diameter breakpoints for *Streptococcus pneumoniae*

	MIC breakpoint (mg/L)				Interpretation of zone diameters (mm)			
Antibiotic	R >	I	S ≤	Disc content (µg)	R ≤	I	S ≥	Comment
Carbapenems								
Ertapenem	0.5	-	0.5	-	-	-	-	Screen for β-lactam resistance with the oxacillin 1 µg disc. Isolates categorised as susceptible can be reported susceptible for ertapenem, imipenem and meropenem. Meropenem is the only carbapenem used for meningitis. For use in meningitis determine the meropenem MIC value. Isolates with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
Imipenem	2	-	2	-	-	-	-	
Meropenem (Infections other than meningitis)	2	-	2	-	-	-	-	
Meropenem (for meningitis)	**1**	**0.5-1**	**0.25**	-	-	-	-	

Setting Breakpoints

- BPs allow prediction of clinical efficacy
- BPs relate to
  - Particular doses
  - Particular infections (Bloodstream)
- BPs give consistent reliable predictive results (but are not absolute)