

Dosing and clinical outcome during antibacterial chemotherapy¹

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1. The slides of the Academy for Infection Management (Educational Resource Slide Kit, Pharmacokinetic/pharmacodynamic considerations for antibiotic therapy) are partly used in this lecture

Problems in the treatment of bacterial infections

- increasing rate of resistance (both in community acquired and nosocomial infections)
- widespread emerging of multi- and panresistant bacteria
- limited efficacy of infection control measurements
- no new antibiotics in the pipelines

Improving the probability of SUCCESS

- The outcome depends on the interrelationship of the host, the pathogen and the antibiotic
- no way to influence the patient
- no way to influence the pathogen
- but we can improve the quality of antimicrobial therapy

Improving the probability of SUCCESS

- Possibilities:
- -early diagnosis and treatment
- -knowledge of local resistance patterns
- for the optimal empiric therapy
- -improvement of the efficacy of antibiotic therapy through the use of pk/pd approach

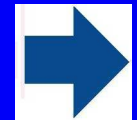
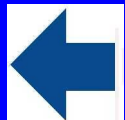
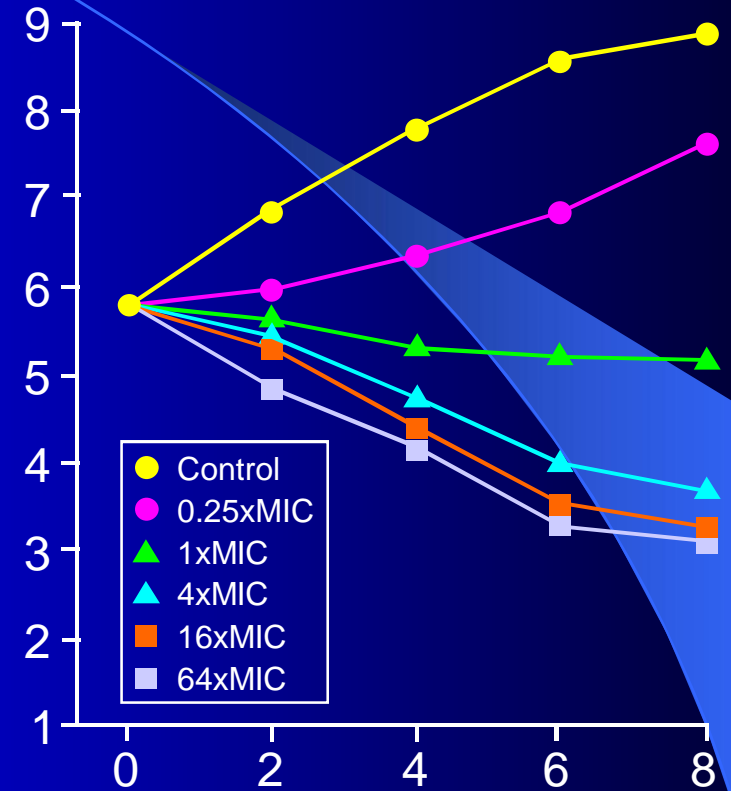
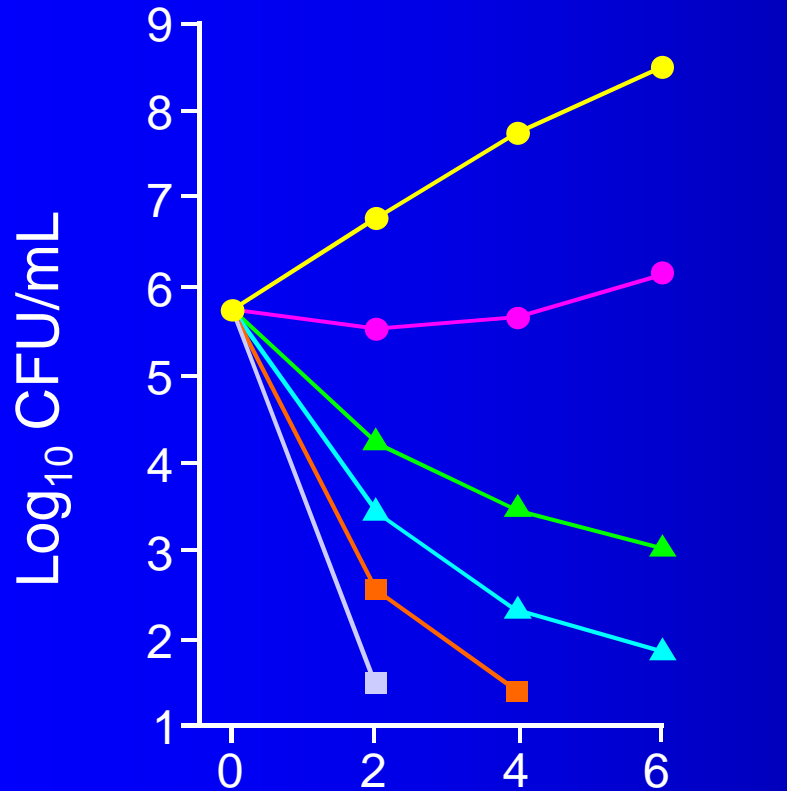
Goals of antimicrobial therapy

- **Minimum=**
- **-clinical cure**
- **-shortening the duration of the illness**
- **-prevention of complications**

- **maximum=**
- **above +**
- **eradication of the pathogen (prevention of the spread of resistant bugs)**

Basic observations on bacterial killing

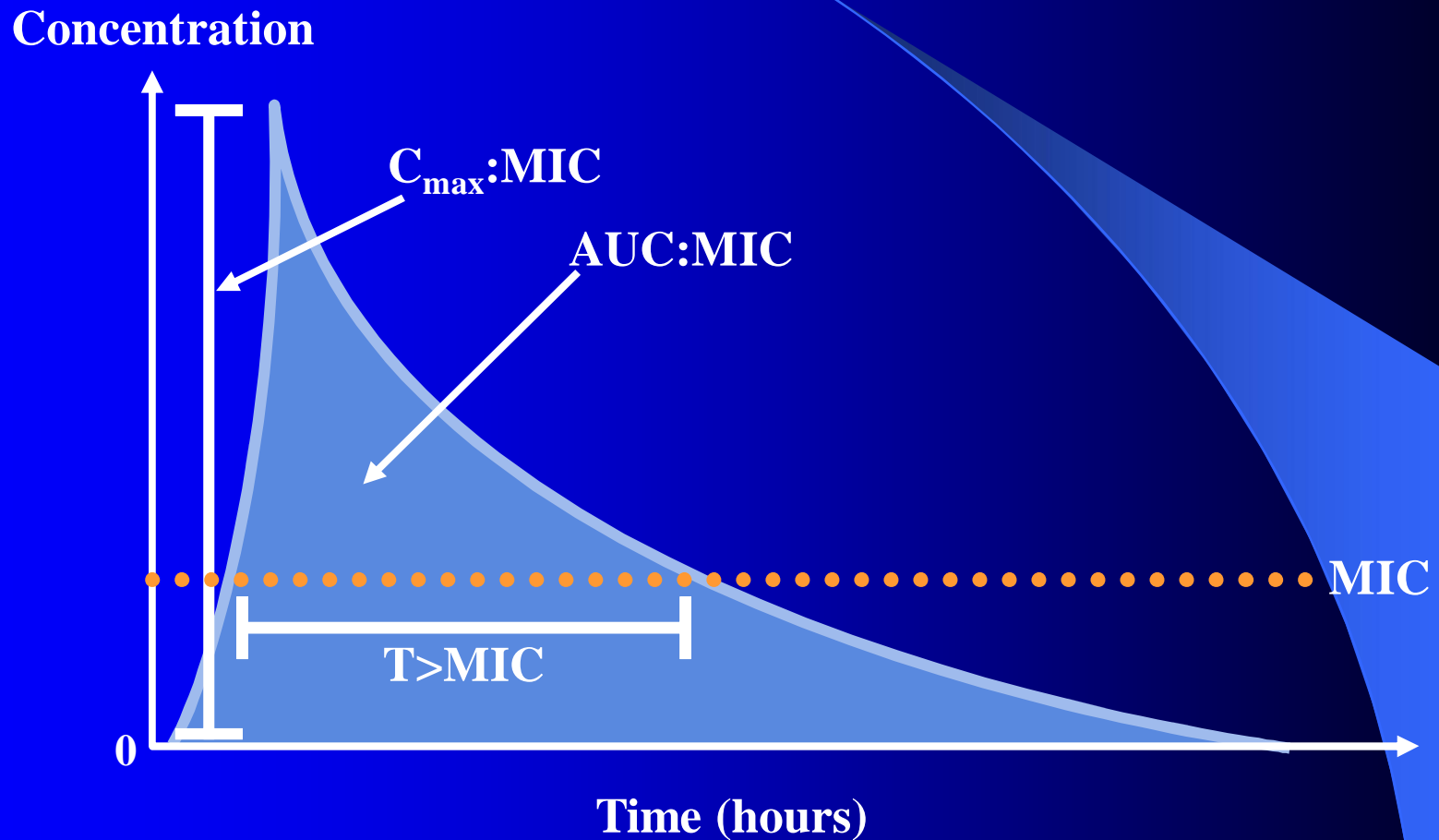
Concentration dependent **Time dependent**



Pharmacokinetic and pharmacodynamic parameters

- **The best available parameter for the in vitro drug potency is the minimum inhibitory concentration (MIC)**
- **Important kinetic parameters used as indices:**
 - **- C_{\max}**
 - **-AUC**
 - **-time above MIC**
- **The outcome always depends on the relationship (ratio) of one of the kinetic parameters and the MIC**
- **Pharmacodynamic relationship is different for different antimicrobial classes**

Pk/pd approach



AUC = Area under the concentration–time curve

C_{\max} = Maximum plasma concentration

Pharmacodynamic parameters predictive of outcome

Parameter correlating with efficacy	C_{\max} :MIC	AUC:MIC	T>MIC
Examples	Aminoglycosides Fluoroquinolones	Azithromycin Fluoroquinolones Ketolides	Carbapenems Cephalosporins Macrolides Penicillins
Organism kill	Concentration-dependent	Concentration-dependent	Time-dependent
Therapeutic goal	Maximise exposure	Maximise exposure	Optimise duration of exposure

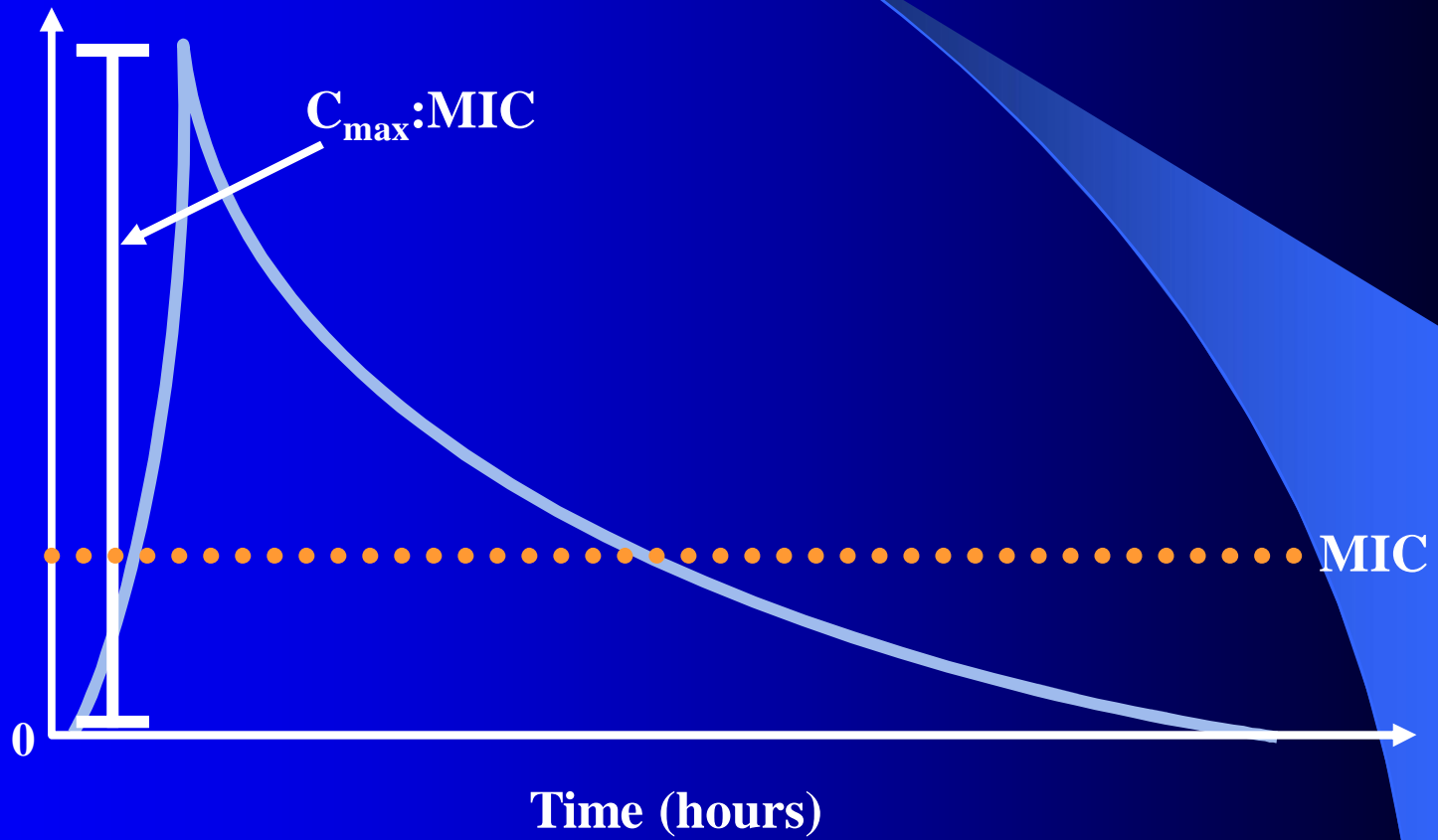
Drusano & Craig. J Chemother 1997;9:38-44

Drusano et al. Clin Microbiol Infect 1998;4 (Suppl. 2):S27-S41

Vesga et al. 37th ICAAC 1997

$C_{\max}:\text{MIC}$

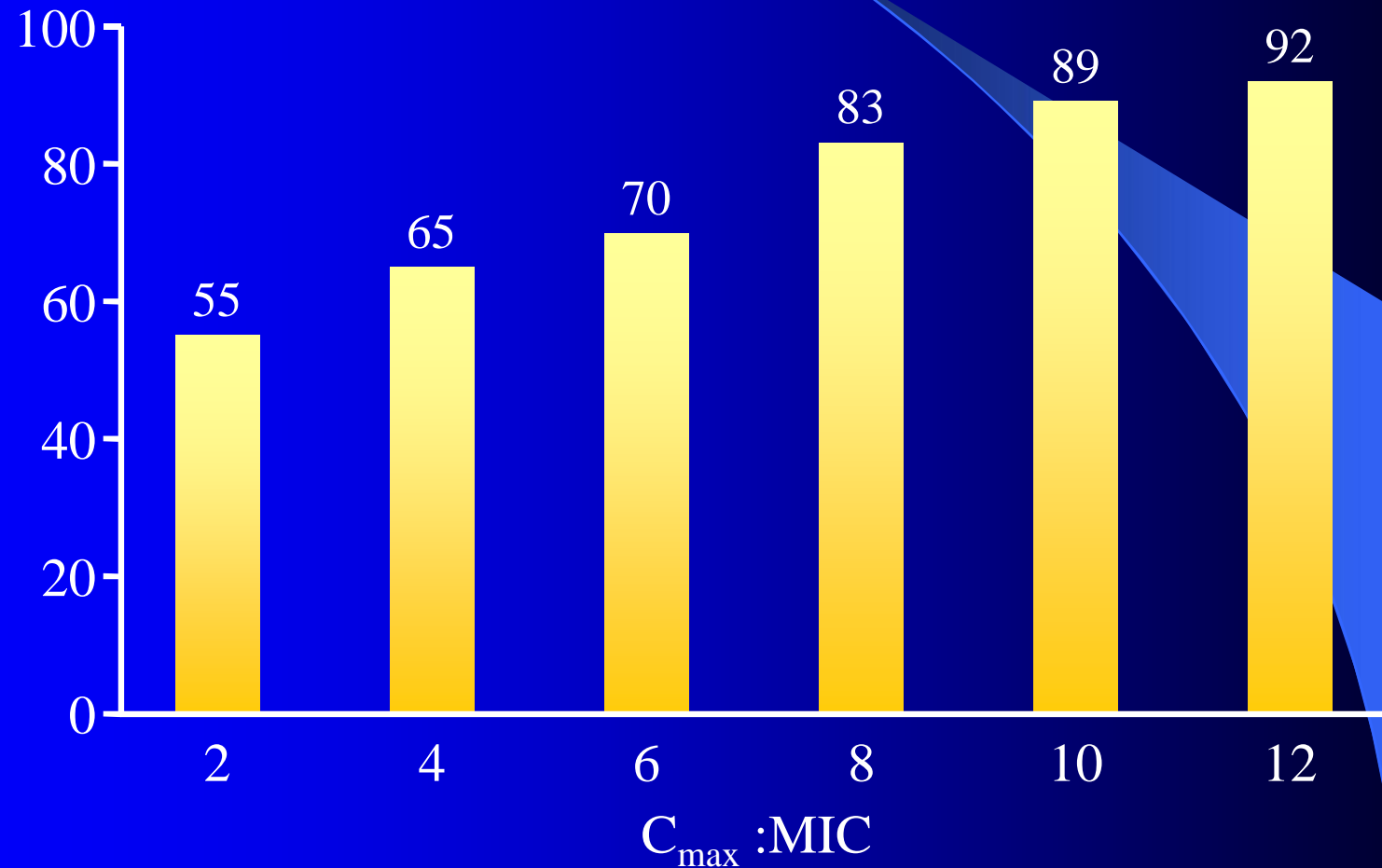
Concentration



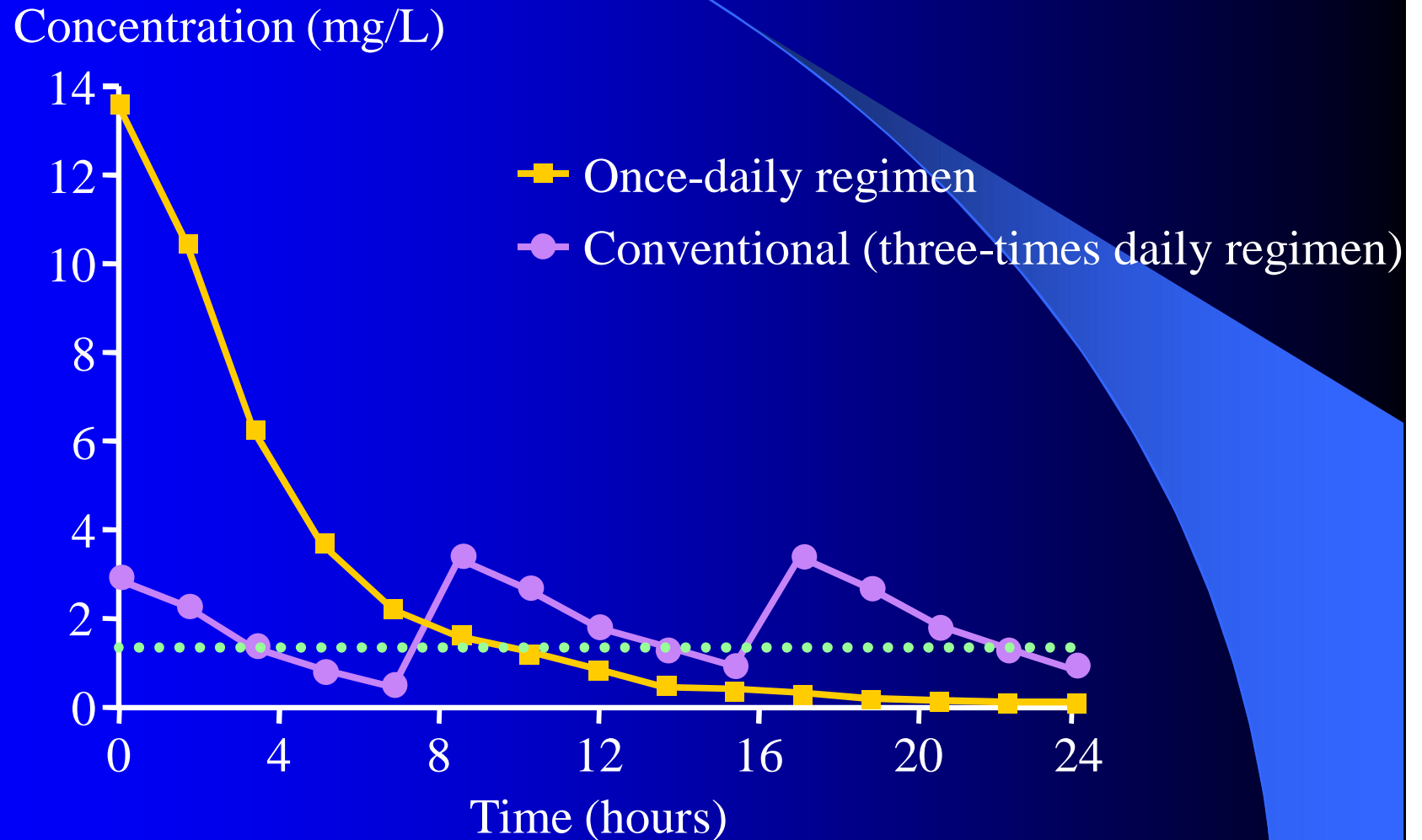
C_{\max} = Maximum plasma concentration

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

Clinical response (%)



Once-daily vs conventional three-times daily aminoglycoside regimens



Aminoglycosides

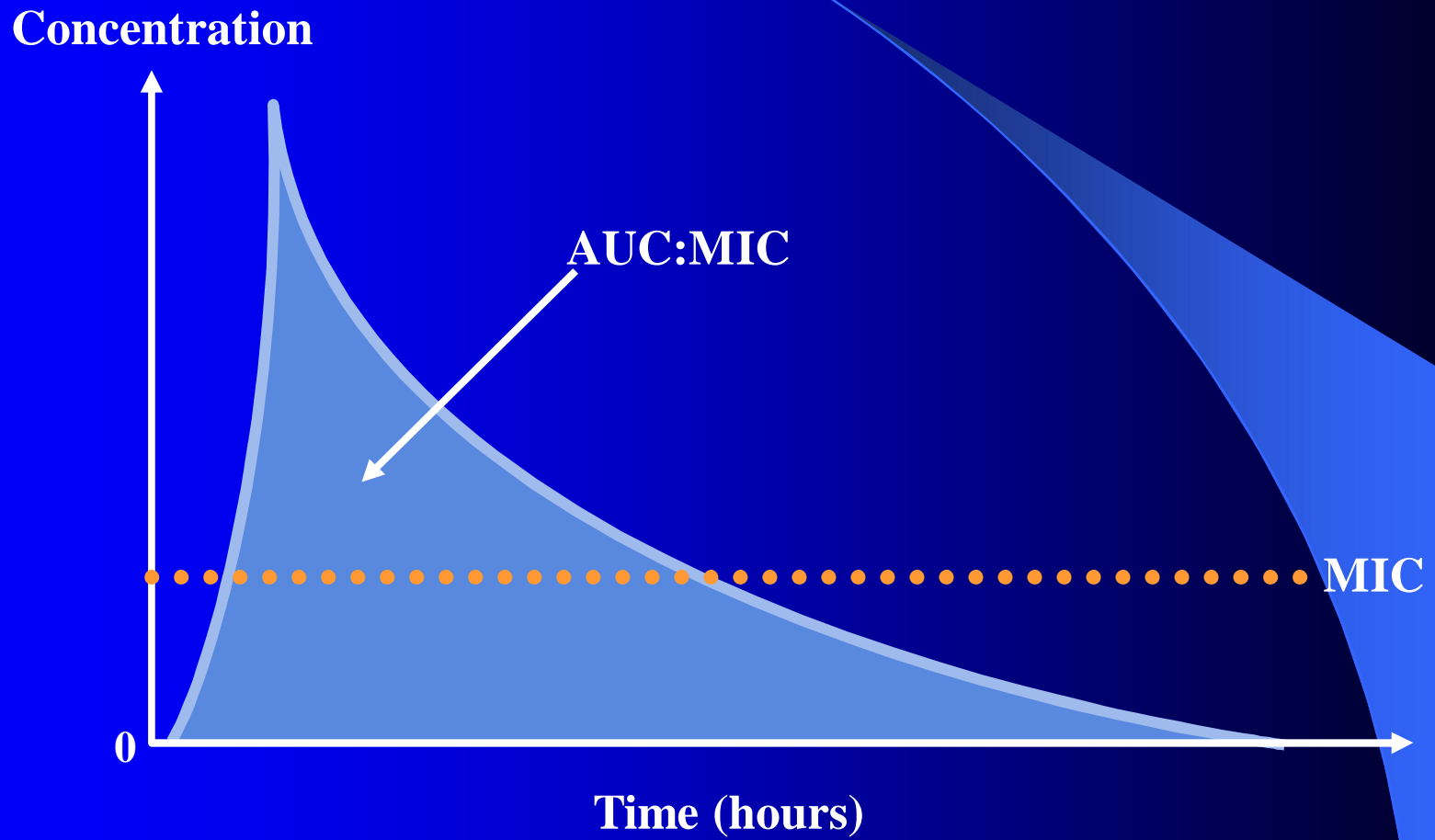
- **Target value: $C_{\max}/MIC = 10$**
- **$C_{\max}:MIC \geq 10$ translates into improvements in the rate and extent of clinical response**
- **Once-daily administration is advocated to maximise efficacy and minimise potential drug accumulation and toxicity**

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

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

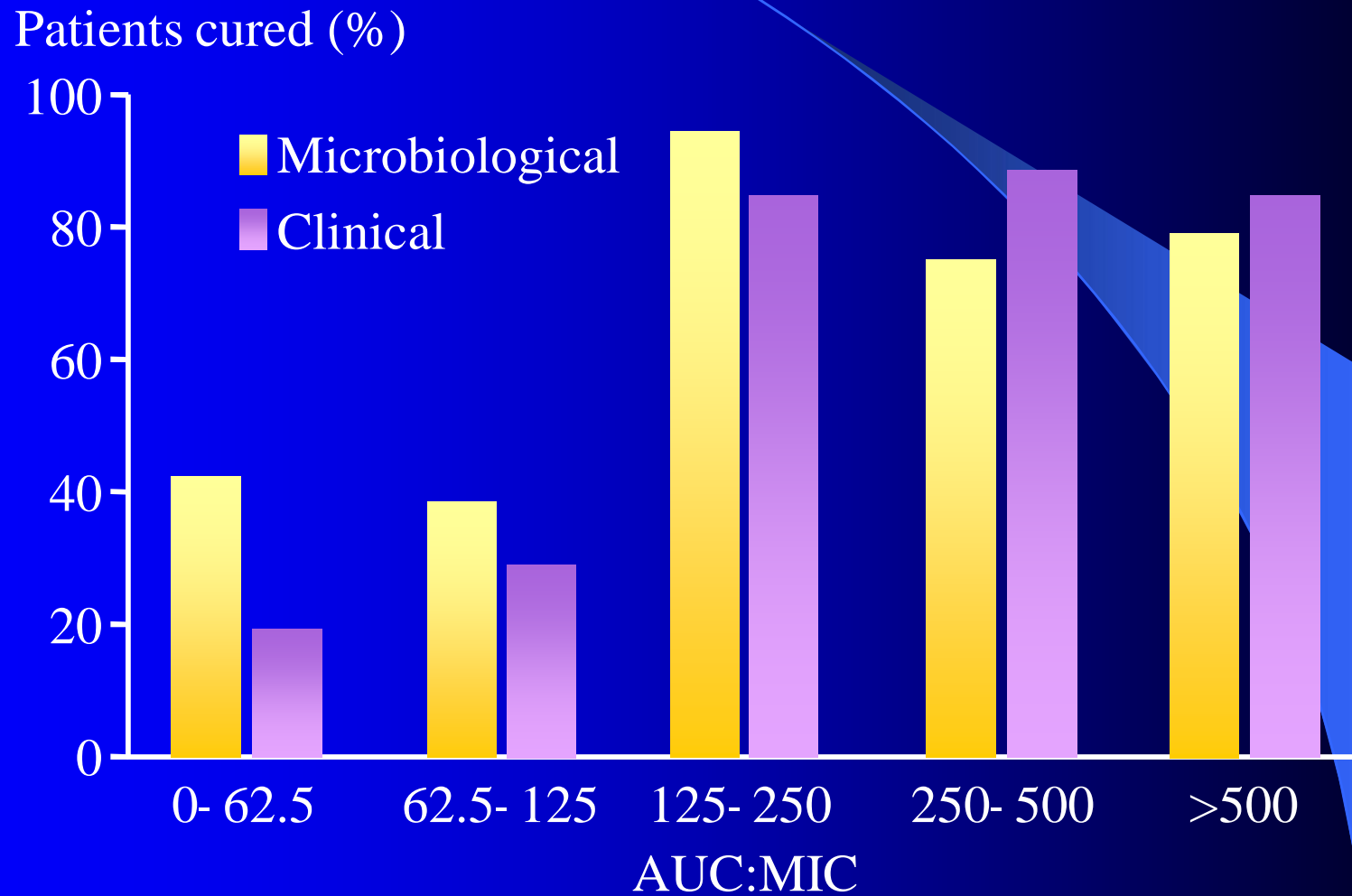
Nicolau et al. Antimicrob Agents Chemother 1995;39:650- 655

AUC:MIC



AUC = Area under the concentration–time curve

Fluoroquinolone therapy for nosocomial pneumonia: correlation between drug exposure and clinical outcome



Fluoroquinolones

- For nosocomial pneumonia treated with ciprofloxacin, $AUC:MIC >125$ results in clinical cure and bacteriological eradication rates $>80\%$
- For community-acquired pneumonia treated with levofloxacin or gatifloxacin, $AUC:MIC >34$ improves probability of pneumococcal bacteriological eradication

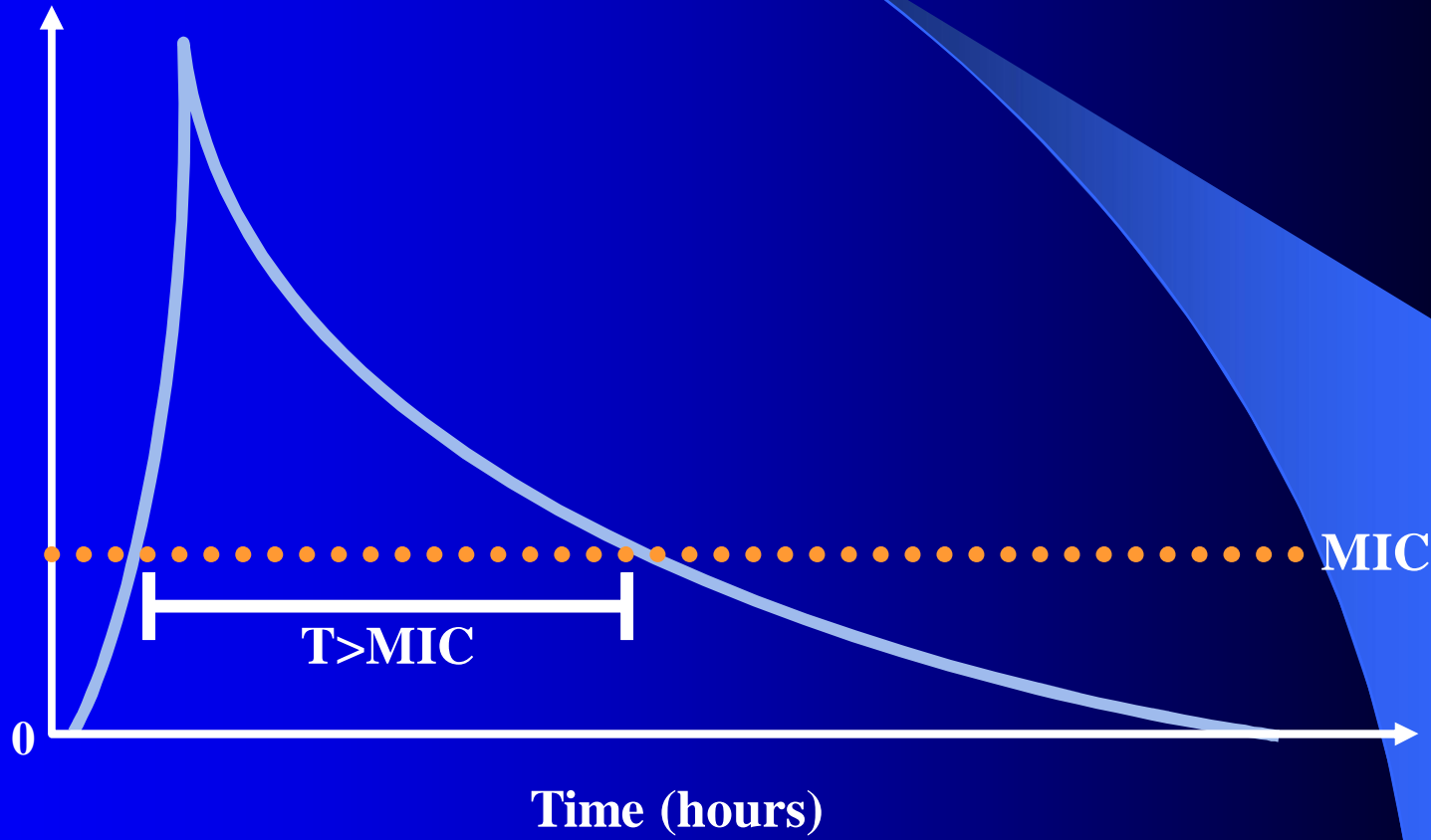
Fluoroquinolones

- target values:
- Gram-negatives $AUC/MIC > 125$
- Gram-positives: $AUC/MIC > 30$

- high doses of fluoroquinolones are recommended

$T > MIC$

Concentration



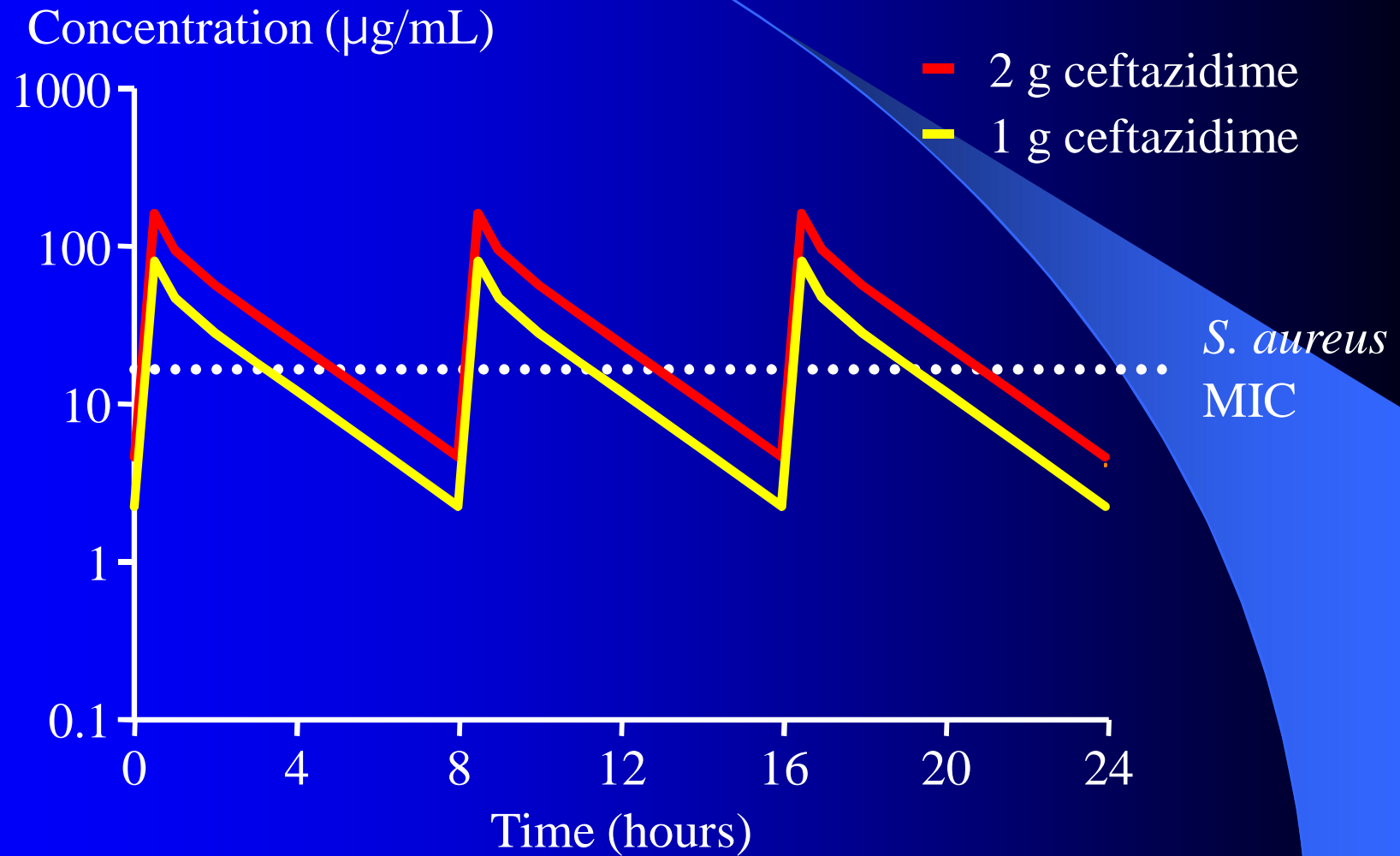
β -lactams: optimising exposure

- The optimum level of exposure varies for different agents within the β -lactam class: approximately $T > MIC$ of:
 - ~ 60–70% for cephalosporins
 - ~ 50% for penicillins
 - ~ 40% for carbapenems

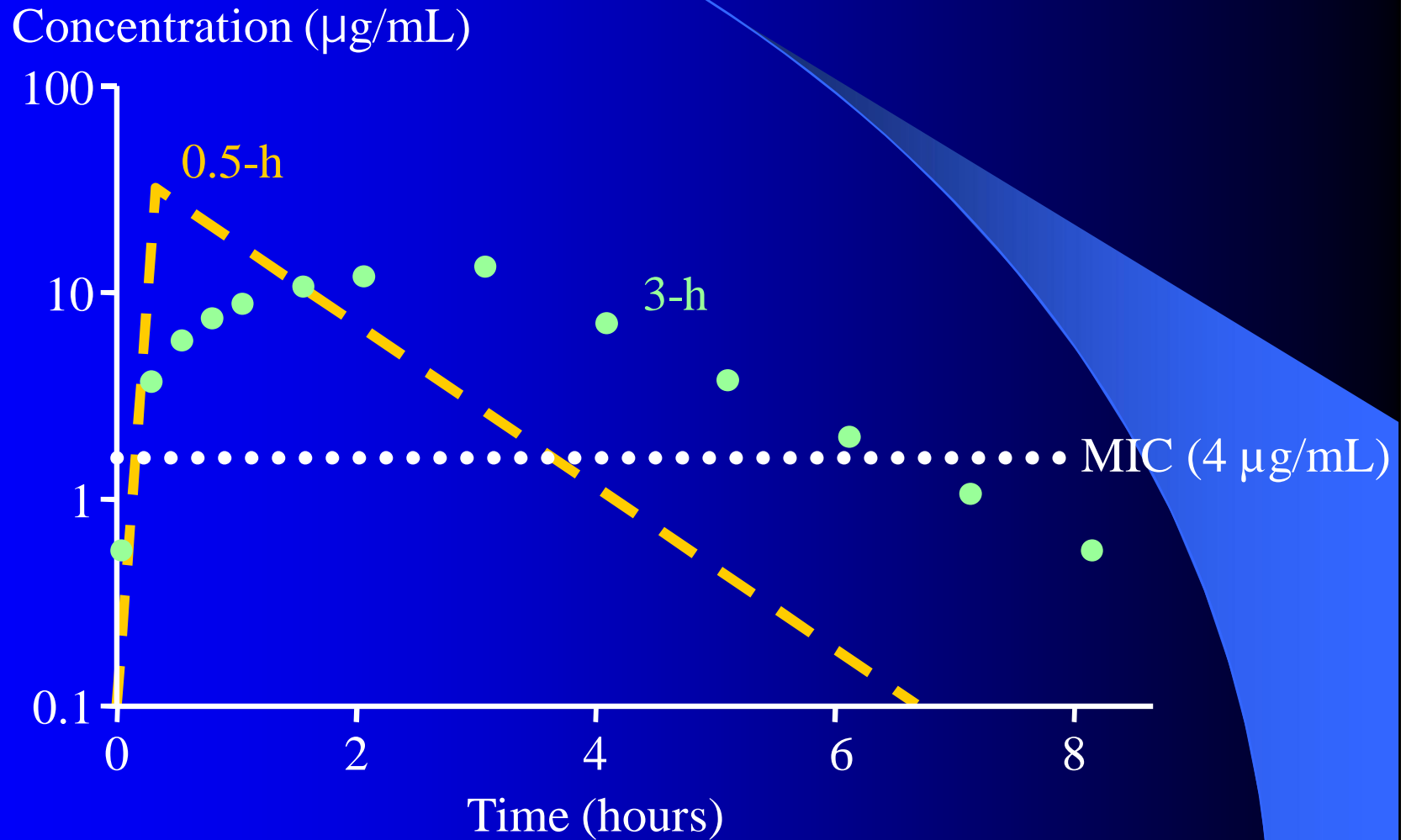
Maximizing T>MIC

- Higher dose
- Increased dosing frequency
- Improved pharmacodynamic profile within class
- Increased duration of infusion

Pharmacodynamics of ceftazidime 1 g and 2 g three-times daily



Meropenem 500 mg administered as a 0.5-h or 3 h-infusion



Pharmacokinetics of meropenem administered
in bolus and 3 h infusion in healthy volunteers
A.A.C. 2005, 49, 1337

Parameter	Bolus injection	3-h infusion	
		1 g	2 g
C_{\max} ($\mu\text{g/ml}$)	112,52	30,24	67,09
AUC_{0-8}	136,27	186,16	388,58

Pharmacokinetics of meropenem administered
in bolus and 3 h infusion in healthy volunteers
A.A.C. 2005, 49, 1337

Parameter	Bolus injection	3-h infusion	
		1 g	2 g
%T > MIC ($\mu\text{g/ml}$) of			
16	28,33	37,78	57,89
8	45,89	58,11	72,89
4	57,00	72,67	85,56
1	74,67	93,56	98,56

Monte Carlo simulation of 180 *P.aeruginosa* strains isolated in Hungary (Ludwig et al ECCMID 2005)

Calculated target attainment rates (%) for selected beta-lactams

%T>MIC	meropenem			imipenem			ceftazidime		cefepime		piperacillin/tazobactam		
	500 mg q8h	1 g q8h	500 mg q6h	500 mg q8h	1 g q8h	500 mg q6h	1 g q8h	2 g q8h	1 g q12h	2 g q12h	3.375 g q6h	4.5 g q8h	4.5 g q6h
20	80.64	84.30	83.86	70.74	75.94	72.84	87.24	92.14	74.16	80.44	87.62	86.34	88.12
30	77.28	84.30	78.94	69.46	70.82	72.42	81.54	88.82	70.16	76.56	82.58	78.52	83.44
40 ^a	71.28	78.42	77.12	64.46	69.28	71.30	73.82	82.58	65.38	72.00	76.78	69.94	78.60
50 ^b	62.58	71.88	72.56	53.04	65.48	67.72	64.52	75.26	59.58	67.40	71.00	56.44	72.40
60	54.38	71.88	67.50	37.84	57.30	60.60	53.08	66.36	51.94	62.02	61.70	36.86	64.66
70	47.02	58.94	60.82	23.82	43.84	50.06	41.14	56.48	40.78	54.86	46.44	18.62	52.90

Monte Carlo simulation of 180 *P.aeruginosa* strains isolated in Hungary (Ludwig et al ECCMID 2005)

Pharmacodynamic target attainment (%) of prolonged infusions for selected beta-lactams

%T>MIC	3-hour infusions		4-hour infusions			
	meropenem	meropenem	P/T*	P/T*	cefepime	cefepime
	1 g q8h	2 g q8h	4.5 g q8h	4.5 g q6h	1 g q8h	2 g q8h
40 ^a	83.80	88.12	81.94	82.68	72.28	80.52
50 ^b	79.80	84.22	80.68	81.28	71.20	79.16
60	77.30	82.34	74.36	81.16	67.12	74.98
70	71.84	78.08	67.90	77.54	65.66	73.44

Importance of $T > MIC$ in the treatment of infection

Carbenicillin plus intermittent or continuous infusion
cefamandole

- 235 documented infections in febrile cancer patients
 - cure rate: 65% continuous infusion; 57% intermittent
- Profoundly granulocytopenic patients
 - cure rate: 65% continuous infusion; 21% intermittent

Continuous infusion: consider stability issues

- Allows maximisation of $T > MIC$ for drugs with a short half-life
- Generally can achieve maximisation at reduced dosage
- Reduced dosage minimises adverse events and cost

Consensus principle strategies to optimise outcomes and minimise resistance

- Antibiotics are indicated only in bacterial infections
 - importance of accurate diagnosis
- Antibiotic choices should be based on local susceptibility patterns
- Maximise the reduction in bacterial load with the aim of bacterial eradication
- Pharmacodynamic parameters assist appropriate choices of agents and dosage