TDM of antibiotics

(Laboratory testing guideline in the intensive care unit)

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LDRI LOUVAIN DRUG RESEARCH INSTITUTE

Disclosures

Industry support for work on investigational compounds from

- Cempra Pharmaceuticals [1]
- GSK
- Melinta Therapeutics [2]
- The Medicine Company [3]
- MerLion Pharmaceuticals
- Trius Therapeutics [4]
- Debiopharm

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- the *Fond de la Recherche Scientifique* (F.R.S.-FNRS)
- the *Région Wallone*
- the European Union (FP7 programme)

Influenced by my participation to the

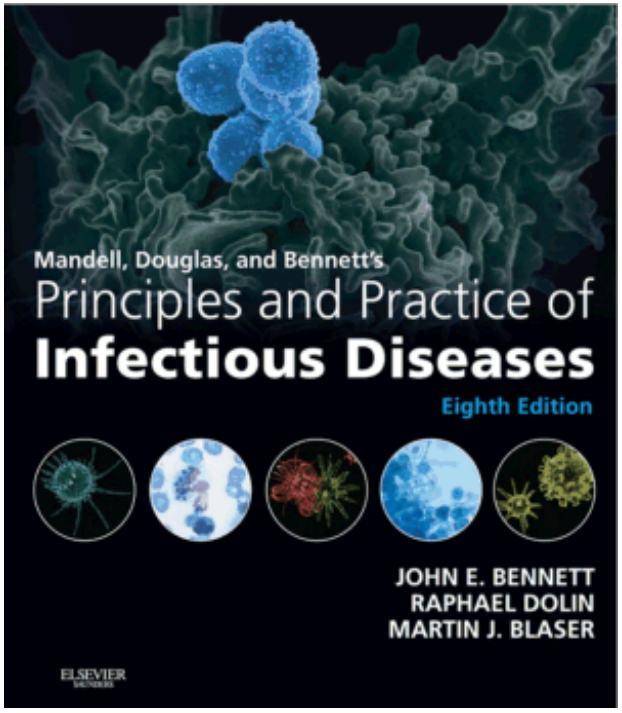
- Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
- EUCAST steering committee (2008-2010) and General Assembly (current)
- the Governance Body of DRIVE-AB (2014-2017)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

[1] merged in 2017 with and renamed as Melinta Therapeutics
[2] formerly RibX Pharmaceuticals; world rights holder for delafloxacin (with license to Menarini for EU and other countries)
[3] antibiotic portfolio acquired by Melinta Therapeutics in 2018
[4] acquired by Cubist (2014), which was then acquired by Merck (2016)

Our program

- How to define the right antibiotic ?
- The basis of the antibiotic Pharmacokinetics/Pharmacodynamics (PK/PD)
- TDM of
  - aminoglycosides — once daily dosing: ↗ efficacy - ↘ toxicity
  - vancomycin — AUC driven TDM – continuous infusion
  - fluoroquinolones — rational breakpoints - ↘ emergence of resistance
  - β-lactames — coping with patients' variations and susceptibility loss
  - linezolid — minimizing toxicity
- a few words about the techniques and the need of bedside approach

The right antibiotic treatment ? … I always wondered…



https://expertconsult.inkling.com/read/mandell-douglas-bennetts-infectious-diseases-8/mandell-douglas-and-bennetts/cover

Chapter 17:
Principles of Anti-infective Therapy
George M. Eliopoulos
Robert C. Moellering Jr.*

"In choosing the appropriate antimicrobial agent for therapy for a given infection, a number of factors must be considered.

- First, the **identity of the infecting organism must be known** or, at the very least, it must be possible to arrive at a statistically **reasonable guess as to its identity** on the basis of clinical information.
- Second, information about the **susceptibility of the infecting organism**, or **likely susceptibility**, must be as accurate as possible.
- Finally, a series of f**actors specific to the patient who is being treated** *(and his/her disease)* must be considered to arrive at the optimal choice of antimicrobial agent. "

Here are the questions …

When choosing an antibiotic, do we know

1. for the organism
   - its identity and whether it is causal or not ?
   - its susceptibility to and the main key properties of the proposed antibiotic ?
2. for the patient
   - the antibiotic effectiveness in the specific disease ?
   - **how to dose the antibiotic appropriately ?**
   - **how to prevent / avoid patient- and drug-related side effects ?**
3. for the society
   - **how to prevent emergence of resistance ?**
   - how to get "value for money" ?

<u>This</u> is what we will mainly discuss

Here are the questions …

When choosing an antibiotic, do we know

1. for the organism
   - its identity and whether it is causal or not ?
   - its susceptibility to and the main key properties of the proposed antibiotic ?
2. for the patient
   - the antibiotic effectiveness in the specific disease ?
   - **how to dose the antibiotic appropriately ?**
   - **how to prevent / avoid patient- and drug-related side effects ?**
3. for the society
   - **how to prevent emergence of resistance ?**
   - how to get "value for money" ?

But we cannot ignore this !

Possible answers for the organism …

When choosing an antibiotic, do we know

1. for the organism
   - **its susceptibility to the proposed antibiotic**

Susceptibility

- are *in vitro* methods predictive (and which ones to use) ?
- which interpretive criteria ?

Know the limits of your methods … and your interpretive criteria…

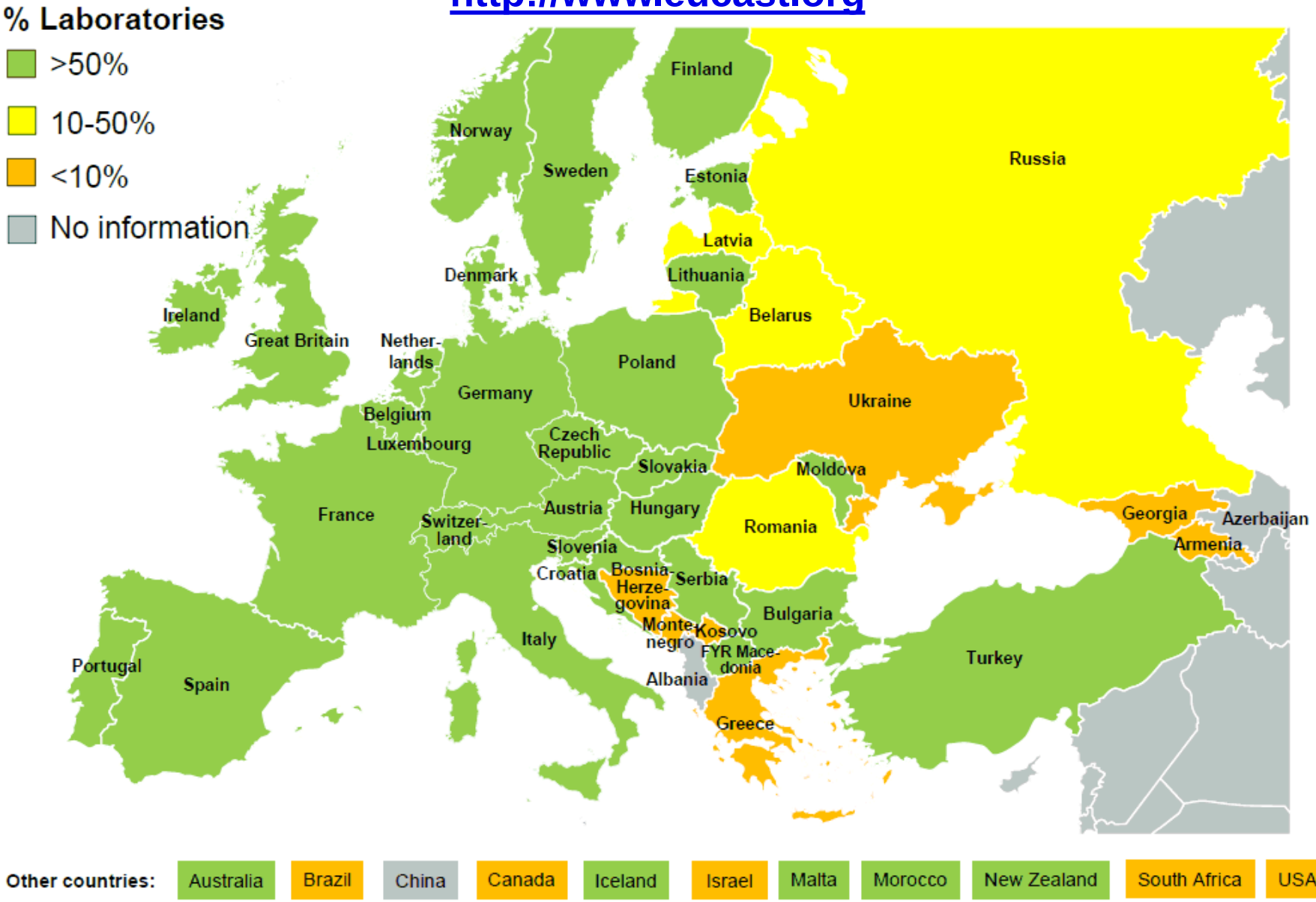
EUCAST European Committee on Antimicrobial Susceptibility Testing
European Society of Clinical Microbiology and Infectious Diseases

CLSI

FDA U.S. Food & Drug Administration

Implementation of EUCAST breakpoints, January 2018

http://www.eucast.org



Possible answers for the patient …

When choosing an antibiotic, do we know

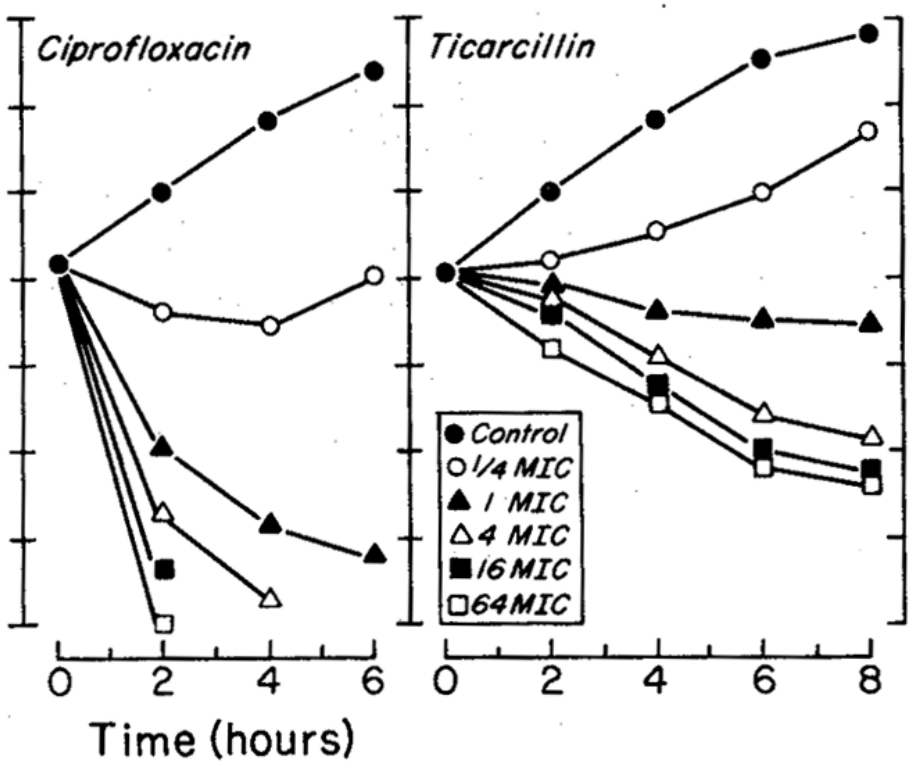
2. for the patient
   - **how to dose the antibiotic appropriately ?**

This is where the PK/PD guys came in (Stockholm, 1989)

Starting PK/PD with a simple *in vitro* microbiological comparison

- bacteria in broth
- increasing concentrations (multiples of MIC)
- measure of the change in CFUs over time

quinolone … **β-lactam …**

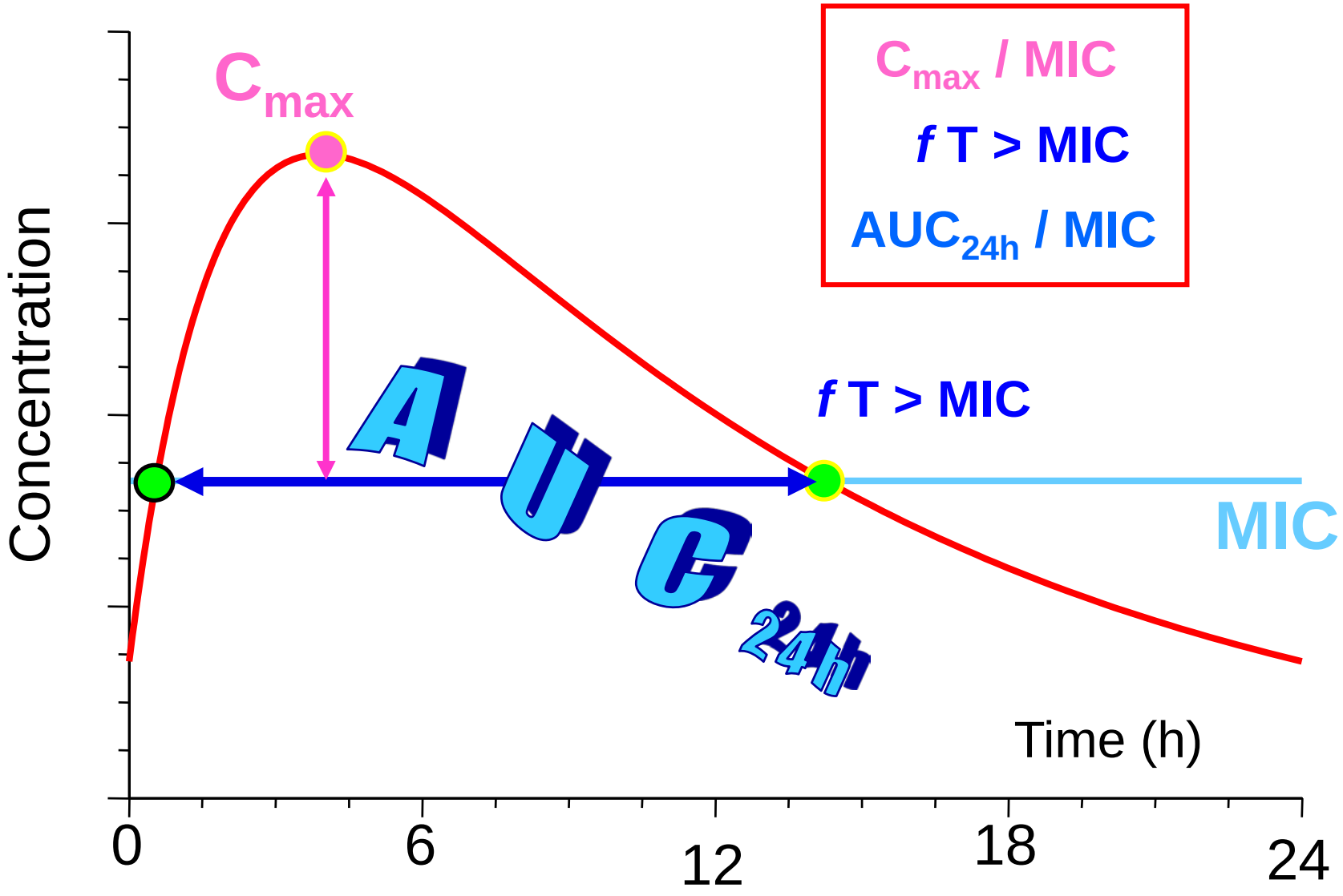


Fast and **concentration**-dépendant

Slow and **time**-dépendant

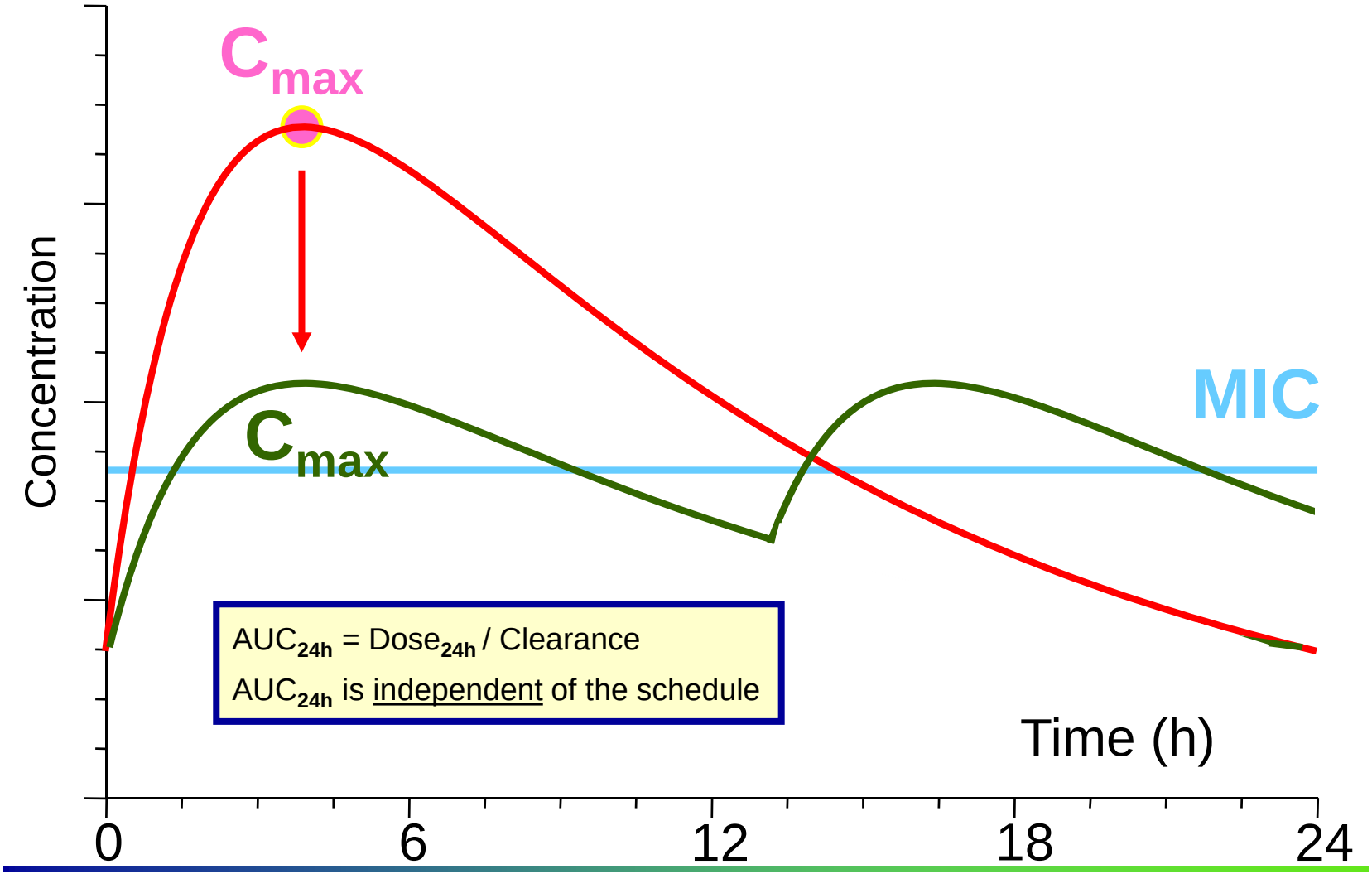
Vogelman & Craig (1986) Jounal of Pediatrics 108:835-840

Moving to patients: PK parameters governing the activity of antibiotics



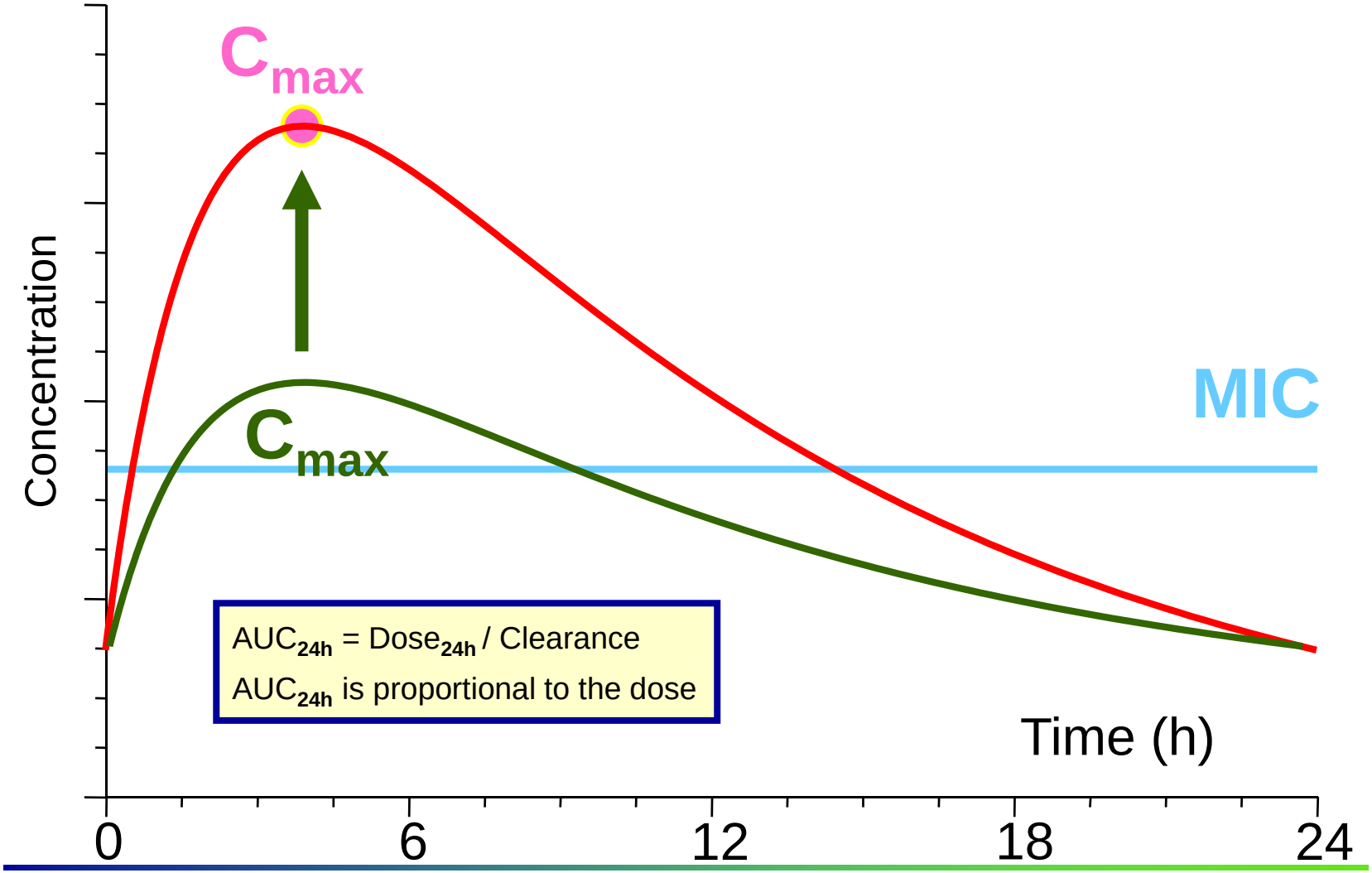
How to determine which PK parameter is critical ?

- If you fractionate the daily dose, you change C_{max} without changing AUC_{24h}



How to determine which PK parameter is critical ?

- If you increase the dose without change of schedule, you increase BOTH C_{max} and AUC_{24h}



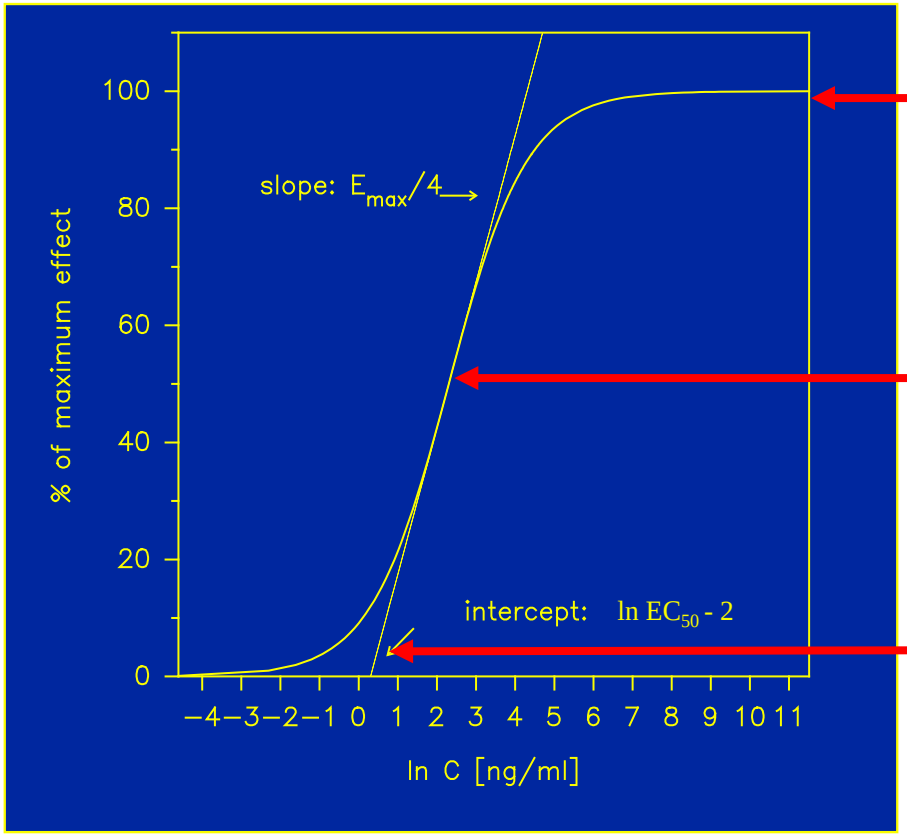
The 3 main patterns of antibiotic PK/PD properties

(W.A. Craig, 2000; revised in 2003)

antibiotic	PK/PD parameter	What to do ?
β-lactams	time > MIC	stay > MIC as needed
macrolides, oxazolidinones, vancomycin…	AUC_{24h} / MIC	give a sufficient total daily dose
quinolones aminoglycosides	peak / MIC and AUC_{24h} / MIC	obtain a peak and aim for a sufficient total daily dose

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig, Infect. Dis. Clin. N. Amer., 17:479-502, 2003

An important consideration: What should we aim for ?



concentration

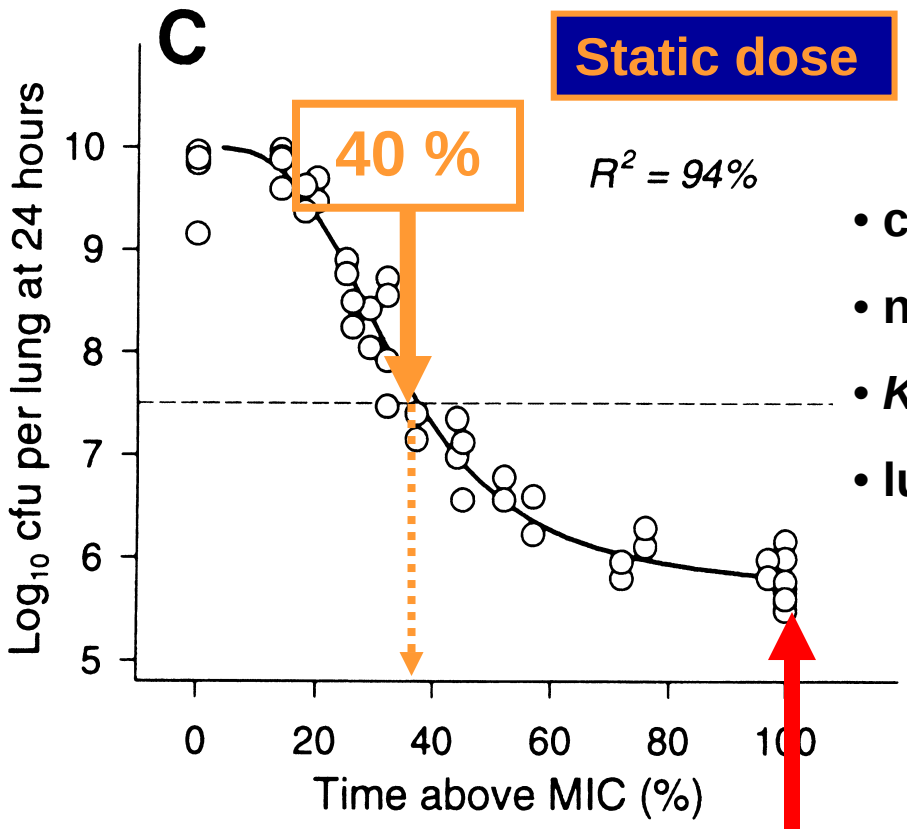
E_{max} — **Maximal effect**

$E_{50\%}$

E_{min} — **Minimal effect**

How to be optimal ?

If you select a β-lactam …

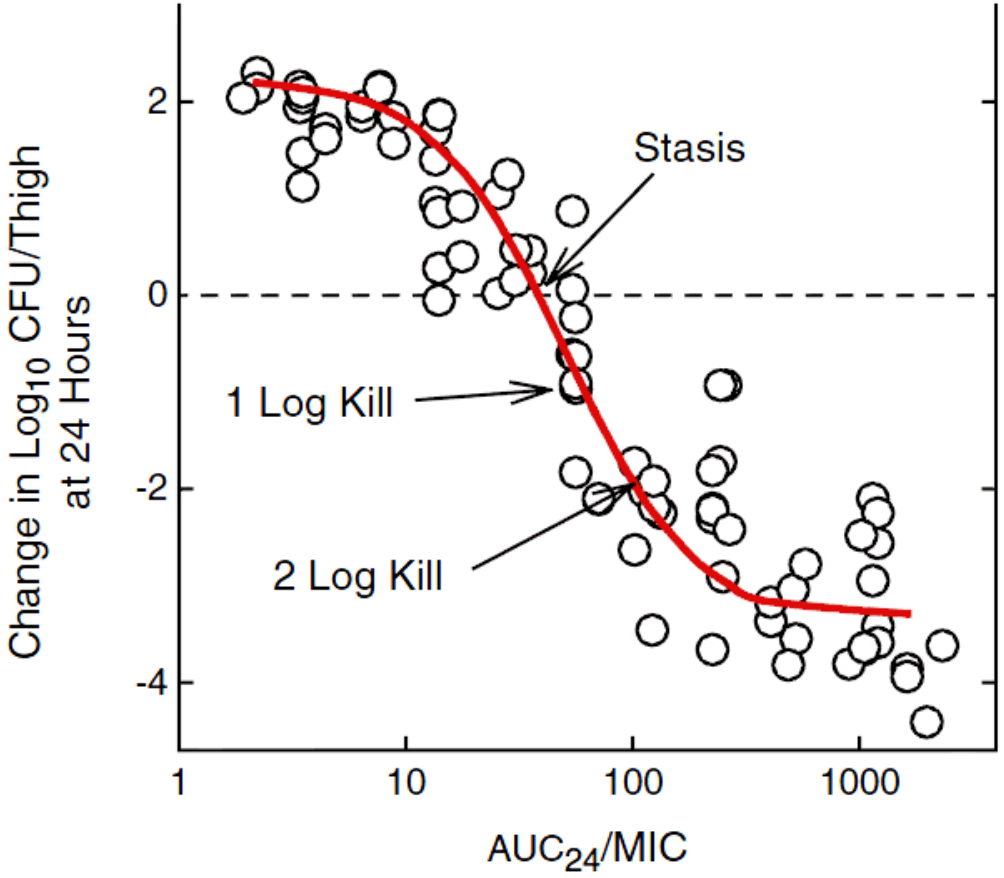


- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection

100 % - Maximal effect

Breakpoint setting…

Fig. 2.6 Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)



Aminoglycosides …

Aminoglycosides are concentration-dependent and need to be given **once-daily** both for increased efficacy and possible reduction of toxicity

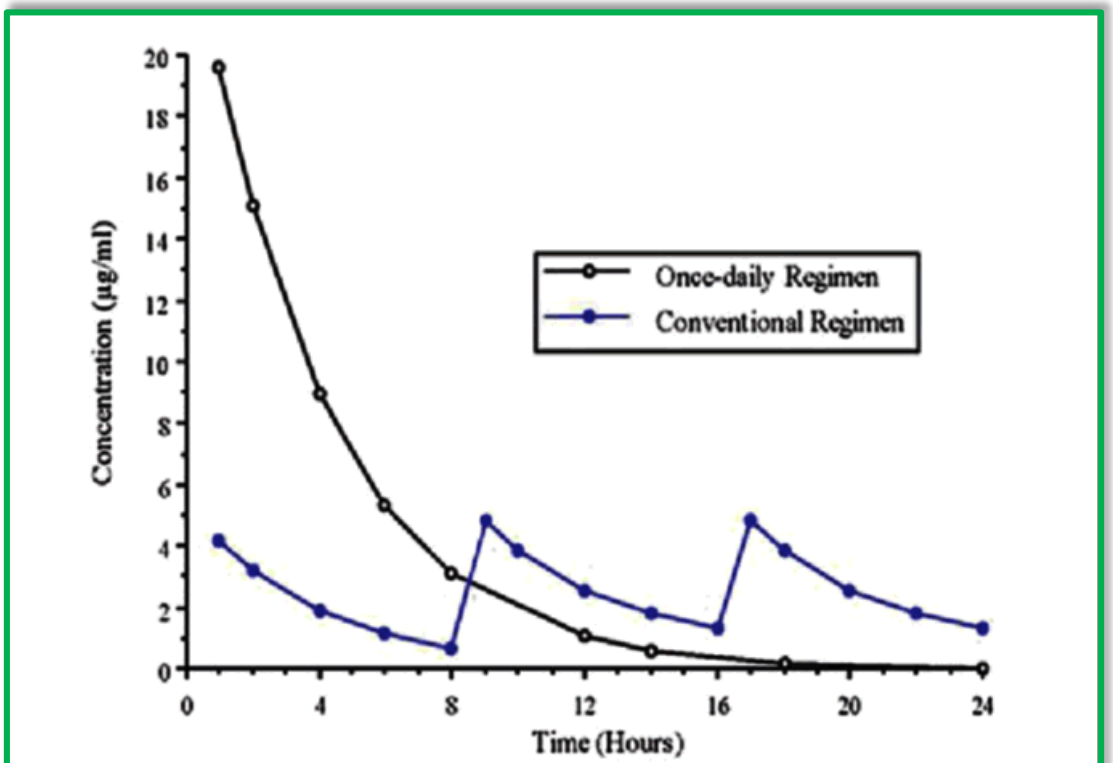


Fig. 9.1 Concentration-time profile comparison of conventional q8h intermittent dosing versus the once-daily daily administration technique

Nicolau et al. Antimicrob Agents Chemother. 1995;39:650-5 - PMID: 7793867

Aminoglycosides …

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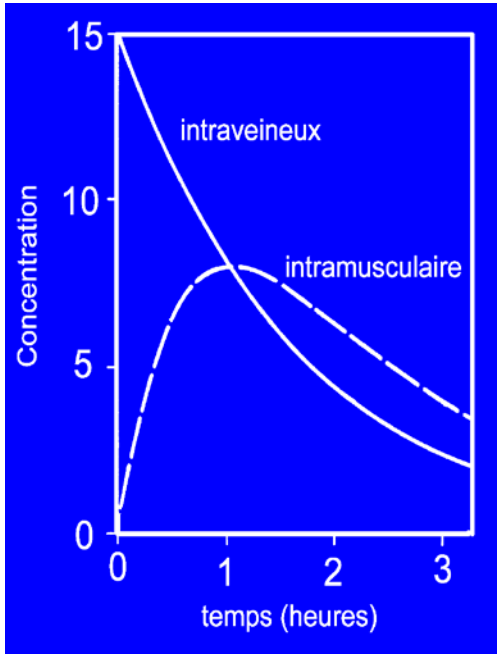


After Schorderet, 1998

1. clinical efficacy is maximal if C_{max} = 8 x MIC

2. select the appropriate route of administration (IV > IM)

3. Compute the desired based on MIC (if available) or breakpoint (see EUCAST documents)

4. Compute the dose (C_{max} x V_d)

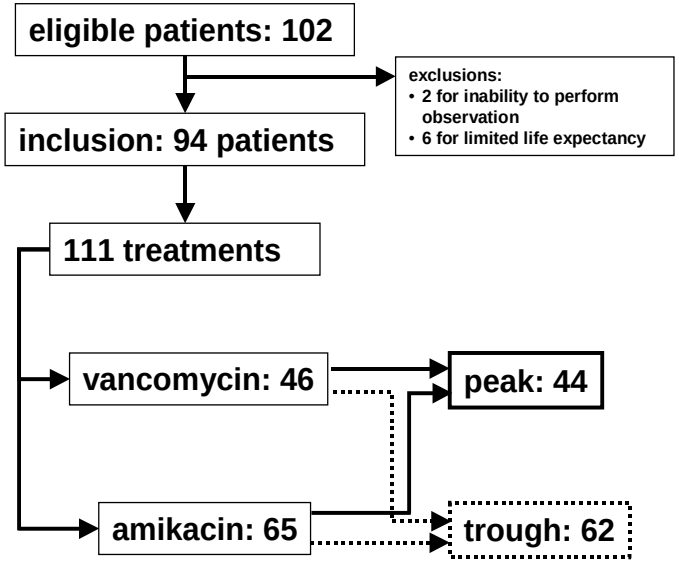
Note: Vd = 0.2 L/kg in "nomal" patients but can be increased to 0.3 L/kg in infected patients)

For most patients:

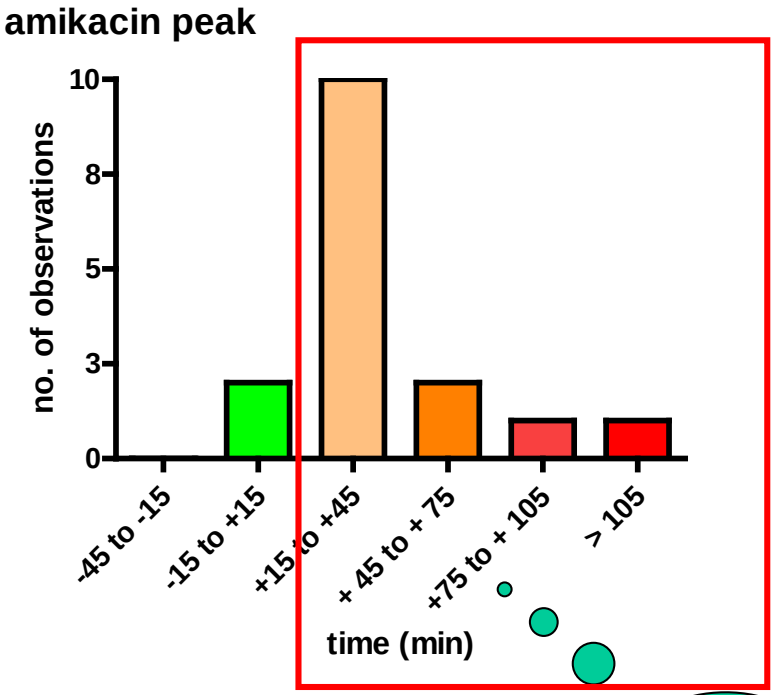
- gentamicin / tobramycin / netilmicin daily dose: 6 mg/kg
  → Cmax: 16 mg/L – will cover up to an MIC of 2 mg/L
- amikacin daily dose 15 mg/kg
  → Cmax: 32 mg/L – will cover up to an MIC of 4 mg/L

Aminoglycoside TDM: correct sampling !!

Observations of a clinical pharmacist about the correct peak sampling



Ampe *et al*., unpublished



A large number of samples were not taken at the defined optimal time

Therapeutic Drug Monitoring: aminoglycosides

Aminoglycosides: The "Nicolau's" nomogram with an 8h sampling time

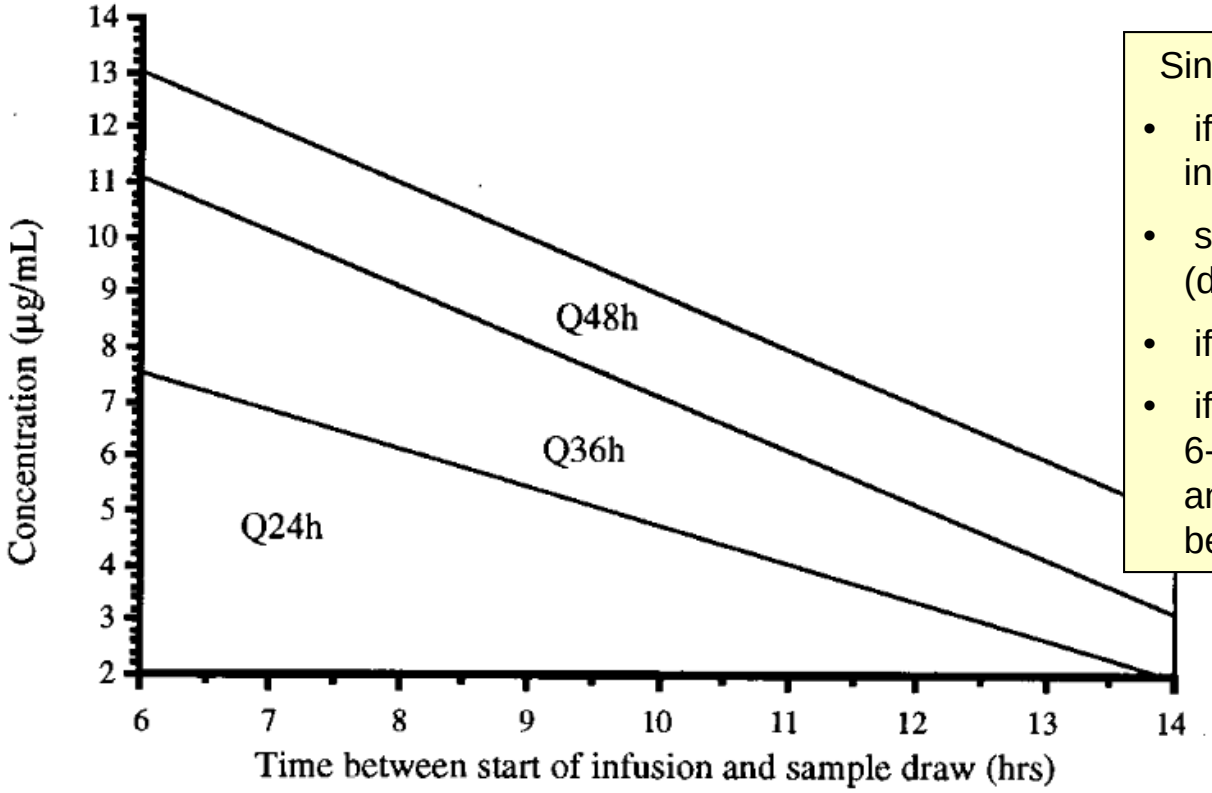


FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

Single concentration measured at 8 h

- if level falls in q24h area, dosing interval is q24h
- same applies for areas q36h q48h (decr. creat. clearance).
- if near line, choose longer interval
- if above the nomogram between the 6- and 14-h time points, stop therapy and monitor for concentr. < 1 mg/L before next dose

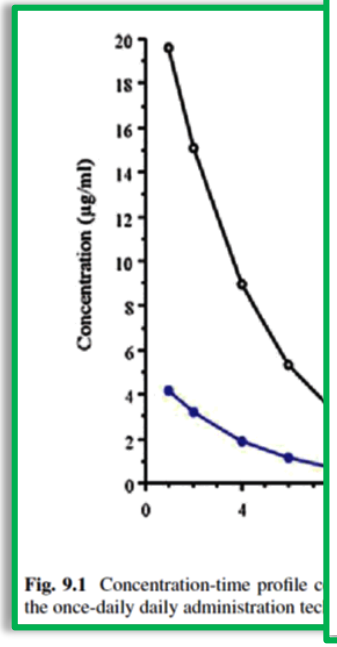
Nicolau et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. PubMed PMID:7793867

Once daily dosing of aminoglycosides: toxicity

When choosing an antibiotic, do we know

2. for the specific patient
   - how to prevent / avoid patient- and drug-related side effects

aminoglycoside
daily both for inc



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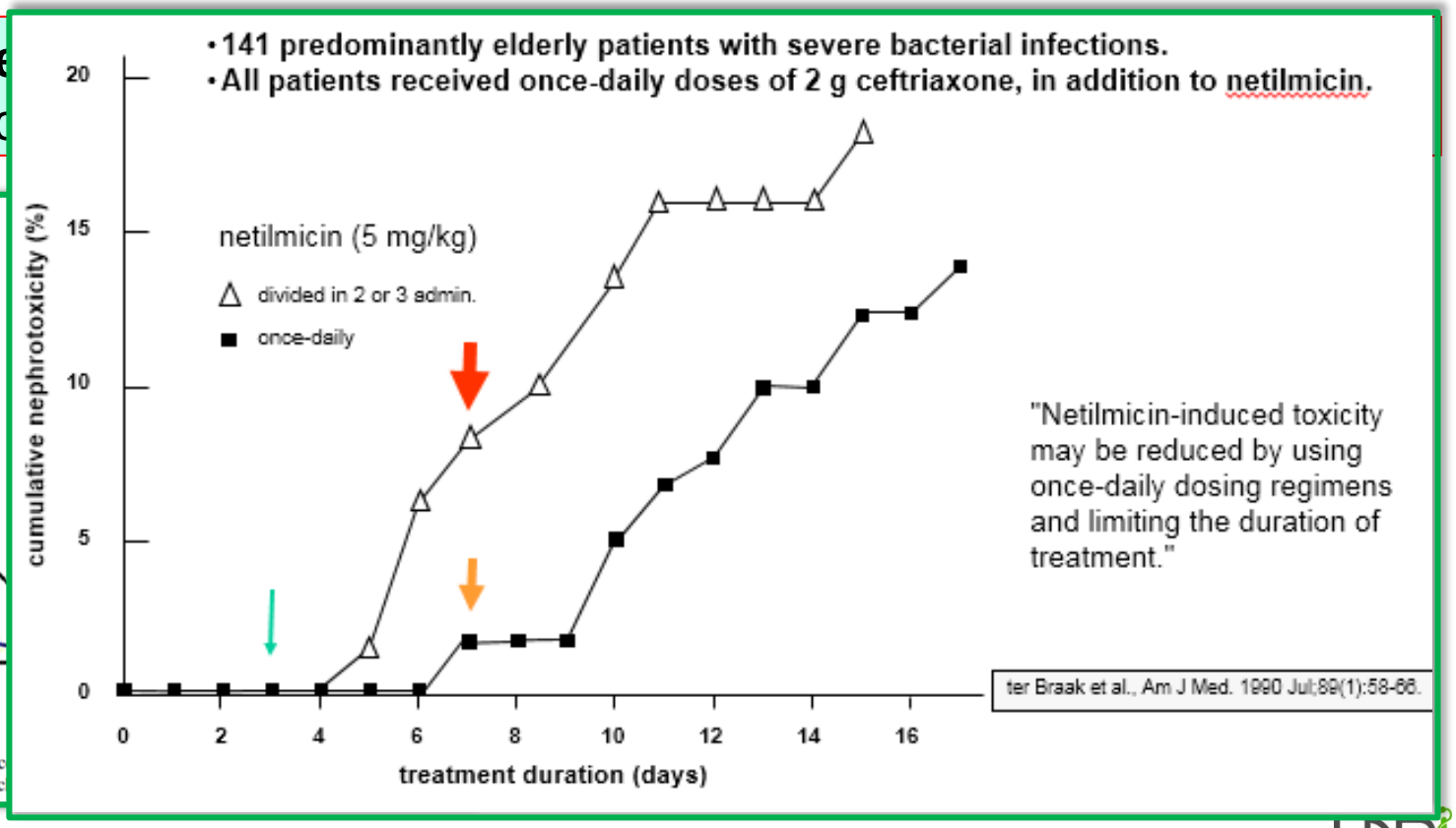

Aminoglycosides: can you do better ?

J Antimicrob Chemother 2016; **71**: 1386–1394
doi:10.1093/jac/dkv491 Advance Access publication 31 January 2016

Journal of Antimicrobial Chemotherapy

A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens: a proof-of-concept study

Alexandre Brasseur[1], Maya Hites[2], Sandrine Roisin[3], Frédéric Cotton[4], Jean-Louis Vincent[1], Daniel De Backer[1], Frédérique Jacobs[2] and Fabio Silvio Taccone[1]*

[1]*Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik, 808-1070 Brussels, Belgium;*
[2]*Department of Infectious Diseases, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik, 808-1070 Brussels, Belgium;*
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Table 3. Characteristics of aminoglycoside dosing

Drug	Initial dose (mg/kg)	Maximal daily dose (mg/kg)	Initial peak (mg/L)	Number of patients with optimal C_{peak}/MIC on day 1	Total dose (mg)
Amikacin ($n=11$)	29 (25–37)	29 (26–67)	77 (66–89)	8	22500 (14250–37875)
Gentamicin ($n=3$)	11 (10–18)	13 (11–18)	27 (21–39)	2	14400 (7900–16800)
Tobramycin ($n=1$)	16	20	15	0	12480

Data are expressed as median (range

Aminoglycosides: can you do better ?

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Journal of
Antimicrobial

A high-dose aminoglycoside regime
therapy for the treatment of MDR p

**Alexandre Brasseur[1], Maya Hites[2], Sandrine Roisin[3], Fr
Frédérique Jacobs[2] an**

[1]*Department of Intensive Care, Erasme Hospital, Université L*
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[4]*Department of Clinical Biochemistry, Erasme Hospital, Universit*

*Corresponding author. Tel: +322-555-5587; F

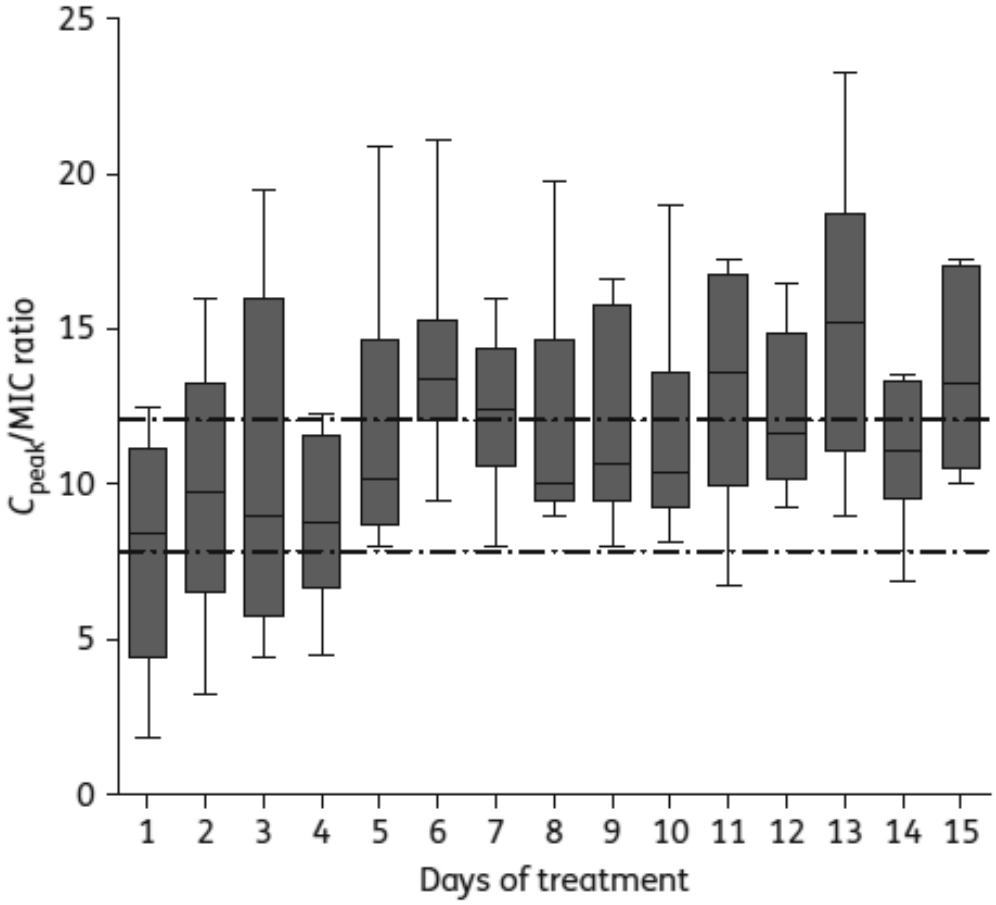

Figure 1. Daily evolution of C_{peak}/MIC ratio. Broken horizontal lines show C_{peak}/MIC ratios of 8 and 12.

Fluorquinolones: the first study of antibiotics PK/PD…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993, p. 1073–1081 Vol. 37, No. 5
0066-4804/93/051073-09$02.00/0

Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

ALAN FORREST, DAVID E. NIX, CHARLES H. BALLOW, THOMAS F. GOSS, MARY C. BIRMINGHAM, AND JEROME J. SCHENTAG*

Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209-1194

Received 19 February 1992/Accepted 5 February 1993

Fluorquinolones: the first study of antibiotics PK/PD…

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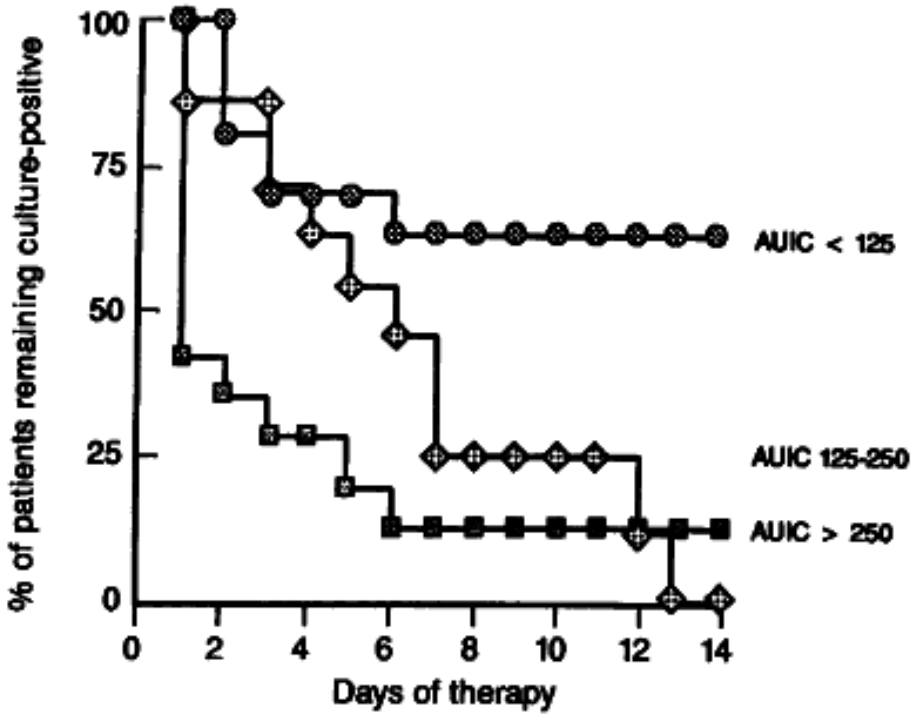

FIG. 5. Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ($P < 0.005$).

PKP/PD of ciprofloxacin: a Japanese testimonial

J Pharm Pharmaceut Sci (www. cspsCanada.org) 11 (4): 111s- 117s, 2008

Investigation of the Clinical Efficacy and Dosage of Intravenous Ciprofloxacin in Patients with Respiratory Infection

Kazuhiro Matsuo[1], Minako Azuma[1], Maki Kasai[2], Itsuka Hanji[1], Itsuki Kimura[1], Takayoshi Kosugi[1], Noriko Suga[1] and Mitsutoshi Satoh[2]

[1] Department of Pharmacy, Toho University Omori Medical Center, 6-11-1 Omorinishi, Ota-ku, Tokyo 143-8540, JAPAN; [2]Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, JAPAN

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Investigation
Ciprofloxacin

Kazuhiro Matsuo[1], Mi
and Mitsutoshi Satoh

[1] Department of Pharm
JAPAN; [2]Department c
Miyama, Funabashi, C

Table 2. Efficacy and pharmacokinetic/pharmacodynamic parameters of CPFX for patients who had *P. aeruginosa* infections.

		Mean±S.D.	N	Range	95%CI	P-value
AUC/MIC	Cures	87.8±23.1	7	60.9–123.0	66.4–109.2	0.0035
	Failures	37.2±23.1	12	1.1–154.2	10.8–63.7	
AUC (mg·min/mL)	Cures	48.6±19.4	42	22.5–113.3	42.5–54.6	0.0342
	Failures	42.2±19.0	52	15.8–87.7	36.9–47.5	
Ccr (mL/min)	Cures	69.3±36.8	40	12.2–147.6	59.6–79.3	0.0686
	Failures	82.0±43.1	41	11.0–170.3	68.4–95.6	
Body weight (kg)	Cures	51.5±12.0	40	24.1–75.0	47.7–55.3	0.3379
	Failures	52.9±16.6	41	29.1–98.0	47.6–58.1	

Creatinine level; Ccr = {[140 – age(years)] X weight(kg)} (X0.85 if female)/{72 X [serumCr(mg/dL)]}. Predictive plasma clearance (CL): CL (mL/min) = weight X (0.167 + 0.00145 X Ccr). Predictive AUC for individual patients were obtained from a modified formula reported by Forrest et al. (1993) [1]: AUC = dose (mg/day)/weight(kg) X (0.167 + 0.00145 CL).

PK/PD breakpoints for fluoroquinolones

Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (µg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[l]	
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.5-1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.5-1
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.5-1
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	1-2
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.5-1

EUCAST breakpoints

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

PK/PD of ciprofloxacin: a special population

Suboptimal Ciprofloxacin Dosing as a Potential Cause of Decreased *Pseudomonas aeruginosa* Susceptibility in Children with Cystic Fibrosis

Emmanuelle Guillot, Pharm.D., Isabelle Sermet, Ph.D., Agnès Ferroni, Ph.D., Stéphanie Chhun, Pharm.D., Gérard Pons, Ph.D., Jean-Ralph Zahar, M.D., and Vincent Jullien, Ph.D.

Guillot et al. Pharmacotherapy. 2010;30:1252-8 - PMID: 21114393

PK/PD of ciprofloxacin: a special population

Suboptimal Ciprofloxacin Dosing as a Potential Cause of Decreased *Pseudomonas aeruginosa* Susceptibility in Children with Cystic Fibrosis

0.25 mg/L may be the max. MIC

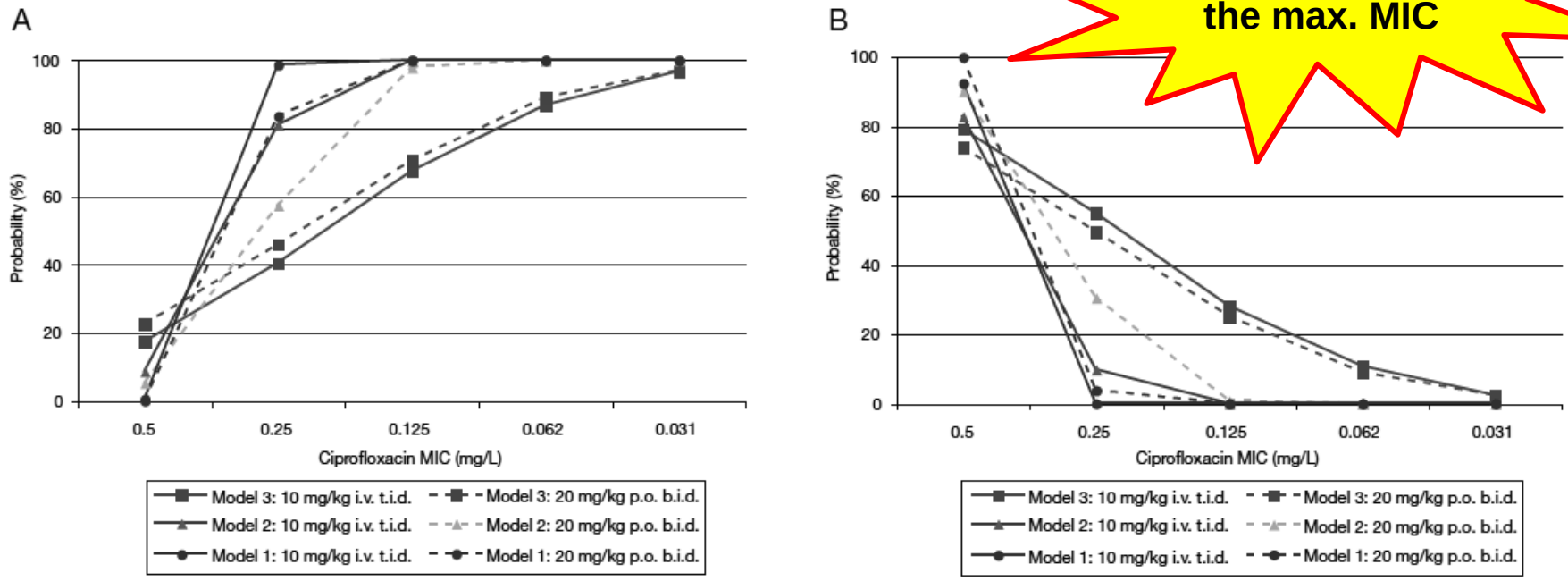

Figure 1. Probability of achieving a 24-hour area under the plasma concentration–time curve (AUC):minimum inhibitory concentration (MIC) ratio greater than 125 (A) or less than 110 (B) for ciprofloxacin against *Pseudomonas aeruginosa* for each respective ciprofloxacin MIC value.

Model 1: 10 mg/kg BID IV 1 day -- 15 mg/kg BID PO 1 day.
Model 2: 10 mg/kg BID IV 1–3 days -- 15 mg/kg BID PO 1 day, or 20 mg/kg TID PO - >3 days.
Model 3: 10 mg/kg IV -- 15 mg/kg BID PO

PK/PD of levofloxacin: limits in MICs

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

Pier Giorgio Cojutti,[a,b] Virginia Ramos-Martin,[c] Isabella Schiavon,[d] Paolo Rossi,[d] Massimo Baraldo,[a,b] William Hope,[c] Federico Pea[a,b]

Institute of Clinical Pharmacology, Santa Maria della Misericordia University Hospital of Udine, Udine, Italy[a]; Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy[b]; Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom[c]; First Division of Internal Medicine Santa Maria della Misericordia University Hospital of Udine, Udine, Italy[d]

PK/PD of levofloxacin: limits in MICs

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CLINICAL THERAPEUTICS

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

TABLE 3 Probabilities of achieving underexposure, normal target exposure, and overexposure with different levofloxacin dosing regimens in older patients in relation to different classes of renal function

Levofloxacin regimen (mg)	Probability[a]														
	0–19			20–39			40–59			60–79			>80		
	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160
125 every 48 h	91.8	8.2	0.0	99.8	0.2	0.0	99.8	0.2	0.0	99.9	0.1	0.0	100.0	0.0	0.0
250 every 48 h	48.5	50.5	1.0	91.4	8.6	0.0	99.0	1.0	0.0	99.6	0.4	0.0	99.9	0.1	0.0
500 every 48 h	6.4	77.2	16.4	32.2	67.0	0.8	81.6	18.4	0.0	95.7	4.3	0.0	97.2	2.8	0.0
750 every 48 h	1.4	53.9	44.7	7.2	86.2	6.6	42.2	57.2	0.6	79.6	20.0	0.4	89.0	11.0	0.0
500 every 24 h	2.3	50.3	47.4	5	81.3	13.7	22.2	76.0	1.8	59.2	40.1	0.7	78.7	21.0	0.3
750 every 24 h	1.1	17.1	81.8	1.7	51.3	47.0	5.8	82.8	11.4	23.2	73.1	3.7	50.3	47.6	2.1
500 every 12 h	0	3.6	96.4	0.2	12.3	87.5	0.1	39.0	60.9	1.5	70.1	28.4	2.8	82.8	14.4

[a]Probability of achieving underexposure (AUC_{24} < 50 mg · h/liter), normal target exposure (AUC_{24} between 50 and 160 mg · h/liter), and overexposure (AUC_{24} > 160 mg · h/liter) with different levofloxacin dosing regimens in older patients in relation to different classes of renal function. The classes of renal function (ml/min/1.73 m^2) are shown in the top row, and those of levofloxacin AUC_{24} (mg · h/liter) are shown in the bottom row in the header.

PK/PD of levofloxacin: limits in MICs

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CLINICAL THERAPEUTICS

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patie
Various Degrees of Renal Funct

TABLE 3 Probabilities of achieving underexposur
in older patients in relation to different classes o

Levofloxacin regimen (mg)	Probability[a] 0–19 <50	0–19 50–160	0–19 >160	20–39 <50	20–39 5
125 every 48 h	91.8	8.2	0.0	99.8	0
250 every 48 h	48.5	50.5	1.0	91.4	8
500 every 48 h	6.4	77.2	16.4	32.2	6
750 every 48 h	1.4	53.9	44.7	7.2	8
500 every 24 h	2.3	50.3	47.4	5	8
750 every 24 h	1.1	17.1	81.8	1.7	5
500 every 12 h	0	3.6	96.4	0.2	1

[a]Probability of achieving underexposure (AUC_{24} < 50 mg ·
mg · h/liter) with different levofloxacin dosing regimens in
m^2) are shown in the top row, and those of levofloxacin A

egimens

	>160
	0.0
	0.0
	0.0
	0.0
	0.3
	2.1
	14.4

$_{24}$ > 160
in/1.73

Levofloxacin regimen (mg)	Probability[a] 0–19 renal function class <50	50–160	>160
125 every 48 h	91.8	8.2	0.0
250 every 48 h	48.5	50.5	1.0
500 every 48 h	6.4	77.2	16.4
750 every 48 h	1.4	53.9	44.7
500 every 24 h	2.3	50.3	47.4
750 every 24 h	1.1	17.1	81.8
500 every 12 h	0	3.6	96.4

under-exposed

over-exposed

PK/PD of levofloxacin: limits in MICs

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CLINICAL THERAPEUTICS

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

TABLE 3 Probabilities of achieving underexposure, normal target exposure, and overexposure with different levofloxacin dosing regimens in older patients in relation to different classes of renal function

Levofloxacin regimen (mg)	Probability[a]														
	0–19			20–39			40–59			60–79			>80		
	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160
125 every 48 h	91.8	8.2	0.0	99.8	0.2	0.0	99.8	0.2	0.0	99.9	0.1	0.0	100.0	0.0	0.0
250 every 48 h	48.5	50.5	1.0	91.4	8.6	0.0	99.0	1.0	0.0	99.6	0.4	0.0	99.9	0.1	0.0
500 every 48 h	6.4	77.2	16.4	32.2	67.0	0.8	81.6	18.4	0.0	95.7	4.3	0.0	97.2	2.8	0.0
750 every 48 h	1.4	53.9	44.7	7.2	86.2	6.6	42.2	57.2	0.6	79.6	20.0	0.4	89.0	11.0	0.0
500 every 24 h	2.3	50.3	47.4	5	81.3	13.7	22.2	76.0	1.8	59.2	40.1	0.7	78.7	21.0	0.3
750 every 24 h	1.1	17.1	81.8	1.7	51.3	47.0	5.8	82.8	11.4	23.2	73.1	3.7	50.3	47.6	2.1
500 every 12 h	0	3.6	96.4	0.2	12.3	87.5	0.1	39.0	60.9	1.5	70.1	28.4	2.8	82.8	14.4

[a]Probability of achieving underexposure (AUC_{24} < 50 mg · h/liter), normal target exposure (AUC_{24} between 50 and 160 mg · h/liter), and overexposure (AUC_{24} > 160 mg · h/liter) with different levofloxacin dosing regimens in older patients in relation to different classes of renal function. The classes of renal function (ml/min/1.73 m^2) are shown in the top row, and those of levofloxacin AUC_{24} (mg · h/liter) are shown in the bottom row in the header.

PK/PD of levofloxacin: limits in MICs

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CLINICAL THERAPEUTICS

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

TABLE 3 Probabilities of achieving underexposure, nor … regimens in older patients in relation to different classes of rena…

Levofloxacin regimen (mg)	Probability[a] 0–19 <50	0–19 50–160	0–19 >160	20–39 <50	20–39 50–160	… >160
125 every 48 h	91.8	8.2	0.0	99.8	0.2	0.0
250 every 48 h	48.5	50.5	1.0	91.4	8.6	0.0
500 every 48 h	6.4	77.2	16.4	32.2	67.0	0.0
750 every 48 h	1.4	53.9	44.7	7.2	86.2	0.0
500 every 24 h	2.3	50.3	47.4	5	81.3	0.3
750 every 24 h	1.1	17.1	81.8	1.7	51.3	2.1
500 every 12 h	0	3.6	96.4	0.2	12.3	14.4

[a]Probability of achieving underexposure (AUC_{24} < 50 mg · h/liter) … AUC_{24} > 160 mg · h/liter) with different levofloxacin dosing regimens in older … /min/1.73 m²) are shown in the top row, and those of levofloxacin AUC_{24} (…

Levofloxacin regimen (mg)	Probability[a] >80 <50	>80 50–160	>80 >160
125 every 48 h	100.0	0.0	0.0
250 every 48 h	99.9	0.1	0.0
500 every 48 h	97.2	2.8	0.0
750 every 48 h	89.0	11.0	0.0
500 every 24 h	78.7	21.0	0.3
750 every 24 h	50.3	47.6	2.1
500 every 12 h	2.8	82.8	14.4

renal function class

under-exposed

over-exposed

PK/PD of levofloxacin: limits in MICs

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

Pier Giorgio Cojutti,[a,b] Virginia Ramos-Martin,[c] Isabella Schiavon,[d] Paolo Rossi,[d] Massimo Baraldo,[a,b] William Hope,[c] Federico Pea[a,b]

Institute of Clinical Pharmacology, Santa Maria della Misericordia University Hospital of Udine, Udine, Italy[a]; Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy[b]; Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom[c]; First Division of Internal Medicine Santa Maria della Misericordia University Hospital of Udine, Udine, Italy[d]

- **The opportunity to define permissible doses of levofloxacin in older patients was further strengthened by the findings of two recent reviews showing that levofloxacin is the fluoroquinolone associated with the highest risk of causing tendon damage**
- **This may further strengthen the valuable role that a real-time therapeutic drug monitoring (TDM)-guided approach to levofloxacin dosage adjustments may have in preventing drug-related toxicity in older patients.**

Vancomycin

- Vancomycin is a AUC_{24h}/MIC-driven antibiotic
- Vancomycin effective AUC_{24h}/MIC should be around 400 (more than for fluoroquinolones) because of its poor tissue penetration
- Yet, most (US) guidelines suggest to only measure trough (C_{min}) levels !

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

Liu et al. Clin Infect Dis. 2011; ;52:e18-55 PMID:: 21208910

Vancomycin

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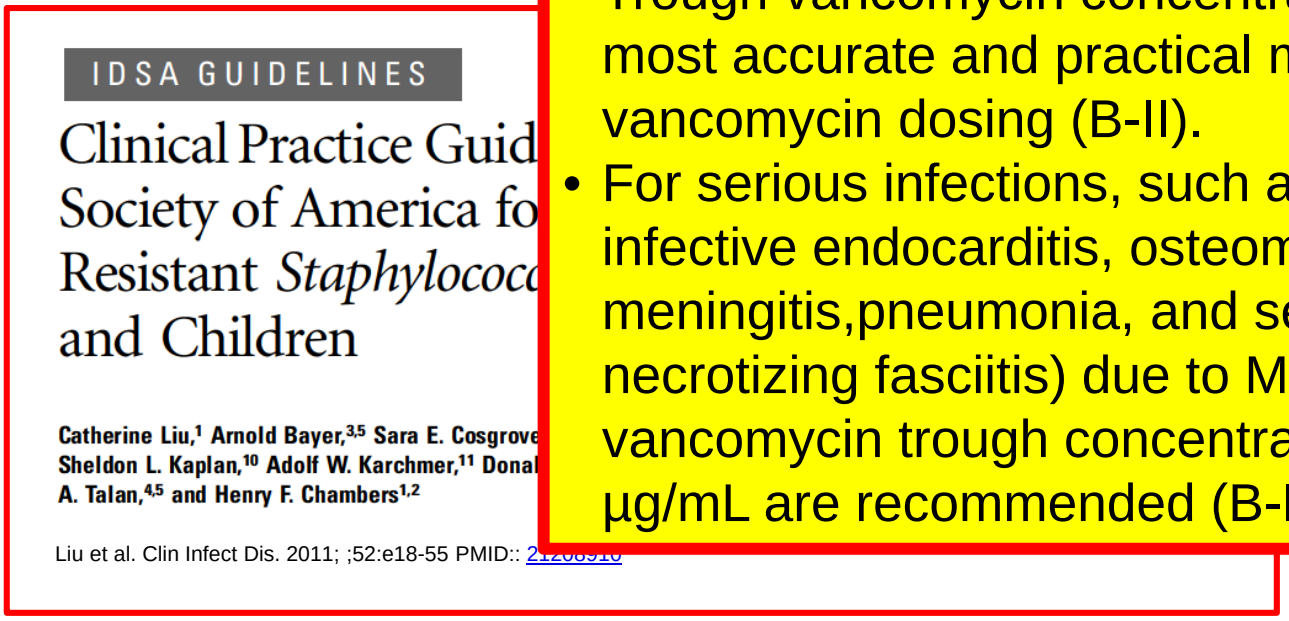
IDSA GUIDELINES

Clinical Practice Guid
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Resistant *Staphylococ*
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Liu et al. Clin Infect Dis. 2011; ;52:e18-55 PMID:: 21208910

- Trough vancomycin concentrations are the most accurate and practical method to guide vancomycin dosing (B-II).
- For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis,pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 µg/mL are recommended (B-II).

Vancomycin: things are moving …

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CLINICAL THERAPEUTICS

A Quasi-Experiment To Study the Impact of Vancomycin Area under the Concentration-Time Curve-Guided Dosing on Vancomycin-Associated Nephrotoxicity

Natalie A. Finch,[a]* Evan J. Zasowski,[b] Kyle P. Murray,[a] Ryan P. Mynatt,[a] Jing J. Zhao,[a] Raymond Yost,[a] Jason M. Pogue,[a] Michael J. Rybak[a,b,c]

Finch et al. Antimicrob Agents Chemother. 2017;61:e01293-17 - PMID: 28923869

Vancomycin: things are moving …

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

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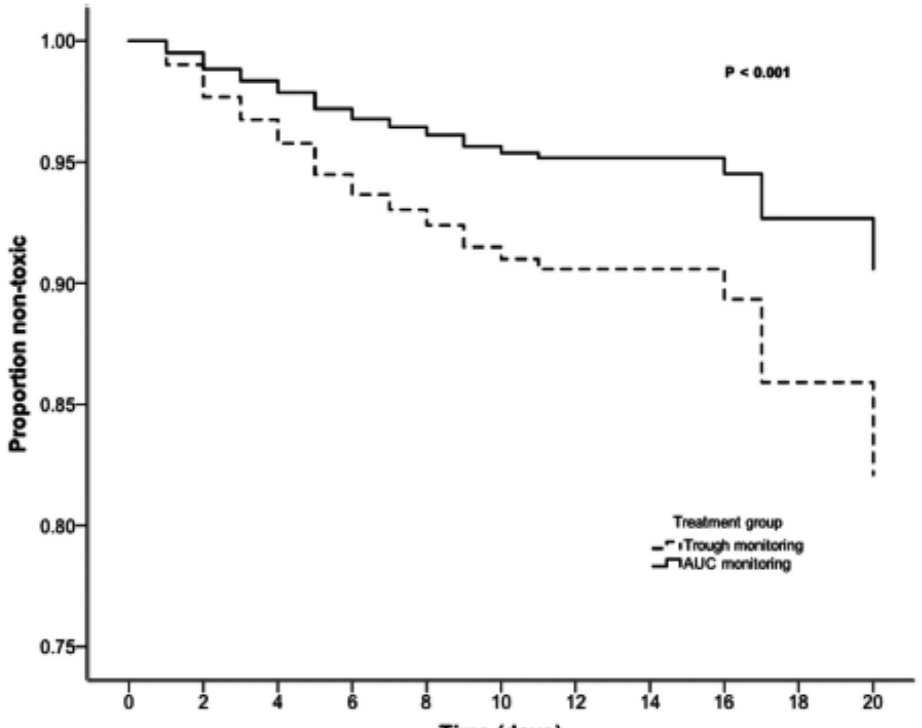
Finch et al. Antimicrob Agents Chemother. 2017;61:e01293-17 - P

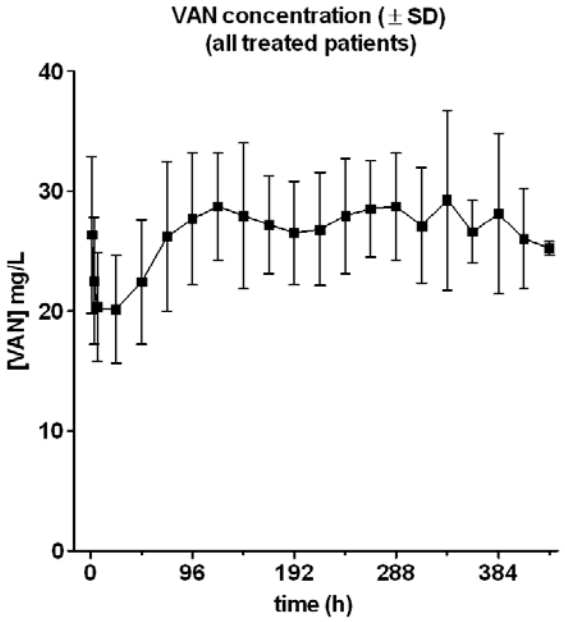


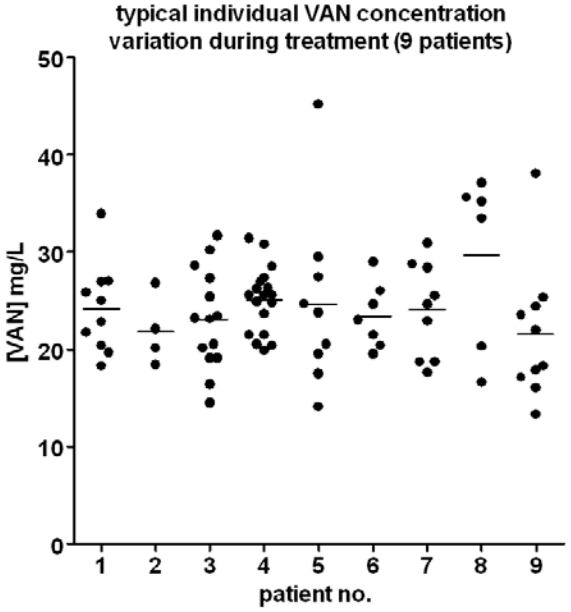
Variable	Hazard Ratio	95% CI	*P* value
AUC-TD	0.501	0.336 – 0.748	0.001
Concomitant furosemide	1.636	1.072 – 2.496	0.022
Elixhauser Comorbidity Index	1.123	1.044 – 1.208	0.002
APACHE II score	1.066	1.042 – 1.091	<0.001
Concomitant IV contrast	1.508	0.972 – 2.339	0.067
Concomitant tobramycin [a]	-	-	-
Duration of therapy, days [a]	-	-	-

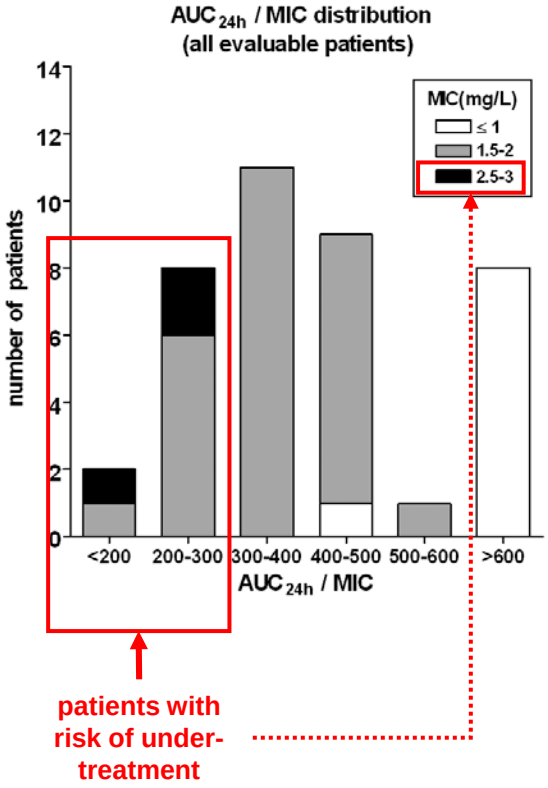
[a] Not retained in final model

FIG 1 Time to nephrotoxicity by Cox proportional hazards regression. AUC-TD, AUC- and trough concentration-guided dosing.

But there could be a better approach: continuous infusion





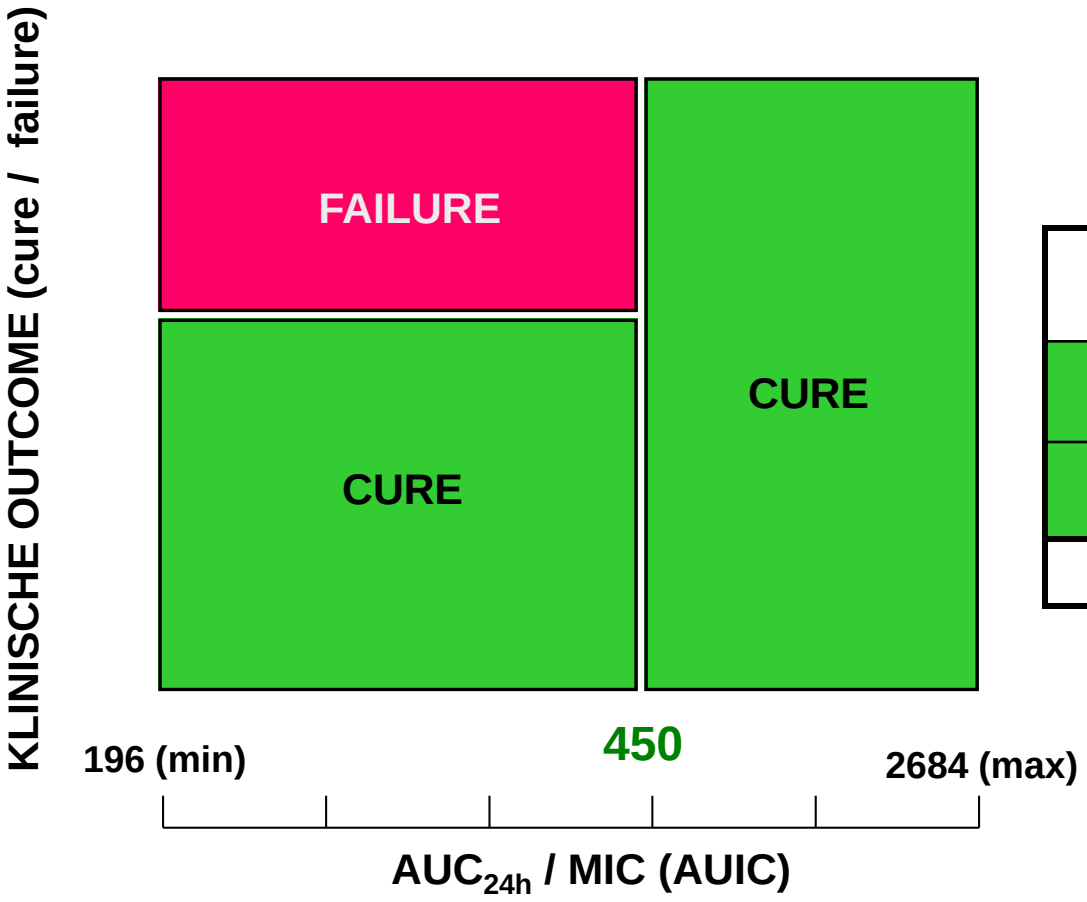


- 54 patients (40 documented infections)
- target concentration: 25-30 mg/L
- loading dose: 20 mg/kg;
- infusion rate: 2.5 g/day
  (adapted to renal function and corrected by therapeutic drug monitoring)

Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

Results are quite clear for efficacy….

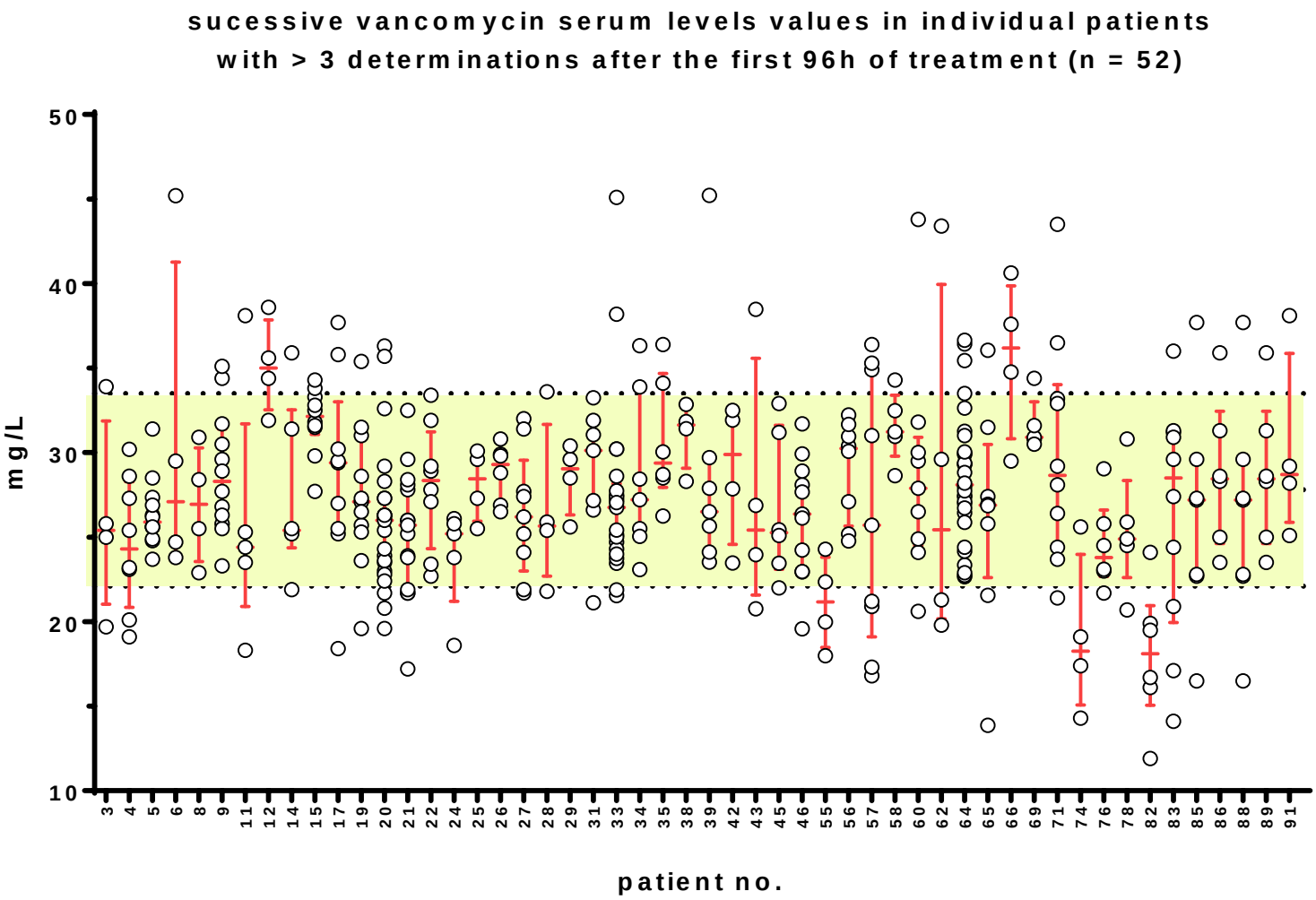
relation between AUC_{24h} / MIC (E-Test) and clinical efficacy (n=19)



AUIC < 450	
cure	failure
5/9	4/9
P < 0.05	

Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

But there still are huge variations in blood levels

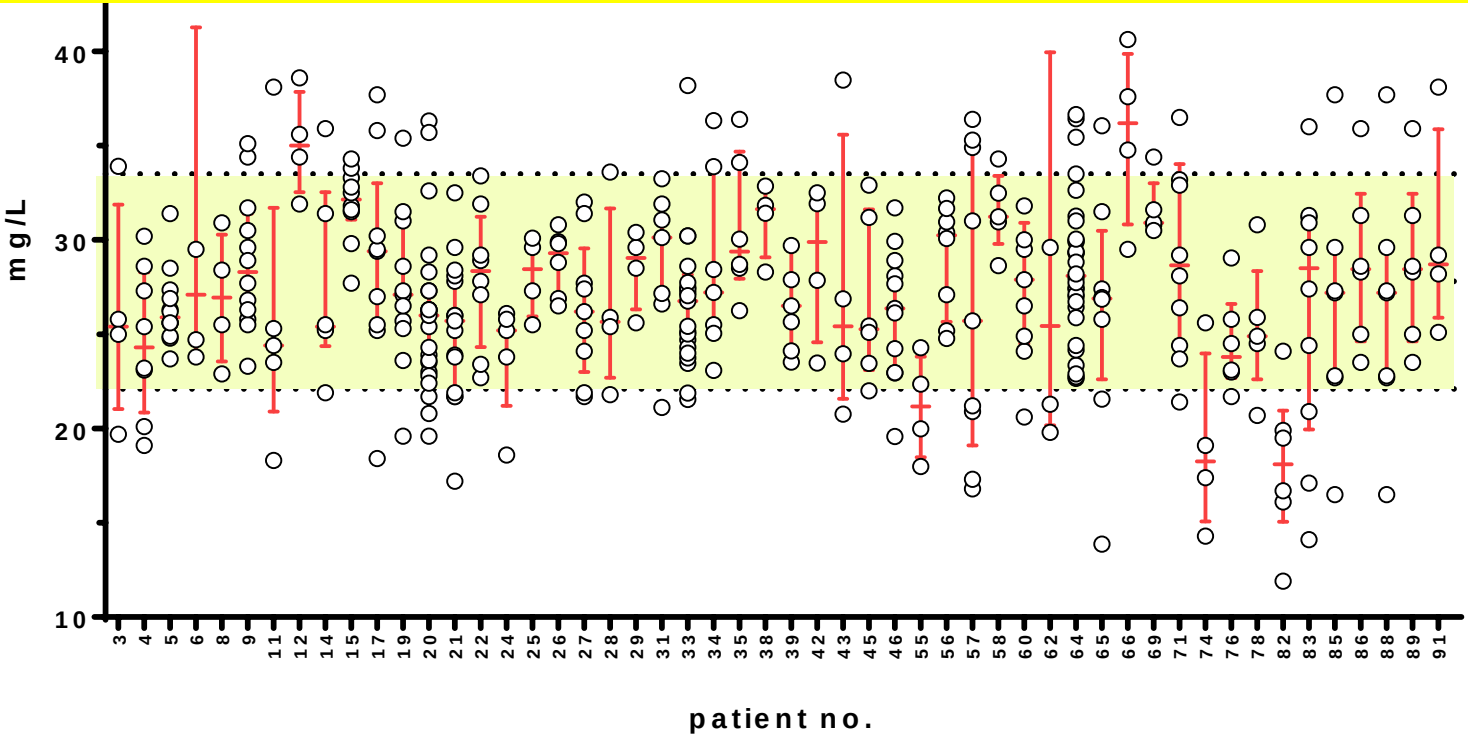


Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

But there still are huge variations in blood levels

sucessive vancomycin serum levels values in individual patients
with > 3 determinations after the first 96h of treatment (n = 52)

Monitoring remains essential



Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

β-lactams

- β-lactams have been long considered as drugs with a very large therapeutic ratio… So, why bother about monitoring them… ?
- but two things have now appeared as critical
  - the rise in MICs, creating a risk of under-treatment with the current dosages
  - the huge variability of PK parameters (V_d and clearance) between patients and over time (ICU)
    → under-treatment
    → toxicity

What is the correct target for a β-lactam ?

Expert Review of Anti-infective Therapy

ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: http://www.tandfonline.com/loi/ierz20

Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/ pharmacodynamics targets: are first conventional doses effective?

Isabelle K. Delattre, Fabio S. Taccone, Frédérique Jacobs, Maya Hites, Thierry Dugernier, Herbert Spapen, Pierre-François Laterre, Pierre E. Wallemacq, Françoise Van Bambeke & Paul M. Tulkens

Delattre et al.Expert Rev Anti Infect Ther. 2017;15:677-88 - PMID: 28571493

What is the correct target for a β-lactam ?

Expert Review of Anti-infective Therapy
ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: http://www.tandfonline.com/loi/ierz20

Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/ pharmacodynamics targets: are first conventional doses effective?

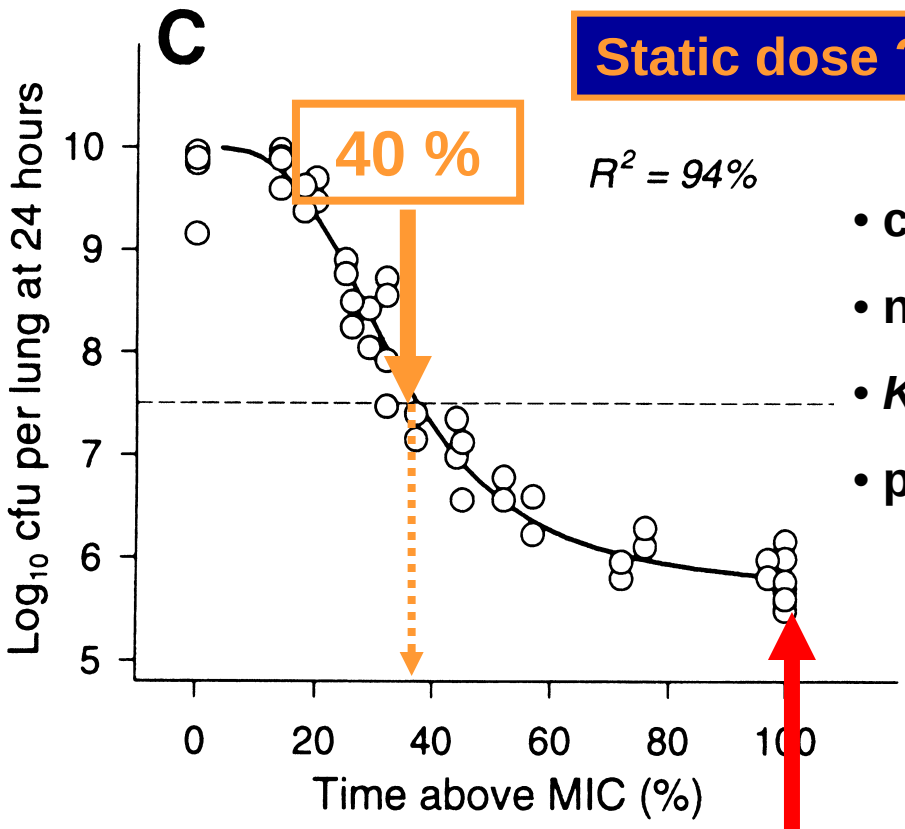
Isa
Du
Fra

Delat

Table 1. Percentage of the dosing interval over which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen (*f*T>MIC) for various β-lactams after bolus dosing in animal infection models [13,16].

	*f*T>MIC	
β-lactams	Bacteriostatic effect	Maximal bactericidal effect
Penicillins	30%	50%
Cephalosporins	35–40%[a]	60–70%[a]
Carbapenems	20%	40%

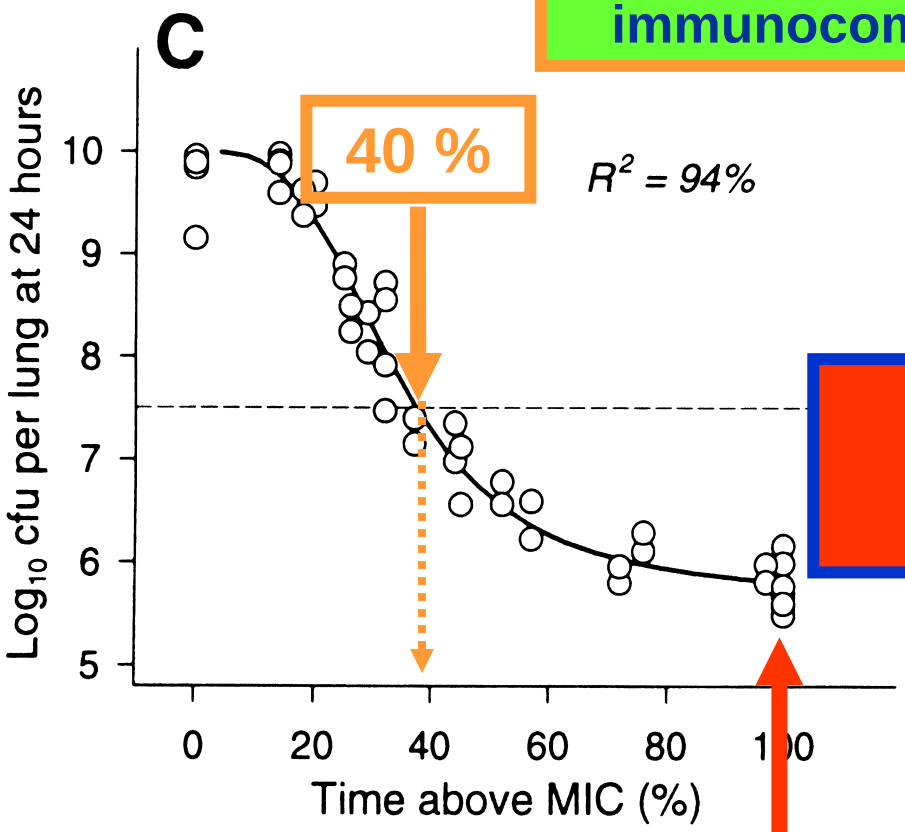
Illustration from animal data…



- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection

100 % - Maximal effect ?

What is the correct dose for your patient



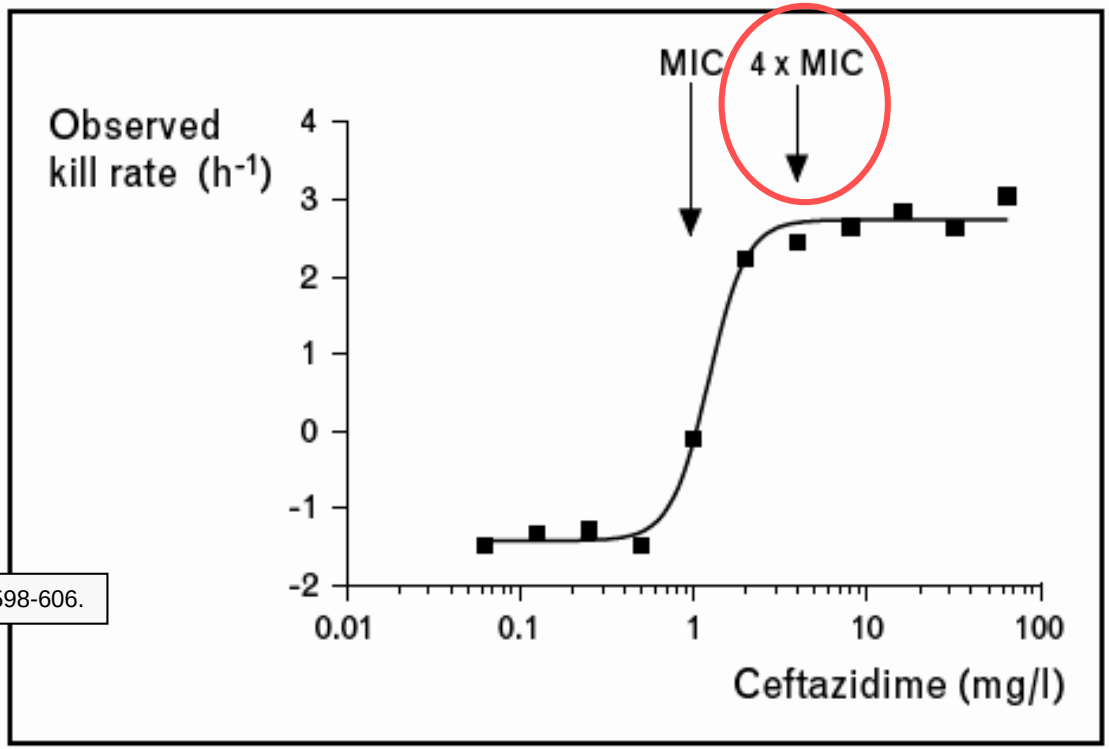
Mild infections in a non-immunocompromised patient

Severe infection in an immunocompromised patient

100 % ?

but maybe even more ?

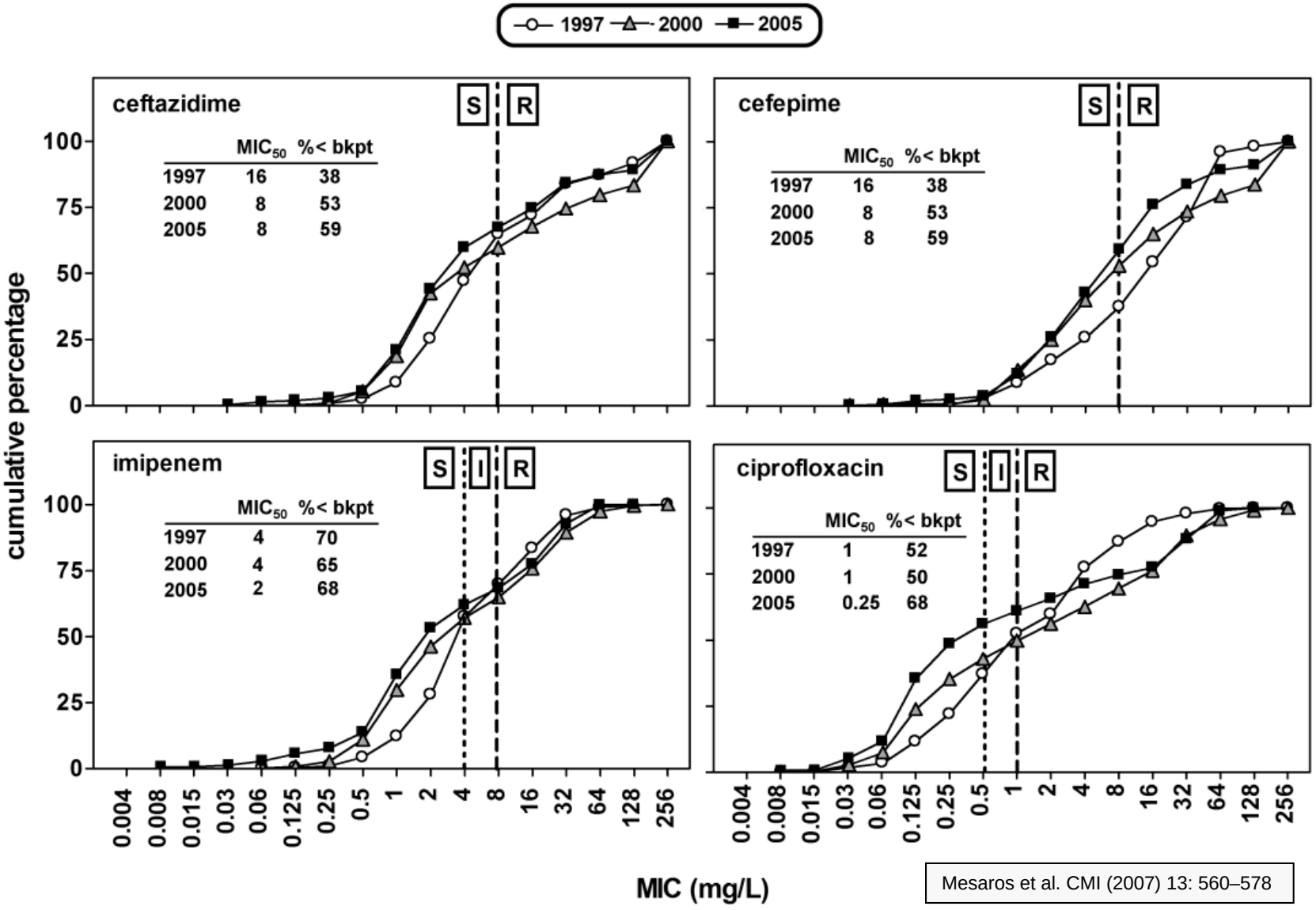
Figure 2 Relationship between concentration of ceftazidime and kill rate



The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

Mouton JW, Vinks AA. Curr Opin Crit Care. 2007 Oct;13(5):598-606.

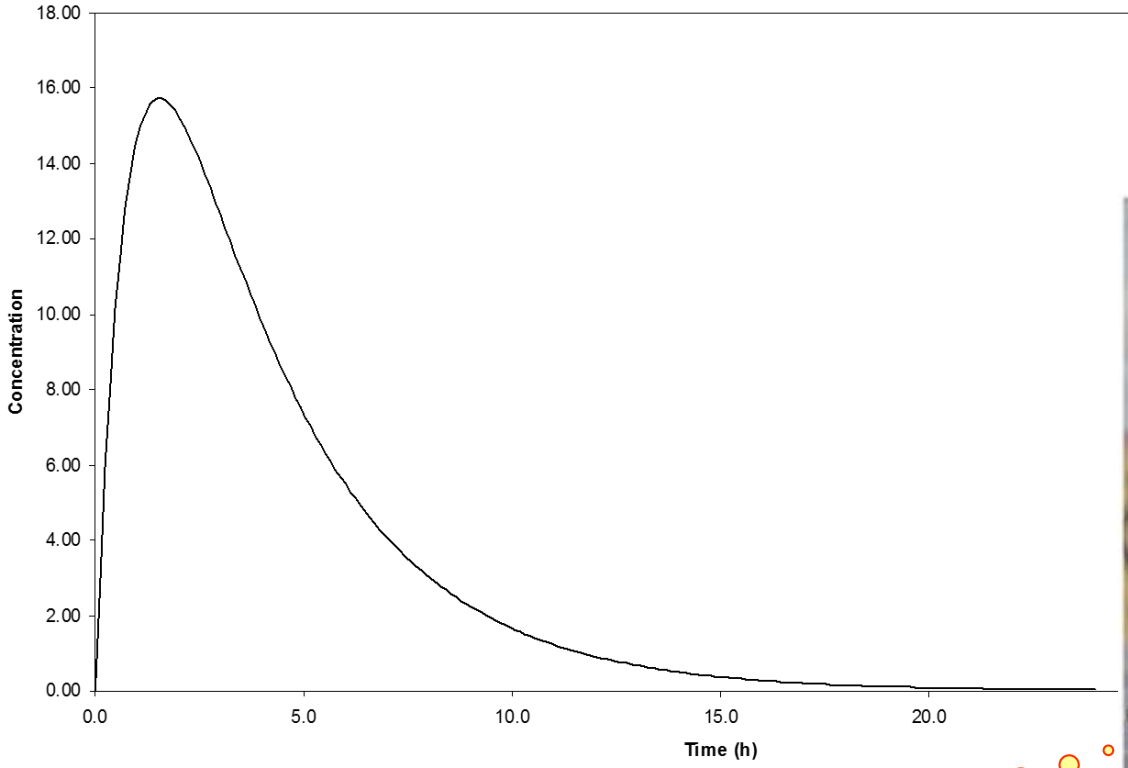
But which MICs ?

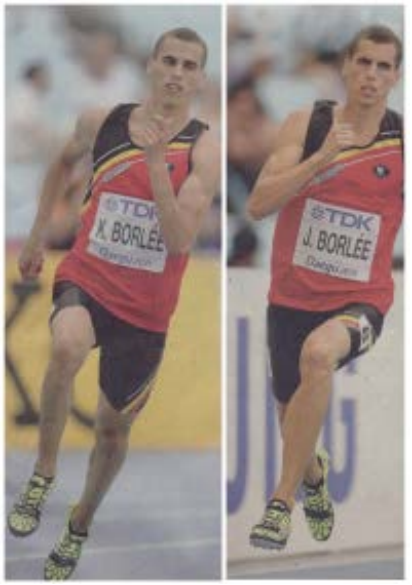


Mesaros et al. CMI (2007) 13: 560–578

But are all patients equal ?

Concentration profile of a β-lactam in volunteers
V_d = 20 L, k_a = 1.2 h^{-1}, k_e = 0.3 h^{-1}





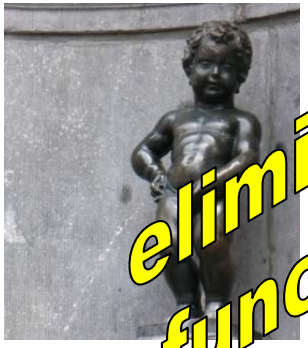
But are all patients really alike

Wat is a "standard" patient ?

physical c

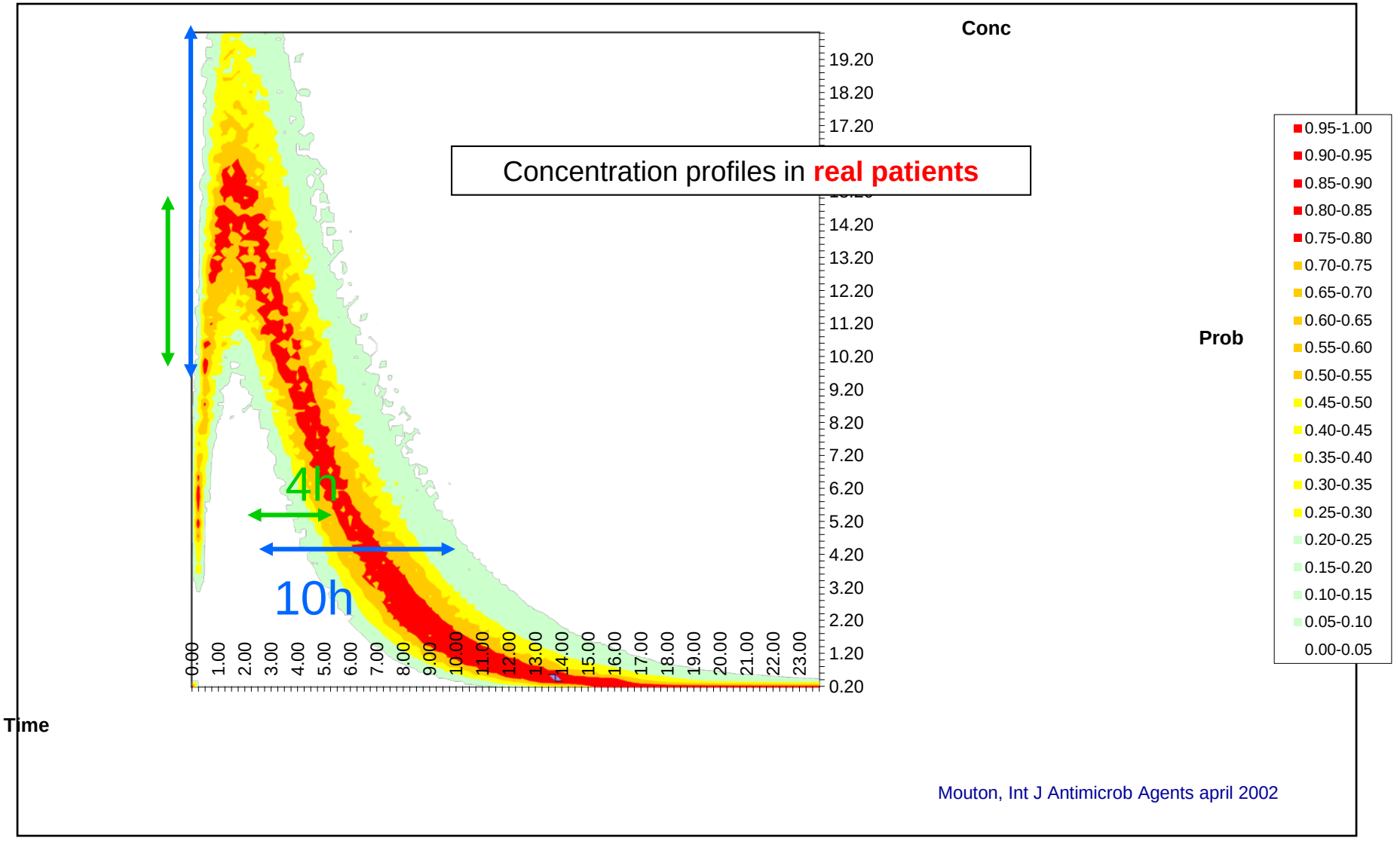
condition

disease



elimination
functions

Here is the daily reality …



Mouton, Int J Antimicrob Agents april 2002

Today, monitoring β-lactams becomes a reality

International Journal of Antimicrobial Agents 36 (2010) 332–339

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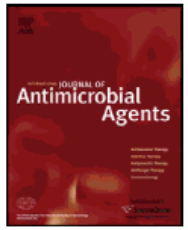

Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

Jason A. Roberts[a,b,c,*], Marta Ulldemolins[a,d], Michael S. Roberts[e,f], Brett McWhinney[g], Jacobus Ungerer[g], David L. Paterson[h,i], Jeffrey Lipman[a,c]

[a] Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia
[b] Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, Australia
[c] Department of Intensive Care, Royal Brisbane and Women's Hospital, Brisbane, Australia
[d] Critical Care Department, Vall d'Hebron University Hospital; Institut de Recerca Vall d'Hebron-Universitat Autònoma de Barcelona (UAB)-CIBER Enfermedades Respiratorias, Barcelona, Spain
[e] Therapeutics Research Unit, The University of Queensland, Brisbane, Australia
[f] School of Pharmacy, University of South Australia, Adelaide, Australia
[g] Department of Chemical Pathology, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia
[h] Department of Infectious Diseases, Royal Brisbane and Women's Hospital, Brisbane, Australia
[i] University of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, Australia

β-lactam monitoring: a typical and early example

International Journal of Antimicrobial Agents 35 (2010) 500–503

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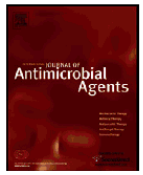
International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag



Short communication

Daily serum piperacillin monitoring is advisable in critically ill patients

Nicolas Blondiaux[a,*], Frédéric Wallet[a], Raphaël Favory[b], Thierry Onimus[b], Saad Nseir[b], René J. Courcol[a], Alain Durocher[b], Micheline Roussel-Delvallez[a]

[a] *Pôle de Microbiologie, Centre de Biologie-Pathologie, Centre Hospitalier Régional Universitaire (CHRU) de Lille, Boulevard du Pr. J. Leclercq, F-59037 Lille, France*
[b] *Service de Réanimation Médicale, Hôpital A. Calmette, Centre Hospitalier Régional Universitaire (CHRU) de Lille, Boulevard du Pr. J. Leclercq, F-59037 Lille, France*

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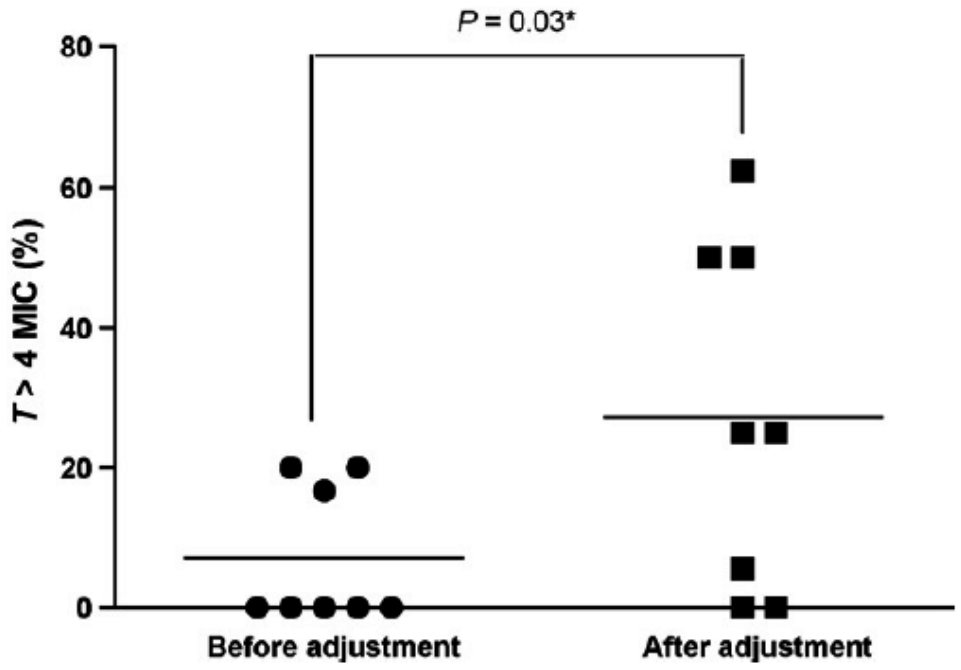

Fig. 1. Change in percentage of time during which the concentration remained above 4x the minimum inhibitory concentration (%$T > 4\times$ MIC) for patients who received dosage adjustment due to below-target serum concentrations. Horizontal bars represent the mean %$T > 4\times$ MIC.

Monitoring of β-lactams in special populations (1)

Wong *et al. BMC Infectious Diseases* 2014, **14**:288
http://www.biomedcentral.com/1471-2334/14/288

REVIEW Open Access

How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients?

Gloria Wong[1†], Fekade Bruck Sime[2,3†], Jeffrey Lipman[1,4] and Jason A Roberts[1,2,4*]

Monitoring of β-lactams in special populations (1)

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BMC Infectious Diseases

REVIEW Open Access

How do we use therapeutic drug monitoring to improve outcor critically ill pati

Gloria Wong[1†], Fekade Bruck Sime[1]

Table 1 Summary of common factors associated with altered pharmacokinetics of antibiotics in critically ill patients

Increased V_d	Decreased Cl	Increased Cl	Variable changes in V_d and/or Cl
Hypoalbuminaemia, leading to increased unbound drug	Renal hypoperfusion	Augmented renal clearance	Extracorporeal interventions (eg RRT, ECMO)
Capillary leakage	Acute kidney injury		
Fluid resuscitation	Renal/hepatic dysfunction		
Third space loss			

Monitoring of β-lactams in special populations (1)

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BMC Infectious Diseases

REVIEW Open Access

How do we use therapeutic drug monitoring to improve outcor
critical

Gloria Wong[1†]

Table 1 Summary of common factors associated with altered pharmacokinetics of antibiotics in critically ill

- In the context of critical illness, there is strong data demonstrating that standard dosing regimens for many antibiotics frequently fail to provide optimal PK/PD exposure in critically ill patients.
- Given that pharmacokinetic exposures can be very difficult-to-predict in some patients, TDM is valuable to identify these patients and guide dose optimization.
- TDM can ensure attainment of PK/PD surrogate indicators of antibiotic efficacy, and therefore potentially improve patient outcome.

Monitoring of β-lactams in special populations (2)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

β-Lactam Dosage Regimens in Septic Patients with Augmented Renal Clearance

Alexandra Jacobs,[a,b] Fabio Silvio Taccone,[a] Jason A. Roberts,[c,d,e,f] Frédérique Jacobs,[b] Frederic Cotton,[g] Fleur Wolff,[g] Jacques Creteur,[a] Jean-Louis Vincent,[a] Maya Hites[b]

Jacobs et al. Antimicrob Agents Chemother. 2018;62:pii: e02534-17 - PMID: 29987138

Monitoring of β-lactams in special populations (2)

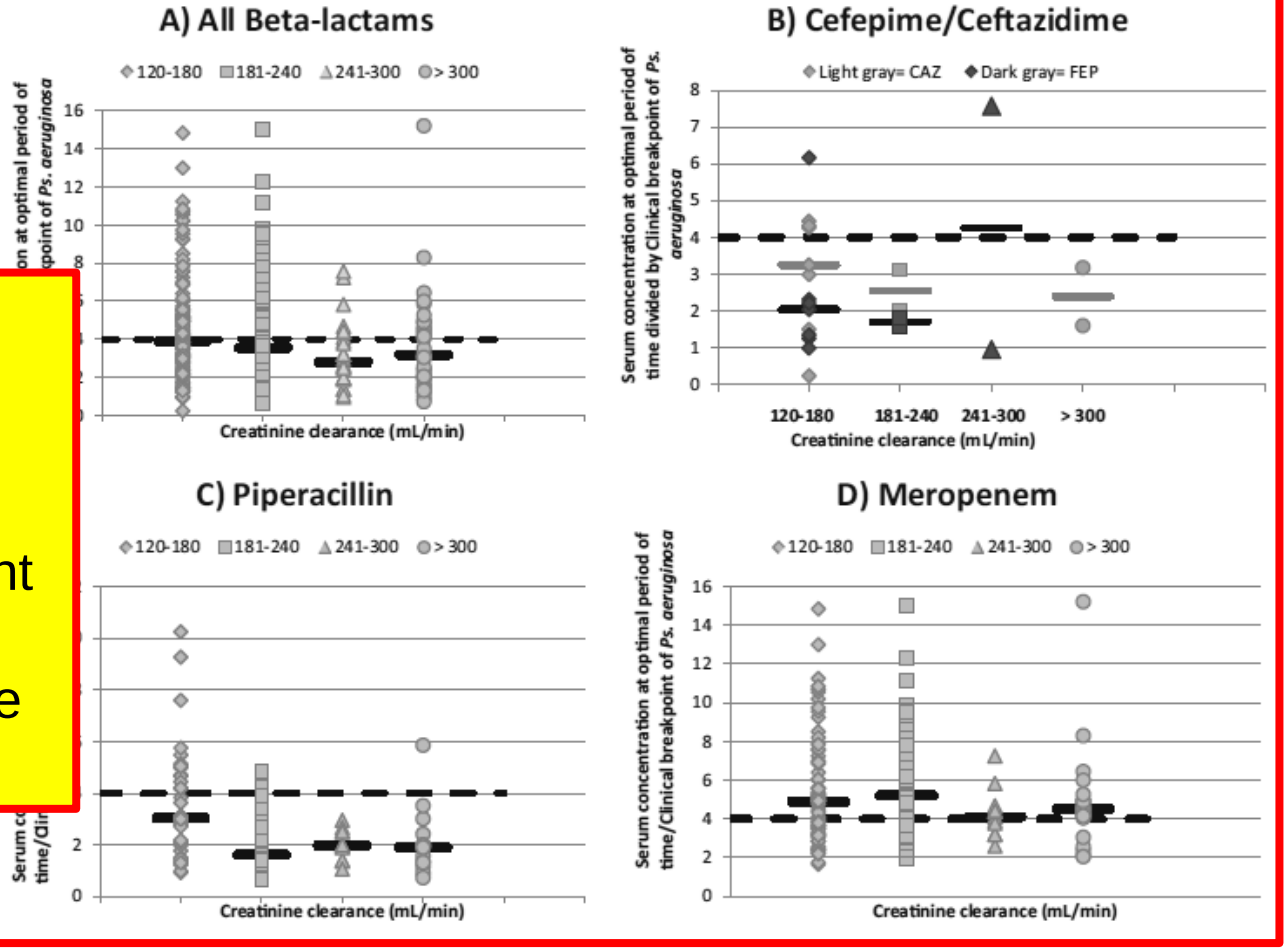
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

β-Lactam Dosage Reg
Augmented Renal Cle

Alexandra Jacobs,[a,b] Fabio Silvio Taccone,[a]
Jacques Creteur,[a] Jean-Louis Vincent,[a] May

Currently, we recommend, when possible, TDM-guided therapy to optimize PK/PD target attainment in critically ill patients and particularly in those at risk of ARC.



Monitoring of β-lactams in special populations (3)

Repeated Piperacillin-Tazobactam Plasma Concentration Measurements in Severely Obese Versus Nonobese Critically Ill Septic Patients and the Risk of Under– and Overdosing*

Boris Jung, MD, PhD[1,2]; Martin Mahul, MD, MSc[1,2]; Dominique Breilh, PharmD, PhD[3]; Rachel Legeron, PharmD[3]; Jeremy Signe, MD[1,2]; Helene Jean-Pierre, MD[4]; Anne-Catrin Uhlemann, MD, PhD[5]; Nicolas Molinari, PhD[6]; Samir Jaber, MD, PhD[1,2]

Jung et al. Crit Care Med. 2017;45:e470-e478 - PMID: 28240688

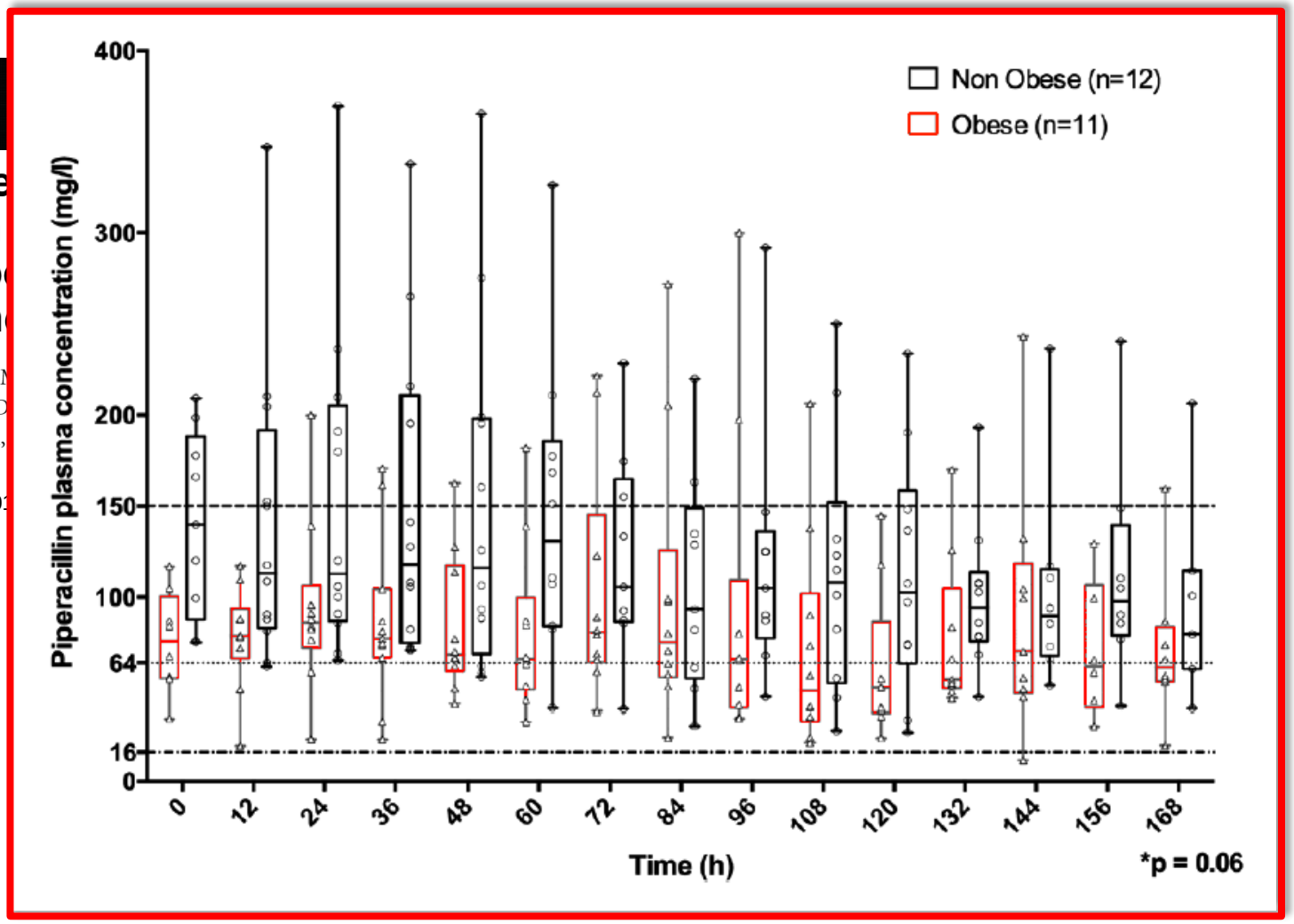
Monitoring of β-lactams in special populations (3)

Online Clinical

**Repeated Pipe
Concentration
Versus Nonob
the Risk of Un**

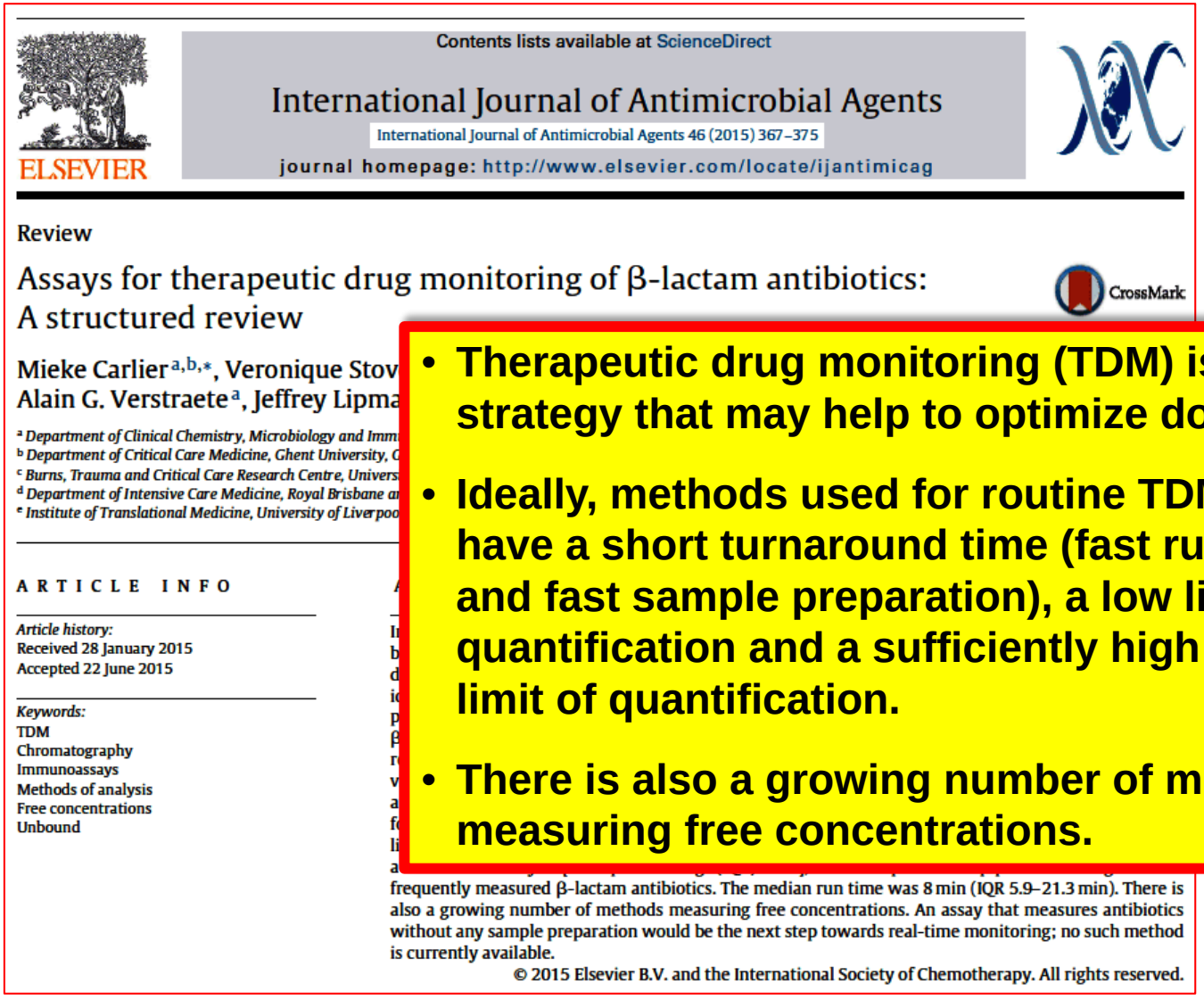
Boris Jung, MD, PhD[1,2]; M
Rachel Legeron, PharmD
Anne-Catrin Uhlemann,

Jung et al. Crit Care Med. 201



Piperacillin blood concentrations (median, quartiles, and individual values) over the 7-d study period for non-obese (*n* = 12) and severely obese (*n* = 11) patients. The *Pseudomonas aeruginosa* minimal inhibitory concentration breakpoint (16 mg/L), 4-fold the breakpoint (64 mg/L), and the potential piperacillin toxic concentration threshold (150 mg/L) are represented as *dashed lines*.. *Between obese and non-obese patients over time, adjusted to SOFA score.

Today, TDM of β-lactams may become a reality



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International Journal of Antimicrobial Agents 46 (2015) 367–375

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Assays for therapeutic drug monitoring of β-lactam antibiotics: A structured review

Mieke Carlier[a,b,*], Veronique Stov
Alain G. Verstraete[a], Jeffrey Lipma

[a] Department of Clinical Chemistry, Microbiology and Imm
[b] Department of Critical Care Medicine, Ghent University, C
[c] Burns, Trauma and Critical Care Research Centre, Univers
[d] Department of Intensive Care Medicine, Royal Brisbane a
[e] Institute of Translational Medicine, University of Liverpoo

ARTICLE INFO

Article history:
Received 28 January 2015
Accepted 22 June 2015

Keywords:
TDM
Chromatography
Immunoassays
Methods of analysis
Free concentrations
Unbound

- **Therapeutic drug monitoring (TDM) is a strategy that may help to optimize dosing.**
- **Ideally, methods used for routine TDM should have a short turnaround time (fast run-time and fast sample preparation), a low limit of quantification and a sufficiently high upper limit of quantification.**
- **There is also a growing number of methods measuring free concentrations.**

frequently measured β-lactam antibiotics. The median run time was 8 min (IQR 5.9–21.3 min). There is also a growing number of methods measuring free concentrations. An assay that measures antibiotics without any sample preparation would be the next step towards real-time monitoring; no such method is currently available.

What about oxazolidinones (linezolid) ?

Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

Drug monitoring and individual dose optimization of antimicrobial drugs: oxazolidinones

Dario Cattaneo, Jan-Willem Alffenaar & Michael Neely

Cattaneo et al. Expert Opin Drug Metab Toxicol 2016;12:533-44 - PMID: 26982718

Linezolid: huge variations in C_{min} …

Expert Opinion on Drug Metaboli
ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage:

Drug monitoring and individual
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Cattaneo et al. Expert Opin Drug Metab Toxicol 2016;12:533-44 - PMID: 269

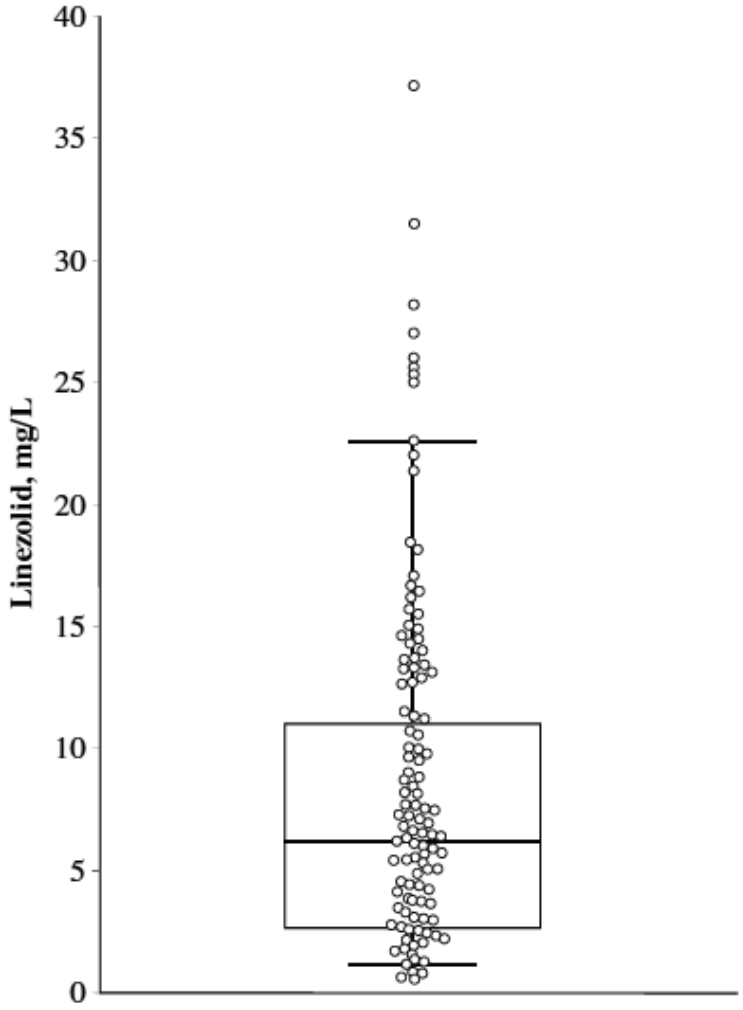

Figure 1. Distribution of linezolid (LZD) plasma trough concentrations measured at the first TDM assessment in 150 patients given the drug at 600 mg bid

Linezolid: many factors affecting its pharmacokinetics…

Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

Drug monitoring and individual dose optimization of antimicrobial drugs: oxazolidinones

Table 2. Factors affecting pharmacokinetics, efficacy, and/or safety of LZD.

	Effect on LZD pharmacokinetics	Effect on clinical outcome
Renal insufficiency	Kidney impairment is associated with reduced LZD clearance [15,20,22,23]	Patients with renal insufficiency are more likely to experience LZD-related adverse events (mainly hematological, neurological, and metabolic complications) [15,20–23,44]
Renal replacement therapy	LZD is partially cleared by dialysis. However, dose reductions are still required to avoid excessive LZD accumulation [28,29]	Patients undergoing peritoneal dialysis [27] or hemodialysis are more likely to experience LZD-related hematologic and metabolic complications [45]
Co-medications	Coadministration of clarithromycin, omeprazole, amiodarone, or amlodipine increases LZD concentrations, whereas rifampicin or levothyroxine decreases LZD exposure.[12]	Patients concomitantly treated with LZD and rifampicin experience less hematological toxicity compared with those given only LZD [41]
Body weight	A significant inverse correlation was reported between body weight and LZD AUC [21,31]	Low body weight (<55 kg) was associated with the development of thrombocytopenia [46]
Obesity	Mild reduction in the plasma concentrations of LZD in obese patients treated with the oral 600 mg bid dose [32,33]	Anecdotal case reports of obese patients failing to reach the PK/PD targets even if treated with higher than conventional doses [36]
Duration of LZD treatment		Duration of LZD treatment of more than 15 days was significantly associated with the development of thrombocytopenia [23,47]
Age	A significant direct association was reported in adults between age and LZD AUC [31]	Patients experiencing hematological toxicity were older compared to patients who tolerated LZD treatment [15]

Toxicodynamics: what drives linezolid toxicity…

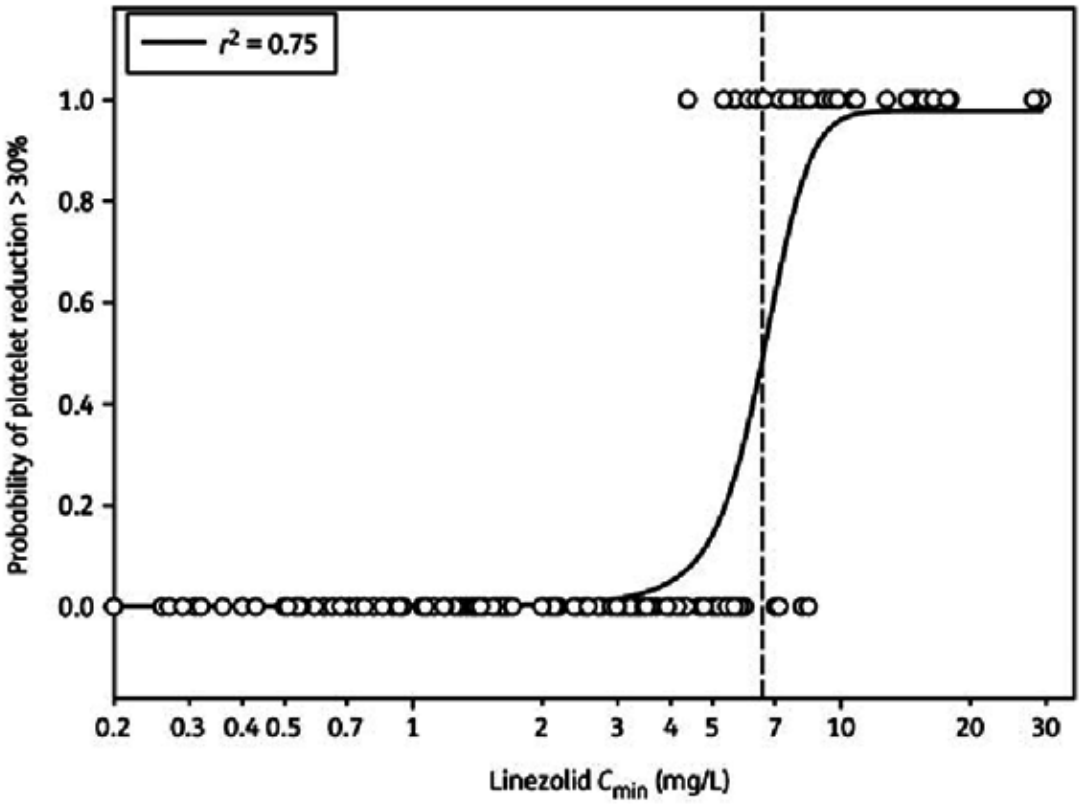

Fig. 16.13 Linezolid C_{min} and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the C_{min} observed over time in each patient with (*top*) or without (*bottom*) thrombocytopenia. The *continuous line* represents the result of the logistic regression model. The *vertical broken line* identifies the C_{min} value predicting 50 % probability of thrombocytopenia

Theuretzbacher U, PK/PD of Oxazolidinones In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinvk, H. Derendorf & JW Mouton eds, Springer, 2014, p 401-443

Where are we now ?

1. know your antibiotic and its PD parameter
   - ➢ time-, AUC_{24h}-, of C_{max}- driven
2. look for the pertinent PK data and the recommended dosages …
3. compute the pertinent "PK/PD parameter – MIC" ratio / target that will ensure efficacy
   - – β-lactams: *f* T > MIC = 30 to 100 % of the dosing interval
   - – aminoglycosides: C_{max} = 8 x MIC
   - – fluoroquinolones: AUC_{24h}/MIC = 30 (min.) -125 (preferred)
   - – vancomycin: AUC_{24h}/MIC = 400
   - – macrolides: AUC_{24h}/MIC = 30
   - – tetracyclines (incld. tigecycline): AUC_{24h}/MIC = 7-10
   - – linezolid: avoid C_{min} > 7 mg/L (for toxicity)

Check the drug label and pertinent publications … or rely on a clinical pharmacist !

4. Check your local epidemiology for MICs … → Ask your microbiologist

Beyond the patient, answers for the Society …

When choosing an antibiotic, do we know

3. for the society
   - **how to prevent emergence of resistance ?**

This is probably a **most difficult challenge** because

- resistance genes are already present in nature (**resistome**)
- bacteria quickly adapt to new environments (**mutation/selection**)

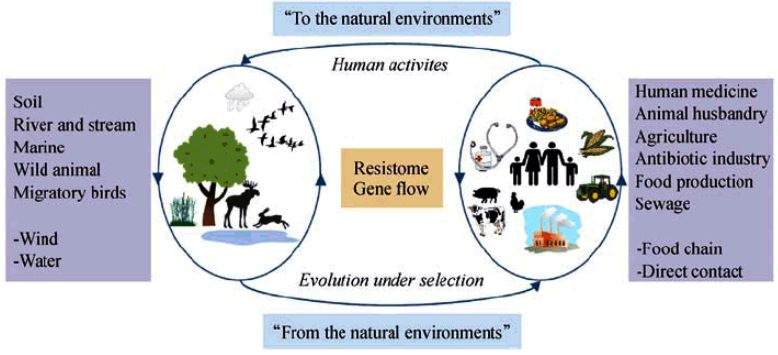

Fig. 1 The antibiotic resistome gene flow in environments, human, and animals. We propose that the antibiotic resistome gene flow is "form the natural environments" and "to the natural environments." The natural environments are the reservoirs for antibiotic resistome. The original ARGs in environmental bacteria can be captured by human or animal pathogens and gradually evolved under the antibiotic selection pressure and become qualified. These ARGs or ARG-bearing bacteria are then disseminated back to the natural environments due to the human activities on producing and using antibiotics. In most cases, the ARGs are more easily transferred within respective ecological niches (the natural environments, and the human- and animal-associated environments). This resistance gene flow scenario is not very applicable to antibiotic resistance caused by chromosomal mutation.

Hu et al. Front Med 2017;11:161-168 - PMID: 28500429

Answers for the Society …

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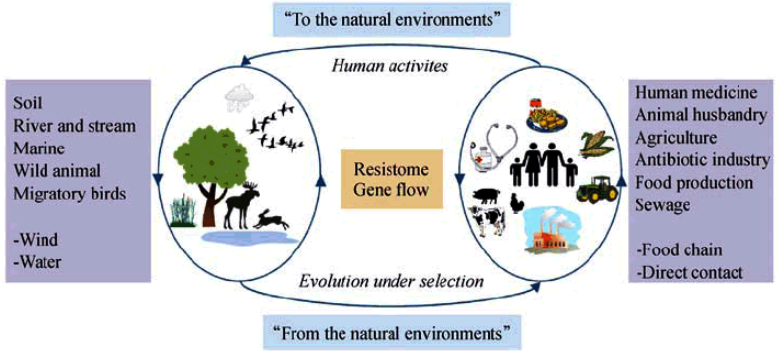
- bacteria quickly adapt to new environments (**muta**

If everyone were cast in the same mould, there would be no such thing as beauty – Darwin



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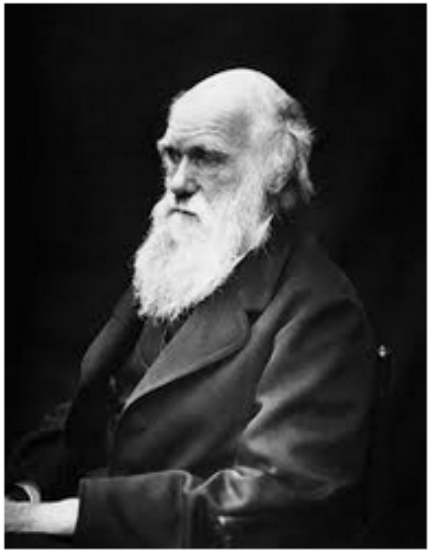
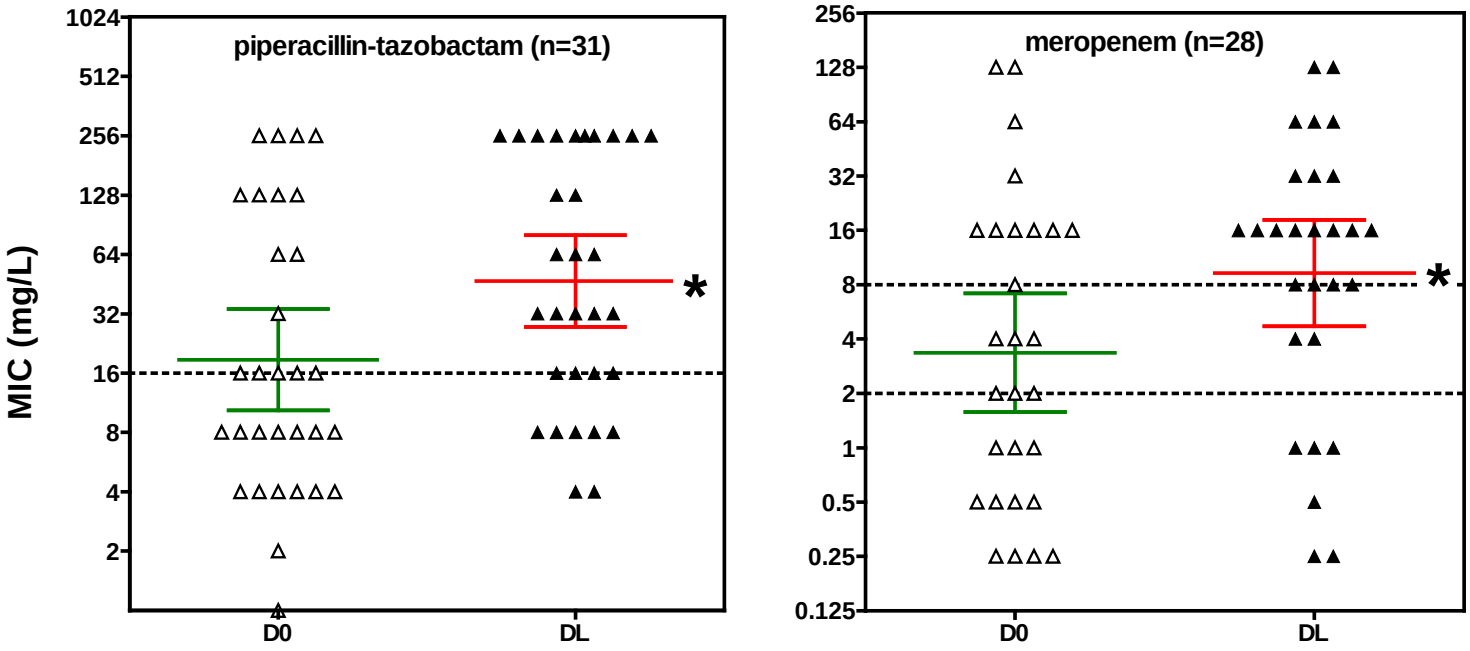


Hu et al. Front Med 2017;11:161-168 - PMID: 28500429

MIC may increase during treatment !



Change in MIC of antibiotics used in empiric antipseudomonal therapy (nosocomial pneumonia; intensive care units) towards the isolate identified before onset of therapy (D0) *vs*. the last isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using both raw and $\log_2$ transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

Riou et al. Int J Antimicrob Agents. 2010 Dec;36(6):513-22.

Optimization may prevent emergence of resistance

J Antimicrob Chemother 2017; **72**: 1421–1428
doi:10.1093/jac/dkx001 Advance Access publication 31 January 2017

Journal of Antimicrobial Chemotherapy

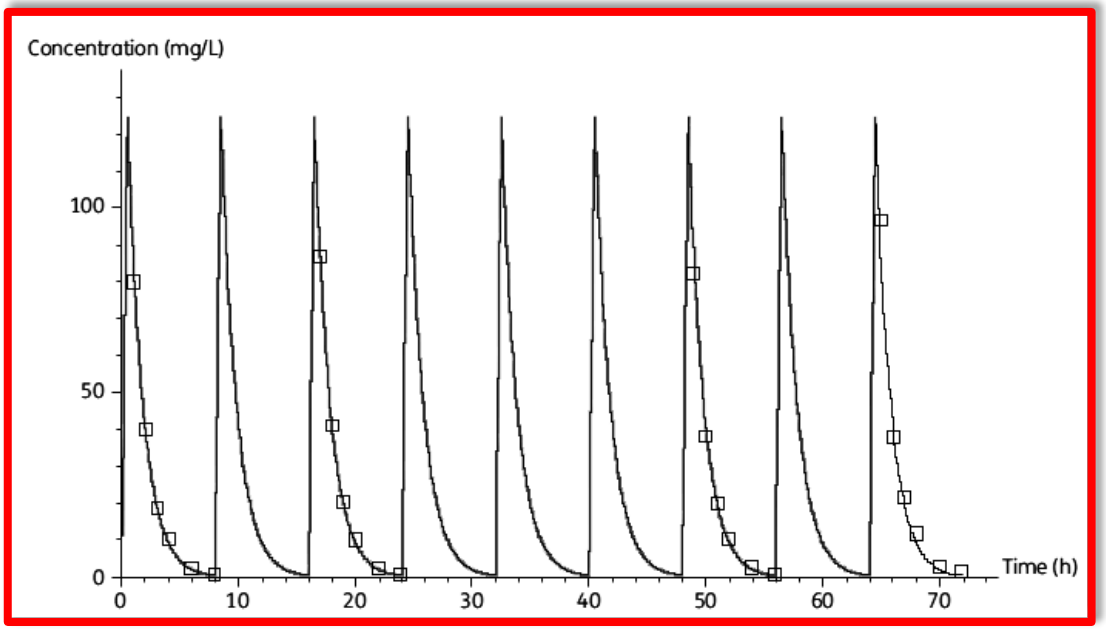
Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam[1]*, Kai-Tai Chang[1], Jian Zhou[1], Kimberly R. Ledesma[1], Kady Phe[1], Song Gao[1], Françoise Van Bambeke[2], Ana María Sánchez-Díaz[3], Laura Zamorano[4], Antonio Oliver[4] and Rafael Cantón[3]

[1]University of Houston, Houston, TX, USA; [2]Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; [3]Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; [4]University Hospital Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain

Tam *et al.* J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

Simulation of serum concentration levels (hollow fibers model)



Optimization may prevent emergence of resistance

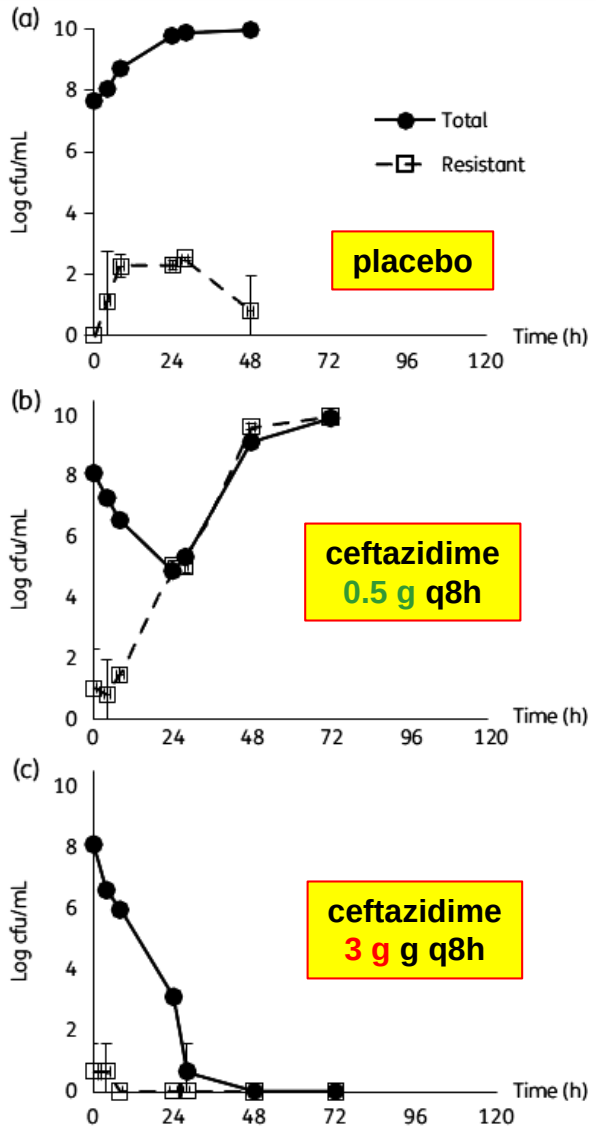


Figure 2. Typical bacterial profiles for WT *P. aeruginosa*. Placebo control (a). Ceftazidime at 500 mg every 8 h (C_{min}/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h (C_{min}/MIC = 7.7) (c). Data are shown as mean ± SD.

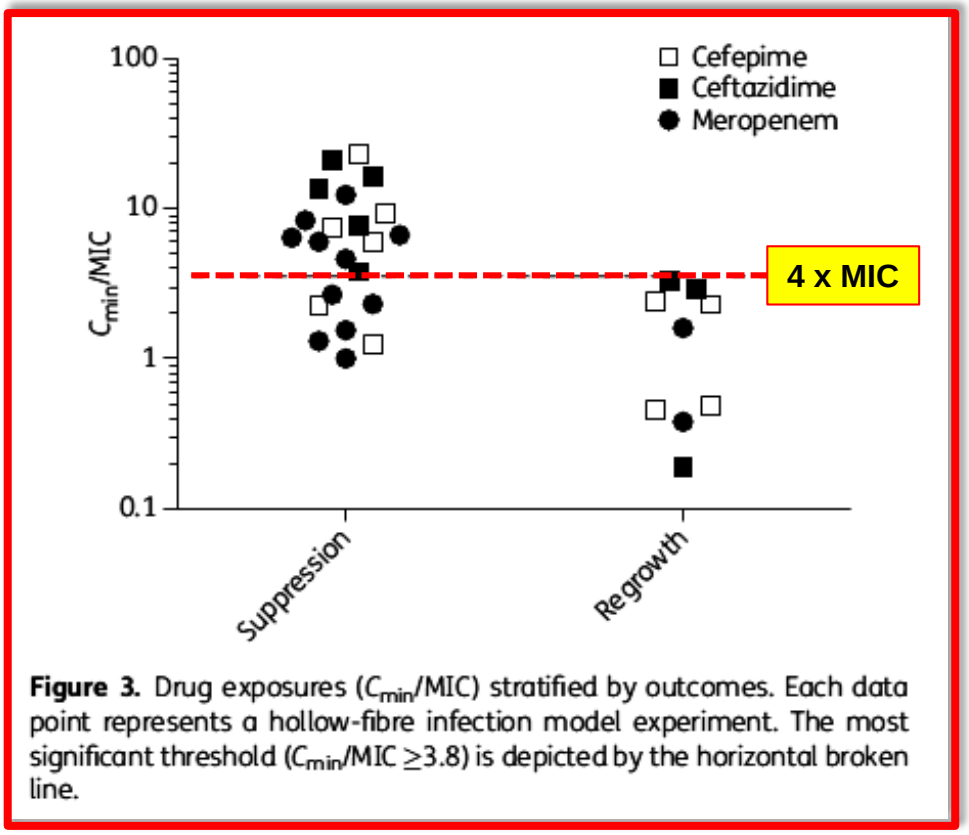
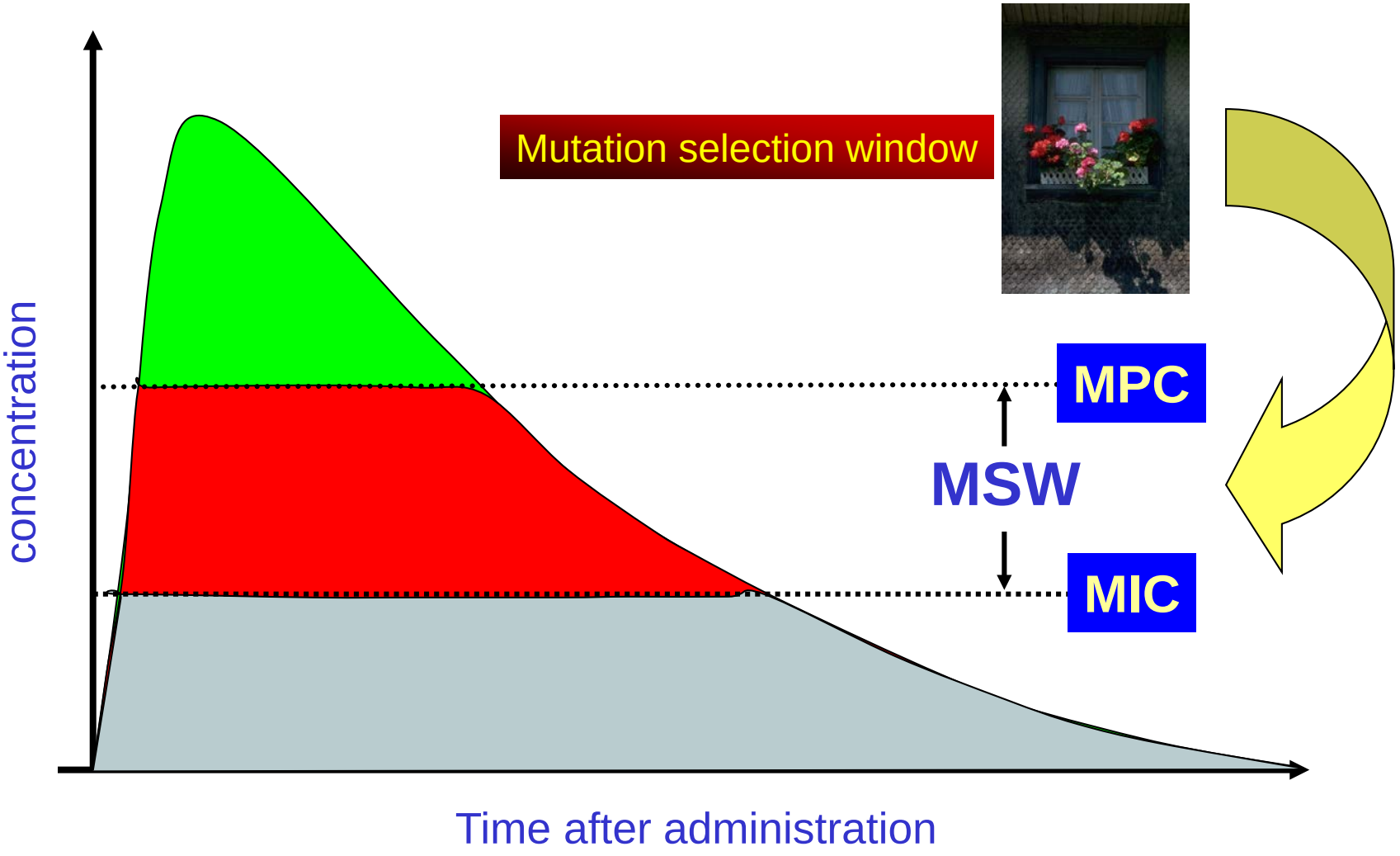


Figure 3. Drug exposures (C_{min}/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold (C_{min}/MIC ≥3.8) is depicted by the horizontal broken line.

To prevent emergence of resistance, C_{min} of β-lactams must stay > 4 x MIC (mean), which commands higher dosages…

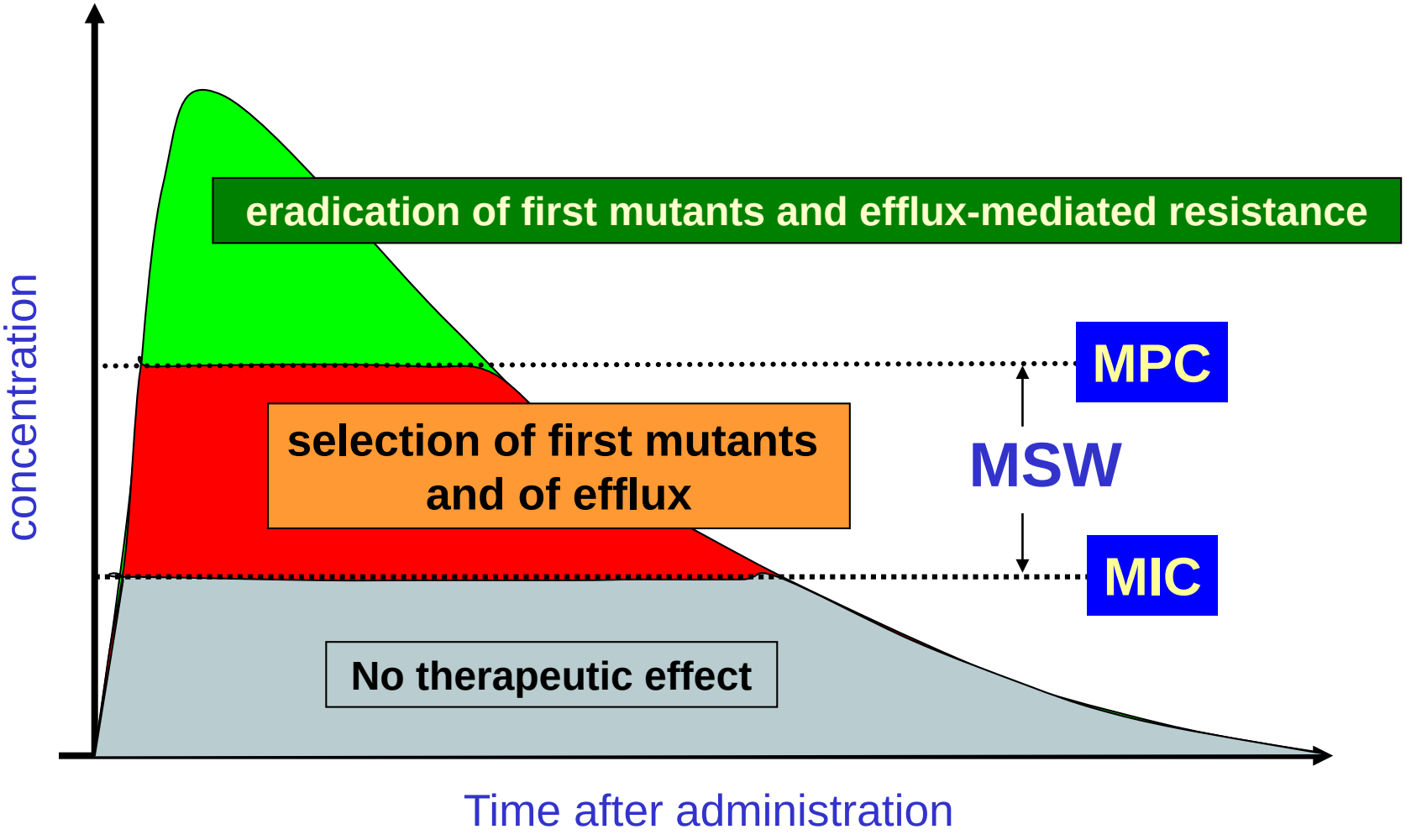
Tam et al. J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

Avoiding the window for selection of resistance



concept taken from Drlica & Zhao, *Rev. Med. Microbiol*. 2004, 15:73-80
and *Journal of Antimicrobial Chemotherapy* 2008, 62:434–436

Avoiding the window for selection of resistance



concept taken from Drlica & Zhao, *Rev. Med. Microbiol*. 2004, 15:73-80
and *Journal of Antimicrobial Chemotherapy* 2008, 62:434–436

AUC_{24h} / MIC = 125 en C_{max} / MIC > 10 as parameters for efficacy and prevention of resistance of fluoroquinolones: which MICs can you cover with standard treatments ?

Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\ h}$ (mg × h/L) total/free	Proposed PK/PD upper limit of sensitivity (µg/ml) for: Efficacy[b]	Proposed PK/PD upper limit of sensitivity (µg/ml) for: Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

TDM of antibiotics …