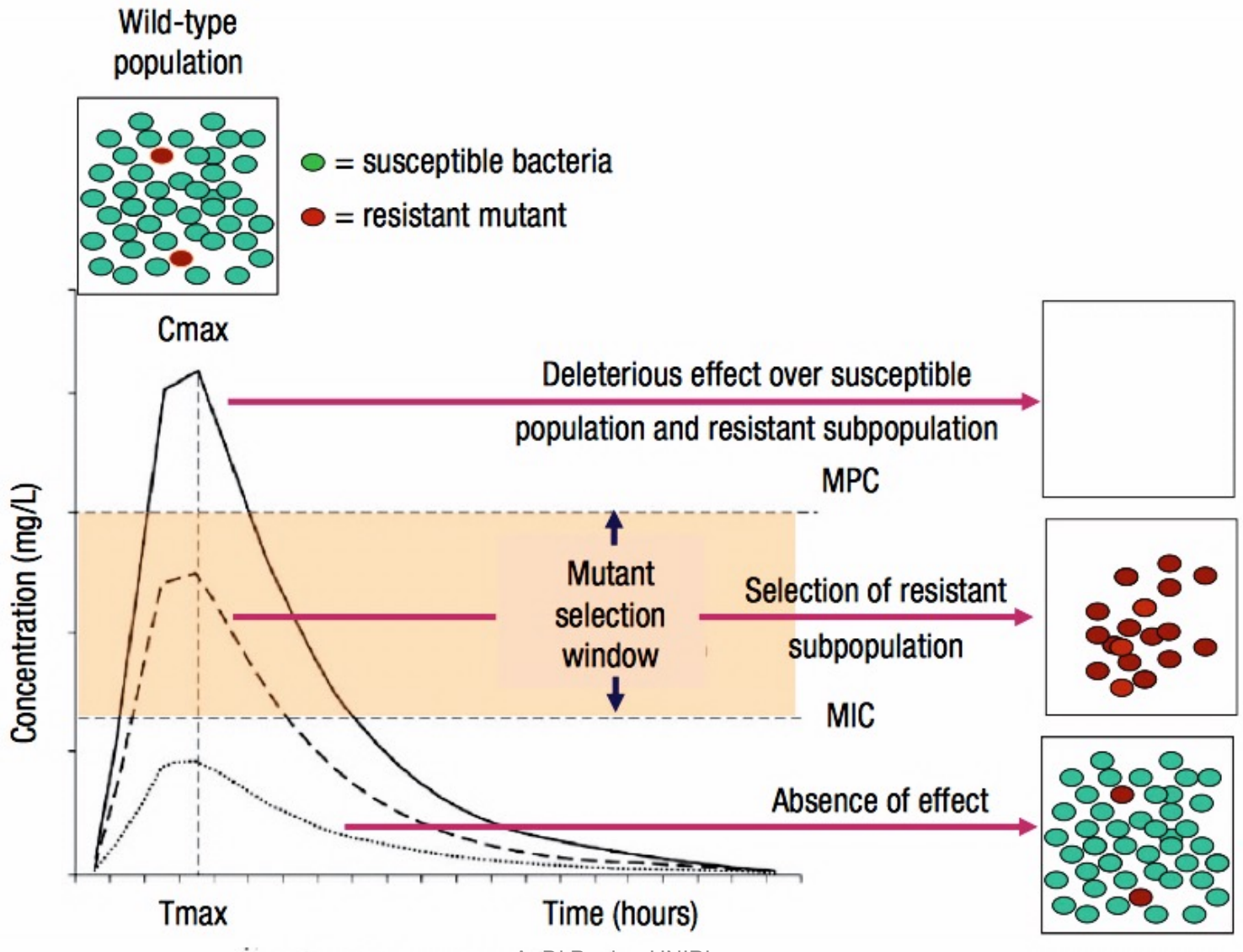
Meeting
Antibiotic
Stewardship

30 - 31 Maggio 2018, Ranica
Istituto di Ricerche
Farmacologiche Mario Negri

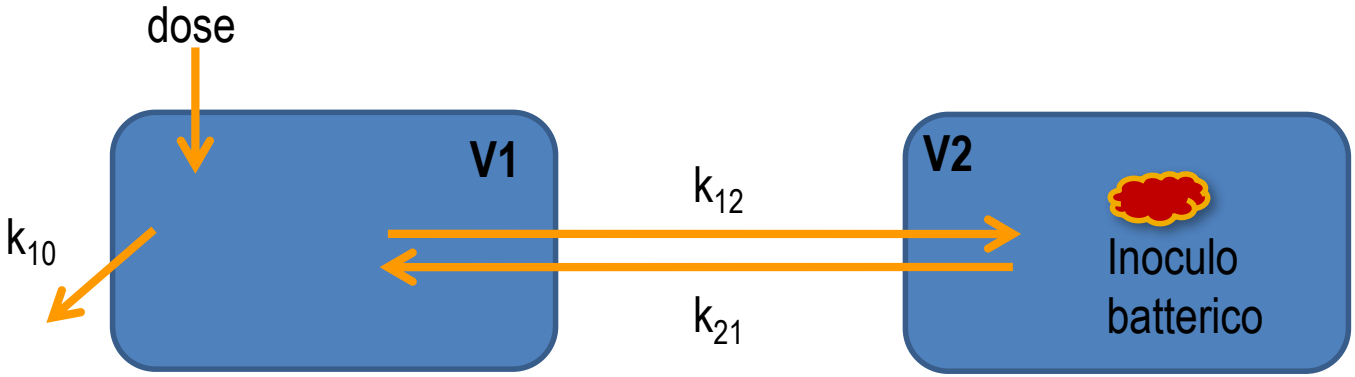
PK/PD con casi clinici

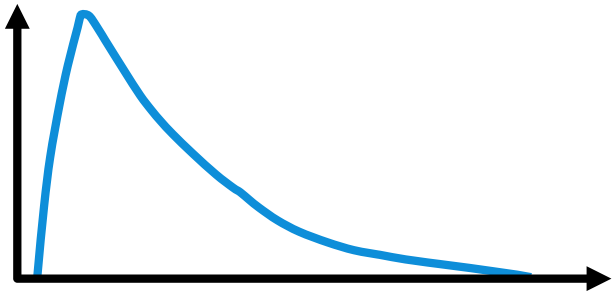
Antonello Di Paolo
Università di Pisa
AOU Pisana

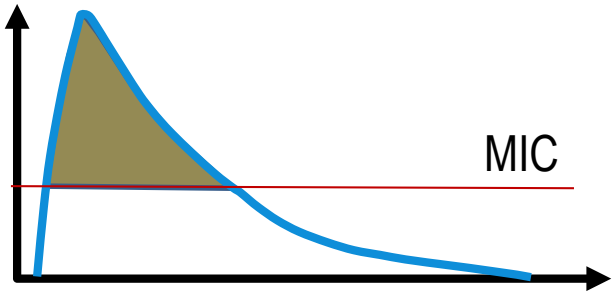
Appropriatezza = efficacia



Farmacocinetica e farmacodinamica







AUC
C_{max}
CL, $t_{1/2}$

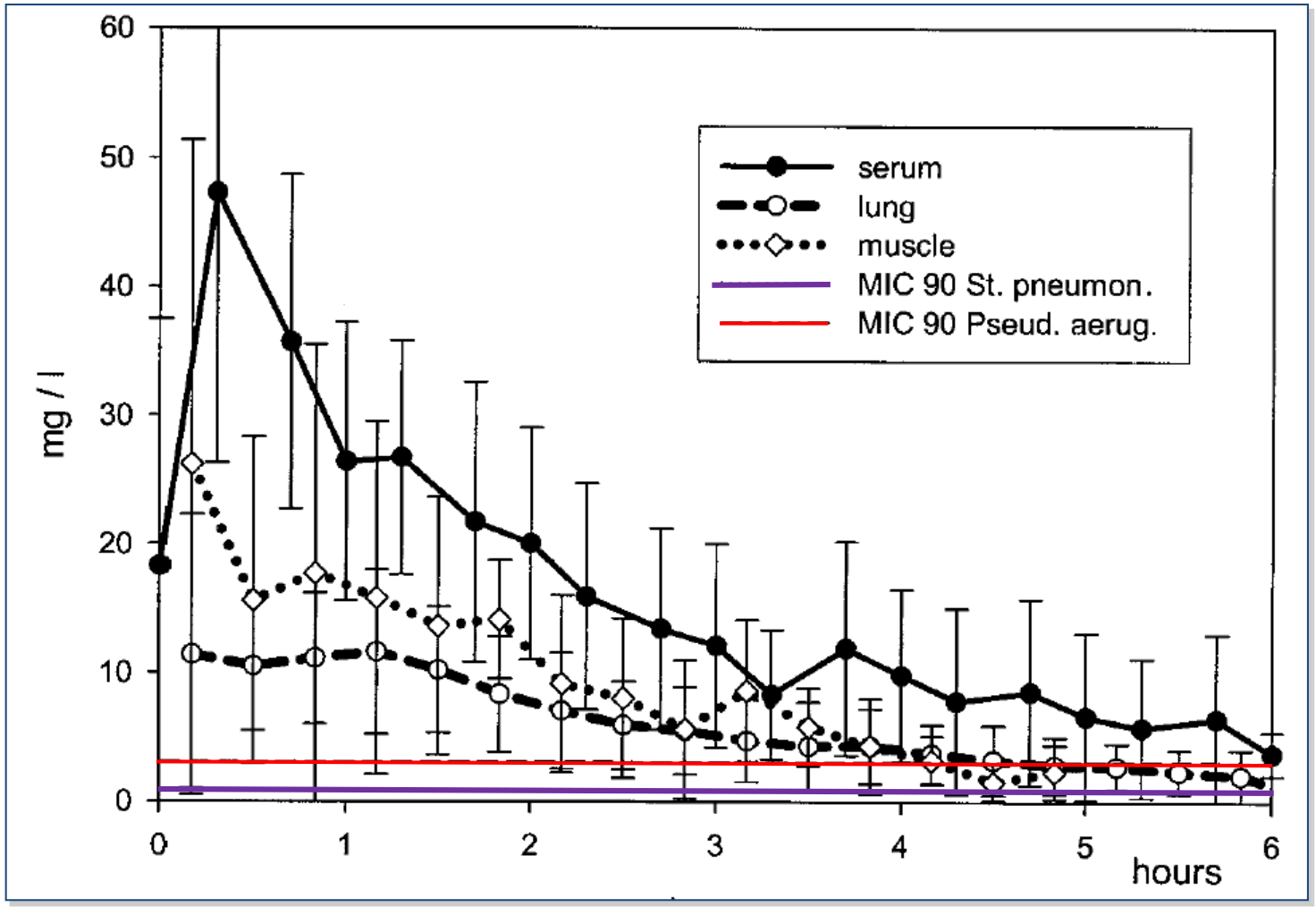
AUC/MIC
C_{max}/MIC
T/MIC

Correlazioni PK/PD

Antibiotici	Farmacodinamica	Dosaggio
Penicilline **Cefalosporine**	Killing tempo-dipendente Breve o assente PAE Correlazione PD-PK:**T>MIC**	Prolungare il tempo di esposizione all'antibiotico Mantenere i livelli sierici >alle MIC (ridurre gli intervalli o infusione continua)
Carbapenemici **Glicopeptidi** **Eritromicina**	Killing tempo-dipendente Prolungato PAE Correlazione PD-PK:**T>MIC**	Prolungare il tempo di esposizione all'antibiotico Livelli sierici possono essere < alle MIC (ridurre gli intervalli)
Aminoglicosidi **Fluorochinoloni** **Claritromicina** **Azitromicina**	Killing concentrazione dipendente Prolungato PAE Correlazione PD-PK: **Picco/MIC** o **AUC/MIC**	Ottenere alti livelli sierici ed elevate concentrazioni tissutali (aumentare le dosi e prolungare gli intervalli)

Carbapenemi

Meropenem 1 g x 3 / die



Spettro esteso

Eliminazione renale

Basso legame farmaco-proteico

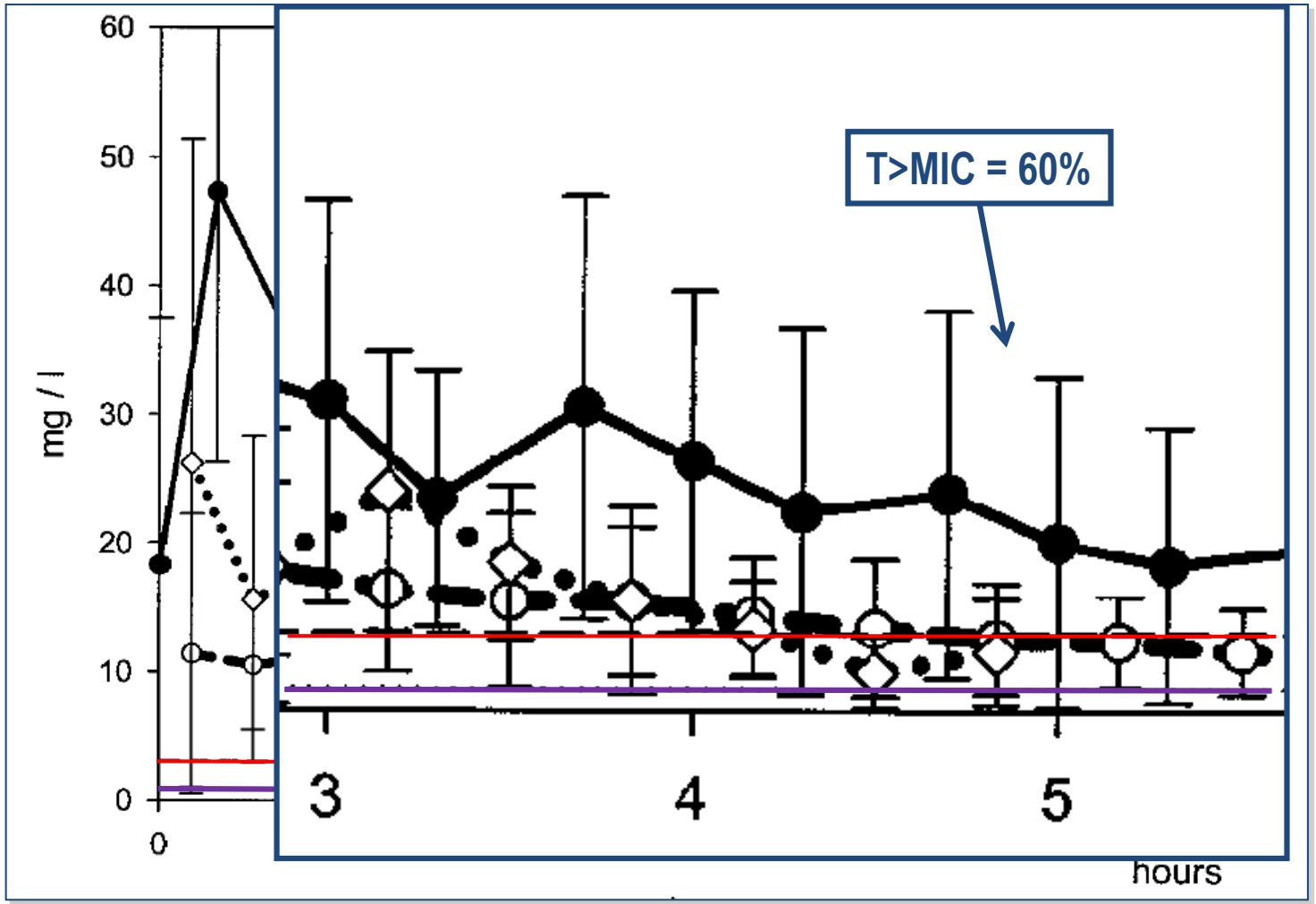
Obiettivo

T>MIC >40%

Tomaselli et al. Antimicrob Agents Chemother 2004;48:2228

Carbapenemi

Meropenem **1 g x 3 / die**



Spettro esteso

Eliminazione renale

Basso legame farmaco-proteico

Obiettivo

T>MIC >40%

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Meropenem

Regimen	Target attainment, %	
	Non–ESBL producers	ESBL producers
Meropenem, 1 g q8h[a]	98	97
Imipenem, 500 mg q6h[a]	98	98
Ertapenem, 1 g q24h[a]	94	78
Levofloxacin[b]		
500 mg q24h	88	11
750 mg q24h	91	13
Gatifloxacin, 400 mg q24h[b]	85	8
Ciprofloxacin, 400 mg q12h[b]	88	2

NOTE. q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h. Adapted from Moczygemba LR, Frei CR, Burgess DS. Pharmacodynamic modeling of carbapenems and fluoroquinolones against bacteria that produce extended-spectrum beta-lactamases. Clin Ther 2004;26:1802, 1804 [55], with permission from Excerpta Medica, Inc.

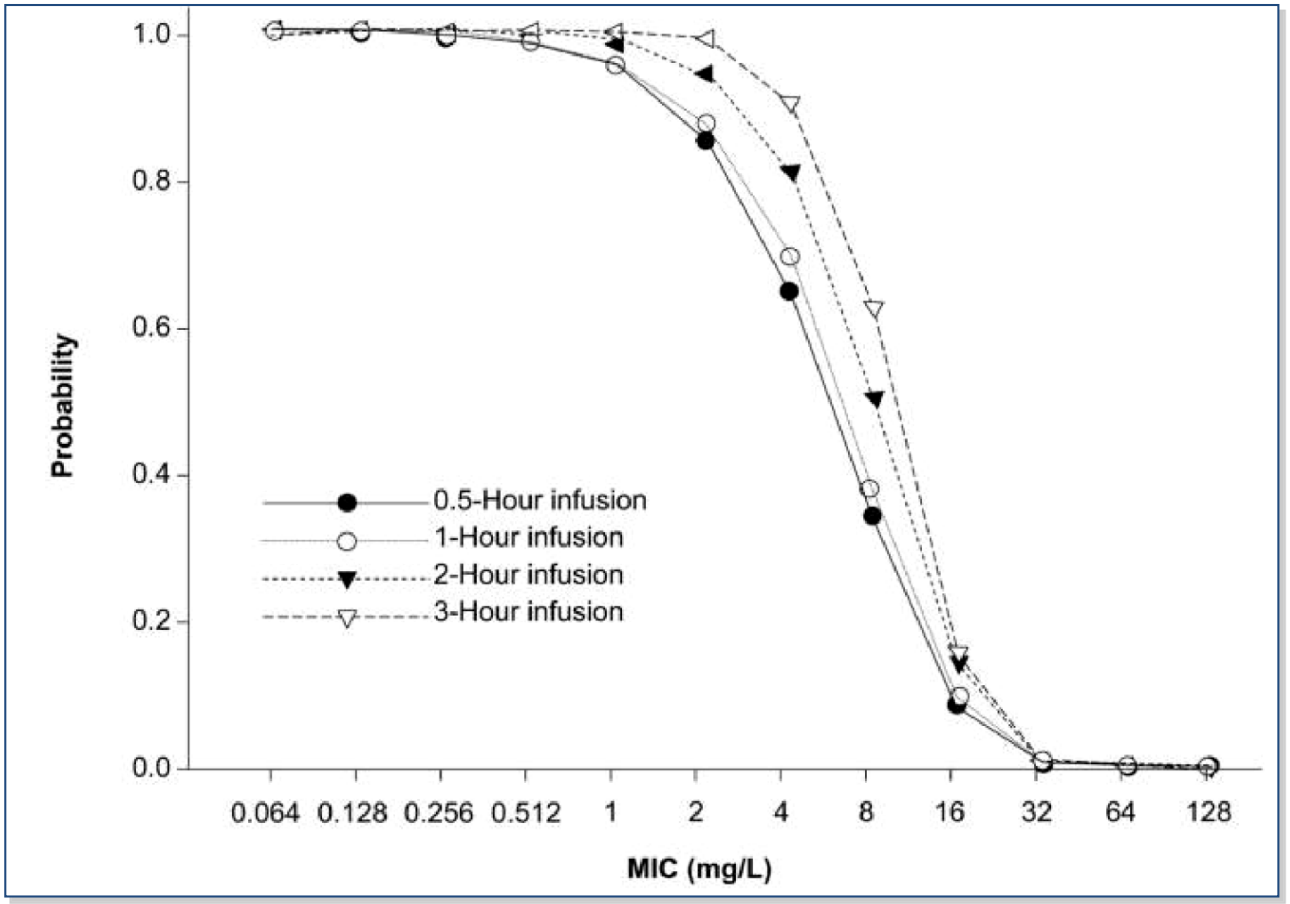
[a] Bactericidal target assessed as free-drug concentration greater than the MIC for ≥40% of the dosing interval.

[b] Bactericidal target assessed as total free-drug area under the concentration-time curve/MIC ratio of ≥125.

Nicolau. Clin Infect Dis 2008;47:S32

Carbapenemi

Meropenem **1 g x 3 / die**



Probabilità di raggiungere L'obiettivo

T>MIC >40%

Infusione di 30'

65%

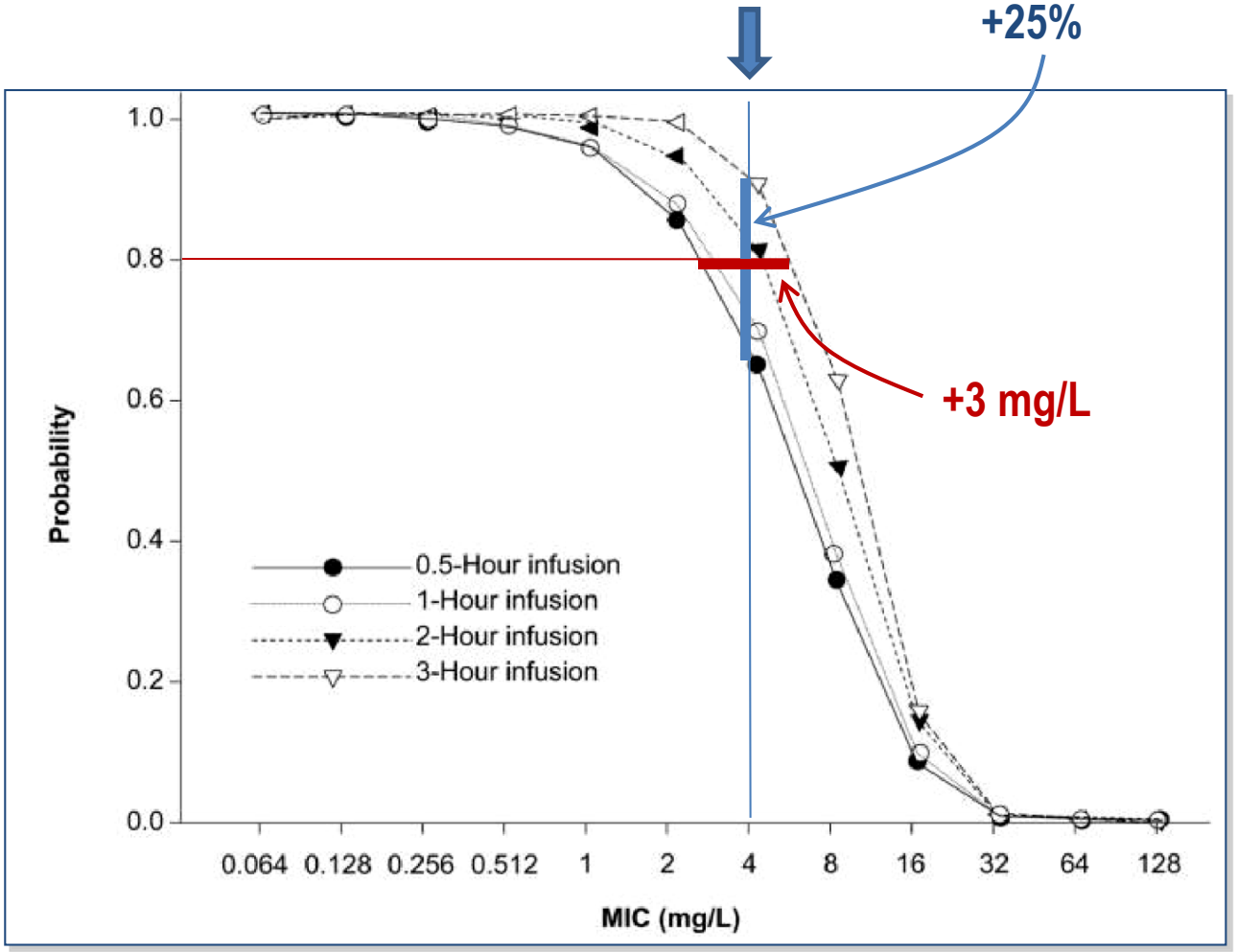
Infusione di 3 h

90%

Li et al. J Clin Pharmacol 2006; 46:1171

Carbapenemi

Meropenem **1 g x 3 / die**



Probabilità di raggiungere L'obiettivo

T>MIC >40%

Infusione di 30'

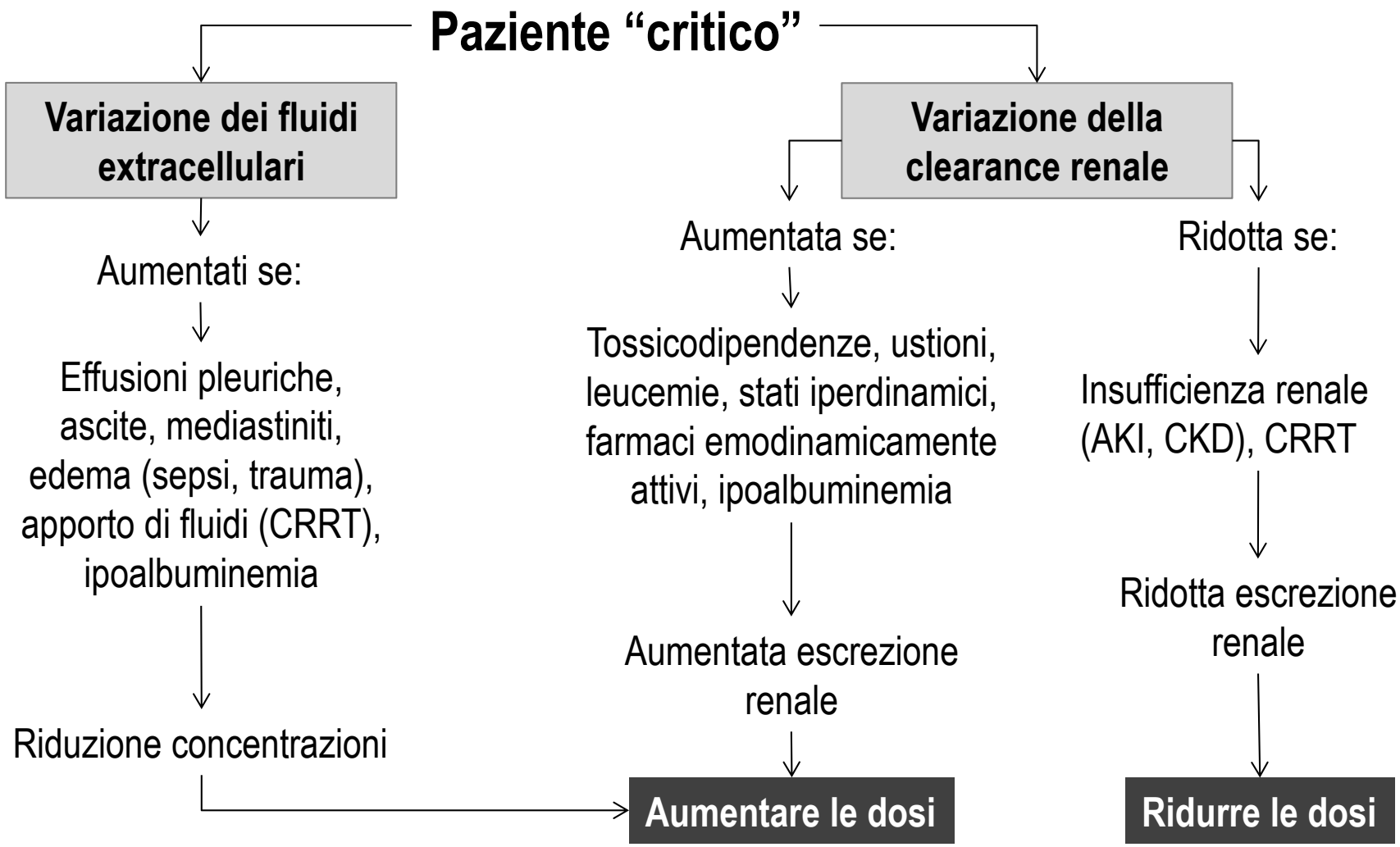
65%

Infusione di 3 h

90%

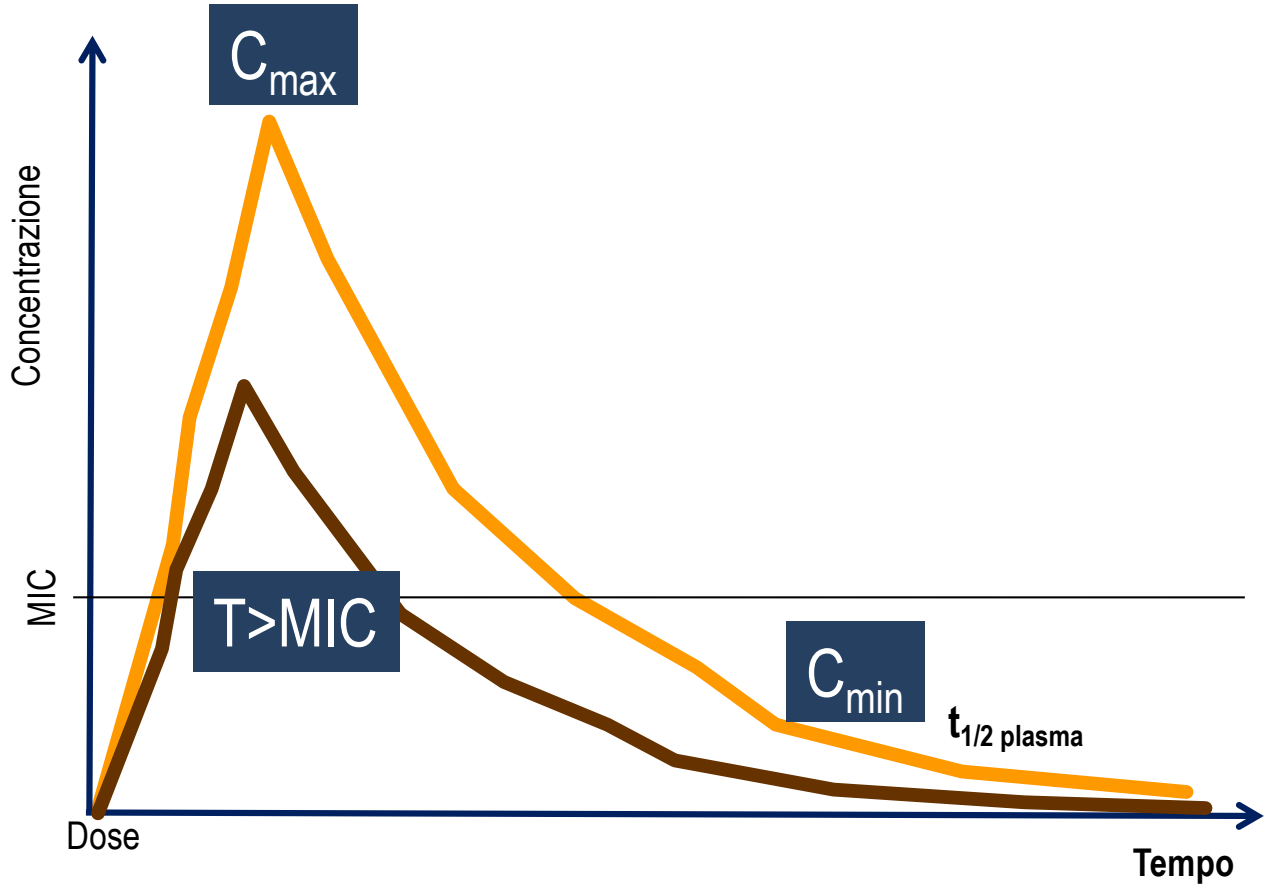
Li et al. J Clin Pharmacol 2006; 46:1171

Variabilità PK degli antibiotici nel paziente critico



Pea et al. *Clin Pharmacokinet* 2005;44:1009-1034

Cause di variabilità PK: la sepsi



Grave sepsi

Risposta infiammatoria

Danno endoteliale

Aumentata permeabilità capillare

Edema interstiziale

"Terzo spazio"

Caratteristiche generali degli antimicrobici

idrofili

β-lattamici
Glicopeptidi
Aminoglicosidi
Oxazolidinoni

- Limitato volume di distribuzione
- Prevalentemente eliminati immodificati dal rene

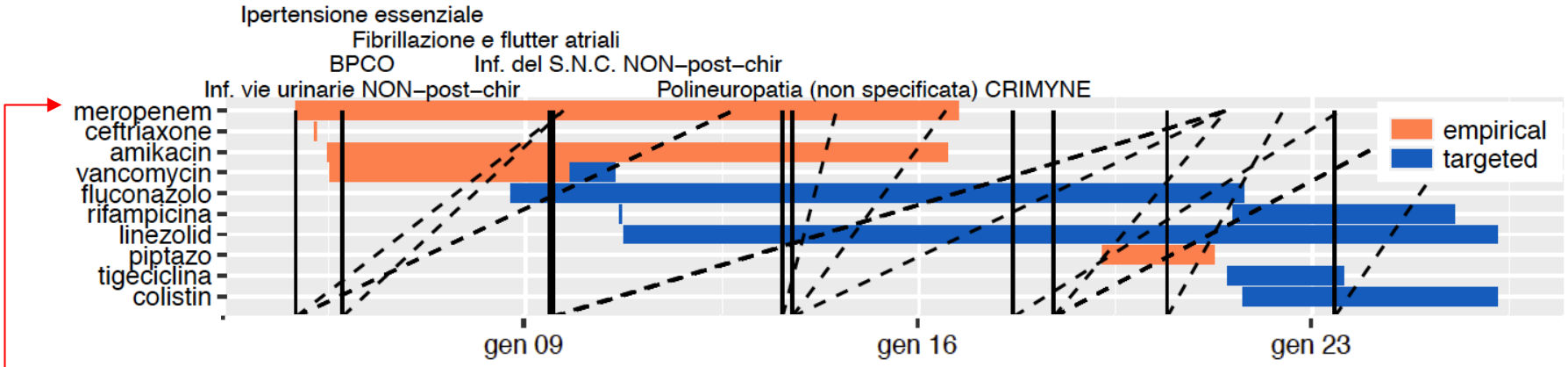
liposolubili

Macrolidi
Fluorochinoloni
Tetracicline
Rifampicina

- Ampio volume di distribuzione, diffondono attraverso le membrane cellulari
- Prevalentemente eliminati dal fegato previa biotrasformazione

Pea et al. *Clin Pharmacokinet* 2005;44:1009-1034

Paziente 886



Principio Attivo	Terapia	Via Somm	Data Inizio	Date Fine	NTot	TTra (h)	NDay	Durata (h)	Dose
amikacin	Empirical	e.v. bolo	2017-01-05 11:39	2017-01-16 12:17	12	24.00	1	0.50	1 g/dose
ceftriaxone	Empirical	e.v. bolo	2017-01-05 06:00	2017-01-05 06:45	1			0.75	2 g/dose
colistin	Targeted	e.v. bolo	2017-01-21 18:00	2017-01-26 06:59	10	12.00	2	1.00	4.5e+06 UI/dose
fluconazolo	Targeted	e.v. bolo	2017-01-08 17:46	2017-01-21 18:30	14	24.00	1	0.50	0.8 g/dose
linezolid	Targeted	e.v. bolo	2017-01-10 17:51	2017-01-11 06:54	2	12.05	2	1.00	0.6 g/dose
linezolid	Targeted	e.v. bolo	2017-01-11 18:00	2017-01-23 06:53	24	12.00	2	1.00	0.6 g/dose
linezolid	Targeted	e.v. bolo	2017-01-23 17:58	2017-01-26 06:53	6	12.00	2	1.00	0.6 g/dose
meropenem	Empirical	e.v. bolo	2017-01-04 22:10	2017-01-05 06:30	2	7.83	3	0.50	1 g/dose
meropenem	Empirical	e.v. bolo	2017-01-05 14:00	2017-01-16 17:00	34	8.00	3	3.00	2 g/dose
piptazo	Empirical	e.v. bolo	2017-01-19 06:00	2017-01-21 05:59	7	8.12	3	0.00	4.5 g/dose
rifampicina	Targeted	e.v. bolo	2017-01-10 16:07	2017-01-10 17:07	1			1.00	0.6 g/dose
rifampicina	Targeted	e.v. bolo	2017-01-21 14:00	2017-01-22 14:17	2	23.78	1	0.50	0.6 g/dose
rifampicina	Targeted	e.v. bolo	2017-01-23 12:00	2017-01-25 12:38	3	24.07	1	0.50	0.6 g/dose
tigeciclina	Targeted	e.v. bolo	2017-01-21 11:35	2017-01-21 12:35	1			1.00	0.1 g/dose
tigeciclina	Targeted	e.v. bolo	2017-01-21 23:49	2017-01-23 13:00	4	12.13	2	1.00	0.05 g/dose
vancomycin	Empirical	e.v. bolo	2017-01-05 12:45	2017-01-05 13:45	1			1.00	1.5 g/dose
vancomycin	Empirical	inf. continua	2017-01-05 13:40	2017-01-09 19:06	1			101.43	1.92 g/day
vancomycin	Targeted	inf. continua	2017-01-09 19:00	2017-01-10 14:12	1			19.20	1.92 g/day

Meropenem nel paziente settico

Assessment of pharmacokinetic changes of meropenem during therapy in septic critically ill patients

- 15 pazienti settici ricoverati in reparti di terapia intensiva
- Score (mediano, range interquartile)
  - SOFA **4** 2,5
  - CHARLSON **4** 3
  - SAPS II **44** 11,5
- Meropenem in associazione
  - 1 g x 3/die in infusione i.v. di 30 min

Goncalves-Pereira et al. BMC Pharmacol Toxicol 2014;15:21

PK/PD di meropenem nel paziente settico

Patient N°	V_{ss}	V_{ss}/weight	V_{ss2}/V_{ss}	AUC	Cl	$T_{1/2}$	Peak	Trough	T > 2 mg/L	T > 4 mg/L	T > 8 mg/L
	L	L/Kg	%	L/mg.h	mL/min	h	mg/L	mg/L	100%	90%	70%
1	19.6	0.25	50.6%	157.1	106.7	2.9	63.3	3.0	100%	100%	100%
2	NA	NA	NA	264.7	63.3	1.5	NA	11.9	100%	100%	100%
3	13.6	0.21	56.3%	253.3	65	2.6	94.1	8.6	100%	100%	85%
4	13.6	0.17	78.4%	160.1	103.3	1.7	102.3	4.8	100%	85%	50%
5	13.4	0.16	51.8%	129.2	128.3	1.3	80.1	2.7	100%	90%	65%
6	32.7	0.42	93.7%	134.9	123.3	3.4	52.0	3.0	100%	100%	100%
7	18.6	0.23	73.6%	479.2	35	6.4	84.7	NA	100%	100%	100%
8	14.9	0.25	88.7%	465.9	35	5.0	91.3	NA	100%	100%	75%
9	6.7	0.07	90.4%	232.5	71.7	1.4	192.5	4.4	100%	75%	50%
10	13.0	0.16	58.4%	139.5	120	1.5	85.1	2.4	100%	75%	50%
11	20.9	0.30	68,6%	107.3	155	1.9	58.6	2.9	100%	100%	100%
12	13.6	0.18	79.2%	304.2	55	3.5	119.8	8.6	75%	50%	35%
13	17.1	0.27	34.9%	81.4	205	1.3	56.9	0.6	100%	100%	55%
14	22.5	0.28	53.1%	120.7	138.3	2.1	48.4	4.1	100%	100%	100%
15	13.0	0.13	68.6%	315.3	53.3	3.3	124.2	12.5	100%	90%	70%
Geometric mean	15.7	0.2	63.1%	190.2	73.3	2.3	85.9	3.8	100%	100%	100%
95% CI	12.7-19.4	0.15-0.27	52.7-75.5%	138.4-261.4	45-120	1.8-3.1	69.2-106.6	2.3-6.2			

T>MIC

Goncalves-Pereira et al. BMC Pharmacol Toxicol 2014;15:21

PK/PD di meropenem nel paziente settico

Finally we evaluated ability of conventional dose of meropenem to achieve a time over minimal inhibitory concentration (T > MIC) of 100%, assuming a MIC of 2 mg/L (the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for *Pseudomonas aeruginosa*).

T > 2 mg/L	T > 4 mg/L	T > 8 mg/L
100%	90%	70%
100%	100%	100%
100%	100%	100%
100%	100%	85%
100%	85%	50%
100%	90%	65%
100%	100%	100%
100%	100%	100%
100%	100%	75%
100%	75%	50%
100%	75%	50%
100%	100%	100%
75%	50%	35%
100%	100%	55%
100%	100%	100%
100%	90%	70%
100%	100%	100%

T>MIC

Goncalves-Pereira et al. BMC Pharmacol Toxicol 2014;15:21

Meropenem: conclusioni

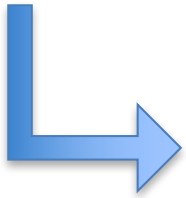
- We confirmed the PK **adequacy** of the commonly used dose of meropenem to treat an unselected population of septic critically ill patients not receiving renal replacement therapy.
- As a result we did **not find any evidence** that the generalized use of meropenem TDM would be useful or cost-effective.
- **Identification** of sub-groups of patients most likely to benefit from this pratice should be performed before the general use of TDM monitoring can be recommended.

Goncalves-Pereira et al. BMC Pharmacol Toxicol 2014;15:21

Paziente 886

Antibiotico	Tracheoaspirato Klebsiella pneumoniae ss. pneumoniae
Amikacina	R (>32,000)
Amoxicillina(A.CLAV.	R (>16,000)
Cefepime	R (>32,000)
Cefotaxime	R (>32,000)
Ceftazidime	R (>32,000)
Ciprofloxacina	R (>2,000)
Colistina	S (<=0,5 mg/L)
Ertapenem	R (>4,000)
Fosfomycin	R (64,000)
Gentamicina	I (4,000)
Imipenem	R (>8,000)
Meropenem	R (>8,000)
Piperacillin/tazobac	R (>64,000)
Tigecycline	I (2,000)
Trimetoprim/Sulfam.	R (>160,000)

Antibiogrammi del 2017-01-17



Carbapenems[1]	MIC breakpoint (mg/L)	
	S ≤	R >
Doripenem	1	2
Ertapenem	0.5	1
Imipenem[2]	2	8
Meropenem	2	8

EUCAST Clinical Breakpoint Tables v. 8.1, valid from 2018-05-15

Meropenem e infezioni da *K. pneumoniae* produttrice di carbapanemasi (KPC)

- Meropenem è un **betalattamico ad ampio spettro**, impiegato largamente nella **terapia di infezioni nosocomiali** per la rapida e buona distribuzione nella maggior parte dei tessuti e dei fluidi.[1,2]
- In associazioni polichemioterapiche, il farmaco trova impiego nel trattamento delle **gravi infezioni** da ***K. pneumoniae*-KPC**, che sono caratterizzate da una elevata percentuale di decessi[3].

[1]Drusano e Hutchison, Scand J Infect Dis Suppl 1995; [2]EMA Meropenem summary of product characteristics, WC500018555.pdf, 2015; [3]Tumbarello et al, J Antimicrobial Chemother 2015

Meropenem e infezioni da *K. pneumoniae* produttrice di carbapanemasi (KPC)

- L'**attività battericida di meropenem** è predetta da parametri farmacocinetico-farmacodinamici (**PK/PD**) quali il tempo durante il quale le concentrazioni libere di farmaco sono superiori alla minima concentrazione inibitoria (***f*T>MIC**)[1-5] e dai valori di concentrazione minima plasmatica (C_{min}) superiori a 4 volte il valore di MIC (**C_{min}>4×MIC**).[6]

[1]Jaruratanasirikul et al, Int J Antimicrob Agents 2011; [2]Antimicrob Agents Chemother 2005; [3]MacGowan. Curr Opin Pharmacol 2011; [4]Mouton et al. J Antimicrob Chemother 2005; [5]Drusano. Clin Infect Dis 2003; [6]Craig. Clin Infect Dis 1998

Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients

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Eur J Clin Pharmacol
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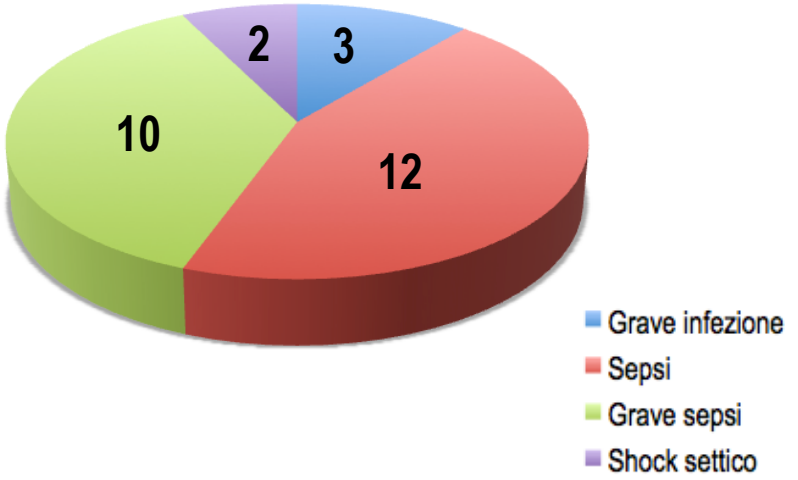
Parametro	Pazienti (n=27)
Età (anni)	62±12 (61)
Peso corporeo (kg) *	76,2±30,3 (68)
Altezza (cm) *	170,3±7,3 (170)
BSA (m^2) *	1,9±0,3 (1,8)
BMI (kg/m^2)	26,1±8,9 (23,4)
Creatininemia (mg/dL)	1,3±1,0 (0,9)
Albuminemia (g/L)	24,3±6,6 (23,1)
Diuresi (mL/die)	2032±950 (2000)

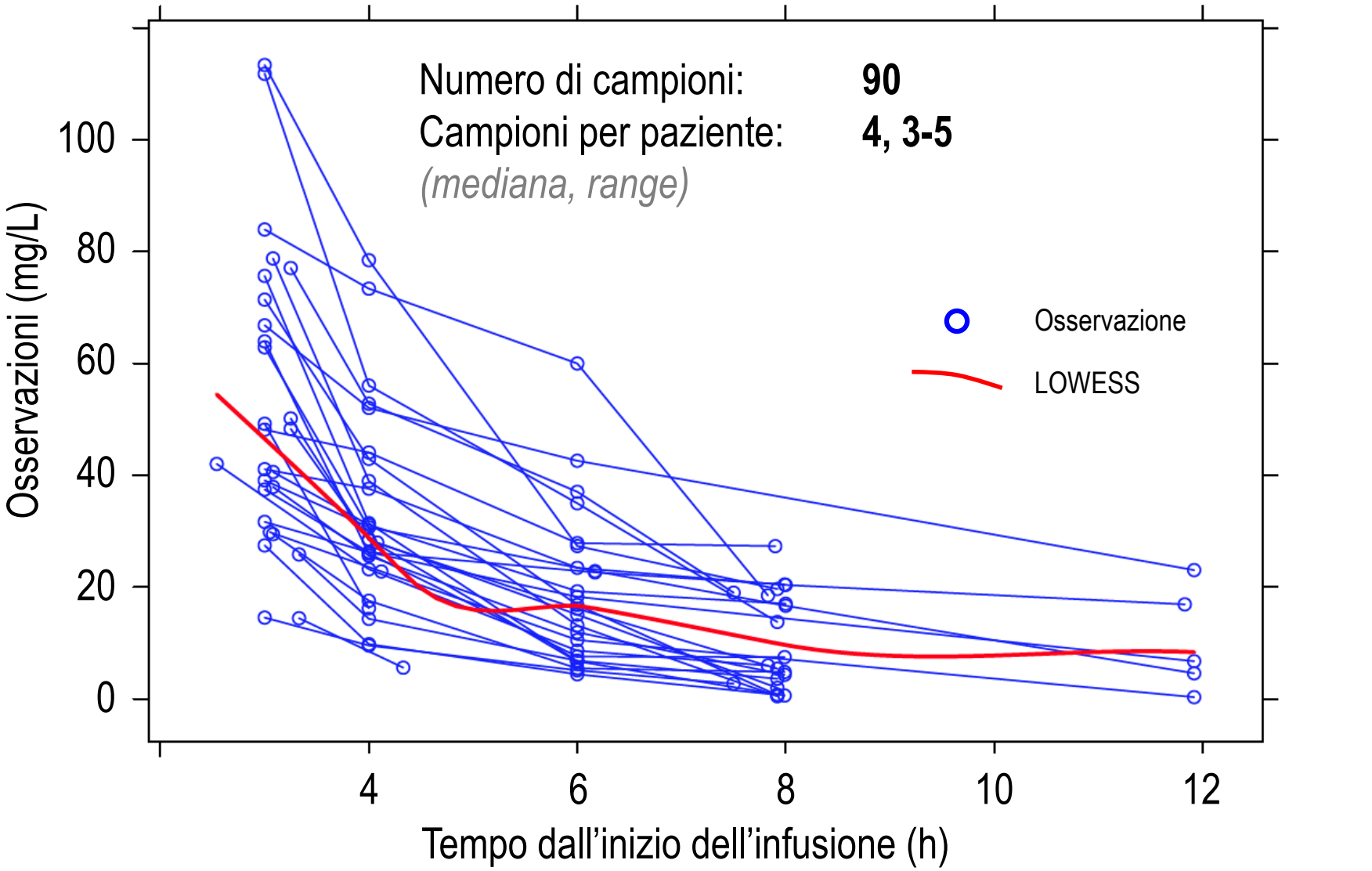


Meropenem	Pazienti
1g x 2	2
1g x 3	2
2g x 2	5
2g x 3	17
3g x 3	1

Note. I valori sono espressi come media±deviazione standard (mediana); *, differenze statisticamente significative per genere (test *t* di Student). **Abbreviazioni**: BSA, superficie corporea; BMI; indice di massa corporea

Andamento temporale delle concentrazioni plasmatiche di meropenem

Mattioli et al. Eur J Clin Pharmacol 2016;72:839-48



Modello farmacocinetico: risultati

Modello farmacocinetico finale

Modello monocompartimentale

$$CL\ (L/h) = 2{,}181 \times [1 + SEX] \times [1 + SEPSI] \times EXP(ETA_1)$$

$$V\ (L) = 8{,}305 \times (ALB/22)^{0{,}521} \times (ETÀ/61)^{0{,}517} \times EXP(ETA_2)$$

Uomo, no sepsi = 6,22 L/h
Donna, sepsi = 12,04 L/h

Covariate

SEX
- 1 > Uomini
- 1,760 > Donne

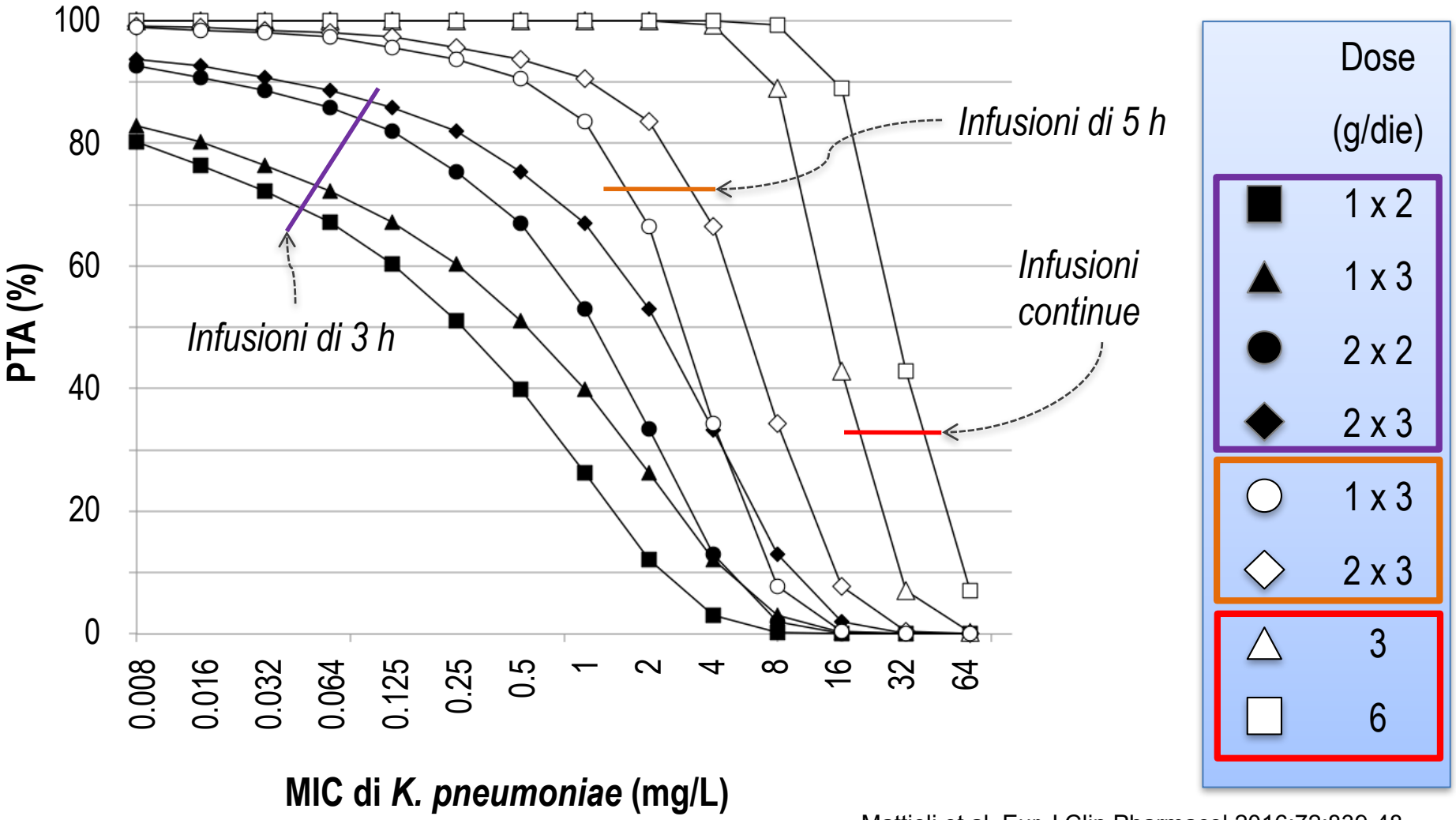
SEPSI
- 0,427 > Sepsi
- 1 > Sepsi grave, shock settico

CL, clearance; V, volume di distribuzione
IIV, variabilità interindividuale

Mattioli et al. Eur J Clin Pharmacol 2016;72:839-48

Probabilità di raggiungere l'obiettivo (PTA)

C_{min}>4xMIC



Mattioli et al. Eur J Clin Pharmacol 2016;72:839-48

Meropenem e funzionalità renale

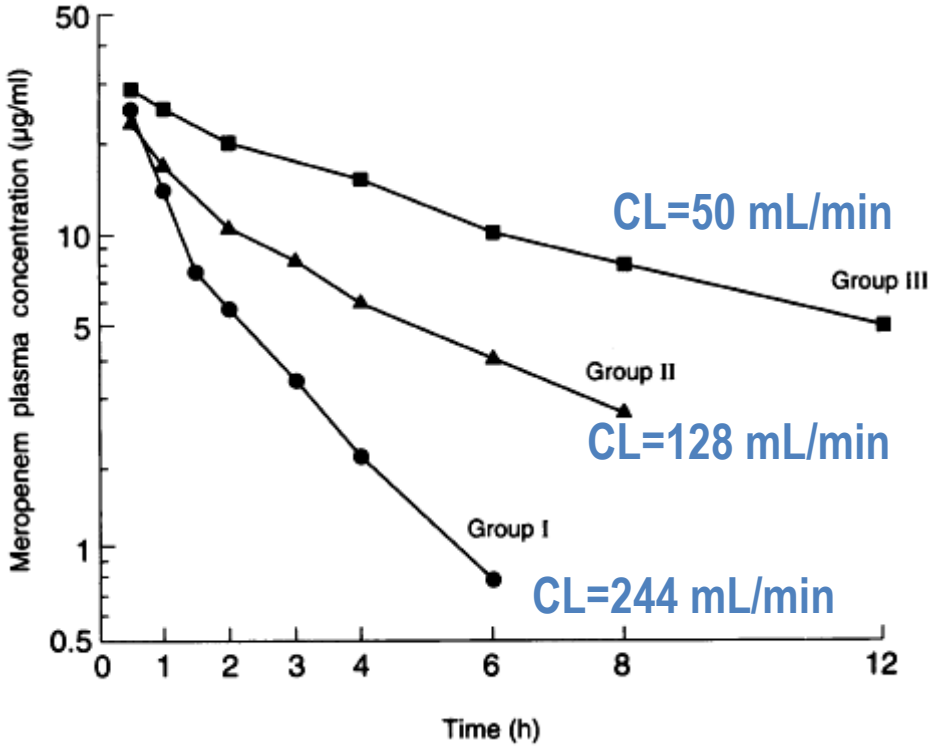


TABLE 1. Subject characteristics

Group	Subject no.	Age	Sex[a]	Wt (kg)	Serum creatinine concn (mg/dl)	CL_{CR} (ml/min)
I	1	55	F	40	0.5	68.0
	2	68	F	34	0.8	62.5
	3	49	F	43	0.8	57.3
	4	30	F	62	1.1	55.7
II	5	61	M	85	1.6	37.3
	6	48	M	65	2.2	34.5
	7	48	M	66	1.8	32.7
	8	60	F	43	1.3	32.0
III	9	66	M	52	4.0	21.5
	10	46	F	58	2.7	16.2
	11	61	F	58	5.3	11.3
	12	76	M	52	4.2	7.1
	13	74	F	50	7.0	4.3

Chimata et al. Antimicrob Agents Chemother 1993;37:229-33

Funzionalità renale e *renal replacement therapy* (RRT)

Fattori di variabilità

1) Meccanismo di clearance (diffusione *vs*. convezione)

2) Tipo di RRT (intermittente *vs*. continuo)

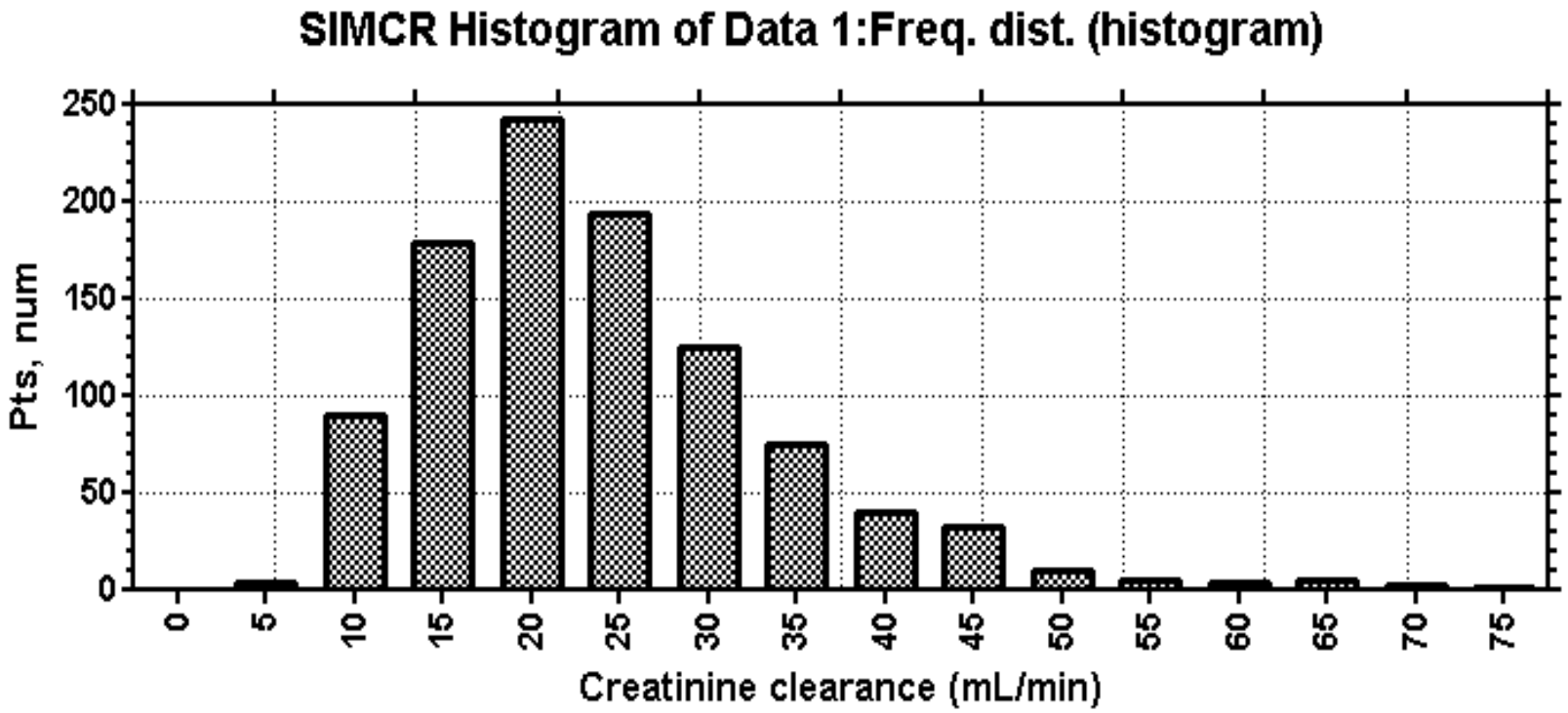
3) Caratteristiche tecniche (tipo ed età della membrana, durata e flusso, diluizione pre- o post-filtro)

4) Caratteristiche fisico-chimiche e farmacocinetiche

Pea et al, Clin Pharmacokinet 2007;46:997
Churchwell e Mueller, Semin Dial 2009; 22:185
Heintz et al. Pharmacother 2009;29:562

Simulazione clearance creatinina

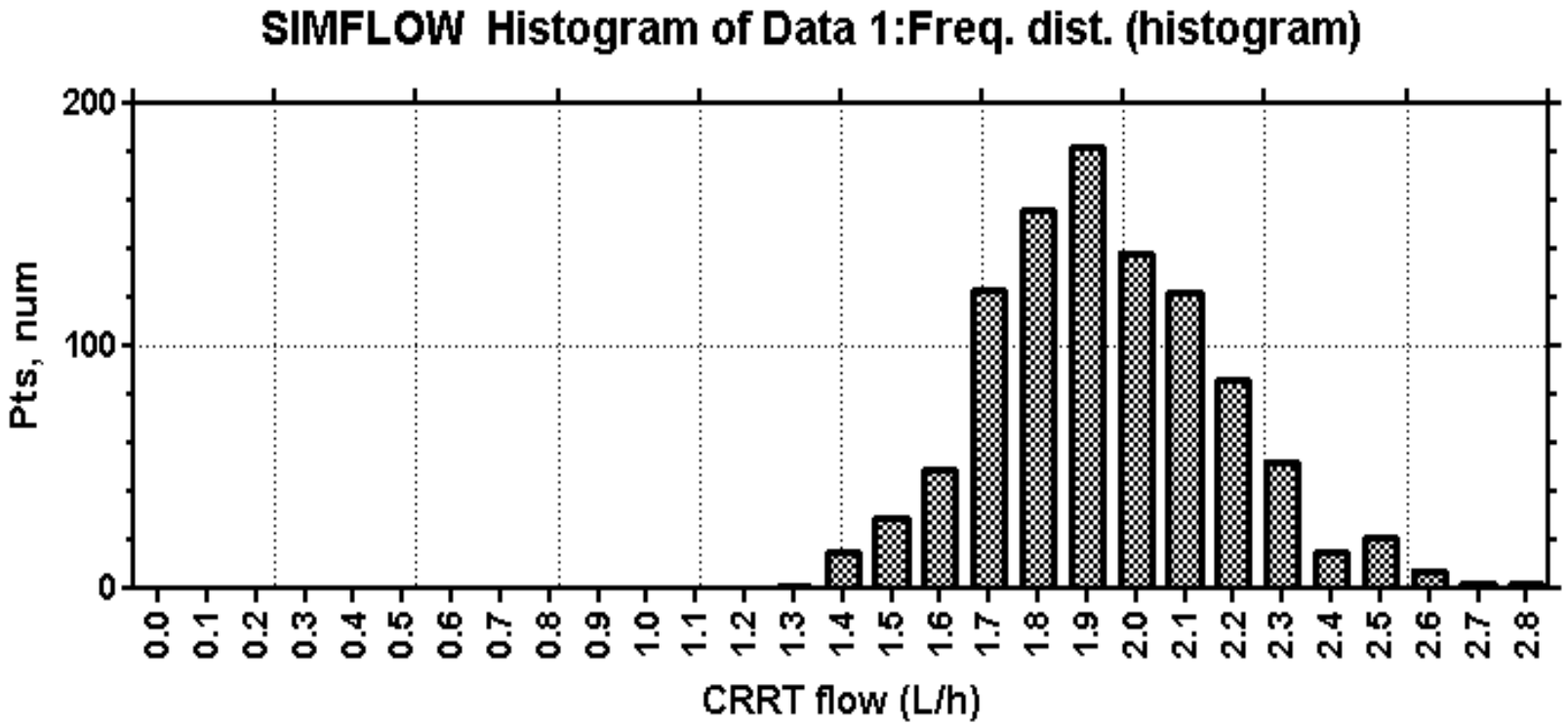
Clearance della creatinina:
Valore medio: 20 mL/min
Variabilità interindividuale: 40,85%



Simulazione flusso CRRT

Parametri per la simulazione (Isla et al, Clin Pharmacokinet 2008;47(3):173)

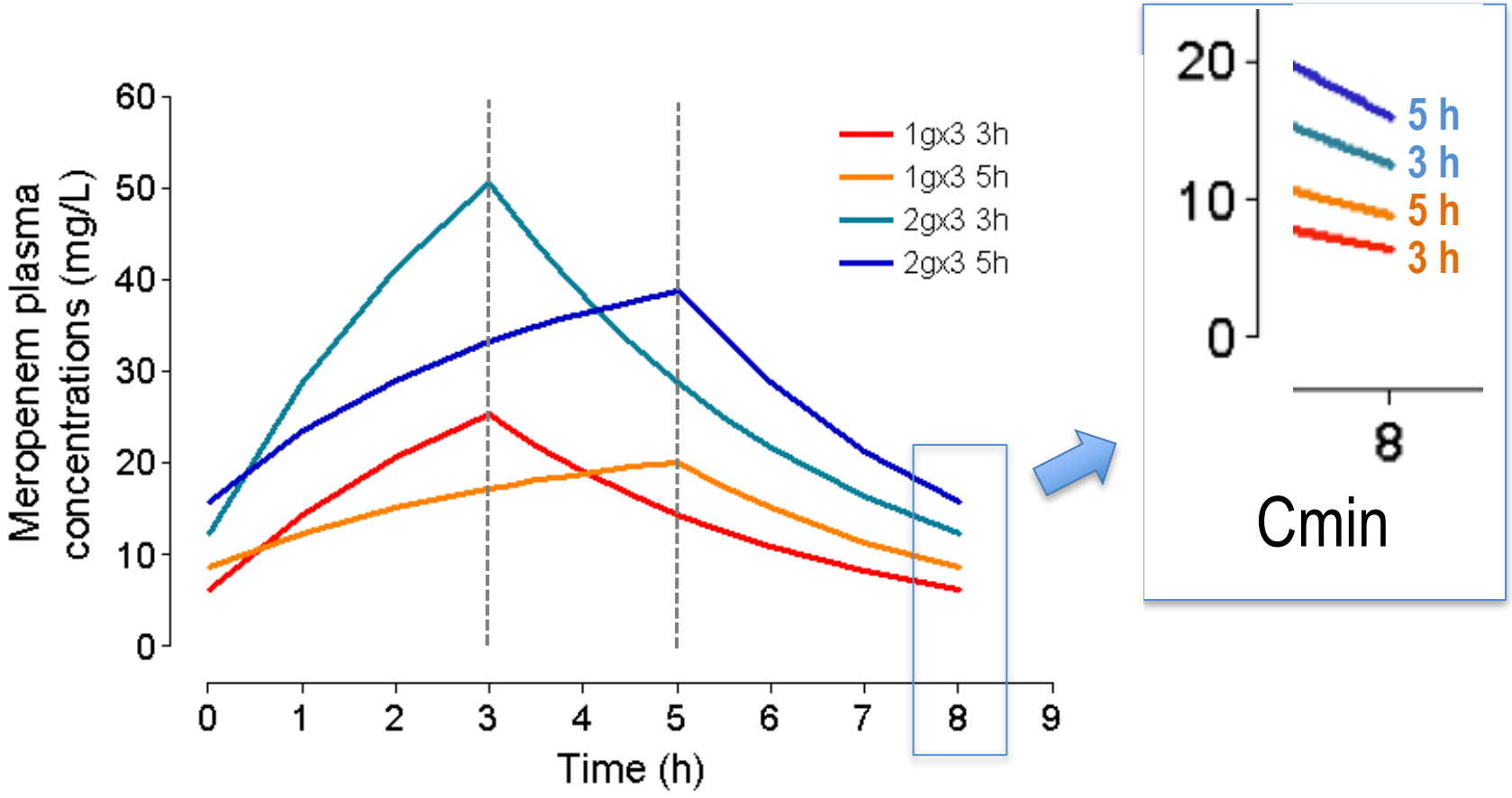
Flusso: 1910±616,4 mL/Min [1000-2800 mL/min]



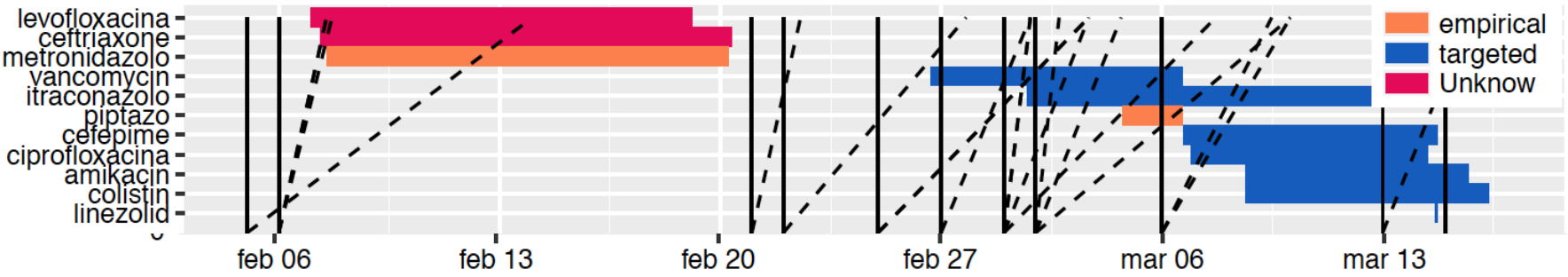
Meropenem, CRRT e infusioni prolungate

1000 individui

Meropenem 1-2 g in infusione i.v. di 3-5 ore x3/die



Paziente 3992



Antibiogrammi del 2017-03-06

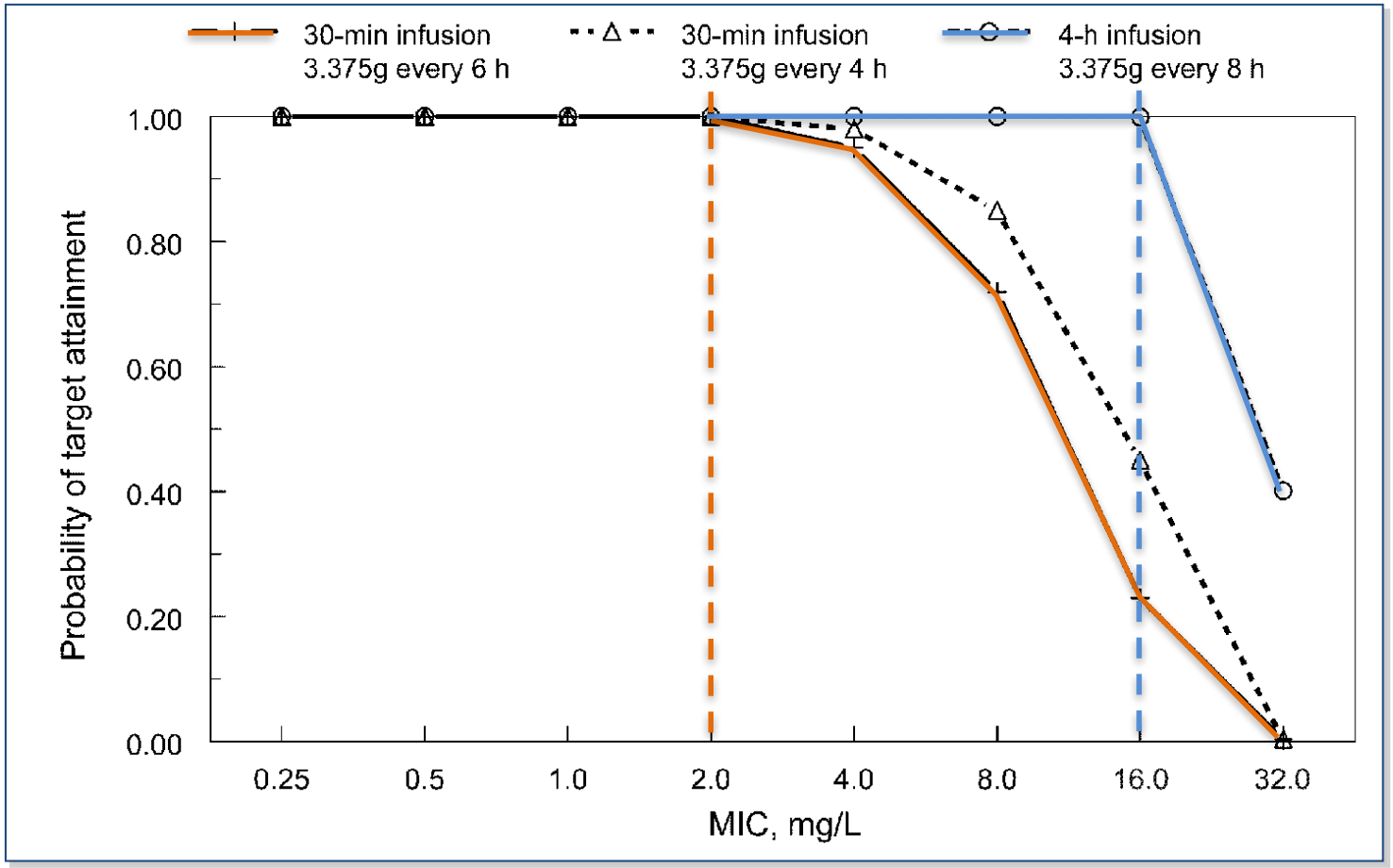
Antibiotico	Broncolavaggio Klebsiella pneumoniae	Urinocoltura Catetere Vescicale Klebsiella pneumoniae	Broncolavaggio Pseudomonas aeruginosa
Amikacina	S (<=2)	S (4)	S (4)
Amoxicillina/A.CLAV.	R (>=32)	R (>=32)	R (>=32)
Cefepime	R (>=64)	R (32)	S (2)
Cefotaxime	R (>=64)	R (>=64)	R (>=64)
Ceftazidime	R (>=64)	R (>=64)	S (4)
Ciprofloxacina	R (>=4)	R (>=4)	S (<=0,25)
Colistina	S (<=0,5)	S (<=0,5)	S (<=0,5)
Ertapenem	R (>=8)	R (>=8)	R (4)
Fosfomicina		S (<=16)	
Gentamicina	S (<=1)	S (<=1)	S (4)
Imipenem	R (>=16)	R (>=16)	S (2)
Meropenem	R (>=16)	R (>=16)	S (0,5)
Piperacillina/tazobactam	R (>=128)	R (>=128)	S (<=4)
Trimetoprim/Sulfam.	R (>=320)	R (>=320)	R (80)

Paziente 3992

Principio Attivo	Terapia	Via Somm	Data Inizio	Date Fine	NTot	TTra (h)	NDay	Durata (h)	Dose
amikacin	Targeted	e.v. bolo	2017-03-08 15:26	2017-03-08 16:26	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-10 16:17	2017-03-10 17:17	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-12 15:43	2017-03-12 16:43	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-15 16:02	2017-03-15 17:02	1			1.00	0.25 g/dose
cefepime	Targeted	inf. continua	2017-03-06 16:32	2017-03-14 11:09	1			186.62	4.03 g/day
cefepime	Targeted	inf. continua	2017-03-14 11:09	2017-03-14 17:14	1			6.08	2.11 g/day
ceftriaxone	Unknown	e.v. bolo	2017-02-07 07:30	2017-02-20 08:55	14	23.92	1	0.50	2 g/dose
ciprofloxacina	Targeted	e.v. bolo	2017-03-06 22:05	2017-03-11 21:19	11	11.92	2	0.00	0.4 g/dose
ciprofloxacina	Targeted	e.v. bolo	2017-03-12 10:22	2017-03-14 10:23	5	11.94	2	0.00	0.4 g/dose
colistin	Targeted	inalatoria	2017-03-08 15:27	2017-03-16 07:44	24	7.90	3		1e+06 UI/dose
colistin	Targeted	e.v. bolo	2017-03-08 19:10	2017-03-09 08:23	2	12.22	2	1.00	1e+06 UI/dose
colistin	Targeted	e.v. bolo	2017-03-09 20:15	2017-03-16 08:41	13	12.24	2	1.00	1e+07 UI/dose
itraconazolo	Targeted	SNG	2017-03-01 17:46	2017-03-16 06:27	30	11.97	2	0.00	0.2 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-06 23:59	2017-02-08 00:08	2	23.15	1	1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-08 22:59	2017-02-08 23:59	1			1.00	0.25 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-08 23:20	2017-02-09 00:20	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-11 00:07	2017-02-11 01:07	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-13 00:04	2017-02-13 01:04	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-14 23:07	2017-02-15 00:07	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-16 22:27	2017-02-16 23:27	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-19 01:05	2017-02-19 02:05	1			1.00	0.5 g/dose
linezolid	Targeted	e.v. bolo	2017-03-14 16:15	2017-03-14 17:15	1			1.00	0.6 g/dose
metronidazolo	Empirical	e.v. bolo	2017-02-07 12:27	2017-02-20 05:58	52	6.02	4	0.50	0.5 g/dose
piptazo	Empirical	e.v. bolo	2017-03-04 18:17	2017-03-04 19:17	1			1.00	4.5 g/dose
piptazo	Empirical	inf. continua	2017-03-04 19:51	2017-03-06 15:45	1			43.90	9.07 g/day
vancomycin	Targeted	e.v. bolo	2017-02-26 16:01	2017-02-26 17:01	1			1.00	1 g/dose
vancomycin	Targeted	inf. continua	2017-02-26 17:02	2017-02-27 11:40	1			18.63	2 g/day
vancomycin	Targeted	inf. continua	2017-02-27 11:45	2017-03-02 12:45	1			73.00	1.44 g/day
vancomycin	Targeted	inf. continua	2017-03-02 12:45	2017-03-03 16:45	1			28.00	1.15 g/day
vancomycin	Targeted	inf. continua	2017-03-03 17:22	2017-03-04 11:28	1			18.10	0.8 g/day
vancomycin	Targeted	inf. continua	2017-03-04 11:28	2017-03-04 17:58	1			6.50	0.61 g/day
vancomycin	Targeted	inf. continua	2017-03-04 17:58	2017-03-06 15:45	1			45.78	0.38 g/day

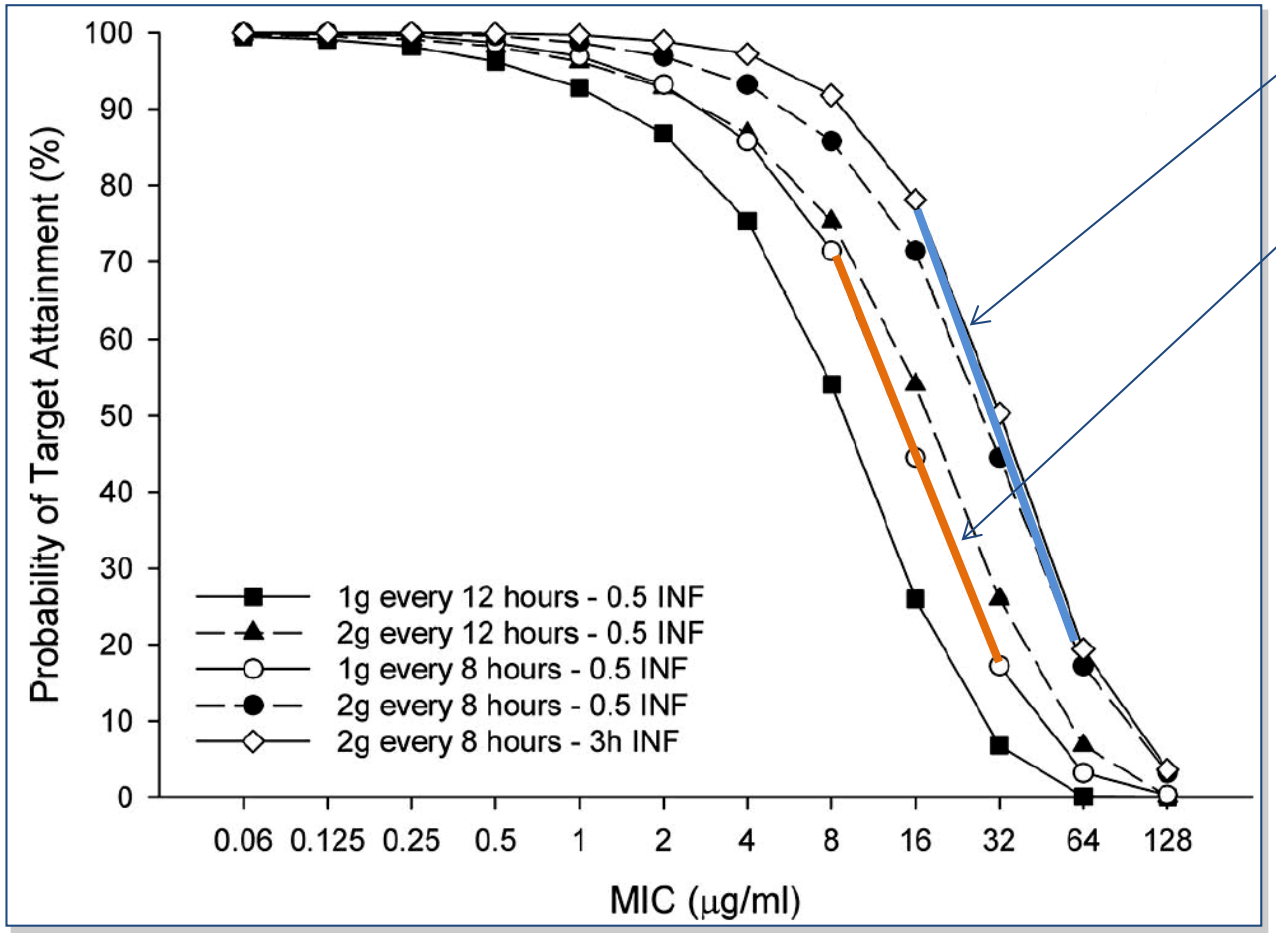
Piperacillina/tazobactam

PTA e durata dell'infusione



Nicasio et al. Antimicrob Agents Chemother 2009;53:1476

Cefepime



Nicasio et al. Antimicrob Agents Chemother 2009;53:1476

Messaggio chiave

- Per gli antimicrobici con *killing* tempo-dipendente:
- Il valore di C_{max} è governato dalla velocità di infusione
- Il valore di C_{min} dalla durata dell'infusione e dalle capacità emuntorie del paziente

- Problema: qual è la stabilità del farmaco in soluzione a temperatura ambiente e quali farmaci possono essere presenti nella stessa sacca?

Antibatterici tempo-dipendenti

Stabilità delle soluzioni per infusione

Antibiotic	Time of stability at room temperature (+25°C; hours)	Maximum concentration tested (mg/l)
Piperacillin/tazobatam [52]	>72	128,000
Ceftazidime [52]	24	120,000
Cefepime [52]	13	50,000
Imipenem [52]	3.30	8,000
Meropenem [52]	5.15	64,000
Vancomycin [53]	>696	NA

Pea e Viale. Critical Care 2009;13:214

Vancomicina in infusione continua
Compatibilità con altri farmaci

Compatible: aminoglycosides, ciprofloxacin/levofloxacin, clarithromycin, clindamycin, fluconazole, meropenem, metronidazole, penicillin G and rifampin (insulin, morphine)

Inconclusive findings: Aztreonam, cephalosporins, imipenem and piperacillin

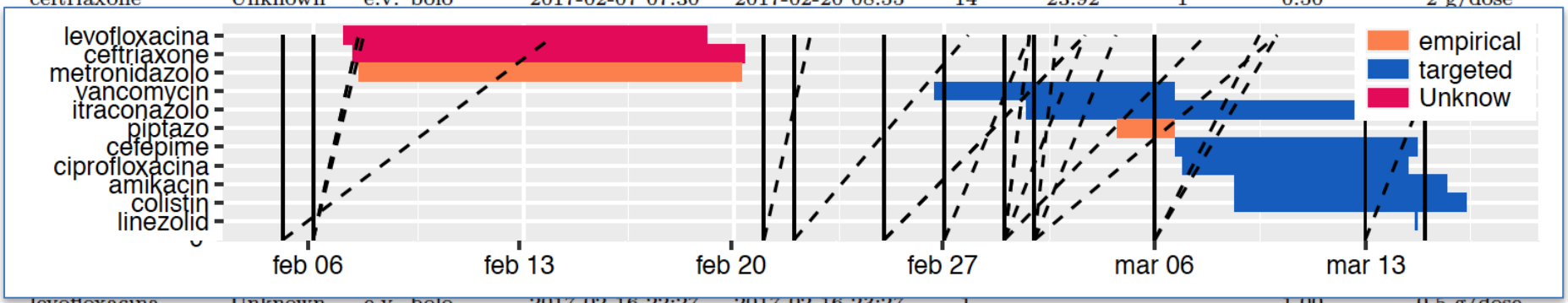
Incompatible: amphotericin B, trimethoprim–sulfamethoxazole, moxifloxacin, piperacillin-tazobactam, imipenem, ceftazidime (furosemide, methylprednisone)

Waineo et al. Journal of Clinical Pharmacy and Therapeutics, 2015, 40, 259–265

Paziente 3992

Farmaco	Dose di carico	Dose di mantenimento	Note
	20-25 mg/kg	10-15 mg/kg q 24 h	CVVHD, per flussi di dializzato di 1-4 L/h
Vancomicina	20-25 mg/kg	500 mg q 12 h	CVVH, per flussi di dializzato di 1-4 L/h
		1000-2000 mg q 24 h	CVVH

Principio Attivo	Terapia	Via Somm	Data Inizio	Date Fine	NTot	TTra (h)	NDay	Durata (h)	Dose
amikacin	Targeted	e.v. bolo	2017-03-08 15:26	2017-03-08 16:26	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-10 16:17	2017-03-10 17:17	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-12 15:43	2017-03-12 16:43	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-15 16:02	2017-03-15 17:02	1			1.00	0.25 g/dose
cefepime	Targeted	inf. continua	2017-03-06 16:32	2017-03-14 11:09	1			186.62	4.03 g/day
cefepime	Targeted	inf. continua	2017-03-14 11:09	2017-03-14 17:14	1			6.08	2.11 g/day
ceftriaxone	Unknown	e.v. bolo	2017-02-07 07:30	2017-02-20 08:55	14	23.92	1	0.50	2 g/dose



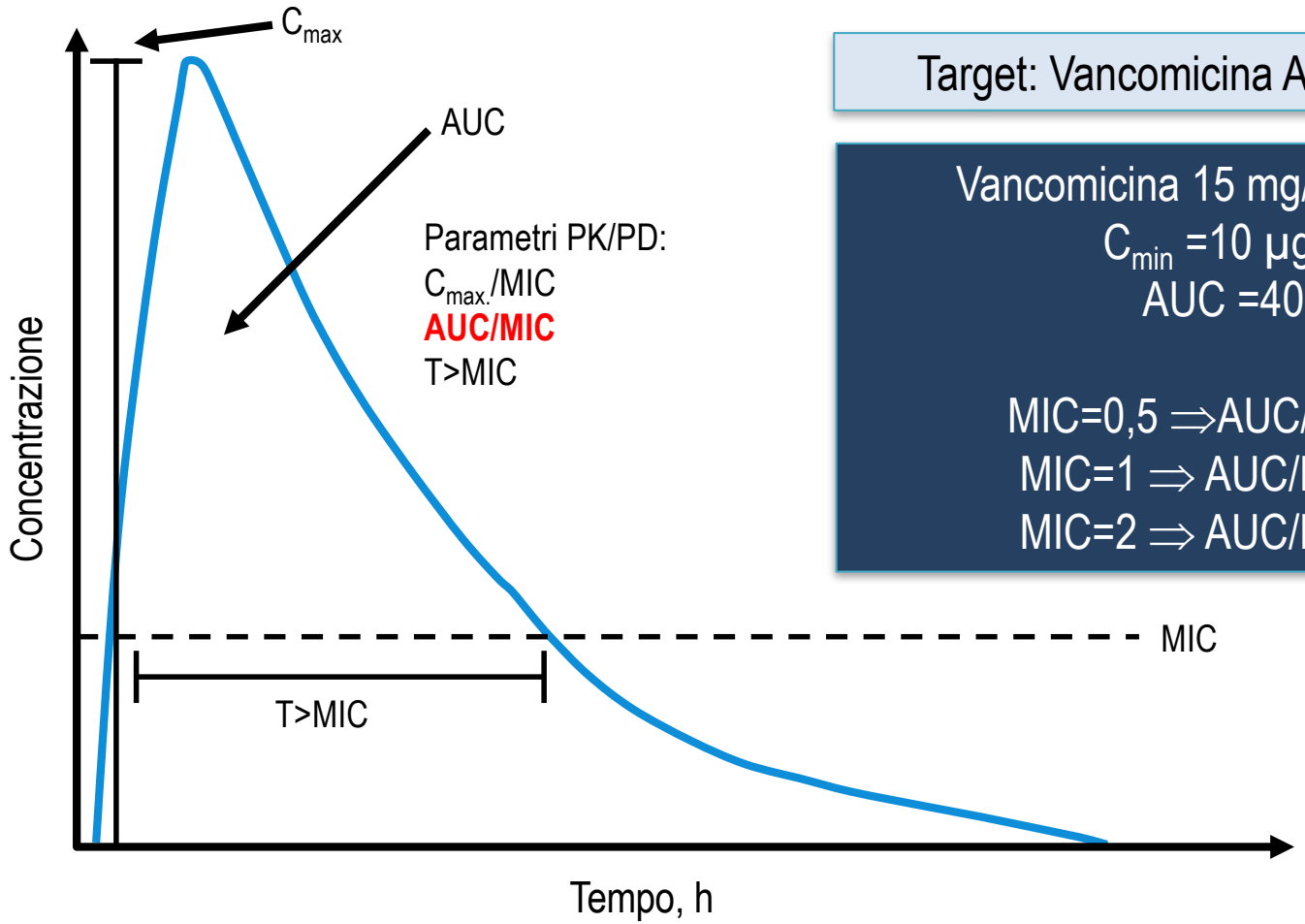
levofloxacina	Unknown	e.v. bolo	2017-02-16 22:27	2017-02-16 23:27	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-19 01:05	2017-02-19 02:05	1			1.00	0.5 g/dose
linezolid	Targeted	e.v. bolo	2017-03-14 16:15	2017-03-14 17:15	1			1.00	0.6 g/dose
metronidazolo	Empirical	e.v. bolo	2017-02-07 12:27	2017-02-20 05:58	52	6.02	4	0.50	0.5 g/dose
piptazo	Empirical	e.v. bolo	2017-03-04 18:17	2017-03-04 19:17	1			1.00	4.5 g/dose
piptazo	Empirical	inf. continua	2017-03-04 19:51	2017-03-06 15:45	1			43.90	9.07 g/day
vancomycin	Targeted	e.v. bolo	2017-02-26 16:01	2017-02-26 17:01	1			1.00	1 g/dose
vancomycin	Targeted	inf. continua	2017-02-26 17:02	2017-02-27 11:40	1			18.63	2 g/day
vancomycin	Targeted	inf. continua	2017-02-27 11:45	2017-03-02 12:45	1			73.00	1.44 g/day
vancomycin	Targeted	inf. continua	2017-03-02 12:45	2017-03-03 16:45	1			28.00	1.15 g/day
vancomycin	Targeted	inf. continua	2017-03-03 17:22	2017-03-04 11:28	1			18.10	0.8 g/day
vancomycin	Targeted	inf. continua	2017-03-04 11:28	2017-03-04 17:58	1			6.50	0.61 g/day
vancomycin	Targeted	inf. continua	2017-03-04 17:58	2017-03-06 15:45	1			45.78	0.38 g/day

Disponibilità TDM

- Immunometria:
  - Vancomicina
  - Amikacina
  - Gentamicina
  - Teicoplanina

  } Controllo concentrazioni plasmatiche
  Aggiustamento posologia
- HPLC/LC-MS:
  - Meropenem
  - Piperacillina/tazobactam
  - …

PK/PD di vancomicina e regime posologico



Target: Vancomicina AUC/MIC >350

Vancomicina 15 mg/kg q12h i.v.
C_{min} =10 µg/ml
AUC =400

MIC=0,5 ⇒AUC/MIC 800
MIC=1 ⇒ AUC/MIC 400
MIC=2 ⇒ AUC/MIC 200

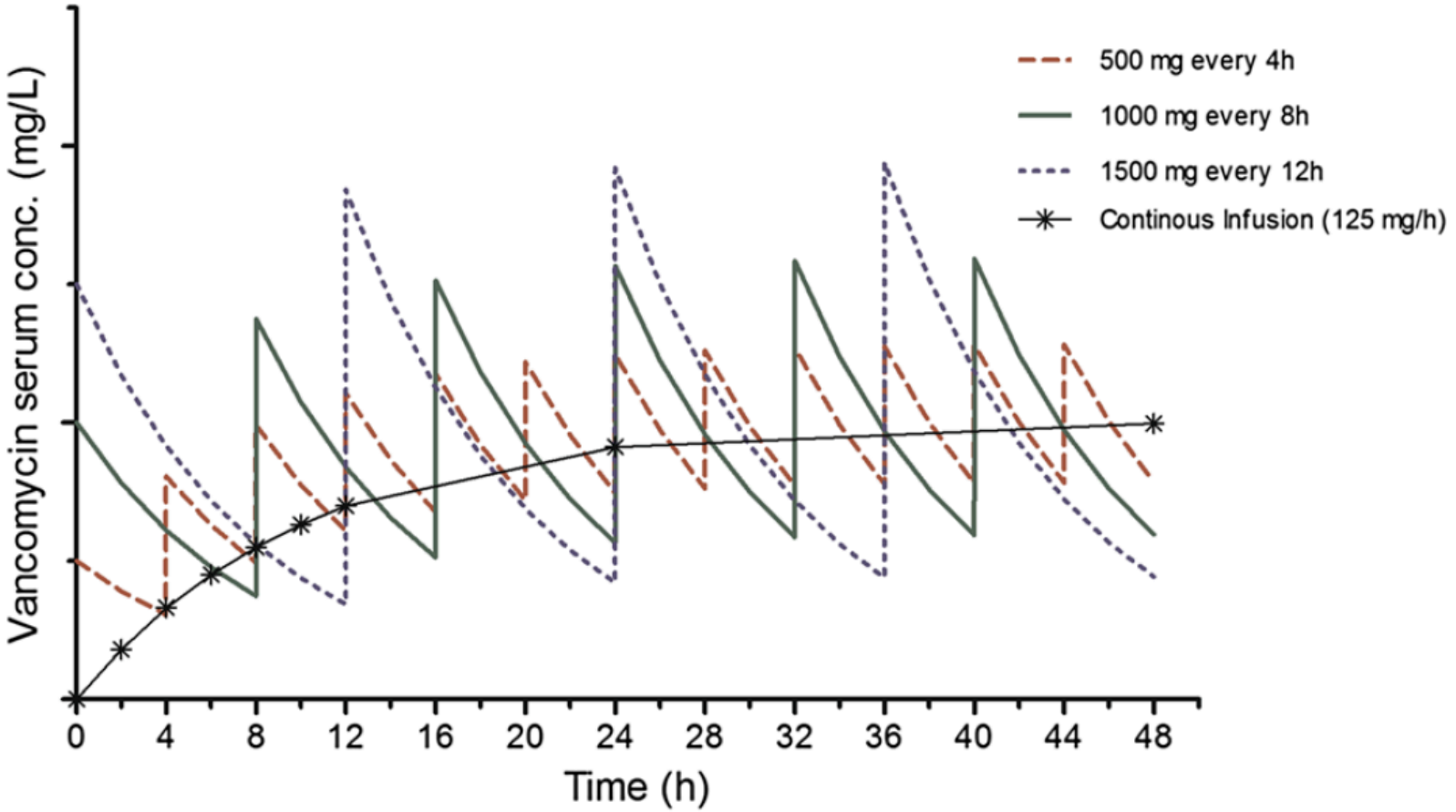
Scaglione et al. Expert Rev Anti Infect Ther 2006; 4: 479

Vancomycin Dosing and Monitoring: Critical Evaluation of the Current Practice

Fawzy Elbarbry[1]

Eur J Drug Metab Pharmacokinet
https://doi.org/10.1007/s13318-017-0456-4

The observation that trough concentrations above 20 mg/L achieved with intermittent infusion are associated with higher risk of nephrotoxicity compared to steady-state concentrations between 20 and 30 mg/L achieved with continuous infusion



The pharmacokinetic/pharmacodynamic rationale for administering vancomycin via continuous infusion

Journal of Clinical Pharmacy and Therapeutics, 2015, **40**, 259–265

M. F. Waineo BS, T. C. Kuhn BS and D. L. Brown PharmD

AUC target = 400 hxmg/L

Nephrotoxic AUC = 700 hxmg/L (C_{ss} >28 mg/L)

MIC ≤ 1 mg/L

Loading dose 15–20 mg/kg

Target C_{ss}[b] (mg/L)	Target AUC_{24} (mg•h/L)	Daily dose[c] (mg/day)	Hourly Dosing Rate[c] (mg/h)	C_{min} (mg/L)
27·5	660	27•CrCl + 140	1·1•CrCl + 6	**15-20**
25	600	25•CrCl + 130	1·0•CrCl + 5·5	
22·5	540	22•CrCl + 120	0·92•CrCl + 5	**10-15**
20	480	20•CrCl + 110	0·83•CrCl + 4·5	
17·5	420	17•CrCl + 100	0·71•CrCl + 4	

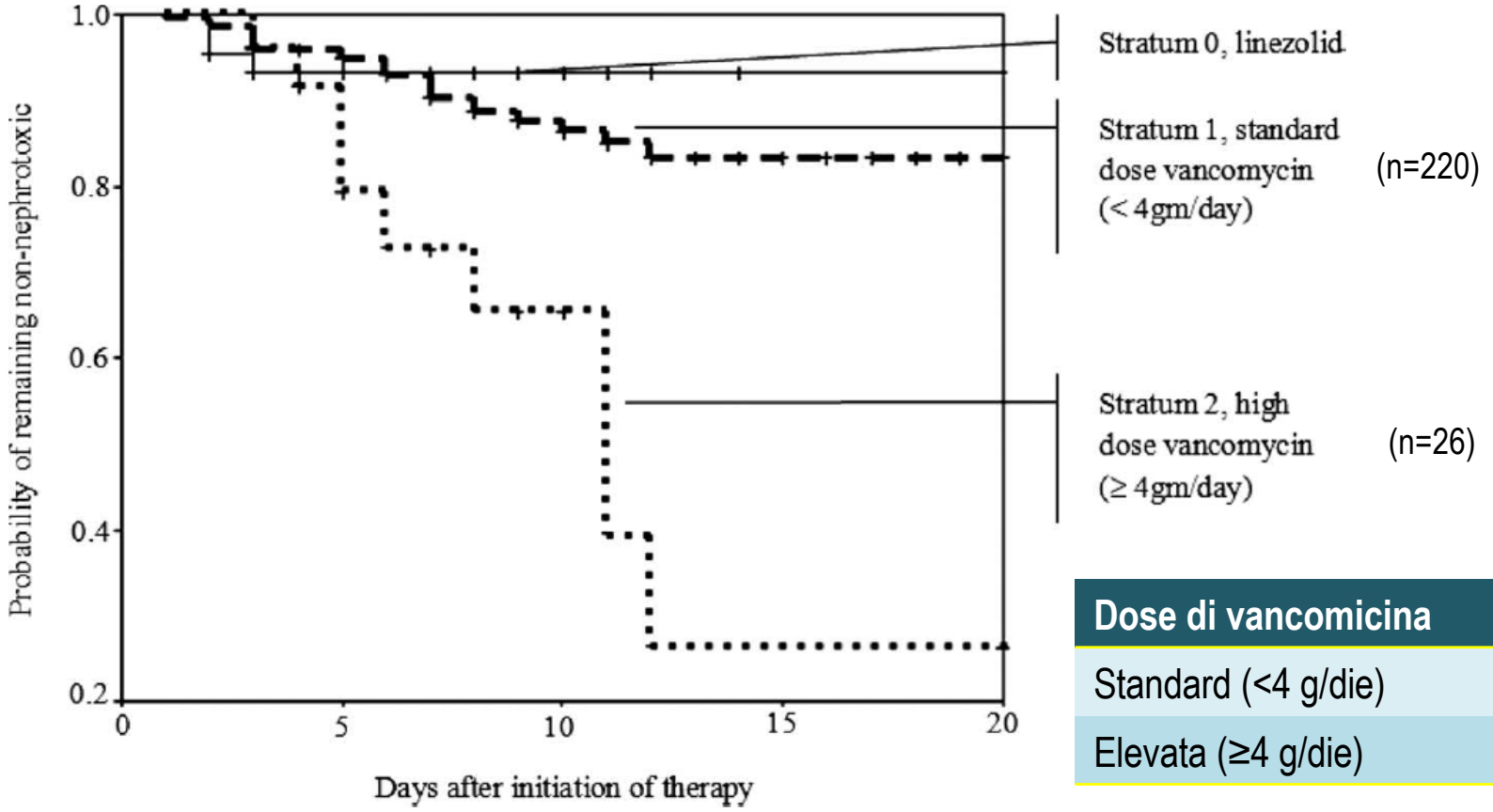
30 mg/kg/die*

*Pea e Viale. Clin Pharmacokinet, 2008;47:147–152.

Alte dosi di vancomicina e rischio di nefrotossicità

Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity▽

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1330–1336



Dose di vancomicina	C_{min}, µg/ml
Standard (<4 g/die)	9
Elevata (≥4 g/die)	18

*Nefrotossicità: aumento della creatininemia ≥0,5 mg/dl

J Antimicrob Chemother 2018; **73**: 199–203
doi:10.1093/jac/dkx356 Advance Access publication 11 October 2017

Journal of Antimicrobial Chemotherapy

Prospective evaluation of a continuous infusion vancomycin dosing nomogram in critically ill patients undergoing continuous venovenous haemofiltration

Jonathan H. Sin[1]*, Kelly Newman[1], Ramy H. Elshaboury[1], D. Dante Yeh[2], Marc A. de Moya[2] and Hsin Lin[1]

$$CL_{vanc}(L/h) = [CVVH\ intensity\ (mL/kg/h) - 0.392] \div 8.368$$

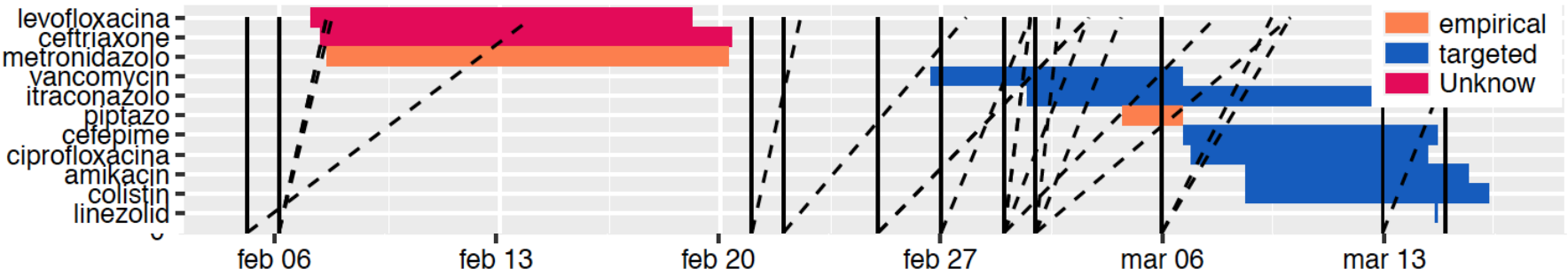
$$\text{Dosage via continuous infusion}\,(mg/24\,h) = CL_{vanc}\,(L/h) \times 20\,(mg/L) \times 24(h), \text{where } 20\,mg/L \text{ is the desired concentration}$$

$$AUC_{24} = \text{serum concentration at steady-state}\ (mg/L) \times 24\ (h)$$

Continuous Infusion Dosing Nomogram	
CVVH intensity (mL/kg/h)	Dose infused over 24 h (mg)
10–15	1000
15.1–20	1250
20.1–25	1500
25.1–30	1750
>30	2000

Concentration at 24 h ($n = 52$)	
15–25 mg/L (therapeutic)	43 (82.7%)
>25 mg/L (supratherapeutic)	7 (13.5%)
<15 mg/L (subtherapeutic)	2 (3.8%)
Concentration at 48 h ($n = 33$)	
15–25 mg/L (therapeutic)	27 (81.8%)
>25 mg/L (supratherapeutic)	4 (12.1%)
<15 mg/L (subtherapeutic)	2 (6.1%)
Concentration at 72 h ($n = 24$)	
15–25 mg/L (therapeutic)	18 (75%)
>25 mg/L (supratherapeutic)	4 (16.7%)
<15 mg/L (subtherapeutic)	2 (8.3%)

Paziente 3992



Antibiogrammi del 2017-03-06

Antibiotico	Broncolavaggio Klebsiella pneumoniae	Urinocoltura Catetere Vescicale Klebsiella pneumoniae	Broncolavaggio Pseudomonas aeruginosa
Amikacina	S (<=2)	S (4)	S (4)
Amoxicillina/A.CLAV.	R (>=32)	R (>=32)	R (>=32)
Cefepime	R (>=64)	R (32)	S (2)
Cefotaxime	R (>=64)	R (>=64)	R (>=64)
Ceftazidime	R (>=64)	R (>=64)	S (4)
Ciprofloxacina	R (>=4)	R (>=4)	S (<=0,25)
Colistina	S (<=0,5)	S (<=0,5)	S (<=0,5)
Ertapenem	R (>=8)	R (>=8)	R (4)
Fosfomicina		S (<=16)	
Gentamicina	S (<=1)	S (<=1)	S (4)
Imipenem	R (>=16)	R (>=16)	S (2)
Meropenem	R (>=16)	R (>=16)	S (0,5)
Piperacillina/tazobactam	R (>=128)	R (>=128)	S (<=4)
Trimetoprim/Sulfam.	R (>=320)	R (>=320)	R (80)

Therapeutic drug monitoring of amikacin in septic patients

- 63 critically ill patients who required AMK administration for the treatment of severe infection (severe sepsis or septic shock)
- **Loading dose (LD)**:
  - MIC ≤ 4 mg/L ➔ LD = 18-24 mg/kg
  - MIC = 4-16 mg/L ➔LD = 25-30 mg/kg
- **Daily maintenance dose** adapted using TDM: **C_{max}/MIC > 8**, **C_{min} < 5 mg/L**

15 mg/kg
11,2 ± 1,8
2,4 ± 0,5
6,8 ± 0,6
155 ± 30

Volontari sani

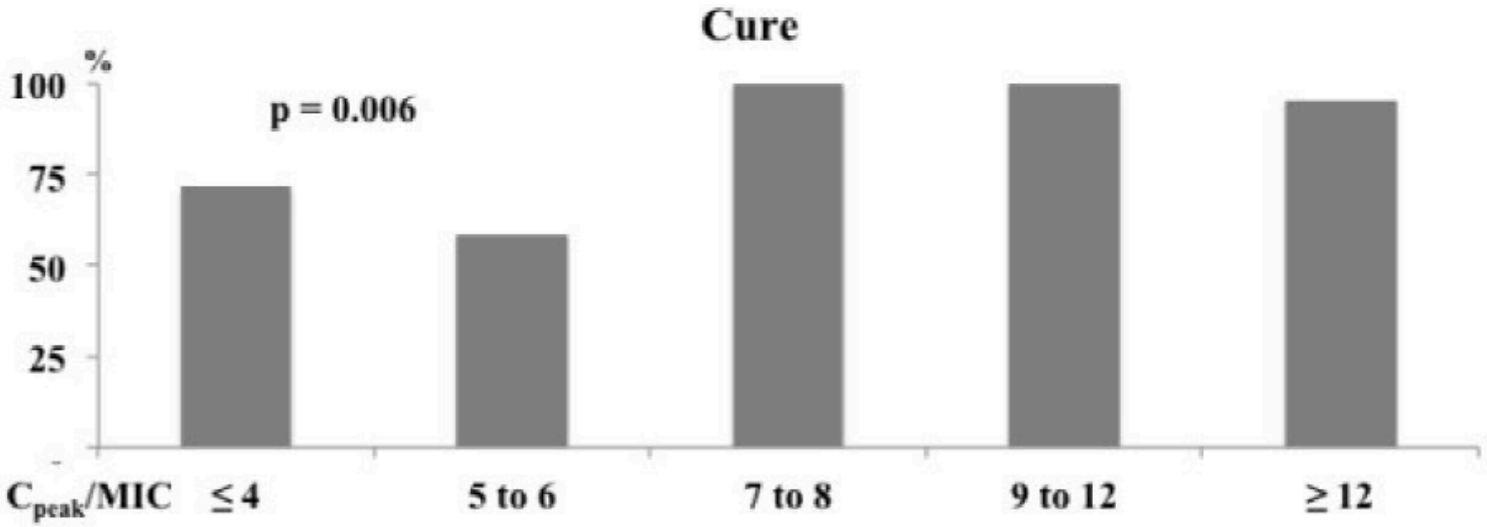
Parameter	CrCl ≥50 mL/min (*n* = 46)	CrCl <50 mL/min (*n* = 17)
Vd (L)	25.7 (8.5-49.3)	38.8 (8.4-46.7)
Vd (L/kg)	0.40 (0.12-1.03)	0.66 (0.2-0.8)*
$t_{1/2}$ (h)	4.9 (0.8-11.0)	7.8 (3.2-19.1)*
CL (mL/min)	3.4 (1.5-25.8)	3.3 (0.6-9.9)
AUC_{0-24} (mg*h/L)	361 (58-1045)	507 (153-1867)

Garraffo et al. Antimicrob Agents Chemother 1990;34:614-21

Duszynska et al. Critical Care 2013, 17:R165

Amikacina, sepsi e PK/PD

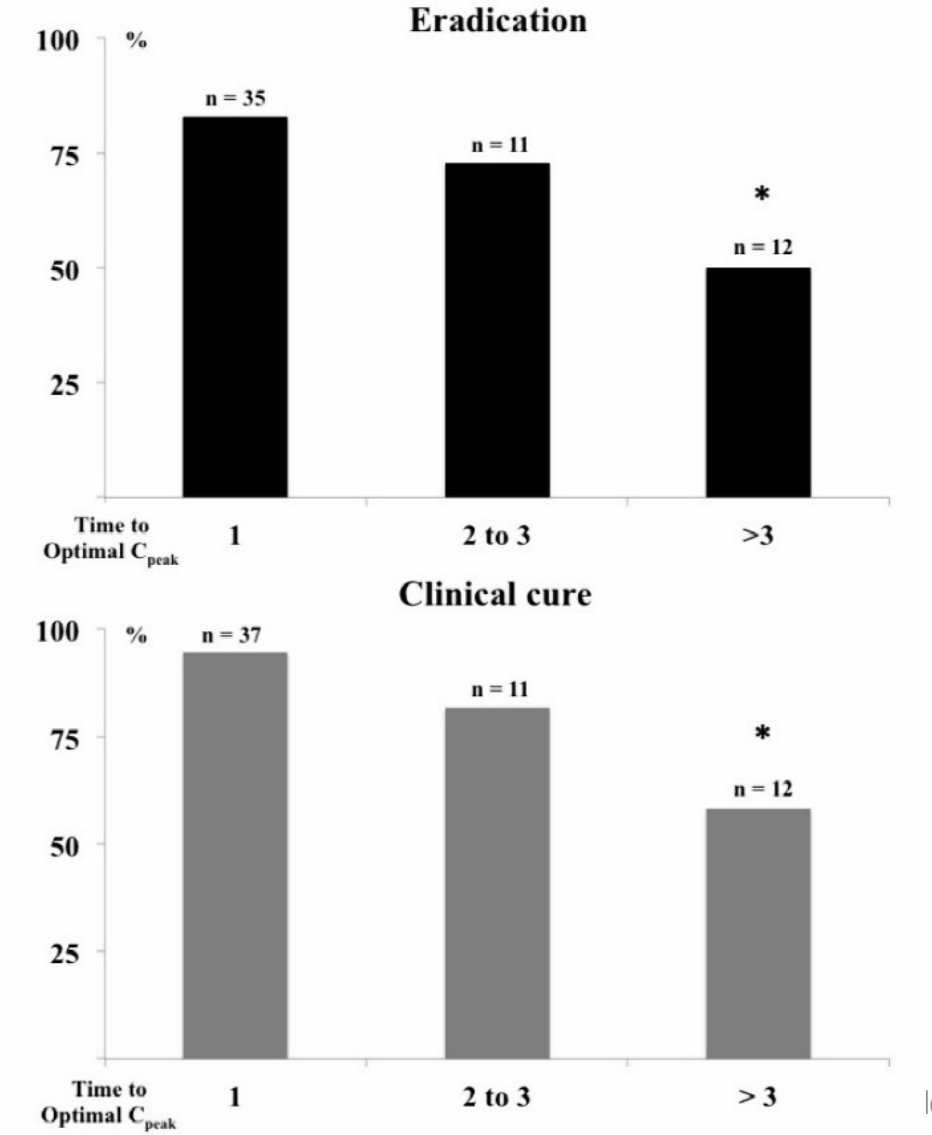
		Dose administration				
		24 hrs	36 hrs	48 hrs	72 hrs	
Dose management	Increased	14	2	4	3	23
	Unchanged	11	3	2	-	16
	Decreased	15	2	4	3	24
		40	7	10	6	63



Duszynska et al. Critical Care 2013, 17:R165

Amikacina, sepsi e PK/PD

Tempo al raggiungimento del C_{max}/MIC



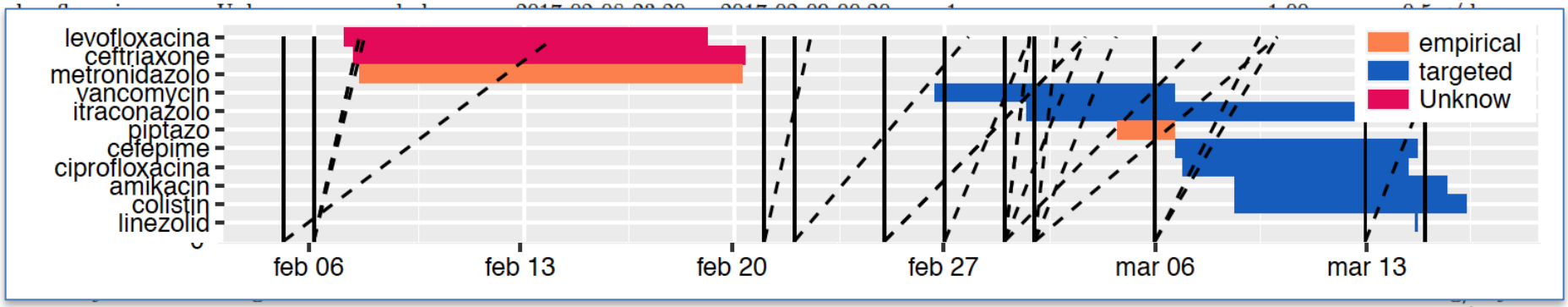
TDM resulted in adjustment of AMK therapy in most of our septic patients.

Early achievement of an optimal C_{peak}/MIC ratio may have an impact on clinical and microbiological responses, but not on outcome.

Duszynska et al. Critical Care 2013, 17:R165

Paziente 3992

Principio Attivo	Terapia	Via Somm	Data Inizio	Date Fine	NTot	TTra (h)	NDay	Durata (h)	Dose
amikacin	Targeted	e.v. bolo	2017-03-08 15:26	2017-03-08 16:26	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-10 16:17	2017-03-10 17:17	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-12 15:43	2017-03-12 16:43	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-15 16:02	2017-03-15 17:02	1			1.00	0.25 g/dose
cefepime	Targeted	inf. continua	2017-03-06 16:32	2017-03-14 11:09	1			186.62	4.03 g/day
cefepime	Targeted	inf. continua	2017-03-14 11:09	2017-03-14 17:14	1			6.08	2.11 g/day
ceftriaxone	Unknown	e.v. bolo	2017-02-07 07:30	2017-02-20 08:55	14	23.92	1	0.50	2 g/dose
ciprofloxacina	Targeted	e.v. bolo	2017-03-06 22:05	2017-03-11 21:19	11	11.92	2	0.00	0.4 g/dose
ciprofloxacina	Targeted	e.v. bolo	2017-03-12 10:22	2017-03-14 10:23	5	11.94	2	0.00	0.4 g/dose
colistin	Targeted	inalatoria	2017-03-08 15:27	2017-03-16 07:44	24	7.90	3		1e+06 UI/dose
colistin	Targeted	e.v. bolo	2017-03-08 19:10	2017-03-09 08:23	2	12.22	2	1.00	1e+06 UI/dose
colistin	Targeted	e.v. bolo	2017-03-09 20:15	2017-03-16 08:41	13	12.24	2	1.00	1e+07 UI/dose
itraconazolo	Targeted	SNG	2017-03-01 17:46	2017-03-16 06:27	30	11.97	2	0.00	0.2 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-06 23:59	2017-02-08 00:08	2	23.15	1	1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-08 22:59	2017-02-08 23:59	1			1.00	0.25 g/dose



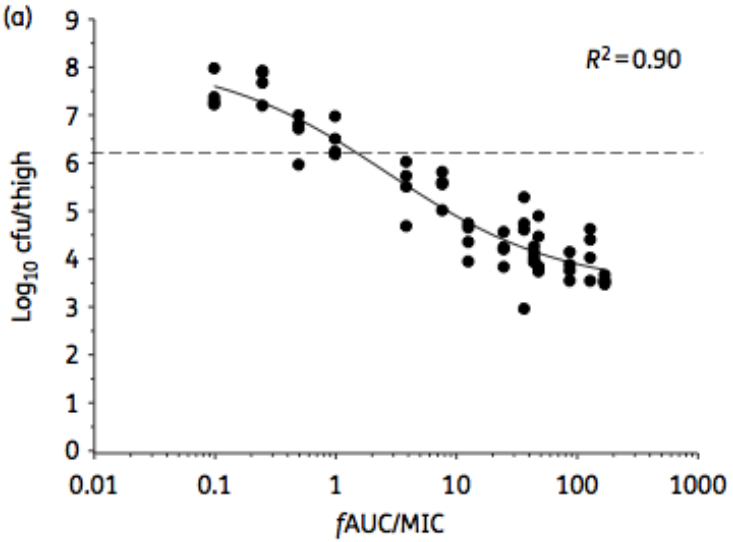
vancomycin	Targeted	inf. continua	2017-03-02 12:45	2017-03-03 16:45	1			28.00	1.15 g/day
vancomycin	Targeted	inf. continua	2017-03-03 17:22	2017-03-04 11:28	1			18.10	0.8 g/day
vancomycin	Targeted	inf. continua	2017-03-04 11:28	2017-03-04 17:58	1			6.50	0.61 g/day
vancomycin	Targeted	inf. continua	2017-03-04 17:58	2017-03-06 15:45	1			45.78	0.38 g/day

J Antimicrob Chemother 2010; **65**: 1984–1990
doi:10.1093/jac/dkq226 Advance Access publication 23 June 2010

Journal of Antimicrobial Chemotherapy

*f*AUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against *Acinetobacter baumannii* in murine thigh and lung infection models

Rajesh V. Dudhani[1], John D. Turnidge[2,3], Roger L. Nation[1]† and Jian Li[1]*†



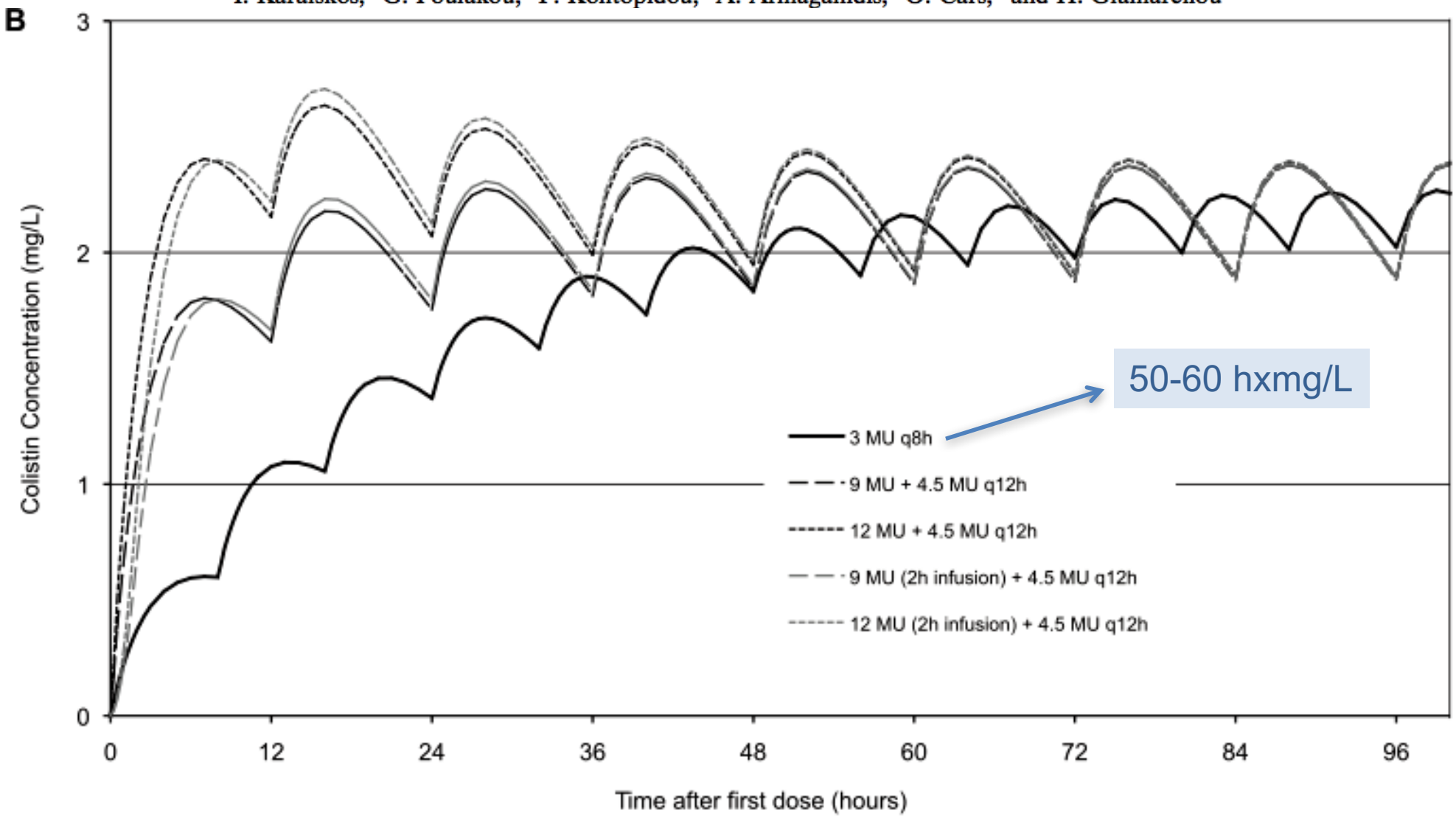
	*f*AUC/MIC		
Kill effect	ATCC 19606	248-01-C.248[a]	N-16870.213[a]
Thigh infection model			
Static effect	1.89	6.75	7.41
1 $\log_{10}$ kill	6.98	13.6	11.9
2 $\log_{10}$ kill	43.0	24.7	17.5
Lung infection model			
Static effect	1.57	6.08	6.52
1 $\log_{10}$ kill	8.18	12.9	42.1
2 $\log_{10}$ kill	95.0	22.5	[b]

P. aeruginosa: fAUC/MIC for bacteriostasis = 16-23
fAUC/MIC for 2 log reduction = 37-46

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3430–3436 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.01361-08

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria▽†

D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]



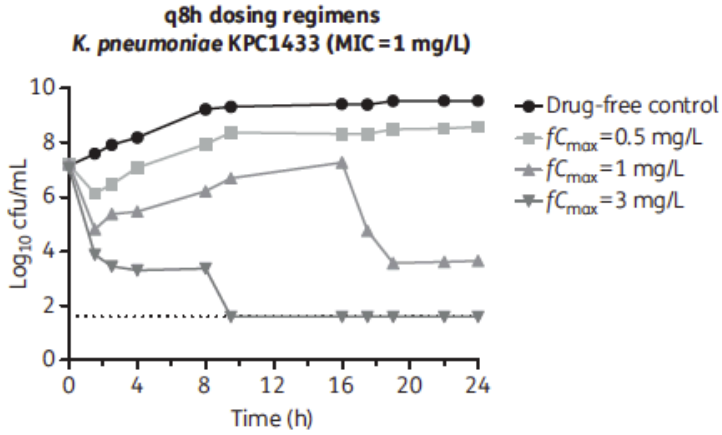
J Antimicrob Chemother 2018; **73**: 953–961
doi:10.1093/jac/dkx522 Advance Access publication 25 January 2018

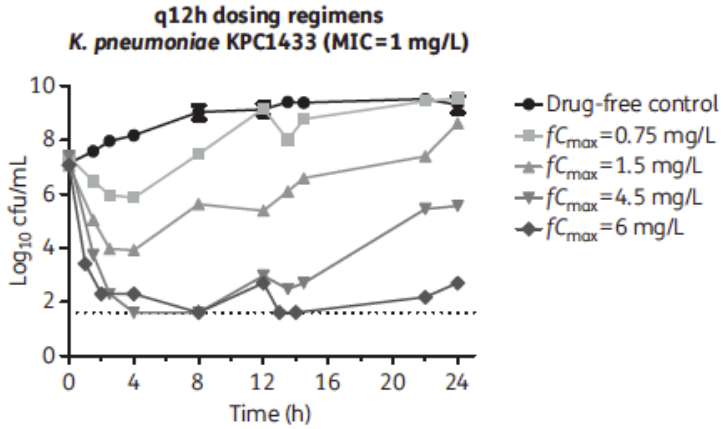
Journal of Antimicrobial Chemotherapy

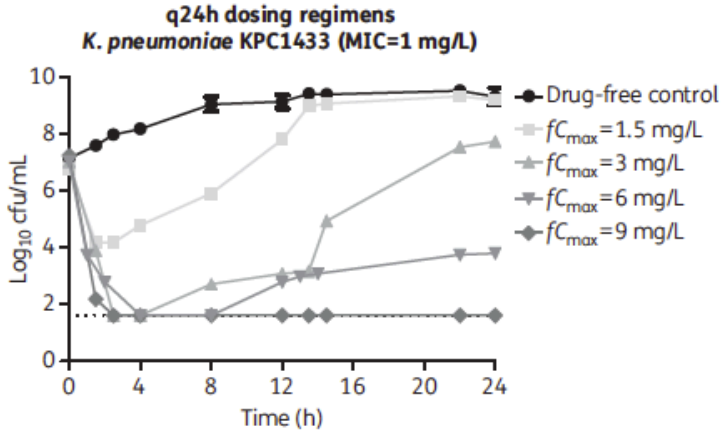
Exploring colistin pharmacodynamics against *Klebsiella pneumoniae*: a need to revise current susceptibility breakpoints

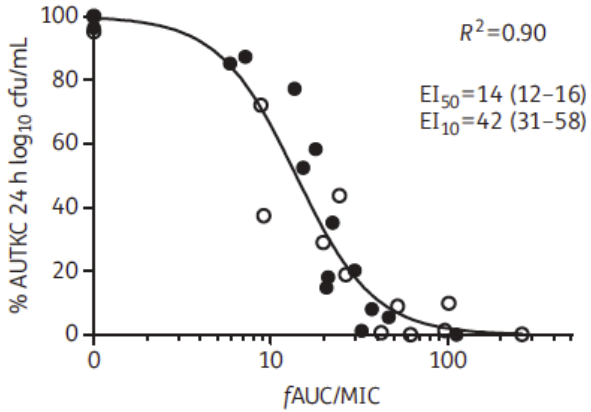
Marilena Tsala[1], Sophia Vourli[1], Panagiota-Christina Georgiou[1], Spyros Pournaras[1,2], Athanasios Tsakris[2], George L. Daikos[3], Johan W. Mouton[4] and Joseph Meletiadis[1,4]*

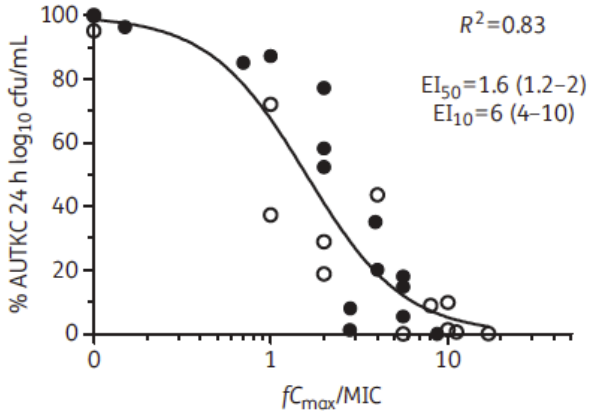
Tsala et al. JAC 2018;73:953-61

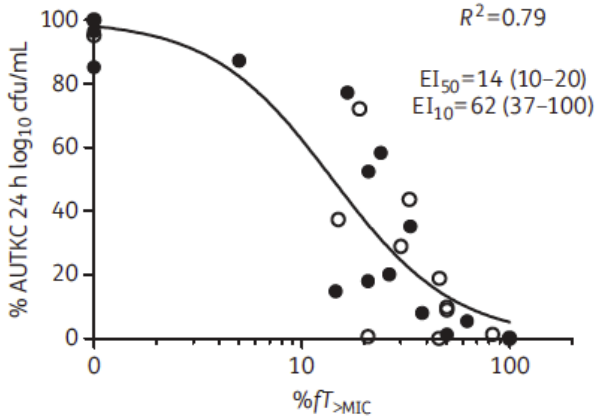












● KPC1433 (MIC=1 mg/L)

J Antimicrob Chemother 2018; **73**: 953–961
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Journal of Antimicrobial Chemotherapy

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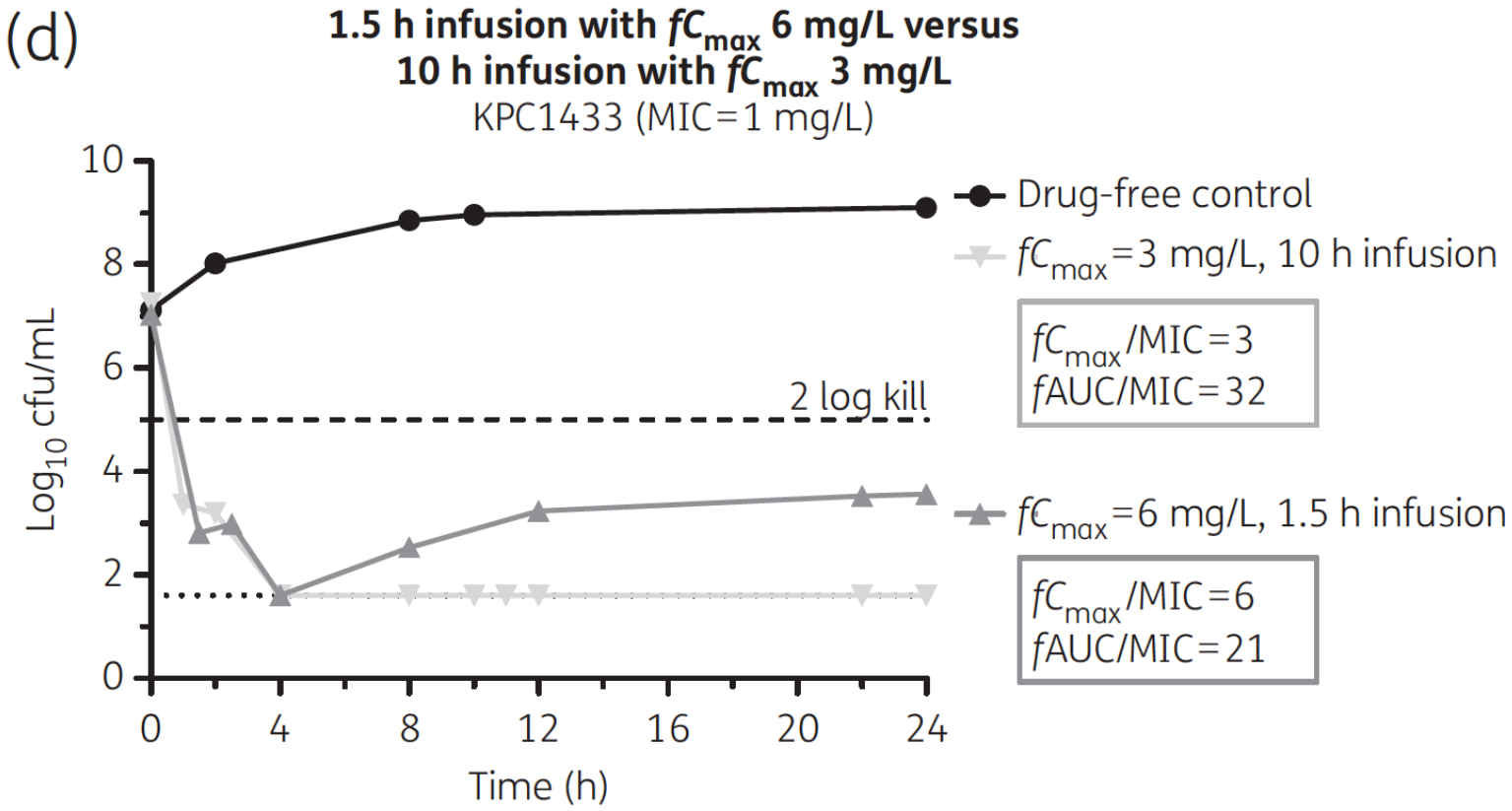

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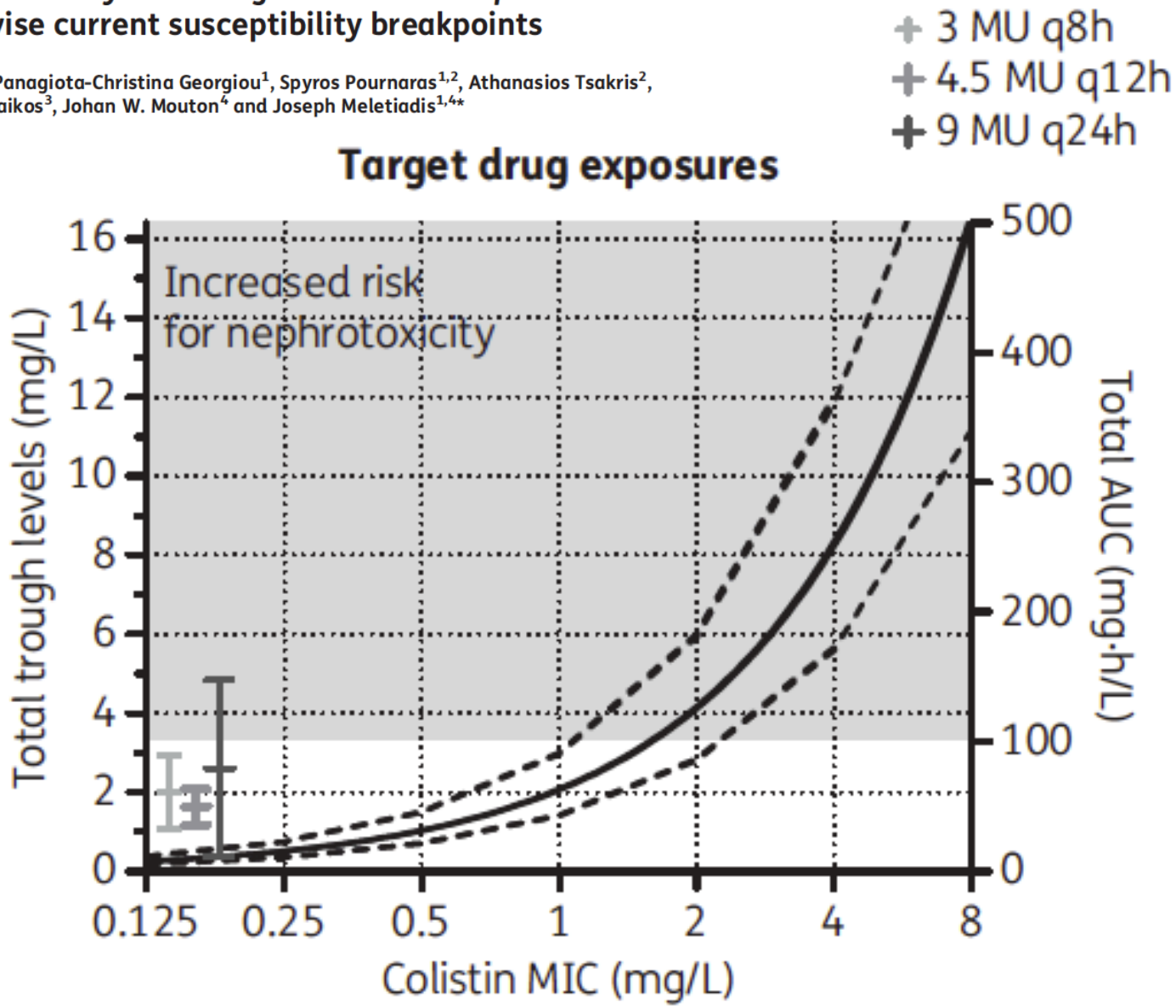

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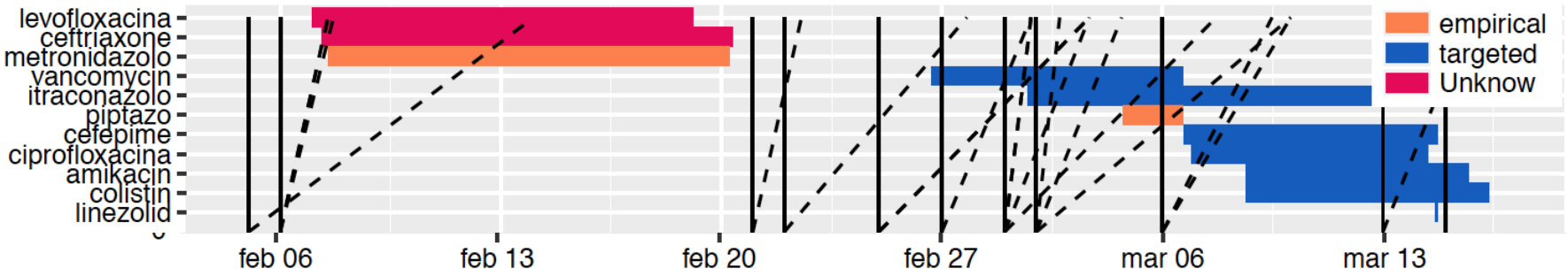
The trough levels required to attain a 2 log kill effect for isolates with increasing MICs are shown in Figure 7. In order to attain the PK/PD target fAUC/MIC>25, the estimated target trough/MIC ratio was 2, indicating that isolates with an MIC up to 1 mg/L could be covered with a non-toxic dosing regimen (trough levels <3.33 mg/L).[12] This could just be achieved with 3 MU q8h and 4.5 MU q12h. However, 1 mg/L is below the breakpoint of 2 mg/L and colistin therapy is therefore marginal at best. Most patients treated with 9 MU q24h could achieve those levels but the large interindividual variation and the fact that one-quarter of the patients would have toxic trough levels indicates the necessity for therapeutic drug monitoring (TDM).

Paziente 3992



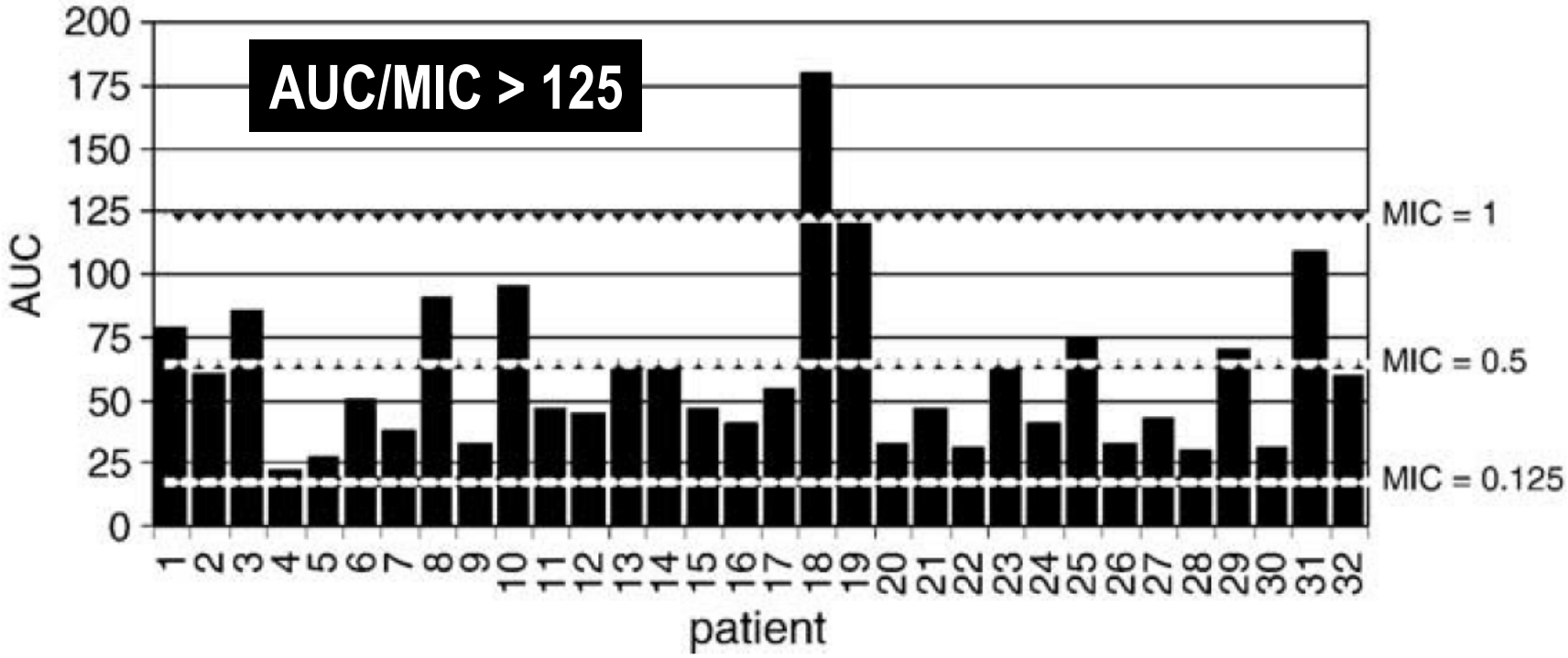
Antibiotico	Broncolavaggio Klebsiella pneumoniae	Urinocoltura Catetere Vescicale Klebsiella pneumoniae	Broncolavaggio Pseudomonas aeruginosa
Amikacina	S (<=2)	S (4)	S (4)
Amoxicillina/A.CLAV.	R (>=32)	R (>=32)	R (>=32)
Cefepime	R (>=64)	R (32)	S (2)
Cefotaxime	R (>=64)	R (>=64)	R (>=64)
Ceftazidime	R (>=64)	R (>=64)	S (4)
Ciprofloxacina	R (>=4)	R (>=4)	S (<=0,25)
Colistina	S (<=0,5)	S (<=0,5)	S (<=0,5)
Ertapenem	R (>=8)	R (>=8)	R (4)
Fosfomicina		S (<=16)	
Gentamicina	S (<=1)	S (<=1)	S (4)
Imipenem	R (>=16)	R (>=16)	S (2)
Meropenem	R (>=16)	R (>=16)	S (0,5)
Piperacillina/tazobactam	R (>=128)	R (>=128)	S (<=4)
Trimetoprim/Sulfam.	R (>=320)	R (>=320)	R (80)

Paziente 3992

Principio Attivo	Terapia	Via Somm	Data Inizio	Date Fine	NTot	TTra (h)	NDay	Durata (h)	Dose
amikacin	Targeted	e.v. bolo	2017-03-08 15:26	2017-03-08 16:26	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-10 16:17	2017-03-10 17:17	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-12 15:43	2017-03-12 16:43	1			1.00	0.75 g/dose
amikacin	Targeted	e.v. bolo	2017-03-15 16:02	2017-03-15 17:02	1			1.00	0.25 g/dose
cefepime	Targeted	inf. continua	2017-03-06 16:32	2017-03-14 11:09	1			186.62	4.03 g/day
cefepime	Targeted	inf. continua	2017-03-14 11:09	2017-03-14 17:14	1			6.08	2.11 g/day
ceftriaxone	Unknown	e.v. bolo	2017-02-07 07:30	2017-02-20 08:55	14	23.92	1	0.50	2 g/dose
ciprofloxacina	Targeted	e.v. bolo	2017-03-06 22:05	2017-03-11 21:19	11	11.92	2	0.00	0.4 g/dose
ciprofloxacina	Targeted	e.v. bolo	2017-03-12 10:22	2017-03-14 10:23	5	11.94	2	0.00	0.4 g/dose
colistin	Targeted	inalatoria	2017-03-08 15:27	2017-03-16 07:44	24	7.90	3		1e+06 UI/dose
colistin	Targeted	e.v. bolo	2017-03-08 19:10	2017-03-09 08:23	2	12.22	2	1.00	1e+06 UI/dose
colistin	Targeted	e.v. bolo	2017-03-09 20:15	2017-03-16 08:41	13	12.24	2	1.00	1e+07 UI/dose
itraconazolo	Targeted	SNG	2017-03-01 17:46	2017-03-16 06:27	30	11.97	2	0.00	0.2 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-06 23:59	2017-02-08 00:08	2	23.15	1	1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-08 22:59	2017-02-08 23:59	1			1.00	0.25 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-08 23:20	2017-02-09 00:20	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-11 00:07	2017-02-11 01:07	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-13 00:04	2017-02-13 01:04	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-14 23:07	2017-02-15 00:07	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-16 22:27	2017-02-16 23:27	1			1.00	0.5 g/dose
levofloxacina	Unknown	e.v. bolo	2017-02-19 01:05	2017-02-19 02:05	1			1.00	0.5 g/dose
linezolid	Targeted	e.v. bolo	2017-03-14 16:15	2017-03-14 17:15	1			1.00	0.6 g/dose
metronidazolo	Empirical	e.v. bolo	2017-02-07 12:27	2017-02-20 05:58	52	6.02	4	0.50	0.5 g/dose
piptazo	Empirical	e.v. bolo	2017-03-04 18:17	2017-03-04 19:17	1			1.00	4.5 g/dose
piptazo	Empirical	inf. continua	2017-03-04 19:51	2017-03-06 15:45	1			43.90	9.07 g/day
vancomycin	Targeted	e.v. bolo	2017-02-26 16:01	2017-02-26 17:01	1			1.00	1 g/dose
vancomycin	Targeted	inf. continua	2017-02-26 17:02	2017-02-27 11:40	1			18.63	2 g/day
vancomycin	Targeted	inf. continua	2017-02-27 11:45	2017-03-02 12:45	1			73.00	1.44 g/day
vancomycin	Targeted	inf. continua	2017-03-02 12:45	2017-03-03 16:45	1			28.00	1.15 g/day
vancomycin	Targeted	inf. continua	2017-03-03 17:22	2017-03-04 11:28	1			18.10	0.8 g/day
vancomycin	Targeted	inf. continua	2017-03-04 11:28	2017-03-04 17:58	1			6.50	0.61 g/day
vancomycin	Targeted	inf. continua	2017-03-04 17:58	2017-03-06 15:45	1			45.78	0.38 g/day

Ciprofloxacina, sepsi e PK/PD

Ciprofloxacin 400 mg bid IV leads to inadequate AUC/MIC and C_{max}/MIC ratios in many cases.
Effective killing concentrations were only achieved in pathogens with MIC less than 0.25.
As bacteria in intensive care unit patients often exceed this threshold, we recommend to use higher doses of ciprofloxacin (1200 mg daily) to ensure optimal bacterial killing and avoid antibiotic resistance.



Van Zanthen et al. J Critical Care 2008;23:422

Conclusioni

- L’appropriatezza della terapia antibatterica nel paziente settico permette il rapido raggiungimento di concentrazioni battericide e un miglior esito clinico, soprattutto se esiste la disponibilità di un servizio di TDM.
- Numerosi fattori possono influenzare la farmacocinetica degli antibatterici nel paziente settico.
- Per alcuni farmaci, la somministrazione in infusioni prolungate, compatibilmente con la stabilità in soluzione acquosa, sembra essere associata ad una maggiore efficacia.