

# **Farmacocinetica e farmacodinamica in corso di CRRT-CPFA**

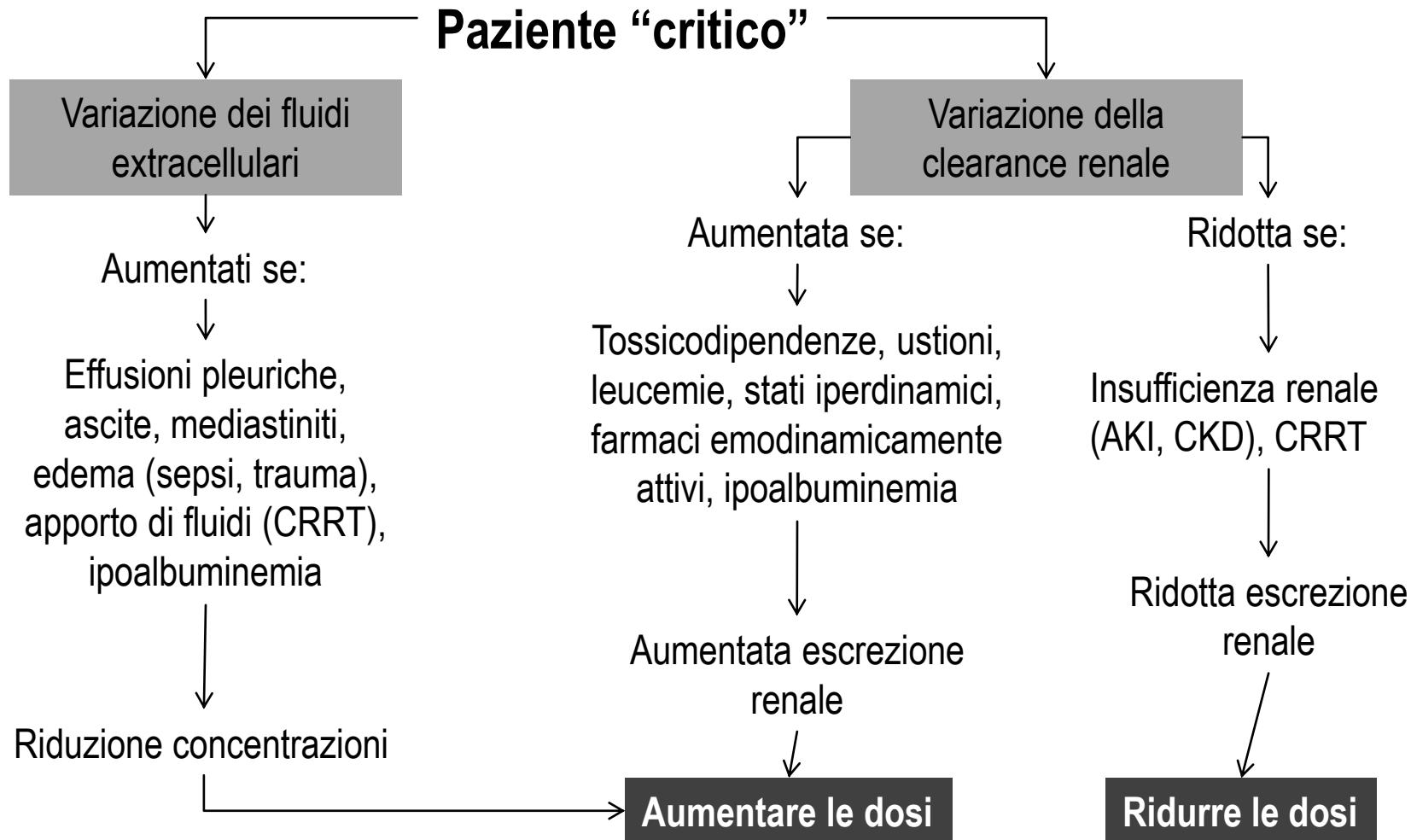
Antonello Di Paolo  
Pisa

Istituto Mario Negri, Ranica (BG)  
20 maggio 2014

# Strategie integrate in antibioticoterapia

Fattori	Area	Competenza
Tipo e gravità di malattia Condizioni cliniche del paziente (es., comorbidità)	Internistica Infettivologica Rianimatoria	Gestione clinica, farmacologica e di sostegno del paziente
Agente eziologico Fenotipo/genotipo di resistenza	Microbiologica Infettivologica	Esami culturali microbiologici Esami molecolari
Variabilità cinetica inter- e intra-individuale dei farmaci	Farmacologica Laboratoristica	Monitoraggio terapeutico dei farmaci Aggiustamento del dosaggio

# Variabilità PK degli antibiotici nel paziente critico



# Caratteristiche generali degli antimicobici

idrofili

**β-lattamici**  
**Glicopeptidi**  
**Aminoglicosidi**  
**Oxazolidinoni**

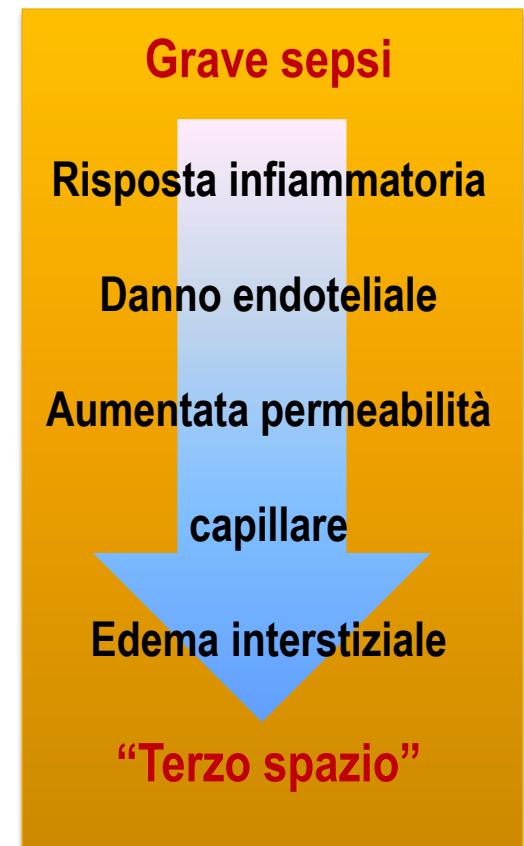
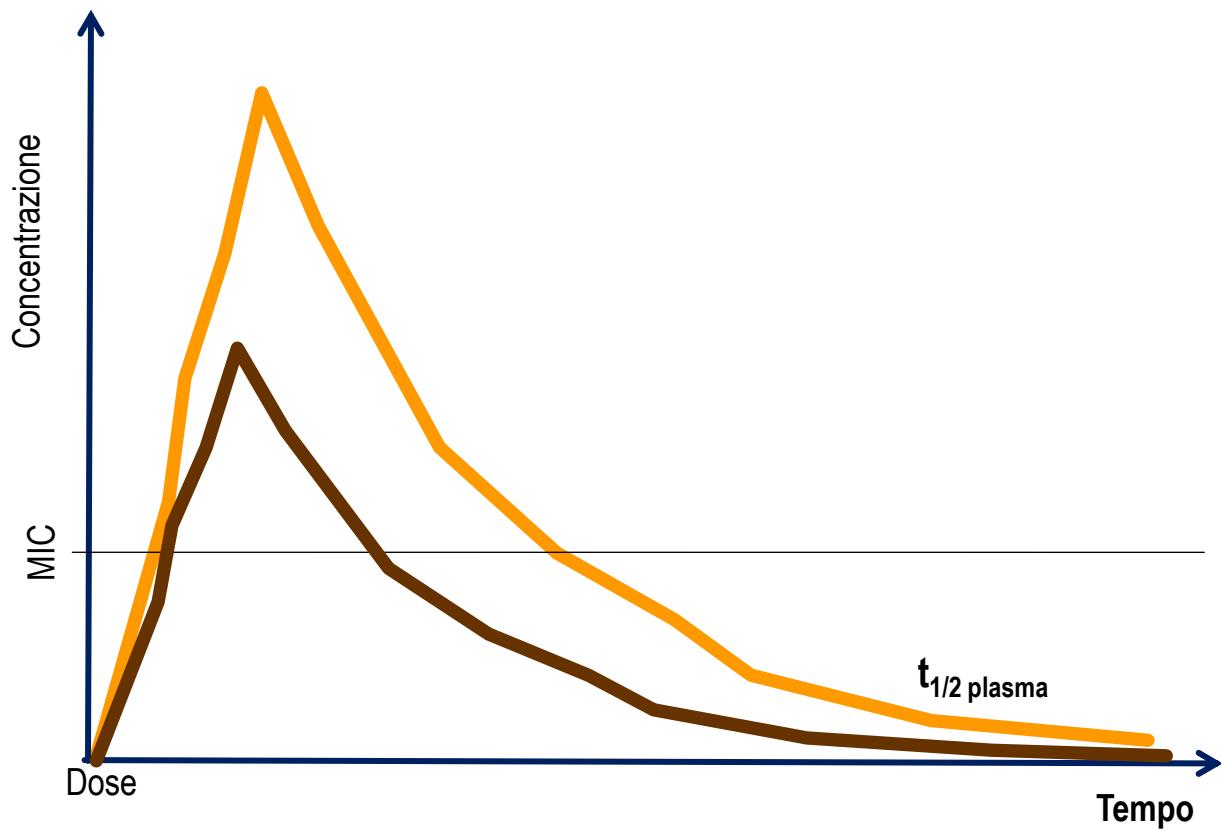
- Limitato volume di distribuzione
- Inefficaci contro patogeni intracellulari
- Prevalentemente eliminati immodificati dal rene

liposolubili

**Macrolidi**  
**Fluorochinoloni**  
**Tetracicline**  
**Rifampicina**

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

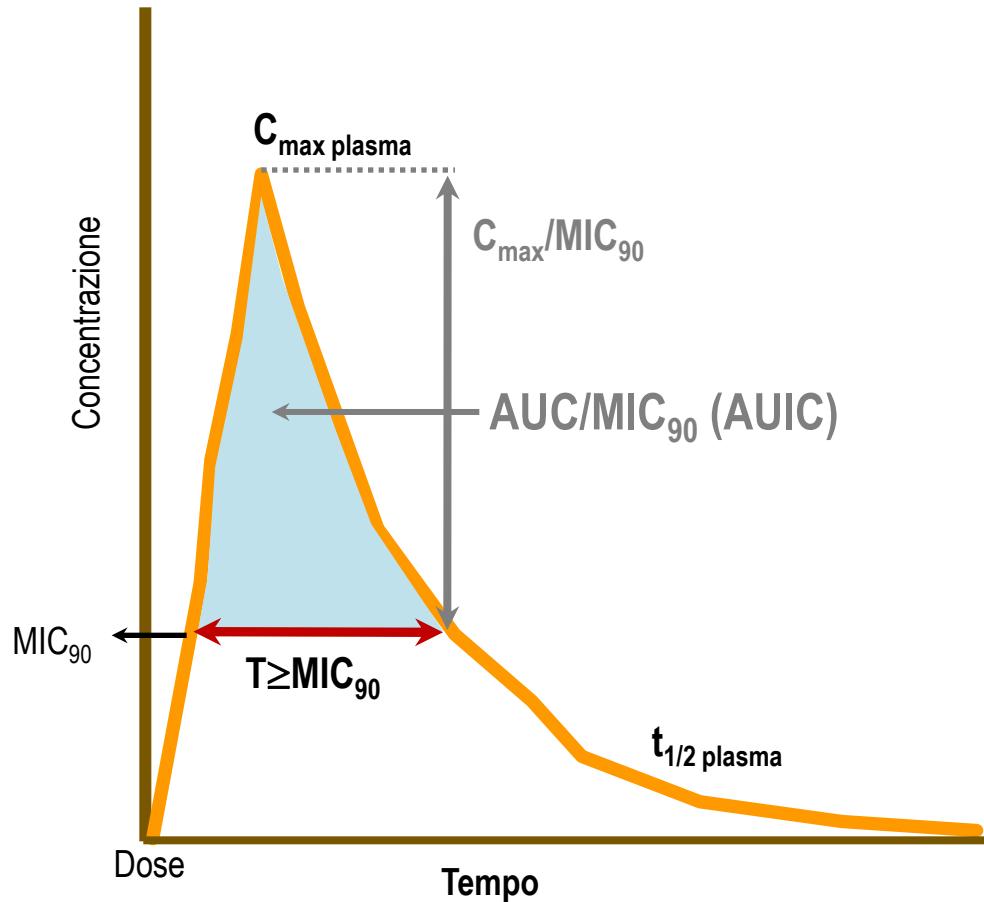
# Cause di variabilità PK: la sepsi



# Correlazioni PK/PD

Antibiotici		Dosaggio
Penicilline Cefalosporine	Tempo-dipendente <b>(T&gt;MIC)</b>	PAE breve  Prolungare il tempo di esposizione all'antibiotico Mantenere i livelli sierici > alle MIC (ridurre gli intervalli o infusione continua)
Carbapenemici Gli copeptidi Eritromicina	Concentrazione- dipendente <b>(Cmax/MIC AUC/MIC)</b>	PAE prolungato  Prolungare il tempo di esposizione all'antibiotico Livelli sierici possono essere < alle MIC (ridurre gli intervalli)
Aminoglicosidi Fluorochinoloni Claritromicina Azitromicina		Ottenere alti livelli sierici ed elevate concentrazioni tissutali (aumentare le dosi e prolungare gli intervalli)

# Parametri PK/PD



Betalattamici

Glicopeptidi

Teicoplanina

Macrolidi

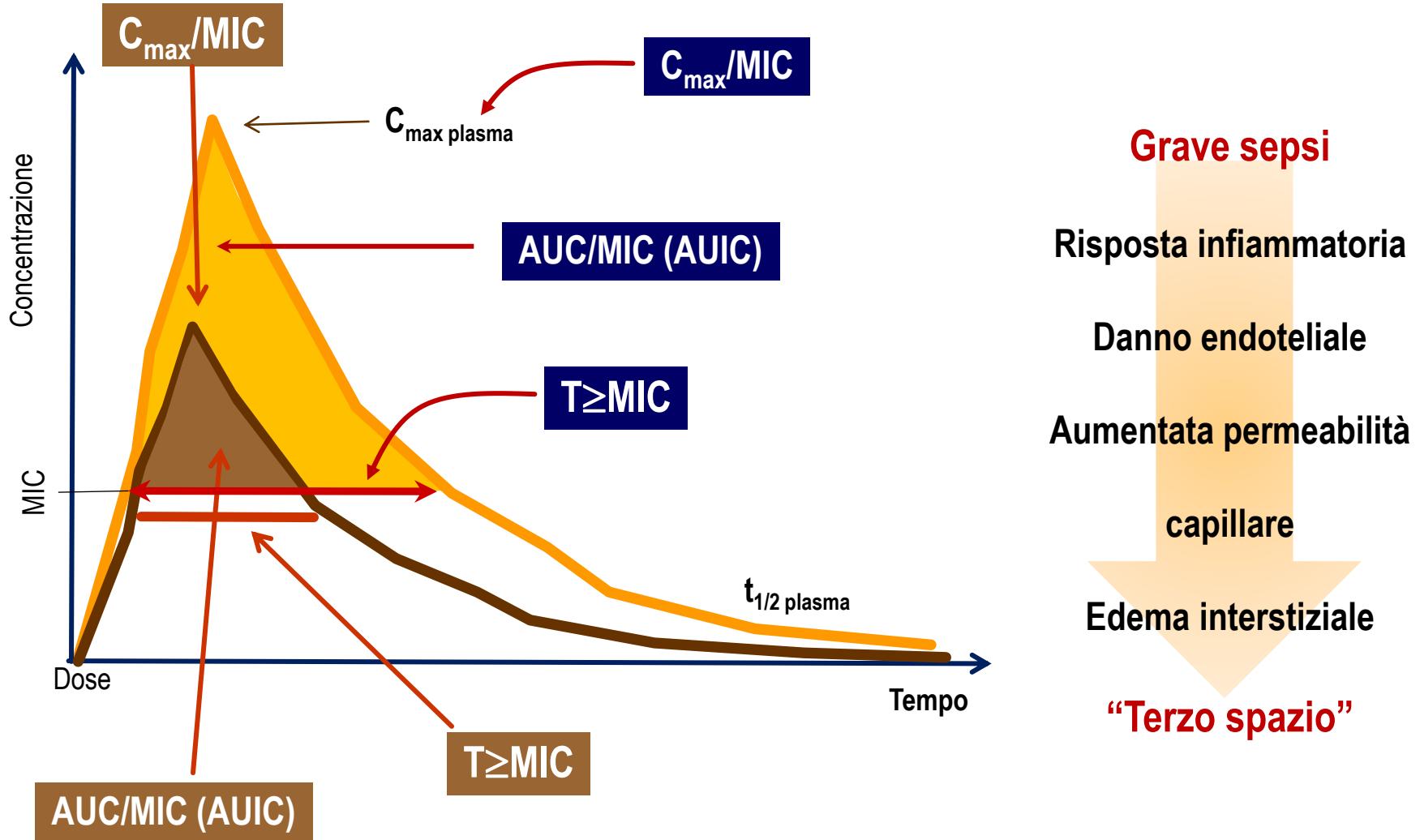
Eritromicina

Oxazolidinoni

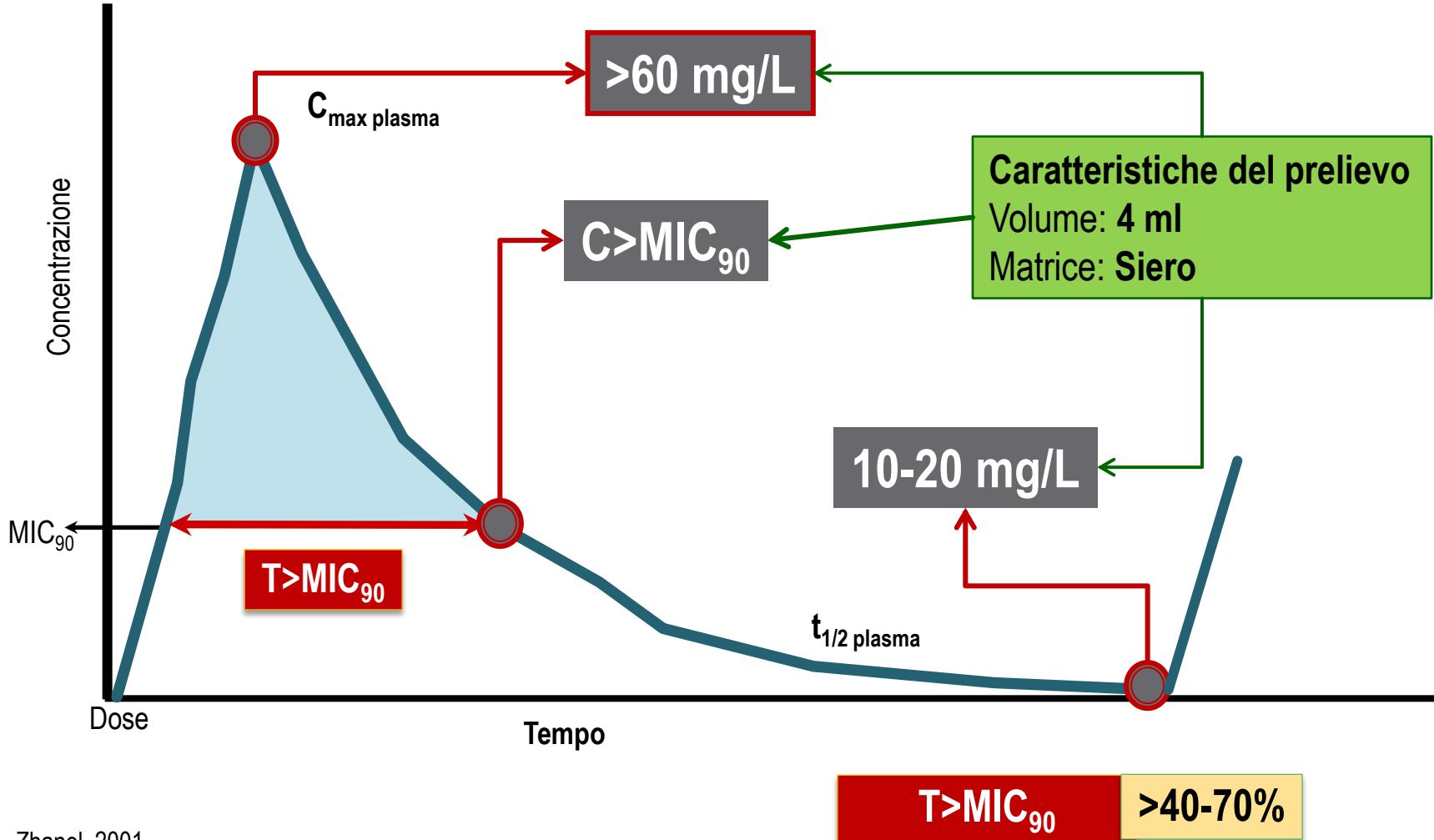
Linezolid

Cefalosporine 60-70%  
Penicilline 50%  
Carbapenemi 40%

# Cause di variabilità PK: la sepsi



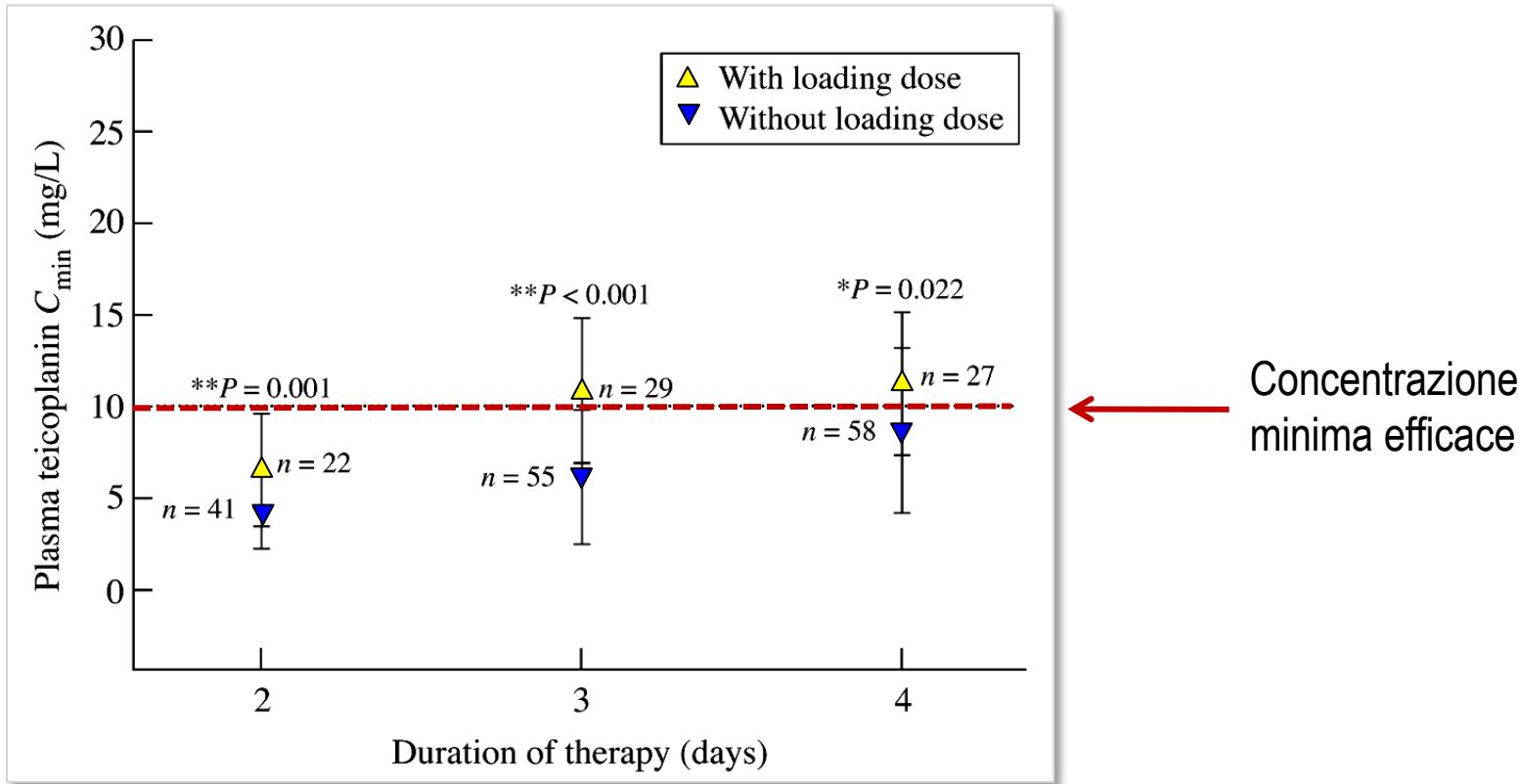
# TDM di teicoplanina



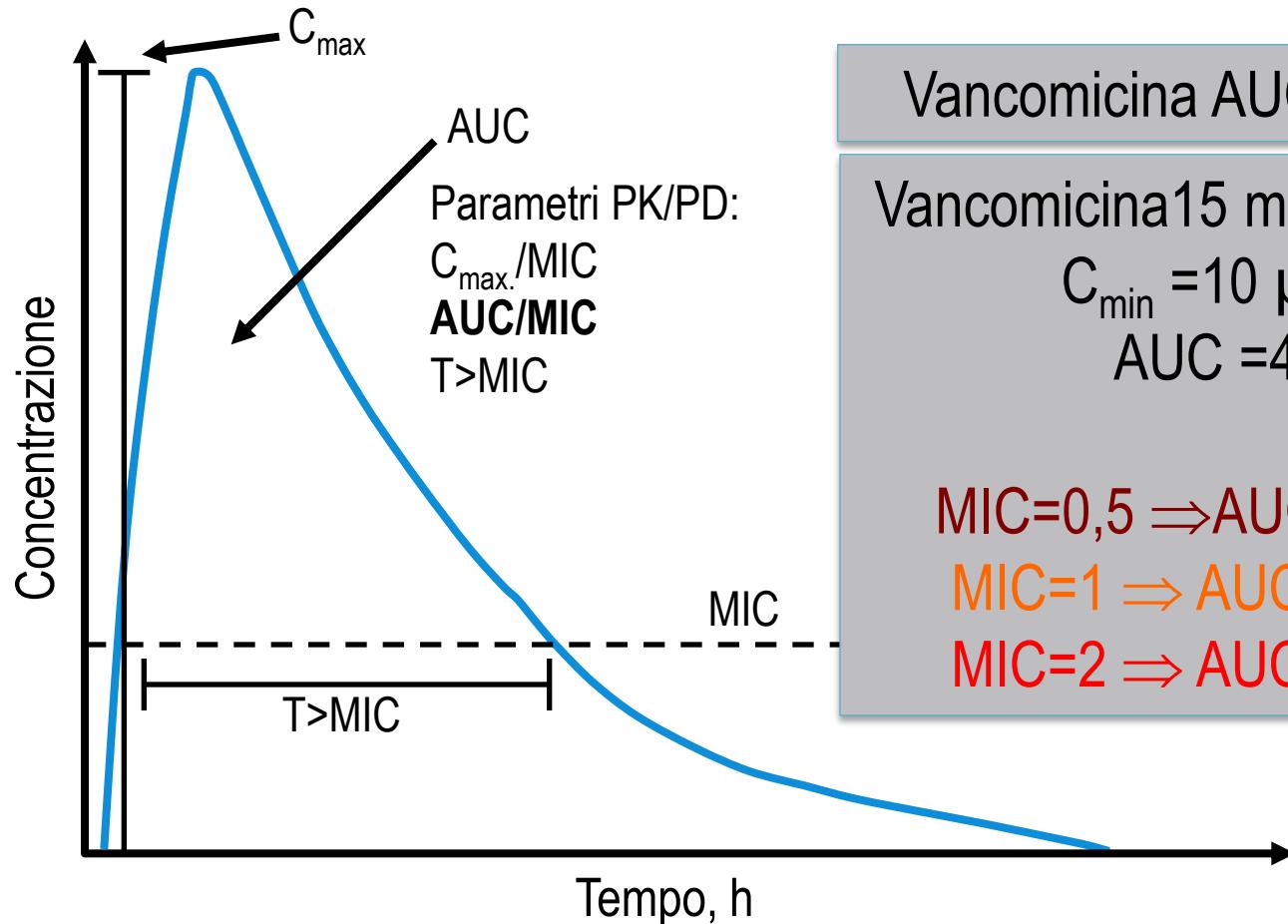
Zhanel, 2001

Del Mar Fernandez et al, 2006

# Teicoplanina: dosi di carico



# PK/PD divancomicina e regime posologico



Vancomicina AUC/MIC >350

Vancomicina 15 mg/kg q12h i.v.

$$C_{\min} = 10 \mu\text{g/ml}$$

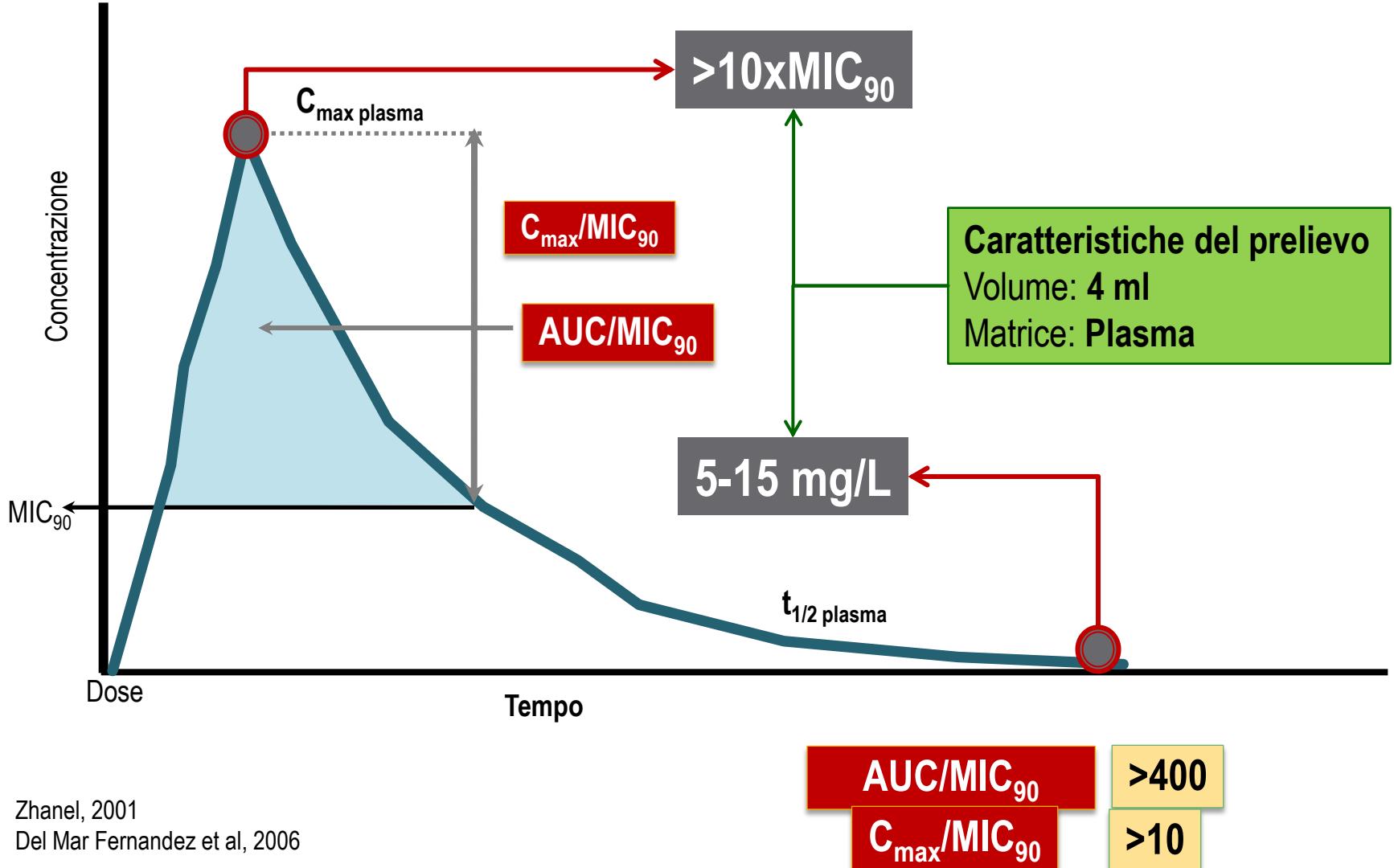
$$\text{AUC} = 400$$

$$\text{MIC} = 0,5 \Rightarrow \text{AUC/MIC} 800$$

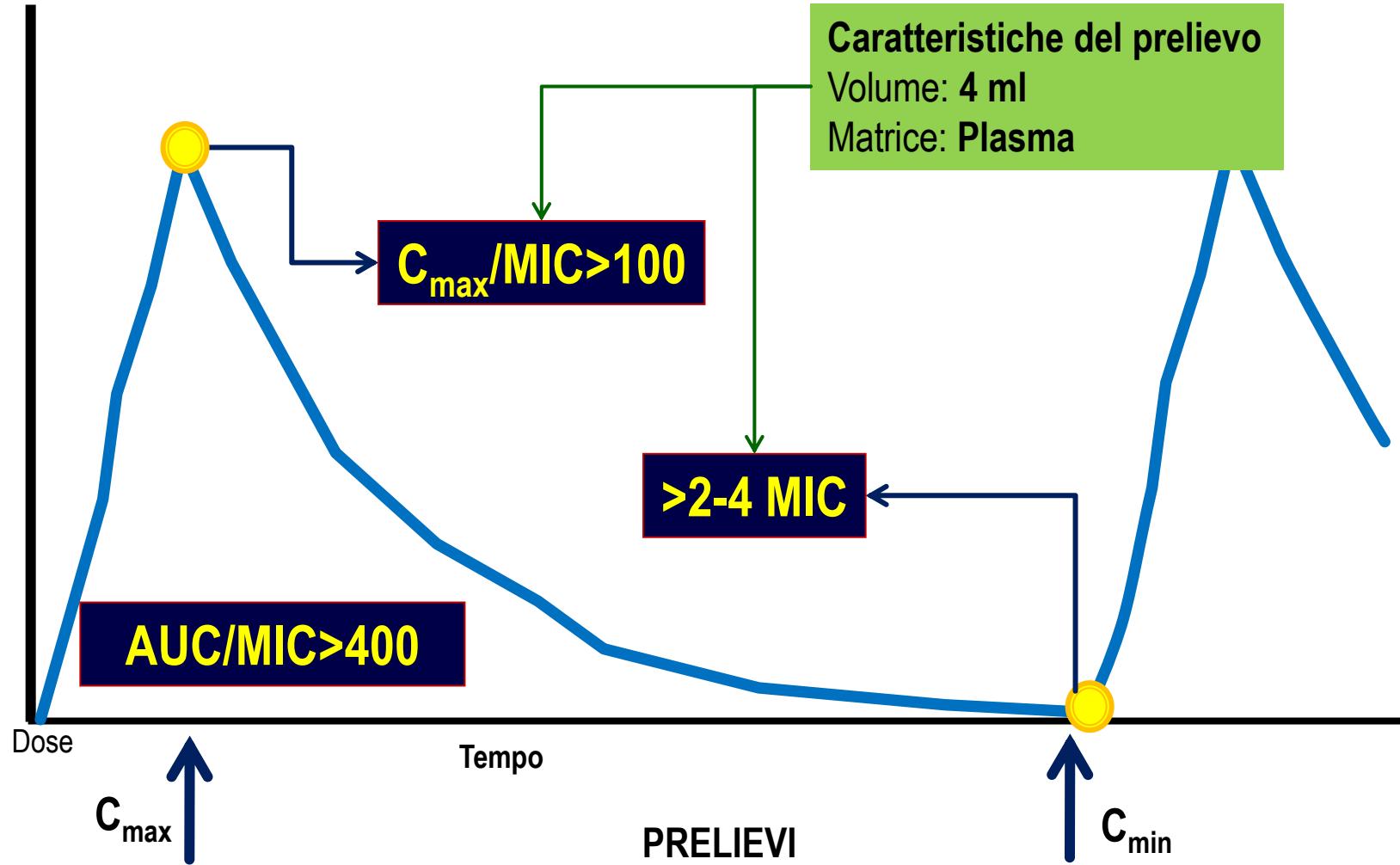
$$\text{MIC} = 1 \Rightarrow \text{AUC/MIC} 400$$

$$\text{MIC} = 2 \Rightarrow \text{AUC/MIC} 200$$

# TDM di vancomicina

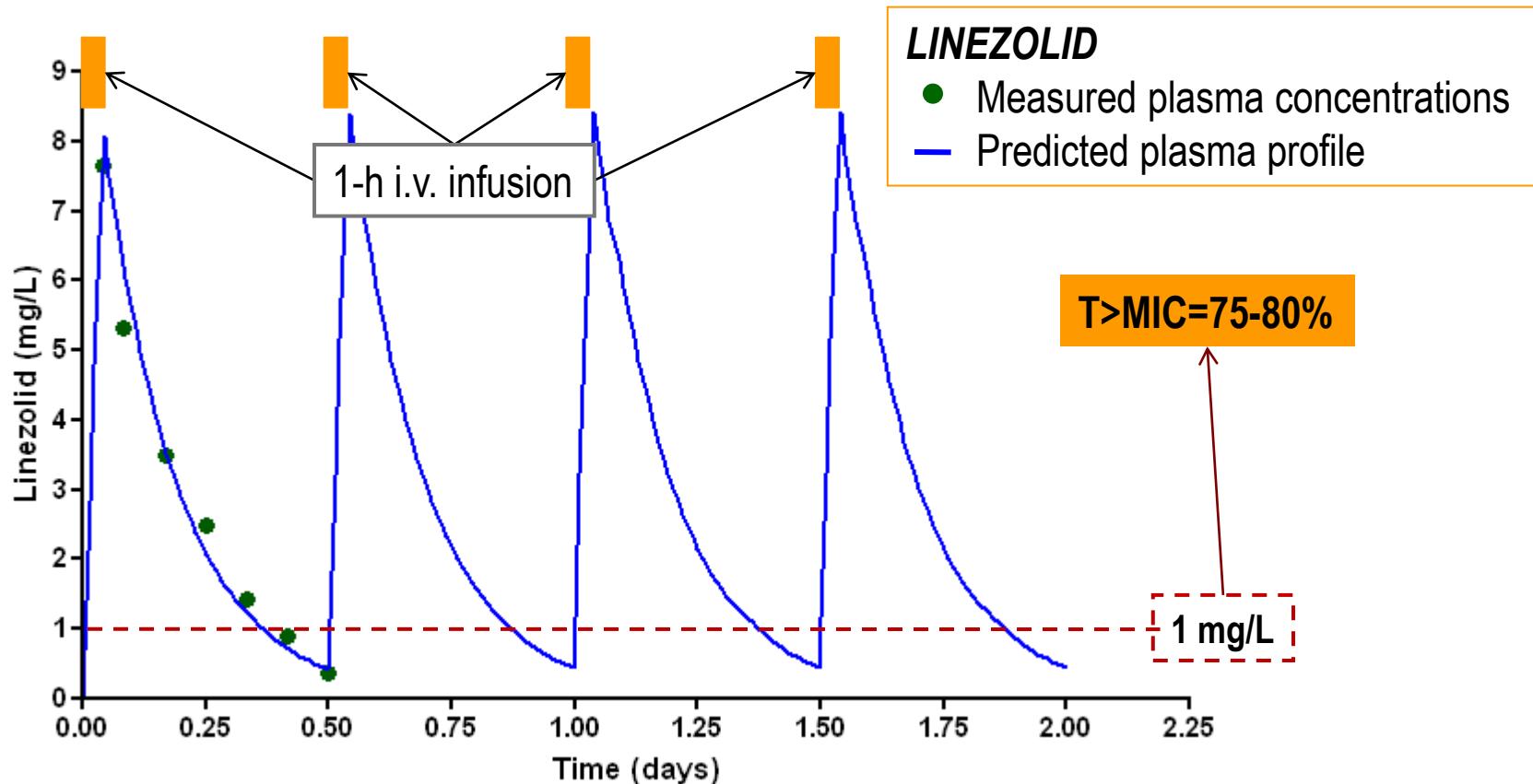


# TDM di daptomicina



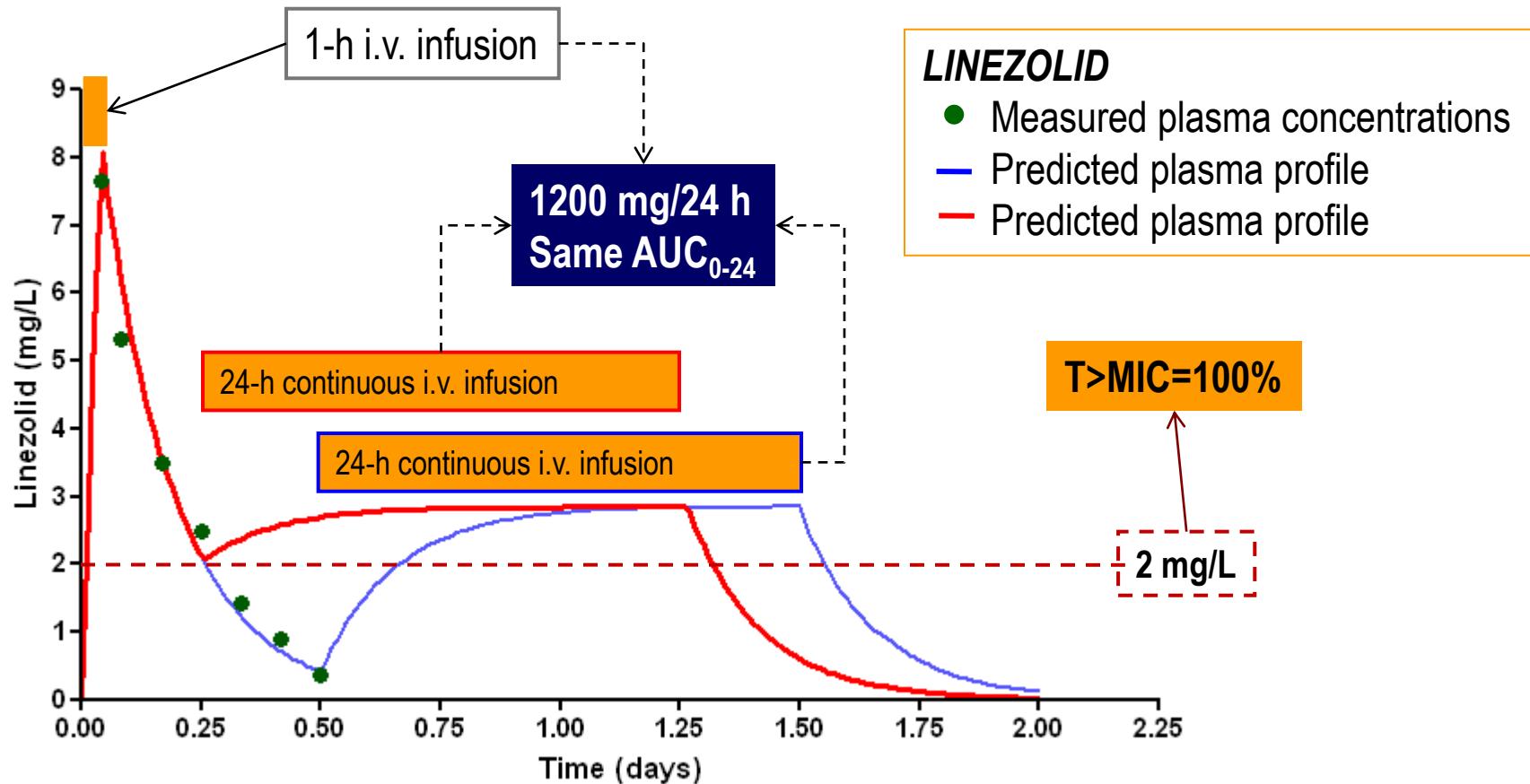
# Predizione del profilo plasmatico

Plasma profile of linezolid in an ICU patient: predicted concentrations after standard schedule administration



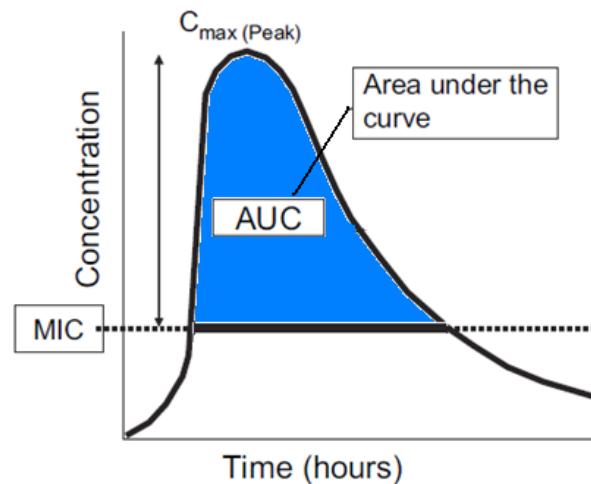
# Infusione continua con dose da carico

Plasma profile of linezolid in an ICU patient: predicted plasma concentrations after a 24-h continuous infusion administration

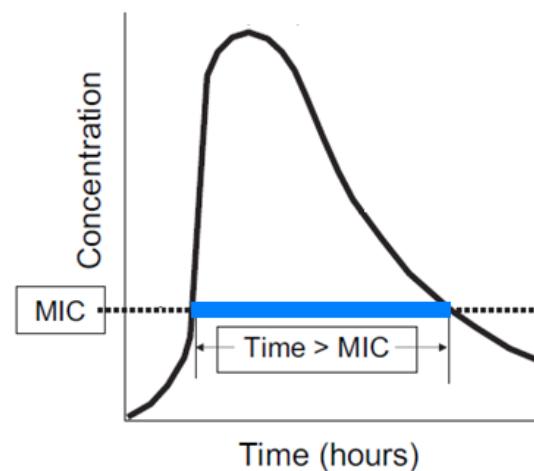


# Antifungini: concentrazione o tempo?

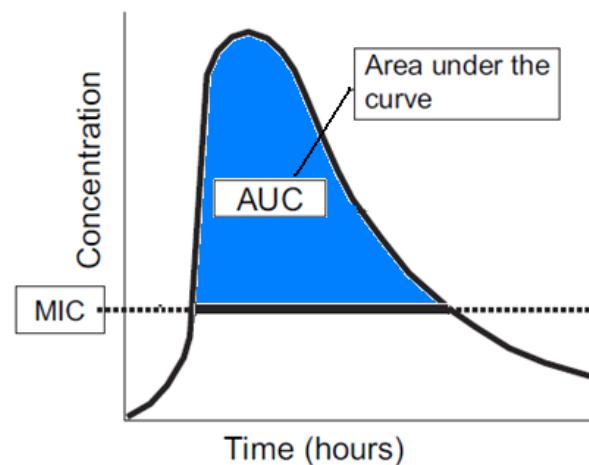
$C_{max}/MIC$  o  $AUC/MIC$   
Lungo PAFE



$T > MIC$   
PAFE breve o assente



$AUC_{24}/MIC$   
Lungo PAFE



Amfotericina B  
Echinocandine

Flucitosina

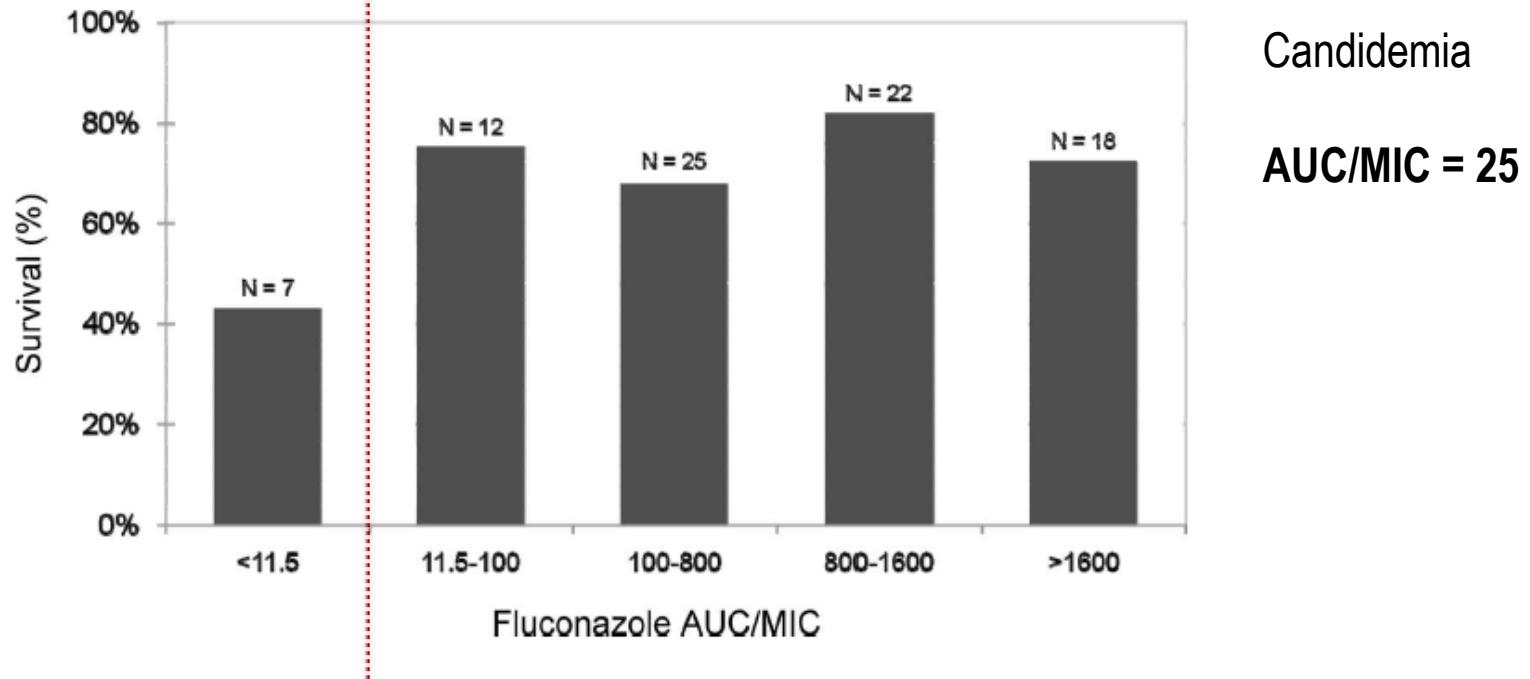
Triazoli

# Antifungini e TDM

Farmaco	Correlazione con		Variabilità farmacocinetica
	Efficacia	Tossicità	
Fluconazolo	SI	NO	SI (paz. critico)
Itraconazolo	SI	NO	SI (assorbimento)
Posaconazolo	SI	NO	SI (assorbimento)
Voriconazolo	SI	SI	SI (metabolismo)
Caspofungina	SI	NO	NO
Anidulafungina	SI	NO	NO
Micafungina	SI	NO	NO
Amfotericina B	SI	NO	NO

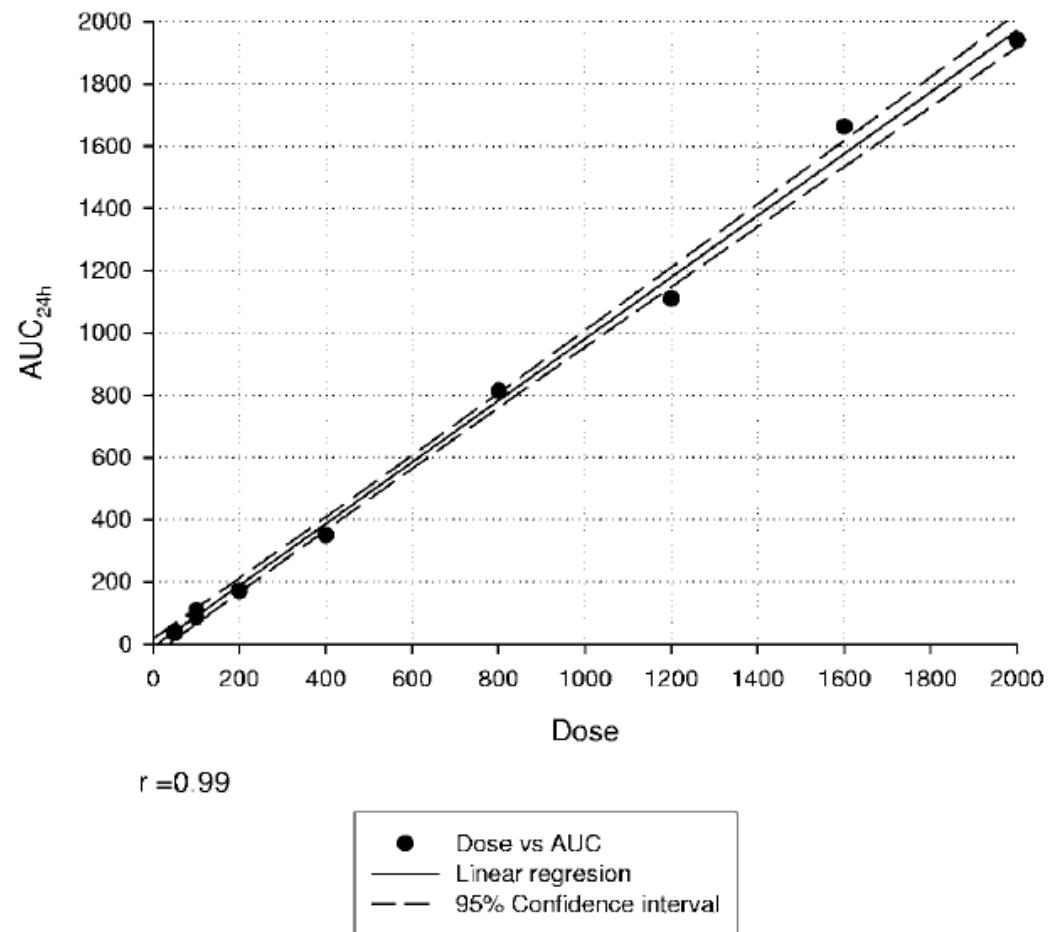
# AUC/MIC per fluconazolo

*...a fluconazole area under the concentration-time curve/MIC of <11.5 or MIC of >64 was associated with increased patient mortality ( $P < 0.09$ ).*



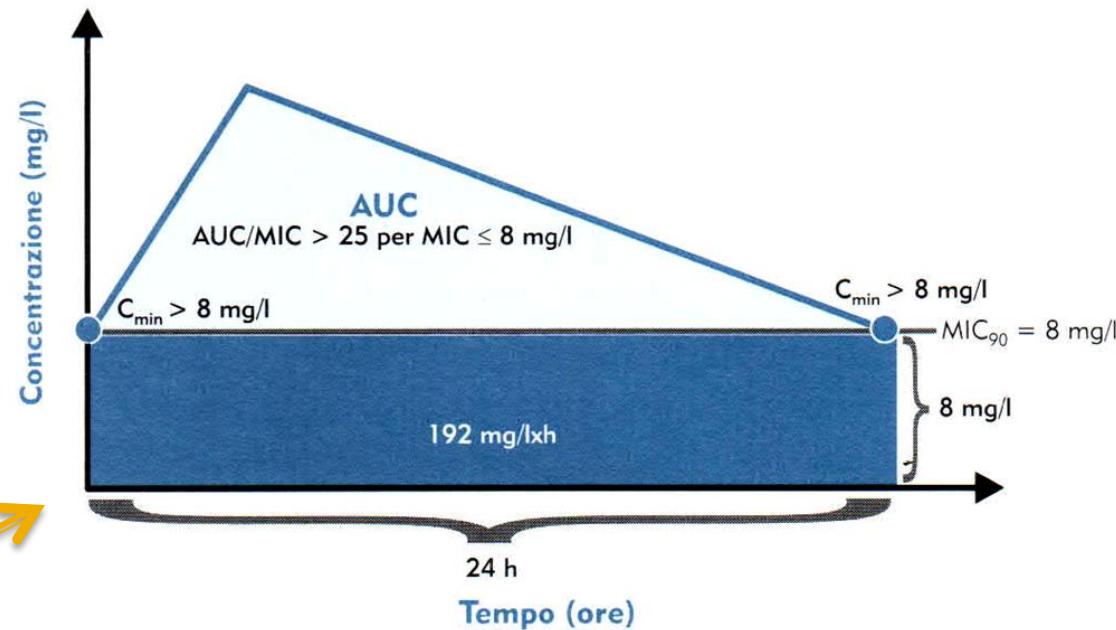
# Cinetica lineare di fluconazolo

Dose in mg/day	AUC24h
50	39.0
50	38.8
50	34.7
100	86.9
100	93.0
100	107.0
100	106.0
100	106.0
200	170.0
400	350.0
800	813.3
1200	1110.3
1600	1661.7
2000	1939.0

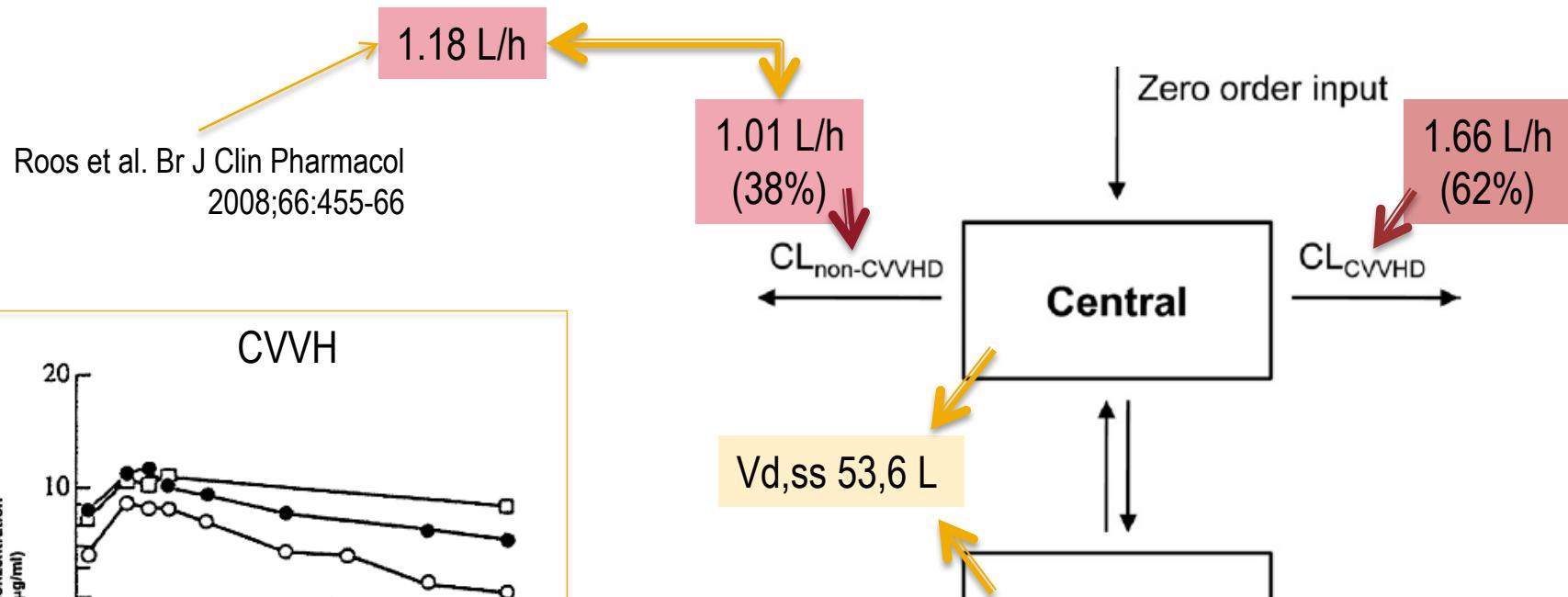


# TDM di Fluconazolo

Dose in mg/day	AUC24h
50	39.0
50	38.8
50	34.7
100	86.9
100	93.0
100	107.0
100	106.0
100	106.0
200	170.0
400	350.0
800	813.3
1200	1110.3
1600	1661.7
2000	1939.0



# Fluconazolo e renal replacement therapies



...the predicted efficiency of  $CL_{CVVHDF}$  decreased to 36.8% when filters were in use >48 h...

Pittrow et al. Mycoses 1999;42:17-19

Patel et al. Antimicrob Agents Chemother 2011;55:5868-73

# Modelli matematici e simulazione

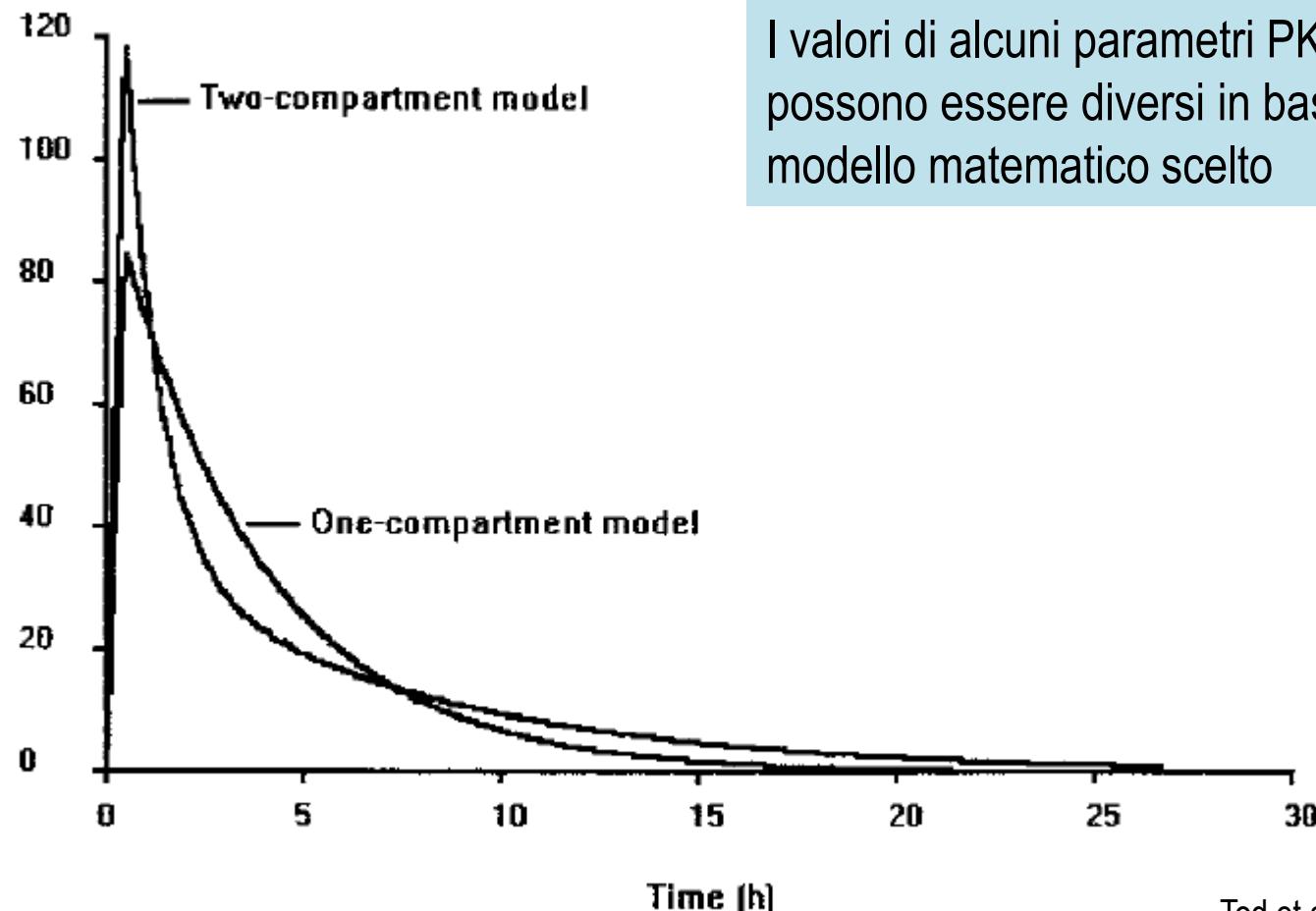
Variabilità temporale  
Diverse condizioni cliniche  
Diverse tecniche di dosaggio  
Differenti approcci metodologici  
Personale coinvolto nello studio  
Numerosità degli studi



Ricerca in letteratura  
Recupero dei parametri PK  
Simulazione delle condizioni iniziali  
Simulazioni degli schemi adottati

# Modelli matematici e simulazione

Concentration (mg/liter)



Tod et al, AAC 1998

# Meropenem e funzionalità renale

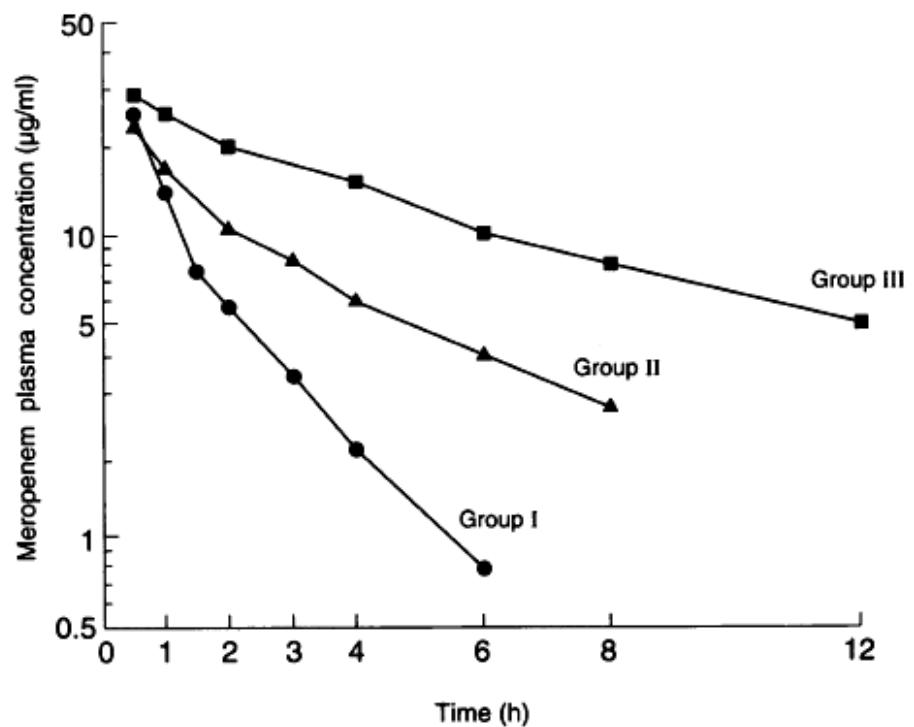


TABLE 1. Subject characteristics

Group	Subject no.	Age	Sex <sup>a</sup>	Wt (kg)	Serum creatinine concn (mg/dl)	CL <sub>CR</sub> (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

# Meropenem e funzionalità renale

TABLE 3. Meropenem pharmacokinetic data<sup>a</sup>

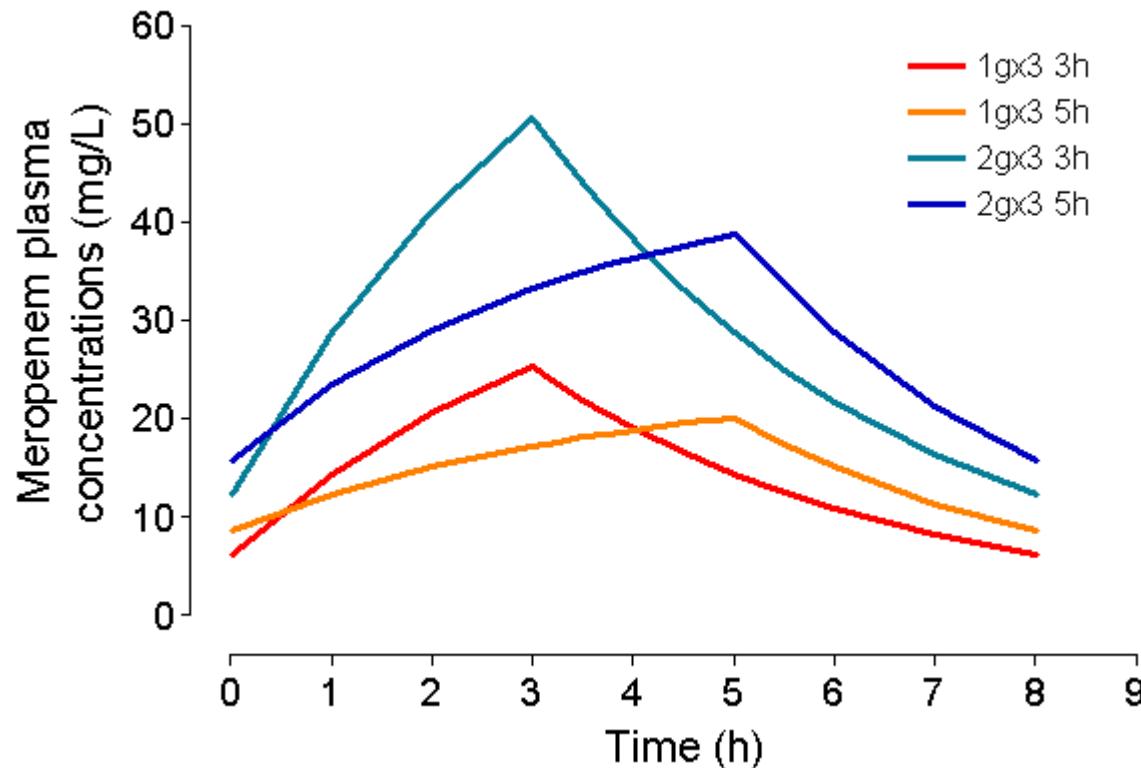
Group	Subject no.	$t_{1/2}$ (h)	AUC ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )	CL (ml/min)	$\text{CL}_R$ (ml/min)	$\text{CL}_R/\text{CL}_{CR}$ ratio
I	1	1.71	24.0	347.2	263.9	3.88
	2	0.61	50.7	164.4	73.6	1.18
	3	2.31	35.8	232.8	74.3	1.30
	4	1.54	36.0	231.5	95.4	1.71
$\text{Mean} \pm \text{SD}$		$1.54 \pm 0.70$	$36.6 \pm 11.9$	$244.0 \pm 75.9$	$126.8 \pm 92.0$	$2.02 \pm 1.26$
II	5	4.45	40.2	207.3	80.0	2.14
	6	4.01	88.5	94.2	26.6	0.77
	7	2.46	63.3	131.6	66.7	1.76
	8	2.53	106.5	78.2	11.9	0.28
$\text{Mean} \pm \text{SD}$		$3.36 \pm 1.02$	$74.6 \pm 29.0$	$127.8 \pm 57.5$	$46.3 \pm 32.3$	$1.24 \pm 0.86$
III	9	4.52	112.2	74.3	32.2	1.50
	10	3.58	136.3	61.1	21.9	1.35
	11	5.69	173.1	48.1	9.5	0.84
	12	4.94	235.6	35.4	5.8	0.82
$\text{Mean} \pm \text{SD}$		$5.00 \pm 1.05$	$186.8 \pm 68.5$	$49.8 \pm 18.2$	$15.4 \pm 11.3$	$1.25 \pm 0.41$

<sup>a</sup>  $t_{1/2}$ , half-life; AUC, area under the concentration-time curve; CL, meropenem clearance from plasma;  $\text{CL}_R$ , renal clearance;  $\text{CL}_{CR}$ , creatinine clearance.

# Meropenem e CRRT

1000 individui

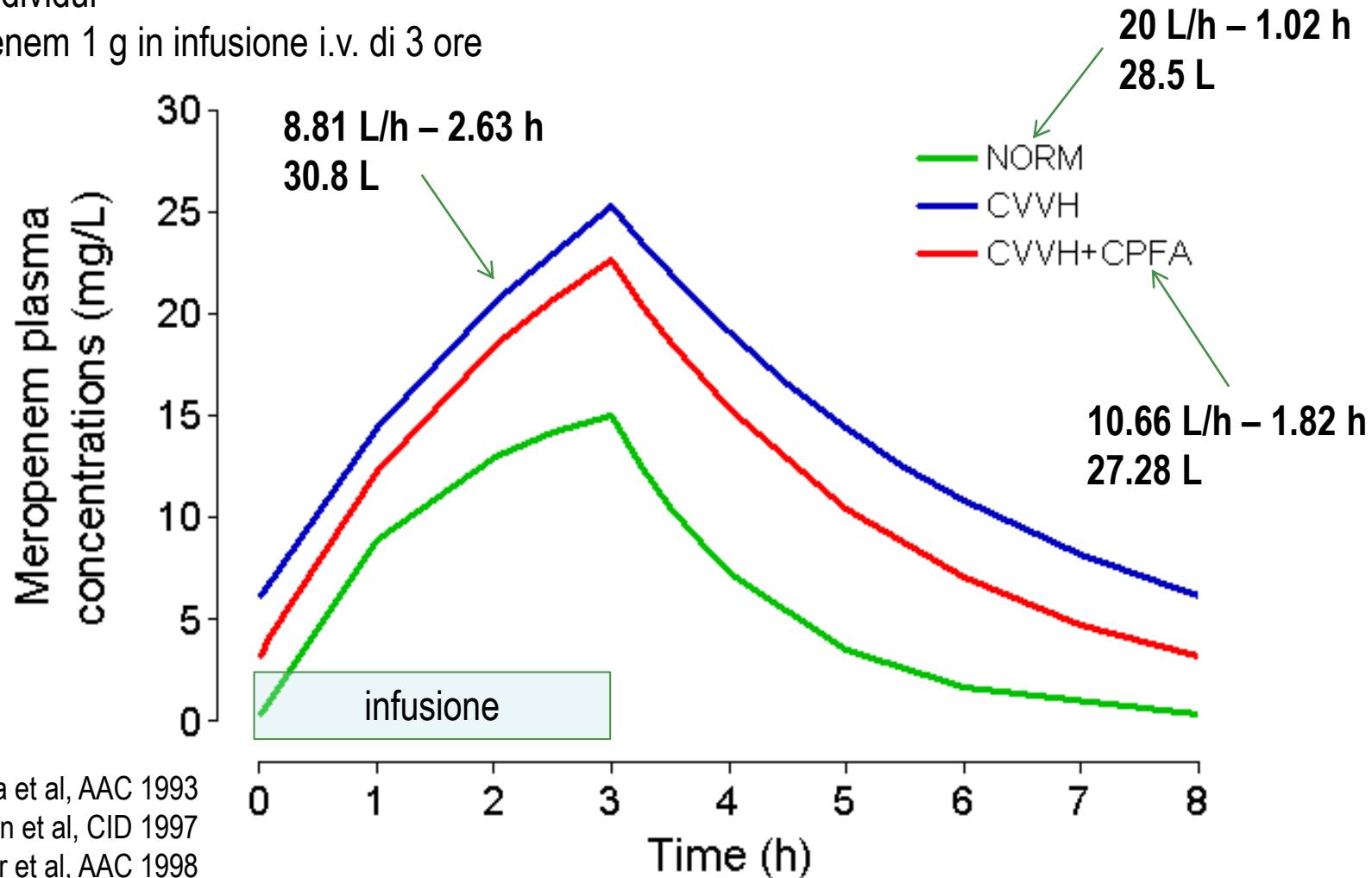
Meropenem 1-2 g in infusione i.v. di 3-5 ore



# Meropenem, CRRT e CPFA

1000 individui

Meropenem 1 g in infusione i.v. di 3 ore



Chimata et al, AAC 1993

Moon et al, CID 1997

Thalhammer et al, AAC 1998

# Meropenem, CRRT e PK/PD

1000 individui

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

Schema

1gx3 3h

1gx3 5h

2gx3 3h

2gx3 5h

CRRT

Paz. Con Cmin<MIC

11%

2%

3%

0%

Paz. Con T>MIC>40%

100%

100%

100%

100%

No CRRT

Schema

1gx3 3h

1gx3 5h

2gx3 3h

2gx3 5h

Paz. Con Cmin<MIC

91.8%

72.7%

78.4%

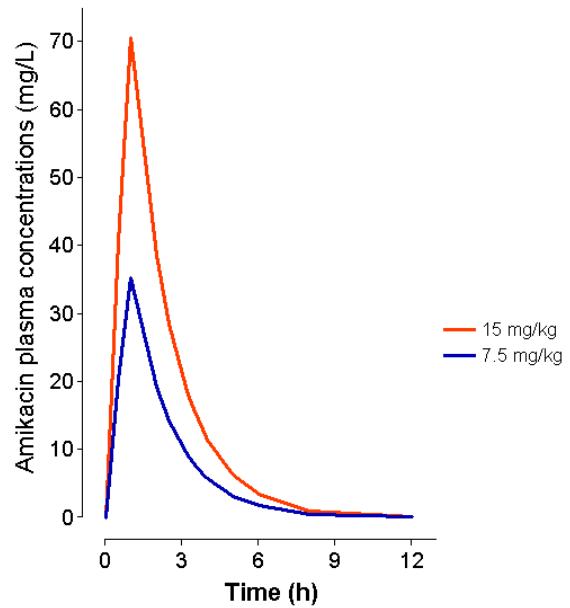
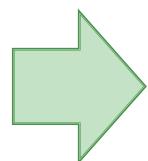
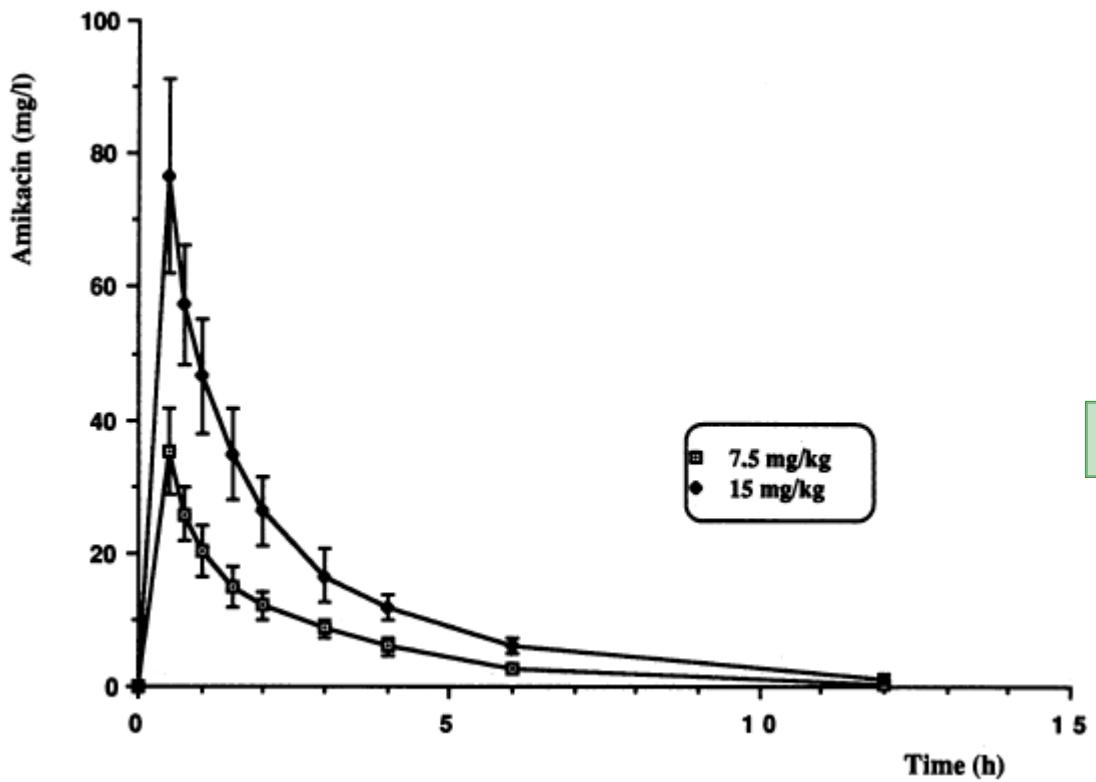
50.8%

Paz. Con T>MIC>40%

84.3%

96.2%

# Amikacina



Garraffo et al, AAC 1988

# Amikacina

Parameter <sup>b</sup>	Amikacin dose	
	7.5 mg/kg	15 mg/kg
$V_1$ (liter)	11.00 ± 2.975	11.154 ± 1.776
$k_{el}$ ( $h^{-1}$ )	0.742 ± 0.246	0.62 ± 0.088
$CL_T$ (liter · $h^{-1}$ )	7.60 ± 1.003	6.77 ± 0.552
$t_{1/2\beta}$ (h)	1.9 ± 0.211	2.37 ± 0.534
$V_{area}$ (liter)	17.83 ± 2.253	17.96 ± 1.648
AUC (mg · h/liter) <sup>c</sup>	66.64 ± 15.742	154.53 ± 29.91

Garraffo et al, AAC 1988

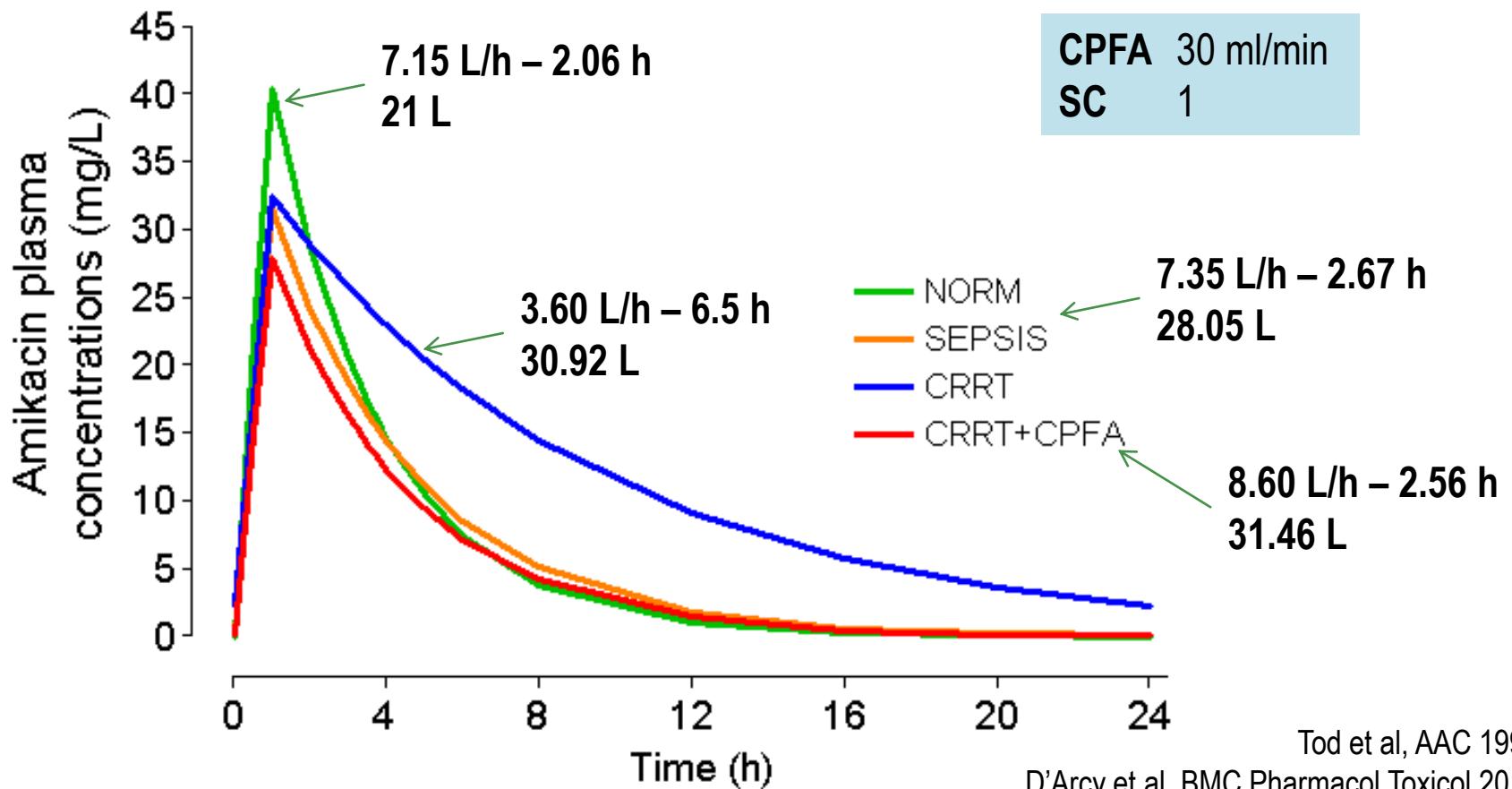


	15 mg/kg
$V$ (L)	11.17 ± 1.11
$Kel$ ( $h^{-1}$ )	0.62 ± 0.09
$CL_t$ (L * $h^{-1}$ )	6.82 ± 0.66
$t_{1/2b}$ (h)	1.15 ± 0.16
AUC (mg * h/L)	155.5 ± 14.93

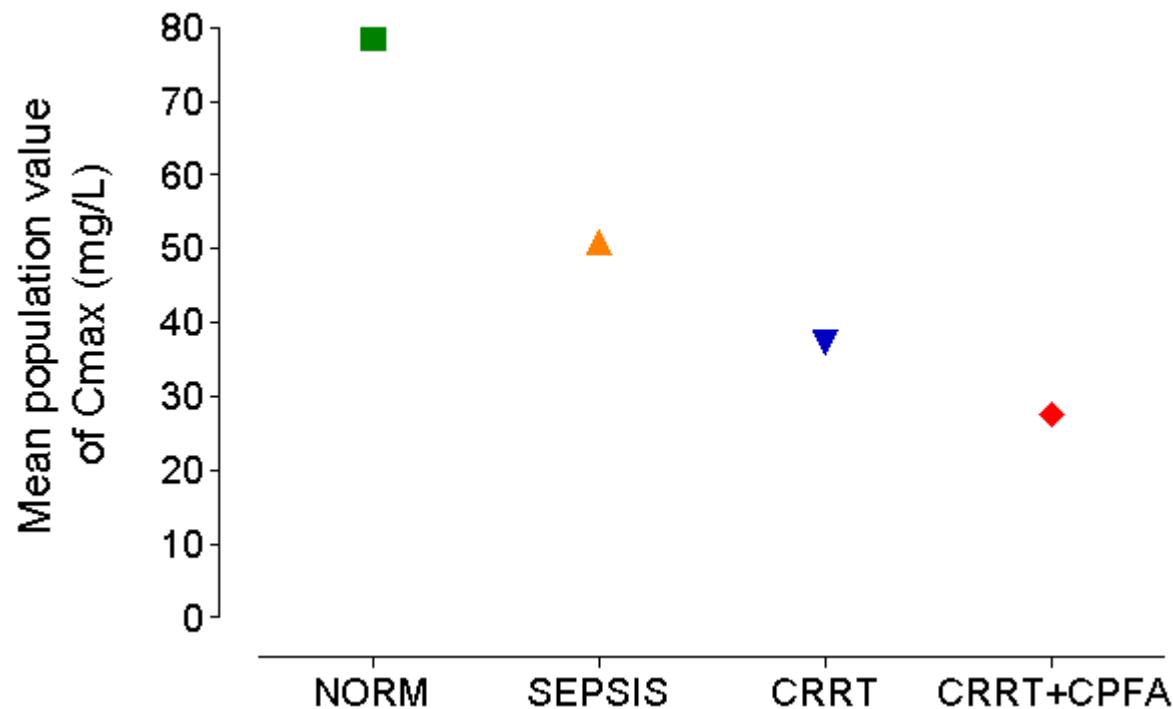
# Amikacina, CRRT e CPFA

1000 individui

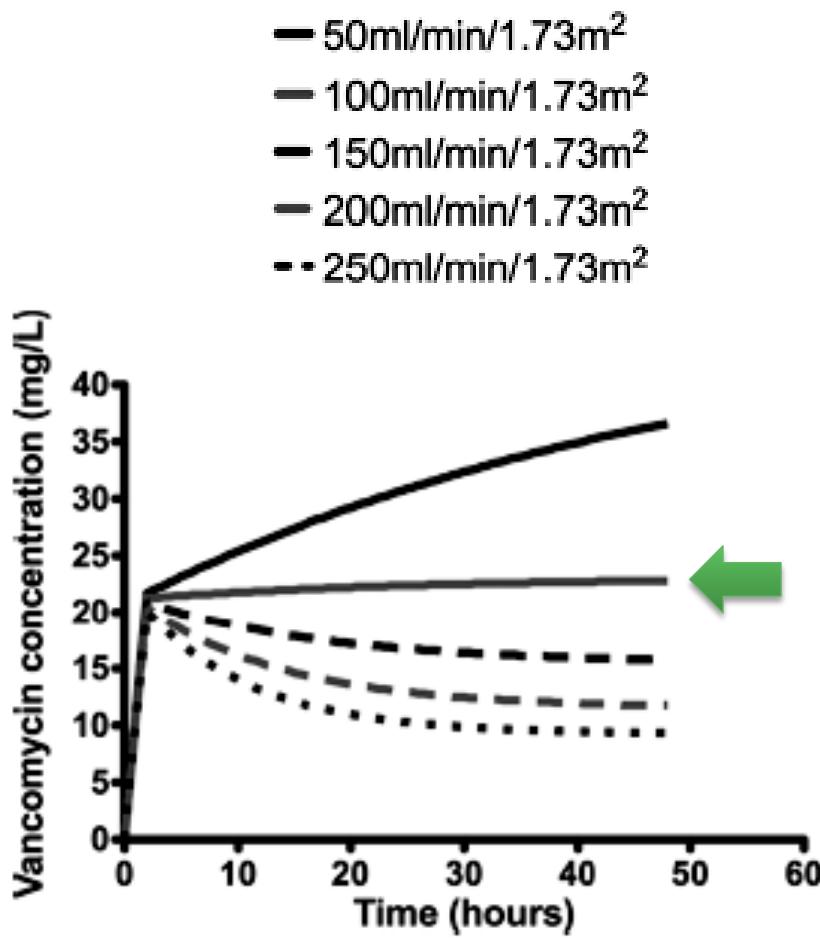
Amikacin 1000 mg in infusione i.v. di 1 ora



# Amikacina, CRRT, CPFA e PK/PD

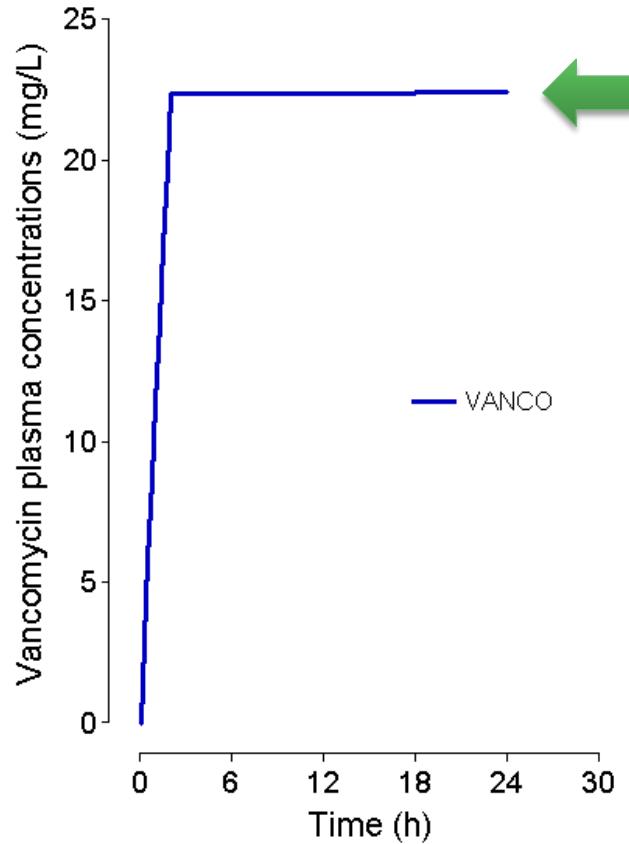


# Vancomicina e funzionalità renale



Roberts et al, AAC, 2011

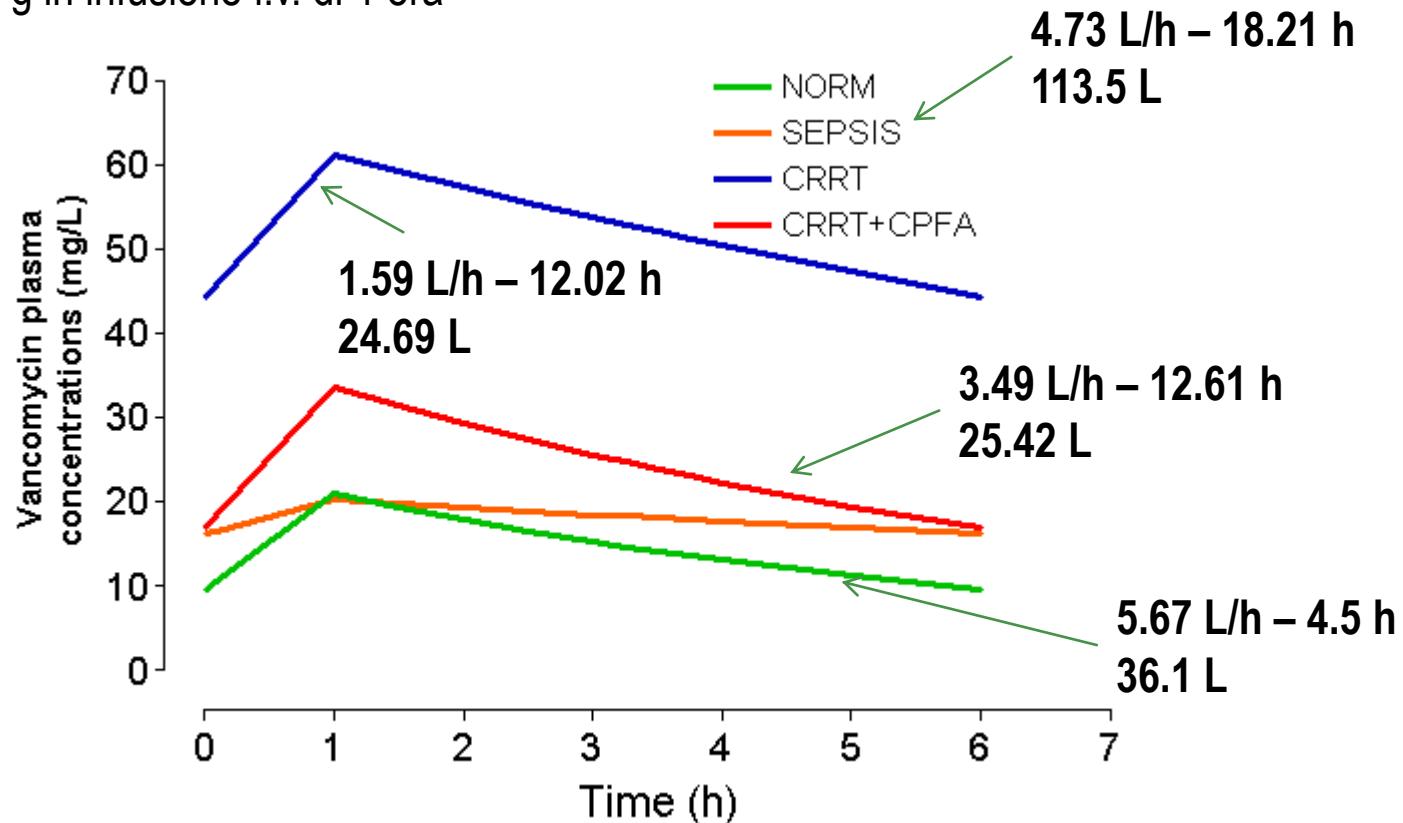
Dose di carico di 35 mg/kg = 2450 mg/die in 2 ore  
Dose di 35 mg/kg = 2450 mg/die in infusione continua  
Peso paziente=70 kg, Vd=105 L



# Vancomicina, CRRT e CPFA

1000 individui

Vancomicina 0,5 g in infusione i.v. di 1 ora



Boeckh et al, AAC 1988

Chaijamorn et al, IJAA 2011

Roberts et al, AAC, 2011

# Vancomicina, CRRT e PK/PD

No CRRT

Schema	0,5gx4	2g inf cont
AUC/MIC>500	0.40%	2.40%
Paz. Con Cmin<10	37.6%	31.6%
Paz. Con Cmin<20	60.3%	50.7%

CRRT

Schema	0,5gx4	2g inf cont
AUC/MIC>500	78.70%	78.70%
Paz. Con Cmin<10	26.9%	25.5%
Paz. Con Cmin<20	34.1%	31.7%

# Fluconazolo, CRRT e CPFA

1000 individui

Fluconazolo 800 mg in infusione i.v. di 1 ora

