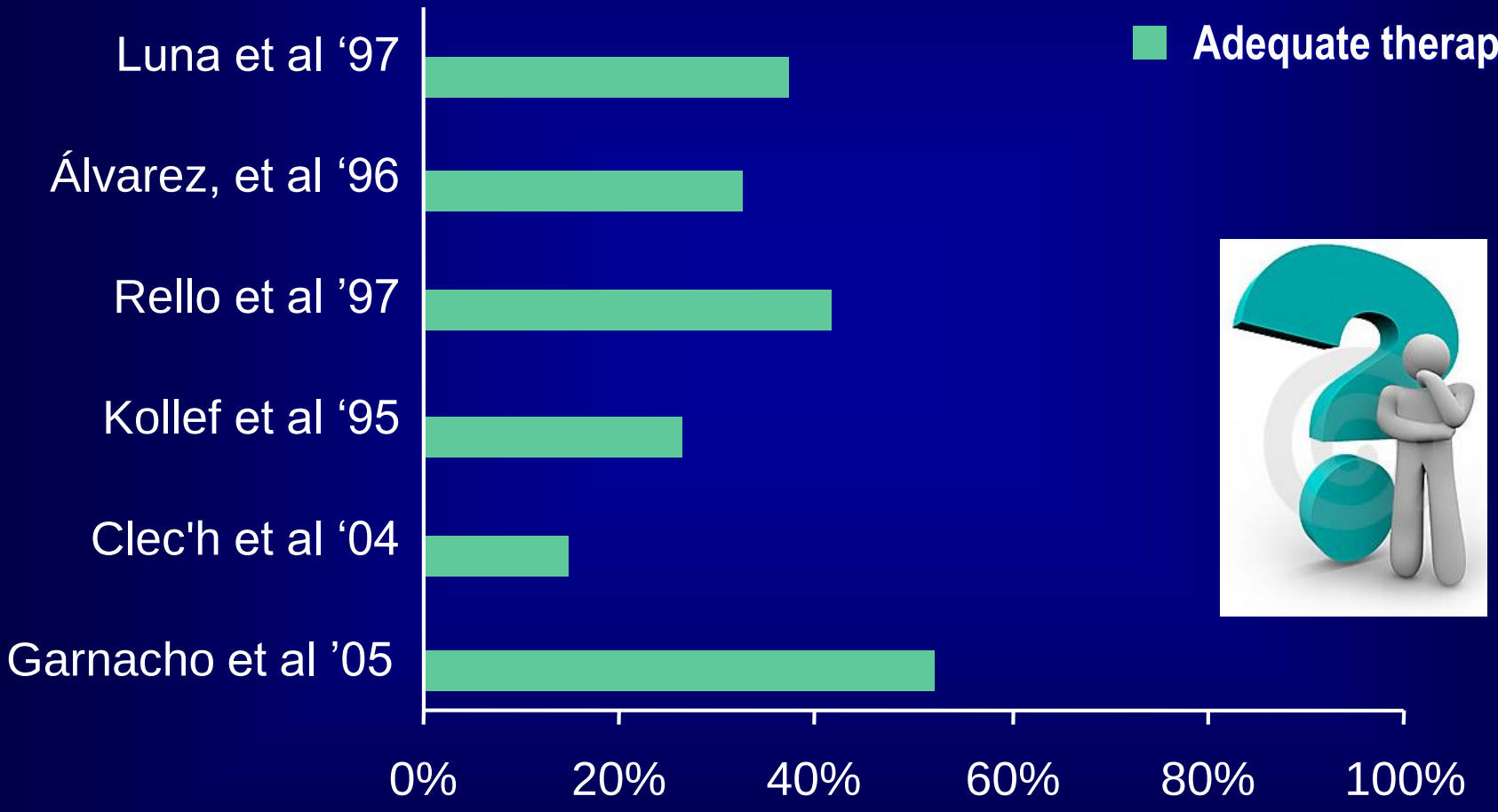
Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

# Il contributo della farmacologia clinica ai programmi di Antimicrobial Stewardship

Dario Cattaneo
UOSD Farmacologia Clinica

# Mortality impact of **adequate**** therapy in patients with ventilator-associated pneumonia




**The bug is in vitro susceptible to the drug !


La MIC (*minima concentrazione inibente*) è un parametro derivato *in vitro* che acquista significato clinico quando viene correlata cone le caratteristiche farmacocinetiche di un antibiotico. Solo cosi si possono avere buone indicazioni di predittività di effecia *in vivo*…

La farmacocinetica studia l'evoluzione temporale delle concentrazioni di un farmaco e dei suoi metaboliti nei diversi fluidi e tessuti dell'organismo mediante l'analisi dei processi che ne regolano:

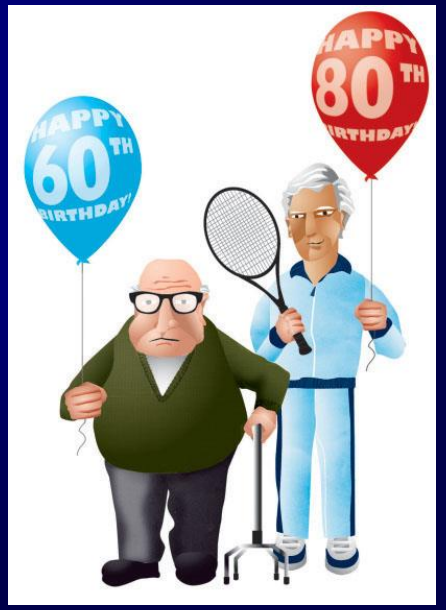
- Assorbimento
- Distribuzione
- Metabolismo
- Eliminazione

} "ciò che l'uomo fa al farmaco"

- ✓ ***quale è la dose giusta di farmaco?***
- ✓ ***ogni quanto va somministrata?***
- ✓ ***Ci sono differenze tra i pazienti?***

# La farmacocinetica degli antibiotici cambia soprattutto nel paziente “complesso”…

- ✓ anziani…
- ✓ con insufficienza renale…
- ✓ con insufficienza epatica…
- ✓ in politerapia…
- ✓ scompensati…
- ✓ con variazioni nei volumi corporei…
- ✓ massa grassa ridotta…
- ✓ in nutrizione parenterale…
- ✓ immunodepressi…
- ✓ multicolonizzati….



# Variabilità "real life" delle concentrazioni ematiche di diversi antibiotici nei pazienti complessi…

| farmaco | Concentrationi ematiche (mg/L)* | Variabilità |
|---|---|---|
| Meropenem | 12.1 (2.4 – 18) | 6.7-fold |
| Piperacillin | 105.0 (74.4 – 204.0) | 3.8-fold |
| Tazobactam | 3.8 (3.4 – 21.8) | 10.5-fold |
| Vancomycin | 12.0 (9.8 – 16.0) | 1.9-fold |
| Ciprofloxacin | 3.7 (3.0 – 5.6) | 3.9-fold |

*median (interquartile range)

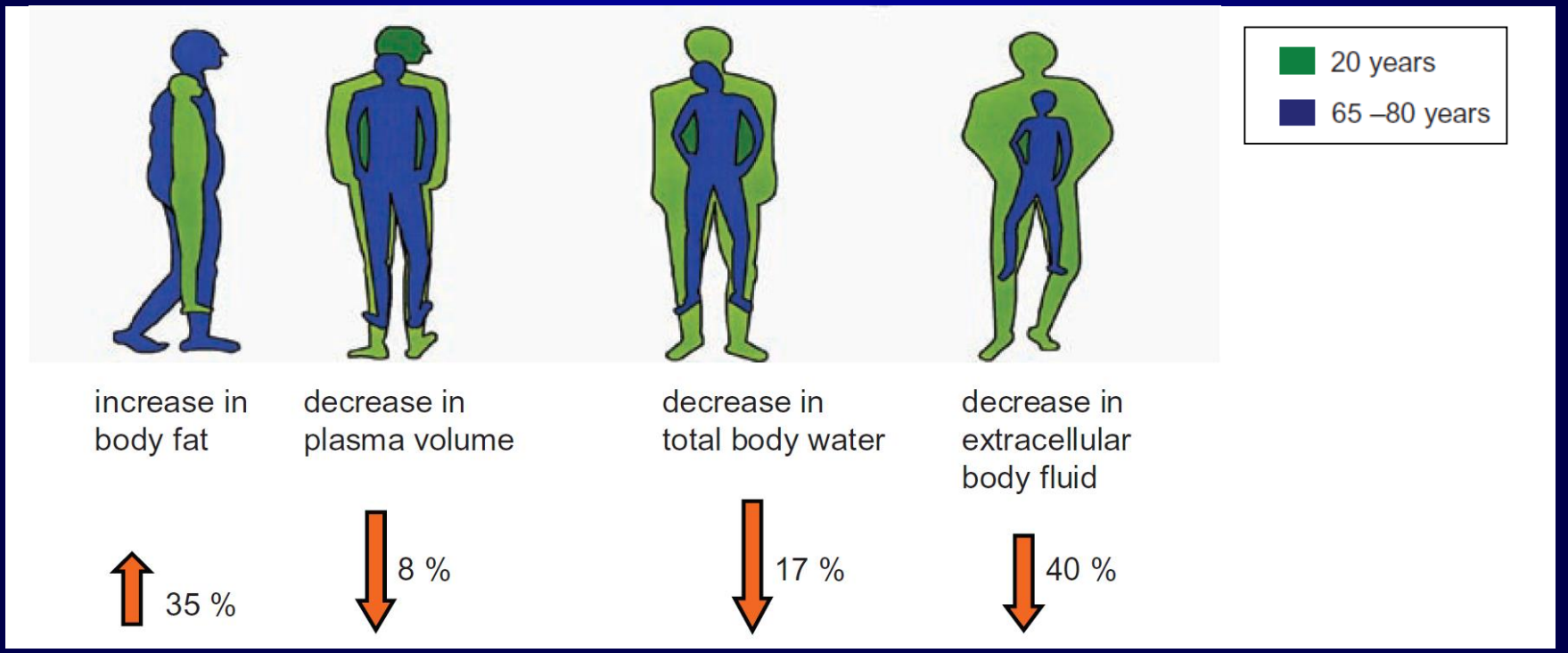
Stesso farmaco…stessa dose somministrata…

*- Roberts, Crit Care Med 2012 -*

***Come si spiega***
***questa variabilità?***

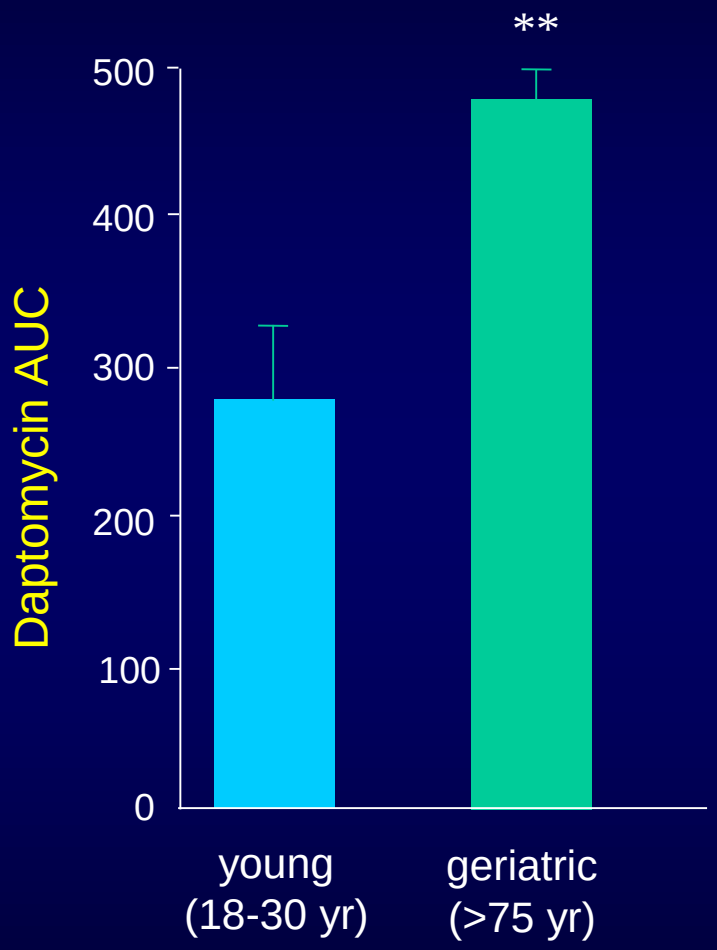
# Common clinical conditions: aging...

| Physiologic change | Result | PK parameter | PK effect |
|---|---|---|---|
| Reduced muscle mass and total water | Accumulation of hydrophilic drugs | Volume of distribution | Increase of drug plasma concentrations |
| Increased body fat | Accumulation of lipophilic drugs | Volume of distribution | Increase of drug half-life |



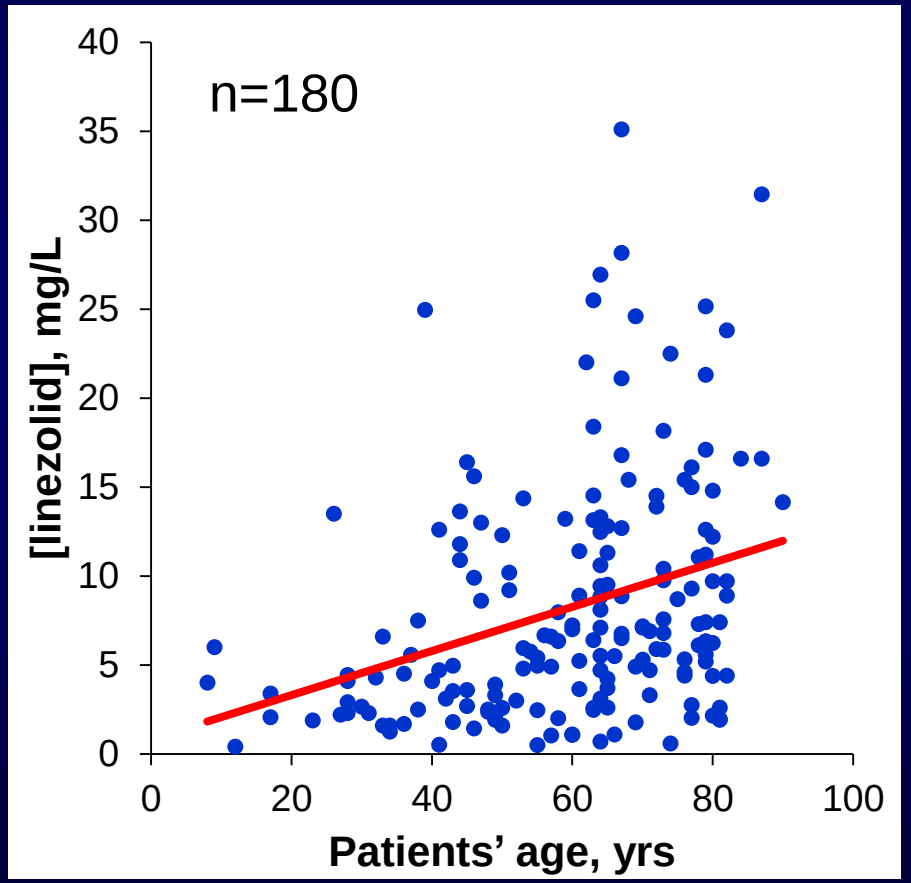

*- Klotz, Drug Metab Rev 2009 -*

**Single-Dose Pharmacokinetics of Daptomycin in Young and Geriatric Volunteers**



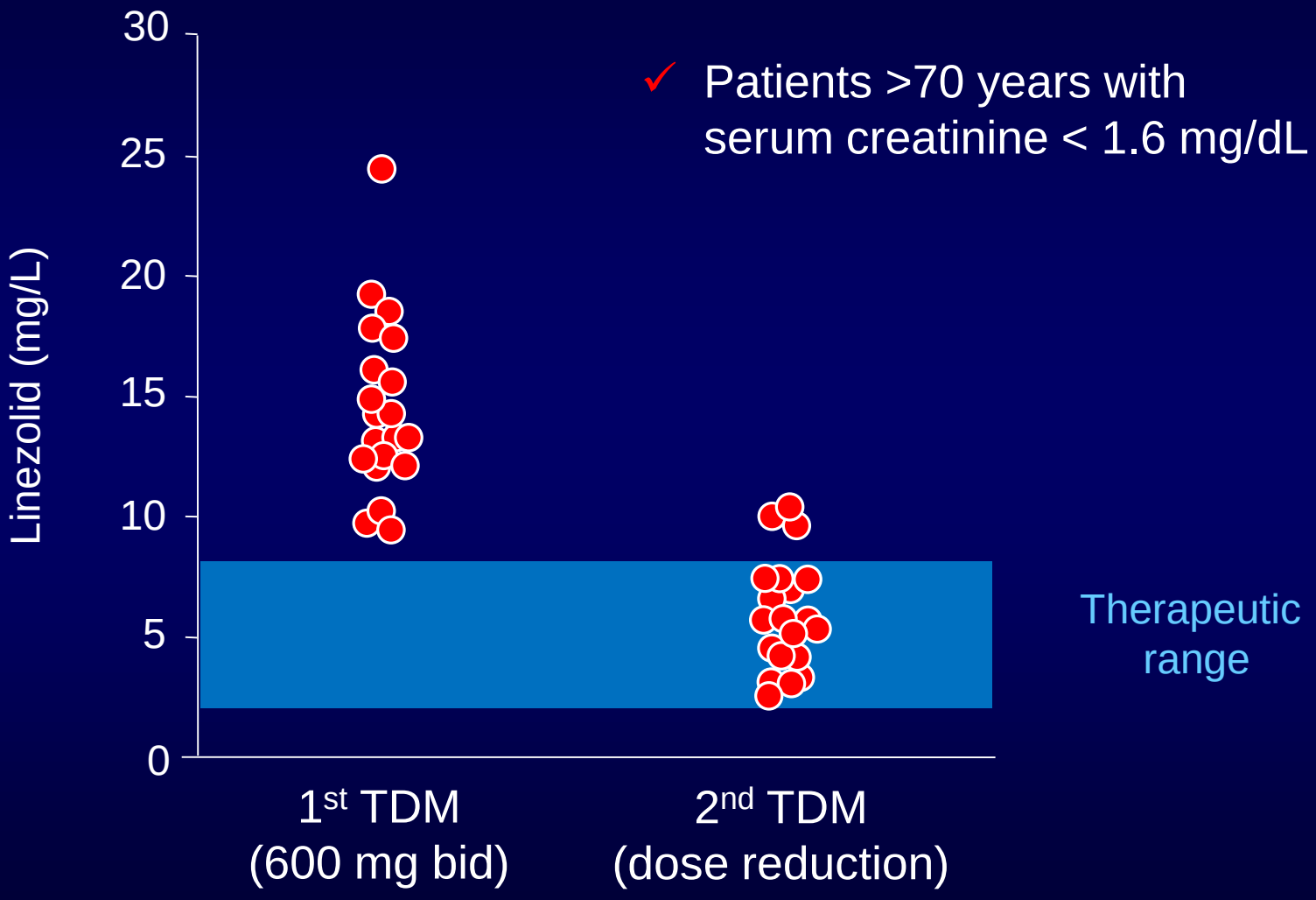

*- Dvorchik, J Clin Pharmacol 2006 -*

| Age quartiles | [Linezolid]$_{trough}$ |
|---|---|
| ≤ 40 yrs | 4.6 ± 4.9 mg/L |
| 40 – 60 yrs | 6.1 ± 4.5 mg/L |
| 60 – 80 yrs | 10.0 ± 7.0 mg/L** |
| > 80 yrs | 12.6 ± 9.3 mg/L** |




*- Cattaneo, IJAA 2016-*

# Is it time to revise linezolid doses in elderly patients?



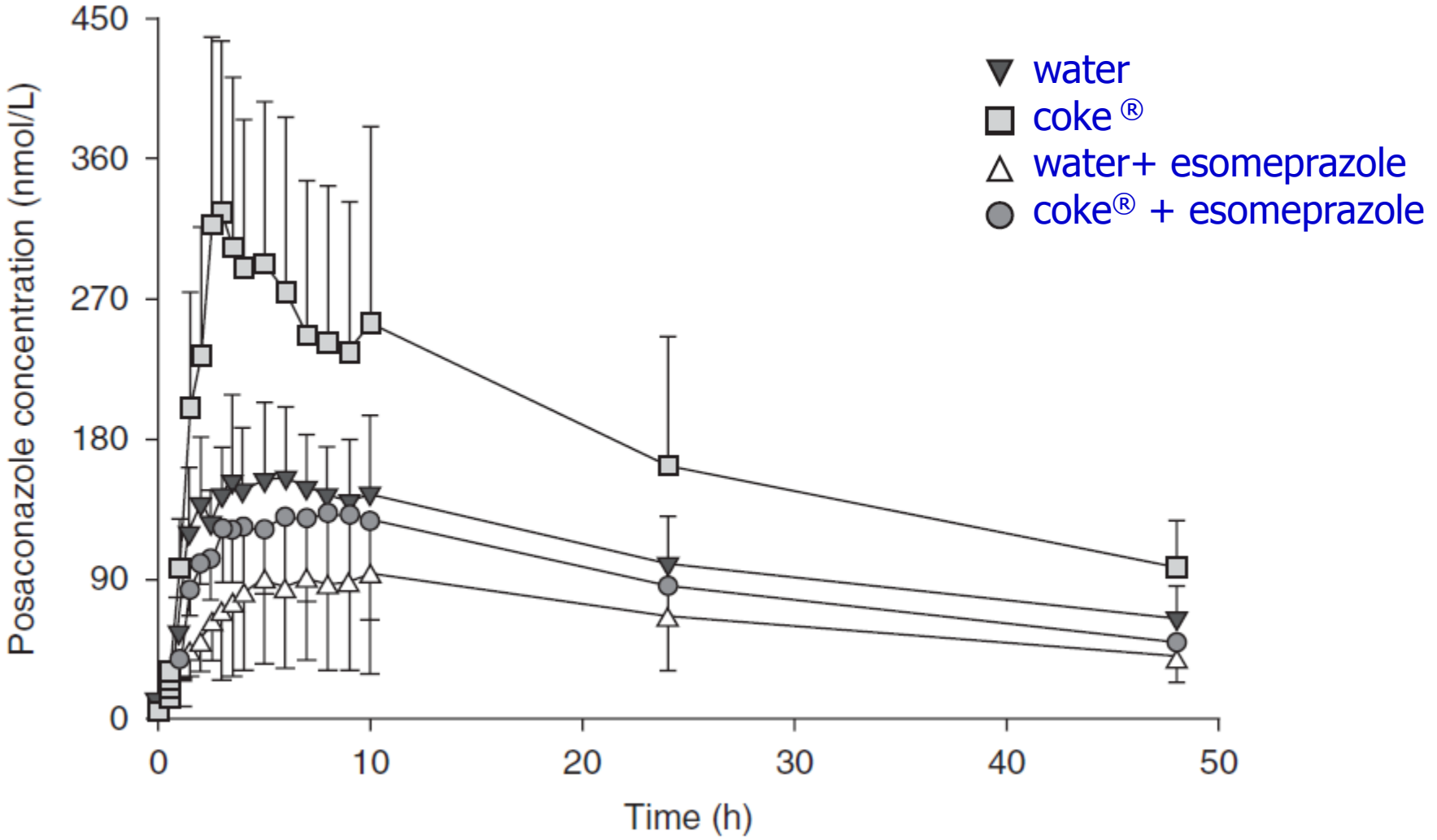

*- Cattaneo, Eur J Clin Pharmacol 2017 -*

# …senza dimenticare il ruolo delle politerapie...

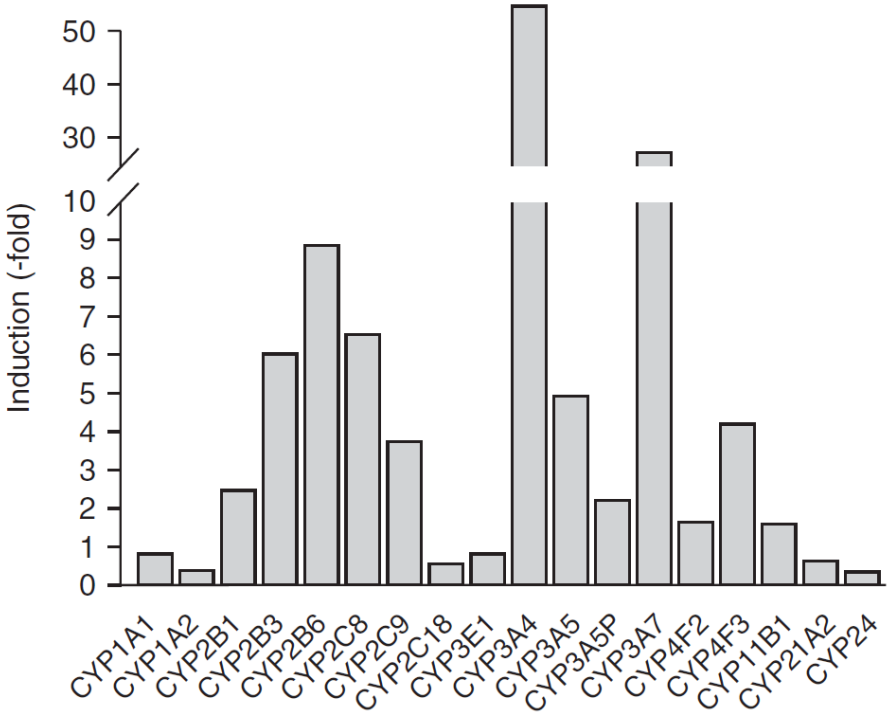
| Parameter | No. (%) of cases by linezolid $C_{min}$: | | *P* value |
|---|---|---|---|
| | ≥10 mg/liter (*n* = 33) | <10 mg/liter (*n* = 247) | |
| Linezolid administration route | | | |
| Intravenous | 21 (63.6) | 157 (63.6) | 0.847 |
| Oral | 12 (36.4) | 90 (36.4) | 0.845 |
| Linezolid dosage, median (IQ range) (mg/kg/q12h) | | | |
| Overall | 9.3 (7.5–10.2) | 8.0 (7.1–10.0) | 0.067 |
| Intravenous | 10.0 (7.9–10.0) | 8.0 (7.1–10.0) | 0.071 |
| Oral | 7.9 (7.9–10.3) | 8.5 (7.1–10.0) | 0.876 |
| Cotreatments | | | |
| Omeprazole | 26 (78.8) | 68 (27.5) | <0.001 |
| Amiodarone | 7 (21.2) | 6 (2.4) | <0.001 |
| Amlodipine | 7 (21.1) | 13 (5.2) | 0.003 |

*- Pea, AAC 2010 -*

# Variazioni nel pH possono determinare modifiche significative nell'assorbimento di un farmaco…



# Effects of rifampicin on cytochrome P450 (CYP) enzymes expression




Clin Pharmacokinet 2003; 42 (9): 819-850
0312-5963/03/0009-0819/$30.00/0

Eur J Clin Pharmacol (2015) 71:643–644
DOI 10.1007/s00228-015-1833-z

LETTER TO THE EDITORS

**Prolonged inductive effect of rifampicin on linezolid exposure**

**Cristina Gervasoni · Francesco R. Simonetti · Chiara Resnati · Nitin Charbe · Emilio Clementi · Dario Cattaneo**

"…the inductive effect of rifapicin on linezolid metabolism may persist up to 2-3 weeks after stopping the drug…"

# Quanto sono frequenti le DDIs…???

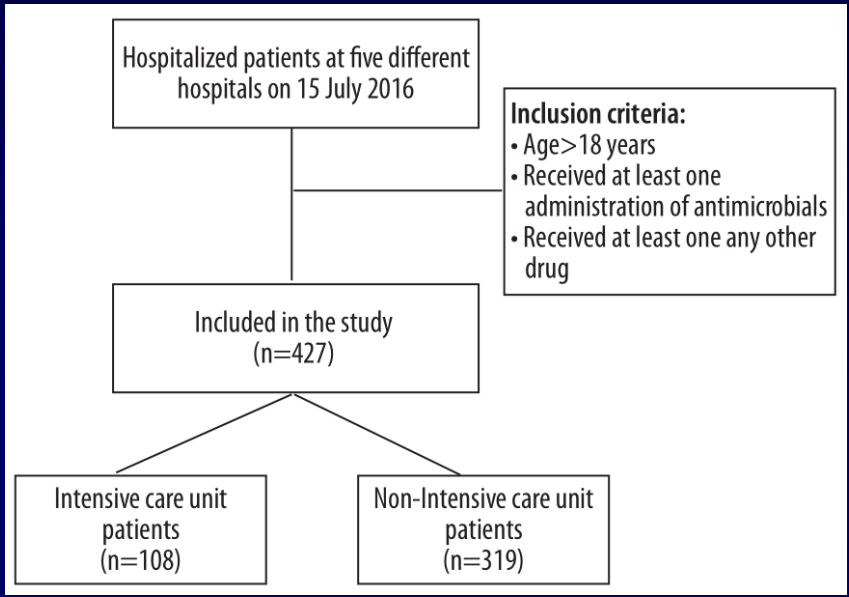
**Potential Drug–Drug Interactions Among Critically Ill Pediatric Patients in a Tertiary Pulmonary Center**

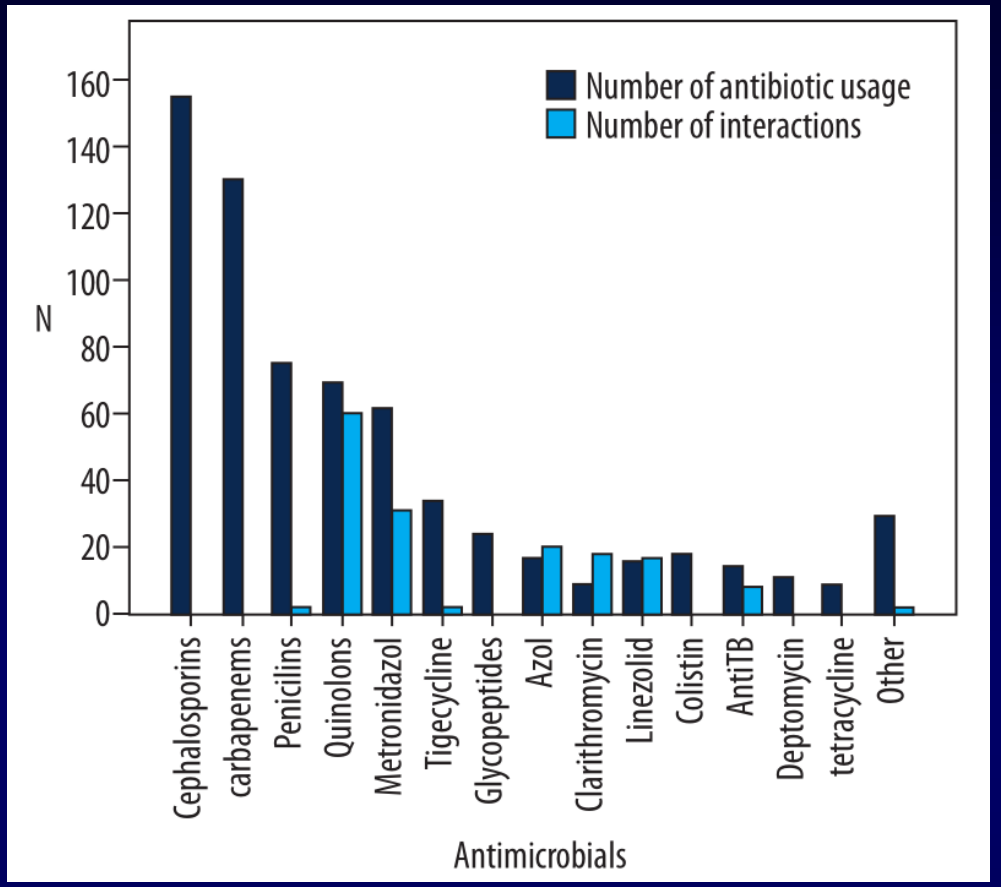
| Most Commonly Prescribed Drugs | Percentage of Prescriptions |
|---|---|
| Acetaminophen | 59.6% |
| Budesonide | 52.6% |
| Salbutamol | 49.1% |
| Ceftriaxone | 42.1% |
| Pantoprazole | 38.6% |
| Meropenem | 35.1% |
| Vancomycin | 36.8% |
| Azithromycin | 31.6% |
| Clindamycin | 28.1% |
| Zinc sulfate | 22.8% |
| Potassium chloride | 21.1% |
| Sodium chloride | 21.1% |

- ✓ Nearly 40% of the patients were exposed to at least 1 major and/or contraindicated interaction during ICU admission

The Journal of Clinical Pharmacology
2018, 58(2) 221–227

# Potential Drug–Drug Interactions with Antimicrobials in Hospitalized Patients: A Multicenter Point-Prevalence Study




| | Contraindicated | Major | Moderate | Minor | Total (%) |
|---|---|---|---|---|---|
| PDDIs with antimicrobials | 5 | 61 | 78 | 9 | 153 (26.4) |
| Other PDDIs | 7 | 159 | 229 | 31 | 426 (73.6) |
| Total (%) | 12 (2.0) | 220 (38.0) | 307 (53.0) | 40 (7.0) | 579 (100.0) |

GAP

Contents available at **PubMed**
**www.aidsreviews.com**

PERMANYER

**AIDS** Rev. 2019;21:1-10

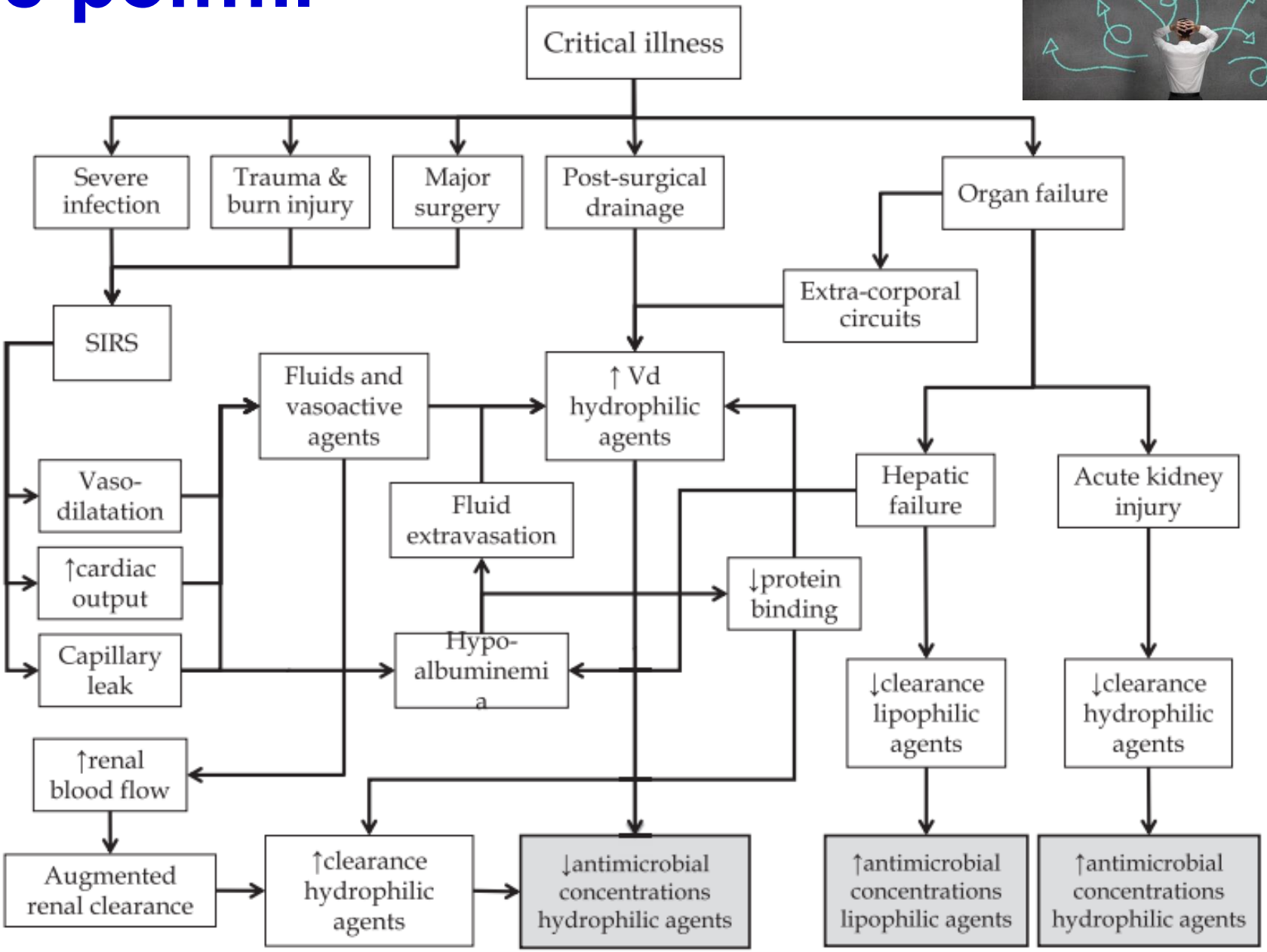
# Management of Polypharmacy and Drug-drug Interactions in HIV Patients: A 2-year Experience of a Multidisciplinary Outpatient Clinic

*Cristina Gervasoni[1,2], Tiziana Formenti[2] and Dario Cattaneo[1,3]*

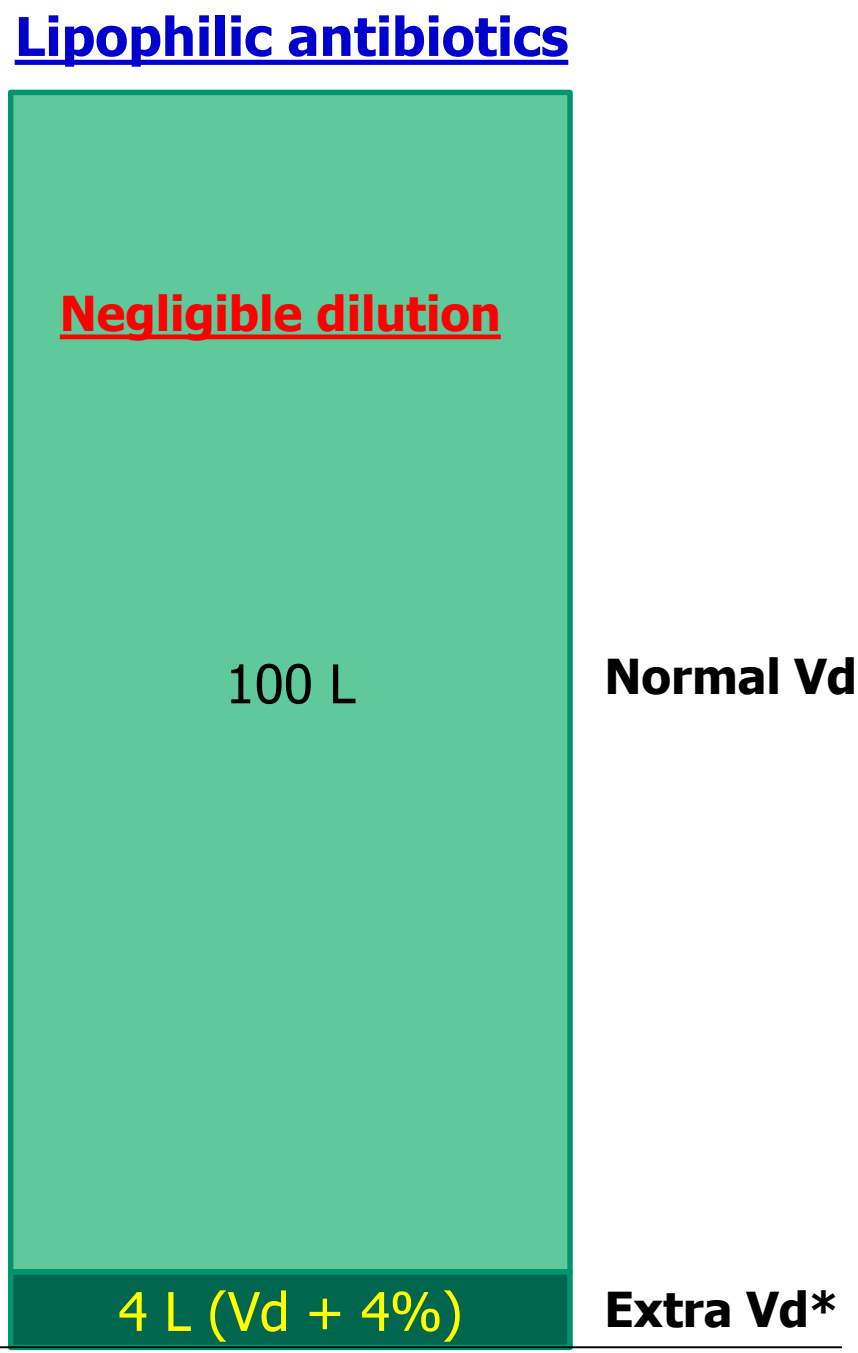
*[1]Gestione Ambulatoriale Politerapie Outpatient Clinic, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy; [2]Department of Infectious Diseases, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy; [3]Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy*

# ..e poi…..

S.I. Blot et al. / Advanced Drug Delivery Reviews 77 (2014) 3–11



*edema, accumulo di liquido extracellulare, accumulo volemico, capillary leakage, ecc



*edema, accumulo di liquido extracellulare, accumulo volemico, capillary leakage, ecc

**Lipophilic antibiotics**

**Negligible dilution**

100 L

**Normal Vd**

**4 L (Vd + 4%)**

**Extra Vd***

**High dilution**

**Hydrophilic antibiotics**

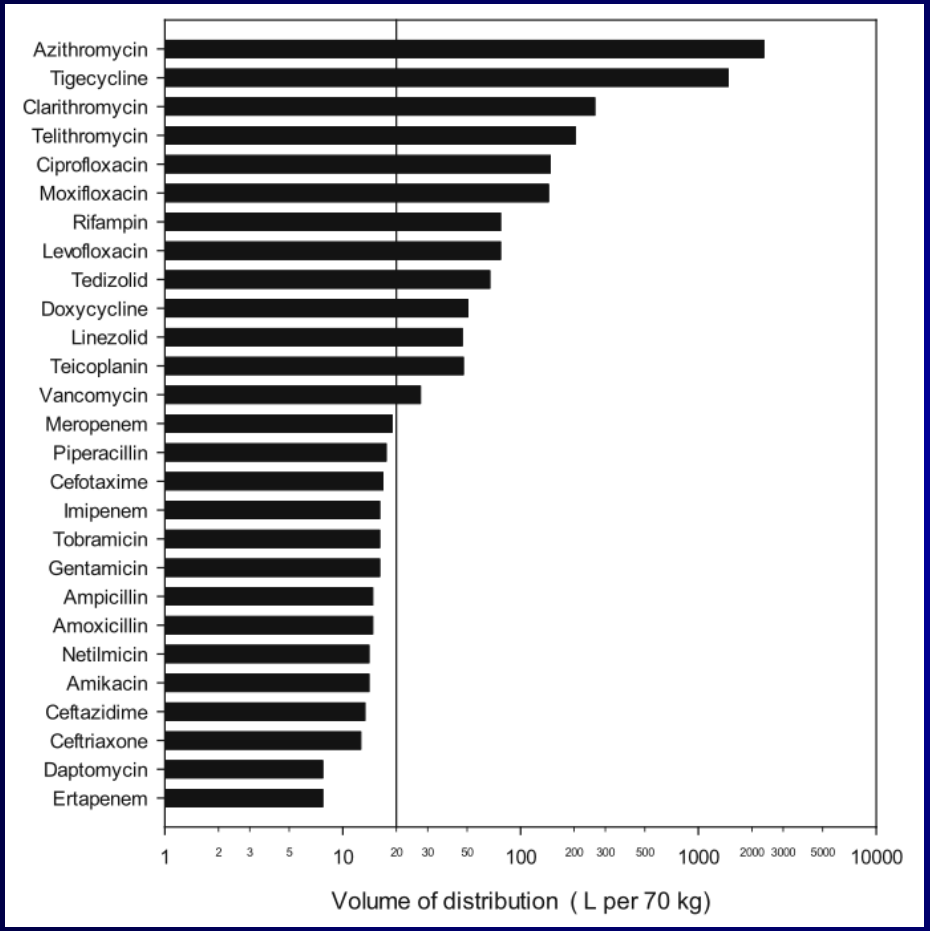
**Normal Vd**

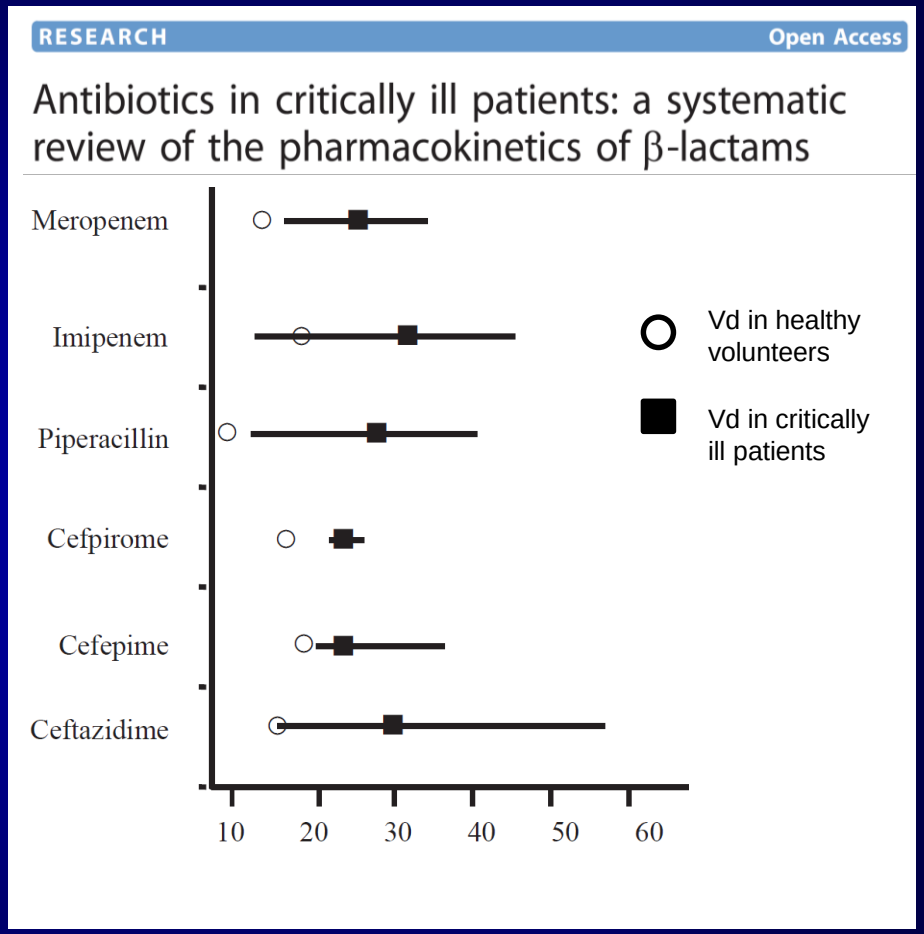
10 L

**Extra Vd***

4 L (Vd + 40%)

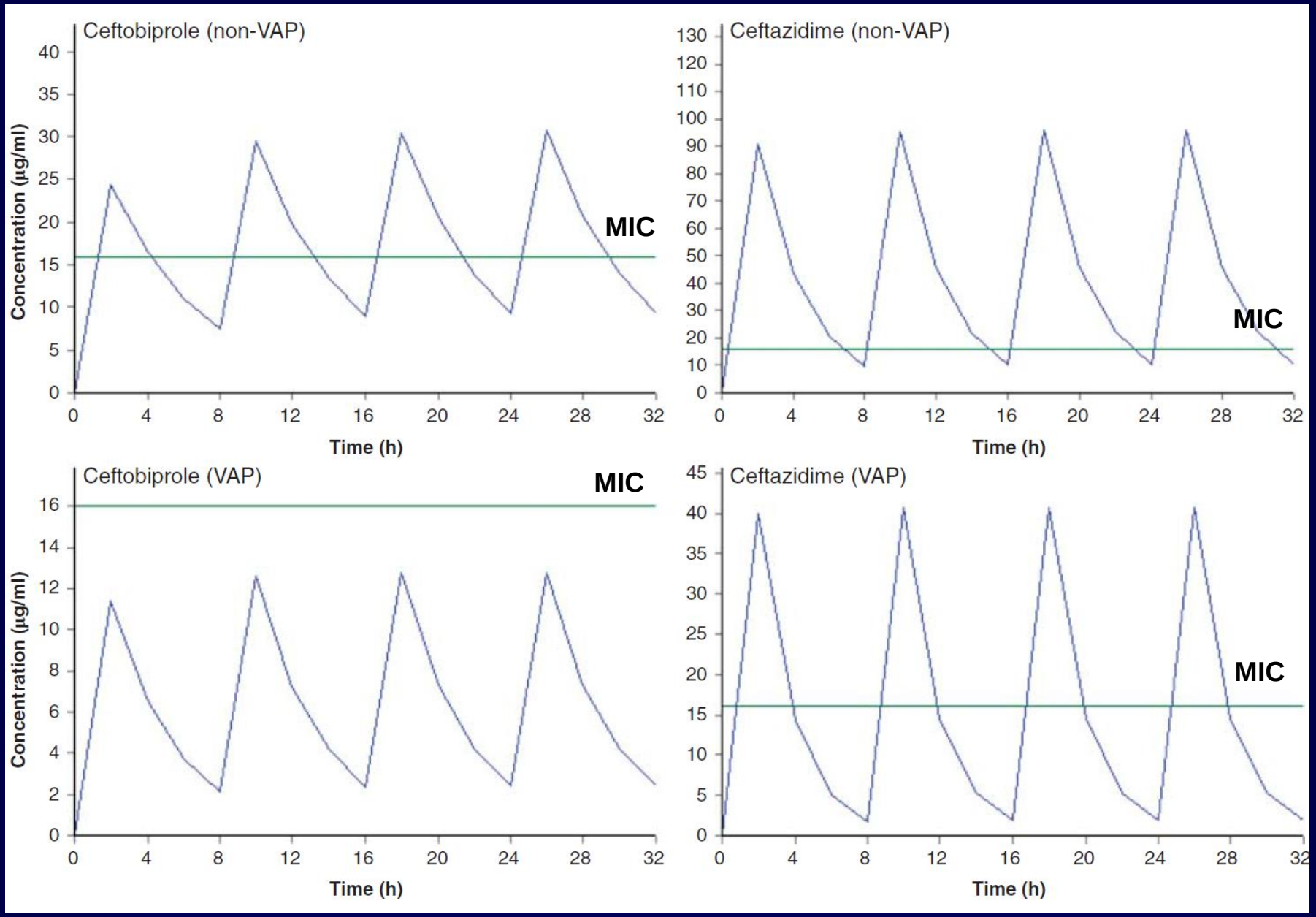
# Quali farmaci sono più a rischio…?




*- Pea, Clin Pharmacokinet 2018 -*

*- Pereira, Critical Care 2011 -*




"…In VAP patients ceftobiprole elimination is increased by 40% and Vd is doubled..."

*- Lagacé-Wiens, EODMT 2013 -*

**Spiegando risultati inattesi…**

# A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

**Table 2. Primary Endpoint: Clinical Cure at Test of Cure (Intent-to-Treat and Clinically Evaluable Analysis Sets)**

| | Ceftobiprole | | Ceftazidime/Linezolid | | |
|---|---|---|---|---|---|
| Analysis Set Group | No. | No.[a] (%) | No. | No.[a] (%) | Difference (%)[b] |
| Intent-to-treat | | | | | |
| All patients | 391 | 195 (49.9) | 390 | 206 (52.8) | −2.9 |
| HAP (excluding VAP) | 287 | 171 (59.6) | 284 | 167 (58.8) | 0.8 |
| VAP | 104 | 24 (23.1) | 106 | 39 (36.8) | −13.7 |
| HAP, mechanically ventilated | 69 | 21 (30.4) | 70 | 19 (27.1) | 3.3 |
| Clinically evaluable | | | | | |
| All patients | 251 | 174 (69.3) | 244 | 174 (71.3) | −2.0 |
| HAP (excluding VAP) | 198 | 154 (77.8) | 185 | 141 (76.2) | 1.6 |
| VAP | 53 | 20 (37.7) | 59 | 33 (55.9) | −18.2 |
| HAP (excluding VAP), mechanically ventilated | 38 | 21 (55.3) | 37 | 15 (40.5) | 14.7 |

***Conclusions.*** Ceftobiprole is a safe and effective bactericidal antibiotic for the empiric treatment of HAP (excluding VAP). Further investigations are needed before recommending the use of ceftobiprole in VAP patients.

*- Awad, CID 2014 -*

# Quindi ceftobiprolo non potrà mai essere utilizzato (*off-label*) per la terapia delle VAP?

**Pharmacokinetics, safety and tolerability of high-dose ceftobiprole medocaril administered as prolonged infusion in ICU patients**

| Parameter | Low[a] $CL_{CR}$ 50–79 mL/min [$n = 5$] | Normal[b] $CL_{CR}$ 80–150 mL/min [$n = 20$] | High[b] $CL_{CR}$ >150 mL/min [$n = 6$] |
|---|---|---|---|
| $C_{max}$ (mg/L) | 51.6 ± 11.2 | 37.8 ± 7.3 | 27.6 ± 7.3 |
| $t_{max}$ (h) | 4.7 (3.4–6.0) | 4.0 (3.5–4.5) | 3.9 (3.5–4.0) |
| $AUC_{last}$ (mg·h/L) | 405 ± 93.2 | 269 ± 116 | 180 ± 75.3 |
| $t_{½}$ (h) | 4.5 ± 1.0 | 3.8 ± 1.6 | 3.8 ± 1.2 |
| $V_{SS}$ (L) | 23.7 ± 6.6 | 23.1 ± 6.3 | 29.4 ± 7.5 |
| $CL_T$ (L/h) | 3.8 ± 0.6 | 5.2 ± 1.2 | 7.4 ± 1.5 |
| Protein binding (%) | 19.1 ± 4.4 | 20.5 ± 7.3 | 21.6 ± 3.5 |

Data are expressed as mean ± standard deviation, except for $t_{max}$, which is expressed as median (range)

*$AUC_{last}$* area under the plasma concentration–time curve from time zero to the last measurable concentration, $C_{max}$ maximum plasma concentration, *$CL_{CR}$* creatinine clearance, *$CL_T$* total systemic clearance, $t_{½}$ elimination half-life, *$t_{max}$* time to $C_{max}$, $V_{SS}$ volume of distribution at steady state

[a] Ceftobiprole 1000 mg administered as a 4-h infusion every 12 h

[b] Ceftobiprole 1000 mg administered as a 4-h infusion every 8 h

*- Torres, Clin Pharmacokinet 2016 -*

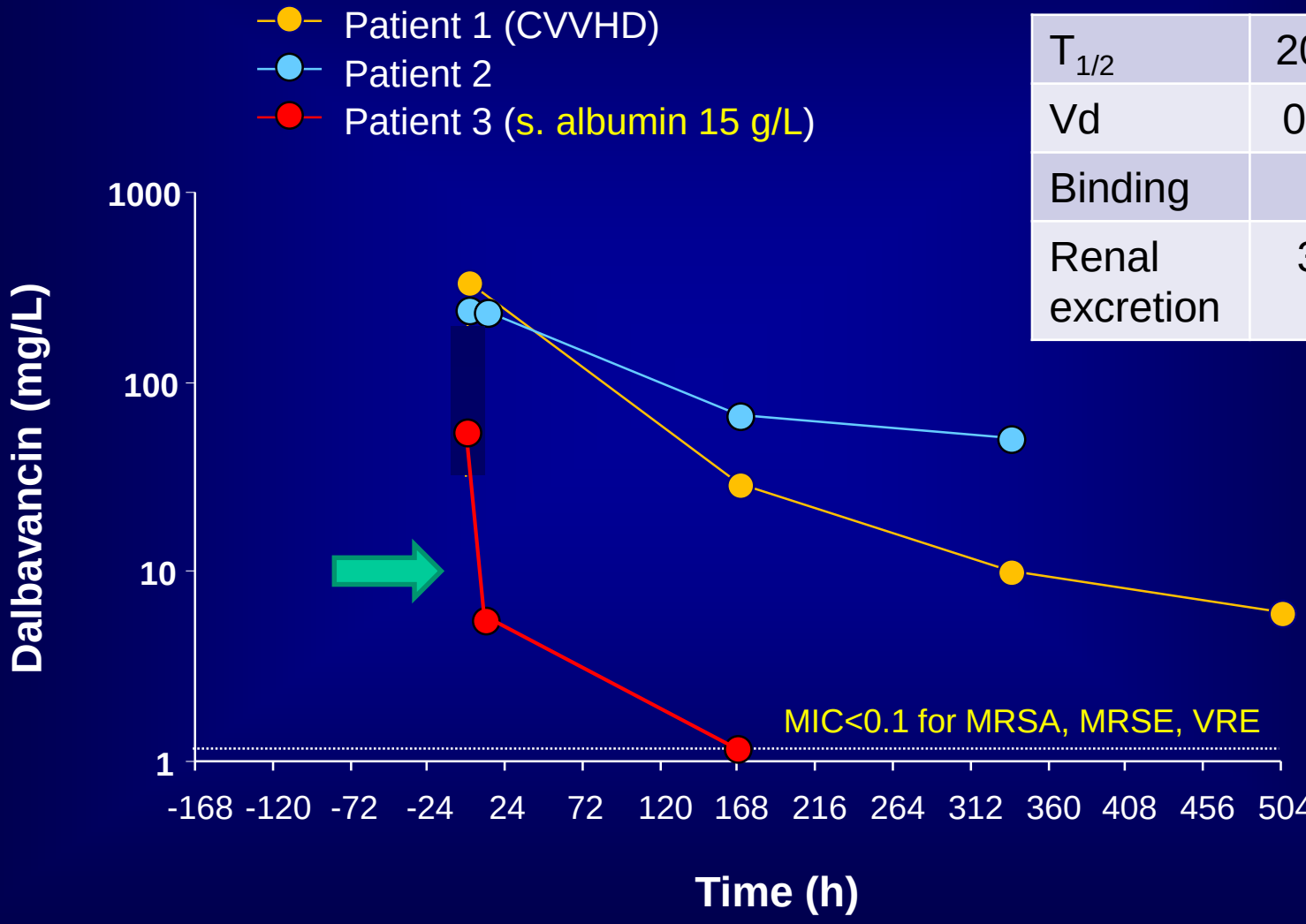
# Changes in drug clearance for highly bound antibacterials in patients with hypoalbuminemia

| Drug | % Protein binding in healthy volunteers | Change in clearance in ICU patients[a] |
|---|---|---|
| Aztreonam [26, 27] | 60 | 15 % increase |
| Ceftriaxone [10, 16] | 85–95 | 99 % increase |
| Daptomycin [28, 29] | 90–93 | 151 % increase |
| Ertapenem [30, 31] | 85–95 | 113 % increase |
| Ertapenem [14] | 85–95 | 462 % increase |
| Flucloxacillin [13, 32] | 95 | 10 % increase |
| Fusidic acid [33, 34] | 95–97 | 94 % increase |

[a]with serum albumin < 2 g/dL

*- Roberts, Clin Pharmacokinet 2013 -*

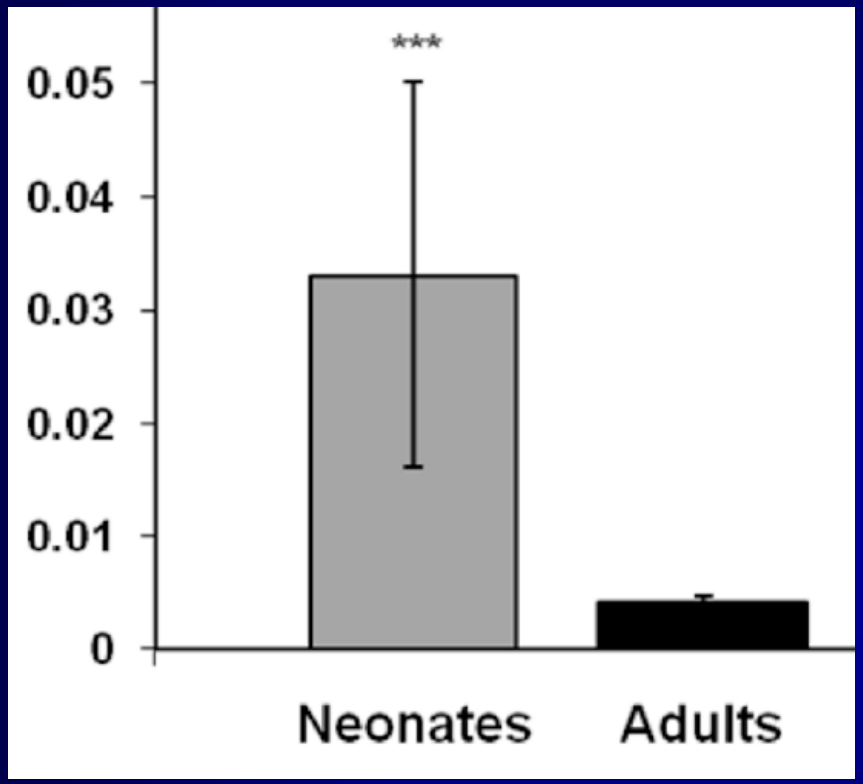
# PK of of dalbavancin in ICU patients…




| | |
|---|---|
| $T_{1/2}$ | 204 hours |
| Vd | 0.22 L/kg |
| Binding | 93% |
| Renal excretion | 35-50% |

*- Corona et al, submitted -*

# …As well as for antifungal drugs…




| | Adult | Neonate |
|---|---|---|
| drug CL (ml/min/Kg) | 0.17±0.01 | 0.79±0.09** |

*- Yanni, Biophar Drug Disp 2011 -*

Mean micafungin AUC in different subjects treated with the same dose

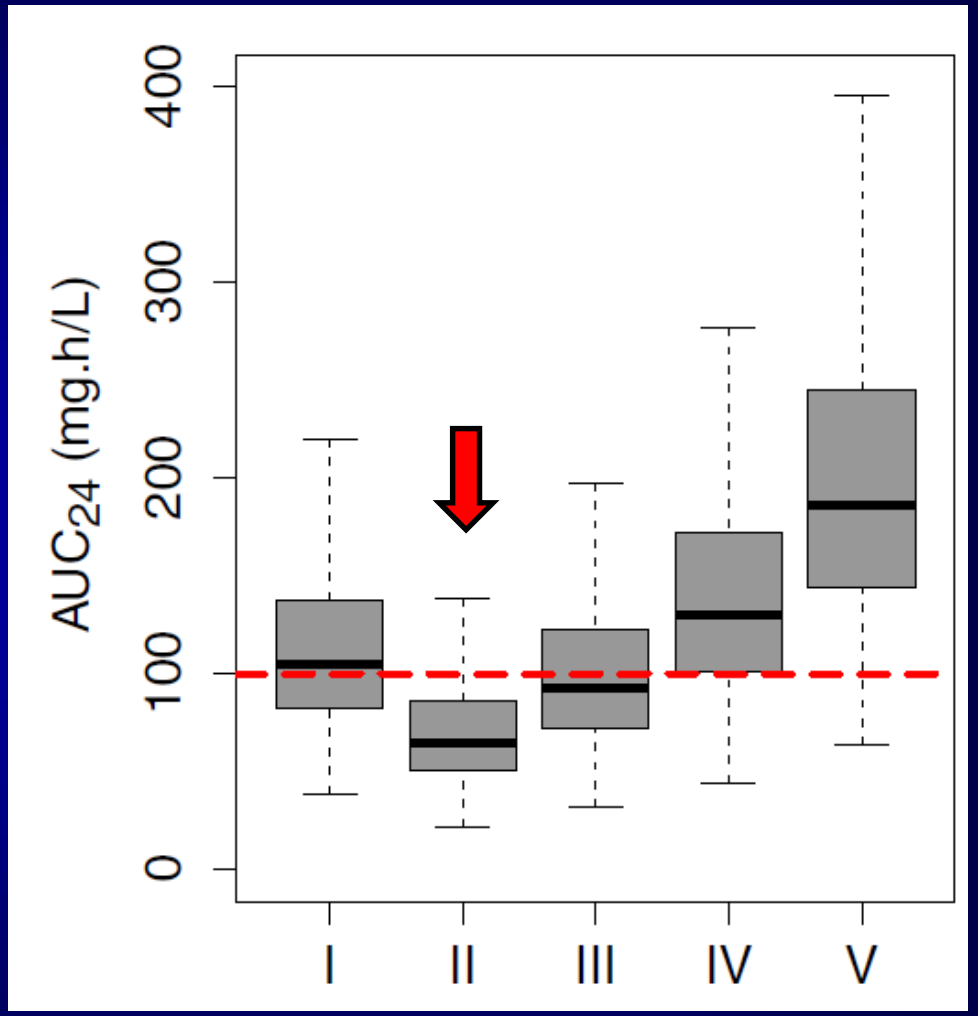
| | **Micafungin AUC** (mg*h/mL) |
|---|---|
| albumin <2.5 mg/L | 87 |
| albumin >2.5 mg/L | 99 |
| ICU patients | 78 |
| Non-ICU patients | 100 |
| Healthy volunteers | 135 |

*- Jullien, JAC 2016 -*

# ...Hypoalbuminemia and hepatic insufficiency…

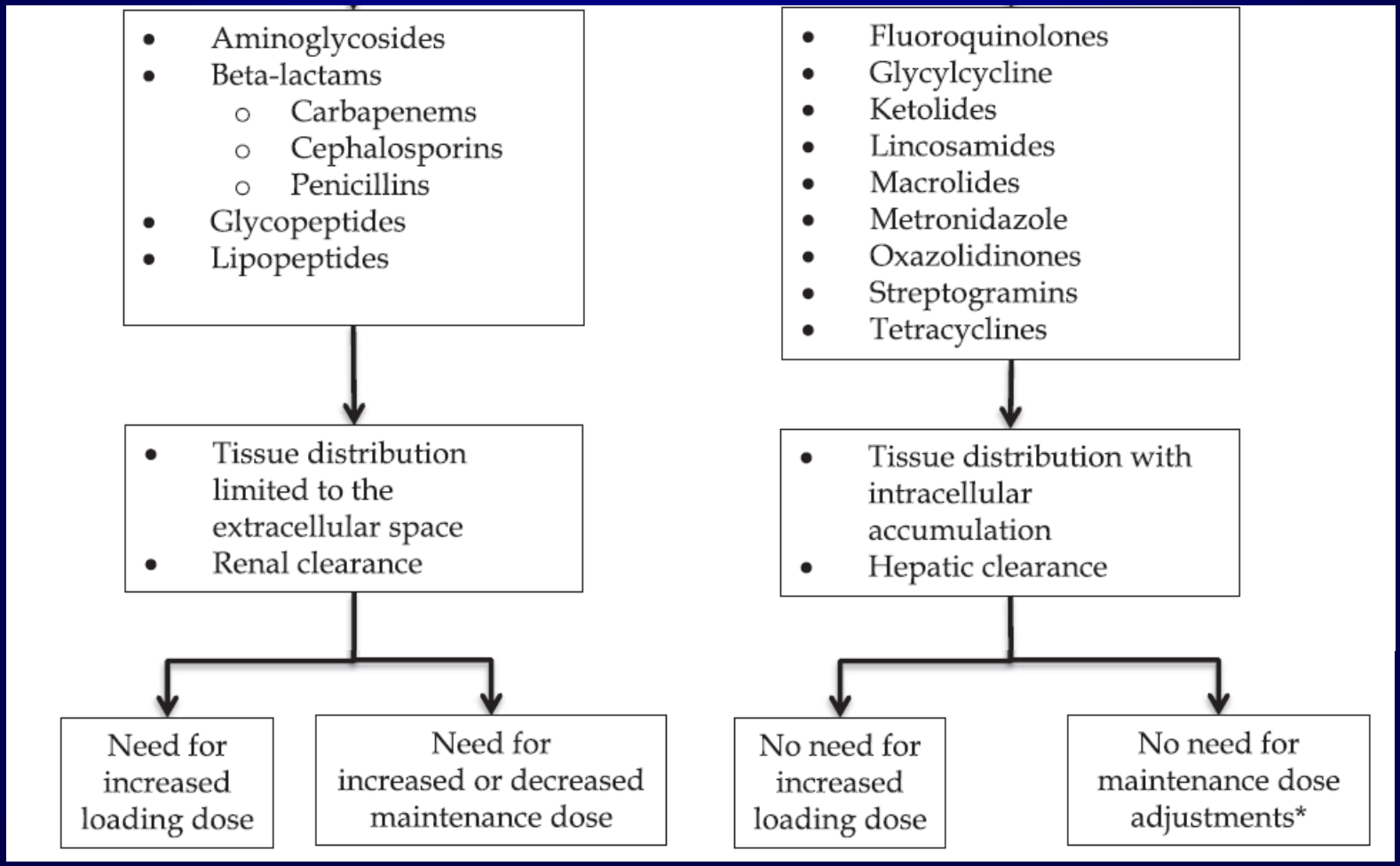
Caspofungin PK data from 21 ICU patients were used to simulate various drug dosing regimens by PopPK models:

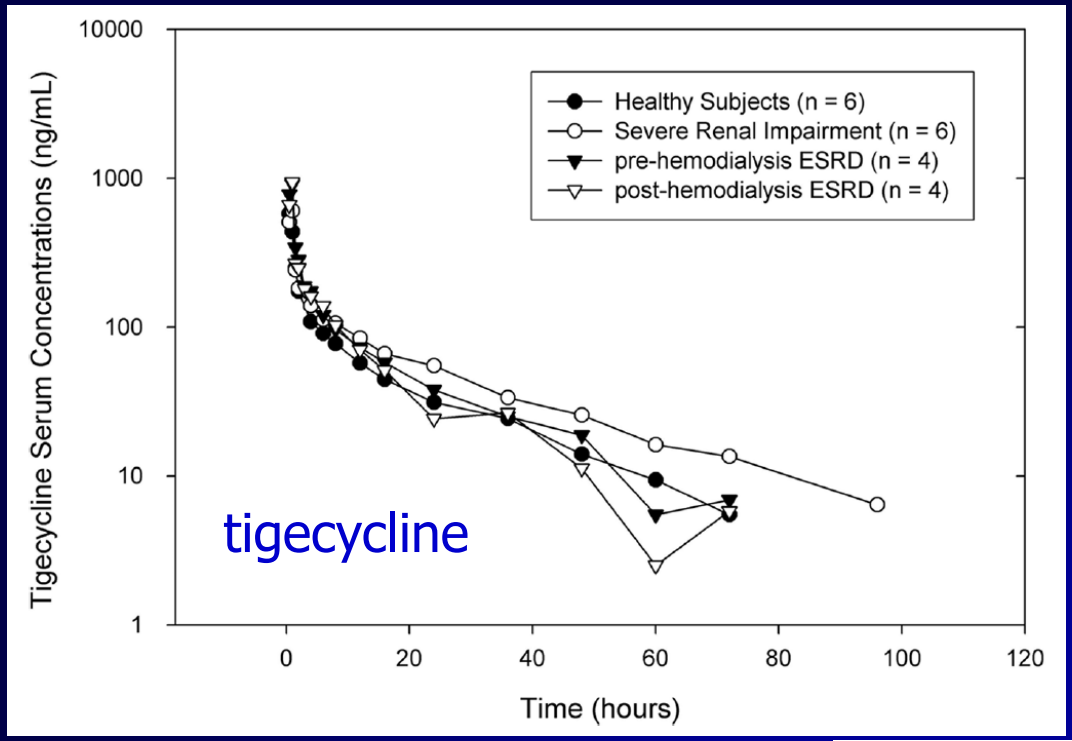
Licensed regimens:
(I) 70/50 mg or 70/70 mg (for BW>80 Kg)
(II) (II) 70/35 mg (for Child-Pugh score B);
Adapted regimens:
(III) 100/50 mg (for Child-Pugh score B)
(IV) 100/70 mg
(V) 100/100 mg




*- Martial, Clin Pharmacokinet 2016 -*

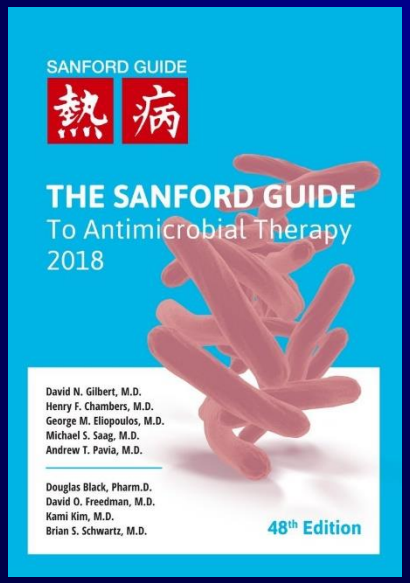
# Nei pazienti con insufficienza renale si modifica principalmente la farmacocinetica degli antibiotici più idrofili...

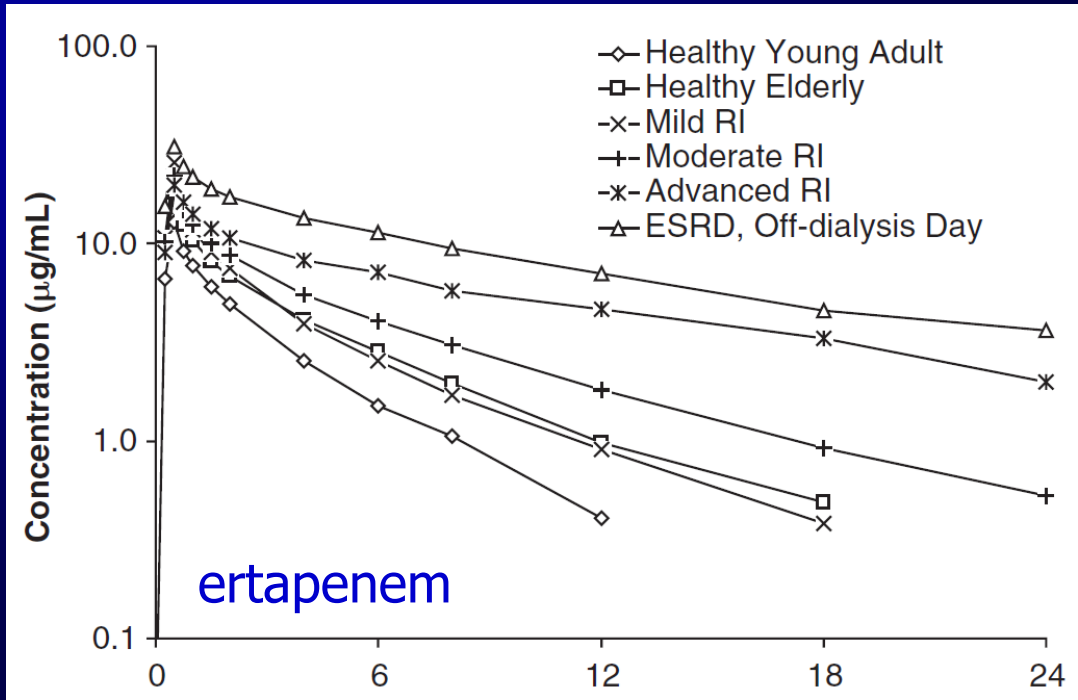





*- Mistry, J Clin Pharmacol 2006 -*

*- Korth-Bradley, J Clin Pharmacol 2011 -*



# …non sempre però tutto è cosi chiaro...

## Linezolid compresse

*Riassunto delle Caratteristiche del Prodotto –* *(Fonte: A.I.FA.)*

Pazienti con insufficienza renale:

Dopo singole dosi di 600 mg è stato osservato un incremento di 7-8 volte della esposizione ai due metaboliti primari del linezolid nel plasma di pazienti con insufficienza renale grave (cioè, clearance della creatinina < 30 ml/min). Non è stato tuttavia osservato un incremento della AUC del farmaco invariato. Sebbene si sia rilevata una certa eliminazione dei principali metaboliti del linezolid mediante emodialisi, dopo singole dosi di 600 mg i livelli plasmatici dei metaboliti erano sostanzialmente più elevati dopo dialisi rispetto a quelli osservati in pazienti con funzionalità renale normale o con insufficienza renale lieve o moderata.

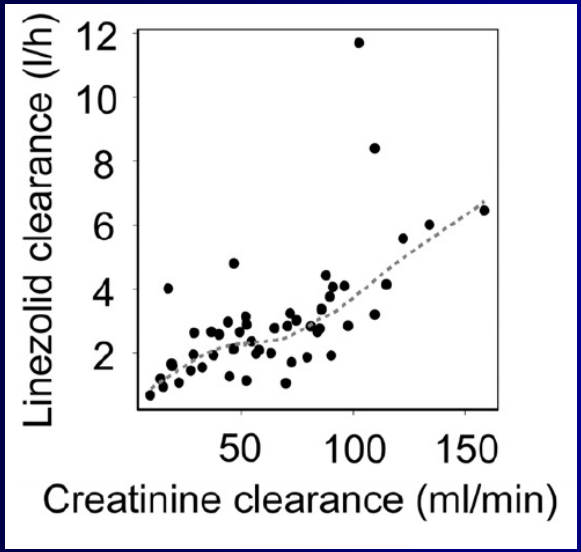
| Parameter | Healthy Subjects $CL_{CR}$ > 80 mL/min | Moderate Renal Impairment 30 < $CL_{CR}$ < 80 mL/min | Severe Renal Impairment 10 < $CL_{CR}$ < 30 mL/min |
|---|---|---|---|
| | | Linezolid | |
| $AUC_{0-\infty}$, µg h/mL | 110 (22) | 128 (53) | 127 (66) |
| $t_{1/2}$, hours | 6.4 (2.2) | 6.1 (1.7) | 7.1 (3.7) |

10.0 DATA DI REVISIONE DEL TESTO Indice

*Questo paragrafo risponde alle domande: Quando è stato rivisto e corretto da AIFA il testo di questa scheda tecnica di **Linezolid**?*

31/03/2015

# …non sempre però tutto è cosi chiaro...




*- Sasaki, AAC 2011 -*

| eGF-MDRD (ml/min)[a] | No. (%) of patients | Median $C_{min}$ in mg/liter (IQR)[b] |
|---|---|---|
| 0–40 | 11 (14.1) | 10.40 (2.32–18.40) |
| 41–80 | 31 (39.7) | 7.40 (3.10–11.90) |
| >80 | 36 (46.2) | 1.921 (0.85–5.85) |

*- Morata, AAC 2013 -*

| Effect on clinical outcome |
|---|
| Patients with renal insufficiency are more likely to experience LZD-related adverse events (mainly hematological, neurological, and metabolic complications) [15,20–23,44] |
| Patients undergoing peritoneal dialysis [27] or hemodialysis are more likely to experience LZD-related hematologic and metabolic complications [45] |

*- Cattaneo, Exp Opin Drug Metab Toxicol 2016 -*

# Comparative analyses involving patients that did or did not develop linezolid-related hematologic toxicity

| | pts without tox (m ± SD) | pts with tox (m ± SD) | P-value |
|---|---|---|---|
| Age (years) | 60.3 ± 22.5 | 76.3 ± 22.5 | 0.042 |
| Body Mass Index (Kg/m$^2$) | 24.2 ± 6.3 | 24.5 ± 0.4 | |
| **Creatinine Cl. (mL/min)** | **62.1 ± 32.2** | **34.3 ± 19.6** | **0.042** |
| AST (UI/L) | 61.6 ± 72.8 | 23.3 ± 4.4 | |
| ALT (UI/L) | 92.1 ± 116.3 | 21.3 ± 10.1 | |
| [LZD] day 3 (mg/L) | 12.3 ± 4.2 | 4.1 ± 2.6 | 0.002 |
| LZD dose (mg/12h) | 575 ± 72 | 600 ± 0 | |
| Days of LZD treatment | 7 ± 4 | 10 ± 6 | |

*- Cattaneo, Int J Antimicrob Agents 2013 -*

"…ricordiamoci inoltre che in alcuni pazienti (pazienti con shock settico, diabetici iperfiltranti) si può osservare un aumento della clearance renale con conseguente rischio di sottodosaggio del farmaco…"

| antibiotico | Clearance del farmaco nel volontario sano | Clearance del farmaco nel paziente critico |
|---|---|---|
| Cefpirome | 102 mL/min | 158 mL/min |
| Ceftriaxone | 19.8 mL/min | 41 mL/min |
| Ceftazidime | 116 mL/min | 125 mL/min |
| Piperacillin | 188 mL/min | 396 mL/min |
| **Ertapenem** | **29.5 mL/min** | **200 mL/min** |

*- Udy, Clin Pharmacokinet 2010 -*

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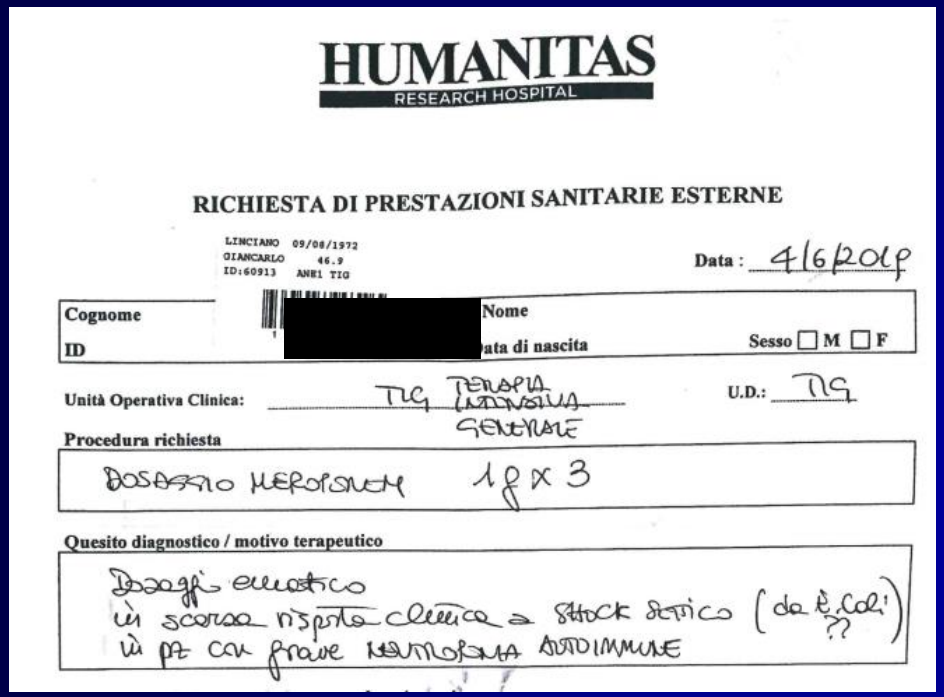


HUMANITAS
RESEARCH HOSPITAL

RICHIESTA DI PRESTAZIONI SANITARIE ESTERNE

LINCIANO 09/08/1972
GIANCARLO 46.9
ID:60913 ANNI TIO

Data : 4/6/2016

Cognome [redacted] Nome
ID ata di nascita Sesso ☐ M ☐ F

Unità Operativa Clinica: TIG TERAPIA INTENSIVA GENERALE U.D.: TIG

Procedura richiesta
DOSAGGIO MEROPENEM 1g x 3

Quesito diagnostico / motivo terapeutico
Dosaggi ematici
in scarsa risposta clinica → SHOCK SETTICO (da E. Coli ??)
in pz con grave NEUTROPENIA AUTOIMMUNE

Estimated creatinine Clearance: 500 mL/min!!!

TDM1
Meropenem <LOQ

Increased meropenem dose

TDM2
Meropenem: 1 mg/L*

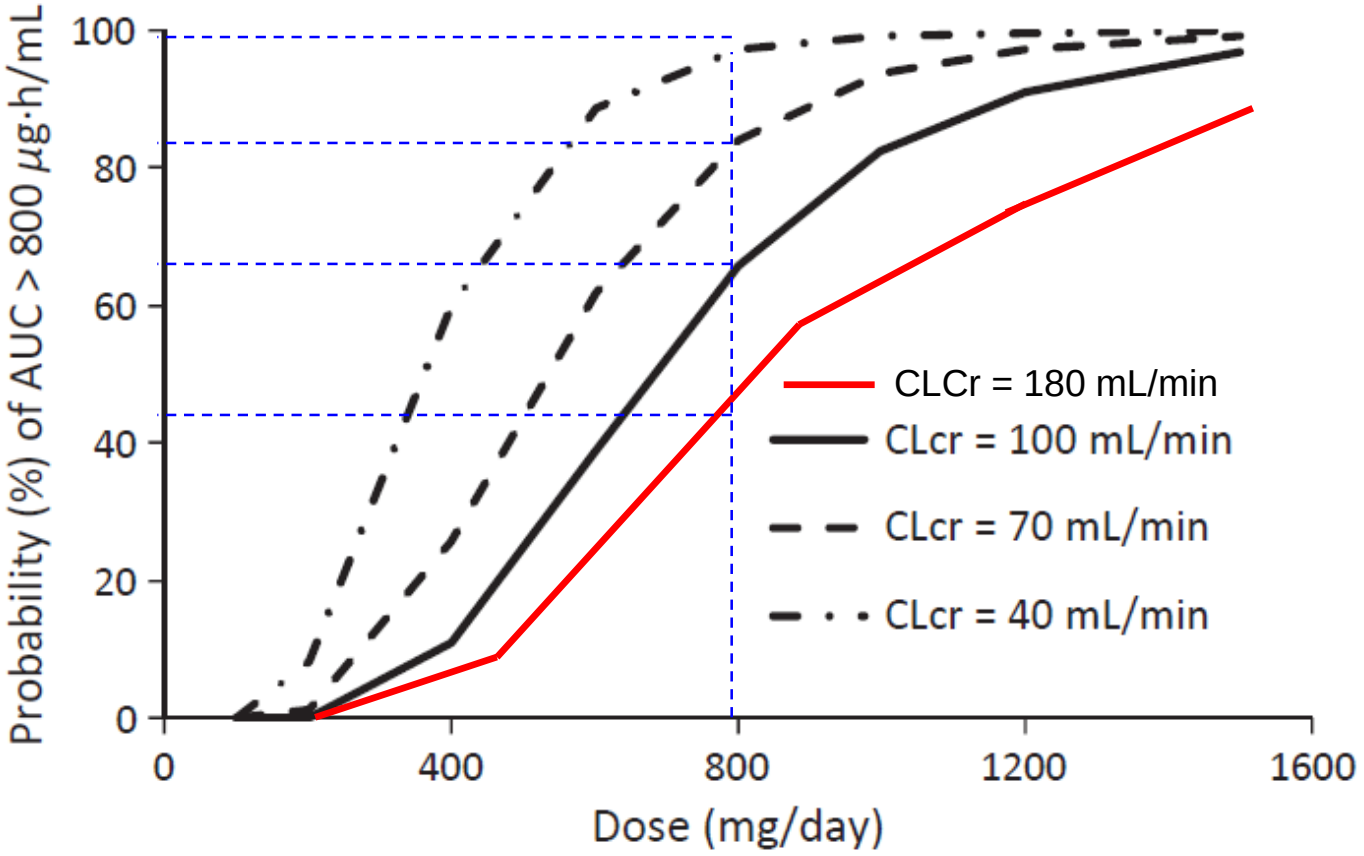
Increased meropenem dose

TDM3
Meropenem: 4,1 mg/L*

*MIC<2 mg/L

# ..this is true also for fluconazole…

Pharmacokinetics of fluconazole in critically ill patients




*Journal of Clinical Pharmacy and Therapeutics*, 2012, **37**, 356–363

# E poi ci sono le procedure dialitiche…..

| | Vancomycin | Meropenem | Cefepime | Piperacillin Tazobactam |
|---|---|---|---|---|
| Dose for normal renal function | 15–20 mg/kg q8–12 h | 1 g q8 h | 1–2 g q8-12 h | 3.375 g q6 h |
| Dose in CRRT | 500 mg q24–48 h | 500 mg q24 h | 2 g q24 h | 2.25 g q6 h |
| Dose in EHD[2] | No data | No data | No data | No data |
| Dose in IHD[3] | 15 mg/kg after HD | 500 mg q24 h | 1 g q24 h (+1 g after HD) | 2.25 g q12 h (+0.75 g after HD) |
| Dose in PD[4] | 7.5 mg/kg q2–3 days | 500 mg q24 h | 1–2 g q48 h | 2.25 g q6 h |

AUC, area under the curve; MIC, minimum inhibitory concentration; T, time; CRRT, continuous renal replacement therapy; IHD, conventional intermittent hemodialysis; EHD, prolonged or extended hemodialysis; HDI, intermittent hemodialysis; PD, peritoneal dialysis.

*- Zamoner, Pharmacol Res Perspect 2017 -*

# Le cose non vanno meglio per le nuove molecole…..

| Clearance creatinine | 30-50 mL/min | 10-30 mL/min | Intermittent dialysis | CVVHD |
|---|---|---|---|---|
| Telavacin | 7,5 mg/Kg every 24 h | 10 mg/kg every 48h | No data | No data |
| Dalbavancin | 1 g d1 + 0.5 g d7 | 750 mg d1+ 375 mg d7 | 1 g d1 + 0.5 g d7 | No data |
| Oritavancin | 1,2 g d1 | No data | No data | No data |

CVVHD: continuous veno-venous hemodialysis

# The issue of continuous venovenous hemofiltration procedures in ICU (CVVHD): preliminary results of an ongoing study

$$Sc = \frac{[drug]_{ultrafiltrate}}{[drug]_{plasma}}$$

| Drug | Sieving coefficient (Sc) |
|---|---|
| Vancomicin | 1,11 |
| Ciprofloxacin | 0,98 |
| Meropenem | 0,86 |
| Piperacillin | 0,80 |
| Levofloxacin | 0,79 |
| trimethoprim | 0,74 |
| Linezolid | 0,72 |
| Sulfametox. | 0,57 |
| Voriconazole | 0,29 |
| Rifampicin | 0,25 |
| Teicoplanin | 0,11 |
| Caspofungin | 0,02 |

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CURRENT OPINION

# Improving antibiotic dosing in special situations in the ICU: burns, renal replacement therapy and extracorporeal membrane oxygenation

*Janattul-Ain Jamal*[a], *Caleb J.P. Jason A. Roberts*[a,b,c]

Received: 3 June 2017 | Accepted: 7 September 2017

DOI: 10.1111/jcpt.12636

REVIEW ARTICLE

WILEY Journal of Clinical Pharmacy and Therapeutics

## Pharmacokinetic changes of antibiotic, antiviral, antituberculosis and antifungal agents during extracorporeal membrane oxygenation in critically ill adult patients

J. Hahn PharmD[1] | J. H. Choi PharmD[1] | M. J. Chang PhD[1,2]

## EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO is a highly invasive intervention that assists critically ill patients with severe lung and/or heart dysfunction. Generally, ECMO may cause increases in $V_d$ for certain drugs as well as the possible binding of drugs in the ECMO circuit [72]. However, the variable characteristics of ECMO technologies and settings (e.g. composition of tubing, flow rates and machine specifications) make comparisons between different pharmacokinetic studies challenging.

# …che fare per “pesare” tutti questi fattori???

EXPERT REVIEW OF CLINICAL PHARMACOLOGY, 2016
VOL. 9, NO. 7, 961–979
http://dx.doi.org/10.1586/17512433.2016.1172209

Taylor & Francis
Taylor & Francis Group

REVIEW

## Therapeutic drug monitoring of anti-infective agents in critically ill patients

Nynke G. L. Jager[a], Reinier M. van Hest[a], Jeffrey Lipman[b,c], Fabio S. Taccone[d] and Jason A. Roberts[b,c,e]

***“TDM is defined as the regular measurement of drugs concentrations requiring close 'titration' of doses in order to ensure that there are sufficient levels in the blood to be therapeutically effective, while avoiding potentially toxic excess”***

Ospedale Luigi Sacco
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UOSD Medicina di Laboratorio-Farmacologia Clinica
Farmacocinetica Tel. 02 50319619 Fax 02 50319646

UNIVERSITÀ DEGLI STUDI DI MILANO

COGNOME_____NOME_____

CODICE A BARRE DEL PRELIEVO

□ M □ F Data di nascita_____/_____/_____

Reparto:_____ Data e ora del prelievo:_____

Medico Richiedente_____

**SETTORE DI FARMACOCINETICA (PK) – Modulo di richiesta esami** M FACL 6 01 Rev.18 /P FACL 06

**SANGUE:** provetta da 4 ml con **EDTA** (tappo **VIOLA** cod 368861);
per dosaggi di 1-2 farmaci usare 1 provetta, per più di due farmaci usare 2 provette.
**NON** congelare prelievo

*Antiretrovirali*

- ❑ cod.51 P-Atazanavir
- ❑ cod.52 P-Darunavir
- ❑ cod.53 P-Efavirenz
- ❑ cod.54 P-Etravirina
- ❑ cod.55 P-Lopinavir
- ❑ cod.56 P-Maraviroc
- ❑ cod.57 P-Nevirapina
- ❑ cod.58 P-Raltegravir
- ❑ cod.59 P-Tipranavir
- ❑ cod.42 P-Amprenavir
- ❑ cod.43 P-Tenofovir
- ❑ cod.28 P-Saquinavir
- ❑ cod.14 P-Ritonavir
- ❑ cod.8016 P-Rilpivirina
- ❑ cod.8017 P-Elvitegravir
- ❑ cod.8018 P-Dolutegravir

*Altri Antinfettivi*

- ❑ cod.37 P-Teicoplanina
- ❑ cod.38 P-Levofloxacina
- ❑ cod.39 P-Rifampicina
- ❑ cod.45 P-Linezolid
- ❑ cod.46 P-Ciprofloxacina
- ❑ cod.47 P-Sulfametoxazolo
- ❑ cod.48 P-Trimetoprim
- ❑ cod.8012 P-Meropenem (**cons. +4°C**)
- ❑ cod.8013 P-Piperacillina (**cons. +4°C**)
- ❑ cod. 9 P-Voriconazolo
- ❑ cod.8007 P-Posaconazolo
- ❑ cod.8020 P-Isavuconazolo
- ❑ cod.8021 P-Itraconazolo
- ❑ cod.8019 P-Caspofungina
- ❑ cod. 44 P-Ribavirina

*Antiepilettici*

- ❑ cod.21 P-Lamotrigina
- ❑ cod.22 P-Etosuccimide
- ❑ cod.23 P-Zonisamide
- ❑ cod.24 P-Rufinamide
- ❑ cod. 2 P- Levetiracetam
- ❑ cod.15 P-Topiramato
- ❑ cod.18 P-Felbamato
- ❑ cod.20 P-Oxcarbazepina
- ❑ cod.8014 P-Perampanel
- ❑ cod.8015 P-Lacosamide

*Antipsicotici/antidepressivi*

- ❑ cod. 25 P-Citalopram/ Escitalopram
- ❑ cod. 29 P-Quetiapina
- ❑ cod. 30 P-Paroxetina
- ❑ cod. 31 P-Aripiprazolo
- ❑ cod. 32 P-Olanzapina (**cons. +4°C**)
- ❑ cod. 33 P-Risperidone (**cons. +4°C**)
- ❑ cod. 34 P-Haloperidolo
- ❑ cod. 35 P-Clozapina
- ❑ cod. 36 P-Paliperidone (**cons. +4°C**)
- ❑ cod. 41 P-Fluoxetina (**cons. +4°C**)
- ❑ cod. 93 P-Duloxetina
- ❑ cod. 94 P-Flufenazina
- ❑ cod. 95 P-Clomipramina (**cons. +4°C**)
- ❑ cod. 96 P-Venlafaxina (**cons. +4°C**)
- ❑ cod. 98 P-Ziprasidone
- ❑ cod. 99 P-Sertralina

*Immunosoppressori*

- ❑ cod.461 Sg-Ciclosporina
- ❑ cod.8026 Sg-Sirolimus
- ❑ cod.8025 Sg-Everolimus
- ❑ cod.8024 Sg-Tacrolimus
- ❑ cod.8023 P-Acido micofenolico

*Varie*

- ❑ cod.49 P-Ibuprofene

**SANGUE:**
una provetta da 4 ml tappo **ROSA** cod 368813

- ❑ cod. 550 S-Chinidina
- ❑ cod. 500 S-Valproato
- ❑ cod. 546 S-Carbamazepina
- ❑ cod. 431 S-Fenobarbitale
- ❑ cod. 597 S-Fenitoina
- ❑ cod. 460 S-Primidone
- ❑ cod. 521 S-Gentamicina
- ❑ cod. 522 S-Vancomicina
- ❑ cod. 433 S-Litio
- ❑ cod. 472 S-Teofillina
- ❑ cod. 8005 S-Amikacina
- ❑ cod. 8006 S-Paracetamolo

**Profilo farmacocinetico (AUC)**
Per misure del farmaco/i ripetute nell'arco della giornata indicare tempi dei prelievi:

- ❑C0 ora prelievo .....
- ❑ **ora assunzione farmaco** .....
- ❑ C1 ora prelievo .....
- ❑ C2 ora prelievo .....
- ❑ C3 ora prelievo .....
- ❑ C4 ora prelievo .....
- ❑ C5 ora prelievo .....

- ❑ Gentamicina
- ❑ Amikacina
- ❑ Vancomicina
- ❑ Teicoplanina
- ❑ Ciprofloxacina
- ❑ Levofloxacina
- ❑ Rifampicina
- ❑ Linezolid
- ❑ Meropenem
- ❑ Piperacillina
- ❑ Trimetoprim/SMTX
- ❑ Voriconazolo
- ❑ Posaconazolo
- ❑ Isavuconazolo
- ❑ Itraconazolo
- ❑ Caspofungina

A breve

- ❑ Dalbavancina
- ❑ Fosfomicina
- ❑ Ceftazidime/avibactam
- ❑ Ampicillina
- ❑ Cefepime

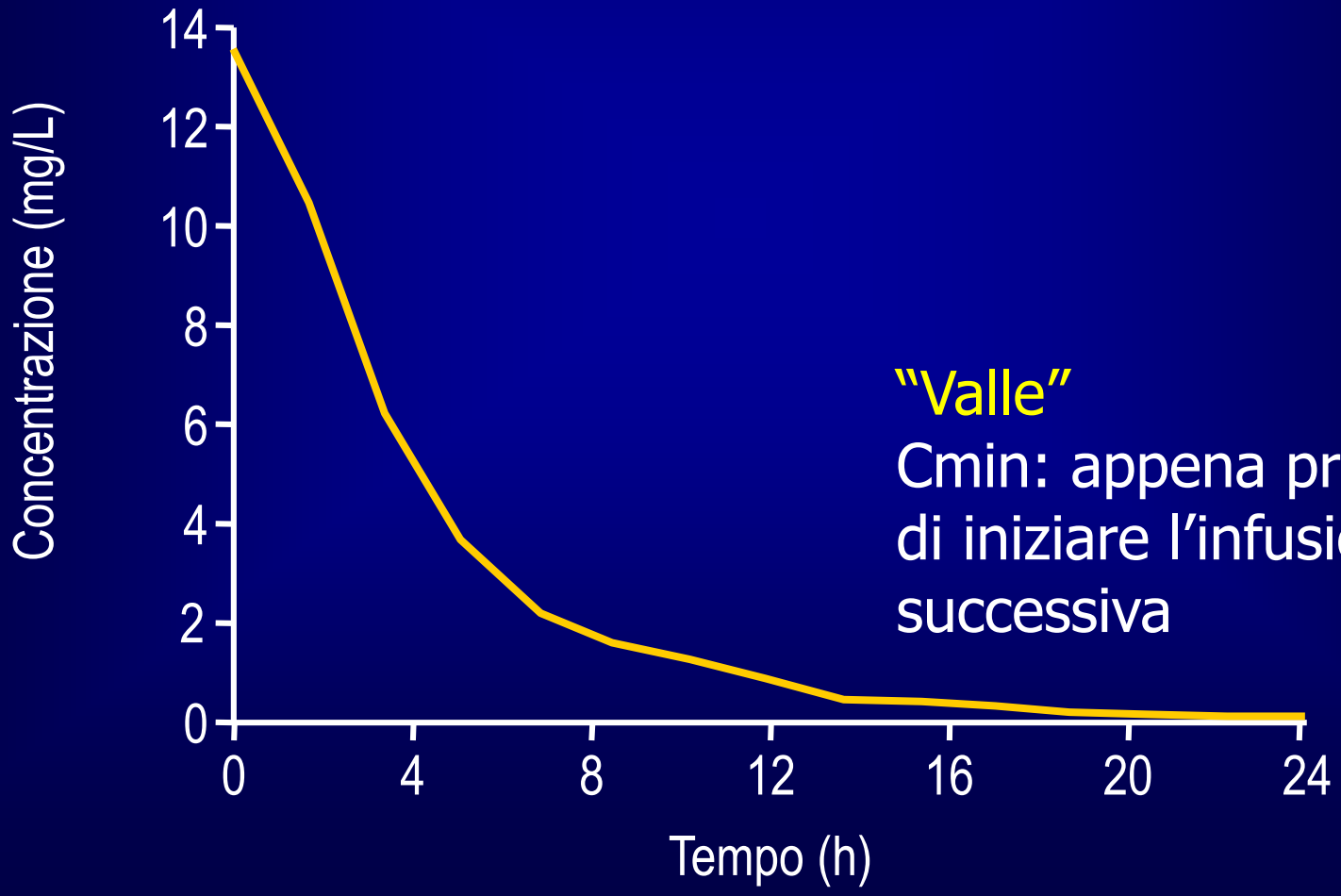
# *Un pò di informazioni pratiche….*

| Farmaco | Concentrazioni Basali (Cmin, mg/L) | Concentrazioni di picco (Cmax, mg/L) |
|---|---|---|
| Gentamicina | 0.5 – 2.0 | 5 – 10 |
| Vancomicina | 10 – 20 | 30 – 40 |
| Teicoplanina | 10 – 60 | |
| Linezolid | 2 – 8 | |
| Levofloxacina | | 5 – 15 |
| Rifampicina | | 8 – 24 |
| Amikacina | <1.0 | 40-60 |
| sulfametoxazolo | | 100-150 |
| Ciprofloxacina | 0.5 – 3.0 | |
| Meropenem | Cmin>MIC | |
| piperacillina | Cmin>MIC | |

***Cmin, Cmax….o che altro???***

# .. somministrazione E.V...

"Picco"
Cmax: 30 minuti dopo il termine dell'infusione




"Valle"
Cmin: appena prima di iniziare l'infusione successiva

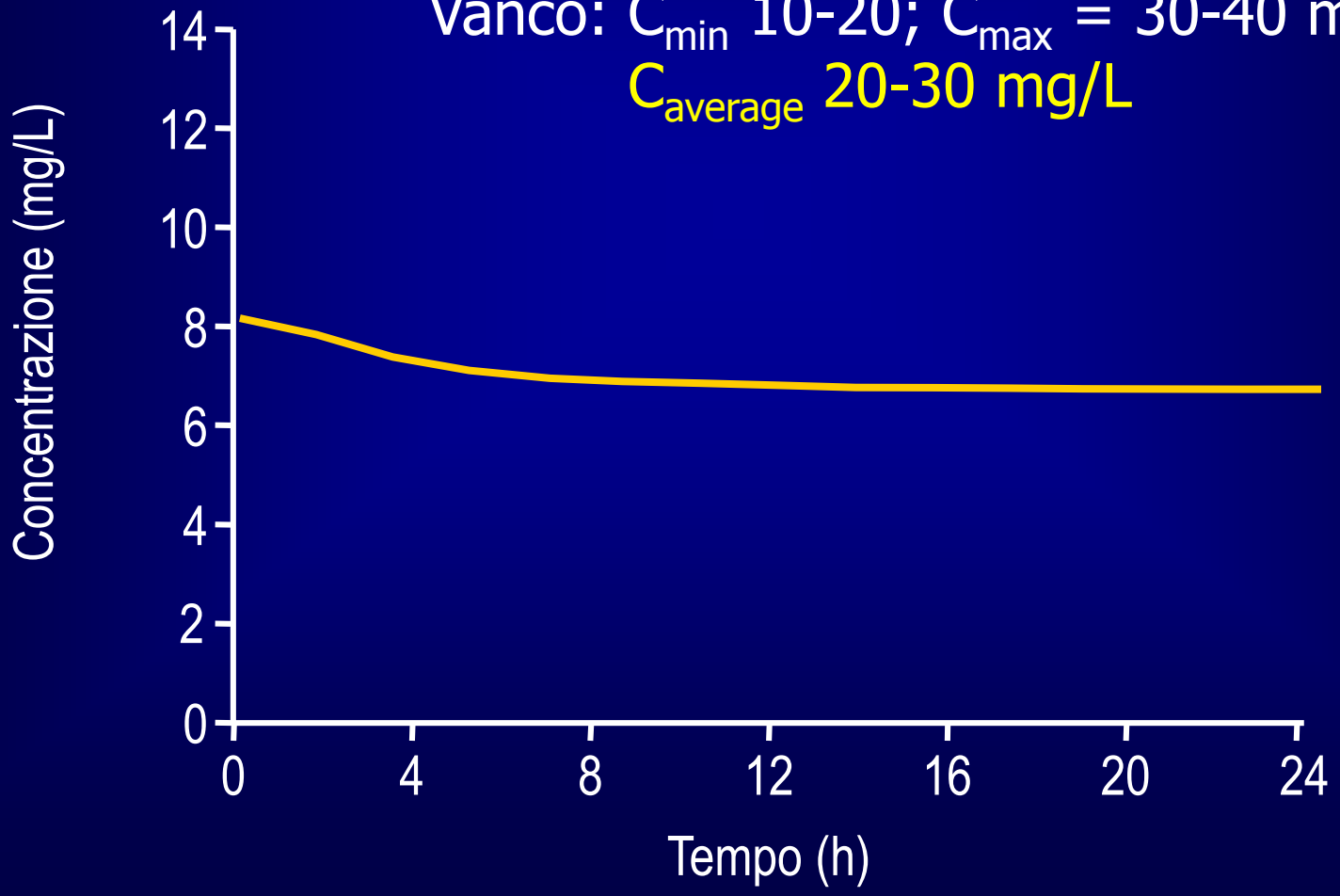
# .. Infusione continua...

"Picco" = "valle"

Posso campionare in qualsiasi momento...

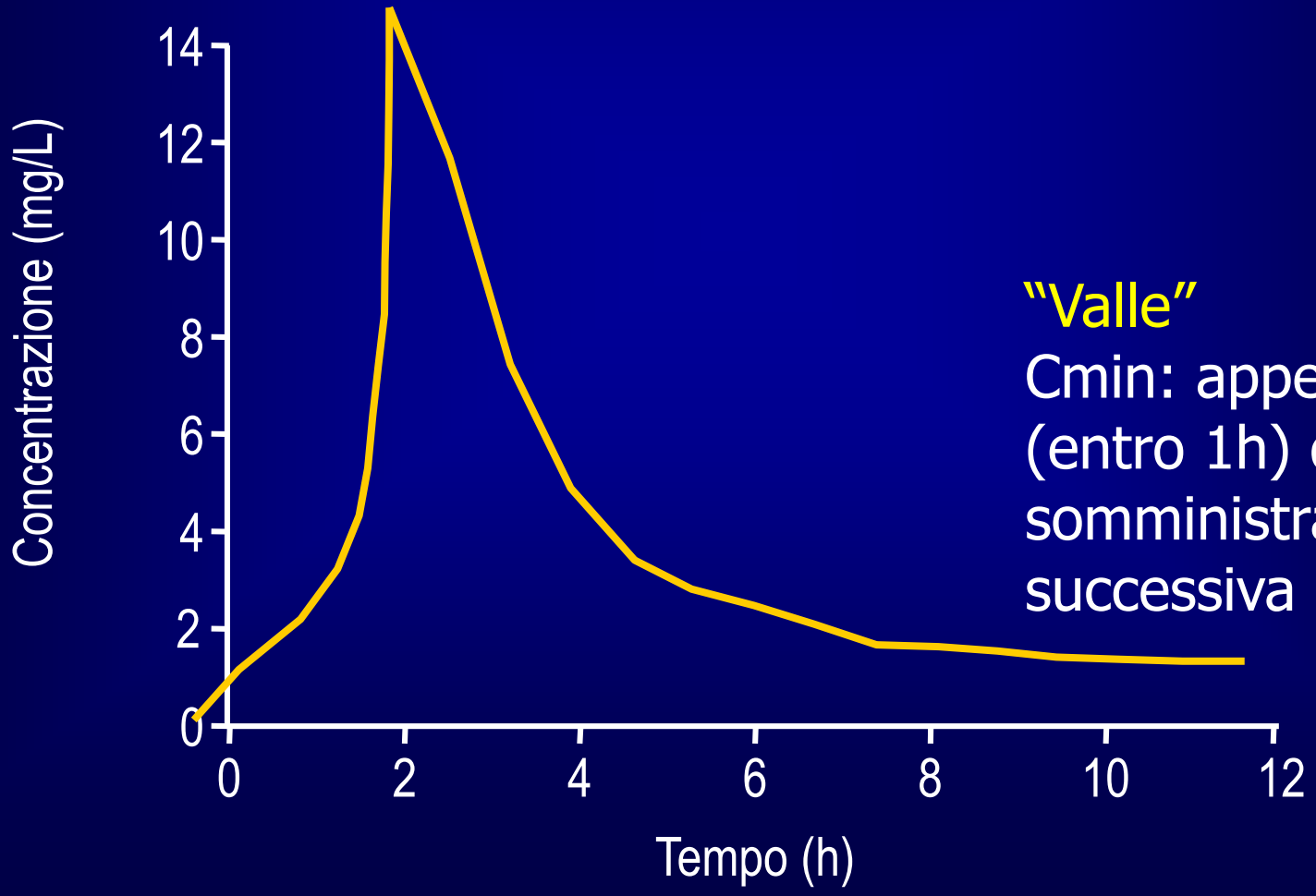
Vanco: $C_{min}$ 10-20; $C_{max}$ = 30-40 mg/L

$C_{average}$ 20-30 mg/L



# .. somministrazione per OS...

"Picco"
Cmax: 2 ore dopo la somministrazione




"Valle"
Cmin: appena prima (entro 1h) della somministrazione successiva

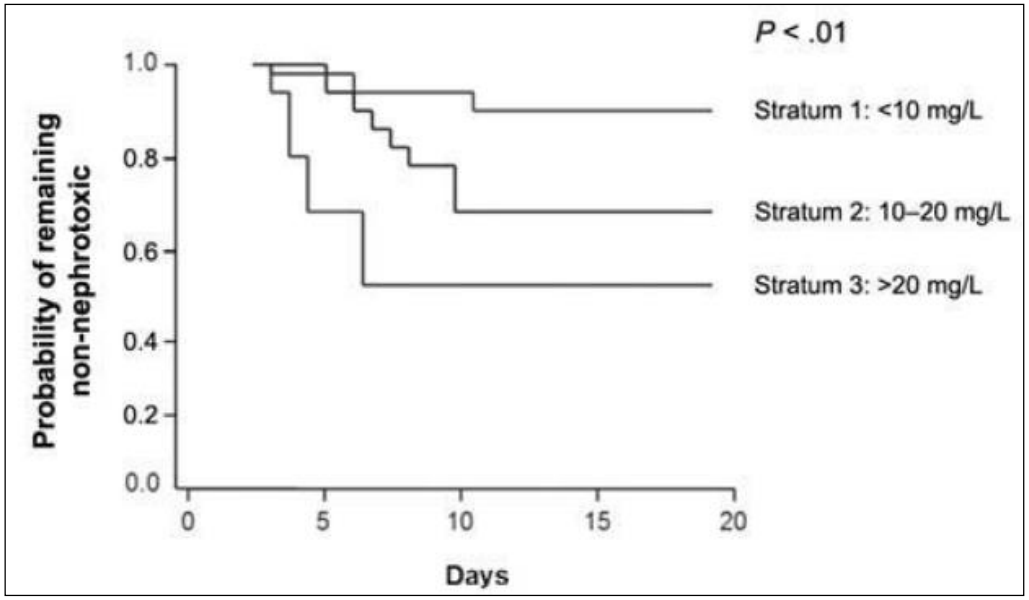
# Vancomycin: our “top player” (3000 TDM/year)

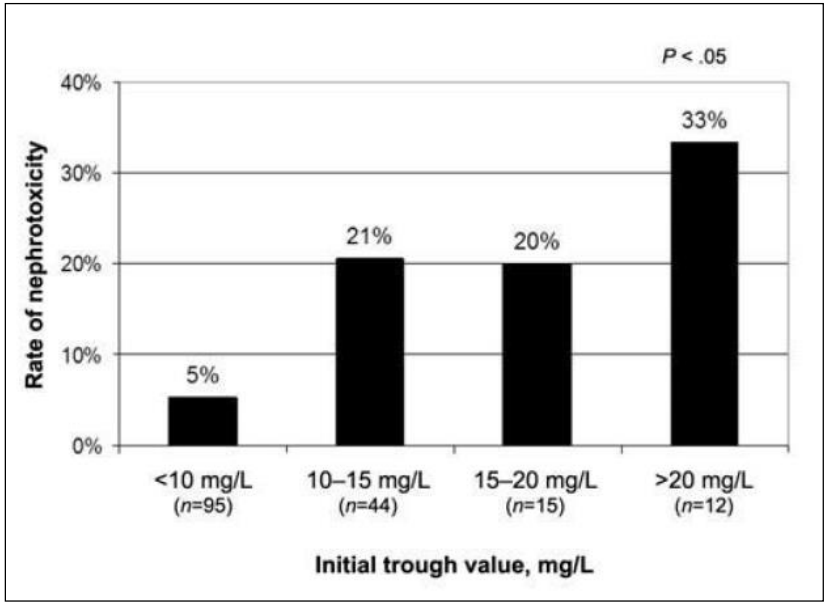
Clinical Infectious Diseases

## Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

**Table 1. Bivariate Analysis of the Relationship between the Vancomycin Exposure Profile and Nephrotoxicity**

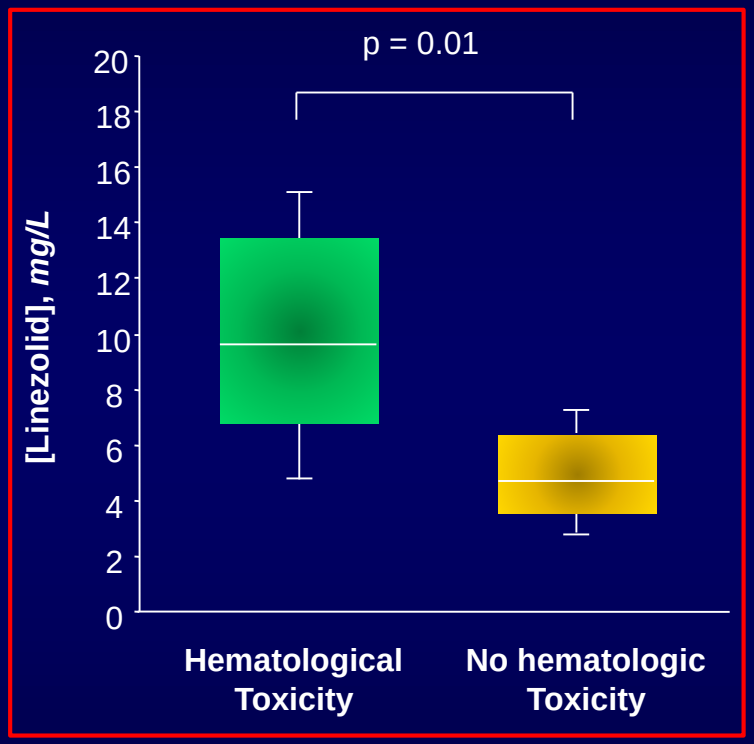
| Antibiotic exposure profile | Patients with nephrotoxicity ($n$ = 21) | Patients without nephrotoxicity ($n$ = 145) | $P$ |
|---|---|---|---|
| Initial vancomycin trough value, mean mg/L ± SD | 14.6 ± 8.3 | 9.6 ± 5.1 | .014 |
| Initial vancomycin trough value ⩾9.9 mg/L | 16 (76.2) | 56 (38.6) | .001 |



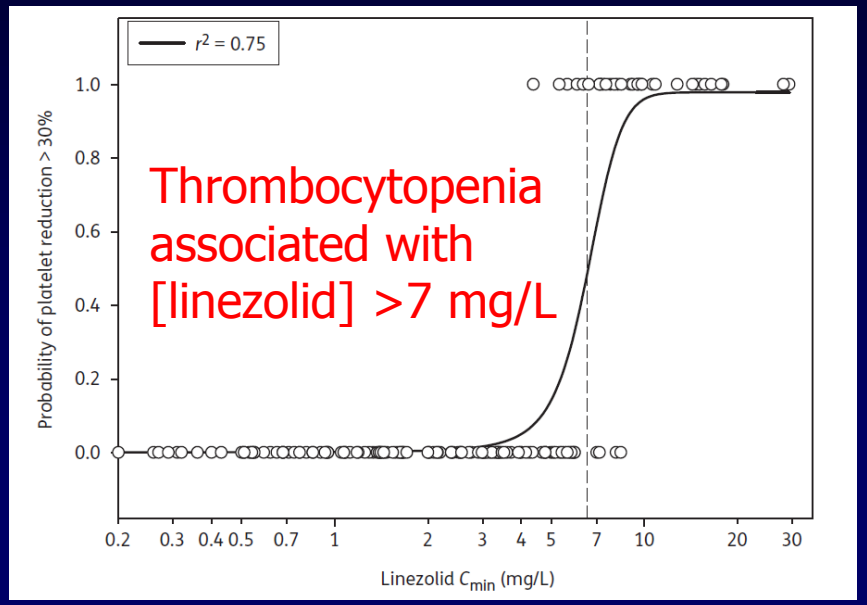




*- Lodise, CID 2009 -*

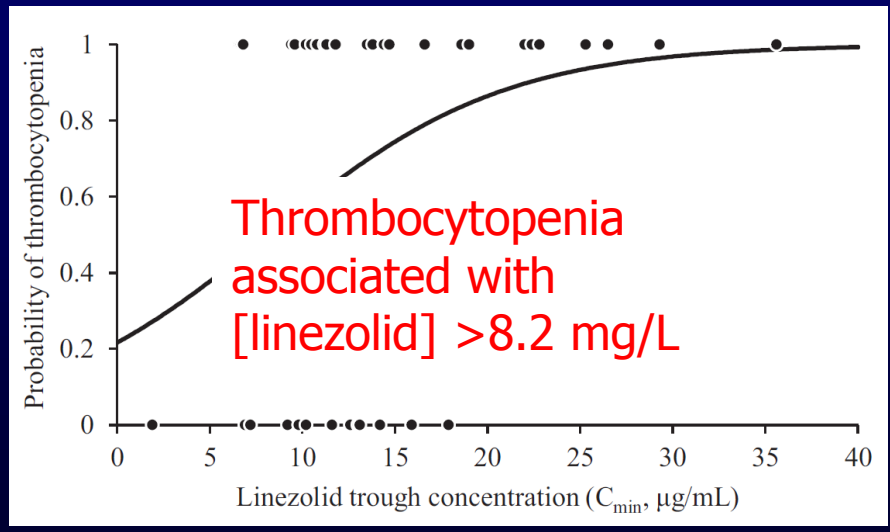
# The issue of drug overexposure: the case of linezolid…




*- Cattaneo, Int J Antimicrob Agents 2013 -*




*- Pea, JAC 2012 -*

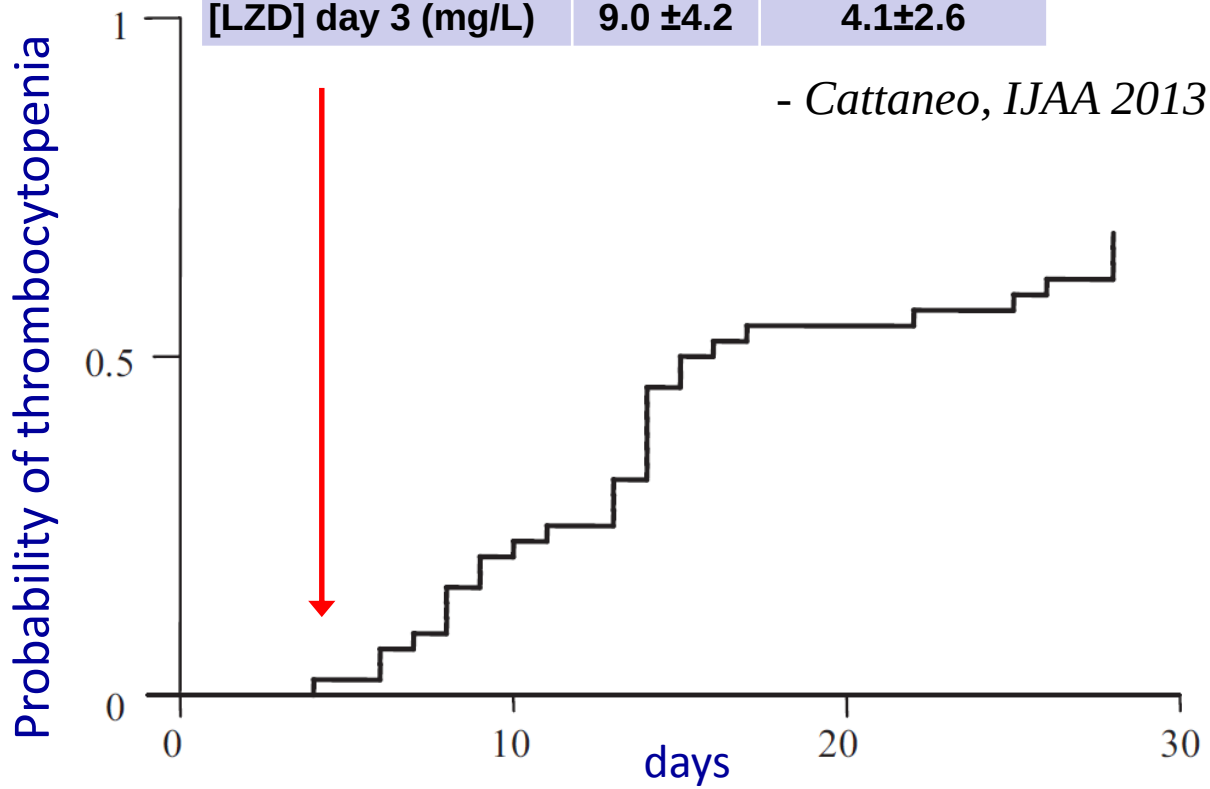



*- Matsumoto Int J AA 2014 -*

# With a window of opportunity…

| | pts with toxicity | pts without toxicity |
|---|---|---|
| [LZD] day 3 (mg/L) | 9.0 ±4.2 | 4.1±2.6 |

*- Cattaneo, IJAA 2013 -*




*- Matsumoto, Int J Antimicrob Agents 2014 -*

# Therapeutic drug monitoring of anti-infective agents

| Drug | TDM target |
|---|---|
| Amikacin | $C_{max}$ 40-60 mg/L |
| Ciprofloxacin | $C_{min}$ 0.5-3.0 mg/L |
| Colistin | 2-5 mg/L |
| Daptomycin | $C_{min}$ <25 mg/L |
| Gentamicin | $C_{min}$ 0.5-2.0 mg/L or $C_{max}$ 5-10 mg/L |
| Levofloxacin | $C_{max}$ 5-15 mg/L |
| Linezolid | $C_{min}$ 2-8 mg/L |
| Meropenem | - |
| Piperacillin | - |
| Posaconazole | $C_{min}$ 0.7-3.0 mg/L |
| Rifampicin | $C_{max}$ 8-24 mg/L |
| Sulfamethoxazole | $C_{max}$ 100-150 mg/L |
| Tobramycin | $C_{max}$ >10 mg/L or $C_{min}$ <1.0 mg/L |
| Teicoplanin | $C_{min}$ 10-60 mg/L |
| Trimethoprim | $C_{min}$ 1-4 mg/L or $C_{max}$ 5-10 mg/L |
| Vancomycin | $C_{min}$ 10-20 mg/L or $C_{max}$ 30-40 mg/L |
| Voriconazole | $C_{min}$ 1.5-5.0 mg/L |

*- Jager, Exp Rev Clin Pharmacol 2016 -*

..ma è davvero cosi corretto fornirvi dei cutoff minimi di efficacia per le concentrazioni di antibiotici?

- ✓Il farmaco
- ✓Il paziente
- ✓Il patogeno…

# ..ma è davvero cosi corretto fornirvi dei cutoff minimi di efficacia per le concentrazioni di antibiotici?

Inizio terapia  con linezolid alla dose di 600 mg bid…
Dopo 3-4 giorni eseguo TDM (conc. Trough)…
Conc. trough linezolid 3.2 mg/L (range: 2 – 8 mg/L)

**I° scenario**

✓ MIC: 0.5 mg/L

Nell'arco delle 12 ore sono sempre abbondantemente sopra la MIC, potrei teoricamente scendere con la dose di linezolid…

**II° scenario**

✓ MIC: 4.0 mg/L

Nell'intervallo di tempo tra 2 somministrazioni le conc. Di linezolid scendono sotto la MIC: rischio di fallire il trattamento se non salgo con la dose

Il batterio resistente a dosaggi convenzionali di un dato antimicrobico può diventare sensibile se si utilizzano dosaggi più elevati (purchè tollerati….).

Quando posso salire con le dosi?
MIC non troppo distante da Breakpoint…

| | A | B |
|---|---|---|
| MIC | 64 | 4 |
| BPs | 8 | 2 |
| MBQ | 0.125 | 0.5 |
| CAT | R | I |

Con l'antibiotico A è impossibile pensare di poter trattare con successo l'infezione aumentando le dosi. Con l'antibiotico B ad alte dosi il ceppo può diventare sensibile…

Quoziente MBQ: breakpoint / MIC

MBQ <1 patogeno resistente
MBQ >1 patogeno sensibile
MBQ ~1 intermedio (incerto)

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST has decided to change the definitions of susceptibility testing categories S, I and R as shown below. Results of several consultations on the new definitions are available on the EUCAST website under “Consultations”.

S - Susceptible, standard dosing regimen: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.

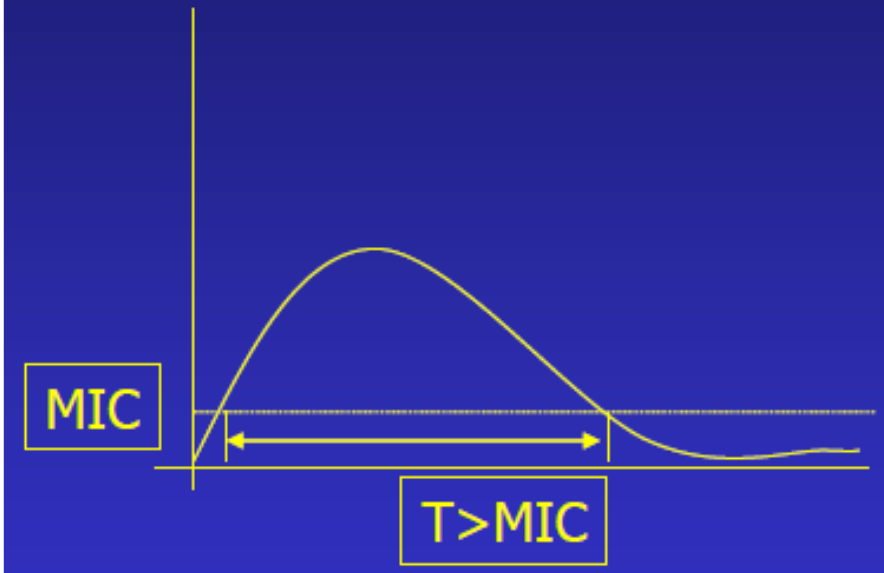
**I – Susceptible, increased exposure*: A microorganism is categorised as "Susceptible, Increased exposure*" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.**

R - Resistant: A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.

***Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.**

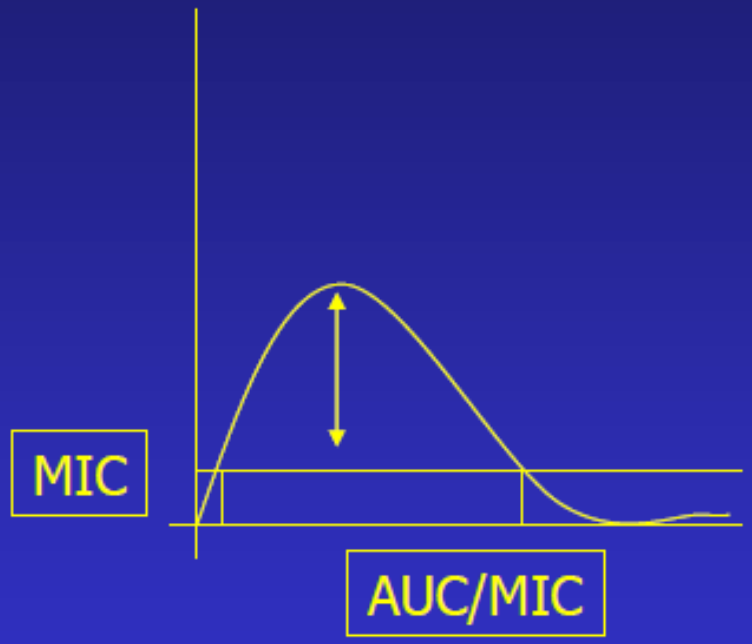
# Combinando insieme I parametri farmacocinetici con quelli farmacodinamici…

**Tempo in cui la concentrazione sierica si mantiene > delle MIC (T>MIC)**



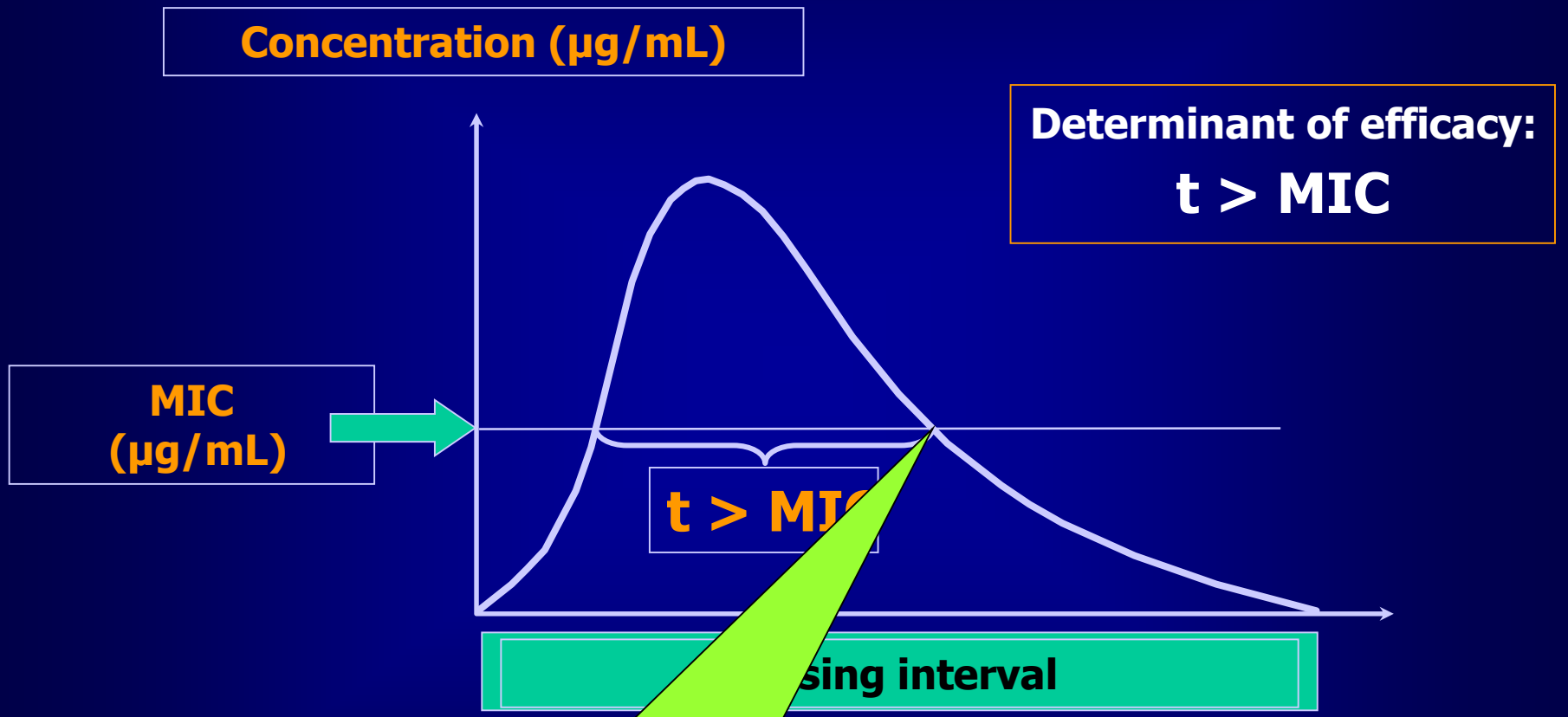

**Tempo-dipendenti**

**Area sotto la curva concentrazione-tempo diviso la MIC (AUC/MIC)**

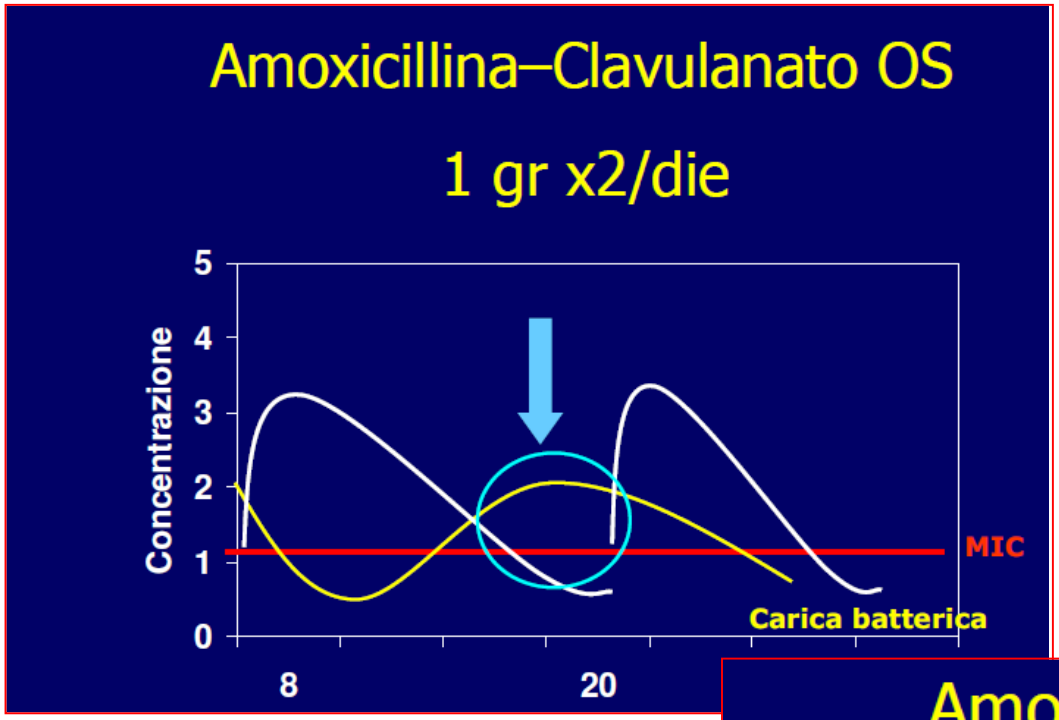



**Concentrazione-dipendenti**

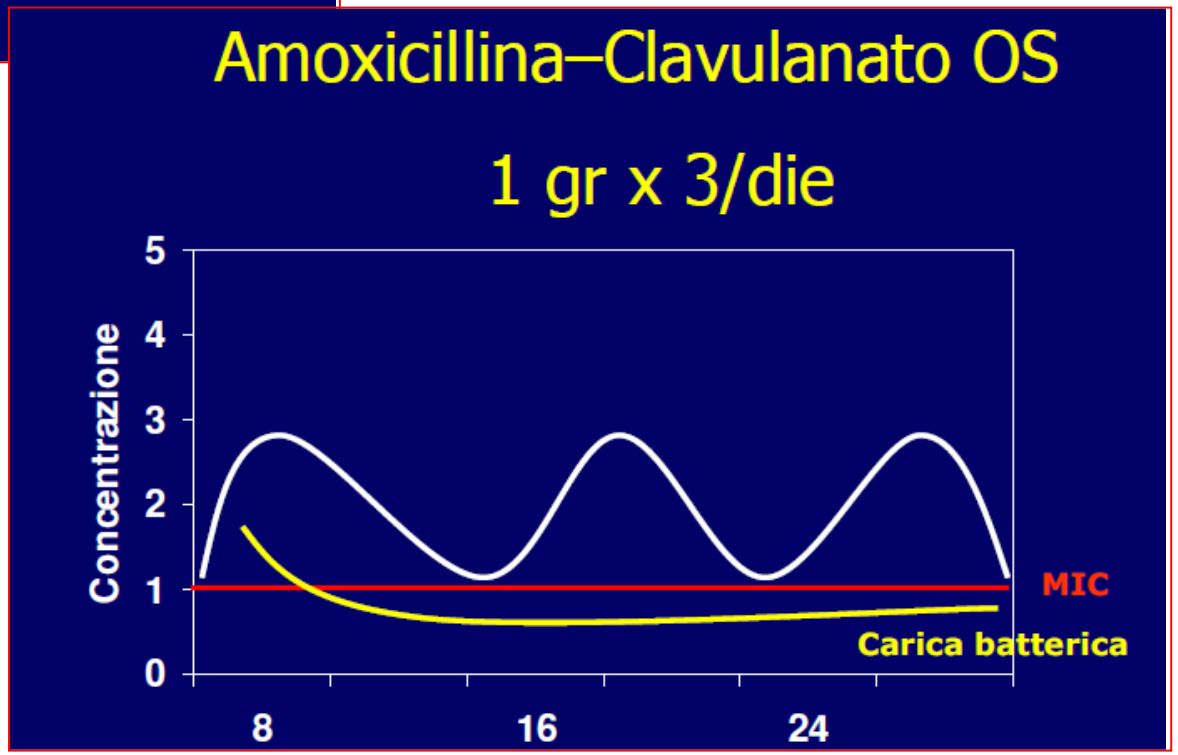
# Antimicrobic time-dependent



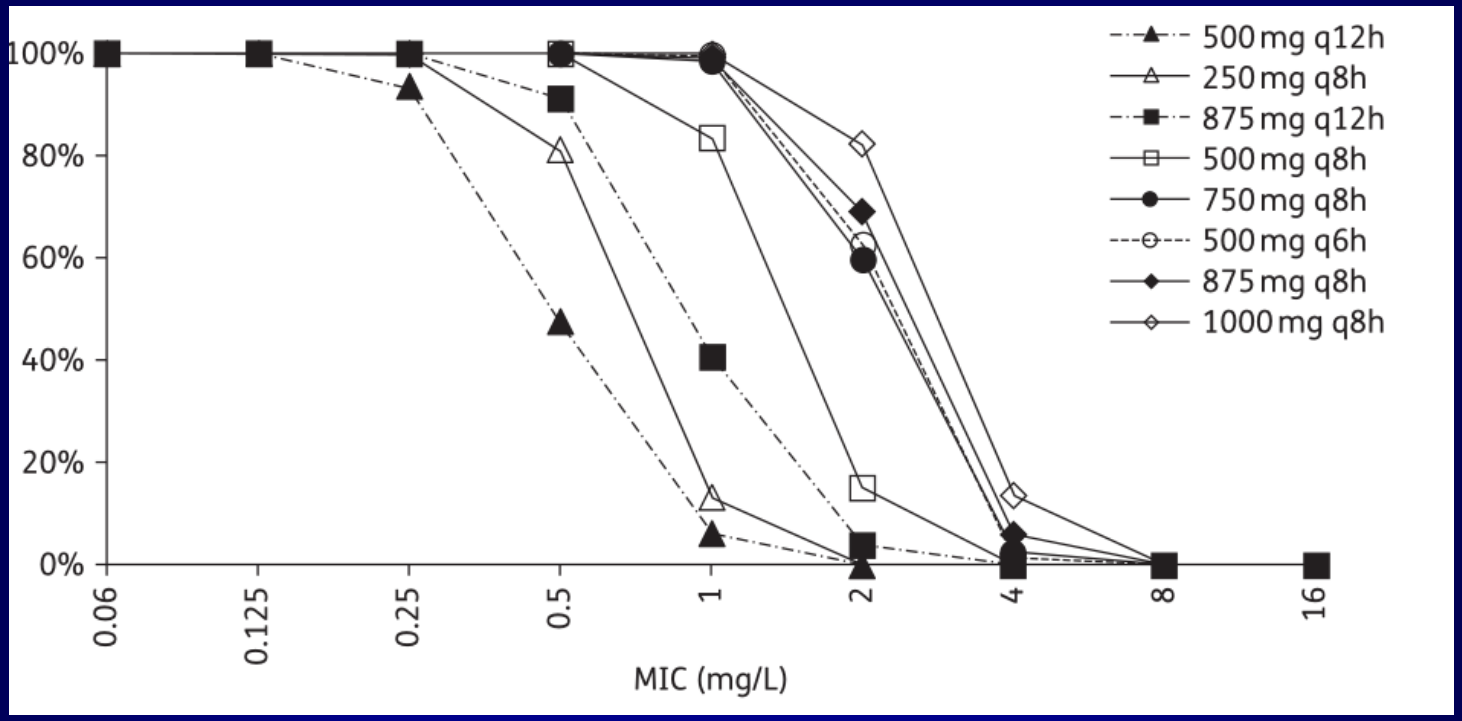

target:
$C_{min}$ > MIC




**..un concetto utile per risolvere alcuni "dubbi amletici"…**



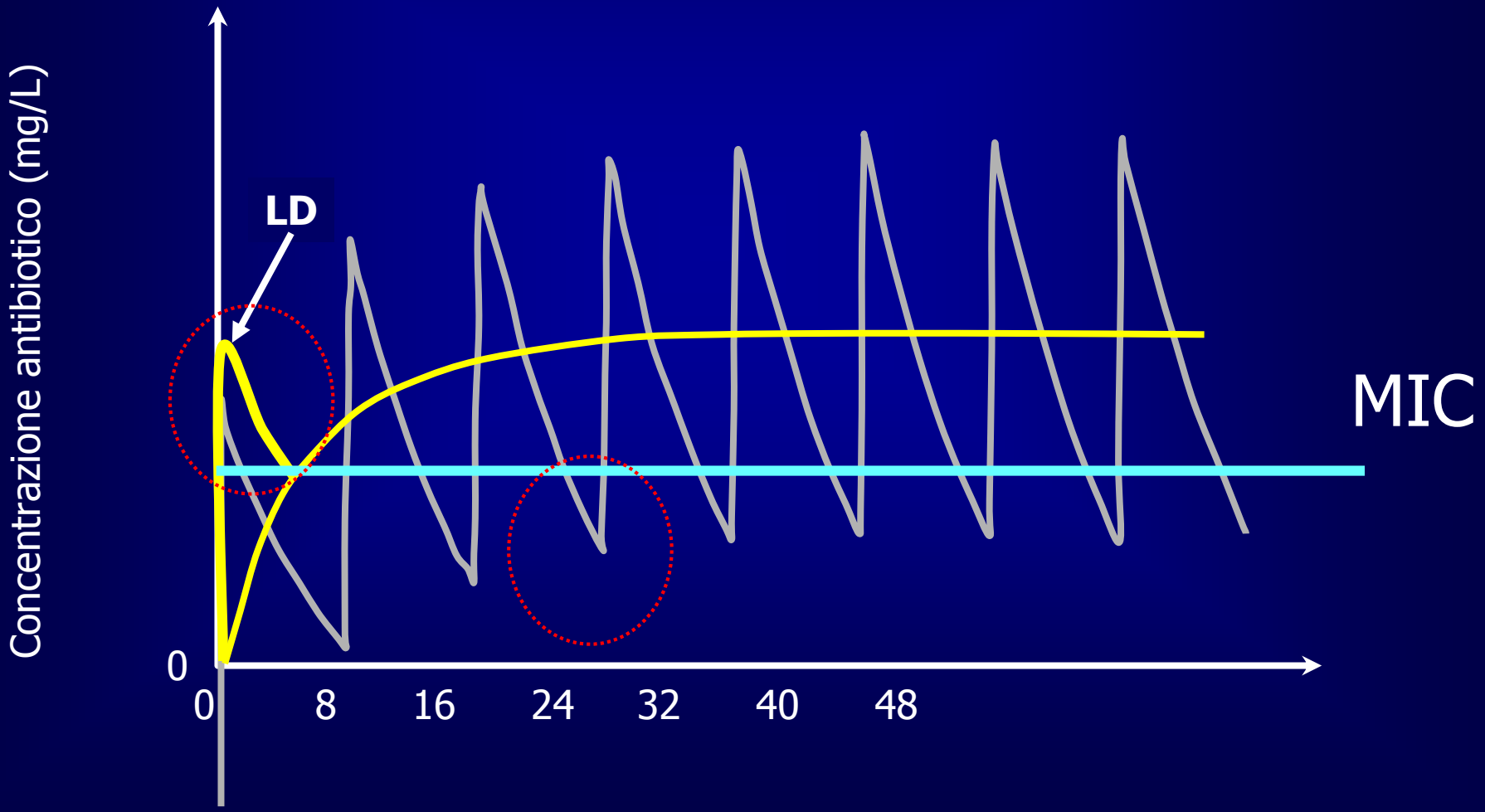
# Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints



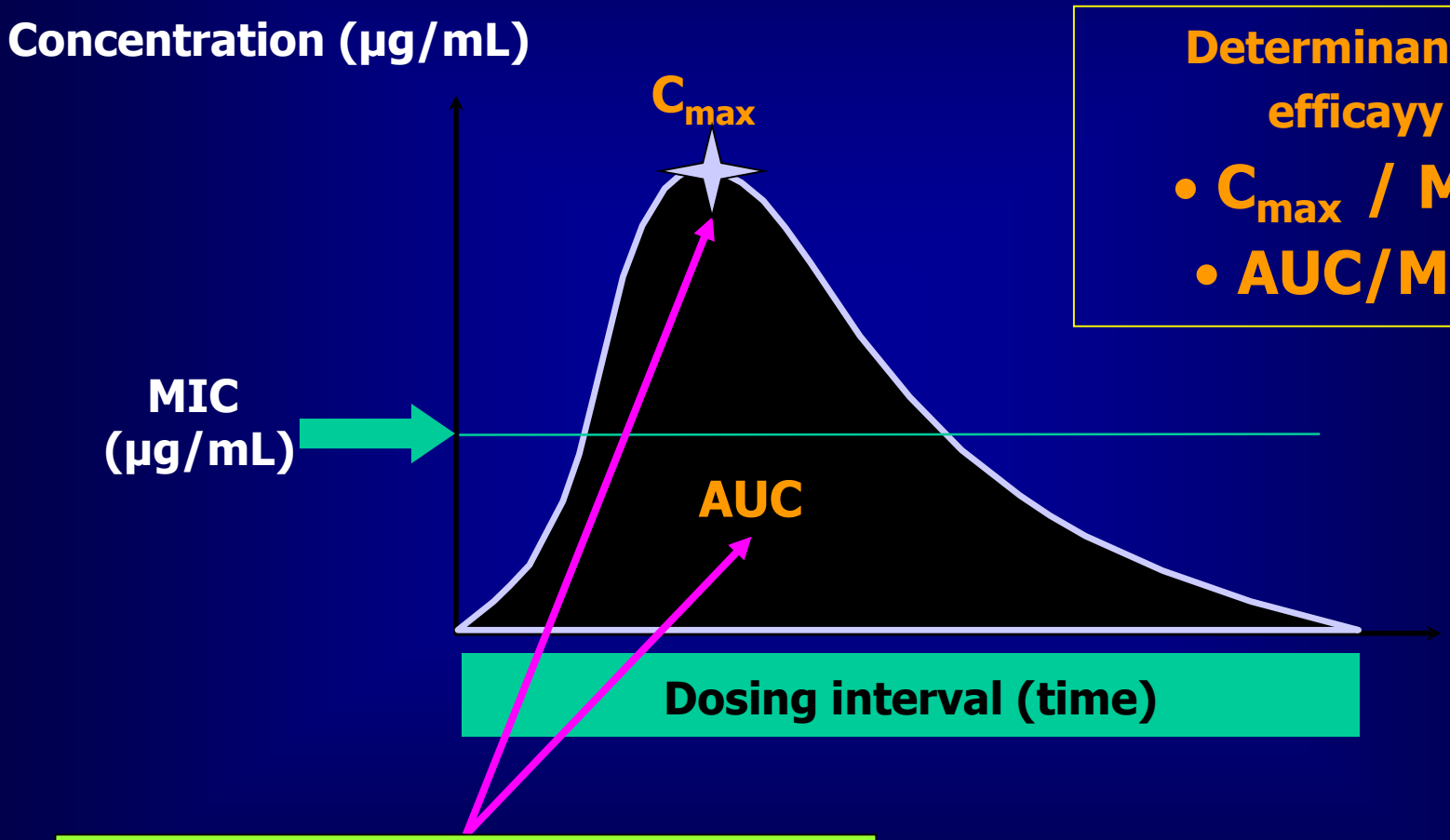

- ✓ The amoxicillin absorption rate appears to be saturable, which results in a non-linear increase in $C_{max}$ and a later $T_{max}$ for higher doses. Increasing the dose results in a larger %fT>MIC due to this delayed absorption, despite the non-proportional increase in $C_{max}$ . Undoubtedly, a smaller interval between doses leads to a larger fT>MIC

*- De Velde, JAC 2016 -*

# Per gli antibiotici tempo-dipendenti l'infusione continua rappresenta un'importante opzione per massimizzare gli effetti terapeutici



# Antimicrobic Concentration-Dependent




**Determinant of efficayy**

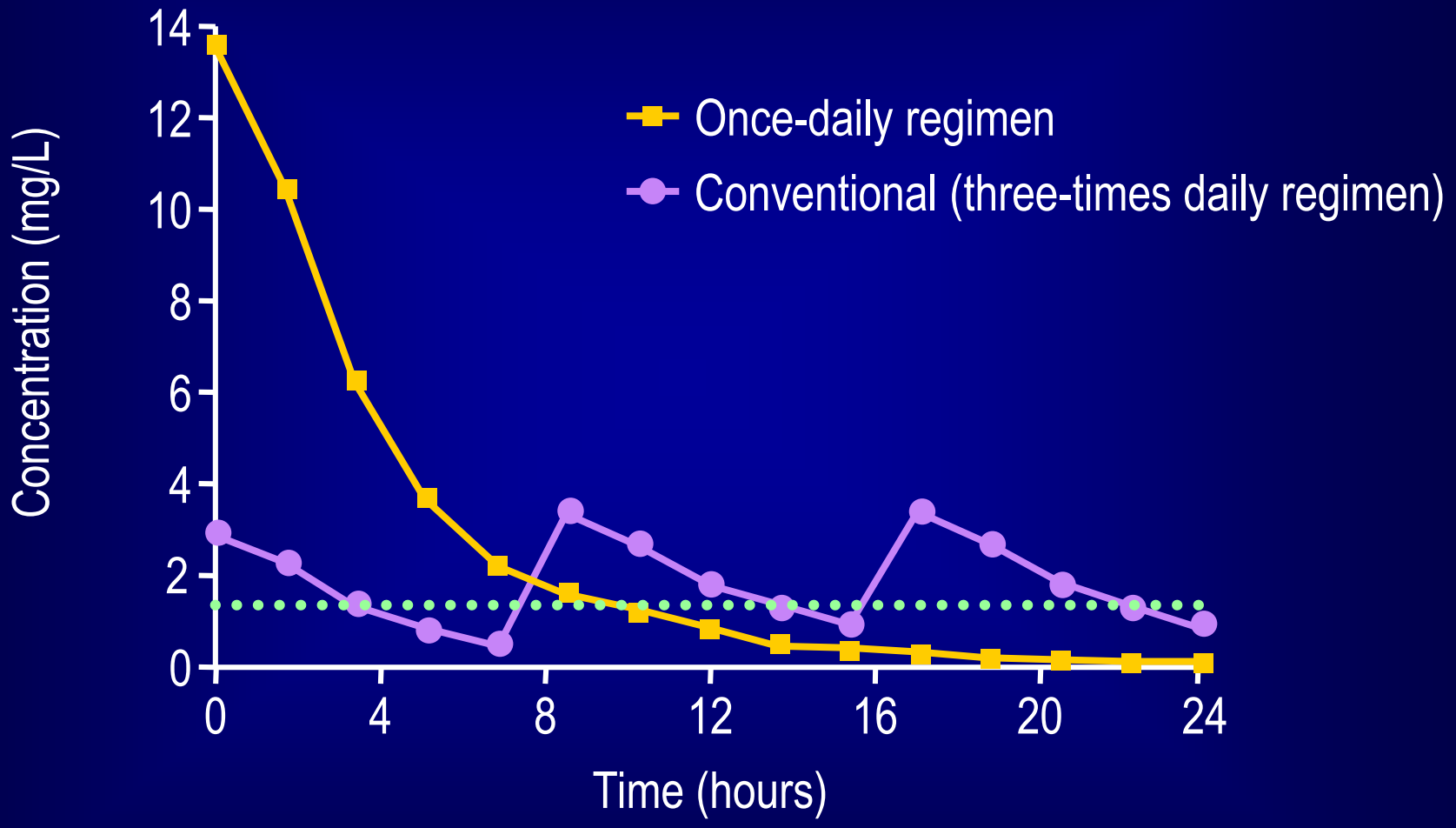
- $C_{max}$ / MIC
- AUC/MIC

**targets:**

$C_{max}$/MIC > 10

AUC/MIC > 125

# Once-daily vs conventional three-times daily aminoglycoside regimens




Il regime once-daily ha una maggior probabilità di raggiungere il valore ideale di Cmax / MIC

| Maximize duration of exposure | Maximize amount of drug exposure | Maximize concentrations |
|---|---|---|
| T > MIC | $AUC_{0-24\ h}$ / MIC | $C_{max}$/MIC |
| Carbapenems | Azithromycin | Aminoglycosides |
| Cephalosporins | Clindamycin | Daptomycin |
| Erythromycin | Linezolid | Fluoroquinolones |
| Linezolid | Tetracyclines | Ketolides |
| Clarithromycin | Fluoroquinolones | Metronidazole |
| Lincosamides | Aminoglycosides | Quinupristin/dalfopristin |
| Penicillins | Quinupristin/dalfopristin | |
| | Tigecycline | |
| | Vancomycin | |

**Effetto Tempo>MIC dipendente**

Somministrazione continua o a brevi intervalli

**Effetto AUC>MIC dipendente**

Frequenza di somministrazione meno rilevante (critica esposizione)

**Effetto $C_{max}$>MIC dipendente**

Alte dosi a lunghi intervalli

# Oggi sappiamo quali sono i target PK/PD…

**TABLE 1. Example Studies Describing a Correlation Between Antibiotic Exposure and Patient Outcome**

| Drug Class | Patient Group | Target Exposure |
|---|---|---|
| Aminoglycosides | $C_{max}$/MIC ≥ 8 | Increased clinical cure for *Pseudomonas aeruginosa* bloodstream infections |
| | $AUC_{0-24}$/MIC ≥ 72 | Increased clinical cure for lower respiratory tract infections |
| Carbapenem | $C_{min}$/MIC > 5 | Increased clinical and microbiologic cure in lower respiratory tract infections |
| Cephalosporins | 100% $T_{>MIC}$ | Increased microbiologic and clinical cure in serious infections |
| Quinolones | $AUC_{0-24}$/MIC ≥ 125 | Increased microbiologic and clinical cure in seriously ill patients |
| Vancomycin | $AUC_{0-24}$/MIC ≥ 451 | Increased survival in critically ill patients associated with methicillin-resistant *Staphylococcus aureus* septic shock |
| Linezolid | $AUC_{0-24}$/MIC ≥ 85 | Increased clinical cure in severely ill patients with blood stream infections |
| Tigecycline | $fAUC_{0-24}$/MIC ≥ 0.9 | Increased clinical success in hospital acquired pneumonia |

*- Roberts, Crit Care Med 2017 -*

# ...Time>MIC-dependent...

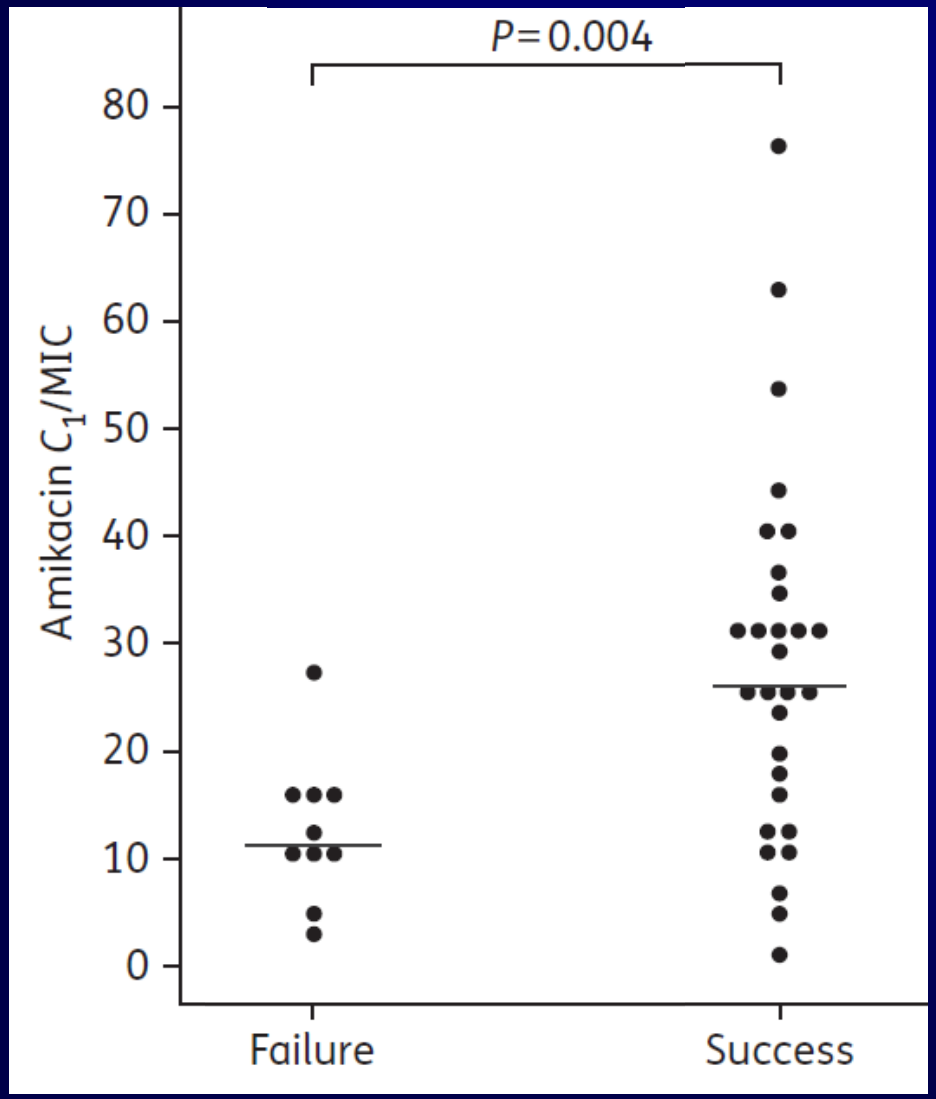
## Meropenem by Continuous Versus Intermittent Infusion in Ventilator-Associated Pneumonia due to Gram-Negative Bacilli

**Table 5.** Clinical Cure Rates of Ventilator-Associated Pneumonia

| Rate | Continuous Infusion, n (%) | Intermittent Infusion, n (%) | OR (95% CI) | p Value |
|---|---|---|---|---|
| All cases | 38 (90.47) | 28 (59.57) | 6.44 (1.97 to 21.05) | <0.001 |
| Microorganism | | | | |
| *Pseudomonas aeruginosa* | 11 (84.61) | 6 (40) | 8.25 (1.33 to 51.26) | 0.02 |
| other | 27 (93.10) | 22 (68.75) | 6.13 (1.21 to 30.98) | 0.02 |
| MIC (µg/mL) | | | | |
| 0.25–0.49 | 21 (100) | 23 (76.67) | 7.09 (0.72 to 56.38) | 0.03 |
| ≥0.50 | 17 (80.95) | 5 (29.41) | 7.84 (2.26 to 46.09) | 0.003 |

*Ann Pharmacother* 2006;40:219-23.

# Impact of imipenem and amikacin pharmacokinetic/pharmacodynamic parameters on microbiological outcome of Gram-negative bacilli ventilator-associated pneumonia




...for drugs that are $C_{max}$/MIC-dependent you can measure $C_{max}$ for efficacy, and eventually $C_{min}$ for toxicity...

*J Antimicrob Chemother* 2015; **70**: 1487–1494

# ...AUC/MIC-dependent...

## Vancomycin AUC/MIC Ratio and 30-Day Mortality in Patients with *Staphylococcus aureus* Bacteremia

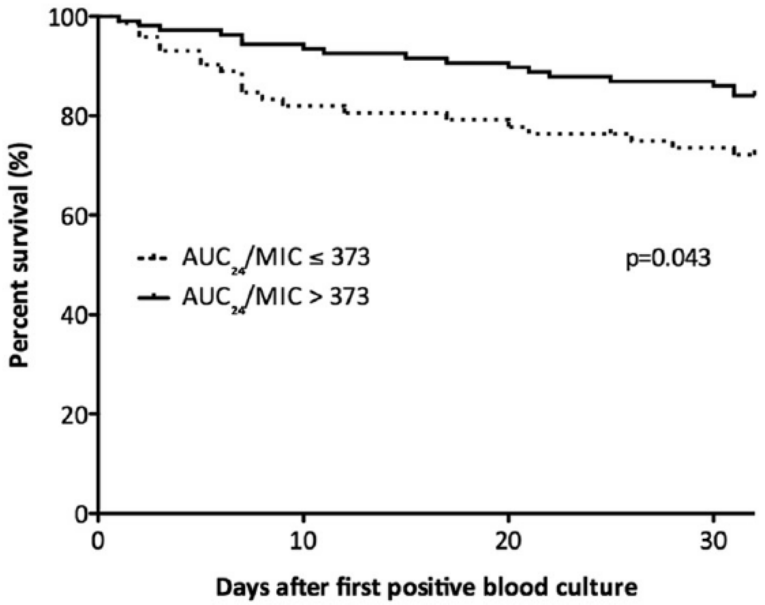
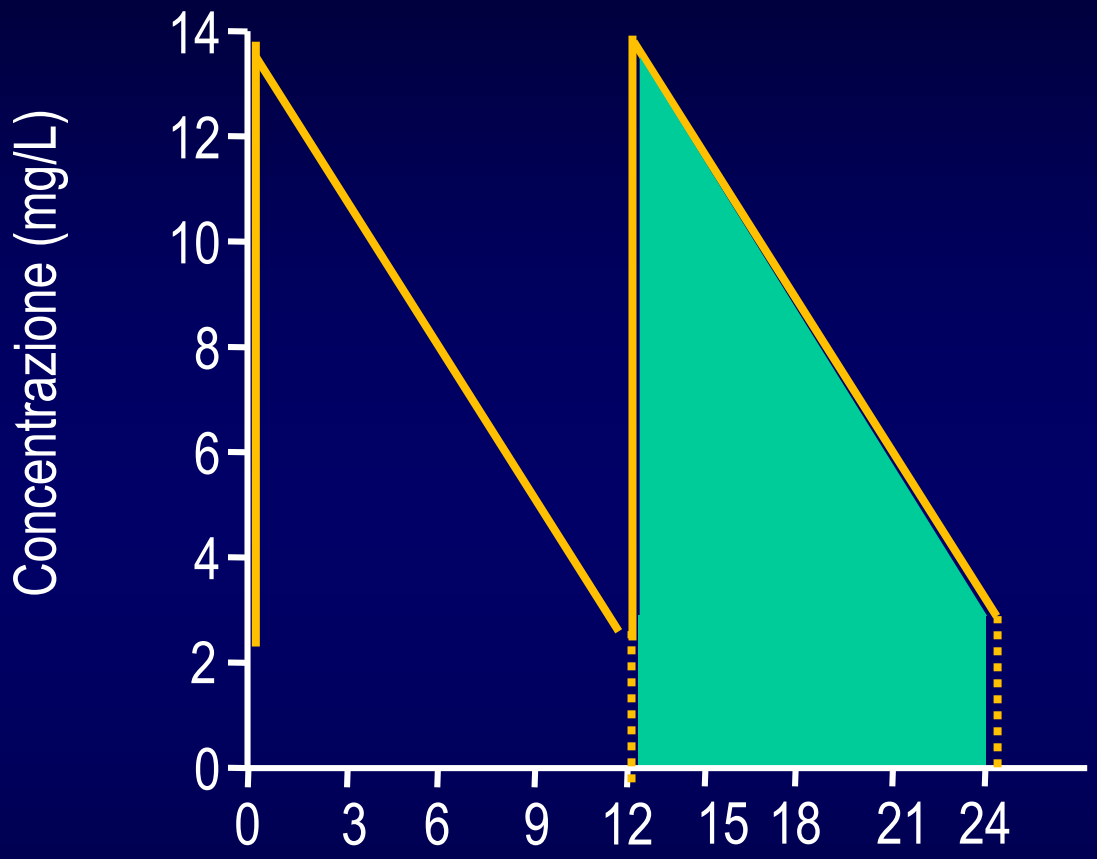



TABLE 4 Final multivariable logistic regression model of factors associated with 30-day mortality in SAB ($n = 182$)[a]

| | Univariable analysis | Multivariable analysis | | |
|---|---|---|---|---|
| Variable[b] | *P* value | OR | 95% CI | *P* value |
| Age ≥ 70 years | 0.008 | 3.61 | 1.59–8.17 | 0.002 |
| Male sex | 0.163 | | | |
| Pneumonia | 0.174 | | | |
| Sepsis syndrome | 0.029 | 3.24 | 1.16–9.08 | 0.025 |
| Vancomycin AUC/MIC > 373 | 0.043 | 0.44 | 0.20–0.99 | 0.049 |
| Elevated vancomycin MIC[c] | 0.063 | | | |
| CWI ≥ 3 | 0.170 | | | |
| Pitt bacteremia score ≥ 4 | 0.001 | 3.74 | 1.64–8.56 | 0.002 |
| Immunosuppression | 0.019 | | | |

*- Holmes, AAC 2013 -*

# Ma l'AUC si può misurare nella pratica clinica??

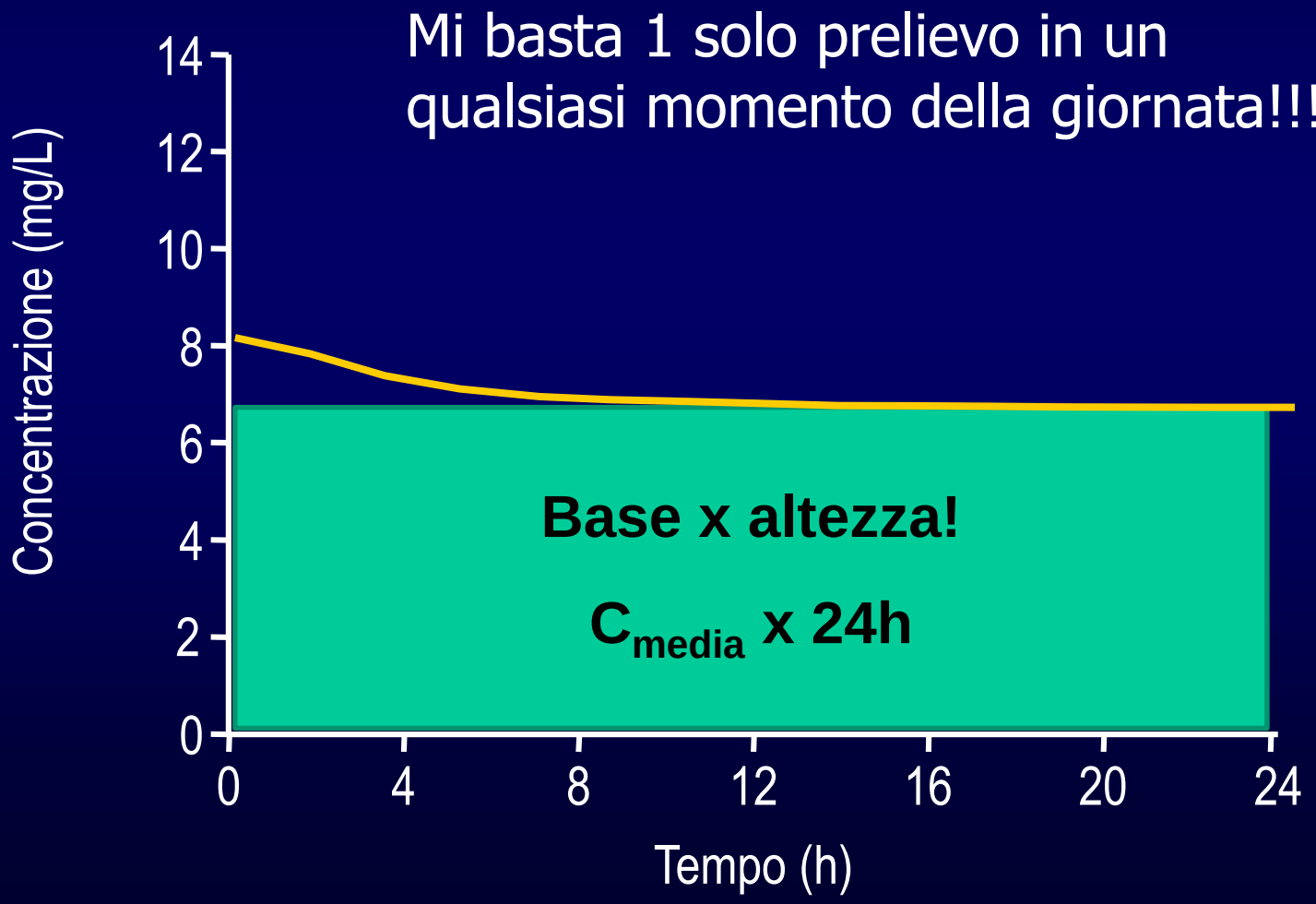



Bastano 2 prelievi!!
Picco e valle

$AUC_{0-12}$ = $base_{maggiore}$ (picco) + $base_{minore}$ x altezza (12 ore) / 2

$AUC_{0-24}$ = $AUC_{0-12}$ x 2 …..o più semplicemente (picco+valle) x 12….

# .. ancora più semplice se è infusione continua...



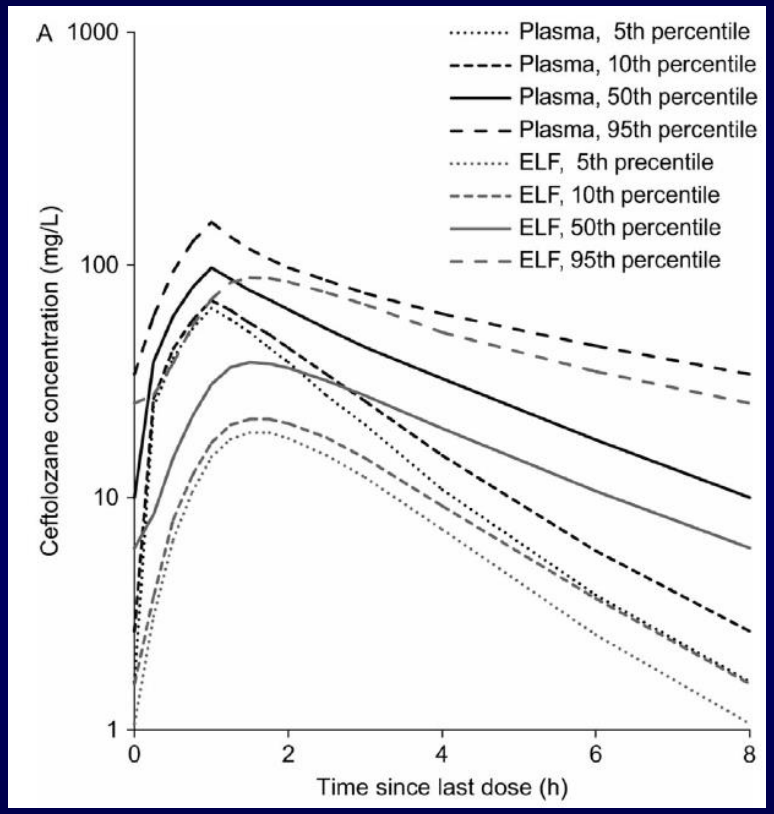
# È infne non dimentichiamo mai di verificare la penetrazione tissutale…

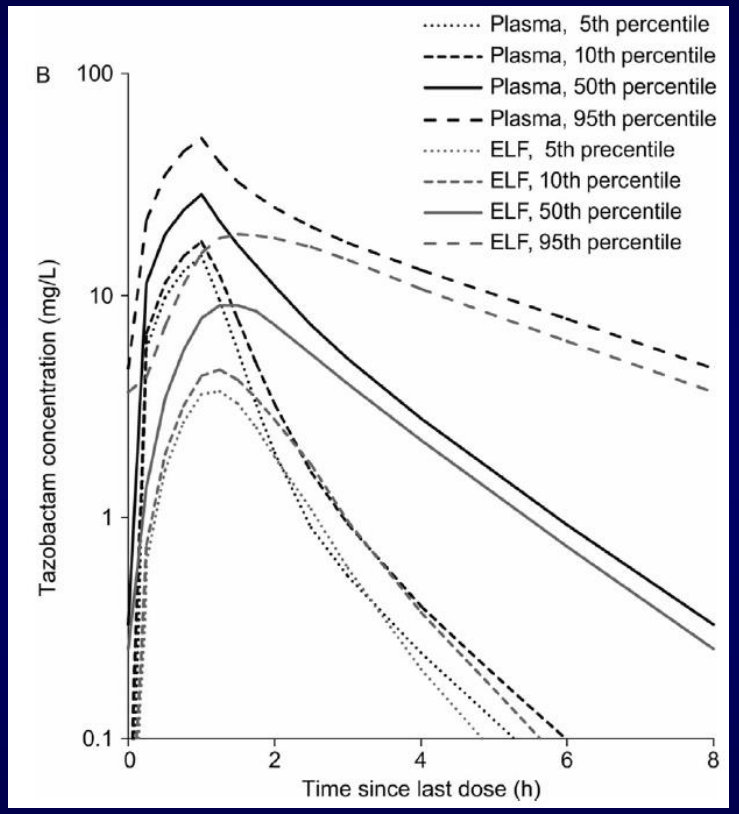
| Antibiotic | Penetration ratio % (ELF/plasma) |
|---|---|
| Ceftaroline | 10-25% |
| Ceftobiprole | 20-30% |
| Ceftolozane/tazobactam | 45-50% |
| Ceftazidime/avibactam | 30-40% |
| Dalbavancin | 30-40% |
| Eravacycline | 300-600% |
| Telavancine | 60-70% |
| Tedizolid | 200-300% |
| Vancomycin | 20-50% |

ELF: epithelial lining fluid

# Ceftolozane/Tazobactam Pharmacokinetic/ Pharmacodynamic-Derived Dose Justification for Phase 3 Studies in Patients With Nosocomial Pneumonia

ELF: epithelial lining fluid
PTA: probability of target attainment
UTIs: urinary tract infections
IAIs: intra-abdominal infections




With a plasma-to-ELF ratio of 50%, a doubling of the currently approved dose for UTIs and IAIs is needed to achieve a 90% PTA for nosocomial pneumonia (ie from 1.5 to 3.0 g)

*- Xiao, J Clin Pharmacol 2016 -*

P1288

# Dose selection of ceftazidime-avibactam in patients with nosocomial pneumonia, including ventilator-associated pneumonia, based on preclinical efficacy, preclinical pharmacokinetic/pharmacodynamic and clinical pharmacokinetic data

Shampa Das,[1] Wright W. Nichols,[2] James Li[2]
[1]AstraZeneca Pharmaceuticals, Macclesfield, UK; [2]AstraZeneca Pharmaceuticals LP, Waltham, MA, USA

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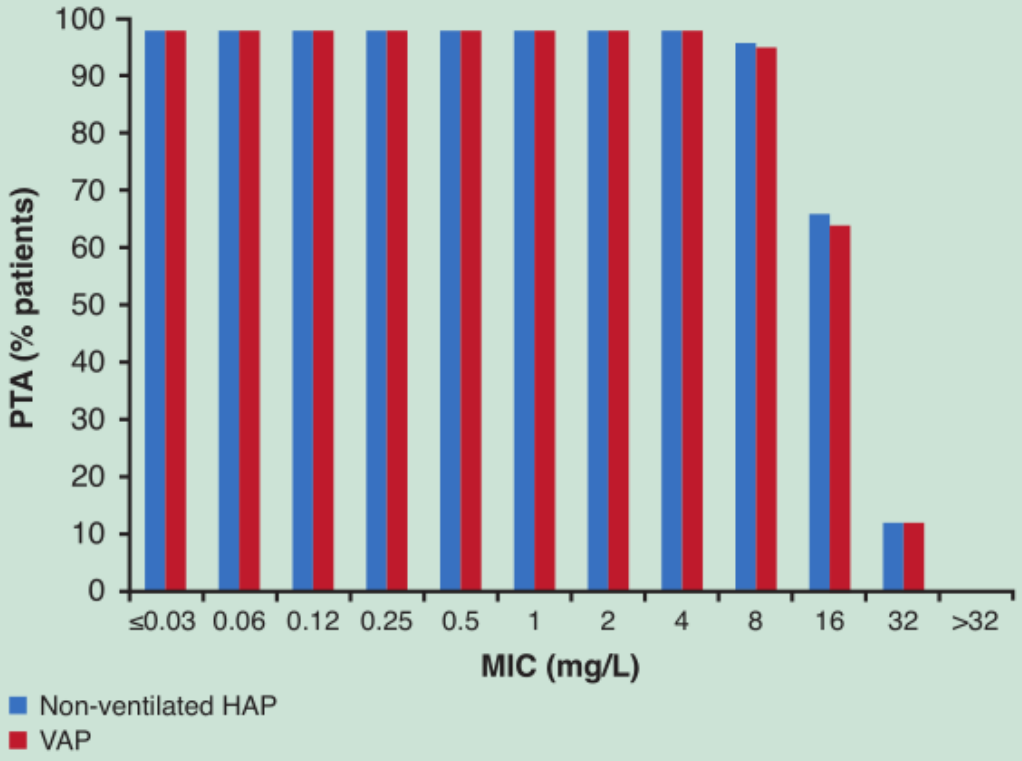
✓ Ceftazidime/avibactam 2000/500 mg q8h

**Figure 4.** *Probability of ceftazidime-avibactam PK/PD target attainment in patients with non-ventilated healthcare-acquired pneumonia (HAP) or VAP by MIC*




*- Das, 27th ECCMID, 2017 -*

# …Lo stesso vale anche per altri distretti….

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Review

## Antibiotic penetration into bone and joints: An updated review

Abrar K. Thabit*, Dania F. Fatani, Maryam S. Bamakhrama, Ola A. Barnawi, Lana O. Basudan, Shahad F. Alhejaili

### Highlights

- Despite the rigid structure of bone, many antibiotics demonstrated a good penetration profile.
- Diffusion into synovial fluid was exhibited by many antibiotics despite their variation in pharmacokinetic properties.
- Only penicillin, flucloxacillin, and metronidazole showed lower than optimum penetration profiles.
- Antibiotics with good penetration profiles in bone and joints represent potential options for the treatment of osteomyelitis and septic arthritis.

International Journal of Infectious Diseases 81 (2019) 128–136

***…è davvero cosi importante conoscere e ottimizzare PK/PD degli antibiotici…???***

# Antibioticoresistenza: ogni anno in Europa 33mila morti, più di quelli causati da influenza, tubercolosi e Aids messi insieme. Studio Ecdc


06 NOV - Lo studio spiega che il 75% del carico di malattia è dovuto a infezioni associate all 'assistenza sanitaria (HAI) e che la riduzione di questo attraverso adeguate misure di prevenzione e controllo delle infezioni, nonché la gestione antibiotica, potrebbe essere un obiettivo raggiungibile in ambito sanitario e mostra che il 39% del carico è causato da infezioni batteriche resistenti a antibiotici di ultima generazione. Leggi >