La terapia antibiotica nel paziente con insufficienza renale: confronto con il nefrologo…

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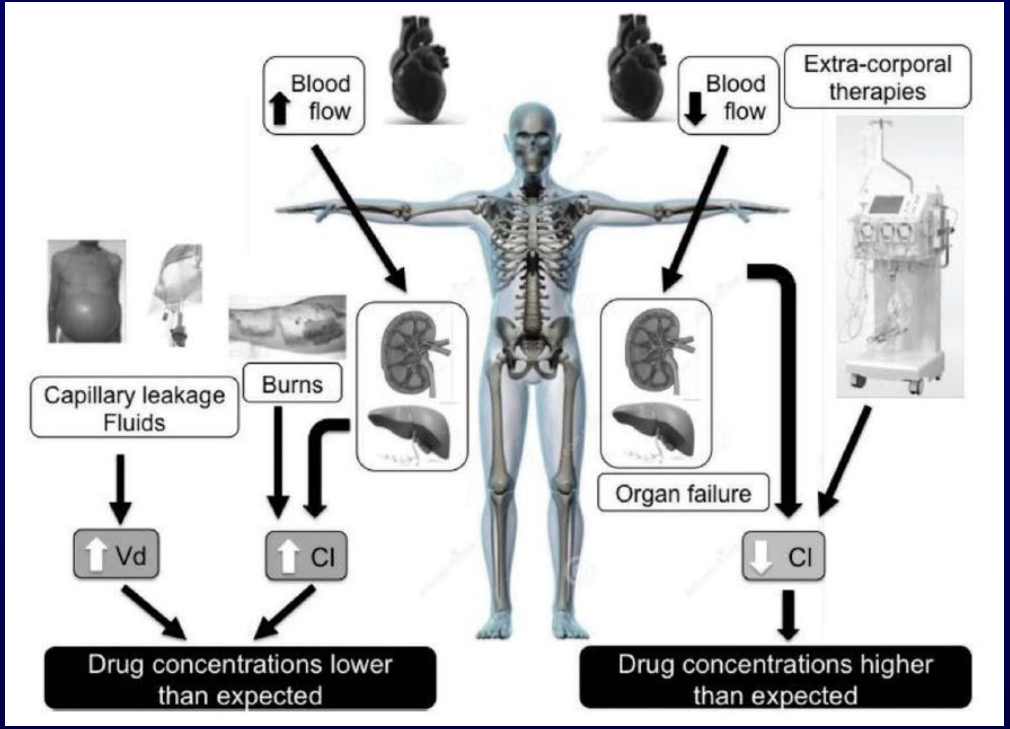
Il paziente critico come modello…

- ✓ patients' age…
- ✓ altered fluids volumes…
- ✓ acute/chronic renal insufficiency…
- ✓ hyperfiltration…
- ✓ hypoalbuminemia…
- ✓ liver impairment…
- ✓ polytherapies…
- ✓ obesity/undernutrition…
- ✓ pregnancy…
- ✓ adherence…
- ✓ genetic background…
- ✓ …



EXPERT REVIEW OF CLINICAL PHARMACOLOGY, 2016

Variability of antibiotic concentrations in critically ill patients

Drug	Trough concentration (mg/L)*	Variability
Meropenem	12.1 (3.4 – 21.8)	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

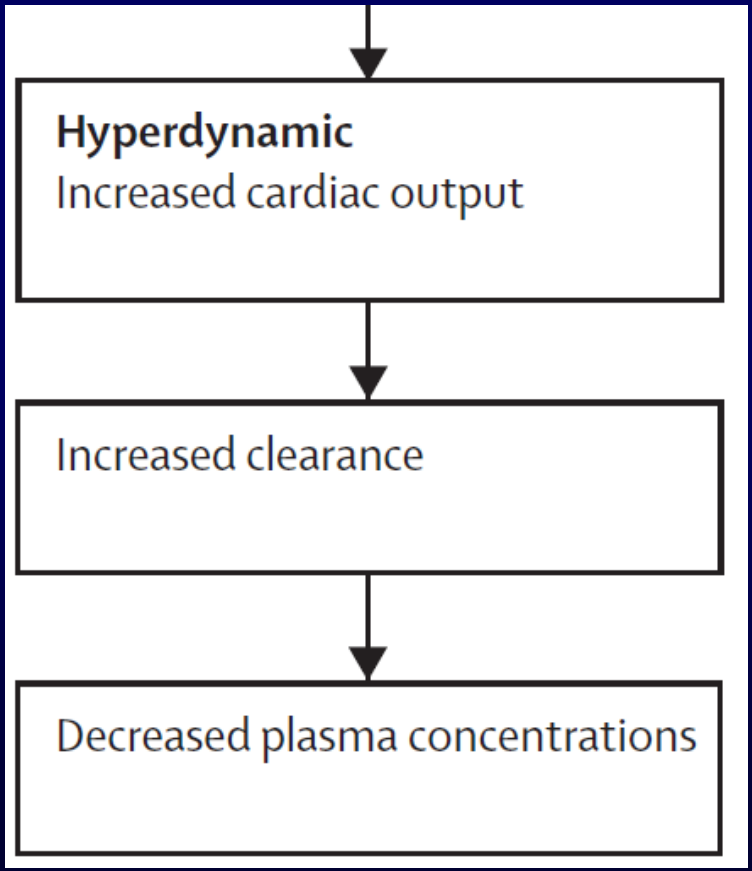
*median (interquartile range)

- Roberts, Crit Care Med 2012 -

How to explain such variability…?!?

…In addition to known variables (age, DDIs, etc), critically ill patients may have also peculiar conditions that can affect the pharmacokinetics of antibiotics…

Critical illness



- Roberts, Lancet Infect Dis 2014 -

"..Augmented renal clearance can result in elevated renal elimination and subtherapeutic plasma concentrations, although whether this process solely involves augmented filtration or altered tubular secretion/reabsorption remains uncertain…"

Antibacterials	Drug CL in healthy subjects	Drug CL in critically ill pts
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 -

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Dosing Guidance for Intravenous Colistin in Critically Ill Patients

✓ The model-derived post hoc parameter estimates from the population PK modeling were used to compute the colistin $AUC_{0–24}$ for each patient

$$\text{Loading dose of CBA (mg)} = C_{ss,avg} \text{ target (mg/L)} \times 2.0 \times \text{ideal body weight (kg)}$$

$$\text{Daily dose of CBA (mg)} = C_{ss,avg} \text{ target (mg/L)} \times 10^{(0.0048 \times \text{CrCl} + 1.825)}$$

$C_{ss,avg}$ target : 2.0 mg/L

Suggested loading and daily colistin doses in various categories of patients

Dose	Category of Critically Ill Patient	Dosing Suggestions[a]
Loading dose	All patient categories	Equation 1: Loading dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × 2.0 × ideal body weight (kg) To achieve a $C_{ss,avg}$ of 2 mg/L in a patient with an ideal body weight of 75 kg, the loading dose would be 300 mg CBA (9 million IU), the suggested maximum loading dose. The 1st regular daily dose should be administered 12 h later.
Daily dose[b]	Not receiving RRT	Equation 2[c]: Daily dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × $10^{(0.0048 \times CrCl + 1.825)}$ See Table 3 ("look-up" table) for the daily dose to target a plasma colistin $C_{ss,avg}$ of 2 mg/L, depending on the patient's creatinine clearance.
	Receiving RRT	The baseline daily dose of colistimethate for a $C_{ss,avg}$ of 2 mg/L in a patient with creatinine clearance of 0 mL/min is 130 mg/d of CBA (3.95 million IU/d) (see Table 3)[d]; the supplement to the baseline daily dose needed during receipt of RRT is 10% of the baseline dose per 1 h of RRT.
	Intermittent hemodialysis	Nondialysis day: CBA dose of 130 mg/d (3.95 million IU/d), ie, baseline dosing for a $C_{ss,avg}$ of 2 mg/L; dialysis day supplement: add 30% or 40% to baseline daily dose after a 3- or 4-h session, respectively.[e] The dialysis session should occur toward the end of a colistimethate dosing interval, and the supplement to the baseline (nondialysis) daily dose should be administered with next regular dose, after the dialysis session has ended.
	SLED	During SLED: add 10% per 1 h of SLED replacement to baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[f]; for a patient receiving a 10-h nocturnal SLED session each day and receiving colistimethate every 12 h, the dose would be (baseline CBA dose of 130 mg/d for a patient with creatinine clearance of 0 mL/min + supplemental dose comprising 10% of the baseline dose per h × 10 h); ie, for this case the CBA dose would be 260 mg/d (7.9 million IU/d). It is suggested that the SLED session begin 1–2 h after the afternoon/evening dose; in such a case, it may be most convenient and safe to administer 130 mg CBA (3.95 million IU) every 12 h.
	CRRT	During CRRT: add 10% per 1 h of CRRT to the baseline daily dose for a $C_{ss,avg}$ of 2 mg/L[g]; the suggested CBA dose is 440 mg/d (~13 million IU/d).

Suggested loading and daily colistin doses in various categories of patients

Dose	Category of Critically Ill Patient	Dosing Suggestions[a]
Loading dose	All patient categories	Equation 1: Loading dose of CBA (mg) = $C_{ss,avg}$ target (mg/L) × 2.0 × ideal body weight (kg) To achieve a $C_{ss,avg}$ of 2 mg/L in a patient with an ideal body weight of 75 kg, the loading dose would be 300 mg CBA (9 million IU), the suggested maximum loading dose. The 1st regular daily dose should be administered 12 h later.
Daily dose[b]	Not receiving RRT	Equation 2[c]: Daily dose of CBA (m See Table 3 ("look-up" table) for th patient's creatinine clearance.
	Receiving RRT	The baseline daily dose of colistim is 130 mg/d of CBA (3.95 millio receipt of RRT is 10% of the ba
	Intermittent hemodialysis	Nondialysis day: CBA dose of 130 supplement: add 30% or 40% should occur toward the end of sis) daily dose should be admin
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	CRRT	During CRRT: add 10% per 1 h of is 440 mg/d (~13 million IU/d).

Table 3. "Look-up" Table of Daily Doses of Colistimethate for a Desired Target colistin $C_{ss,avg}$ of 2 mg/L for Narrow Windows of Creatinine Clearance

Creatinine clearance, mL/min	Dose of Colistimethate for $C_{ss,avg}$ of 2 mg/L[a]	
	CBA, mg/d	Million IU/d
0	130	3.95
5 to <10	145	4.40
10 to <20	160	4.85
20 to <30	175	5.30
30 to <40	195	5.90
40 to <50	220	6.65
50 to <60	245	7.40
60 to <70	275	8.35
70 to <80	300	9.00
80 to <90	340	10.3
≥90	360	10.9

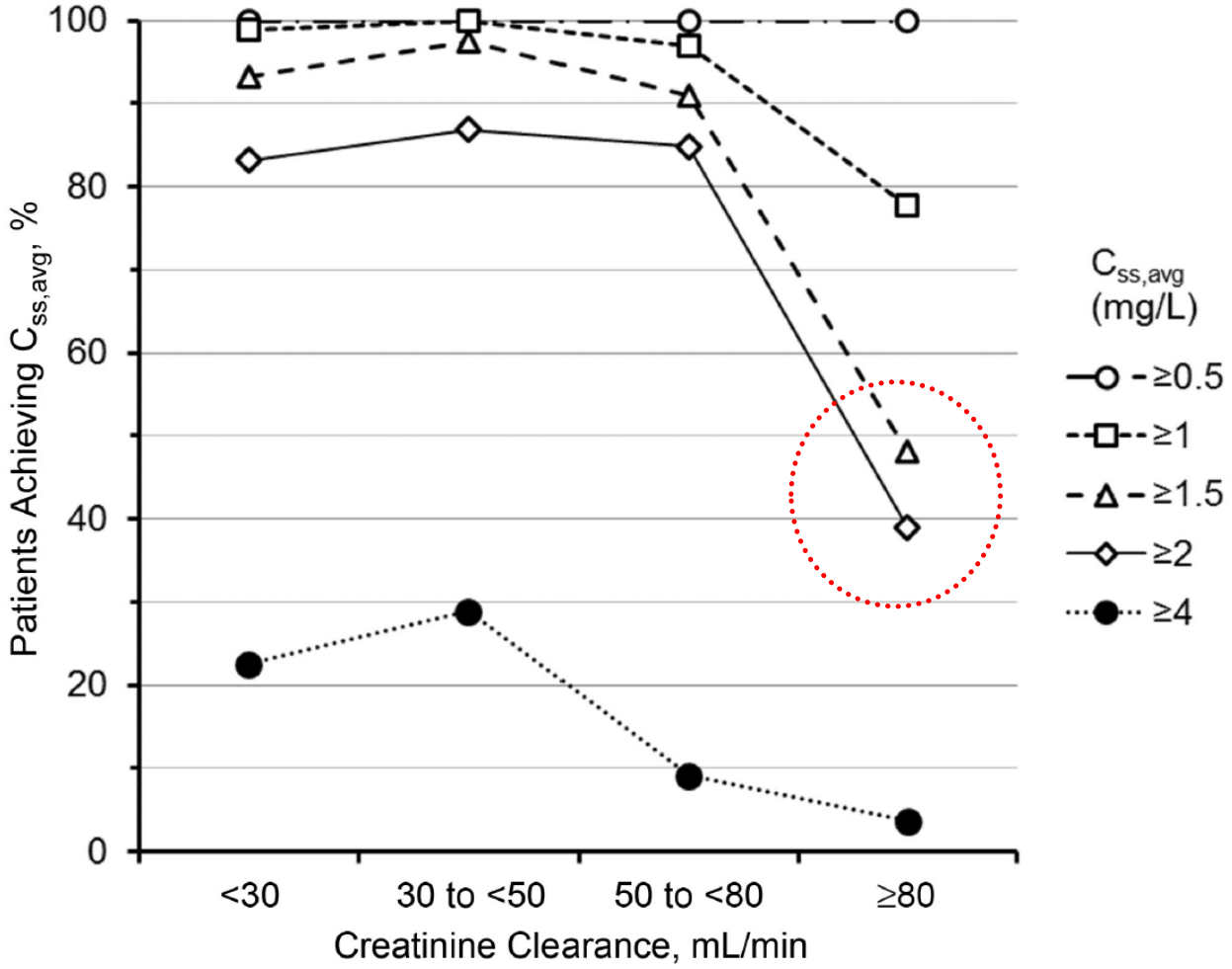


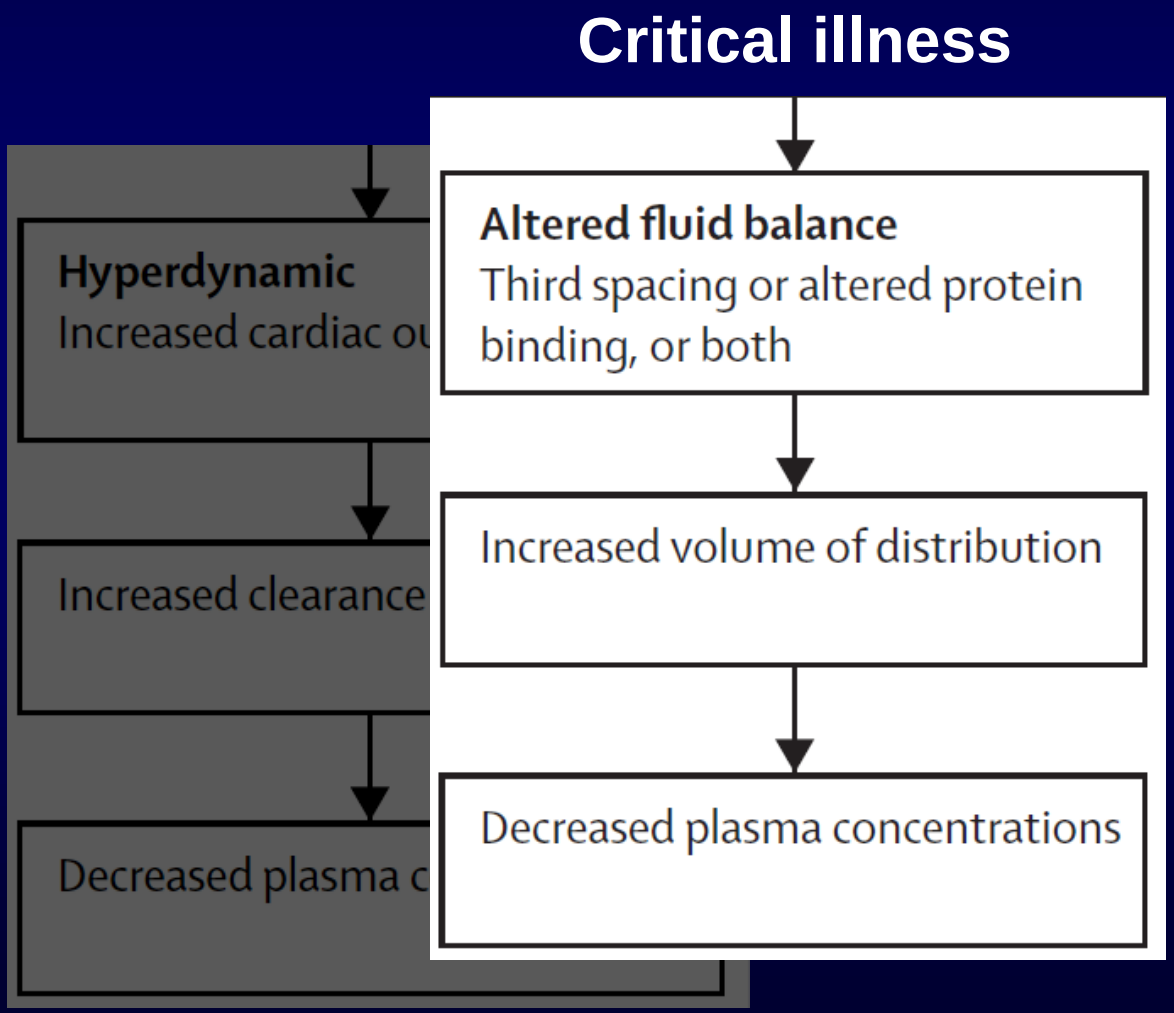
Figure 3. Percentage of patients in each creatinine clearance cluster achieving average steady-state plasma concentrations of colistin ($C_{ss,avg}$) of ≥0.5, ≥1, ≥1.5, ≥2, and ≥4 mg/L using the daily dose of colistimethate in Table 3 relevant to the actual creatinine clearance of each patient.

I modelli proposti falliscono nei pazienti iperfiltranti…

FAQ I

Quanto e in che modo l'iperfiltrazione deve essere considerata nell'aggiustamento posologico di una terapia antibiotica?

…In addition to known variables (age, DDIs, etc), critically ill patients may have also peculiar conditions that can affect the pharmacokinetics of antibiotics…



- Roberts, Lancet Infect Dis 2014 -

"La quota di farmaco libera, non legata alle proteine plasmatiche, viene distribuita ed eliminata dal plasma. Di consequenza, pazienti ipoalbuminemici avranno, a parità di dose di antibiotico somministrata, un aumento nell'eliminazione del farmaco, con consequente ridotta attività terapeutica"

NB: questo vale per farmaci con legame proteico elevato

Highly bound (>70%)	Moderately bound (70-30%)	Minimally bound (<30%)
Cefazolin	Azithromycin	Amikacin
Cefoperazone	Aztreonam	Amoxicillin
Ceftriaxone	Cefotaxime	Ampicillin
Clindamicin	Cefuroxime	Cefepime
Daptomycin	Ciprofloxacin	Ceftazidime
Ertapenem	Clarithromycin	Doripenem
Erythromycin	Levofloxacin	Gentamycin
Minocycline	Linezolid	Imipenem
Rifampicin	Piperacillin	Meropenem
Teicoplanin	Ticarcillin	Norfloxacin
Tigecycline	Vancomycin	Tobramycin

- Ulldemolins, Clin Pharmacokinet 2011 -

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

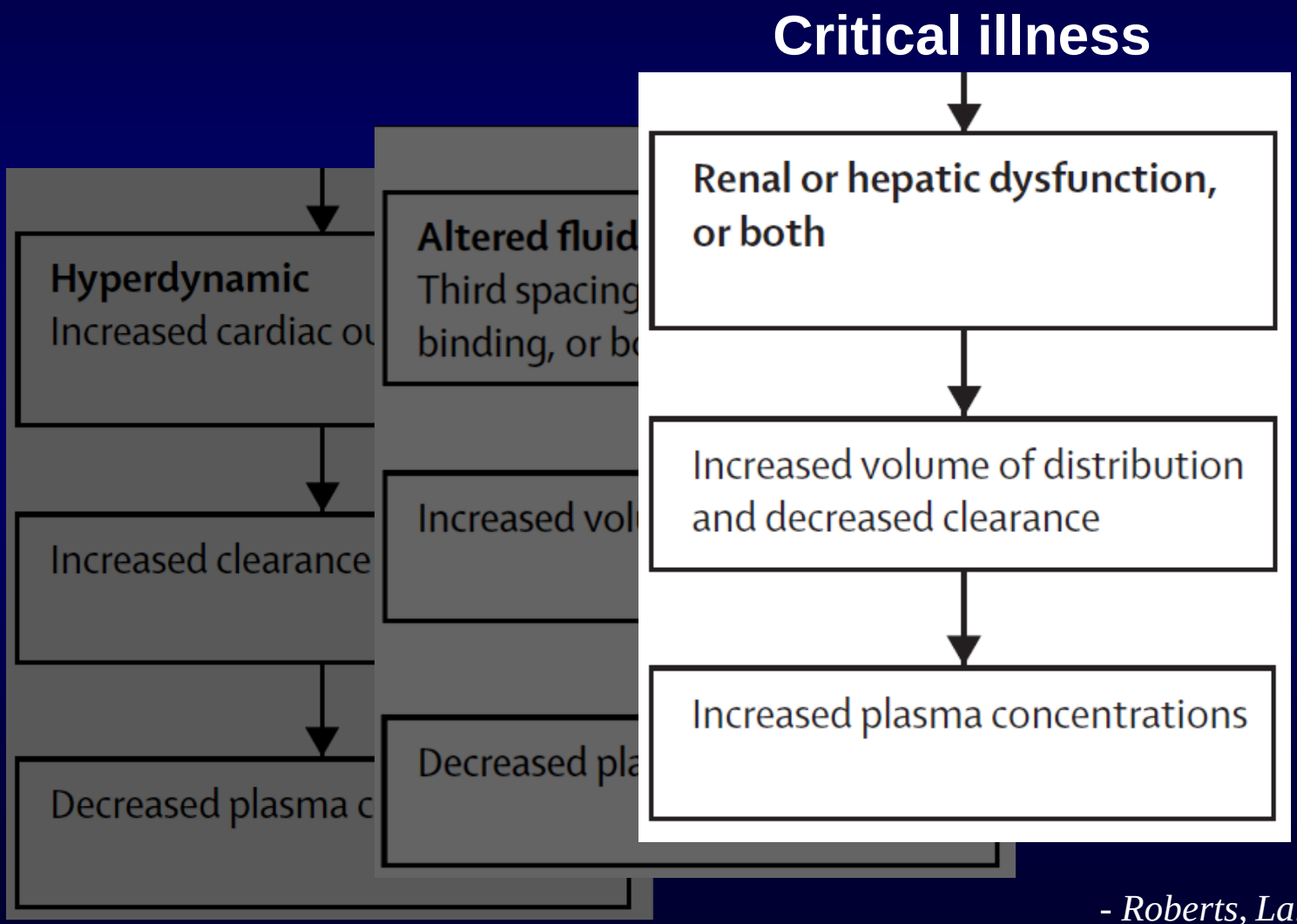
Drug	% Protein binding in healthy volunteers	Change in clearance in ICU patients[a]
Aztreonam [26, 27]	60	15 % increase
Ceftriaxone [10, 16]	85–95	99 % increase
Daptomycin [28, 29]	90–93	151 % increase
Ertapenem [30, 31]	85–95	113 % increase
Ertapenem [14]	85–95	462 % increase
Flucloxacillin [13, 32]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

- Roberts, Clin Pharmacokinet 2013 -

FAQ II

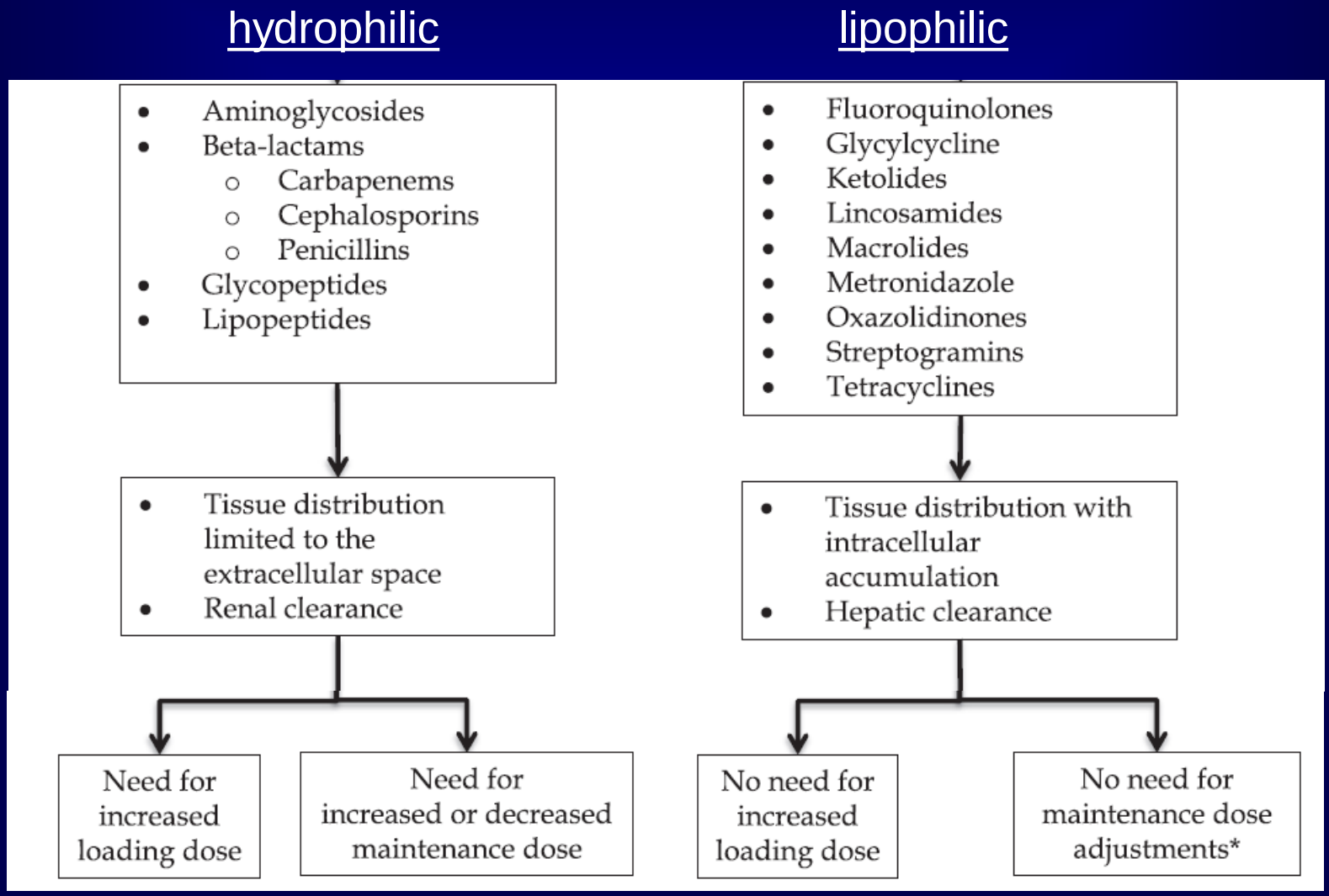
Pensando ai pazienti con patologie proteinuriche che livelli di ipoalbuminemia si possono considerare patologici?
Che valore aggiunto può avere la supplementazione con albumina?

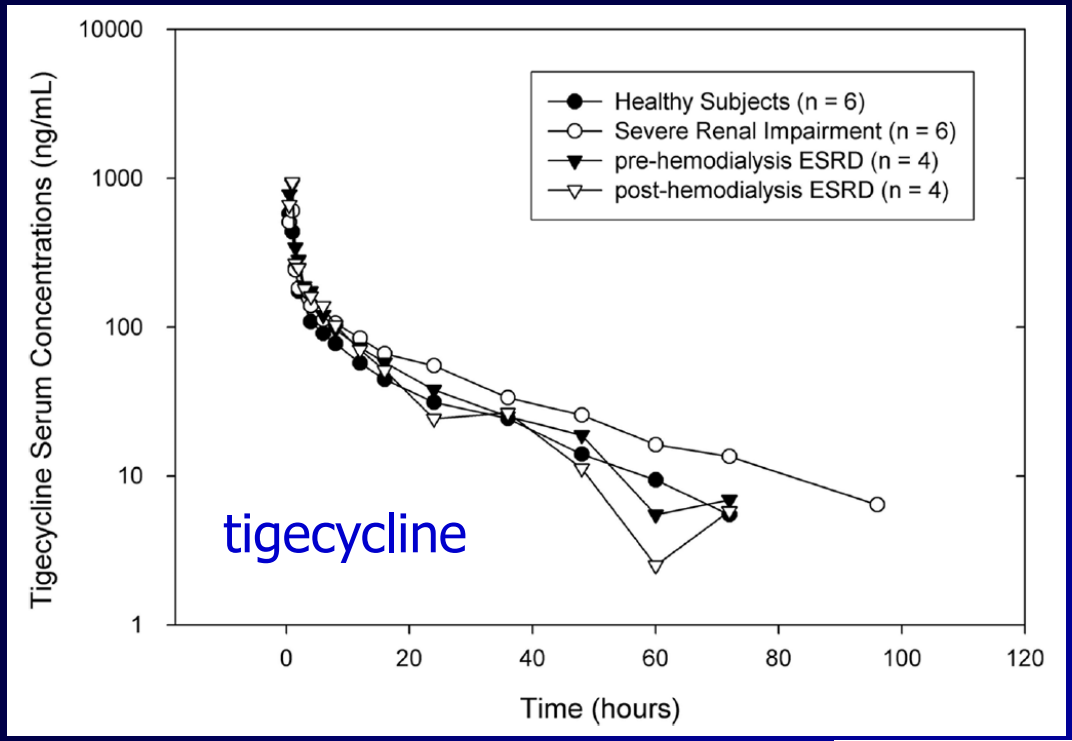
…In addition to known variables (age, DDIs, etc), critically ill patients may have also peculiar conditions that can affect the pharmacokinetics of antibiotics…



- Roberts, Lancet Infect Dis 2014 -

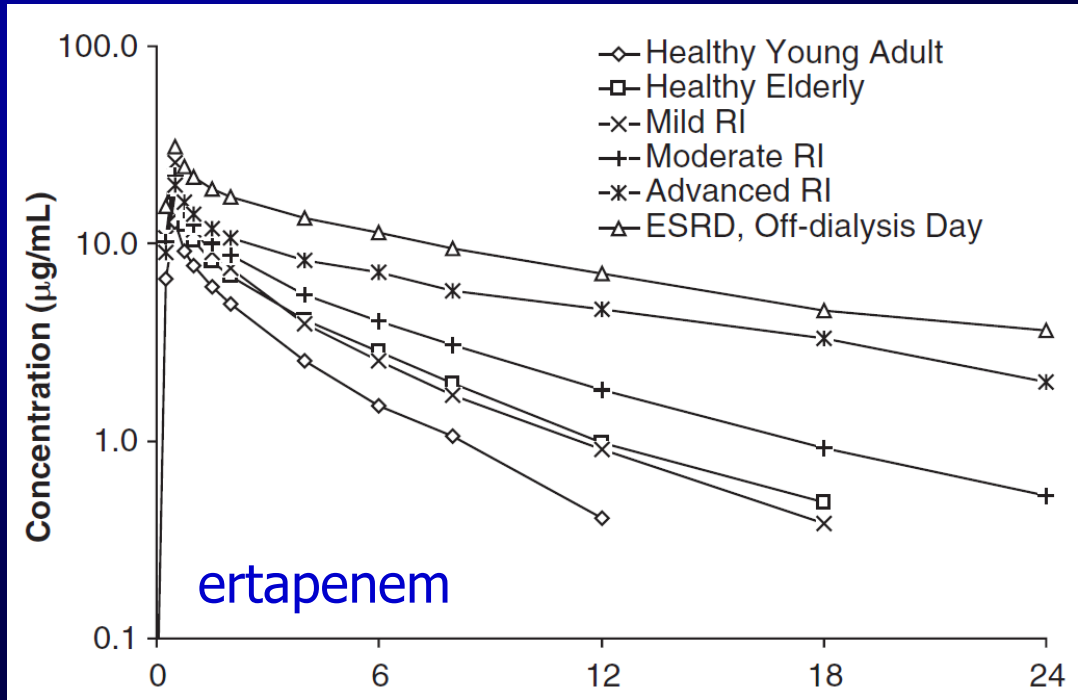
The pharmacokinetics of hydrophilic antibiotics is greatly altered in patients with renal insufficiency…



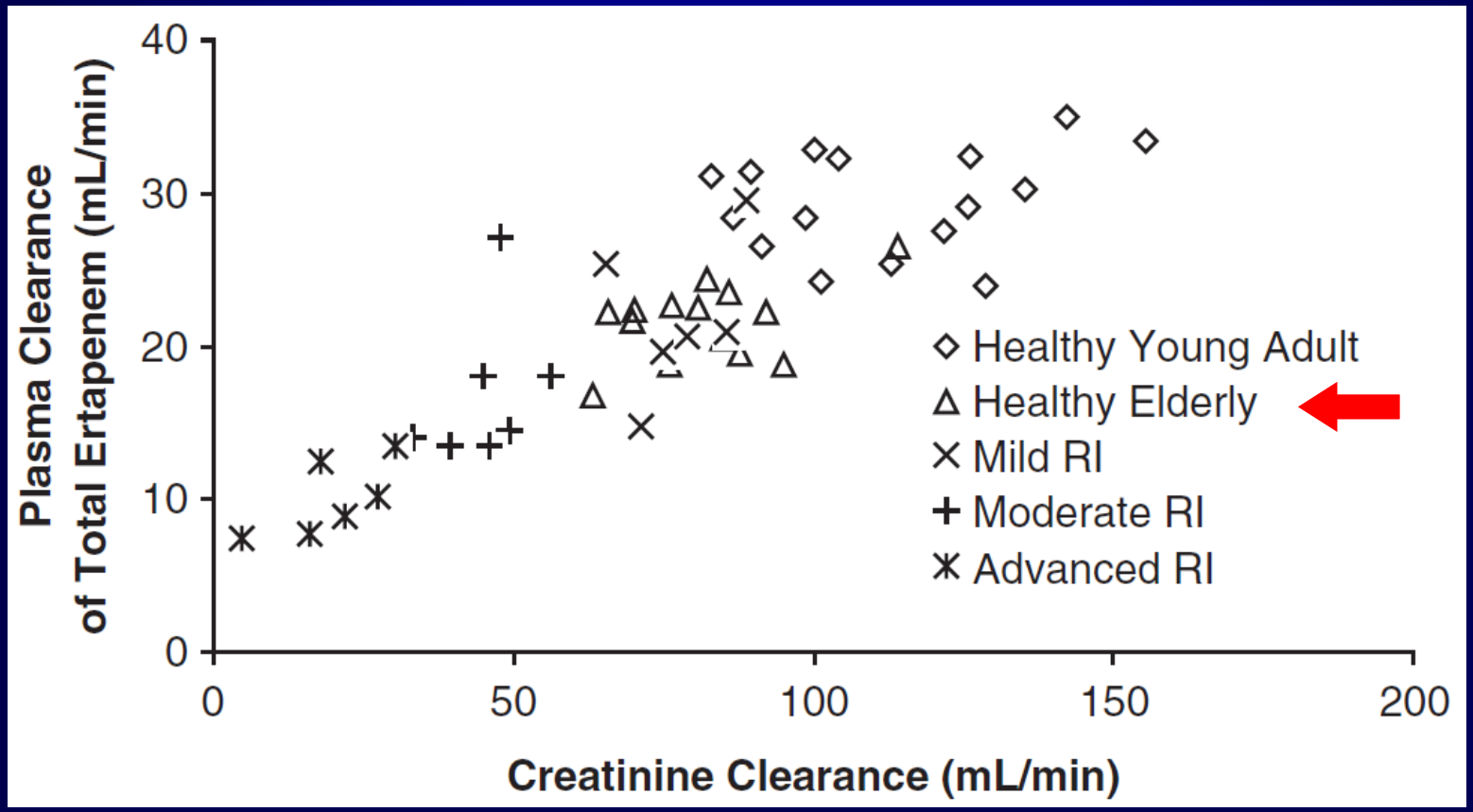


- Korth-Bradley, J Clin Pharmacol 2011 -

- Mistry, J Clin Pharmacol 2006 -



…qui allora è semplice…se conosco la funzione renale del paziene posso stimarmi la clearance del'antibiotico…!!!



- Mistry, J Clin Pharmacol 2006 -

Evaluation of Aminoglycoside Clearance Using the Modification of Diet in Renal Disease Equation Versus the Cockcroft-Gault Equation as a Marker of Glomerular Filtration Rate

RESULTS: Fifty-five patients were included in the final analysis. The primary outcome showed concordance between estimated and actual aminoglycoside clearance was 0.53 (95% CI 0.18 to 0.88) for the CG equation and 0.41 (95% CI 0.04 to 0.78) for the MDRD equation. Subgroup analysis also favored CG as a better predictor of CrCl. This signified a stronger correlation between the CG equation and aminoglycoside clearance.

- ✓ Creatinine
- ✓ Creatinine clearance?
- ✓ cystatin C
- ✓ MDRD?
- ✓ Cockcroft-Gault?
- ✓ Nankivell?
- ✓ GFR by iohexol, inulin or iothalamate?

- Ryzner, Annals Pharmacother 2010 -

FAQ III

Quali equazioni per la predizione del GFR sono più affidabili? Quali utilizzare nel paziente con IRC?

…inoltre non sempre tutto è bianco o nero: il caso di linezolid…

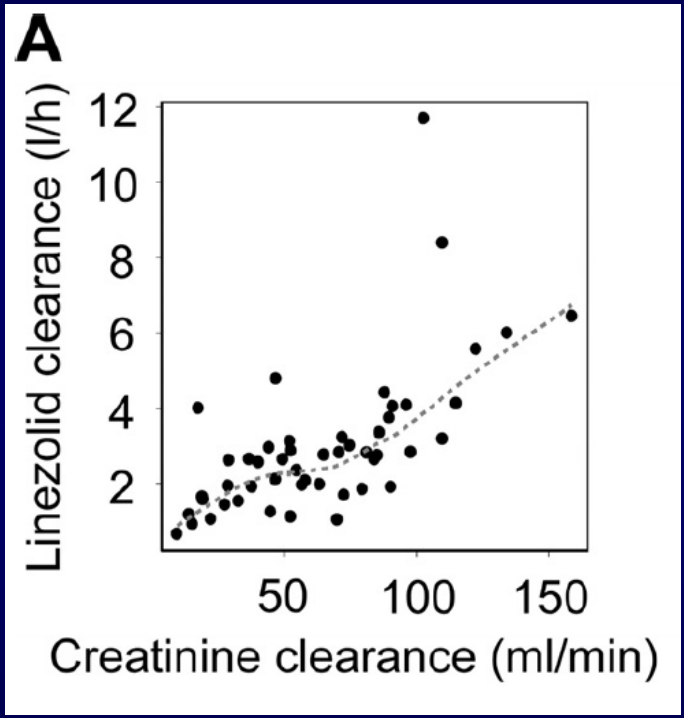
- ✓ Nonrenal clearance accounts for approximately 65% of the total clearance of linezolid;
- ✓ The pharmacokinetics of linezolid are not altered in patients with any degree of renal insufficiency;

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)

- ✓ **No dose adjustment is recommended for patients with renal insufficiency**

-USP-NF monograph-

...these data, however, are not confirmed in the real life clinical scenarios....



A clear relationship between renal function and linezolid clearance has been firmly established

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)

- Sasaki, Antimicrob Agents Chemother 2011 -

- Morata, Antimicrob Agents Chemother 2013 -

Linezolid accumulates in patients with renal dysfunction leading to hematologic toxicity

Table 2. Factors affecting the development of thrombocytopenia during linezolid therapy

Factor	OR (95% CI)	*P* value
Age ≥65 years	4.9 (0.8–29.1)	0.12
Gender male	0.3 (0.04–1.6)	0.23
Weight <50 kg	2.3 (0.5–11.7)	0.44
CL_{CR} <60 mL/min	39.0 (3.8–399.8)	0.0002
Duration of linezolid treatment ≥14 days	1.8 (0.4–7.8)	0.48
Linezolid trough concentration[a] >7.5 mg/L	90.0 (7.3–1115.9)	<0.0001
Intravenous administration of linezolid	0.5 (0.1–2.3)	0.47
Previous vancomycin use	0.5 (0.1–2.3)	0.47

- Nukui, J Antimicrob Chemother 2013 -

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

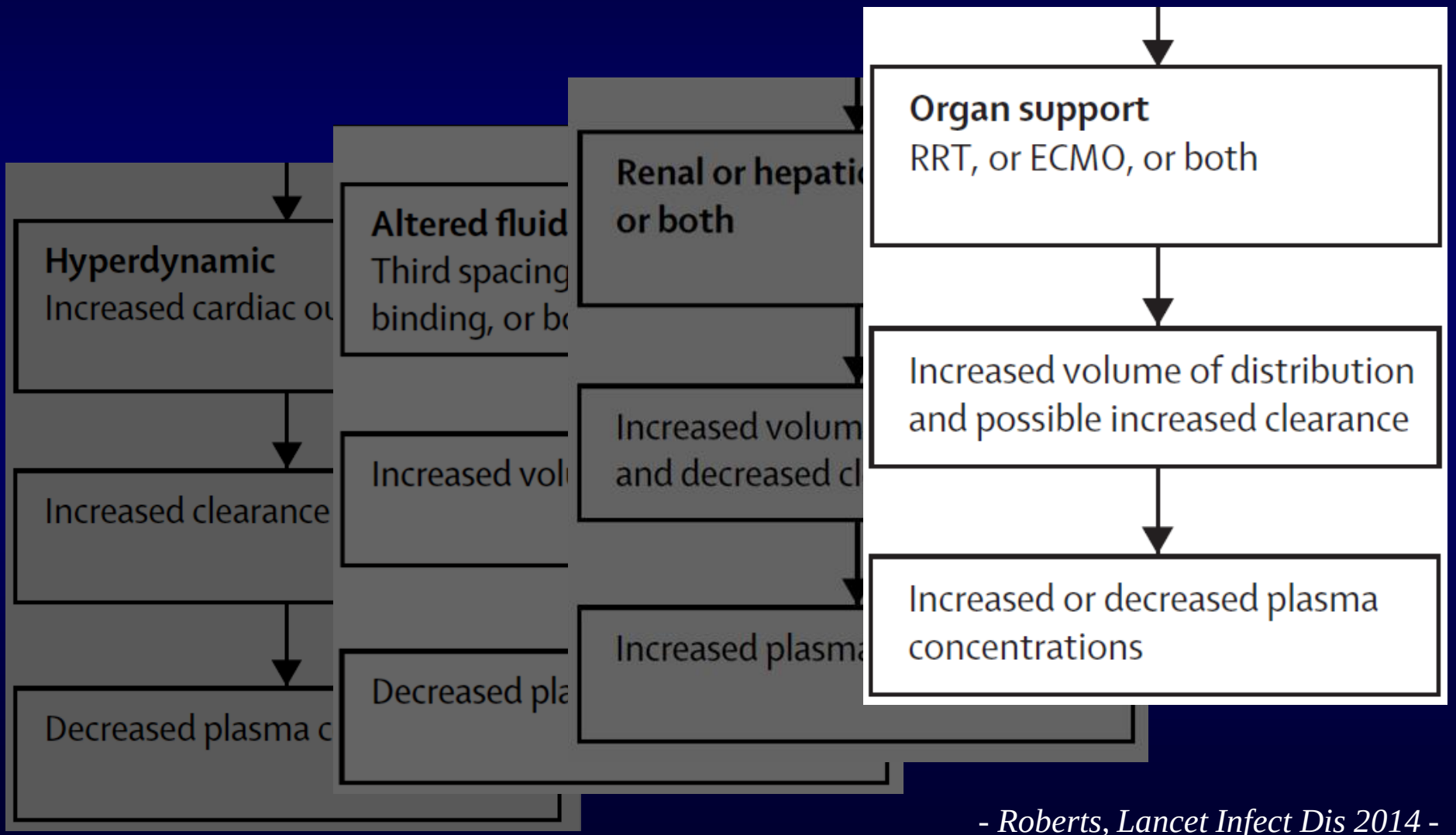
	pts without tox (m ± SD)	pts with tox (m ± SD)	P-value
Age (years)	60.3 ± 22.5	76.3 ± 22.5	0.042
Body Mass Index (Kg/m^2)	24.2 ± 6.3	24.5 ± 0.4	
Creatinine Cl. (mL/min)	**62.1 ± 32.2**	**34.3 ± 19.6**	**0.042**
AST (UI/L)	61.6 ± 72.8	23.3 ± 4.4	
ALT (UI/L)	92.1 ± 116.3	21.3 ± 10.1	
[LZD] day 3 (mg/L)	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 -

FAQ IV

Quale dose di linezolid suggerire nel paziente con IRC?

…In addition to known variables (age, DDIs, etc), critically ill patients may have also peculiar conditions that can affect the pharmacokinetics of antibiotics…



- Roberts, Lancet Infect Dis 2014 -

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REVIEW

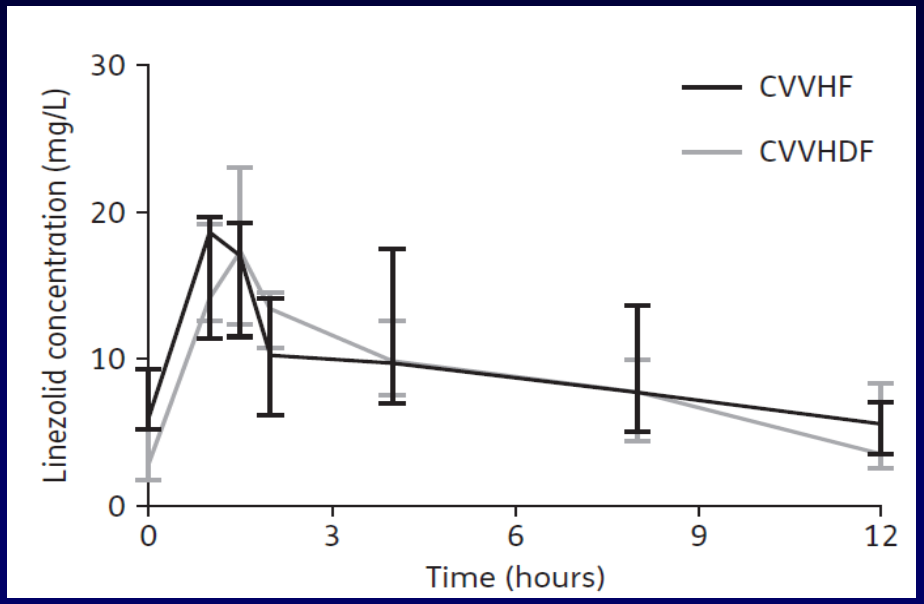
Pharmacokinetics and pharmacodynamics of antibiotics in critically ill acute kidney injury patients

Welder Zamoner, Fernanda M. de Freitas, Durval S. S. Garms, Mariele Gobo de Oliveira, André L. Balbi & Daniela Ponce

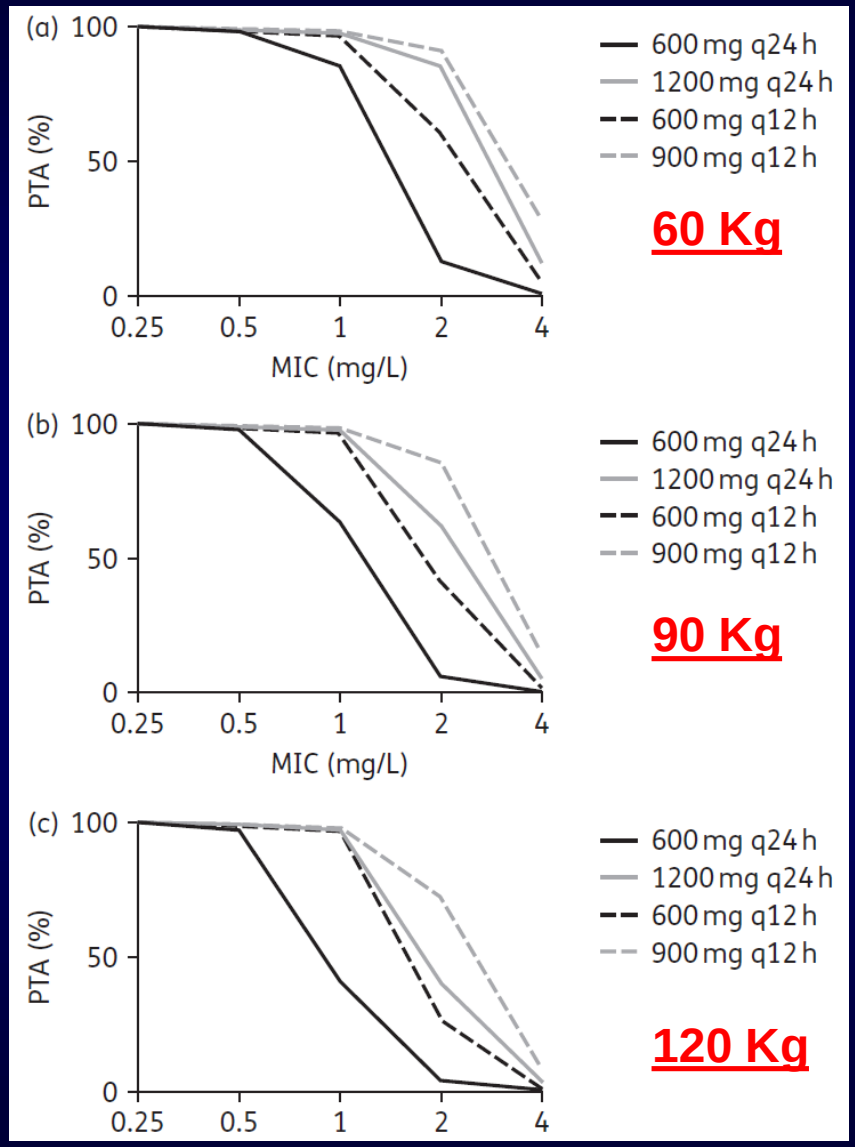
	Vancomycin	Meropenem	Cefepime	Piperacillin Tazobactam
Dose for normal renal function	15–20 mg/kg q8–12 h	1 g q8 h	1–2 g q8-12 h	3.375 g q6 h
Dose in CRRT	500 mg q24–48 h	500 mg q24 h	2 g q24 h	2.25 g q6 h
Dose in EHD[2]	No data	No data	No data	No data
Dose in IHD[3]	15 mg/kg after HD	500 mg q24 h	1 g 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.

Pk of linezolid in critically ill patients on continuous venovenous haemofiltration vs. continuous venovenous haemodiafiltration



- ✓CVVHDF was associated with a 21% higher linezolid CL than CVVHF
- ✓Increasing patient weight and decreasing SOFA score were associated with increasing linezolid CL
- ✓Suboptimal achievement of therapeutic targets occurs at the MIC of 2 mg/L using 600 mg iv every 12 h



- Rogers, JAC 2016 -

Is it time to revise linezolid doses in peritoneal dialysis patients? A case series

J Antimicrob Chemother 2015
doi:10.1093/jac/dkv184
Advance Access publication 3 July 2015

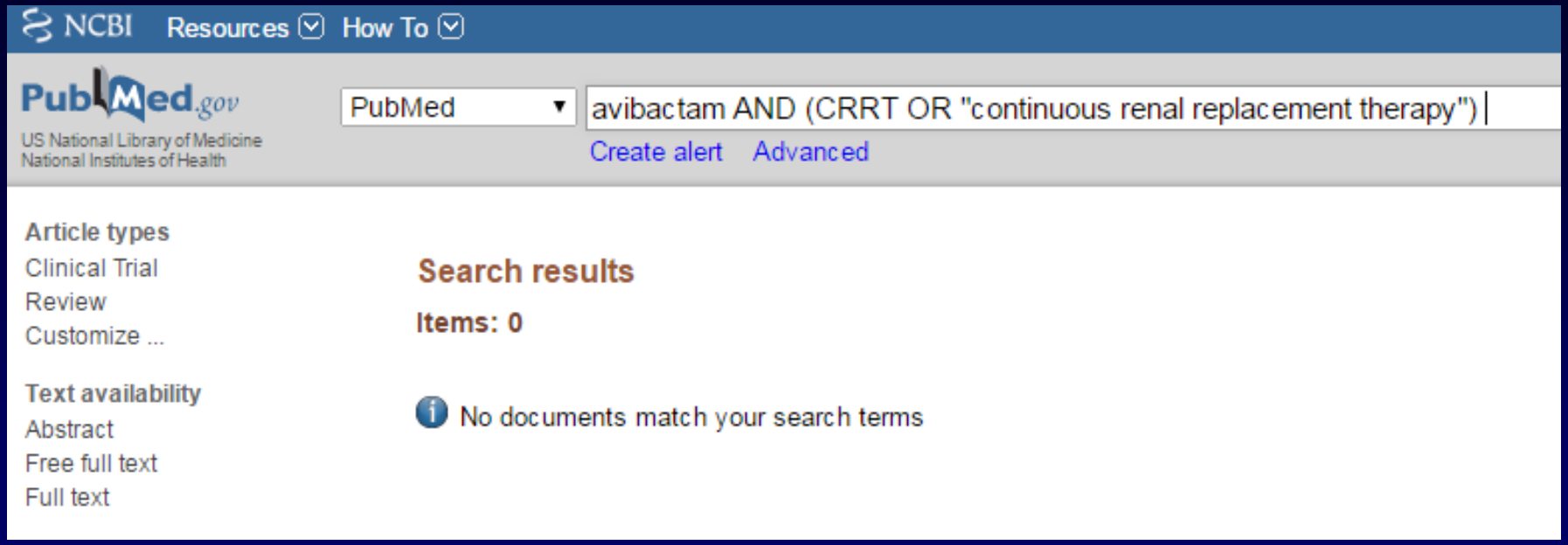
Cristina Gervasoni[1]*, Roberto Bergia[2], Valeria Cozzi[3], Emilio Clementi[4,5] and Dario Cattaneo[3]

- ✓ 1st: 66-year-old man on PD since 2012 given linezolid to treat lumbar spondylodiscitis. This resulted in a progressive reduction in platelet count, reaching a nadir of 53×10^3 cells/mL. Linezolid trough concentration: 25.5 mg/L.

- ✓ 2nd: 74-year-old woman on PD since 2010 given linezolid for leg ulcers. Linezolid trough concentrations: 22.5 mg/L.

- ✓ 3rd: 87-year-old woman on PD since 2013 given linezolid for Enterococcus faecalis peritonitis.The patient experienced pancytopenia and an increase in blood lactate values. Linezolid trough concentrations: 30 mg/L.

- ✓ 4th : 57-year-old woman on PD since 2009 given linezolid for MDR Staphylococcus epidermidis peritonitis. Linezolid was withdrawn 20 days later due to severe pancytopenia. Three days later, the patient experienced severe lactic acidosis and was transferred to the ICU, where she died. A plasma sample collected nearly 90 h after stopping linezolid revealed a plasma concentration of 1.5 mg/L (estimated trough: 20–30 mg/L).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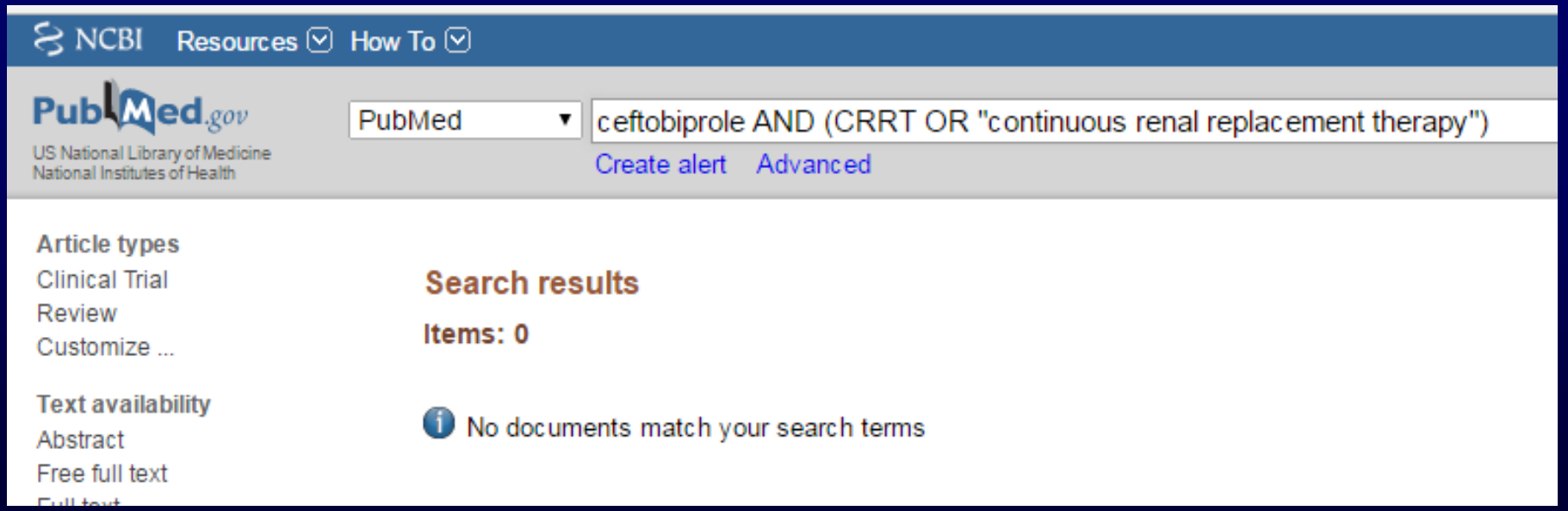
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FAQ V

Cosa devo rispondere a chi mi chiede come aggiustare la posologia dei nuovi antibiotici in pazienti che fanno CRRT?

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

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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"

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 -

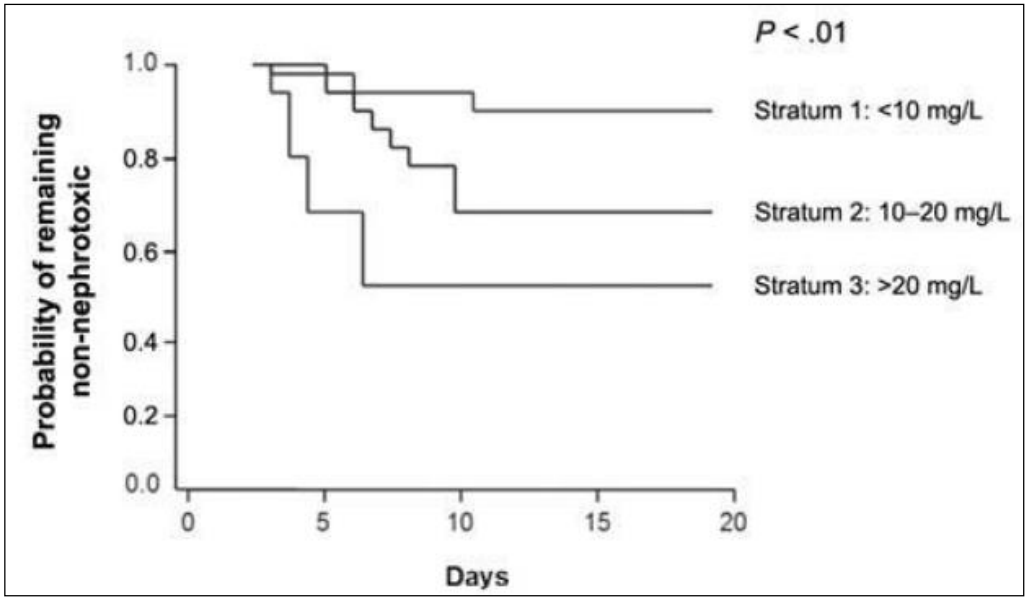
Vancomycin: our “top player” (3000 TDM/year)

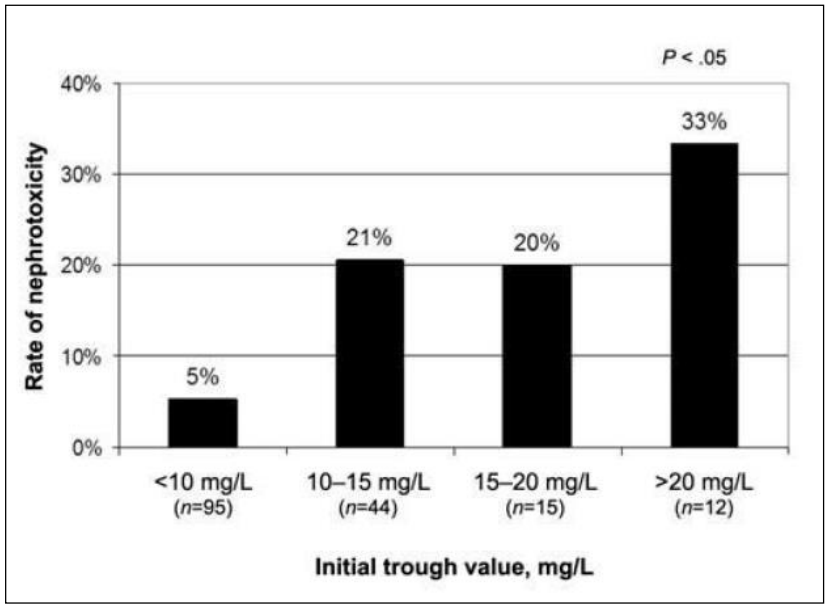
Clinical Infectious Diseases

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

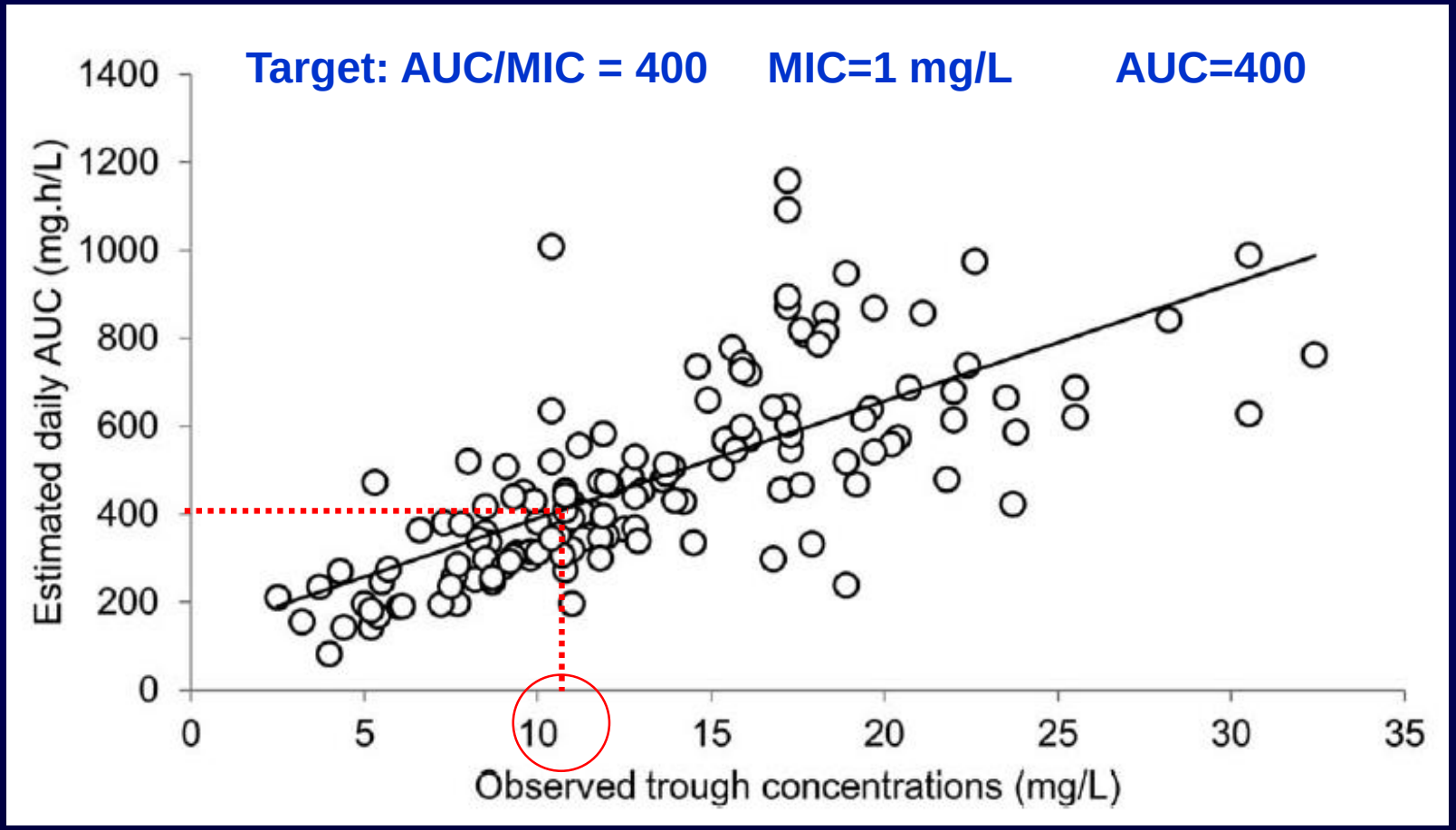
Antibiotic exposure profile	Patients with nephrotoxicity (n = 21)	Patients without nephrotoxicity (n = 145)	P
Initial vancomycin trough value, mean mg/L ± SD	14.6 ± 8.3	9.6 ± 5.1	.014
Initial vancomycin trough value ⩾9.9 mg/L	16 (76.2)	56 (38.6)	.001





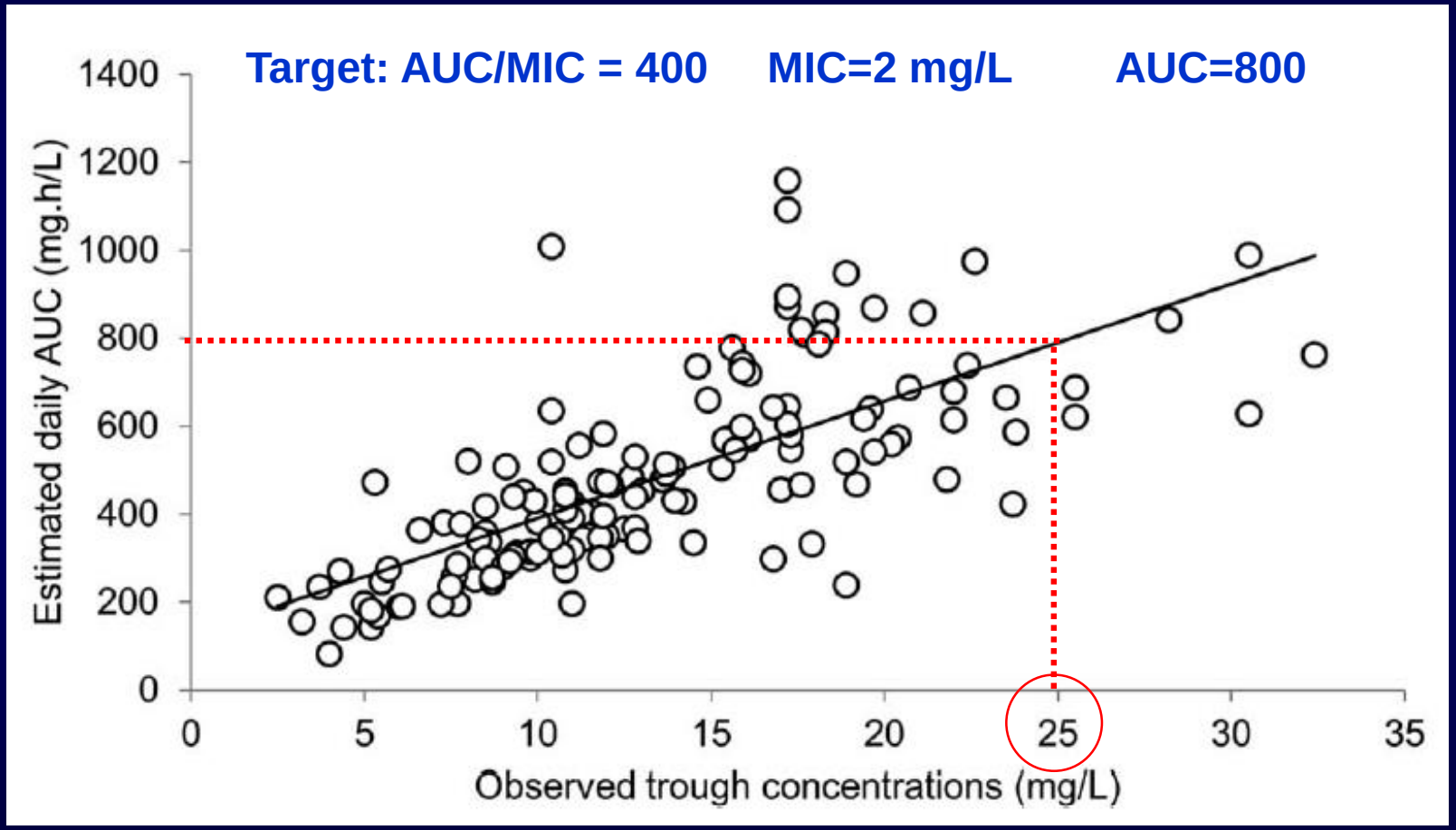
- Lodise, CID 2009 -

…but increased vancomycin concentrations may be required to treat resistant pathogens..



- Kamel, Ther Drug Monit 2017 -

…but increased vancomycin concentrations may be required to treat resistant pathogens..



- Kamel, Ther Drug Monit 2017 -

Paziente XX

11/11/2016: infusione gentamicina
al termine dell'infusione di gentamicina si misura una Cmax di 15 mg/L (MIC = 1 mg/L, Cmax/MIC=15)

12/11/2016, prima di somministrare la dose successiva di gentamicina si misura Cmin = 4.5 mg/L

NON somministro gentamicina!
Fino a quando Cmin non è scesa sotto i 2 mg/L (la letteratura piu recente suggerisce che le Cmin di gentamicina dovrebbero essere <1 mg/L..) non somministro la dose successiva…

Commento del medico di reparto: "ma io devo somministrare gentamicina tutti i giorni…"

FAQ VI

Quanto viene realmente utilizzato/considerato il TDM per aggiustare la posologia nel paziente con IRC?