BETALATTAMICI: COME OTTIMIZZARNE L'IMPEGO TRAMITE TDM

Dott. Davide Mangioni
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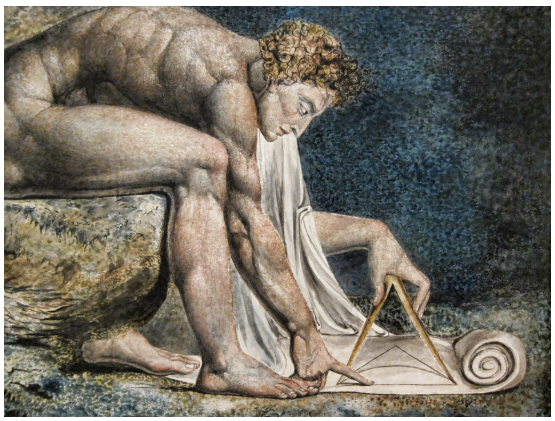
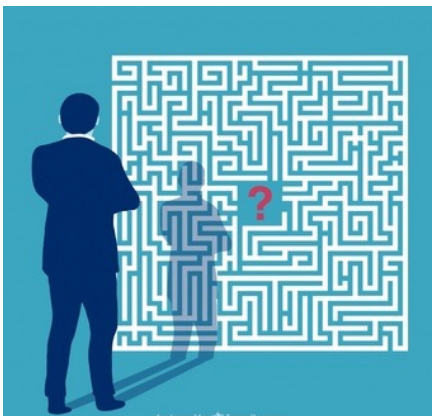
Policlinico di Milano

1

L'antibiogramma …



… e il TDM



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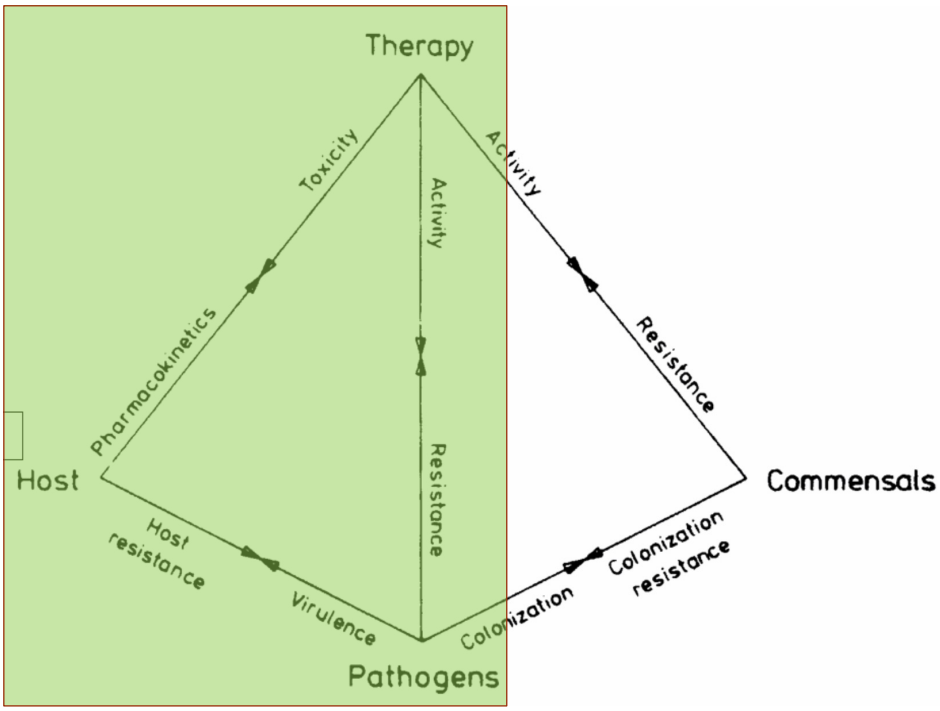

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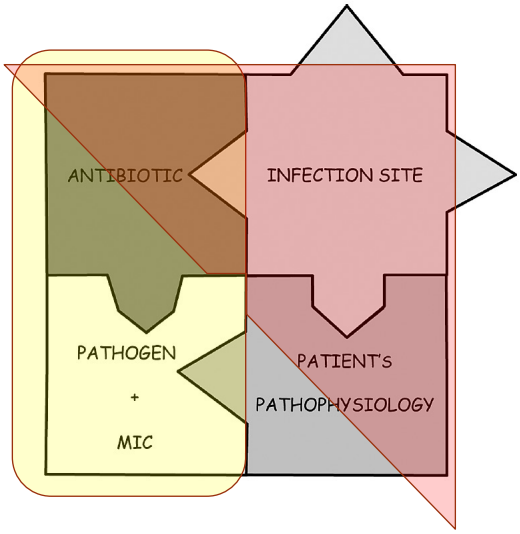
PHARMACODYNAMICS PHARMACOKINETICS



Pea F & Viale P. *Critical Care* 2009

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QUANDO UTILIZZARE IL TDM DEI BETALATTAMICI?

- ALTERAZIONI PK (PAZIENTE CRITICO)
- ALTERAZIONI PD (DIFFICULT-TO-TREAT RESISTANCE)

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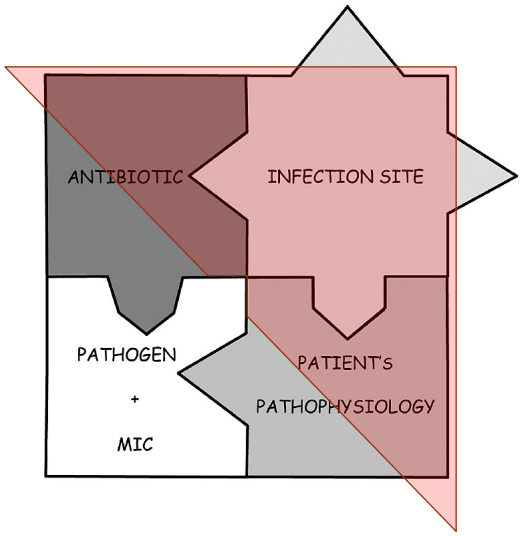
ALTERAZIONI FARMACOCINETICHE



Pea F & Viale P. *Critical Care* 2009

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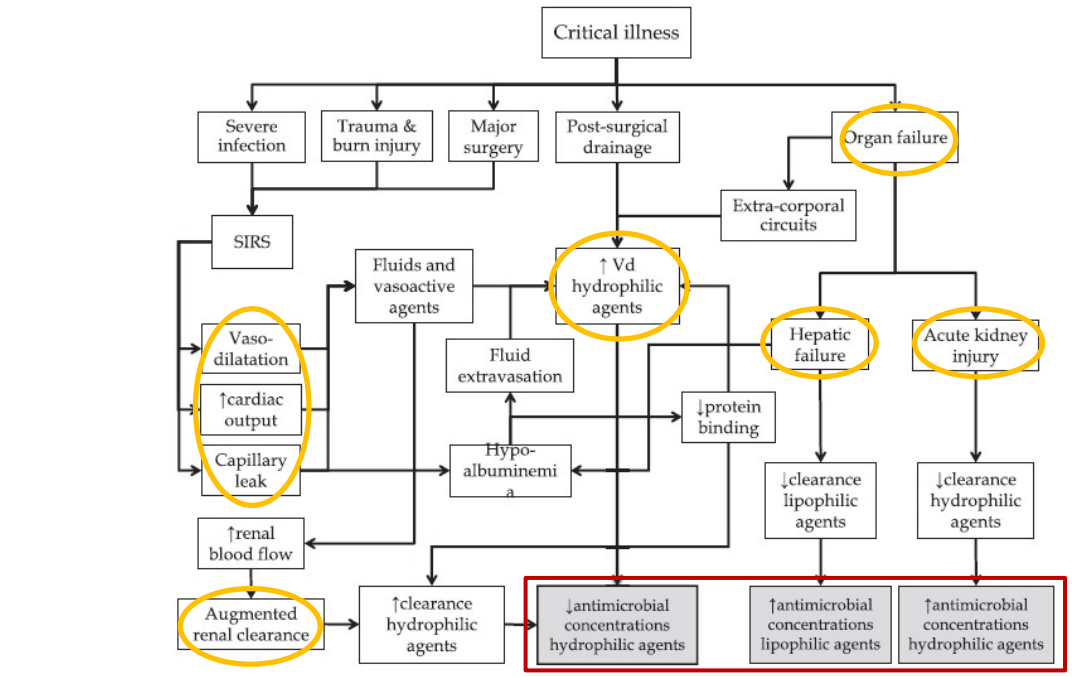

Blot S et al. *Adv Drug Deliv Rev* 2014

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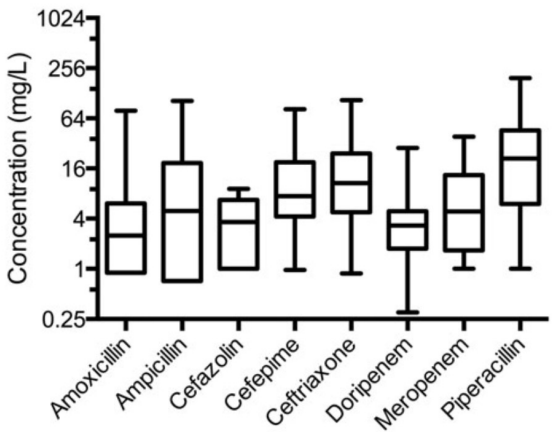
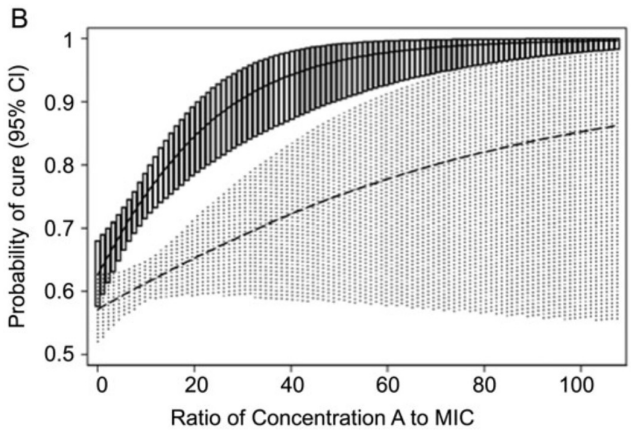
INTER-INDIVIDUAL VARIABILITY





Roberts JA et al. *Clin Inf Dis* 2014

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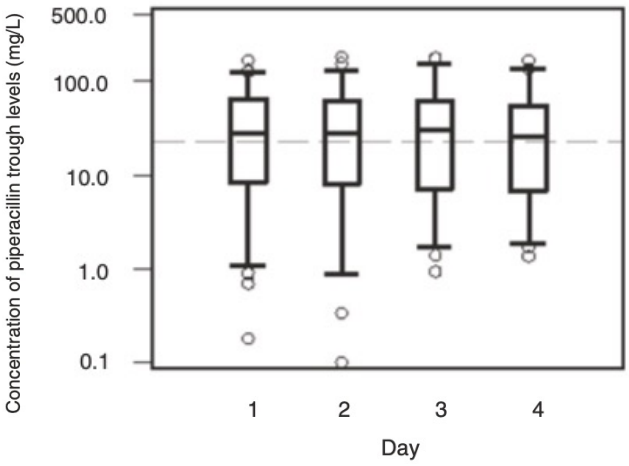
INTER-INDIVIDUAL & INTRA-INDIVIDUAL VARIABILITY



median intra-individual variability of trough piperacillin concentrations of 30% (range, 6 to 129%)

Zander J et al. *Critical Care* 2016

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QUALI FATTORI LEGATI A VARIABILITÀ?

- volume di distribuzione (BMI, terzo spazio)
- clearance (AKI/RRT o ARC)
- età
- condizioni cliniche (rapide variazioni, pazienti critici)

Table 2 Multivariate binary logistic regression in ICU patients, analysis predicting attainment achieving PDT of (A) 100% $fT >$ MIC and (B) 100% $fT > 4\times$MIC as the dependent factor

Predictor variables	100% $fT >$ MIC OR (95% CI)	100% $fT > 4\times$MIC OR (95% CI)
Male gender	**0.32 (0.12–0.81)**	0.60 (0.23–1.51)
Age (years)	1.03 (0.99–1.07)	0.98 (0.94–1.01)
BMI (mg/kg^2)	0.98 (0.91–1.05)	**0.91 (0.83–0.99)**
Serum urea (mmol/L)	**1.09 (1.03–1.17)**	**1.05 (1.00–1.10)**
eGFR ≥ 90 (mL/min/1.73 m^2)	0.69 (0.25–1.94)	**0.14 (0.03–0.49)**
SOFA score	1.05 (0.96–1.16)	0.95 (0.85–1.05)
CRRT	**6.54 (1.47–48.61)**	2.26 (0.73–6.97)
Sepsis	1.18 (0.38–3.88)	1.31 (0.43–3.88)

Abdulla A et al. *Critical Care* 2020

10

QUALI FATTORI LEGATI A VARIABILITÀ?

- sito di infezione
  - infezioni con *source control* inefficace
    - endocarditi o infezioni endovascolari con *focus* non rimuovibile
    - ascesso con mancato/incompleto drenaggio
  - infezioni in sito anatomico con scarsa penetrazione
    - infezioni SNC
    - osteomieliti
    - prostatiti
    - HAP/VAP

Muller AE et al. *Drugs* 2018

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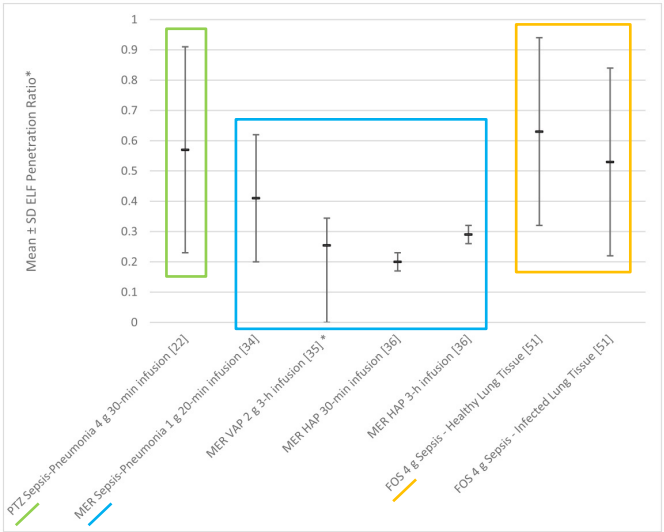
QUALI FATTORI LEGATI A VARIABILITÀ?



Heffernana AJ et al. *Int J Antimicrob Agents* 2019

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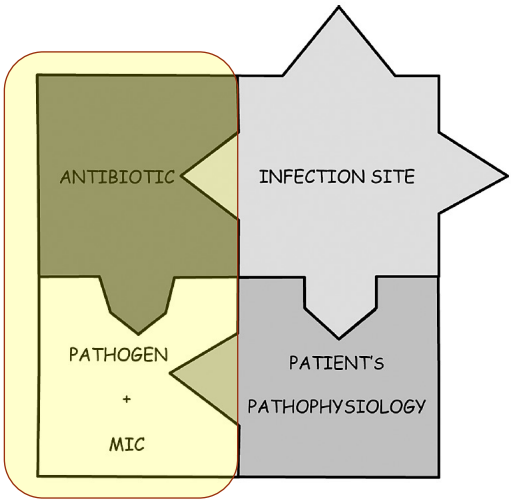
ALTERAZIONI FARMACODINAMICHE



Pea F & Viale P. *Critical Care* 2009

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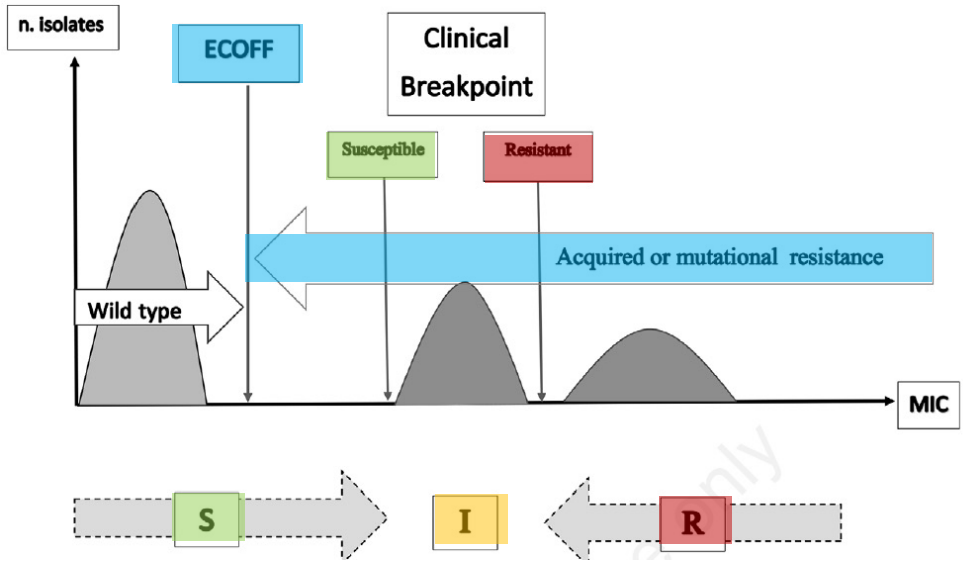
TARGET PK/PD DEI BETALATTAMICI



Tascini C. et al., *Italian Journal of Medicine* 2016

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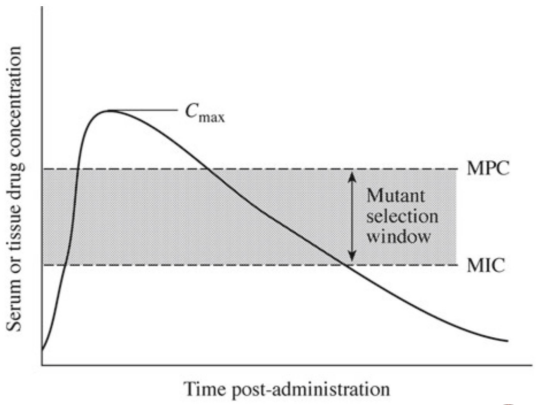
TARGET PK/PD DEI BETALATTAMICI

- paziente non critico: 50-70% *f*T > (k) x MIC
- paziente critico (sepsi, ICU) 100% *f*T > (k) x MIC

100% *f*T ≥ 4-8 x MIC

- inaccuratezza determinazione della MIC (± 1-2 diluizioni)
- inaccuratezza misurazione TDM del farmaco (± 15%)
- variabilità diffusione del farmaco nella sede di infezione
- prevenzione selezione di farmacoresistenza



Guilhaumou R et al. *Critical Care* 2019

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RISCHIO INEFFICACIA/TOSSICITÀ

BAL: Pseudomonas aeruginosa

carica 1.000.000 UFC/ml

Antibiotico	RSI	MIC
amikacina	S	2
cefepime	S	8
ceftazidime	R	32
ceftazidime/avibactam	R	32
ciprofloxacina	R	>2
fosfomicina		64
imipenem	R	2
meropenem	I	4
piperacillina/tazobactam	S	16

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CEFEPIME

Table 1 Convulsing activity of beta-lactams compared to penicillin G, from [67, 69, 70]

Beta-lactam	Relative pro-convulsive activity (reference: penicillin G = 100)
Cefazolin	294
Cefepime	160
Penicillin G	*100*
Imipenem	71
Aztreonam	42
Ampicillin	21
Ceftazidime	17
Meropenem	16
Ceftriaxone	12
Piperacillin	11
Cefotaxime	8,8
Cefoxitine	1,8

Guilhaumou R et al. *Critical Care* 2019

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CEFEPIME

Characteristic	Value
Median age (IQR)	69 years (54–75)
Sex (female), *n* (%)	69 (51%)
Pre-existing CNS disease, *n* (%)	11 (8%)
Cerebral vascular disease	6 (4%)
Encephalopathy	2 (1%)
Other[a]	3 (2%)
Renal function dysfunction	108 (80%)
Creatinine clearance, median (IQR)	26.5 (17–56) ml/min
History of alcohol use disorder, *n* (%)	3 (2%)
Co-administered neurotoxic drug(s), *n* (%)[b]	21 (16%)
Patient location, *n* (%)	
ICU	60 (44%)
Non-ICU	14 (10%)
Unreported	61 (45%)

CNS central nervous system
[a]Other pre-existing CNS diseases included encephalitis, spina bifida, dementia
[b]Reported neurotoxic medications include amikacin, ciprofloxacin, metronidazole, cytarabine, cyclosporine, tacrolimus, phenytoin

Characteristic	Value
Cefepime dosing	
Median dose over 24 hours (IQR), g	3.5 (2–5.9)
Median frequency of dosing (IQR), hours	12 (12–24)
Appropriately dosed for renal function, *n* (%)	
No	65 (48%)
Yes	35 (26%)
Unable to assess	35 (26%)
Indication, *n* (%)	
Febrile neutropenia	11 (8%)
Pneumonia	37 (27%)
Other[a]	31 (23%)
Not reported	56 (41%)
Drug concentrations, mg/L	
Median serum, n = 21 (range)	45 (15–284)
Median trough, n = 13 (range)	38 (15–224)
Median CSF, n = 4 (range)	13 (6–18)
Median for appropriately dosed patients, n = 7 (range)	60 (22–74)
Median for inappropriately dosed patients, n = 10 (range)	39 (15–284)
Trough for appropriately dosed patients, n = 6 (range)	54 L (37–65)
Median onset of neurotoxic effects (IQR), days	4 (2–6)

Payne EL et al. *Critical Care* 2017

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CEFEPIME

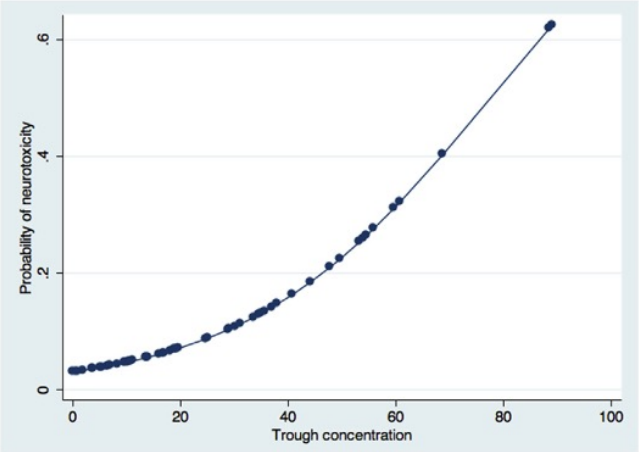

Fig. 1. Estimated probability of the occurrence of neurotoxicity according to cefepime plasma concentrations in patients with measured trough levels ($n = 55$).

Huwyler T et al. *Clin Microbiol Infect* 2017

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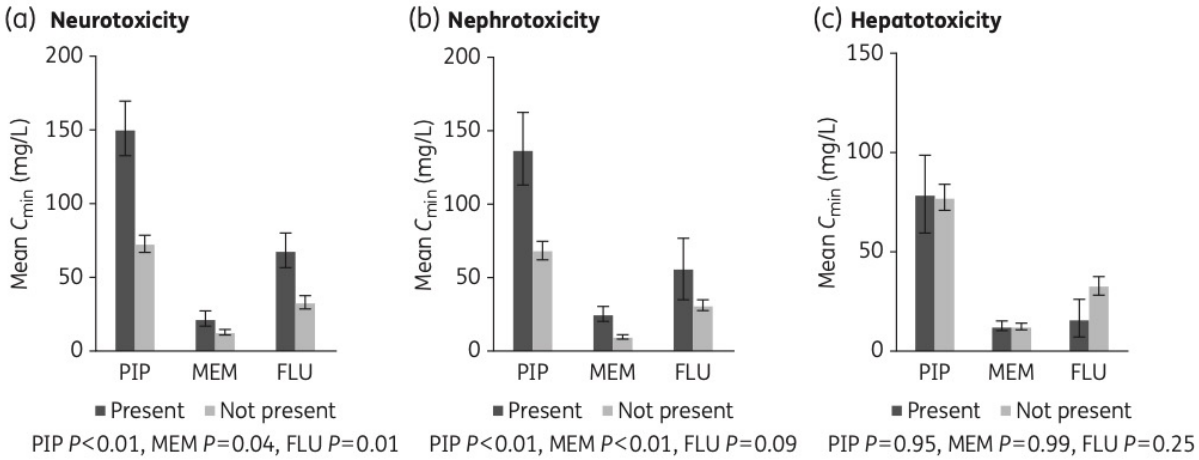
PIPERACILLINA/TAZOBACTAM E MEROPENEM



Imani S et al. *J Antimicrob Chemother* 2017

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COME UTILIZZARE IL TDM DEI BETALATTAMICI?

- COME GESTIRE I FARMACI PRE-TDM
- COME ESEGUIRE UN CORRETTO TDM E COME GESTIRE IL RISULTATO

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OTTIMIZZARE IL TRATTAMENTO PRE-TDM

	Step 1	Step 2	Step 3		
	PD index of choice	First dose	Daily dose (ARC – normal kidney function)	Daily dose (AKI)	Daily dose (CRRT)
Beta-lactams	T > MIC	Increased (up to double dose)	Continuous infusion	Reduced dose (except first 24h)	Unadjusted dose
Aminoglycosides	C_{max} / MIC	Doubled	Once daily (with TDM)	According to TDM	According to TDM
Glycopeptides	AUC / MIC	Weight-based (up to double dose)	Continuous infusion	According to TDM	According to TDM
Fluoroquinolones	AUC / MIC	Unchanged	q8h	According to residual CrCL	According to residual CrCL
Linezolid	AUC / MIC	Unchanged to increased	Unchanged	Unchanged	Increased dose – consider TDM
Colistin	AUC / MIC	Increased (up to 9 MIU)	Unchanged	According to residual CrCL	May need higher dose (up to 15 MUI)

Timsit JF et al. *Intensive Care Med* 2019

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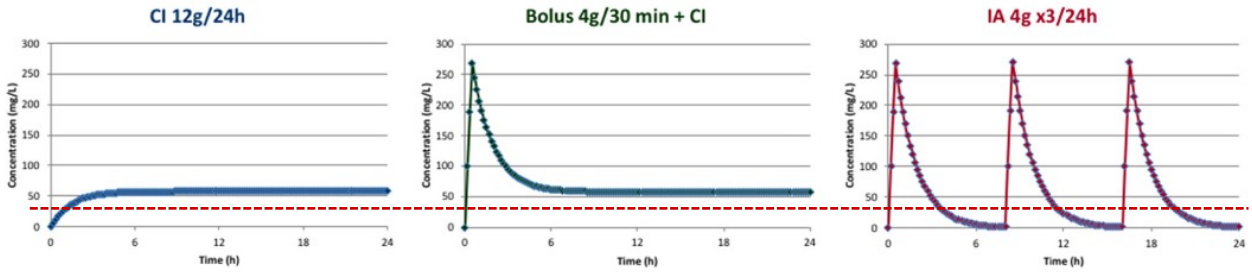
OTTIMIZZARE IL TRATTAMENTO PRE-TDM

- **dose di carico** (indipendente da fx renale)
  - sempre in caso di infusione continua del farmaco
  - nel paziente critico (alto volume di distribuzione) raccomandata anche in caso di infusione frazionata



Guilhaumou R et al. *Critical Care* 2019

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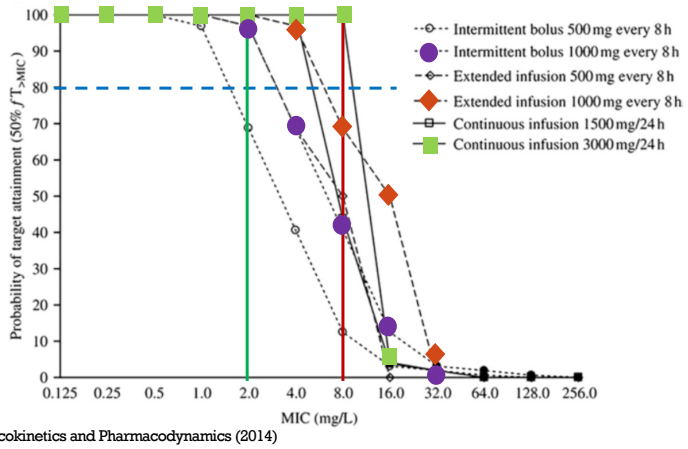
OTTIMIZZARE IL TRATTAMENTO PRE-TDM

- **infusione prolungata o continua**, in particolare se
  - valori di MIC non ottimali



Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics (2014)

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OTTIMIZZARE IL TRATTAMENTO PRE-TDM

- **infusione prolungata o continua**, in particolare se
  - paziente critico, sepsi/shock settico
  - HAP/VAP
  - infezioni severe da gram negativi non fermentanti

Variable	All Factors Included in the Model		Final Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Factors predicting hospital mortality censored at 30 d				
APACHE II score, per 1-point increase	1.08 (1.05–1.11)	<0.001	1.08 (1.05–1.11)	<0.001
Renal replacement therapy	2.48 (1.40–4.39)	0.002	3.02 (1.76–5.18)	<0.001
Study		0.01		0.003
Dulhunty and colleagues (25)	0.70 (0.23–2.15)	0.54	0.66 (0.26–1.67)	0.38
Abdul-Aziz and colleagues (24)	2.89 (1.33–6.24)	0.01	2.55 (1.35–4.79)	0.01
Dulhunty and colleagues (20) (reference group)	1.00		1.00	
Respiratory dysfunction on admission	1.86 (1.15–3.00)	0.01	1.71 (1.07–2.75)	0.03
Infection by NFGNB*	2.85 (1.35–6.04)	0.01	2.72 (1.32–5.62)	0.01
Age, per 1-yr increase	1.02 (1.00–1.03)	0.02	1.02 (1.00–1.03)	0.03
Cardiovascular dysfunction on admission	1.68 (1.03–2.75)	0.03	1.72 (1.06–2.80)	0.02
Hematological dysfunction on admission	1.78 (0.97–3.25)	0.06	—	—
Renal dysfunction on admission	1.41 (0.87–2.28)	0.17	—	—
Continuous infusion	0.52 (0.08–3.21)	0.48	0.62 (0.41–0.94)	0.03

Roberts JA et al. *Am J Respir Crit Care Med* 2016

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COME ESEGUIRE UN CORRETTO TDM E COME GESTIRE IL RISULTATO

- dosaggio **a 24-48h da inizio** del trattamento/modifica posologia/variazioni cliniche significative (inizio RRT, somministrazione amine, ..)
  - C_{min} nei 30' pre-somministrazione successiva
  - C_{ss} in qualsiasi momento dopo 24h da inizio infusione continua

- nei casi di infezione SNC, richiedere **TDM plasma + liquor**, in particolare
  - presenza di DVE
  - mancata risposta clinica, patogeni con MIC non ottimali

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COME ESEGUIRE UN CORRETTO TDM E COME GESTIRE IL RISULTATO

- rapportare C_{min}/C_{ss} a **target terapeutici**

	Free fraction (%)	Recommended target concentrations[#]		MIC threshold[£] [130]
		Documented infection	Non-documented infection	
Amoxicillin	≈ 80%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 80 mg/L	Cmin 40–80*mg/L[§] Css 40–80 mg/L	8 mg/L (ECOFF *E. coli*)
Cefazolin	≈ 15–20%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 80 mg/L	Cmin 40–80 mg/L[§] Css 40–80 mg/L	2 mg/L (ECOFF *S. aureus*)
Cefepime	80%	*f*Cmin or *f*Css ≥ 4× MIC Cmin < 20 mg/L Css < 35 mg/L	Cmin 5–20 mg/L Css 5–35 mg/L	1 mg/L (*Enterobacteriaceae*)[§§]
Cefotaxime	≈ 60–80%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 60 mg/L	Cmin 25–60 mg/L Css 25–60 mg/L	4 mg/L (ECOFF *S. aureus*)
Ceftazidime	≈ 90%	*f*Cmin or *f*Css ≥ 4× MIC Cmin or Css < 80 mg/L	Cmin 35–80 mg/L[§] Css 35–80 mg/L	8 mg/L (ECOFF *P. aeruginosa*)
Ceftriaxone	≈ 10%	*f*Cmin ≥ 4× MIC Cmin < 100 mg/L	Cmin 20–100 mg/L	0.5 mg/L (ECOFF *E. cloacae*)
Cloxacillin	≈ 10%	*f*Cmin or *f*Css ≥ 4× MIC Cmin ou Css < 50 mg/L	Cmin 20–50 mg/L[§] Css 20–50 mg/L	0.5 mg/L (ECOFF *S. aureus*)
Ertapenem	≈ 10%	*f*Cmin ou *f*Css ≥ 4× MIC Cmin < 10 mg/L	Cmin 5–10 mg/L	0.125 mg/L (*H. influenzae*)[§§§]
Imipenem	≈ 80%	*f*Cmin ≥ 4× MIC Cmin < 5 mg/L	Cmin 2.5–5 mg/L	0.5 mg/L (ECOFF *E. coli*)
Meropenem	≈ 100%	*f*Cmin ou *f*Css ≥ 4× MIC Cmin ou Css < 16 mg/L	Cmin 8–16 mg/L[§] Css 8–16 mg/L	2 mg/L (ECOFF *P. aeruginosa*)
Piperacillin	≈ 80%	*f*Cmin ou *f*Css ≥ 4× MIC Css < 160 mg/L	Css 80–160 mg/L	16 mg/L (ECOFF *P. aeruginosa*)

Guilhaumou R et al. *Critical Care* 2019

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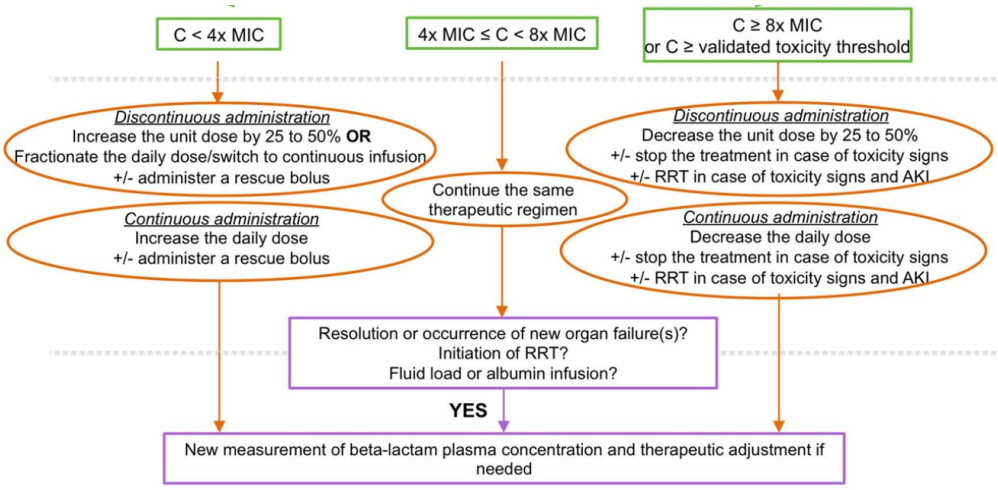
COME ESEGUIRE UN CORRETTO TDM E COME GESTIRE IL RISULTATO

- modificare trattamento se necessario e verificare nuovo TDM



Guilhaumou R et al. *Critical Care* 2019

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BETALATTAMICI: COME OTTIMIZZARNE L'IMPEGO TRAMITE TDM

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