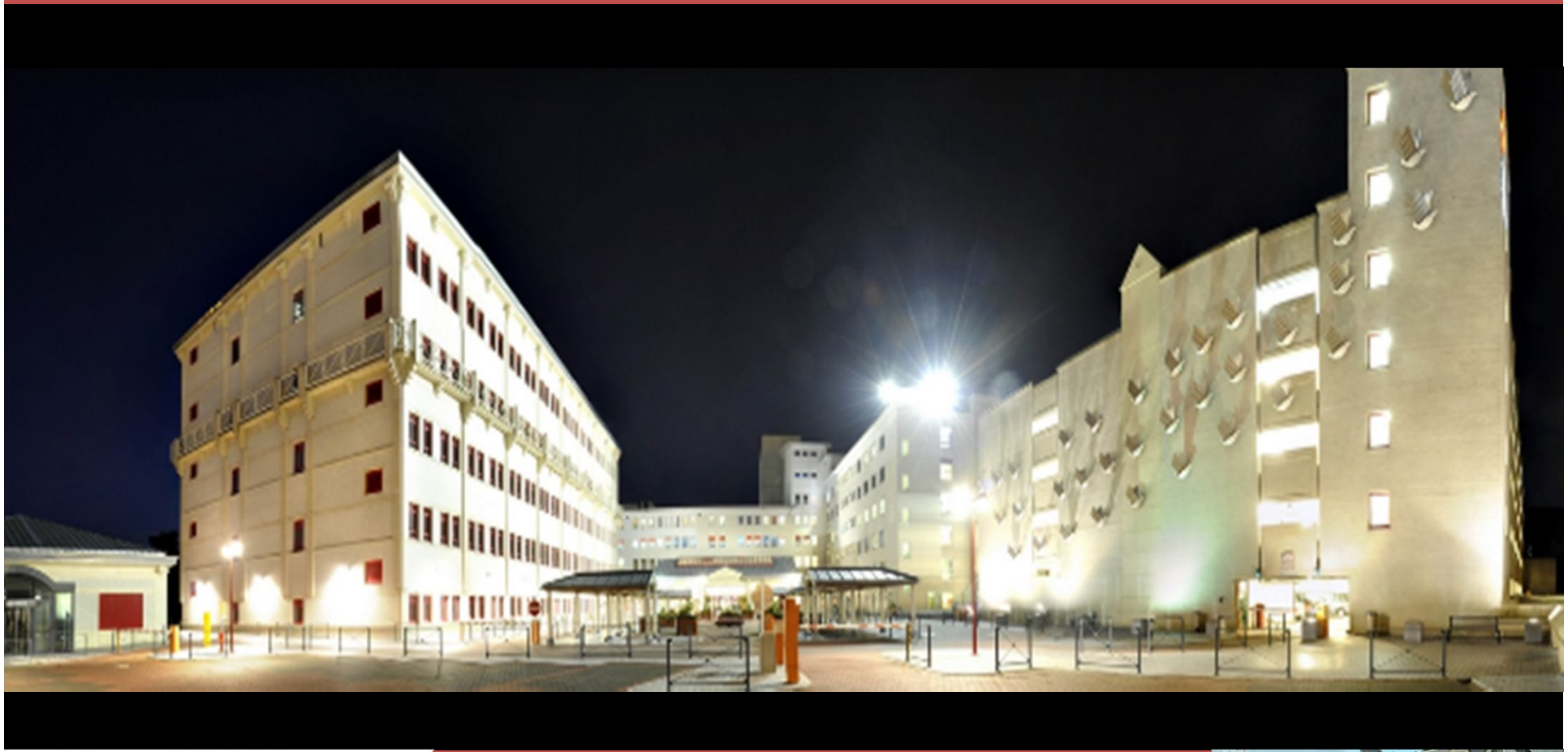
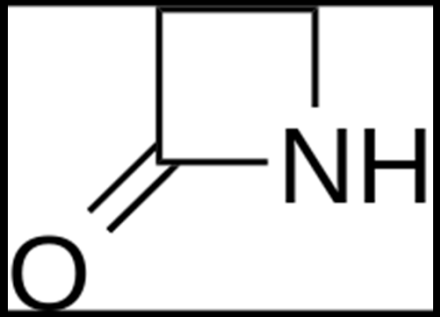
Increased dosing of β-lactams = Increased Toxicity ?

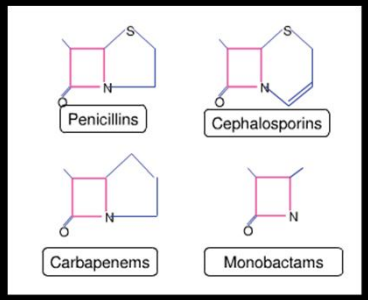


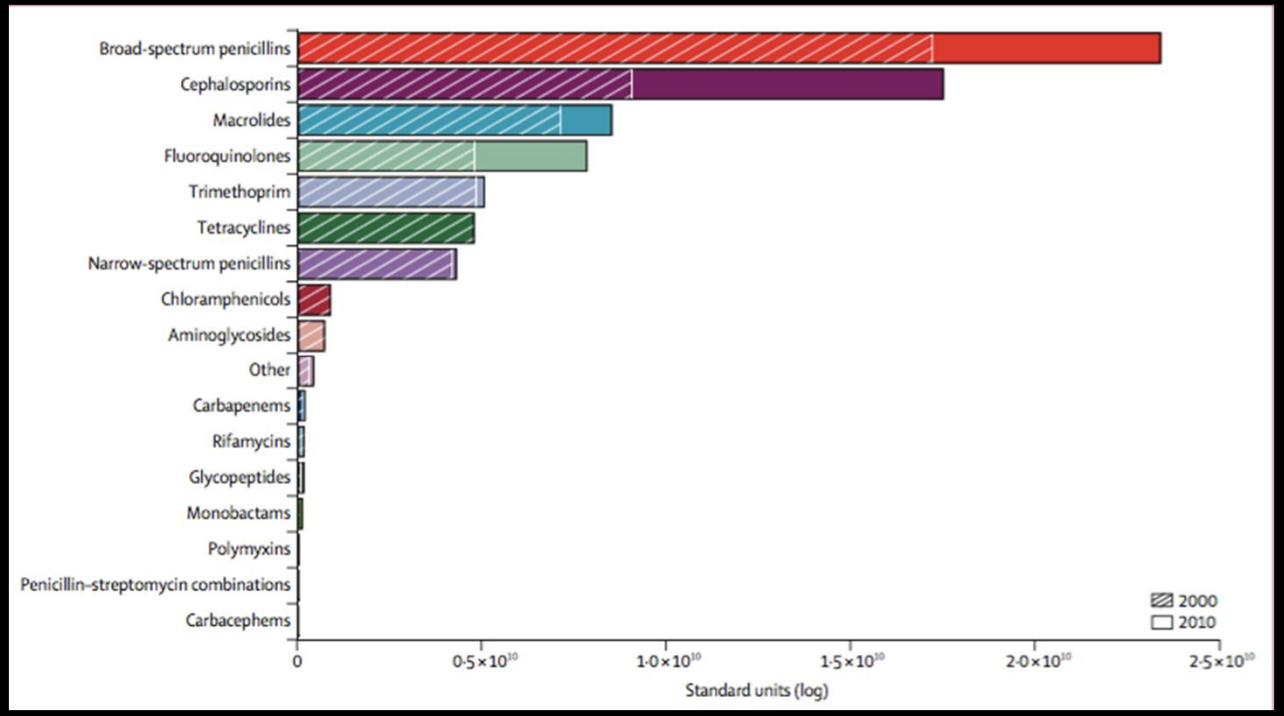
CHU AMBROISE PARÉ

Dr Marjorie Beumier
Intensive Care department
Hôpital Ambroise Paré

β-lactams







Standard dosing = Wide Therapeutic Index

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Increased dosing – WHY?

COMBINATION

APPROPRIATE THERAPY

ADEQUATE THERAPY

EARLY THERAPY

OPTIMAL THERAPY

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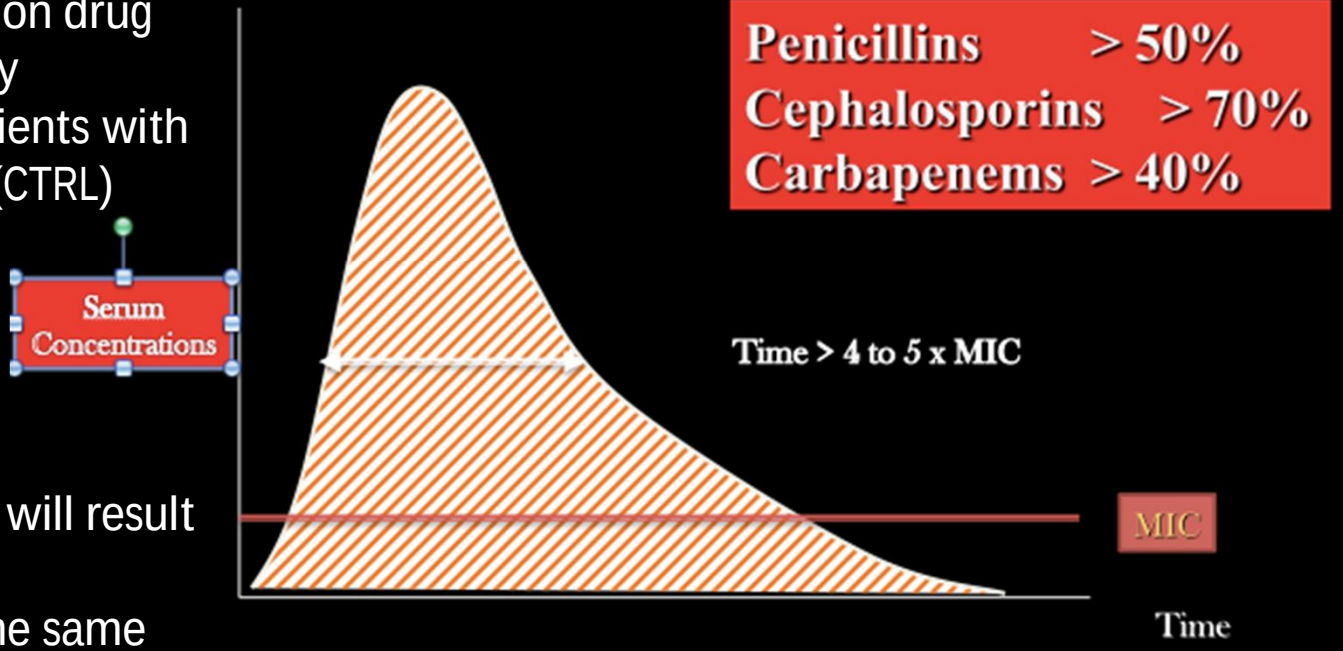
Increased dosing – WHY?

Drug regimens are based on drug PKs assessed in healthy volunteers (HV) or patients with less severe infections (CTRL)

Changes in PK parameters will result in unpredictable drug concentrations using the same regimens than in HV/CTRLs



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Increased dosing – WHY?

Less susceptible & MDR bacteria

Obese patient

Augmented renal clearance

INCREASED DOSING

Extracorporeal devices (iHD, plasmapheresis)

Massive Blood losses

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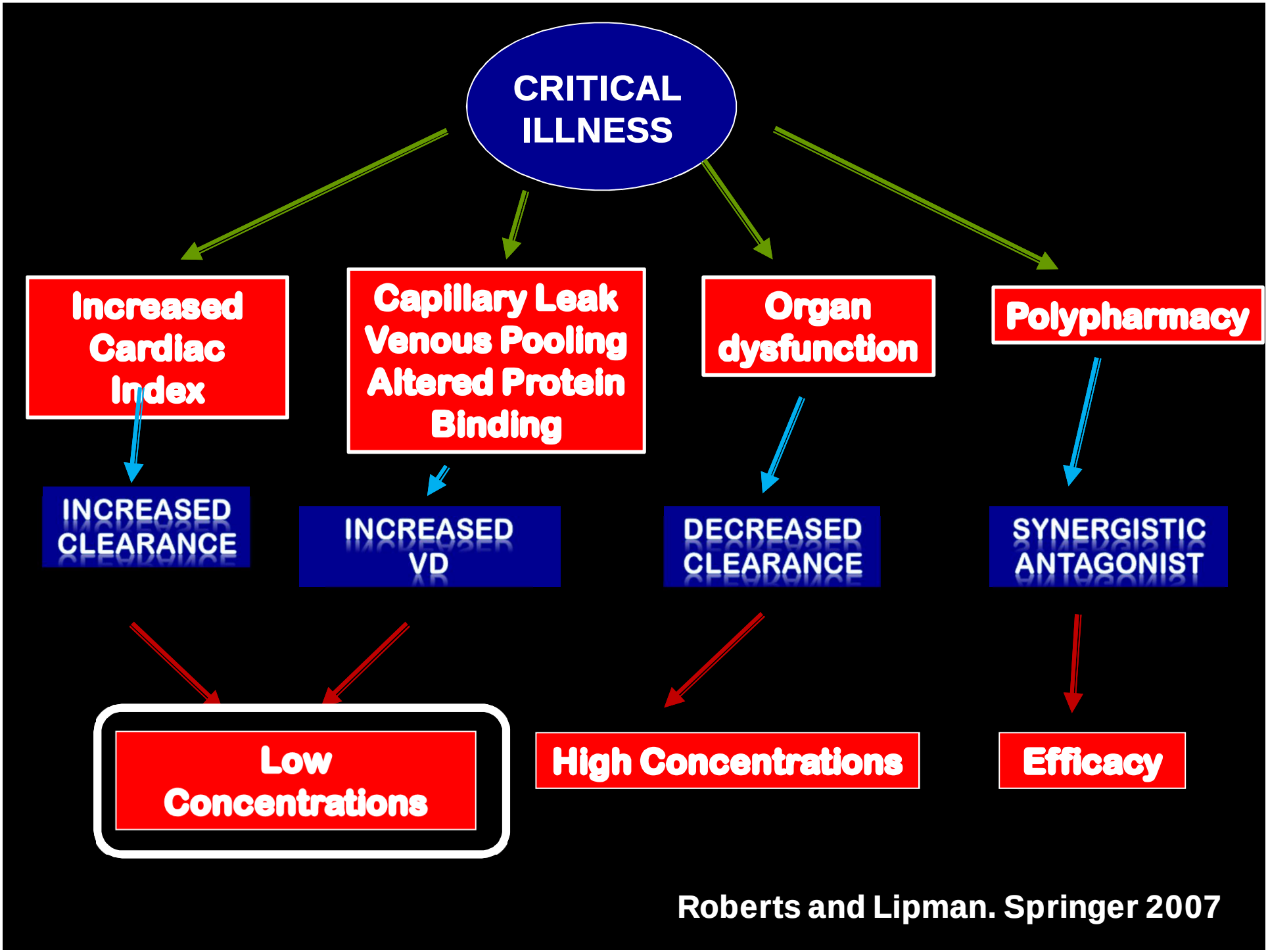
MONS


CRITICAL ILLNESS
Increased Cardiac Index
Capillary Leak Venous Pooling Altered Protein Binding
Organ dysfunction
Polypharmacy
INCREASED CLEARANCE
INCREASED VD
DECREASED CLEARANCE
SYNERGISTIC ANTAGONIST
Low Concentrations
High Concentrations
Efficacy
Roberts and Lipman. Springer 2007

β-lactams toxicity

- Rare - Difficult to diagnose - Underdiagnosed
- Particularly difficult to diagnose in ICU patients
  - Multiple organ failure
  - Polymedication
- Unclear whether this may lead to increased morbidity (and mortality ???)

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Most common toxicities

ALLERGIC	1-10% Cross-reactivity for type I
HEMATOLOGICAL	Agranulocytosis (2-15/million) Thrombopenia/anemia Neutropenia
HEPATOTOXICITY	1/100,000
NEPHROTOXICITY	Intersticial nephritis (*ALL*) AKI/Delayed recovery (*PTAZ*)
NEUROTOXICITY	Rare (*CEF>Others*)

Park Mayo Clin Proc 2005
Clark Pharmacotherapy 2006
Andres Eur J Intern Med 2006
Koklu Ann pharmacother 2003

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Are these toxicities related to dosing?

NEUTROPENIA

Mechanisms?

Direct bone marrow toxicity

IN VIVO

- *24 patients -> myelogram (at different intervals from the nadir of neutropenia)*
- *Lack of well-differentiated myeloid granulocyte precursors - reduction of myelocyte*

IN VITRO

- A dose-dependent **inhibition of granulopoiesis** was found with all the investigated β-lactams

CEF > PTAZ

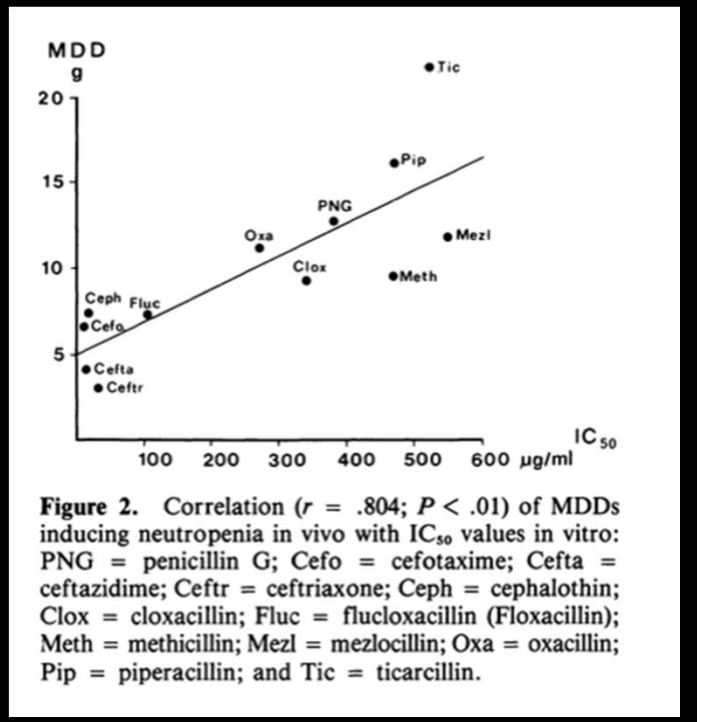

Figure 2. Correlation (r = .804; P < .01) of MDDs inducing neutropenia in vivo with IC_{50} values in vitro: PNG = penicillin G; Cefo = cefotaxime; Cefta = ceftazidime; Ceftr = ceftriaxone; Ceph = cephalothin; Clox = cloxacillin; Fluc = flucloxacillin (Floxacillin); Meth = methicillin; Mezl = mezlocillin; Oxa = oxacillin; Pip = piperacillin; and Tic = ticarcillin.

Neftel. J. Infect. Dis. 1985.

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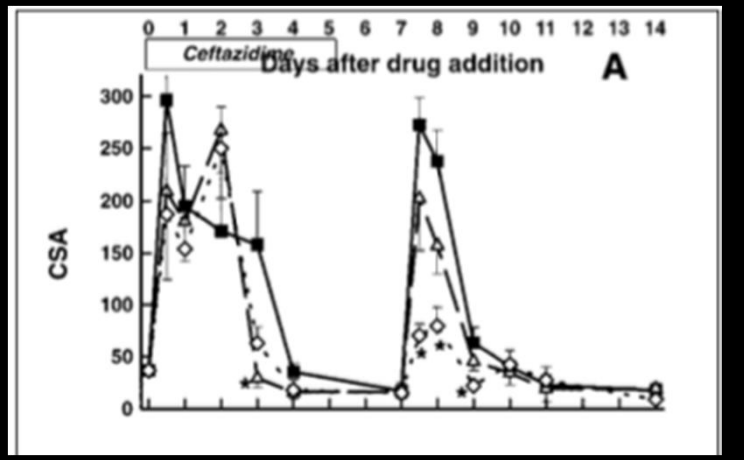
Are these toxicities related to dosing?

NEUTROPENIA

Mechanisms?

- Dose-dependent decrease in **Colony Stimulating Activity** IN VITRO

- Several articles have reported drug-dependent antibodies to neutrophils -> similar to haemolytic anemia



Hauser Stemcell 1998
Rouveix BMJ 1983
Marie JP Presse Med 1986

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Are these toxicities related to dosing?

NEUTROPENIA

- Reversible neutropenia may occur in 5 to 15% of patients receiving BL for more than **10 consecutive days** of IV therapy with β-lactams antibiotics
- 90 % appear after 10 days of Abtherapy

- TZP-induced neutropenia was related to the **cumulative dose** (range 204–612 g) and duration of therapy (range 18–51 days)

- **High doses** BL for endocarditis : 29 patients – neutropenia 7/29 – duration of neutropenia 2-12d
  - Risk factor neutropenia : low count of neutrophils – high doses of BL for long period (14- 24 d)

RESOLUTION AT DRUG DISCONTINUATION

Peralta CID 2003
Olaison JAC 1990

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MONS

Are these toxicities related to dosing?

ANEMIA

- Rare
- Hemolysing antibodies
- 26 cases with PTAZ

THROMBOPENIA

- Antibody-mediated platelet destruction
- Other mechanisms?
- PTAZ may induce a reversible conformation in the platelet membrane generating a neoantigen

Table 5. Beta-lactam antibiotics described as a cause of drug-induced immune thrombocytopenia.

Agent	Platelet count < 20 × 10^9	Re-challenge performed	*In vitro* testing	Mechanism
Amoxicillin	+		+	Drug-dependent binding to specific platelet protein
Ampicillin	+		+	Increase in drug-dependent-platelet-associated
Methicillin				
Penicillin				
Piperacillin				
Cephamandole	+			
Ceftazidime	+		+	Like methicillin
Cephalothin	+	+	+	Like amoxicillin
Ceftizoxime			+	Like methicillin

RESOLUTION AT DRUG DISCONTINUATION

Lindenbaum 1996
Gharpure 1993
Bougie 2003
Shamsuddine 2015

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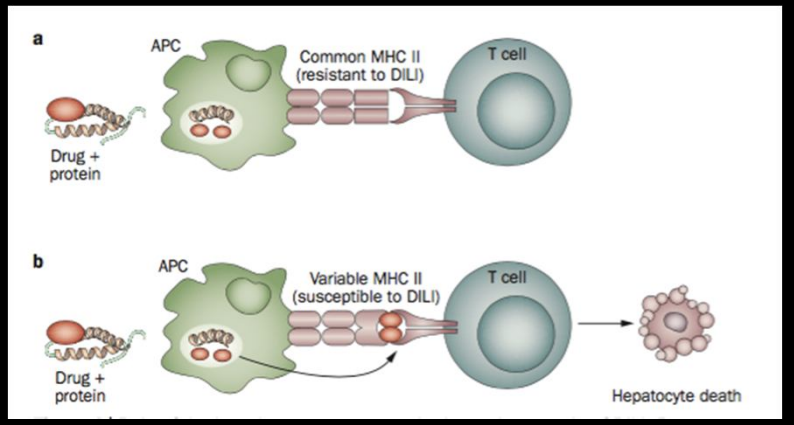
Are these toxicities related to dosing?

HEPATOTOXICITY

Amoxiclav

- Mild hepatocellular or cholestatic liver injury
- 10 per 100,000 patients treated
- Life-threatening acute liver failure: few case reports (extra-hepatic manifestations)
- Mechanism of hepatotoxicity is unclear
  - *Immuno-allergy – HLA predisposition*
  - *Not clear if correlated to dosing*



PTAZ - CEF

- May induce DILI
- Minor clinical significance

Rodriguez 1996
Tujios 2011
Gresser U 2001
Larrey 1992
Zhong Fang 2013

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Are these toxicities related to dosing?

HEPATOTOXICITY

Ceftriaxone

High biliary concentrations (150-fold blood concentrations) -> More likely to induce “sludge”

Characteristics	Ceftriaxone 2 g/day (n = 434)	Ceftriaxone 4 g/day (n = 37)	P value
Duration of therapy (days), median (IQR)	8 (6–10)	7 (6–10)	0.574
Concomitant drug, n (%)			
Proton-pump inhibitor	157 (36.2)	17 (45.9)	0.287
Antiepileptic drug	31 (7.1)	4 (10.8)	0.342
Acetaminophen (>1500 mg/day for ≥3 consecutive days)	3 (0.7)	0 (0)	1
Macrolide	45 (10.4)	2 (5.4)	0.565
Clindamycin	36 (8.3)	4 (10.8)	0.541
Metronidazole	2 (0.5)	2 (5.4)	0.033
Antituberculosis drug (INH and/or RFP)	0 (0)	4 (10.8)	<0.001
Laboratory data at baseline, median (IQR)			
AST (IU/L)	26 (19–38.8)	28 (18–47)	0.732
ALT (IU/L)	18 (13–30.8)	25 (13–40)	0.123
ALP (IU/L)	254 (198.3–335)	217 (179–319)	0.095
T-bil (mg/dL)	0.6 (0.4–1.0)	0.7 (0.5–0.9)	0.749
Serum Cr (mg/dL)	0.80 (0.62–1.17)	0.95 (0.66–1.24)	0.312
Outcomes, n (%)			
Liver injury	9 (2.1)	6 (16.2)	<0.001
Mild liver injury	35 (8.1)	12 (32.4)	<0.001

High (4g) vs normal dosing (2g)
Retrospective study

Biliary sludge or stones not assessed

Table 3 Multivariate analysis of factors associated with liver injury

Factors	OR (95 % CI)	P value
Ceftriaxone of 4 g/day	7.23 (2.01–26.00)	0.002
Concomitant use of antiepileptic drug	2.82 (0.68–11.70)	0.151
Propensity score	2.20 (0.25–19.60)	0.48

CI confidence interval, *OR* odds ratio

Richards Drugs 1987

Nakarai Eur J Clin Pharmacol 2016

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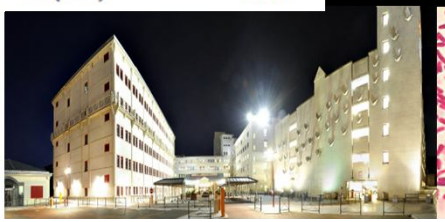


MONS

Are these toxicities related to dosing?

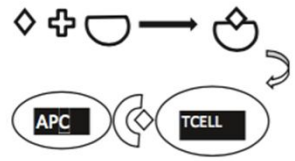
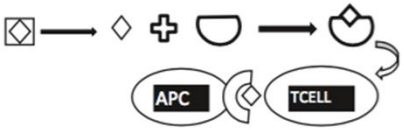
Nephrotoxicity

-AKI increased morbidity and mortality

-Interstitial nephritis

- Delayed T cell mediated HS reaction
- Ampiciliin > 200mg/kg/j
- High dose methycilin Prolonged treatment

Table 1. Mechanisms of Drug-Induced AIN

Mechanism	Illustration	Published Drugs Linked to AIN
Hapten		Penicillins[1,46]: Amoxicillin, Ampicillin, Dicloxacillin, Oxacillin, Benzylpenicillin, Carbenicillin, Cloxacillin, Flucloxacillin, Methicillin, Piperacillin/Tazobactam Cephalosporins[1,46]: Cefaclor, Cefepime Cefamandole, Cefazolin, Cefoperazone, Cefotaxime, Cefotetan, Cefoxitin, Ceftriaxone, Cephalexin, Cephaloridine, Cephalothin, Cephradine NSAIDs Including Salicylates[1,47]: Aceclofenac, Alclofenac Aspirin, Diclofenac, Naproxen
Pro-hapten		Sulfonamide-Containing Drugs[1,8,48-50]: Celecoxib, Chlorthalidone, Chlorpropamide, Furosemide (Frusomide), Hydrochlorothiazide, Trimethoprim-sulfamethoxazole
p-i Concept		Other[1,6,7,51]: Carbamazepine (HLA-B*15:02), Allopurinol (HLA-B*58:01, HLA-B*58:01), Flucloxacillin (HLA-B*57:01)

Recovery after drug discontinuation

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Are these toxicities related to dosing?

Nephrotoxicity

PTAZ MORE NEPHROTOXIC ?

- PTAZ +VAN : increased incidence of nephrotoxicity

  OR = 2.5 – 5.0

- RETROSPECTIVE STUDIES
  - MEM + VAN / PTAZ + VAN / CEF + VAN
  - various definitions of AKI
  - DOSING?
- PROSPECTIVE STUDY
  - 85 patients
  - Higher rate of AKI in PTZ group (37 vs. 7%)
  - Standard Dosing
  - No multivariate analysis

Burgess 2014
Meany 2014
Yami 2017
Moenster 2014
Gomes 2014
Peyko 2014

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Are these toxicities related to dosing?

Nephrotoxicity

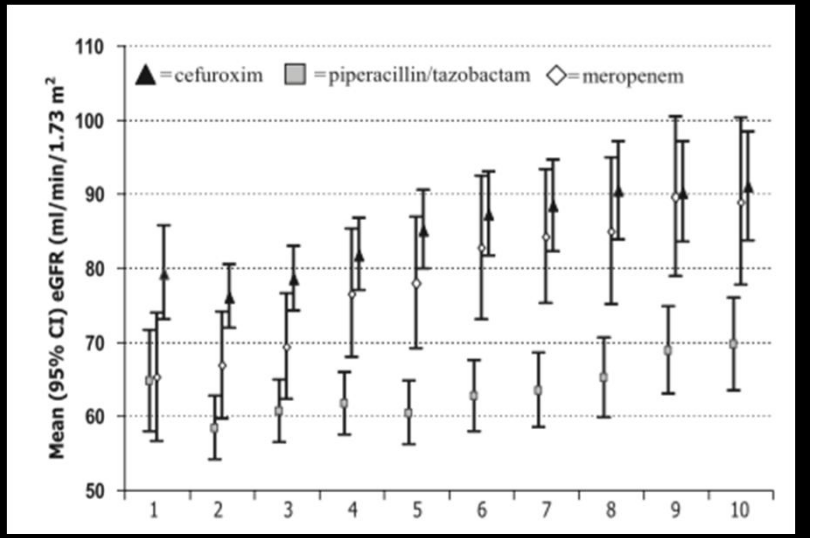
BMJ open accessible medical research

Kidney failure related to broad-spectrum antibiotics in critically ill patients: secondary end point results from a 1200 patient randomised trial

1200 ICU patients – prospective randomised study
Standard Vs High exposure therapy

More AKI in High exposure
Piperacillin/tazobactam : cause of delayed renal recovery in critically ill when compared to other BL

Not related to dosing … More to the drug



Jensen 2012

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Are these toxicities related to dosing?

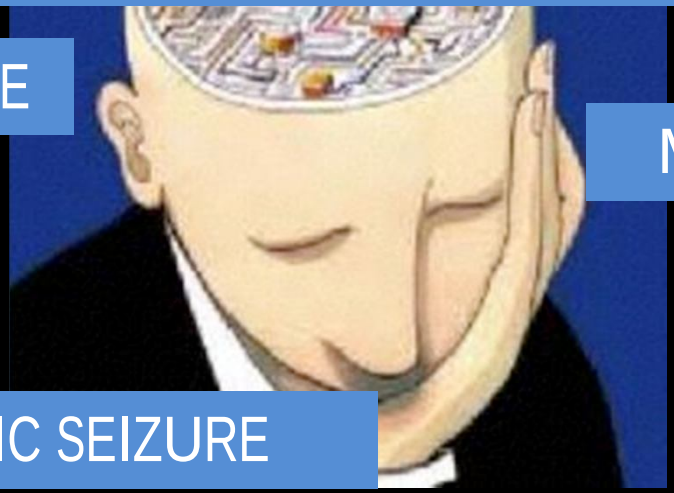
NEUROTOXICITY

NONCONVULSIVE STATUS EPILEPTICUS

DISORIENTATION

-> DIFFICULT TO DIAGNOSE!

SOMNOLENCE



MYOCLONUS

TWITCHING

TONIC CLONIC SEIZURE

Grill Ann Pharmacother. 2008

Chow pharmacotherapy 2003

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Are these toxicities related to dosing?

NEUROTOXICITY

NEUROTOXICITY MECHANISM

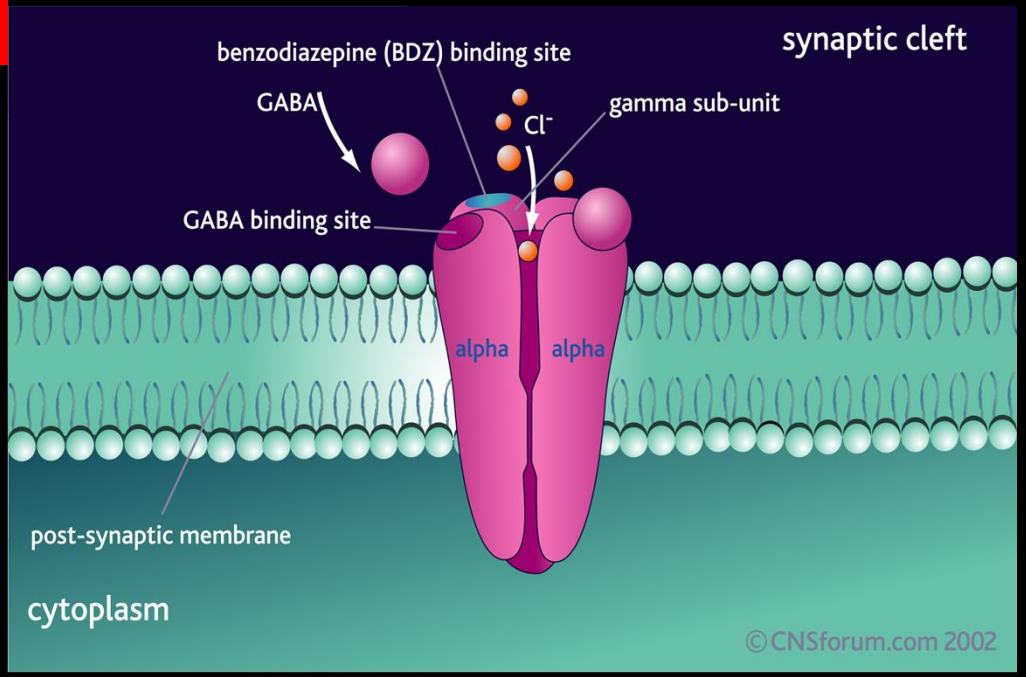
Inhibition of GABA-A receptor function

↓

Neurons hyperexcitability
Depolarization of the post-synaptic membrane

↓

Seizure threshold lowered



Fujimoto Br J Pharmacol. 1995
Sugimoto Neuropharmacology 2003
Chow Eur J Microbiol Infect Dis 2005

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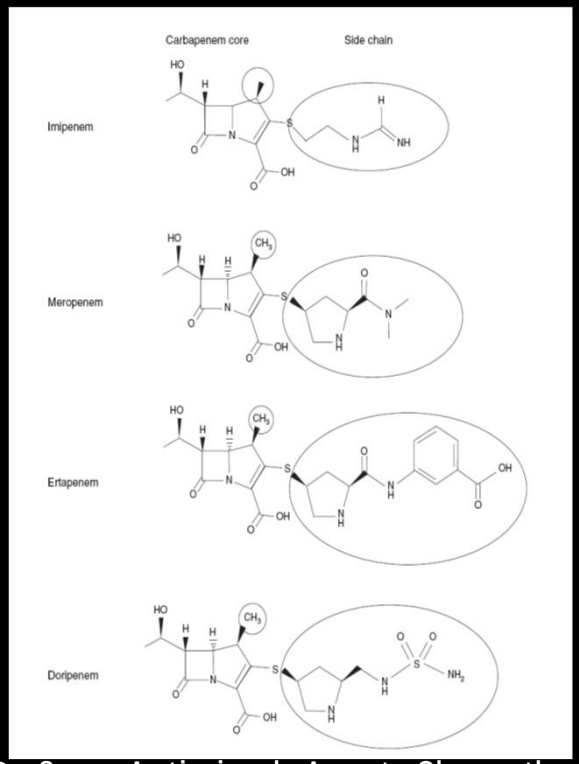
Are these toxicities related to dosing?

NEUROTOXICITY

1. <u>Dose-dependent mechanisms</u>:
More convulsive activity at higher drug concentrations
Cephalosporins > Penicillins

2. <u>Voltage-dependent mechanisms</u>
More basic->better binding to the $GABA_A$
-> higher neurotoxicity

Imipenem >> meropenem > doripenem



De Sarro Antimicrob Agents Chemother. 1995
Sunagawa, J Antibiot 1992
Norby JAC 2000

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Are these toxicities related to dosing?

NEUROTOXICITY

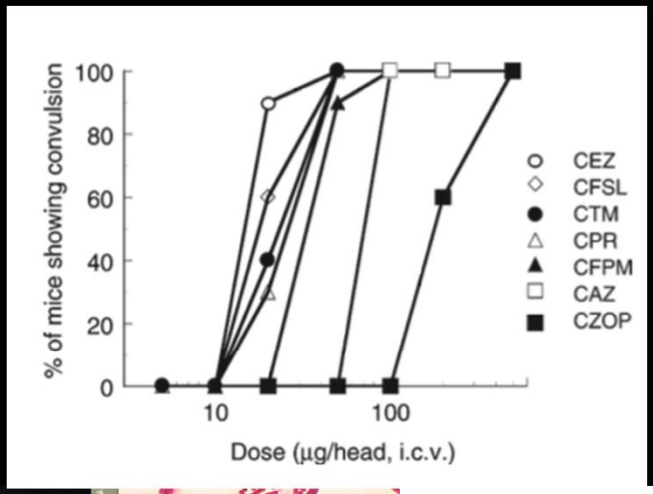
Evidence for the involvement of $GABA_A$ receptor blockade in convulsions induced by cephalosporins

Masahiro Sugimoto [a], Ichiro Uchida [a,*], Takashi Mashimo [a], Shunji Yamazaki [b], Kazuo Hatano [b], Fumiaki Ikeda [b], Yoshitaka Mochizuki [c], Takao Terai [c], Nobuya Matsuoka [b]

Neuropharmacology 45 (2003) 304–314

- Direct injection of AB into the lateral ventricle of mouse brain

- ALL ABs: dose-dependent induced convulsion



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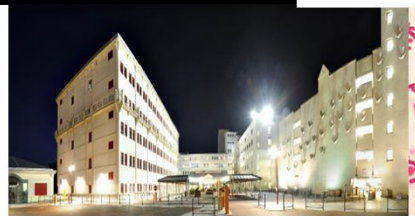

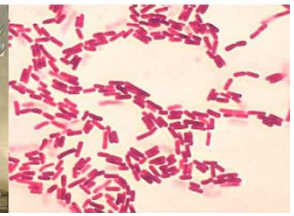

MONS

Are these toxicities related to dosing?

NEUROTOXICITY

Neurotoxic effects associated with antibiotic use: management considerations

Antibiotic class	Number of publications	Neurotoxic effects	Mechanism of neurotoxicity	Risk factors
Beta lactams-	24- Case reports; retrospective reviews; review articles	Encephalopathy with Triphasic waves on EEG Tardive seizures	Inhibition of GABA-A release; Increased glutamate; Induction of endotoxins; Cytokine release	Renal failure Prior CNS disease Older age Excess dosage
Cephalosporins:				
***High risk agents*:**				
1. Cefazolin				
2. Cefesolis				
3. Ceftazidime				
4. Cefoperazone				
5. Cefepime				
***Low risk agents*:**				
1. Cephalexin				
2. Cefatoxime				
3. Ceftriaxone				
Beta-lactams-				Renal failure; low birth weight-neonates
Penicillins:				
1. Benzylpenicillin				
2. Penicllin G				
3. Pipercillin				
4. Ticarillin				
5. Ampicillim				
6. Amoxacillin				
7. Oxacillin				
Beta-lactams	4: Case reports	Encephalopathy Seizures Myoclonus Headache	Inhibition of GABA-A receptors; Possibly binding of glutamate	Renal failure
Carbapenems				
1. Imepenem				
2. Meropenem				
3. Paripenem				
4. Ertapenem				
5. Doripenem				
6. Ceftaroline				

RISK FACTORS

- Renal failure
- Elderly patient
- Pediatric patient
- Pre-existing brain injury

Grill BJCP 2011

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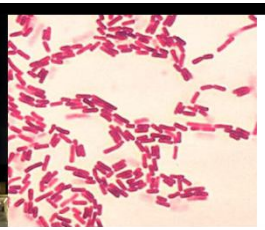

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NEUROTOXICITY

Continuous Epileptiform Discharges in Patients Treated With Cefepime or Meropenem

Gilles Naeije, MD; Sophie Lorent, MPharm; Jean-Louis Vincent, MD, PhD; Benjamin Legros, MD

ARCH NEUROL/VOL 68 (NO. 10), OCT 2011

- Retrospective review of patients treated with meropenem or cefepime in whom EEG has been performed (42 months)

	Patients treated	EEG performed	Continuous epileptiform **discharges**	Prevalence (%)
CEFEPIME	**1120**	**59**	**14**	**1.25**
MEROPENEM	**1572**	**80**	**3**	**0.25**

- Continuous epileptiform discharges : 5-fold more frequent in CEF group
  - Blood serum creatinine concentration: elevated in 5/14 pts
  - Dead 7/14 Pts

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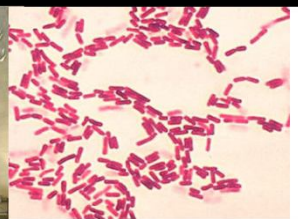


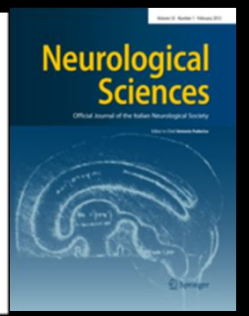
MONS

Are these toxicities related to dosing?

NEUROTOXICITY

Association of antibiotics with status epilepticus

Usha K. Misra, Jayantee Kalita, Satish Chandra, Pradeep P. Nair



117 status epilepticus

12 related to ABs
- 8 convulsivant
- 4 non-convulsivant

- 5 ceftazidim
- 2 piperacillin
- 1 cefepime

Renal failure 6/12 (50%)

Mortality: 8/12 (75%)

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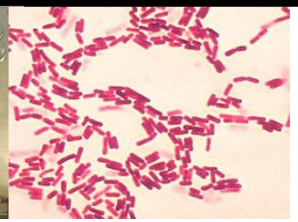


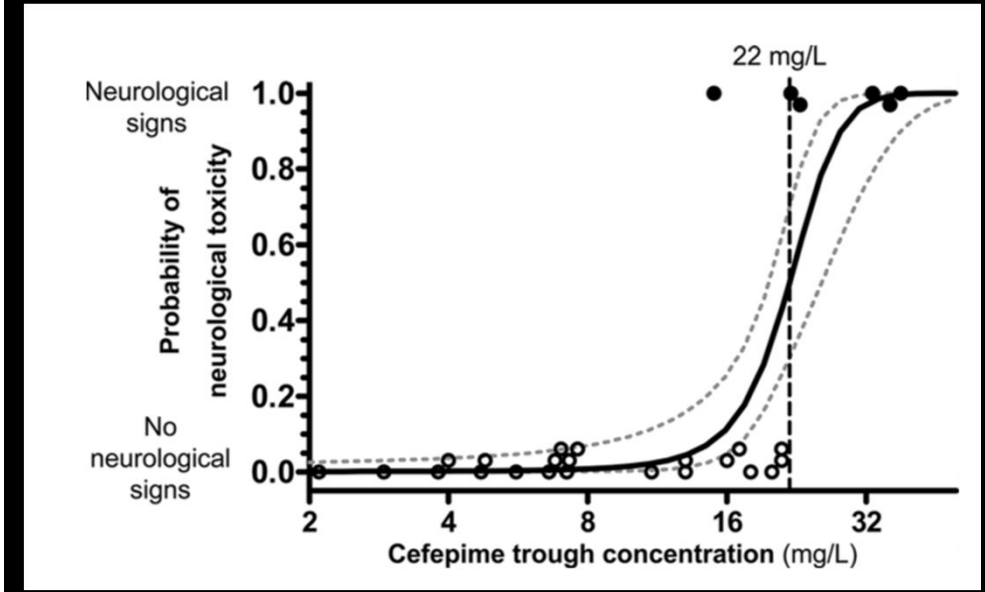
MONS

Are these toxicities related to dosing?

NEUROTOXICITY

High Cefepime Plasma Concentrations and Neurological Toxicity in Febrile Neutropenic Patients with Mild Impairment of Renal Function[▽]

Lamoth AAC 2010



Impaired renal function

Median cefepime trough levels: **28 mg/L**

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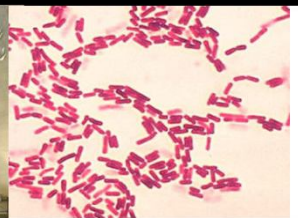

MONS

Are these toxicities related to dosing?

NEUROTOXICITY

Absence of obvious link between supra-therapeutic serum levels of β lactams and clinical toxicity in ICU patients with acute renal failure treated with intermittent hemodialysis

Faten May[1,7*], Najouah El-Helali[2], Jean-François Timsit[3,4,5] and Benoît Misset[1,6]

Retrospective review
108 patients – 180 SEPSIS – 460
measurement of serum BL concentration

96/108 : at least one supratherapeutic level

No correlation with clinical seizure
(univariate analysis)

Table 1 Antibiotics assessed, thresholds used, and trough serum levels (mg/l)

	Upper therapeutic trough level[a]	Observed trough level median (interquartile range)
Piperacillin	20	77 (44–109)
Tazobactam	5	13 (6–20)
Cloxacillin	20	60 (35–103)
Amoxicillin	20	31 (19–42)
Imipenem	3	3 (1.1–4.2)
Clavulanate	0.5	2 (1.3–3.6)
Ceftazidim	20	71 (49–87)
Cefepime	10	27 (16–47)

[a] Five times bacterial modal minimal inhibitory concentration [4, 5]

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MONS

Are these toxicities related to dosing?

NEUROTOXICITY

Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients

RETROSPECTIVE STUDY

ALL ICU PATIENT treated with MEROPENEM (MEM), PIPERACILLIN-TAZOBACTAM (TZP) or CEFTAZIDIME/CEFEPIME (CEF) and AT LEAST 1 TDM PERFORMED (C_{MIN}/MIC)

HYPOTHESIS: Association of serum concentrations with neurological deterioration?

199 patients included (262 TDMs)

Beumier, Minerva Anestesiologica 2015

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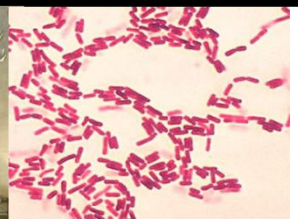

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Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients

Neurological evolution

No Brain Dysfunction -> $nSOFA_{Adm}$ and $nSOFA_{TDM}$ = 0

Brain Improvement -> $nSOFA_{Adm}$ 1-2 + $\Delta nSOFA = 0$

No Clinical Change -> $nSOFA_{Adm}$ 1-2 + $\Delta nSOFA \leq 1$

Persistent Coma -> $nSOFA_{Adm}$ 3-4 + $\Delta nSOFA \leq 2$

Glasgow coma scale	SOFA score
13 – 14	1
10 – 12	2
6 – 9	3
< 6	4

Neurological impairement

- $nSOFA_{Adm} = 0 + \Delta nSOFA \geq 1$
- $nSOFA_{Adm}$ 1-2 + $\Delta nSOFA \geq 1$

Beumier, Minerva Anestesiologica 2015

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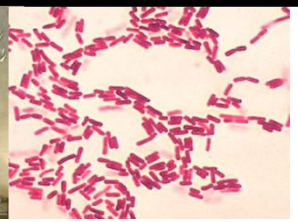
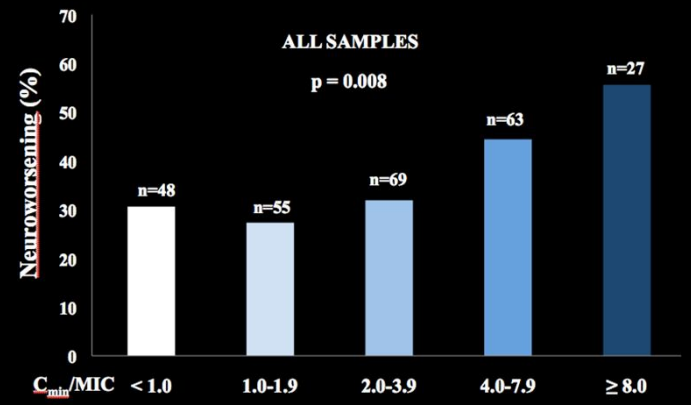
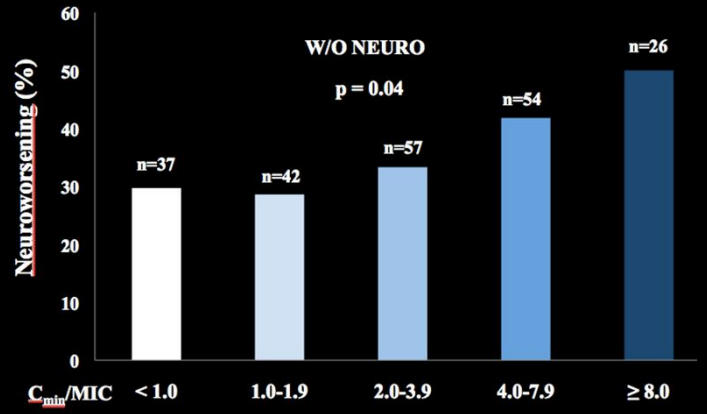


MONS

Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients





Total TDMs = 262

CEF n=47

PTAZ n=85

MEM n=130

Neuroworsening n=94

Variable	Multivariable analysis P value	OR (95% CI)
C_{min}/MIC	0.003	1.12 (1.04-1.20)
Mechanical ventilation	0.01	2.17 (1.20-3.91)
Bilirubin, mg/dL	0.005	1.06 (1.02-1.10)
Anesthetics/Sedatives, N. (%)	0.028	1.97 (1.08-3.59)

Beumier, Minerva Anestesiologica 2015

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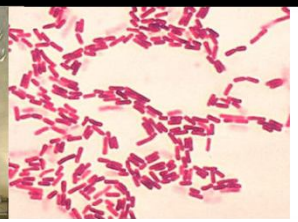

MONS

Is high-dose β-lactam therapy associated with excessive drug toxicity in critically ill patients?

Craig MCDONALD [1], Menino O. COTTA [1-3] *, Peter J. LITTLE [3], Brett MCWHINNEY [4], Jacobus P. J. UNGERER [4], Jeffrey LIPMAN [1, 2], Jason A. ROBERTS [1-3]

Rerospective study – 93 patients
MEM PTAZ high vs standard dose (similar population of patients)
TDM guided

	Meropenem			Piperacillin-tazobactam		
	Licensed-dose (N.=22)	High-dose (N.=28)	P value	Licensed-dose (N.=25)	High-dose (N.=23)	P value
Dosing (g/day)	3.6±2.7	5.1±2.0	0.03	12.5±2.6	18.5±4.6	<0.001
Duration of therapy (days)	6.6±3.8	7.9±4.5	0.28	5.9±3.7	6.7±3.6	0.45
Plasma concentrations obtained	44	81		34	45	
Dose changes n (%)	9	14	0.34	6	8	1.00
Increase	6 (66.7)	12 (85.7)		3 (50)	5 (62.5)	
Decrease	3 (33.3)	2 (14.3)		3 (50)	3 (37.5)	
Treatment courses that achieved 100% $fT_{>MIC}$ (%)	10 (45.5)	15 (53.6)	0.57	10 (40)	12 (52.2)	0.40

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	Meropenem			Piperacillin-tazobactam		
	Licensed-dose (N.=22)	High-dose (N.=28)	P value	Licensed-dose (N.=25)	High-dose (N.=23)	P value
Neurological						
Seizure n (%)	1 (4.5)	2 (7.1)	0.70	0 (0.0)	0 (0.0)	-
Renal (mean values)						
CrCl (mL/min)	128.4±19.9	234.2±94.6	<0.001	95.6±31.7	108.4±31.6	0.17
Need for CRRT						
Incidence n (%)						
Resolved need n (%)	2 (9.1)	0	0.10	2 (8.0)	0	0.16
					0	0.33
Hepatic (mean values)						
Albumin (g/L)					.1±2.4	<0.001
Total Bilirubin (µmol/L)					.1±6.9	0.004
ALP (U/L)					.3±43.0	0.002
ALT (U/L)	149.6±84.1	73.0±15.6	<0.001	40.9±23.3	45.1±18.8	0.50
Hepatic Toxicity						
Hepatocellular derangement n (%)	7					0.90
Cholestasis (%)	3					0.26
Hematological (mean values)						
Platelets (x 10^9/L)	318				.3	0.94
White Cell Count (x 10^9/L)	9				8	0.46
Neutrophils (x 10^9/L)	9				.0	0.07
Hematological toxicity						
Thromocytopenia n (%)	2					0.87
Neutropenia n (%)	1					0.33

NO DIFFERENCES !

BUT...
Dosing adapted to TDM
AIM $fT_{>100\%MIC}$

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How To Manage ?

- Discontinuation of therapy?
  - *What if severe infection ?*
- **CI?**
- **Assessment of drug concentrations ?**
- Extra-corporeal support?
  - *CRRT > iHD?*

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Conclusions

- Increased dosing are sometimes required
- β-lactams= « safe » ABs
- Toxicity (rare) is important to recognize - difficult to diagnose – particularly in ICU patients - Underestimated problem ?
- High doses vs. high blood concentrations
- Patient “at risk” = TDM

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THANK
YOU