Increased dosing of $\beta$-lactams = Increased Toxicity?
β-lactams

Standard dosing = Wide Therapeutic Index
Increased dosing - WHY?

- Early Therapy
- Combination
- Appropriate Therapy
- Adequate Therapy
- Optimal Therapy

Chu Ambroise Pare

Mons
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.

Penicillins > 50%
Cephalosporins > 70%
Carbapenems > 40%

Time > 4 to 5 x MIC
Standard dosing may lead to insufficient drug concentrations (non-ICU).

**Increased dosing – WHY?**

- Less susceptible & MDR bacteria
- Obese patient
- Augmented renal clearance
- Extracorporeal devices (iHD, plasmapheresis)
- Massive Blood losses

**INCREASED DOSING**
CRITICAL ILLNESS

- Increased Cardiac Index
  - Increased Clearance

- Capillary Leak Venous Pooling Altered Protein Binding
  - Increased VD

- Organ dysfunction
  - Decreased Clearance

- Polypharmacy
  - Synergistic Antagonist
  - Efficacy

Low Concentrations
High Concentrations

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 ????)

CHU AMBROISE PARÉ

MONS
# Most common toxicities

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLERGIC</td>
<td>1-10% Cross-reactivity for type I</td>
</tr>
<tr>
<td>HEMATOLOGICAL</td>
<td>Agranulocytosis (2-15/million) Thrombopenia/anemia Neutropenia</td>
</tr>
<tr>
<td>HEPATOTOXICITY</td>
<td>1/100,000</td>
</tr>
<tr>
<td>NEPHROTOXICITY</td>
<td>Interstitial nephritis (ALL) AKI/Delayed recovery (PTAZ)</td>
</tr>
<tr>
<td>NEUROTOXICITY</td>
<td>Rare (CEF&gt;Others)</td>
</tr>
</tbody>
</table>

*References:*
- Park Mayo Clin Proc 2005
- Clark Pharmacotherapy 2006
- Koklu Ann pharmacother 2003
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 IC50 values in vitro: PNG = penicillin G; Cefo = cefotaxime; Cefta = ceftazidime; Ceftr = ceftriaxone; Ceph = cephalothin; Clox = cloxacillin; Fluc = flucloxacillin (Floracillin); Meth = methicillin; Mezl = mezlocillin; Oxa = oxacillin; Pip = piperacillin; and Tic = ticarcillin.

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
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
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.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Platelet count &lt; 20 x 10^9</th>
<th>Re-challenge performed</th>
<th>In vitro testing</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Drug-dependent binding to specific platelet protein</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Increase in drug-dependent-platelet-associated protein</td>
</tr>
<tr>
<td>Methicillin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Like methicillin</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Like amoxicillin</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Like methicillin</td>
</tr>
</tbody>
</table>

RESOLUTION AT DRUG DISCONTINUATION

Lindenbaum 1996
Gharpure 1993
Bougie 2003
Shamsuddine 2015
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
Are these toxicities related to dosing?

HEPATOTOXICITY

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ceftriaxone 2 g/day (n = 434)</th>
<th>Ceftriaxone 4 g/day (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of therapy (days), median (IQR)</td>
<td>8 (6–10)</td>
<td>7 (6–10)</td>
<td>0.574</td>
</tr>
<tr>
<td>Concomitant drug, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proton-pump inhibitor</td>
<td>157 (36.2)</td>
<td>17 (45.9)</td>
<td>0.287</td>
</tr>
<tr>
<td>Antiepileptic drug</td>
<td>31 (7.1)</td>
<td>4 (10.8)</td>
<td>0.342</td>
</tr>
<tr>
<td>Acetaminophen (&gt;1500 mg/day for ≥3 consecutive days)</td>
<td>3 (0.7)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Macrolide</td>
<td>45 (10.4)</td>
<td>2 (5.4)</td>
<td>0.565</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>36 (8.3)</td>
<td>4 (10.8)</td>
<td>0.541</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2 (0.5)</td>
<td>2 (5.4)</td>
<td>0.033</td>
</tr>
<tr>
<td>Antituberculosis drug (INH and/or RFP)</td>
<td>0 (0)</td>
<td>4 (10.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Laboratory data at baseline, median (IQR)

<table>
<thead>
<tr>
<th>Test</th>
<th>Ceftriaxone 2 g/day (n = 434)</th>
<th>Ceftriaxone 4 g/day (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>26 (19–38.8)</td>
<td>28 (18–47)</td>
<td>0.732</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>18 (13–30.8)</td>
<td>25 (13–40)</td>
<td>0.123</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>254 (198.3–335)</td>
<td>217 (179–319)</td>
<td>0.095</td>
</tr>
<tr>
<td>T-bil (mg/dL)</td>
<td>0.6 (0.4–1.0)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.749</td>
</tr>
<tr>
<td>Serum Cr (mg/dL)</td>
<td>0.80 (0.62–1.17)</td>
<td>0.95 (0.66–1.24)</td>
<td>0.312</td>
</tr>
</tbody>
</table>

Outcomes, n (%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ceftriaxone 2 g/day (n = 434)</th>
<th>Ceftriaxone 4 g/day (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver injury</td>
<td>9 (2.1)</td>
<td>6 (16.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild liver injury</td>
<td>35 (8.1)</td>
<td>12 (32.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

High (4g) vs normal dosing (2g)
Retrospective study
Biliary sludge or stones not assessed

Richards Drugs 1987
Are these toxicities related to dosing?

**Nephrotoxicity**

- AKI increased morbidity and mortality
- Interstitial nephritis
  - Delayed T cell mediated HS reaction
  - Ampicillin > 200mg/kg/j
  - High dose methycilin

Prolonged treatment

Recovery after drug discontinuation
Are these toxicities related to dosing?

Nephrotoxicity

- **PTAZ +VAN**: increased incidence of nephrotoxicity
  \[ \text{OR} = 2.5 - 5.0 \]
- **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

PTAZ MORE NEPHROTOXIC?
Are these toxicities related to dosing?

Nephrotoxicity

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
Are these toxicities related to dosing?

- NEUROTOXICITY
- NONCONVULSIVE STATUS EPILEPTICUS
- DISORIENTATION
- SOMNOLENCE
- MYOCLONUS
- TWITCHING
- TONIC CLONIC SEIZURE

-> DIFFICULT TO DIAGNOSE!

Grill Ann Pharmacother. 2008
Chow pharmacotherapy 2003
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
Are these toxicities related to dosing?

**NEUROTOXICITY**

1. **Dose-dependent mechanisms:**
   More convulsive activity at higher drug concentrations
   \[\text{Cephalosporins} > \text{Penicillins}\]

2. **Voltage-dependent mechanisms**
   More basic -> better binding to the GABA\(_A\) -> higher neurotoxicity
   \[\text{Imipenem} \gg \text{meropenem} > \text{doripenem}\]

De Sarro Antimicrob Agents Chemother. 1995
Sunagawa, J Antibiot 1992
Norby JAC 2000
Are these toxicities related to dosing?

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

- Direct injection of AB into the lateral ventricle of mouse brain
- ALL ABs: dose-dependent induced convulsion
Are these toxicities related to dosing?

NEUROTOXICITY

Neurotoxic effects associated with antibiotic use: management considerations

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Number of publications</th>
<th>Neurotoxic effects</th>
<th>Mechanism of neurotoxicity</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams-</td>
<td>24 Case reports; retrospective reviews; review articles</td>
<td>Encephalopathy with Triphasic waves on EEG</td>
<td>Inhibition of GABA-A release; Increased glutamate; Induction of endotoxins; Cytokine release</td>
<td>Renal failure; Prior CNS disease; Older age; Excess dosage</td>
</tr>
<tr>
<td>Beta-lactams- Carbapenems</td>
<td>5 Case reports</td>
<td>Encephalopathy; Seizures</td>
<td>Inhibition of GABA-A receptors; Possibly binding of glutamate</td>
<td>Renal failure; low birth weight-neonates</td>
</tr>
</tbody>
</table>

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

Grill BJCP 2011
• Retrospective review of patients treated with meropenem or cefepime in whom EEG has been performed (42 months)

<table>
<thead>
<tr>
<th></th>
<th>Patients treated</th>
<th>EEG performed</th>
<th>Continuous epileptiform discharges</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEFEPIME</td>
<td>1120</td>
<td>59</td>
<td>14</td>
<td>1.25</td>
</tr>
<tr>
<td>MEROPENEM</td>
<td>1572</td>
<td>80</td>
<td>3</td>
<td>0.25</td>
</tr>
</tbody>
</table>

• Continuous epileptiform discharges: 5-fold more frequent in CEF group
  – Blood serum creatinine concentration: elevated in 5/14 pts
  – Dead 7/14 Pts
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%)
Are these toxicities related to dosing?

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

*La Moth AAC 2010*

Impaired renal function

Median cefepime trough levels: **28 mg/L**
Are these toxicities related to dosing?

**NEUROTOXICITY**

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)
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 ($C_{\text{MIN}}$/MIC)

**HYPOTHESIS:** Association of serum concentrations with neurological deterioration?

199 patients included (262 TDMs)

*Beumier, Minerva Anestesiologica 2015*
Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients

Neurological evolution

No Brain Dysfunction $\rightarrow nSOFA_{Adm}$ and $nSOFA_{TDM} = 0$

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

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

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

Neurological impairment

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

Beumier, Minerva Anestesiologica 2015
Elevated $\beta$-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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable analysis</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{min}}$/MIC</td>
<td>0.003</td>
<td>1.12 (1.04-1.20)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.01</td>
<td>2.17 (1.20-3.91)</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.005</td>
<td>1.06 (1.02-1.10)</td>
</tr>
<tr>
<td>Anesthetics/Sedatives, N. (%)</td>
<td>0.028</td>
<td>1.97 (1.08-3.59)</td>
</tr>
</tbody>
</table>

Beumier, Minerva Anesthesiologica 2015
Retropective study – 93 patients
MEM PTAZ high vs standard dose (similar population of patients)
TDM guided

<table>
<thead>
<tr>
<th></th>
<th>Meropenem</th>
<th></th>
<th></th>
<th>Piperacillin-tazobactam</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing (g/day)</td>
<td>3.6±2.7</td>
<td>5.1±2.0</td>
<td>0.03</td>
<td>12.5±2.6</td>
<td>18.5±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of therapy (days)</td>
<td>6.6±3.8</td>
<td>7.9±4.5</td>
<td>0.28</td>
<td>5.9±3.7</td>
<td>6.7±3.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Plasma concentrations obtained</td>
<td>44</td>
<td>81</td>
<td>0.34</td>
<td>34</td>
<td>45</td>
<td>1.00</td>
</tr>
<tr>
<td>Dose changes n (%)</td>
<td>9 (66.7)</td>
<td>14</td>
<td>0.34</td>
<td>6</td>
<td>8</td>
<td>1.00</td>
</tr>
<tr>
<td>Increase</td>
<td>6 (66.7)</td>
<td>12 (85.7)</td>
<td>0.34</td>
<td>3 (50)</td>
<td>5 (62.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Decrease</td>
<td>3 (33.3)</td>
<td>2 (14.3)</td>
<td>0.34</td>
<td>3 (50)</td>
<td>3 (37.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Treatment courses that achieved 100% fT&gt;MIC (%)</td>
<td>10 (45.5)</td>
<td>15 (53.6)</td>
<td>0.57</td>
<td>10 (40)</td>
<td>12 (52.2)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
NO DIFFERENCES!

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

<table>
<thead>
<tr>
<th></th>
<th>Meropenem</th>
<th></th>
<th></th>
<th>Piperacillin-tazobactam</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure n (%)</td>
<td>1 (4.5)</td>
<td>2 (7.1)</td>
<td>0.70</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Renal (mean values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>128.4±19.9</td>
<td>234.2±94.6</td>
<td>&lt;0.001</td>
<td>95.6±31.7</td>
<td>108.4±31.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Need for CRRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence n (%)</td>
<td>2 (9.1)</td>
<td>0</td>
<td>0.10</td>
<td>2 (8.0)</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Resolved need n (%)</td>
<td>1 (4.5)</td>
<td>0</td>
<td>0.05</td>
<td>2 (9.0)</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>Hepatic (mean values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>3.8±1.1</td>
<td>3.1±2.1</td>
<td>0.17</td>
<td>3.1±1.1</td>
<td>3.1±2.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Total Bilirubin (μmol/L)</td>
<td>1.1±6.9</td>
<td>1.1±6.9</td>
<td>1.1±6.9</td>
<td>1.1±6.9</td>
<td>1.1±6.9</td>
<td>0.002</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>33±23</td>
<td>33±23</td>
<td>1.00</td>
<td>33±23</td>
<td>33±23</td>
<td>0.33</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>149.6±84.1</td>
<td>73.0±15.6</td>
<td>&lt;0.001</td>
<td>40.9±23.3</td>
<td>45.1±18.3</td>
<td>0.50</td>
</tr>
<tr>
<td>Hepatic Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular derangement n (%)</td>
<td>7 (31.8)</td>
<td>5 (21.7)</td>
<td>0.25</td>
<td>4 (16.0)</td>
<td>4 (17.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>Cholestasis (%)</td>
<td>3 (13.6)</td>
<td>3 (13.6)</td>
<td>1.00</td>
<td>3 (13.6)</td>
<td>3 (13.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hematological (mean values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (x 10⁹/L)</td>
<td>318±32</td>
<td>300±34</td>
<td>0.69</td>
<td>318±32</td>
<td>300±34</td>
<td>0.69</td>
</tr>
<tr>
<td>White Cell Count (x 10⁹/L)</td>
<td>9.0±5.8</td>
<td>9.0±5.8</td>
<td>1.00</td>
<td>9.0±5.8</td>
<td>9.0±5.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Neutrophils (x 10⁹/L)</td>
<td>3.8±3.3</td>
<td>3.8±3.3</td>
<td>1.00</td>
<td>3.8±3.3</td>
<td>3.8±3.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Hematological toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromocytopenia n (%)</td>
<td>2 (9.1)</td>
<td>0</td>
<td>0.10</td>
<td>2 (8.0)</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Neutropenia n (%)</td>
<td>1 (4.5)</td>
<td>0</td>
<td>0.05</td>
<td>2 (9.0)</td>
<td>0</td>
<td>0.33</td>
</tr>
</tbody>
</table>
How To Manage?

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

- Increased dosing are sometimes required
- $\beta$-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
THANK YOU