Beta-Lactam Antibiotics in Critically Ill Patients: Is TDM the Solution?

September 20, 2019

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Beta-Lactam Antibiotics in Critically Ill Patients: Is TDM the Solution?

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Objectives

- Explain properties of beta-lactams and pharmacokinetic changes in critically ill patients
- Discuss available evidence for beta-lactam therapeutic drug monitoring for efficacy
- Describe available evidence for beta-lactam therapeutic drug monitoring for safety
- Evaluate the special populations that may benefit from therapeutic drug monitoring of beta-lactams

Pre-assessment question

Which of the following patients represents the best candidate for utilizing TDM of B-lactams?

a. 25 year old male with a TBI complicated by ventriculitis caused by Enterobacter cloacae. Measured CrCl > 220 mL/min
b. 81 year old female with recurrent seizures and delirium and hospital-acquired pneumonia. Pseudomonas aeruginosa is the isolated pathogen. Estimated CrCl ~20 – 30 mL/min
c. 54 year old male with a BMI of 47 kg/m^2^ in septic shock and Morganella morganii bacteremia not improving on current therapy. Estimated CrCl ~10 – 20 mL/min (baseline 70 – 80 mL/min)
d. 38 year old male with 70% TBSA burns and recurrent Acinetobacter baumannii bacteremia throughout his prolonged ICU stay. Estimated CrCl ~ 200 mL/min

B-lactams

- B-lactams are the most commonly used antibiotic in the ICU, accounting for more than 40% of all antibiotic orders
- Broad spectrum of activity, ease of administration and high tolerability in comparison to other antibiotics
- Historically, B-lactams have shown strong clinical effectiveness with fixed dose, empiric regimens
- Recommended first line in many empiric regimens for aerobes and other infectious diseases that are common in the ICU (i.e. hospital-acquired/ventilator-associated pneumonia, intra-abdominal infections, meningitis)

Pharmacokinetics

- B-lactam Pharmacokinetics
  - Bactericidal
  - Hydrophilic
  - Time-dependent killing
  - Renally eliminated (most)
**Concentration-Time Curve**

- Concentration-Time Curve
- T > MIC
- MIC
- Time

**PK/PD Target**

- $fT > MIC$
- $4 - 5 \times MIC$
- 40-100%

**Historic PK/PD Targets**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Bacteriostasis</th>
<th>Bactericidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>40%</td>
<td>60 – 70%</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

**What has changed?**

- **Evolving Pathogens**
  - ↑ in global antimicrobial resistance
  - ↑ MICs for common ICU pathogens

- **Patient Population**
  - ↑ Obesity
  - ↑ Geriatric and immunosuppressed patients

- **Sepsis Management**
  - Early identification
  - Aggressive resuscitation

**PK Changes in Critical Illness**

- Sepsis
  - ↑ Cardiac Output
  - Leaky capillaries
  - Hypoalbuminemia
  - Fluid therapy
  - Normal Organ Function
  - End Organ Dysfunction (renal, hepatic)

  - ↓ CL
  - ↑ Vd
  - Unchanged Vl
  - ↓ CL

- Plasma concentrations
  - Normal plasma concentrations
  - ↑ Plasma concentrations

**PK Changes in Critical Illness**

- Sepsis
  - ↑ Cardiac Output
  - Leaky capillaries
  - Hypoalbuminemia
  - Fluid therapy
  - Normal Organ Function
  - End Organ Dysfunction (renal, hepatic)

  - ↓ CL
  - ↑ Vd
  - Unchanged Vl
  - ↓ CL

- Plasma concentrations
  - Normal plasma concentrations
  - ↑ Plasma concentrations

**Clinical and Experimental Pharmacology and Physiology.** 2012; 39(6): 489-96.

**Individualizing B-lactam Therapy**

- Normal dose
- High dose
- Reduced dose
- Extended infusion

**Drug Properties that Warrant TDM**

1. Narrow therapeutic index
2. Drug toxicity may lead to significant patient harm
3. No clearly defined clinical parameter that allows dose adjustments
4. Correlation between serum concentrations and efficacy/toxicity
5. Unpredictable relationship between dose and clinical outcome
6. Difficult to predict pharmacokinetics

**TDM History: Vancomycin**

- Commonly referred to as “Mississippi mud” soon after its introduction in the 1950s
- Adverse effects prompted TDM of vancomycin peak concentrations
- TDM of vancomycin has since evolved to monitoring of trough concentrations for efficacy which remains a topic of debate
- Primarily used for prevention of toxicity rather than for optimization of clinical efficacy
- The favorable adverse effect profile of β-lactams, high antimicrobial susceptibility, and more homogeneous pharmacodynamic profiles prevented the need for TDM
French Guidelines

- Developed by the French Society of Pharmacology and Therapeutics and the French Society of Anesthesia and Intensive Care Medicine
- Optional recommendations and algorithm to guide β-lactam TDM and dosing in critically ill patients
- Provides recommendations in four areas related to optimization of treatment with β-lactams antibiotics in critical care patients
  - Pharmacokinetic variability
  - Pharmacokinetic/pharmacodynamic relationship
  - Administration modalities
  - Therapeutic drug monitoring

Considerations

What is the optimal PK/PD target?

Which patients and which antibiotics?

When to draw concentrations and how to use them to improve outcomes?

Endpoints

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Positive Clinical Outcome | - Completion of treatment course without change or addition of antibiotic therapy  
- No additional antibiotics commenced with 48 hours of cessation  
- De-escalation to a narrower spectrum antibiotic was excluded from the clinical outcome analysis |
| Negative Clinical Outcome | - Any clinical outcome other than a positive clinical outcome |

TDM for Efficacy

- Prospective multinational pharmacokinetic point-prevalence study
- Included 384 patients across 68 hospitals

DALI

- Determine whether β-lactam antibiotic dosing in critically ill patients achieves concentrations associated with maximal activity
- Determine whether antibiotic concentrations affect patient outcome

- Antibiotics included: amoxicillin-clavulanate, ampicillin, ceftriaxone, cefazolin, cefepime, piperacillin-tazobactam, meropenem, doripenem

Treatment

PK/PD targets: 50% fT > MIC, 50% fT > 4xMIC, 100% fT > MIC, 100% fT > 4xMIC
### Results: Target Attainment

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No. of Patients (n)</th>
<th>Mean</th>
<th>Median</th>
<th>2.5th%-75th%</th>
<th>50th%</th>
<th>75th%-97.5th%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>71</td>
<td>6.0</td>
<td>3.5</td>
<td>2.0-6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>18</td>
<td>12.0</td>
<td>8.3</td>
<td>8.3-12.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>14</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0-4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>14</td>
<td>6.0</td>
<td>5.0</td>
<td>5.0-6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>33</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0-4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doripenem</td>
<td>13</td>
<td>1.75</td>
<td>1.50</td>
<td>1.5-3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>109</td>
<td>12.0</td>
<td>12.0</td>
<td>12.0-16.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>89</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0-4.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Results: Clinical Outcomes

- Clinical cure rate was 66.5% for all patients
- 58.1% of patients treated for infection had a positive clinical outcome
- 72.9% of these patients had a bacterial pathogen isolate and 34.2% of these had a pathogen MIC available
- 67% of patients treated for infection received intermittent bolus dosing and 33% by prolonged infusion
- 16% of patients treated for infection did not achieve 50% $T >$ MIC and were 32% less likely to have a positive outcome

### Critique

**Strengths**
- Multinational, included large number of ICUs
- Landmark trial

**Weaknesses**
- Evaluation of clinical outcomes limited to infected patients
- Lack of MIC data
- Point prevalence design

**Conclusions**
- Significant variability of antibiotic concentrations in critically ill
- PK/PD targets should be higher for critically ill

**TDM to Achieve Appropriate Drug Exposures**
- Single center prospective observational study
- Included 310 patients with 350 infections
- Primary: Describe achievement of unbound β-lactam targets and factors associated with target achievement in critically ill
- Secondary: Identify factors associated with failure to achieve PK/PD targets and negative clinical outcomes
- Antibiotics included in TDM service: ampicillin, benzylpenicillin, dicloxacillin, flucloxacillin, piperacillin-tazobactam, cefazolin, cefalotin, meropenem, ertapenem
- PK/PD target of 100% $T >$ MIC
### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>66%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.4 ± 17.7</td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>2.43 ± 0.56</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.86 (0.60 – 1.46)</td>
</tr>
<tr>
<td>Calculated CrCl (mL/min)</td>
<td>160.5 (93.1 – 163.0)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>68 (13.8%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.0 ± 8.9</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>22 (16 – 27)</td>
</tr>
<tr>
<td>Duration of B-lactam therapy</td>
<td>5 (1 – 7)</td>
</tr>
<tr>
<td>Antibiotic administered as a continuous infusion</td>
<td>21 (4.9%)</td>
</tr>
<tr>
<td>Percentage of standard daily dose</td>
<td>99.4 % ± 45.1</td>
</tr>
</tbody>
</table>

### Target Attainment & Clinical Outcomes

Factors associated with failure to achieve PK/PD targets:
- Augmented renal clearance (CrCl > 130 mL/min)
- Administration by prolonged infusion (continuous or extended)
- Type of B-lactam associated with achievement of all PK/PD targets except 50% fT > MIC

Factors associated with negative clinical outcome:
- Abdominal source of infection
- Failure to achieve PK/PD targets NOT found to be independently associated with negative clinical outcomes

### Results

#### Dosing & PK/PD Data

<table>
<thead>
<tr>
<th>Antibiotic (No. of Patients)</th>
<th>Total</th>
<th>Ampicillin</th>
<th>Benzyl penicillin</th>
<th>Flucloxacillin</th>
<th>Cefazolin</th>
<th>Ceftriaxone</th>
<th>Piperacillin</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dosage</td>
<td></td>
<td>2 g q6h</td>
<td>2.4 g q4h</td>
<td>2 g q4h</td>
<td>1 g q8h</td>
<td>1 g q12h</td>
<td>4.5 g q8h</td>
<td>1 g q8h</td>
</tr>
<tr>
<td>Dose range</td>
<td></td>
<td>1 g q12h</td>
<td>1.2 g q4h</td>
<td>2 g q12h</td>
<td>1 g q8h</td>
<td>1 g q12h</td>
<td>1 g q12h</td>
<td>1 g q12h</td>
</tr>
<tr>
<td>50% fT &gt; MIC</td>
<td></td>
<td>60%</td>
<td>50%</td>
<td>100%</td>
<td>83.3%</td>
<td>100%</td>
<td>96.2%</td>
<td>96.2%</td>
</tr>
<tr>
<td>50% fT &gt; 4 × MIC</td>
<td></td>
<td>53.3%</td>
<td>91.7%</td>
<td>60.0%</td>
<td>96.0%</td>
<td>50.0%</td>
<td>85.5%</td>
<td>50.0%</td>
</tr>
<tr>
<td>100% fT &gt; MIC</td>
<td></td>
<td>53.3%</td>
<td>91.7%</td>
<td>60.0%</td>
<td>96.0%</td>
<td>50.0%</td>
<td>85.5%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

#### Critique

**Strengths**
- Prospective
- Provided information on attainment of unbound concentrations in critically ill

**Limitations**
- Single-center, observational study
- Arbitrary toxicity threshold
- Only 12 culture positive samples, clinical outcomes only assessed in these patients

**Conclusions**
- Suboptimal PK/PD target attainment (particularly in drugs with lower protein binding) in critically ill patients, even with dose adjustment strategies
- Empirically adjusted dosing regimens and conventional dosing regimens are likely inadequate to achieve PK/PD targets in critically ill patients
- Lack of association between target attainment and clinical outcomes

### TDM for Dose Adjustment

- Retrospective observational study
- Included 140 patients in the Burn ICU of a tertiary care hospital with burn infection, healthcare associated pneumonia, blood stream infection, and UTI treated with imipenem, meropenem, piperacillin/tazobactam
- Patients admitted from May 2005 to October 2008 who received conventional dosing regimens
- Patients admitted from November 2008 to June 2011 who received antibiotics with doses adjusted based on TDM results

- Determine the effect of TDM on clinical outcomes in the treatment of healthcare associated infections of critically ill burn patient
- 3 clinical outcomes: clinical outcome, death within first 14 days of treatment and death during hospitalization or hospital mortality
Targets & Outcome definitions

- ≥ 60% fT > MIC for meropenem and imipenem
- 100% fT > MIC for piperacillin

Clinical outcomes:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>Resolution of signs and symptoms of the infection within 14 days of treatment</td>
</tr>
<tr>
<td>Improvement</td>
<td>No change or addition to the antimicrobial treatment</td>
</tr>
<tr>
<td>Improvement</td>
<td>No initiation of additional drugs within 48 hours after discontinuation of therapy</td>
</tr>
<tr>
<td>Worsening</td>
<td>Initiation of antibiotic therapy with broad-spectrum agent other than the 4 studied drugs or death after 48 hours of the onset of treatment</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Death or change of regimen within 48 hours of beginning the initial regimen</td>
</tr>
</tbody>
</table>

Patient Characteristics

<table>
<thead>
<tr>
<th>Infection site</th>
<th>Conventional group, no. (%)</th>
<th>TDM group, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>34 (54)</td>
<td>43 (66)</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>31 (44)</td>
<td>29 (39)</td>
</tr>
<tr>
<td>Burn infection</td>
<td>21 (27)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>UTI</td>
<td>21 (51)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Presence of bacteremia</td>
<td>7 (25)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Other bacteria</td>
<td>4 (14)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>E. coli</td>
<td>9 (33)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>7 (25)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>9 (33)</td>
<td>5 (16)</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional Group, no. (%)</th>
<th>TDM Group, no. (%)</th>
<th>Total, no. (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>23 (36)</td>
<td>30 (39)</td>
<td>53 (38)</td>
<td>0.83</td>
</tr>
<tr>
<td>14-day mortality</td>
<td>9 (14)</td>
<td>12 (16)</td>
<td>21 (15)</td>
<td>0.99</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>N = 56</td>
<td>N = 72</td>
<td>N = 128</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>29 (52)</td>
<td>43 (60)</td>
<td>72 (56)</td>
<td>0.37</td>
</tr>
<tr>
<td>Worsening</td>
<td>27 (48)</td>
<td>29 (40)</td>
<td>56 (43)</td>
<td></td>
</tr>
</tbody>
</table>

Results continued

Multivariate analysis revealed prognostic factors of older age and larger BSA

TDM of antimicrobial treatment did NOT affect prognosis

There are no other published studies that focus on clinical outcomes of TDM vs. no TDM

Critique

Strengths
- Focus on clinical outcomes
- Burn patient population
- Comparison of TDM vs. no TDM

Limitations
- Retrospective, small, single-center cohort study
- Only included 3 β-lactams and 4 types of infections
- No clear explanation for how patients were managed in treatment group
- Variation in handling of samples

Conclusions
- First study to look at TDM vs. no TDM
- Difficult to draw conclusions due to limited information provided

TDM for Safety
Cefepime Neurotoxicity

**Design**
- Single-center, retrospective cohort study
- Included 319 patients treated with cefepime in tertiary care Swiss hospital

**Objectives**
- Determine more stringent therapeutic ranges for cefepime
- Identify individuals at risk for developing cefepime-associated neurotoxicity

**Included**
- Included patients with at least one cefepime plasma concentration available during hospitalization
- Excluded patients with inadequate/uncertain timing of sample, co-application of sulfamethoxazole and lack of adequate neurological assessment

**Primary endpoint**
- Significantly ↑ cefepime trough concentrations (21.6 mg/L vs. 6.3 mg/L, p < 0.001) in individuals with suspected cefepime-associated neurotoxicity
- No individual developed neurotoxicity at concentrations < 7.7 mg/L
- All participants had neurotoxicity at concentrations > 38.1 mg/L
- Probability of neurotoxicity from logistic regression:
  - 25% for cefepime concentrations 12 - 16 mg/mL
  - 50% for cefepime concentrations > 16 mg/mL

**Factors Associated with Neurotoxicity**
- Cefepime trough concentrations inversely correlated with renal function
- Lower eGFR (25 mL/min/1.73 m² vs. 32 mL/min/1.73 m²)
- High cefepime dose adjustment for renal clearance
- Significantly higher in-hospital mortality with cefepime neurotoxicity (7.8% vs. 35.1%, p < 0.001)

**Results**
- 74 of 319 presented neurological symptoms “possibly” related to cefepime administration
- Most frequently encountered symptoms: confusion/agitation/hallucinations and reduced consciousness (including coma)
- Median time to development of neurological signs was 2 days
- Cefepime therapy was modified or stopped in 96% of individuals that developed symptoms
- 81% of these patients exhibited at least partial resolution of symptoms in a median time of 2 days after adjustment or cessation of therapy

**Critique**

**Strengths**
- Focus on safety outcomes
- Broad definition of neurotoxicity symptoms allowed for increased recognition
- Provided evidence on concentrations associated with toxicity

**Limitations**
- Retrospective, single-center cohort study

**Conclusions**
- Maintaining cefepime trough concentrations < 7.5 mg/dL may prevent neurotoxicity from occurring
- Patients with renal insufficiency receiving cefepime should be monitored closely as they are at higher risk of supratherapeutic cefepime concentrations
- TDM may be a useful tool in patients with renal insufficiency to avoid cefepime-associated neurotoxicity
**Summary of Evidence**

- No large randomized controlled trials evaluating use of TDM vs. no TDM
- Small observational studies/case series evaluating use in specific populations (i.e., burn, CRRT, ARC)
- Studies focus on target attainment of PK/PD targets
- Lack of association between achievement of %fT/MIC targets and clinical outcome

**Practical Issues**

- Lack of MIC information
- No commercial B-lactam assay – this means labs must construct and validate their own assays
- Introduction and maintenance of this service would be a significant cost
- Education
- Establishment of goals and dose optimization

**Post-assessment question**

Which of the following patients represents the best candidate for utilizing TDM of B-lactams?

- a. 25 year old male with a TBI complicated by ventriculitis caused by Enterobacter cloacae. Measured CrCl > 220 mL/min
- b. 81 year old female with recurrent seizures and delirium and hospital-acquired pneumonia. Pseudomonas aeruginosa is the isolated pathogen. Estimated CrCl ~ 20 – 30 mL/min
- c. 54 year old male with a BMI of 47 kg/m² in septic shock and Morganella morganii bacteremia not improving on current therapy. Estimated CrCl ~ 10 – 20 mL/min (baseline 70 – 80 mL/min)
- d. 38 year old male with 70% TBSA burns and recurrent Acinetobacter baumannii bacteremia throughout his prolonged ICU stay. Estimated CrCl ~ 200 mL/min

**Recommendations**

- If no access to this service
  - Would not recommend implementing it at this time
  - Not enough evidence to ensure benefit would outweigh significant cost
- If some access to this service
  - Would recommend limiting use to documented infection in the following patients not improving on current dose:
    - ARC
    - CRRT
    - Burn
    - Sepsis
    - AKI
    - Obesity

**Acknowledgements**

- Dusten Rose, PharmD, BCIDP, AAHIVP
- Mitch Daley, PharmD, BCCCP, FCCM
- Molly Curran, PharmD, BCPS, BCCCP

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**Beta-Lactam Antibiotics in Critically Ill Patients: Is TDM the Solution?**

Emmy Gibbons, PharmD
PGY1 Pharmacy Resident
Appendix A: Abbreviations

- AKI: Acute Kidney Injury
- ARC: Augmented Renal Clearance
- BMI: Body Mass Index
- BSA: Body Surface Area
- CI: Continuous Infusion
- CL: Clearance
- CrCl: Creatinine Clearance
- CRRT: Continuous Renal Replacement Therapy
- eGFR: Estimated Glomerular Filtration Rate
- ICU: Intensive Care Unit
- MIC: Minimum Inhibitory Concentration
- PD: Pharmacodynamics
- PK: Pharmacokinetics
- RRT: Renal Replacement Therapy
- TBI: Traumatic Brain Injury
- TDD: Total Daily Dose
- TDM: Therapeutic Drug Monitoring
- Vd: Volume of Distribution
- \%T > MIC: the percentage of time (T) of the dosing interval during which the unbound (free, $f$) serum antibiotic concentration remains at least above the MIC for the targeted organism
Appendix B: French B-lactam optimization guidelines

Infection in a critical care patient

- Start beta-lactam treatment at high dose
  - Administer the first unit dose as a bolus injection

Patient with septic shock/high severity score?
And/or lower respiratory tract infection?
And/or infection due to non-fermenting GNB?
And/or infection due to bacteria with high MIC?

**YES**
- Start immediately the administration of the daily dose by continuous IV infusion*

**NO**
- Start immediately the administration of the daily dose by continuous IV infusion*
- Continue the administration of the daily dose by discontinuous IV injections

- Expected PK variability?
  - And/or renal replacement therapy?
  - And/or beta-lactam toxicity signs?

**NO**
- No beta-lactam therapeutic drug monitoring recommended

**YES**
- Beta-lactam plasma concentration measurement using a validated chromatographic method
  - through concentration in case of discontinuous administration
  - steady-state concentration in case of continuous administration

- C < 4x MIC
  - **Discontinuous administration**
    - Increase the unit dose by 25 to 50% OR
    - Fractionate the daily dose/switch to continuous infusion
    - +/- administer a rescue bolus

- 4x MIC ≤ C < 8x MIC
  - **Continuous administration**
    - Increase the daily dose
    - +/- administer a rescue bolus
  - **Discontinuous administration**
    - Decrease the unit dose by 25 to 50%
    - +/- stop the treatment in case of toxicity signs
    - +/- RRT in case of toxicity signs and AKI

- C ≥ 8x MIC or C ≥ validated toxicity threshold
  - **Continuous administration**
    - Decrease the daily dose
    - +/- stop the treatment in case of toxicity signs
    - +/- RRT in case of toxicity signs and AKI

Resolution or occurrence of new organ failure(s)?
Initiation of RRT?
Fluid load or albumin infusion?

**YES**
- New measurement of beta-lactam plasma concentration and therapeutic adjustment if needed
Appendix C: DALI figures

Table 1: Antibiotic Data for Achievement of PK/PD Targets

<table>
<thead>
<tr>
<th>Dosing &amp; PK/PD Data</th>
<th>Amoxicillin (n = 71)</th>
<th>Ampicillin (n = 18)</th>
<th>Cefazolin (n = 14)</th>
<th>Cefepime (n = 14)</th>
<th>Ceftriaxone (n = 33)</th>
<th>Doripenem (n = 13)</th>
<th>Piperacillin (n = 109)</th>
<th>Meropenem (n = 89)</th>
<th>Total (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage per 24 h, g</td>
<td>6.0 (3.5–6.0)</td>
<td>12.0 (8.3–12.0)</td>
<td>3.0 (3.0–4.0)</td>
<td>6.0 (5.0–6.0)</td>
<td>2.0 (2.0–4.0)</td>
<td>1.75 (1.50–3.0)</td>
<td>12.0 (12.0–16.0)</td>
<td>3.0 (3.0–4.0)</td>
<td></td>
</tr>
<tr>
<td>50% $\text{fT}_{\text{MIC}}$ achieved</td>
<td>52.1%</td>
<td>55.6%</td>
<td>100.0%</td>
<td>78.6%</td>
<td>97.0%</td>
<td>100.0%</td>
<td>80.6%</td>
<td>95.0%</td>
<td>78.9%</td>
</tr>
<tr>
<td>50% $\text{fT}_{4\times \text{MIC}}$ achieved</td>
<td>16.9%</td>
<td>27.8%</td>
<td>50.0%</td>
<td>50.0%</td>
<td>93.9%</td>
<td>69.2%</td>
<td>48.9%</td>
<td>68.8%</td>
<td>48.9%</td>
</tr>
<tr>
<td>100% $\text{fT}_{\text{MIC}}$ achieved</td>
<td>18.3%</td>
<td>33.3%</td>
<td>78.6%</td>
<td>78.6%</td>
<td>93.9%</td>
<td>76.9%</td>
<td>67.0%</td>
<td>69.7%</td>
<td>60.4%</td>
</tr>
<tr>
<td>100% $\text{fT}_{4\times \text{MIC}}$ achieved</td>
<td>11.3%</td>
<td>22.2%</td>
<td>14.3%</td>
<td>71.4%</td>
<td>87.9%</td>
<td>30.8%</td>
<td>30.3%</td>
<td>41.6%</td>
<td>35.0%</td>
</tr>
</tbody>
</table>

Figure 1: The pharmacokinetic/pharmacodynamic (PK/PD) ratios observed at 50% (A) and 100% (B) of the dosing interval
Appendix D: TDM to Achieve Appropriate Drug Exposures Figures

**Table 2:** Demographics and clinical characteristics of the studied patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>66%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.4 ± 17.7</td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>2.43 ± 0.56</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.86 (0.60 – 1.46)</td>
</tr>
<tr>
<td>Calculated CrCl (mL/min)</td>
<td>101.5 (59.1 – 163.0)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>68 (13.8%)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>29.0 ± 8.9</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>22 (16 – 27)</td>
</tr>
<tr>
<td>Repeated sampling (2nd or subsequent)</td>
<td>122 (24.8)</td>
</tr>
<tr>
<td>Duration of B-lactam therapy (days)</td>
<td>5 (3 – 7)</td>
</tr>
<tr>
<td>Antibiotic administered as a continuous infusion</td>
<td>21 (4.3%)</td>
</tr>
<tr>
<td>Percentage of standard daily dose</td>
<td>99.4 % ± 45.1%</td>
</tr>
</tbody>
</table>

**Table 3:** Achievement of predefined PK/PD dose adjustment targets for first TDM of studied B-lactams

<table>
<thead>
<tr>
<th>Dosing &amp; PK/PD Data</th>
<th>Antibiotic (No. of Patients)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ampicillin</td>
<td></td>
</tr>
<tr>
<td>Standard dosage</td>
<td>2 g q6h</td>
<td>1 g q8h</td>
</tr>
<tr>
<td>Dose range</td>
<td>1.2 g q4h – 2.4 g q4h</td>
<td>4.5 g q8h</td>
</tr>
<tr>
<td>50% fT&gt;MIC achieved</td>
<td>60%</td>
<td>90.4%</td>
</tr>
<tr>
<td>50% fT&gt;4MIC achieved</td>
<td>91.7%</td>
<td>92.1%</td>
</tr>
<tr>
<td>100% fT&gt;MIC achieved</td>
<td>52%</td>
<td>53.2%</td>
</tr>
<tr>
<td>100% fT&gt;4MIC achieved</td>
<td>0%</td>
<td>68.5%</td>
</tr>
<tr>
<td>100% fT&gt;10MIC achieved</td>
<td>32%</td>
<td>66.9%</td>
</tr>
<tr>
<td>100% fT-10MIC achieved</td>
<td>16%</td>
<td>36.6%</td>
</tr>
<tr>
<td>Percentage of standard daily dose</td>
<td>80%</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>11.3%</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>17.3%</td>
</tr>
</tbody>
</table>
Figure 2: PK/PD ratios (as unbound concentrations divided by MICs) at 50% and 100% dosing intervals.
### Table 4: Clinical characteristics of treatment groups

<table>
<thead>
<tr>
<th>Infection site</th>
<th>Conventional group, no. (%)</th>
<th>TDM group, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>34 (54)</td>
<td>43 (56)</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>15 (24)</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Burn infection</td>
<td>11 (17)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>UTI</td>
<td>3 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Presence of bacteremia</td>
<td>21 (51)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Agents in blood culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>7 (25)</td>
<td>12 (39)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>9 (33)</td>
<td>5 (16)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>4 (14)</td>
<td>2 (6)</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>5 (18)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (10)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

### Table 5: Clinical outcome and mortality according to treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional Group, no. (%)</th>
<th>TDM Group, no. (%)</th>
<th>Total, no. (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>23 (36)</td>
<td>30 (39)</td>
<td>53 (38)</td>
<td>0.83</td>
</tr>
<tr>
<td>14-day mortality</td>
<td>9 (14)</td>
<td>12 (16)</td>
<td>21 (15)</td>
<td>0.99</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>n = 56</td>
<td>n = 72</td>
<td>n = 128</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>29 (52)</td>
<td>43 (60)</td>
<td>72 (56)</td>
<td>0.37</td>
</tr>
<tr>
<td>Worsening</td>
<td>27 (48)</td>
<td>29 (40)</td>
<td>56 (43)</td>
<td></td>
</tr>
</tbody>
</table>