A retrospective analysis of TDM-guided continuous infusion of Piperacillin/Tazobactam in the ICU
Daniel C. Richter, M.D.
Transparency Declaration

• **Memberships:** Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG)

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• **Accepted Author‘s Fees:** Thieme, Journal of Medical Drug Reviews
Introduction

Right Dose, Right Now: Customized Drug Dosing in the Critically Ill

Jason A. Roberts, PhD, FSHP, Anand Kumar, MD, FCCM; Jeffrey Lipman, MD, FCICM

• Optimal exposure is crucial – especially within the first 24-48 hrs (1,2)
• In terms of β-lactam efficacy: $f_{T > xMIC}$ is predictive
• Extended infusion (i.e. continuous infusion) expand $f_{T > xMIC}$ up to 100%
• TDM as a way to adapt and guide serum concentrations to a defined PK-target
• Trails suggest positive effects (TDM-guided CI and PK target-attainment)(3,4)
• Lack of definite RCTs, lack of experience in clinical routine

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Crass RL et al., CID 2018
Rhodes A et al., ICM, 2017
Abdul-Aziz M et al., JAC, 2016
(1) Roberts JA et al., AJRCCM, 2016
(2) Rhodes A et al., ICM, 2017
(3) Abdul-Aziz M et al., JAC, 2016
Data collection

- Monocentric (interdisciplinary ICU)
- Retrospective analysis
- Database of patients treated with CI of PIP (2008 – 2012)
- $n=484$ patients
- $\sum n=933$ TDM

- Sepsis/septic shock patients \((SEPSIS-2)\)
- Severe infections with organ dysfunction & treatment in the ICU
- Renal replacement therapy (iHD, CVVHD)
- Treatment (empirical & definitive) with PIP/TAZ
Aims of the study

• **Primary objective:**

1. **PK target-attainment within 24 hrs** after treatment initiation
   a. $c(PIP) = 33-64 \text{ mg} \cdot \text{L}^{-1} \Rightarrow 3-4 \cdot \text{MIC resistant Enterobacterales}$
   b. $c(PIP) = 65-99 \text{ mg} \cdot \text{L}^{-1} \Rightarrow$ for resistant non-fermenting pathogens

2. Effect of **TDM-guided PIP dose-adjustments**
### Epidemiology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Severe) Sepsis</td>
<td>187/484</td>
<td>38.6</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>184/484</td>
<td>38.1</td>
</tr>
<tr>
<td>Severe Infection</td>
<td>113/484</td>
<td>23.3</td>
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<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Pneumonia</td>
<td>256</td>
<td>53</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>114</td>
<td>23.6</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>38</td>
<td>7.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal Replacement Therapy</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>79/484</td>
<td>16.3</td>
</tr>
<tr>
<td>CVVHD</td>
<td>71/79</td>
<td>89.9</td>
</tr>
<tr>
<td>iHD</td>
<td>8/79</td>
<td>10.1</td>
</tr>
</tbody>
</table>

- Sepsis: 76.7%
- CVVHD = 89.9% of RRT
- Foci: Pneumonia (53%), Peritonitis (23.6)
Initial target-attainment (day 1)
# Effects of TDM-guided dose-adjustment

<table>
<thead>
<tr>
<th>PIP [mg·L(^{-1})]</th>
<th>&lt;16</th>
<th>16-32</th>
<th>33-64</th>
<th>65-99</th>
<th>≥100</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>24 hrs</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1 (0.2)</td>
<td>48  (9.9)</td>
<td>166 (34.3)</td>
<td>123 (25.4)</td>
<td>146 (30.2)</td>
<td></td>
</tr>
<tr>
<td>% (N)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10.1 (49/484)</td>
<td></td>
<td>59.7 (286/484)</td>
<td></td>
<td></td>
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<tr>
<td>TDM</td>
<td></td>
<td></td>
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<tr>
<td>5 (1.1)</td>
<td>66  (14.7)</td>
<td>280 (62.4)</td>
<td>78 (17.4)</td>
<td>20 (4.5)</td>
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<tr>
<td>d(%)</td>
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<tr>
<td>15.8 (71/449)</td>
<td></td>
<td>79.7 (358/449)</td>
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</table>

- TDM-adjustments increased PK target-attainment
- Significiant increase in prim. target group (33-64 mg·L\(^{-1}\)): + 81%
- Significant reduction in group ≥100 mg·L\(^{-1}\): - 85%
**Renal function**

**High CrCL increases odds for low c(PIP)**
- $<16 \text{ mg}\cdot\text{L}^{-1}$: OR 1.002 95% CI [1.011-1.034], $p<.0005$
- 16-32 mg\cdot\text{L}^{-1}$: OR 1.017 95% CI [1.013-1.022], $p<.0005$

**Age increased the odds for c(PIP) ≥100 mg\cdot\text{L}^{-1}**
- OR 1.044 95% CI [1.029-1.060]; $p<.0005$

1. supports findings of previously conducted trails
2. illustrates the difficulties in predicting $CL_{\text{PIP}}$
3. Risk for target non-attainment: high CrCL, young
Effects of RRT on PIP-dosing

Panel A:
- n=71 (14.6%)
- n=8 (1.7%)
- n=405 (84.1%)

Panel B:
- Dose (median [range]):
  - 8 g [3-12 g]
  - 4 g [2-12 g]
  - 8 g [2-20 g]

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Effect of obesity

Extra-renal clearance (intestinal, deposition)?

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**ICU- & hospital mortality**

<table>
<thead>
<tr>
<th>PIP [mg·L⁻¹]</th>
<th>≤ 16</th>
<th>16-32</th>
<th>33-64</th>
<th>65-99</th>
<th>≥ 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>7 (14.6)</td>
<td>20 (12)*</td>
<td>21 (16.3)</td>
<td>45 (31.9)**</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>10 (21)</td>
<td>23 (13.8)*</td>
<td>26 (20.5)</td>
<td>53 (37.6)**</td>
<td></td>
</tr>
</tbody>
</table>

1. **PK target attainment:** reduction in mortality (ICU & hospital)
2. **higher mortality ≥100 mg·L⁻¹** (toxicity?, Co-morbidities?)
Summary

- CI of PIP leads to **sufficient PK target-attainment**
  - *Low* PIP serum concentrations **rarely occurred** (10.1 & 15.8%) — **EFFICACY!**

- TDMs & dose adjustment measures **increase target-attainment** \( (\text{T}_{\geq \text{MIC}}) \):
  - *High* concentrations probably more relevant (29.1 & 17.8% ≥100mg·L\(^{-1}\)) — **SAFETY!**
    - **Solution**: PK dose-approximation (*data in preparation*)

- **Renal function** is a main risk factor for target non-attainment
  - Use **measured CrCL** rather than calculated CrCL in selected cases?

- **RRT (CVVHD)**: lower CL\(_{\text{pip}}\) & lower PIP-doses administered

- **Obesity**? Probably not a problem until BMI ≤40 kg·m\(^{-2}\)

- Target-attainment might reduce patient mortality \( \rightarrow \) **RCTs needed (BLING III, TARGET)** to confirm!
Thank you very much for your attention

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