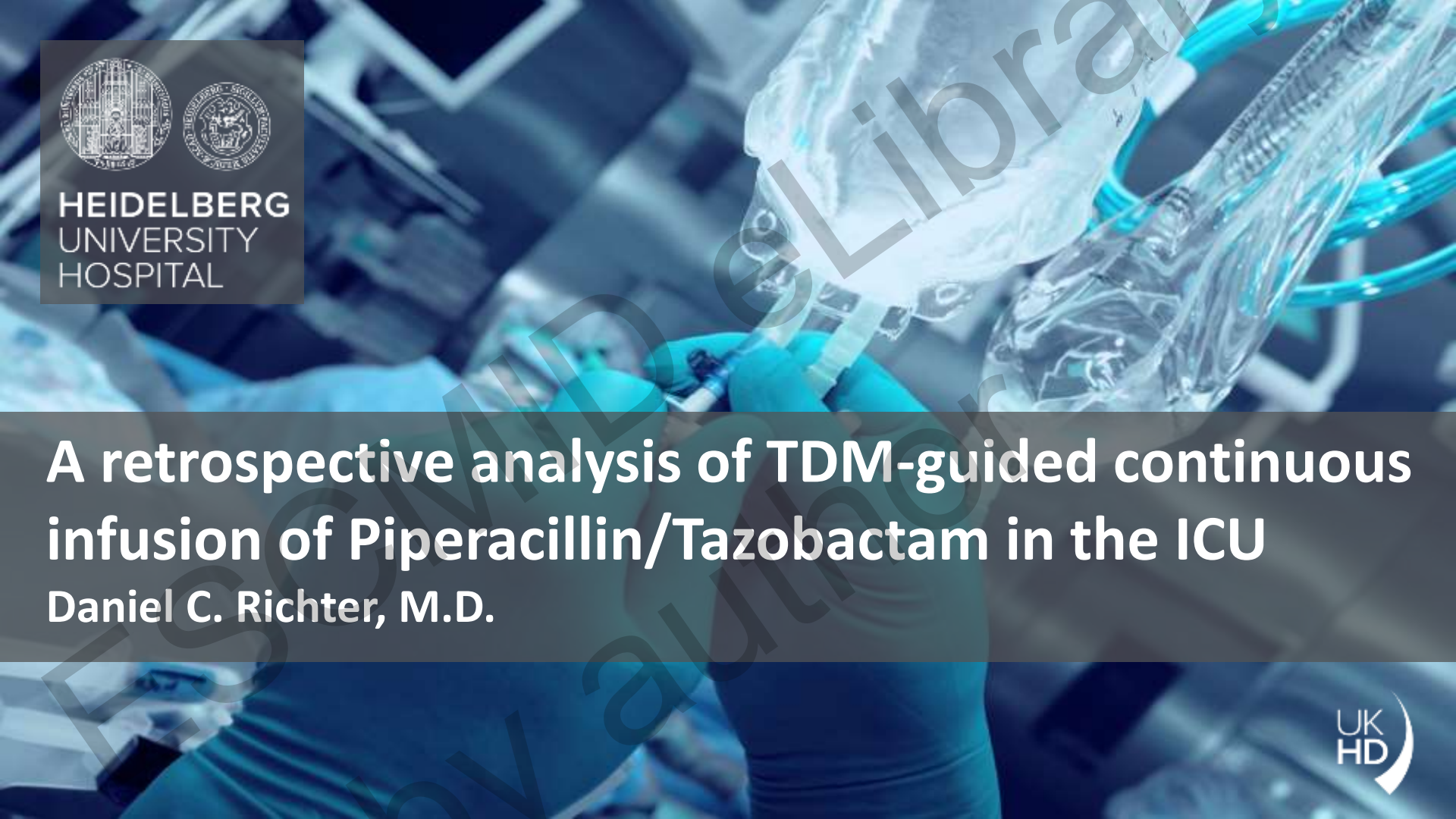

A retrospective analysis of TDM-guided continuous infusion of Piperacillin/Tazobactam in the ICU

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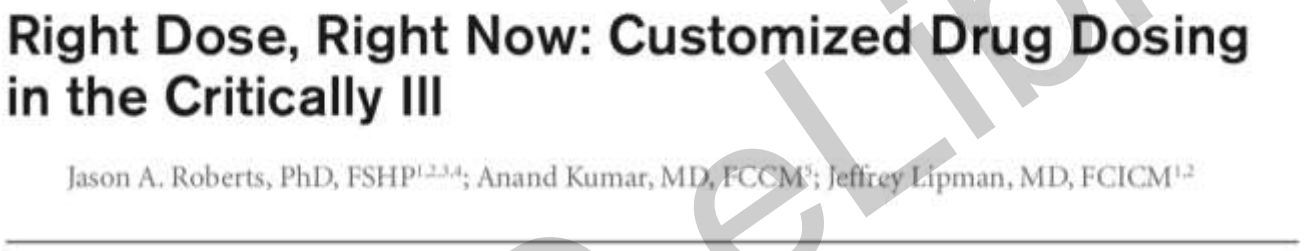
Transperancy Declaration

- **Memberships:** Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG)
- **Financial Support (Travel Expenses):** Pfizer Pharma, Astellas Pharma, Gilead Sciences Inc.
- **Accepted Author‘s Fees:** Thieme, Journal of Medical Drug Reviews

UK HD

Introduction



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

Jason A. Roberts, PhD, FSHP[1,2,3,4]; Anand Kumar, MD, FCCM[5]; Jeffrey Lipman, MD, FCICM[1,2]

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

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

Data collection

- Monocentric (interdisciplinary ICU)
- Retrospective analysis
- Database of patients treated with CI of PIP (2008 – 2012)
- **n=484** patients
- ∑ 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 $mg \cdot L^{-1}$ → 3-4·MIC resistant *Enterobacterales*
     b. c(PIP) = 65-99 $mg \cdot L^{-1}$ → for resistant non-fermenting pathogens
  2. Effect of **TDM-guided PIP dose-adjustments**

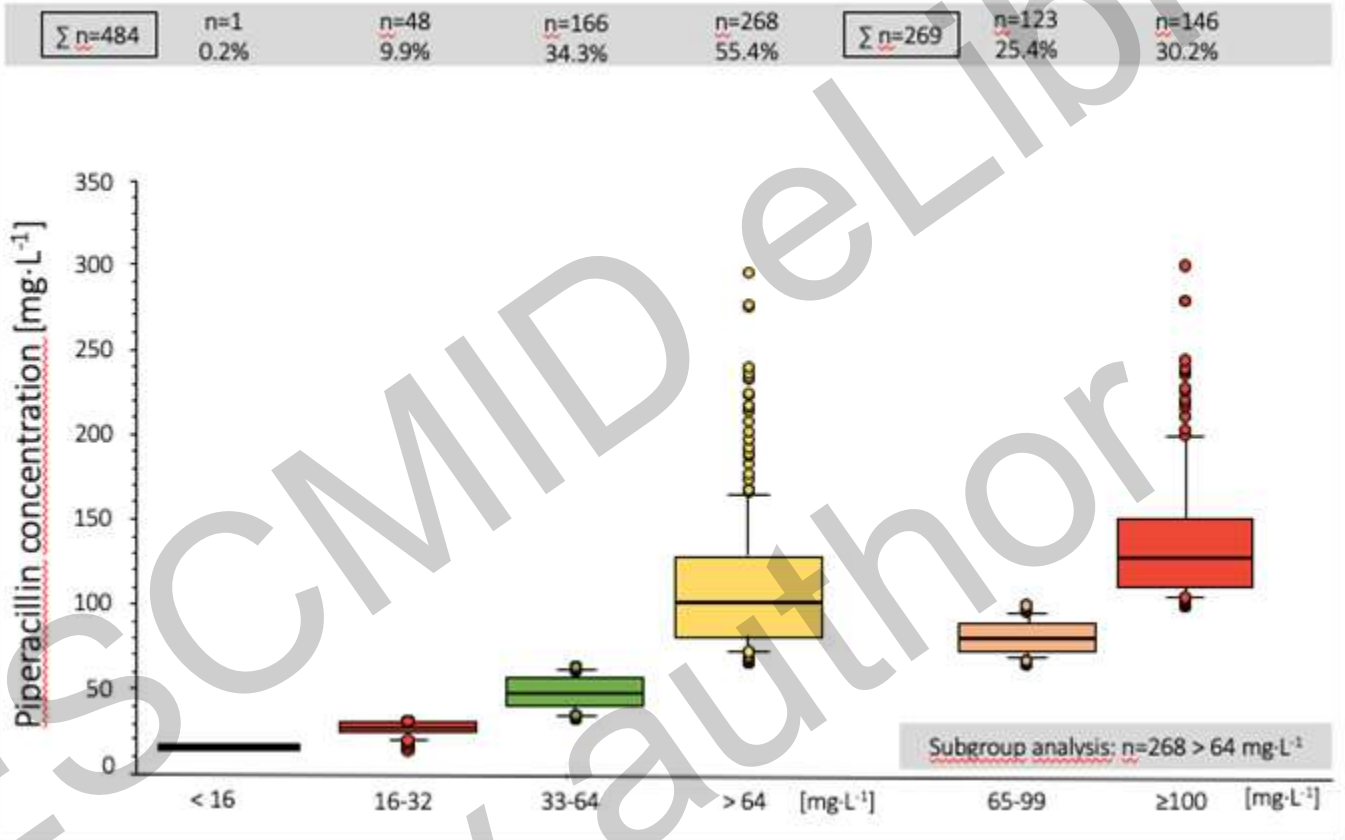
Epidemiology

Diagnosis		
	N	%
(Severe) Sepsis	187/484	38.6
Septic Shock	184/484	38.1
Severe Infection	113/484	23.3
Site of Infection		
	N	%
Pneumonia	256	53
Peritonitis	114	23.6
Urosepsis	38	7.7

Renal Replacement Therapy		
	N	
Overall	79/484	16.3
CVVHD	71/79	89.9
iHD	8/79	10.1

- Sepsis: 76.7%
- CVVHD = 89.9% of RRT
- Foci: Pneumonia (53%), Peritonitis (23.6)

Initial target-attainment (day 1)

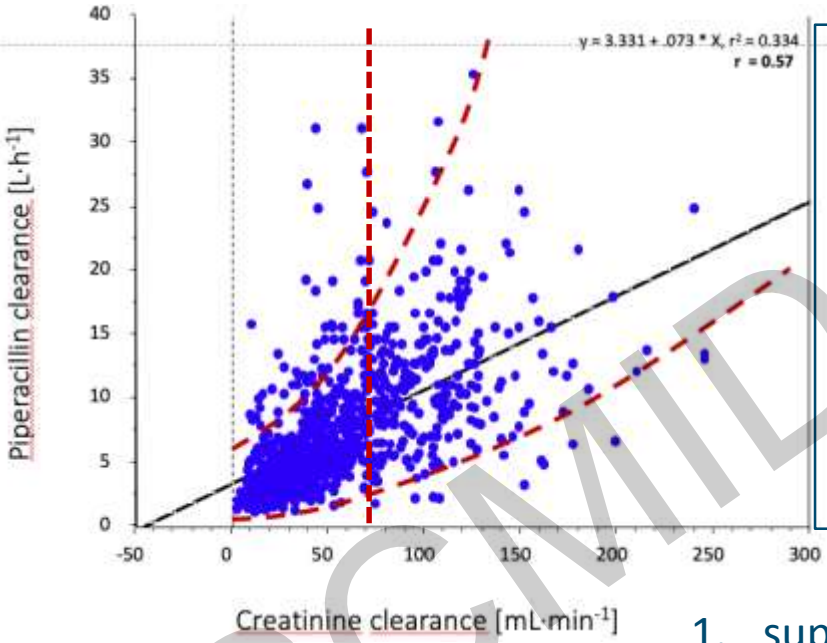


Effects of TDM-guided dose-adjustment

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

- 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)**

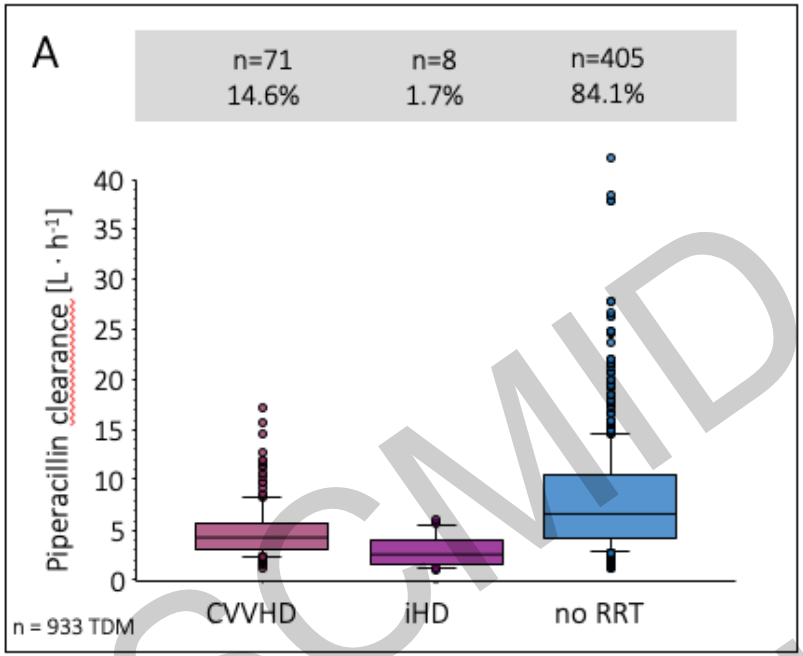
- <16 mg·L^{-1}: OR 1.002 95% CI [1.011-1.034], p<.0005
- 16-32 mg·L^{-1}: OR 1.017 95% CI [1.013-1.022], p<.0005

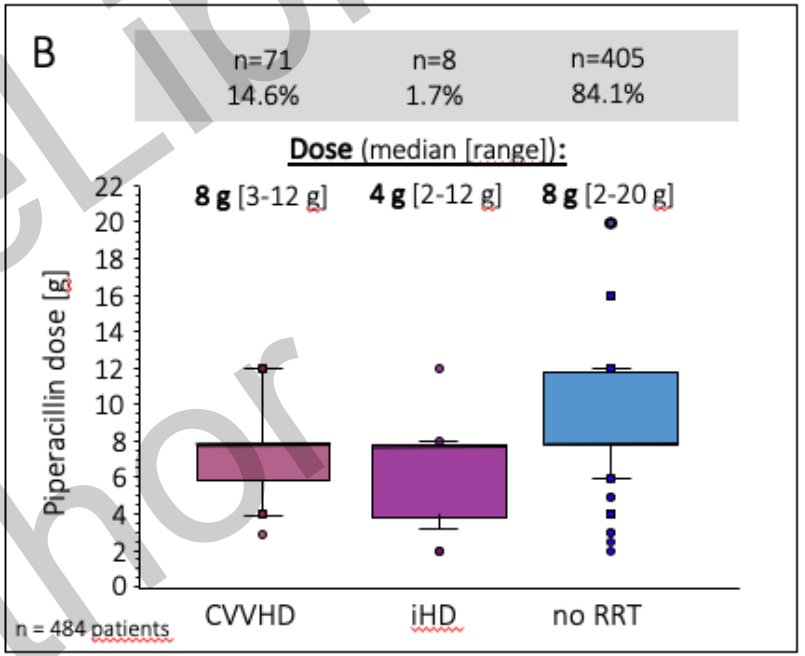
***Age* increased the odds for c(PIP) ≥100 mg·L^{-1}**

- OR 1.044 95% CI [1.029-1.060]; p<.0005

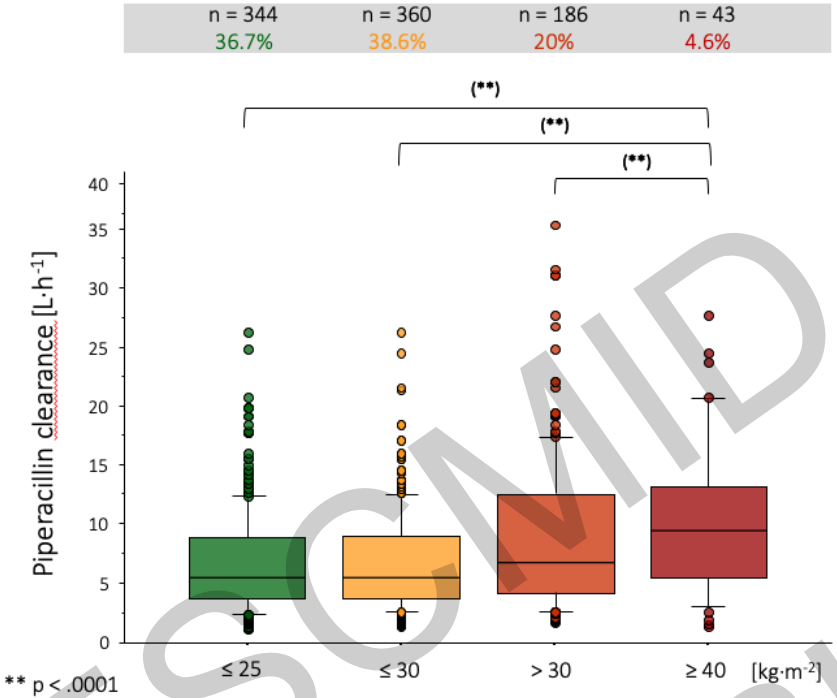
1. supports findings of previously conducted trails
2. illustrates the difficulties in predicting CL_{PIP}
3. Risk for target non-attainment: high CrCL, young

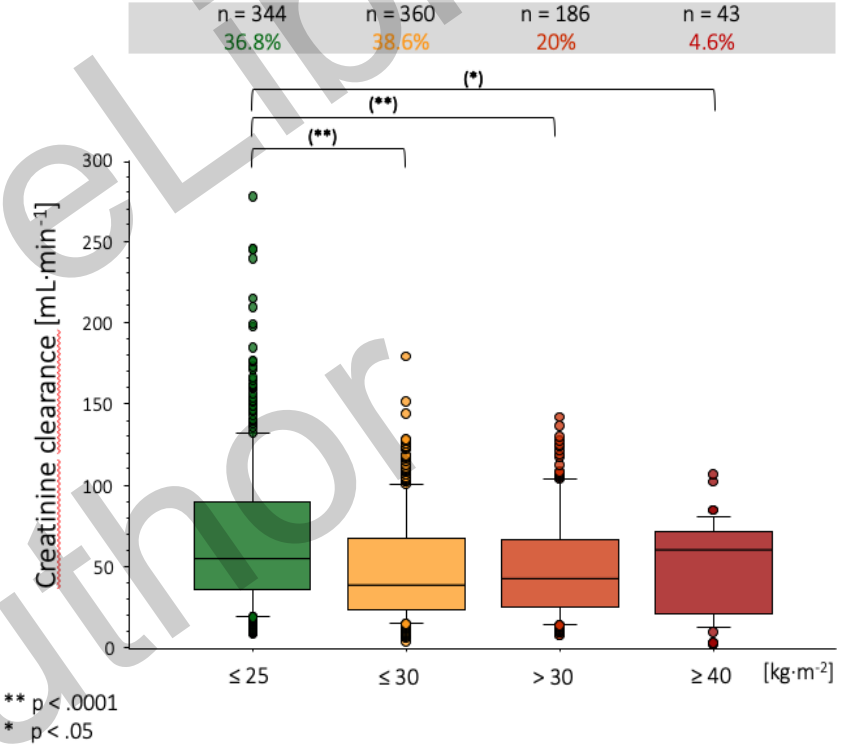
Effects of RRT on PIP-dosing





Effect of obesity





Extra-renal clearance (intestinal, deposition)?

ICU- & hospital mortality

PIP [mg·L^{-1}]	≤ 16	16-32	33-64	65-99	≥ 100
		N (%)			
Mortality ICU		7 (14.6)	20 (12)*	21 (16.3)	45 (31.9)**
Mortality Hospital		10 (21)	23 (13.8)*	26 (20.5)	53 (37.6) **

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 occured** (10.1 & 15.8%) – *EFFICACY!*
- TDMs & dose adjustment measures **increase target-attainment ($fT_{>xMIC}$):**
  - ***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_{PIP} & lower PIP-doses administered
- **Obesity**? Probably not a problem until BMI **≤40 kg·m^{-2}**
- Target-attainment might reduce patient mortality → RCTs needed *(BLING III, TARGET)* to confirm!

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Thank you very much for your attention

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