Prolonged infusions + TDM of β-lactam antibiotics

Dr. Maya Hites
Clinic of Infectious Diseases
Erasme Hospital
BVIKM/SBIMC Spring Symposium
March 30, 2017

The PK of β-lactams in the critically ill are very unpredictible

- Great PK inter and intra-individual variability[1-2]

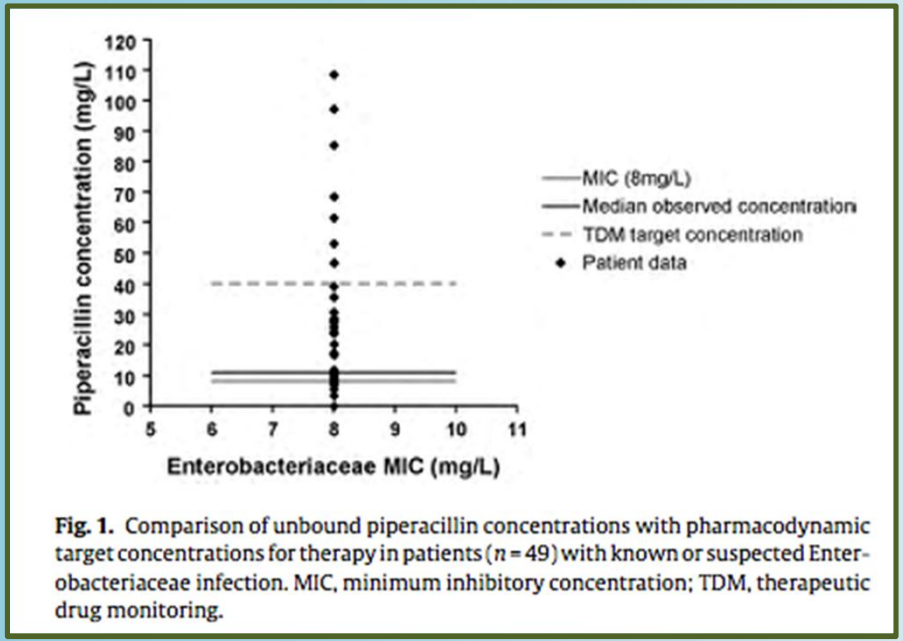


Fig. 1. Comparison of unbound piperacillin concentrations with pharmacodynamic target concentrations for therapy in patients ($n = 49$) with known or suspected Enterobacteriaceae infection. MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

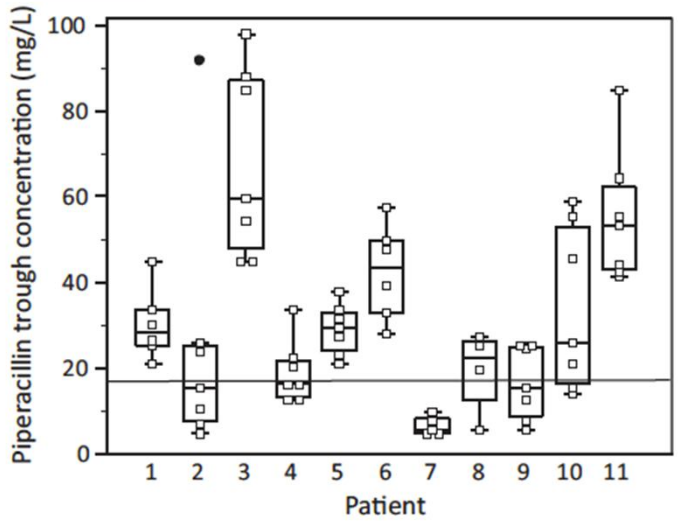
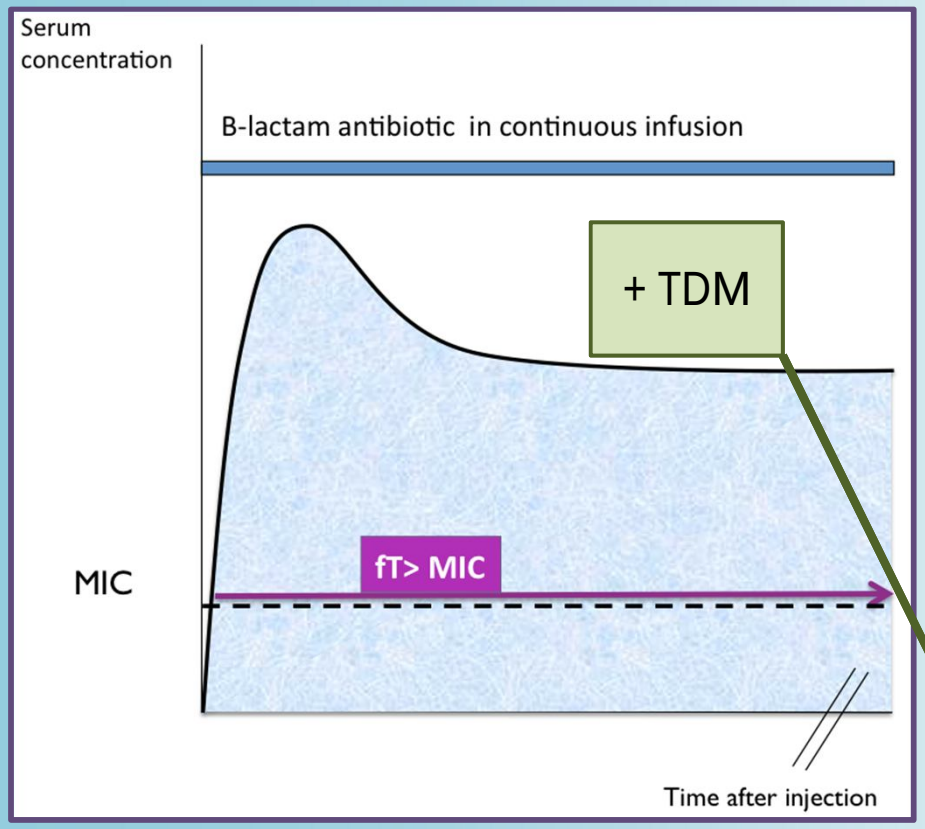


Fig. 2. Box plot of individual patient piperacillin concentrations, also showing the individual concentrations [□, individual values; ●, extreme outlier (outside three times the interquartile range)]. The horizontal black line represents the target minimum inhibitory concentration (MIC) of *Pseudomonas aeruginosa* according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint (16 mg/L).

1. Roberts JA et al. Int J Antimicrob Agents. 2010; 36: 332-39.
2. Carlier M et al. Int J Antimicrob Agents. 2014; 43: 470-73.

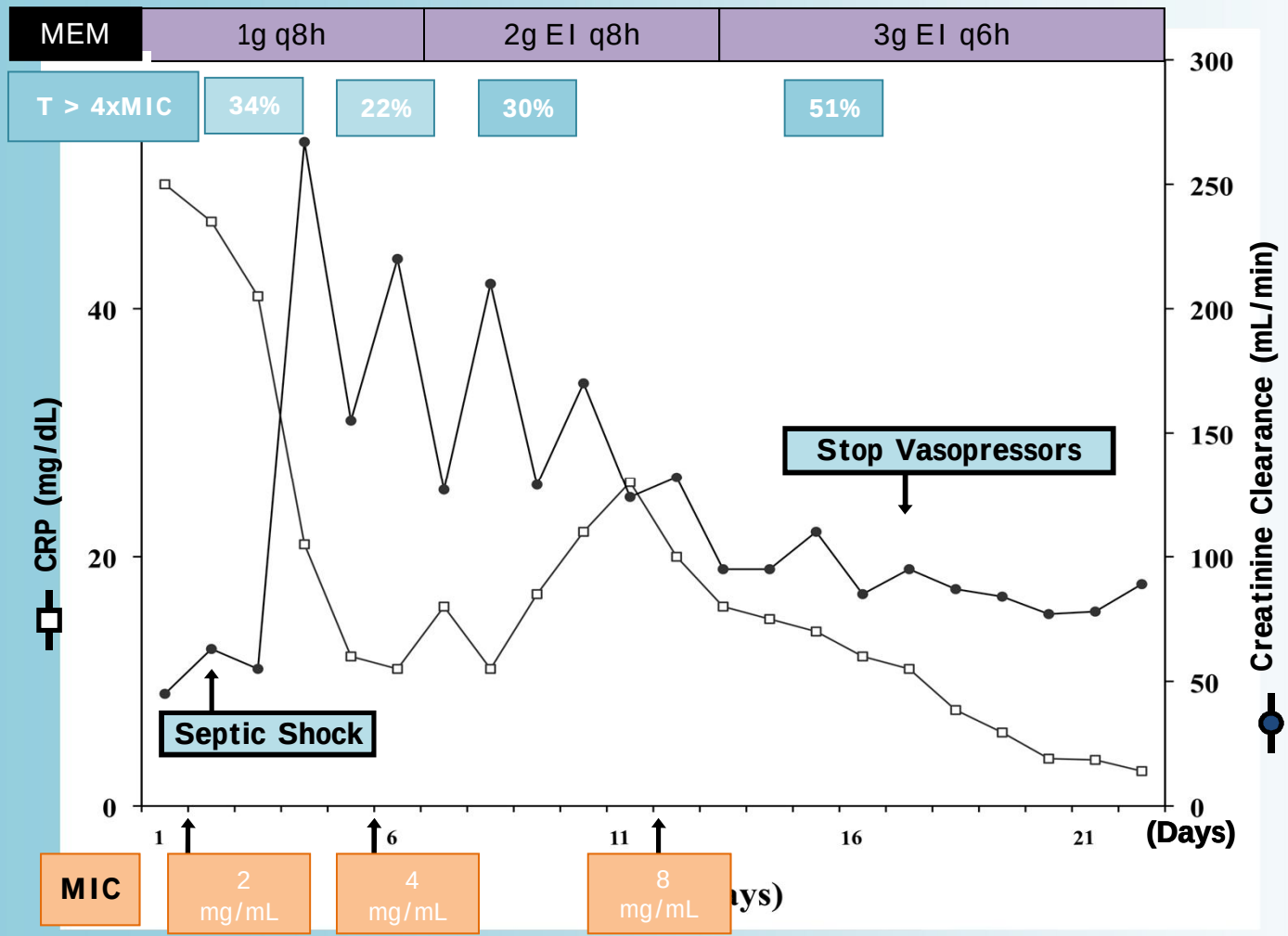
PI of β-lactam antibiotics will result in:



- More predictive PK profiles than with II
- Better chances of PK/PD target attainment

Theoretically TDM will increase our chance of best tailoring the treatment regimen to individual patient's needs

PI + TDM of Meropenem to treat an infection due to a multi-R strain of *P. aeruginosa*



Critically ill patient with ARC

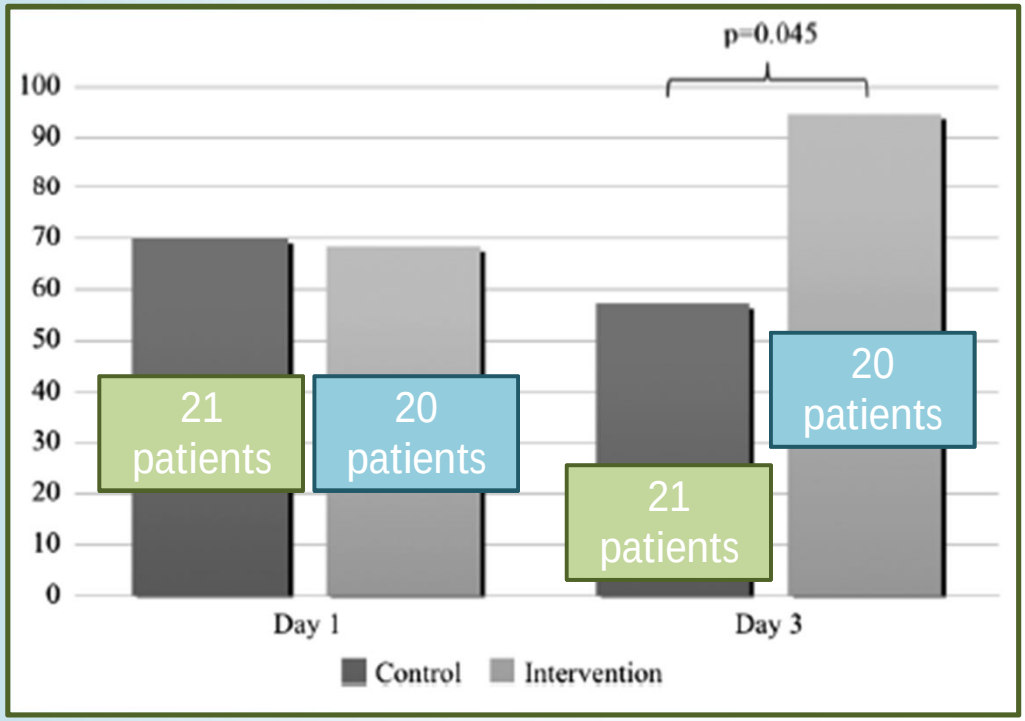
3g EI q6h of MEM

Taccone Antimicrob. Agents Chemother. 2012 56:2129

Jan J. De Waele
S. Carrette
M. Carlier
V. Stove
J. Boelens
G. Claeys
I. Leroux-Roels
E. Hoste
P. Depuydt
J. Decruyenaere
A. G. Verstraete

Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial

- Inclusion criteria: ICU patients needing TZP or MEM with a normal renal function
- CLCR:
  - Control group: 108 mL/min
  - Intervention group: 99 mL/min
- Doses were 33-100% higher than standard dosage regimens



Intensive Care Med (2014) 40: 380-87.

Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial

Fekade Bruck Sime[1,2*], Michael S. Roberts[1–3], Ing Soo Tiong[4,5], Julia H. Gardner[4], Sheila Lehman[4], Sandra L. Peake[6], Uwe Hahn[4], Morgyn S. Warner[5] and Jason A. Roberts[1,7–9]

- RCT in hematology patients with febrile neutropenia needing TZP
- 32 patients included
  - Controls: 16 pts
  - Intervention: 16 pts
- No differences in:
  - duration of fever
  - recovery from neutropenia

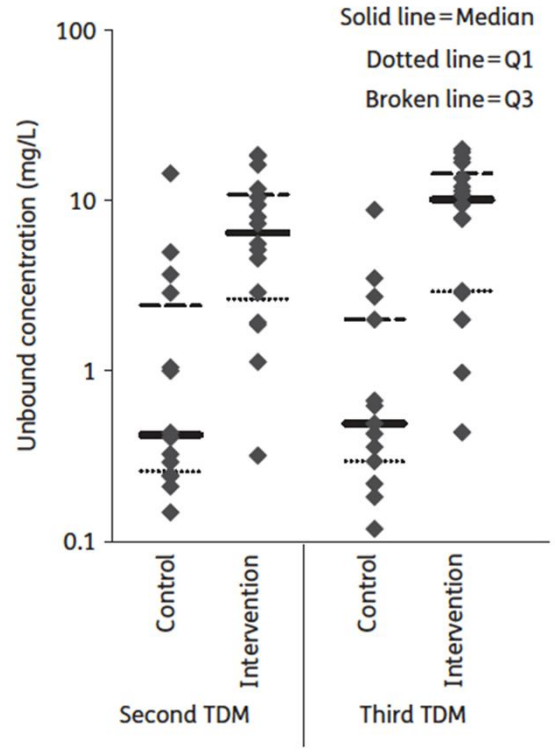


Figure 2. Comparison of unbound trough piperacillin concentrations between the study groups at the second and third TDM. Q1, first quartile; Q3, third quartile.

J Antimicrob Chemother (2015) 70: 2369-75.

In studies performed in the ICU, few RCTs have shown a benefit over mortality

Table 2 Some interventions that have not been shown to be useful in large multicenter trials targeting mortality.

- Tight blood glucose control
- Growth hormone
- Intraaortic balloon counterpulsation
- $ScvO_2$ monitoring
- Glutamine administration
- Blood transfusions
- Albumin solutions
- Steroids in septic shock
- Early parenteral nutrition
- NOS inhibitor in septic shock
- Hemoglobin solution in polytrauma
- HES solutions for fluid therapy
- Glutamine supplementation
- Beta-stimulants in ARDS
- Activated protein C in sepsis
- Bicarbonate in metabolic acidosis
- High-frequency ventilation in ARDS
- Antioxidant supplementation
- Craniectomy in severe brain injury
- Talactoferrin in sepsis
- Embolectomy in stroke
- Pulmonary artery catheter

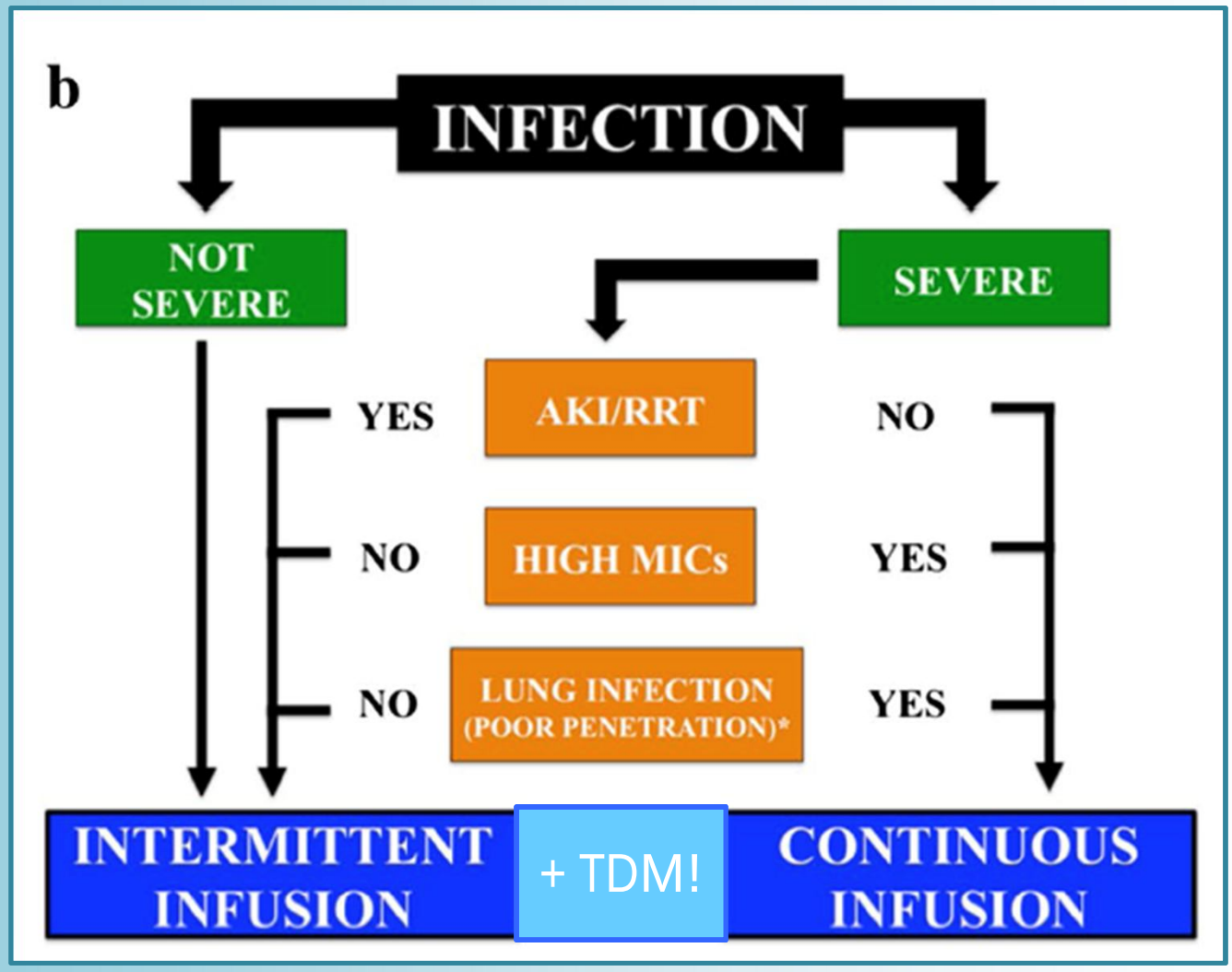
ARDS acute respiratory distress syndrome, *HES* hydroxyethyl starch, *NOS* nitric oxide synthase, $ScvO_2$ central venous oxygen saturation

- Benefits have been shown in sub-groups
- In favor of individualized, personalized therapy
- PI + TDM have their place in this setting!

Vincent JL et al. *Critical Care*. 2015; 19:S10

A ONE-SIZE FITS ALL APPROACH TO DOSING OF B-LACTAM ANTIBIOTICS IN A HETEROGENEOUS POPULATION WILL NOT BE SUCCESSFUL IN IMPROVING PATIENT OUTCOMES!

Algorithm for β-lactam dose optimization in critically ill patients



Taccone FS et al. Intensive Care Med. (2015) 42: 1604-06.

Thank you for your attention!

Case report on PI + TDM of β-lactam antibiotics

Critically ill patient with ARC

Table 1 of 1

Table I. Meropenem therapeutic drug monitoring and dosing regimen changes.

Day of treatment	Unbound meropenem trough concentration	Dosing regimen changes
1		Starting dose of 2 g 8-hourly
2		
3	3.2 mg/L	
4		
5		
6		
7	5 mg/L	
8		
9 10	12 mg/L	Changed to 2 g 6-hourly as extended infusions over 3 h

8 g MEM/day (3h extended infusions)

Cotta MO et al. 2015. J Infect Dis. 47(10): 739-42.

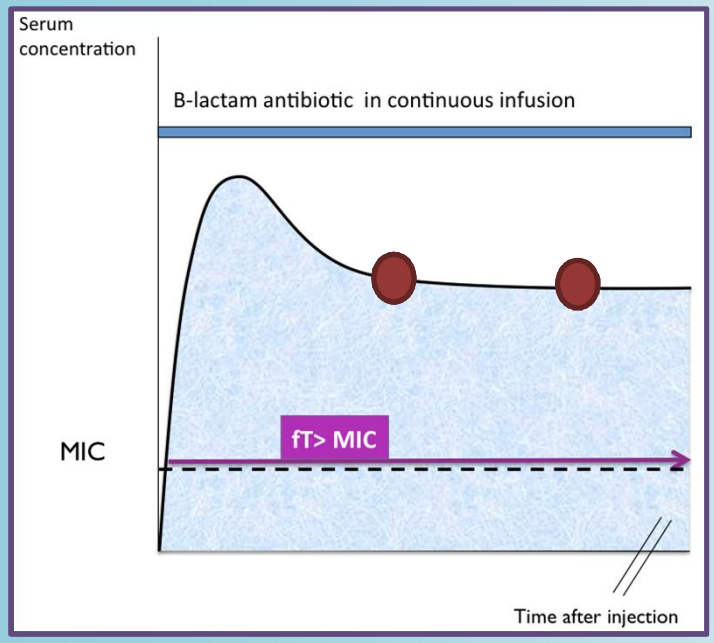
TDM is easier to perform if PI, than if II

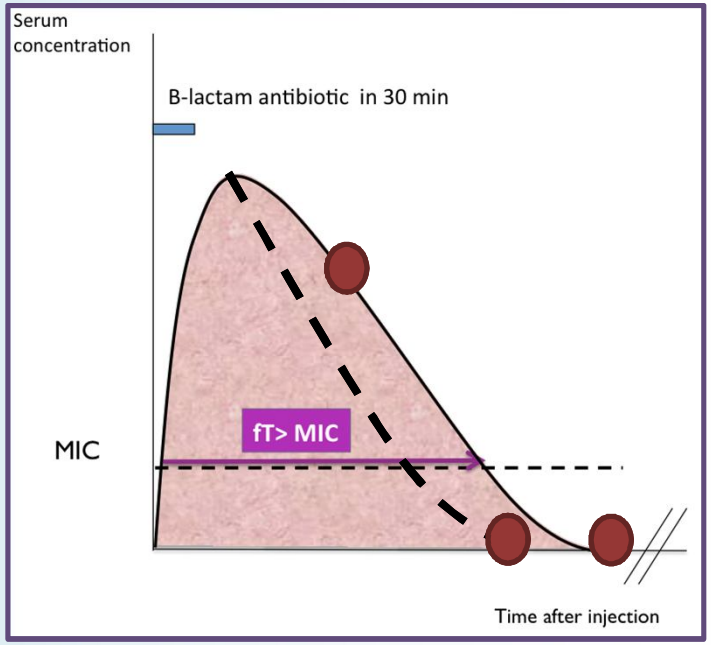
TDM + PI:

- Only 1 serum sample needed
- Serum sample can be taken at any time

TDM + II:

- ≥ 2 serum samples are most informative
- Serum sample must be taken at specific time points:
  - e.g. trough





The PK of β-lactam antibiotics in critically ill patients are different than in healthy volunteers

TDM is easier to perform if PI, than if II

TDM + PI:

- Only 1 serum sample needed
- Serum sample can be taken at any time

TDM + II:

- ≥ 2 serum samples are most informative
- Serum sample must be taken at specific time points:
  - e.g. trough