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EPASG ESCMID PK/PD OF ANTI-INFECTIVES STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

How to apply knowledge on PK/PD and TDM in clinical practice (interactive)

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UNIVERSITÉ DE GENÈVE

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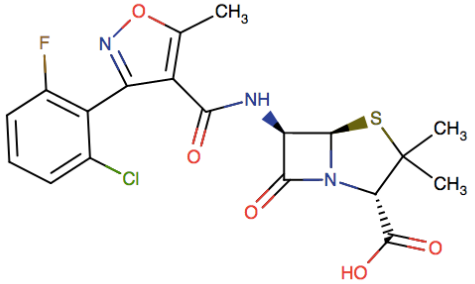
L'ESSENTIEL, C'EST VOUS.

Case 1: A man with MSSA vertebral osteomyelitis

- 72-year-old man with type 2 diabetes mellitus and prostate cancer
- Diagnosed with a methicillin-sensitive *Staphylococcus aureus* (MSSA) catheter infection
- The catheter is removed but he complains of lower back pain
- Imaging reveals a vertebral osteomyelitis; biopsy confirms MSSA (MIC = 1 mg/L)
- IV flucloxacillin 2g q4h (12g/d, maximal dose) is begun

Case 1: A man with MSSA vertebral osteomyelitis



- Flucloxacillin:
  - Half-life 0.75 – 1 hour
  - Volume of distribution 9.7 L
  - Protein binding 91-95%
  - Mostly hepatic metabolism

Case 1: A man with MSSA vertebral osteomyelitis

- After 48 hours, fever has abated & CRP is down
- Trough total flucloxacillin level = 182 mg/L
- You:
  A. Decrease the dose to 1g q4h (6g/d) and recheck levels in 48h
  B. Decrease the dose to 2g q6h (8g/d) and recheck levels in 48h
  C. Do nothing
  D. Check another level in 48h

Case 1: Answer

- Trough total flucloxacillin level = 182 mg/L
- You:
  A. Decrease the dose to 1g q4h (6g/d) and recheck levels in 48h
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  C. Do nothing
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Case 1: Discussion

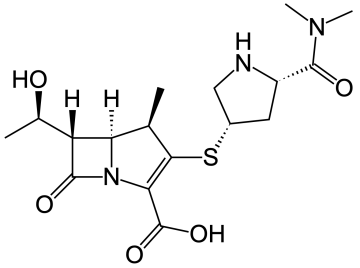
- Flucloxacillin is 95% protein bound so **total** levels will be high!
- Target levels of total fluclox have not been clearly defined
- First do no harm:
  - There are no signs of clinical toxicity
  - Lowering the dose may harm this patient (subtherapeutic dosing)
- Rechecking the level unlikely to change your management

- **Key points:**
  - **Know your antibiotic's PK profile**
  - **Know the way your TDM works (and know its limits!)**

Case 2: Sepsis after car accident

- 27-year-old man recently hospitalized abroad after a car accident with multiple fractures
- Previous growth of ESBL-producing *E. coli* in urine
- Presents with high fever, shivering and hypotension
- Suspected sepsis originating from postoperative skin/skeletal or urinary tract infection
- Started on IV meropenem 1g q8h

Case 2: Sepsis after car accident



- Meropenem:
  - Half-life c. 1 hour
  - Volume of distribution c. 0,3 L/kg
  - Protein binding c. 2 %
  - Mostly renal elimination (c. 70 %)

Case 2: Sepsis after car accident

- Which of the following conditions would have made you adjust initial dosing:
  A. Stable patient vs. critically ill admitted to the ICU
  B. Estimated CL_{creat} 50 vs. 150 mL/min
  C. Weight 80 vs. 160 kg

Case 2: Sepsis after car accident

- The patient is admitted to the ICU
- You decide to perform TDM at mid-dose (4 h) and before next dose (8 h) to ensure therapeutic drug concentrations

A. What concentrations do you aim for and why?

B. In case concentrations are suboptimal,

how would you adjust the dose regimen

(individual dose, interval, …)

Case 2: Discussion

Consider higher-than initial dosing and TDM especially in patients at

- high risk of subtherapeutic concentrations
- high risk of deterioration/mortality if treatment is failing
- high risk of pathogens with increased MICs

PK/PD targets discussed in other session

- In practice mid-dose interval (typically at 3-4 h) and trough values can be used to determine e.g. 50% T > 4 x MIC or 100% T > MIC

- **Key points:**
  - **Know for which patients TDM of beta-lactams is most needed**
  - **Make sure there are guidelines for sampling, PK/PD targets and dose adjustments**

Case 3: *Escherichia coli* pyelonephritis

- 54-year-old woman with hypertension and recurrent urinary tract infections
  - BMI 25 kg/m^2
  - Creatinine clearance 110 ml/min
- Admitted with fever, chills, nausea and left flank pain
  - Temperature 38.5 C, BP 142/86, HR 96, RR 22 (qSOFA=1)
- IV cefepime 2g q8h (maximal dose) is begun
- Urine and blood cultures positive for *E. coli* (MIC cefepime=0.125 mg/L; susceptible to quinolones & co-trimoxazole)
- Defervescence and decreased pain within 24 hours

Case 3: *Escherichia coli* pyelonephritis

- Your intern reminds you that cefepime can cause substantial neurotoxicity
  - He recently presented a paper at journal club on cefepime toxicity and TDM levels*
- You:
  A. Get a trough level of cefepime just before the next dose
  B. Switch to a continuous infusion of cefepime with a new level after 24 hours
  C. Discontinue cefepime and switch to IV ceftriaxone
  D. Watchful waiting, with planned switch to oral therapy in a few days if she continues to respond
  E. Decrease the dose of cefepime to 1g q8h

* Huwyler et al. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. *Clin Microbiol Infect* 2017; 23(7):454-459

Case 3: Answer

- You:
  A. Get a trough level of cefepime just before the next dose
  B. Switch to a continuous infusion of cefepime with a new level after 24 hours
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  D. Watchful waiting, with planned switch to oral therapy in a few days if she continues to respond
  E. Decrease the dose of cefepime to 1g q8h

Case 3: Discussion

- TDM is not necessarily needed here
  - This patient has a relatively “normal” PK profile
  - Cefepime achieves good concentrations in the urine
  - The organism has a low MIC
  - The dose could be decreased if you are worried about toxicity
    - The patient was never septic
  - Cefepime toxicity develops over time
    - Trough levels not necessary if used for only a few days

- **Key points:**
  - **In some populations/organisms/anatomic sites, TDM is not necessary**
  - **Know your drug, bug and host!**

Case 4: Post-neurosurgical meningitis

- 23-y old man with traumatic subarachnoid hemorrhage
- Ventricular drainage, kept sedated at neurointensive care unit
- After 6 days: high fever, increasing CRP >200
- CSF sample indicating bacterial meningitis
- Weight 80 kg, normal renal function
- The patient is started on IV vancomycin 1g q8h (loading dose 30 mg/kg=2.4 g), in combination with cefotaxime 3g q6h

Case 4: Post-neurosurgical meningitis

- Which of the following conditions would have made you adjust initial dosing:
  A. Stable patient vs. critically ill admitted to the ICU
  B. Estimated CL_{creat} 50 vs. 150 mL/min
  C. Weight 80 vs. 160 kg

Case 4: Post-neurosurgical meningitis

- S-vancomycin trough before 3rd dose is 7.3 mg/L (target 15-20 mg/L)
- Grampositive bacteria, probably staphylococci, detected in CSF
- How would you proceed; when do you ask for next concentration determination, and what is the new target level?

A. No change in dosing

B. Increase the individual doses (e.g. 1.5 q8h)

C. Reduce the dose interval (e.g. 1g q6h)

D. Shift to continuous infusion

E. Intraventricular administration

Case 4: Discussion

- Vancomycin PK/PD is AUC-driven (target $AUC_{0\text{-}24h}$/MIC > 400-600) with a narrow therapeutic spectrum
- Suitable targets for trough levels depend on administration mode and dose interval
- More advanced methods or repeated sampling required to assess AUC
- Continuous infusion has some practical benefits and could reduce the risk of toxicity, but AUC is typically lower compared to intermittent dosing

- **Key points:**
  - **Interpretation of TDM results more complicated for AUC-driven drugs**
  - **High blood concentrations does not necessarily mean high drug concentration at the site of infection, remember to consider tissue penetration and local/topical administration**

Case 5: Woman with suspected cholangitis

- 78-year-old, obese woman
- Nausea, vomiting and fever since 2 days
- Presents in the ER with hypotension, confusion, abdominal pain and tenderness in the right upper quadrant
- Abnormal liver function test consistent with cholangitis
- Started on IV piperacillin/tazobactam and gentamicin

Case 5: Woman with suspected cholangitis

- Weight: 120 kg
- Normal S-creatinine 1 month ago but now elevated with an estimated creatinine clearance of 21 ml/min

1) Would you adjust initial dosing of gentamicin?

A. No (standard dose is 7 mg/kg = 840 mg)

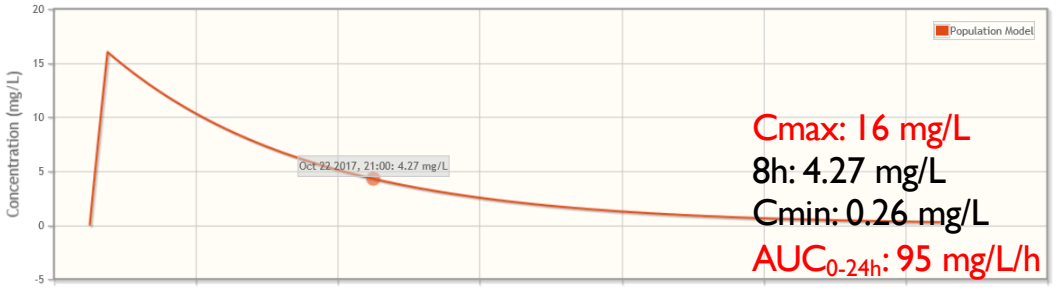
B. Yes, higher dose due to weight (how much?)

C. Yes, lower dose due to impaired renal function (how much?)

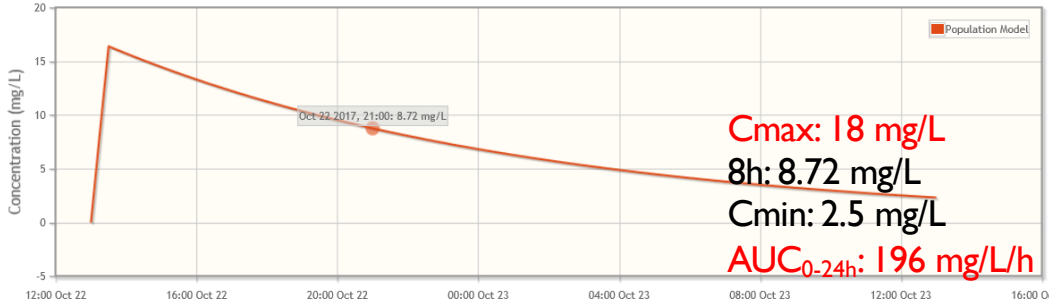
2) Would you use TDM, and if yes: at what time-point?

Case 5: Impact of renal function on patient PK

Normal renal function



Impaired renal function (Cl_{creat} 21mL/min)



Case 5: Discussion

- Cmax/MIC (> 8) and/or $AUC_{0\text{-}24h}$/MIC (> 50-100) determinants of clinical efficacy for aminoglycosides
- Adjusted body weight is used for initial dosing
- Standard initial dosing regardless of renal function for septic shock patients
- TDM at early (1-8 h) time-points can be used to ensure therapeutic levels
- TDM of trough levels routinely used to avoid oto- and nephrotoxicity

- **Key points:**
  - **Cmax/MIC and AUC/MIC important PK/PD parameters for Ags**
  - **Hit hard in critically ill patients, then use TDM (better deaf than dead!)**

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Thank you!

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