PHARMACOKINETICS AND PK/PD OF TEMOCILLIN IN NON-ICU URINARY TRACT INFECTION PATIENTS WITH VARIOUS STAGES OF RENAL INSUFFICIENCY

GERT-JAN WIJNANT (1), PERRIN NGOUGNI POKEM (1), MARIE COESSENS (2), ELEONORA COTTONE (2), LIEVEN GOEMAN (3), STEVEN VERVAEKE (2), FRANÇOISE VAN BAMBEKE (1)

1. Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2. Department of Laboratory Medicine, AZ Delta Hospital, Roeselare, Belgium
3. Department of Urology, AZ Delta Hospital, Roeselare, Belgium

CONTACT: GERT-JAN.WIJNANT@UCLOUVAIN.BE

INTRODUCTION

- **Temocillin** = older intravenous (IV) penicillin antibiotic (°1984), **Revived** as an alternative to carbapenems to treat (mostly) serious urinary tract infection (**UTI**) caused by **(ESBL) Enterobacterales**.
- Belgian Summary of Product Characteristics (**SPC**): **standard dose = 4g/day (2g q12h, IV)**. Higher dose = 6g/day (2g q8h, IV) for intensive care unit (ICU) patients, lower dose = 2g/day (1g q12h, IV) for patients with moderate renal insufficiency (RI).
- **Uncertainties** about **optimal dosing** ~ most PK/PD data from ICU patients.

OBJECTIVE

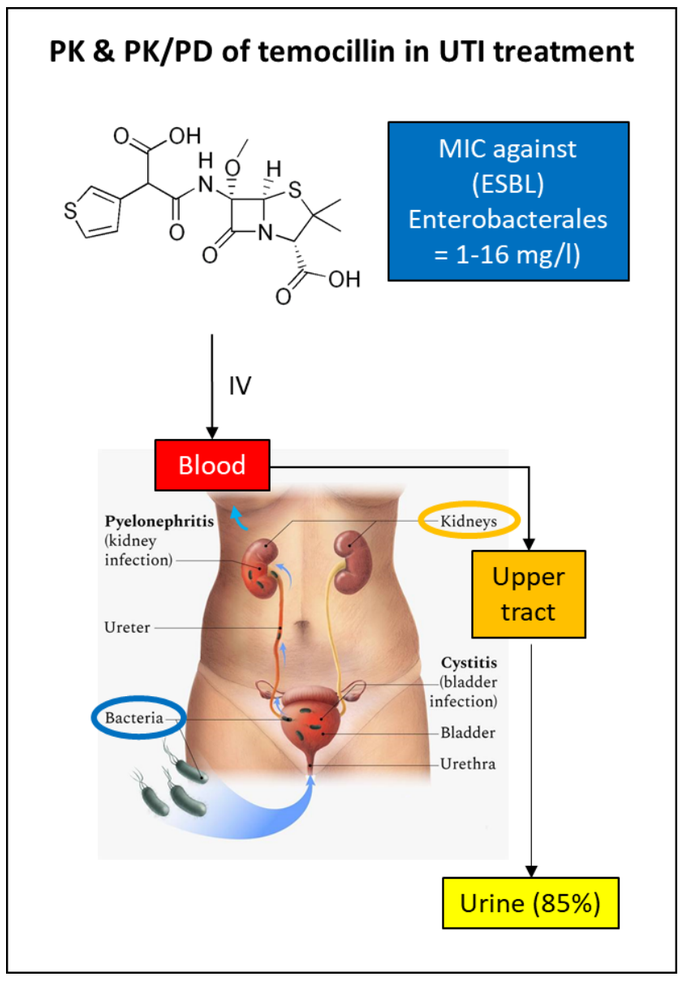
- To evaluate plasma PK and PK/PD of temocillin in non-ICU UTI patients with variable degrees of RI **to propose improved dosing strategies** in this population.

METHODS

- **20 non-ICU UTI patients** (12 ♂ 8 ♀, median age = 72 [35-91] years, median temocillin MIC = 8 [4-32] mg/l, concurrent bacteremia = 14/20) were included. These were retrospectively divided into **3 groups** based on renal function as measured by GFR: **no RI (n=4), mild RI (n=8) and moderate RI (n=8).**
- **All patients:** standard **4g/day** (2g q12h temocillin, IV infusion over 30 min) for a minimum of 4 days. After ≥ 3rd drug dose (SS), venous blood was collected at specific time points over 12 h.
- Total and unbound concentrations in plasma were measured via a validated LC-MS/MS method*.
- Non-compartmental analysis was performed in Pmetrics v1.9 and statistical analysis in Graphpad Prism v4.0. PK/PD-driver temocillin efficacy (time-dependent) = *f*T>MIC = % time that free drug concentrations (*f*) > minimum inhibitory concentration (MIC, EUCAST ECOFF = 16 mg/l) in between dosing intervals (12 hours).

RESULTS

- After 2g temocillin IV administration: patients with **mild and moderate RI** showed significantly decreased drug clearance (Cl, *f*Cl) and **increased plasma drug exposure** (AUC, *f*AUC) as compared to patients without RI.
- ***f*T>MIC** = **25%** (~ 3/12h), **34%** (~ 4/12h) **and 68%** (~ 8/12h) for **patients with no, mild and moderate RI**, **respectively** (figure 1).

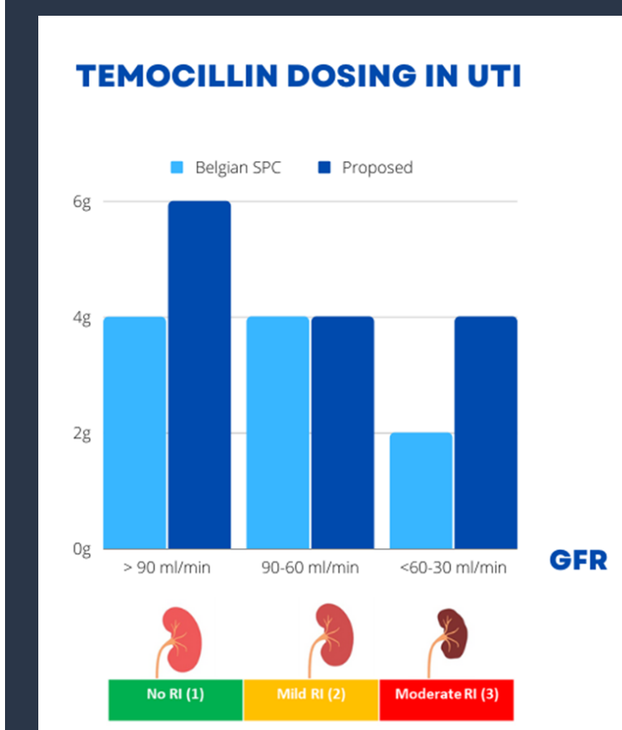


DISCUSSION

Common PK/PD target for penicillins in non-critically ill patients (> 35% *f*T>MIC):

- Patients with mild or moderate RI: 4g/day likely ok
- Patients with normal renal function: 4g/day likely too low. 6g/day: increase *f*T>MIC from 25% (3/12h) to 37.5% (3/8h)
  ~ 2020 EUCAST guidelines: "increased exposure" needed to cover MICs up to 16 mg/l.

These preliminary PK/PD data indicate that SPC doses for temocillin may need to be revised:



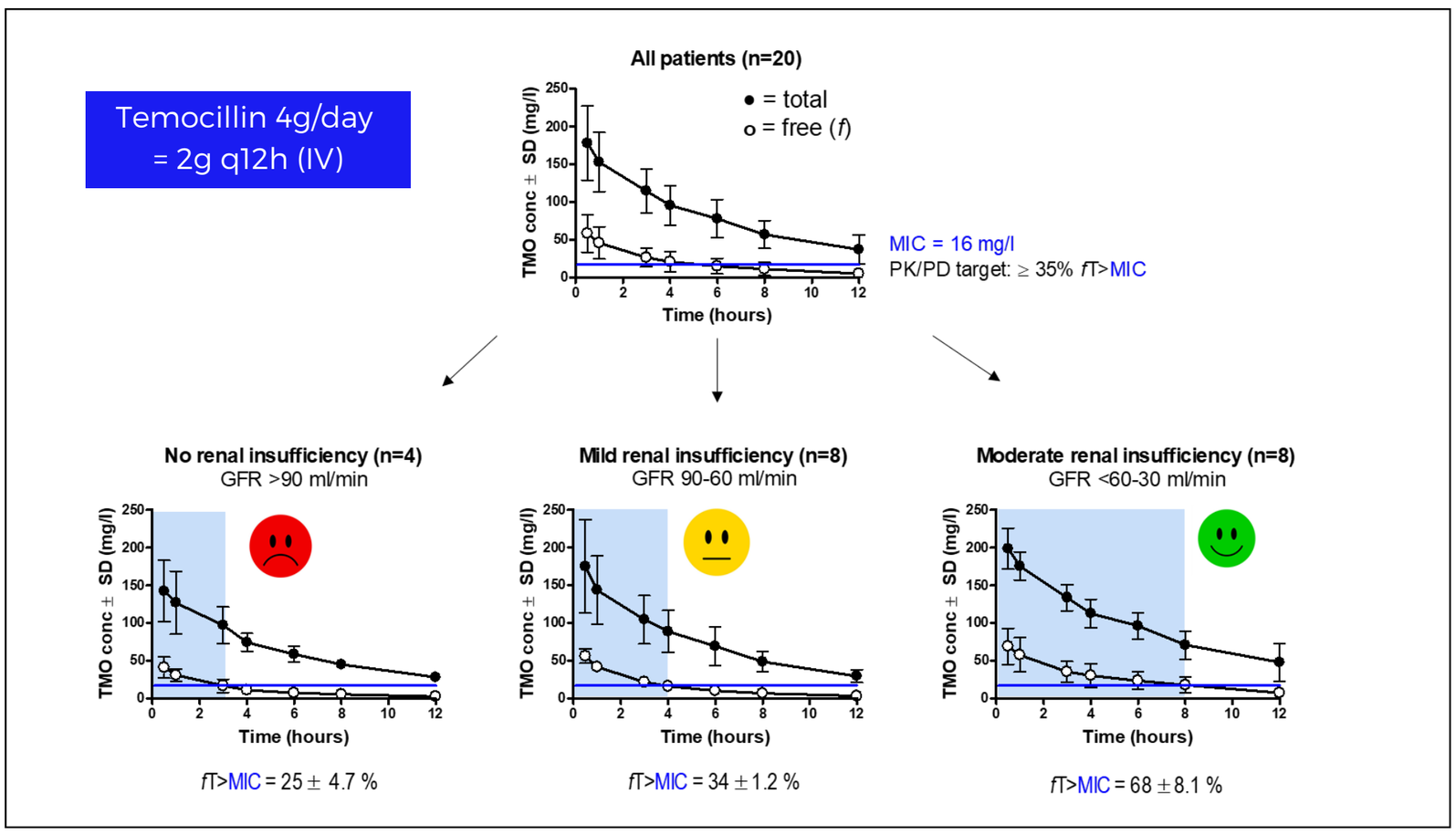


Figure 1: Plasma pharmacokinetics of temocillin after administration of 2g (IV) in non-intensive care unit (non-ICU) urinary tract infection (UTI) patients with no (n=4), mild (n=8), or moderate (n=8) renal insufficiency (RI). The horizontal blue line shows the target MIC (16 mg/l). The blue shaded areas on the graphs represent *f*T>MIC (value under graph: mean ± SEM).

* : Ngougni Pokem, P. et al. Validation of a HPLC-MS/MS assay for the determination of total and unbound concentration of temocillin in human serum. Clin Biochem 48, 542–545 (2015).