J Antimicrob Chemother 2024; **79**: 2204–2212
https://doi.org/10.1093/jac/dkae215 Advance Access publication 10 July 2024

Journal of Antimicrobial Chemotherapy

Pharmacokinetics and pharmacological target attainment of standard temocillin dosing in non-critically ill patients with complicated urinary tract infections

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Received 15 January 2024; accepted 9 June 2024

Objectives: Temocillin, a carbapenem-sparing β-lactam antibiotic, is commonly used at the standard 4 g/day dosage for treating complicated urinary tract infections (cUTIs). However, pharmacokinetic/pharmacodynamic (PK/PD) data supporting this regimen is limited. This study evaluated the plasma pharmacokinetics (PK) and PTA of temocillin in non-critically ill cUTI patients with varying degrees of renal insufficiency (RI).

Methods: In this single-centre clinical study, 22 cUTI patients received a fixed 4 g/day (2 g q12h, *intravenously*) temocillin dose, irrespective of renal function (no RI: $n=5$, mild RI: $n=8$, moderate RI: $n=9$). Plasma samples were collected post-dosing for LC-MS analysis of total and unbound temocillin levels. Monte Carlo simulations were performed based on the established PK/PD target of ≥35% fT > MIC (minimal inhibitory concentration).

Results: Among patients, the highest plasma drug exposure and PK/PD target attainment were observed in those with moderate RI (median $AUC_{0-12h}=1143$ h.mg/L and %fT > MIC = 68%), followed by mild RI patients (median $AUC_{0-12h}=918$ h.mg/L and %fT > MIC = 34%), and the lowest in those with healthy kidney function (median $AUC_{0-12h}=692$ h.mg/L and %fT > MIC = 26%). Simulations indicated that the 4 g/day temocillin dose achieves 90% PTA only for glomerular filtration rate < 60 mL/min and MIC ≤ 8 mg/L.

Conclusion: The standard temocillin dose may need to be increased from 4 to 6 g/day to treat non-critically ill cUTI patients, in line with recent EUCAST recommendations. For patients with moderate RI, who experience higher exposure due to reduced renal drug clearance, 4 g/day temocillin remains appropriate.

Introduction

Temocillin is a narrow-spectrum β-lactam antibiotic with an attractive pharmacological profile to treat complicated urinary tract infections (cUTIs) caused by Enterobacterales in this era of rising Gram-negative drug resistance.[1] The drug is chemically stable to various β-lactamases, including ESBL and AmpC enzymes, making it a possible alternative to last-resort carbapenem agents to treat infections caused by ESBL- and AmpC-producing Enterobacterales.[2,3] Due to its narrow spectrum of antimicrobial activity, temocillin also shows less disturbance of the intestinal microbiota than broad-spectrum third-generation cephalosporins, reducing the risk for the emergence of resistance and *Clostridioides difficile* colonization.[4,5] Finally, following intravenous (IV) administration, the drug is renally cleared and achieves high urinary concentrations, which could contribute to therapeutic efficacy in the context of cUTI.[6]

Like all β-lactam antibiotics, temocillin exerts time-dependent antibacterial activity, meaning that the pharmacokinetic/pharmacodynamic (PK/PD) index correlating to efficacy is the percentage of the time that unbound (free, f) drug concentrations remain above the MIC of the offending pathogen in between dose administrations (%fT > MIC).[6] However, the limited availability of PK/PD and clinical data has caused uncertainties and controversies about optimal dosing strategies.[7,8] A first concern is the standard dose. In countries such as Belgium and the UK, temocillin has been used for many years to successfully treat

non-critically ill cUTI patients at a standard dose of 4 g/day (2 g q12h, IV).[9–12] The high dose of 6 g/day (2 g q8h, IV) was historically reserved for critically ill patients, as per Summary of Product Characteristics (SmPC) instructions.[6] However, in 2020, EUCAST introduced previously non-existing breakpoints for specific Enterobacterales (*Escherichia coli*, *Klebsiella* spp. [except *Klebsiella aerogenes*] and *Proteus mirabilis*), classifying such isolates as 'I: susceptible, increased exposure' for MIC ≤ 16 mg/L and 'R: resistant' for MIC > 16 mg/L).[13–15] Under the new breakpoints, all patients with infections originating from the urinary tract require the 'high exposure' 6 g/day dose, except those with infections restricted to the urinary tract (i.e. cystitis) for whom 4 g/day suffices due to increased drug exposure in urine, close to the infection site. The conclusions of the 'Temocillin: rationale for the EUCAST clinical breakpoints' document[16] state that 6 g/day is required to cover the entire bacterial wild type (MIC 1–16 mg/L) and to obtain satisfactory target attainment rates for ≥35% $fT > MIC$ (a common PK/PD target for penicillins in non-critically ill patients).[6] However, these conclusions were largely based on the outcomes of 2 PK/PD studies performed in critically ill patients with nosocomial infections on the ICU,[17,18] as such data are not available for non-critically ill patients with cUTI. Considering critically ill patients show different pathologies, suffer from more severe illness and experience altered and more variable pharmacokinetics (PK) compared with non-critically ill patients,[19,20] it is debatable whether extrapolation of PK/PD outcomes across these patient populations is appropriate.[21,22] A second concern is temocillin dose adaptation based on renal function. Patients with renal insufficiency (RI) experience increased plasma drug exposure due to reduced renal drug clearance, which could potentially lead to drug-induced toxicity. The SmpC[6] therefore states to decrease the standard dose from 4 g/day (normal kidney function and mild RI) to 2 g/day (moderate RI) and 1 g/day (severe RI and end-stage renal disease, ESDR). However, these dose recommendations are largely based on outdated temocillin PK studies from the 1980s.[19–22]

In this study, we attempt to answer two questions central to the ongoing temocillin dosing debate. First, should the standard dose be increased from 4 g/day to 6 g/day to treat non-ICU cUTI patients, in line with the new EUCAST 'I' breakpoint? Second, how should the standard dose be reduced for patients with RI? To address these questions, we (i) conducted a PK study in non-ICU cUTI patients with variable degrees of RI receiving 4 g/day temocillin, (ii) constructed a population PK model and (iii) performed Monte Carlo simulations to evaluate the PTA for different dose, renal function and MIC scenarios.

Materials and methods

Study setting

Patients were recruited at the Urology Unit of the AZ Delta hospital (Roeselare, Belgium).

Ethics

The study received approval from the local ethics commission (no. B403201938914) and is registered on ClinicalTrial.gov (NCT03557840) per current Good Clinical Practice guidelines and the Declaration of Helsinki. It included only patients having given their informed consent.

Study design

This prospective, single-centre, open-label, non-randomized clinical trial characterized the plasma PK of temocillin in hospitalized, non-ICU patients with cUTI. Patients for whom temocillin was deemed the best treatment option by the attending physician received the drug for at least 4 days and provided informed consent were included in the study. The drug was administrated at a dose of 2 g every 12 h (4 g/day) via IV 30 min intermittent infusion for all patients regardless of renal function (local treatment guidelines). Patients with penicillin or general β-lactam allergy or oversensitivity, age <18 years, participation in another study in the previous 30 days or refusal to provide informed consent were excluded from the study.

Study population

Adult patients who required hospital admission for suspected or confirmed cUTI were included in the study. Within the context of this study, we defined cUTI as 'any infection of, or originating from, the urinary tract that required administration to the Urology ward, but not to the Intensive Care Unit'. Under this definition, patients with any type of cUTI (e.g. cystitis, pyelonephritis, prostatitis, urosepsis), with or without concurrent bloodstream infection, were included. Patients with septic shock resulting from urosepsis were excluded, as this would require ICU admission. Kidney function was estimated based on the Glomerular Filtration Rate (GFR) value calculated via the Chronic Kidney Disease Epidemiology formula and expressed in 'mL/min per 1.73 m^2 of Body Surface Area units'; the GFR units are abbreviated in the text as 'mL/min' for brevity. We retrospectively divided all patients ($n = 22$) into three different stages of RI: no RI (GFR ≥ 90 mL/min, $n = 5$), mild RI (GFR < 90–60 mL/min, $n = 8$) and moderate RI (GFR < 60–30, $n = 9$). No patients with severe RI (GFR < 30 mL/min) or patients with ESRD (GFR < 15 mL/min and requiring dialysis) were included, as these did not present at the Urology ward during the study.

Materials

Temocillin (Negaban®, Eumedica SA, Brussels, Belgium) was prepared in the hospital pharmacy as per the instructions in the SmPC. Ticarcillin disodium was obtained from Sigma–Aldrich Inc. (St. Louis, MO, USA). HPLC/MS-grade methanol and acetonitrile were purchased from J.T. Baker (Deventer, the Netherlands). Formic acid was obtained from Merck KGaA (Darmstadt, Germany). Ultrapure water was obtained from MEDICA-R 7/15 water purification system (Veolia Water Systems, Bucks, UK) and Milli-Q Academic apparatus (Millipore Corporation, Billerica, MA, USA). Human plasma was obtained from healthy volunteers, in agreement with local ethics guidelines.

Blood sampling and plasma isolation

After drug administration (≥4th drug dose, to allow for steady-state conditions) blood was collected via a venous catheter in EDTA-coated tubes at specific time points: 0.5, 1, 3, 4, 6, 8 and 12 h. Blood samples were centrifuged and plasma was isolated and aliquoted (AZ Delta). These samples were stored at −80°C before analysis of temocillin content (UCLouvain).

Temocillin extraction and quantification

Total and unbound temocillin concentrations in plasma were determined via a previously validated LC-MS/MS method.[23] Unbound temocillin was isolated through ultrafiltration of plasma samples using an Amicon® Ultra-15 device (NMWL 30 K; Merck-Millipore, Merck KGaA, Darmstadt, Germany). Calibration lines ranging from 1 to 500 mg/L temocillin and three quality control samples were prepared by spiking blank plasma or ultrafiltrate samples for total and unbound drug, respectively. Temocillin was extracted from patient, calibrator and quality control samples using methanol at a 3:1 ratio. Ticarcillin was added as an internal standard. The LC-MS/MS method used a phenyl column in gradient mode, identified temocillin and ticarcillin in positive electrospray mode using ion transition 415.34 > 339.1 and

Table 1. Demographic, medical and microbiological data for patients enrolled in the study ($n=22$). Study subjects are non-intensive care unit (non-ICU) UTI patients with no ($n=5$), mild ($n=8$) or moderate ($n=9$) RI. All values represent the median and (range)

	Group					
Characteristic	1. No RI (GFR ≥ 90 mL/min)		2. Mild RI (GFR < 90–60 mL/min)		3. Moderate RI (GFR < 60–30 mL/min)	
Patient number per group	5		8		9	
Demography						
Gender (male/female)	3/2		4/4		4/5	
GFR (mL/min)	≥90	(NA)	74	(65–89)	49	(34–58)
Age (years)	51	(35–72)	74	(57–90)	78	(65–91)
Weight (kg)	79.6	(63–93)	74.3	(57–95)	84.3	(52.7–127)
BMI (kg/m^2)	26.8	(23.1–31.9)	26.5	(23.0–31.1)	30.8	(21.1–45.0)
Biochemistry						
Plasma protein (g/L)	68.8	(60.6–78.3)	62.2	(54.6–70.3)	61.0	(52.7–73.1)
Plasma albumin (g/L)	38.7	(32.5–50.6)	33.5	(23.9–39.1)	29.1	(26.2–38)
CRP (mg/L)	76.5	(30.9–118)	109.3	(0.9–385)	94.9	(26.2–328.4)
Microbiology						
UTI	5/5		8/8		9/9	
Urosepsis	1/5		3/8		6/9	
Temocillin MIC (mg/L)	8	(≥4–8)	8	(≥4–32)	8	(≥4– < 32)
Causal organism						
E. coli	2/5		4/8		5/9	
Klebsiella pneumoniae	1/5		1/8		1/9	
Enterobacter cloacae					1/9	
Staphylococcus epidermidis[a]	1/5					
Candida glabrata[a]			1/8			
Enterococcus faecalis[a]					1/9	
No pathogen identified	1/5		2/8		1/9	

[a]Causal pathogen against which temocillin is not active (i.e. Gram-positive bacteria, fungi): no MIC value determined.
NA, not applicable.

385.31 > 160.3, respectively, and had a lower limit of quantification of 1 mg/L. All measured total and free drug concentrations were >1 mg/L. These PK data were then used to build a PK model that was used for Monte Carlo simulations to assess the %fT > MIC for different MICs.

Temocillin %fT > MIC calculation

Temocillin %*f*T > MIC for each patient was calculated based on the individual drug concentration-over-time curves as follows: time that the unbound drug concentrations remain above the target MIC = 16 mg/L (× hours) divided by the duration of the dosing interval (12 h for the 2 g q12h dose)×100%.

Pharmacokinetic modelling and simulations

The population PK model was developed using NONMEM® (version 7.5.0, ICON plc, Dublin, Ireland). One and two compartment models were evaluated to describe plasma PK. Constant and saturable protein binding models were tested to include the unbound concentrations. Covariate model selection was guided by physiological plausibility and graphical inspection of individual PK parameter versus covariate plots. Model selection for nested models was guided using the likelihood ratio test (alpha = 0.05, df = 1, dOFV = 3.84) and the Akaike Information Criterion for non-nested models (lower value indicates better model fit). Goodness-of-fit plots, visual predictive checks and bootstrap analyses were performed for model evaluation. Parameter uncertainty was assessed using the log-likelihood profiling based sampling importance resampling (LLP-SIR) approach.[24]

Using the final population PK model, we computed the (i) % *f*T > MIC (acceptable value = 35%) and (ii) PTA for the *f*T > MIC = 35% target (acceptable value = 90%) for different temocillin doses (1–8 g/day), MICs (0.5–64 mg/L) and GFRs (1–120 mL/min) for 1000 virtual patients. The chosen temocillin PK/PD target (≥35% *f*T > MIC) corresponds to the threshold required for penicillins to achieve a bacteriostatic effect in animal infection models. This target is relatively conservative compared with other and more clinically validated targets for β-lactam antibiotics in non-critically ill patients (i.e. ≥40%–70% *f*T > MIC). We justify this decision by the fact that EUCAST has previously used the same PK/PD target to set temocillin clinical breakpoints, facilitating the comparison of the results.[16]

Microbiological identification and antimicrobial susceptibility testing

Clinical isolates from cUTI patients were typed using a MALDI Biotyper® and the MIC for temocillin was determined by BD Phoenix AP™, as part of standard procedures of the Laboratory Medicine unit of AZ Delta. Temocillin-resistant strains (MIC > 16 mg/L, EUCAST R breakpoint) were retested using the Biomérieux Etest®.

Results

Patient characteristics

Twenty-two cUTI patients ($n=22$) were admitted to the Urology ward of the hospital and enrolled in the study. Overall, the

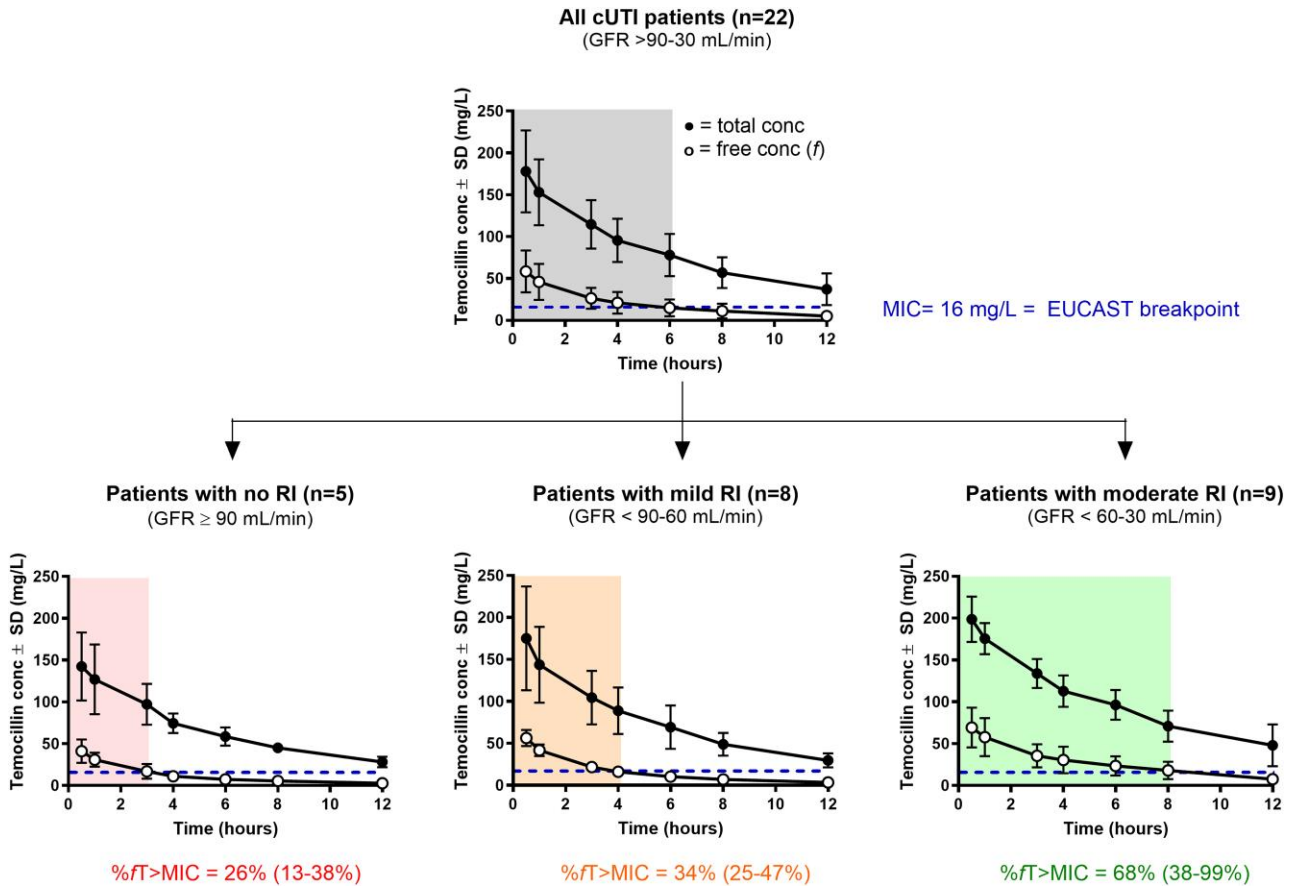

Figure 1. Total and unbound plasma pharmacokinetics of temocillin after administration of 2 g (IV) in non-intensive care unit (non-ICU) urinary tract infection (UTI) patients with no ($n=5$), mild ($n=8$) or moderate ($n=9$) RI. Concentration values are shown as mean ± SD. The horizontal broken line represents a plasma concentration value of 16 mg/L, which is the current EUCAST MIC susceptibility breakpoint for temocillin against *Enterobacterales*. %*f*T > MIC values are shown as median (min–max range). The colored area corresponds to the portion of the dosing interval during which free concentrations remains above a MIC of 16 mg/L. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

majority of patients were elderly (median age = 72; min–max range 35–91 years), overweight (median BMI = 26.6; min–max range 21.1–45.0 kg/m^2) and presented with systemic inflammation (median CRP = 96.0; min–max range 0.9–385 mg/L). Patients presented with variable degrees of RI (median GFR = 70; min–max range 34– ≥ 90 mL/min). To assess the impact of renal function on temocillin PK, patients were retrospectively divided into three groups: group 1 (GFR ≥ 90 mL/min, no RI, $n=5$), group 2 (GFR = < 90–60 mL/min, mild RI, $n=8$) and group 3 (GFR < 60–30 mL/min, moderate RI, $n=9$). Demographic, medical and microbiological parameters for the 3 groups are presented in Table 1. The characteristics and details on temocillin treatment for individual patients are shown in Table S1 (available as Supplementary data at *JAC* Online).

Plasma pharmacokinetics of temocillin

Following administration of 2 g temocillin (via 30 min intermittent infusion), plasma concentration-over-time profiles were determined and are shown in Figure 1. Key PK parameters were calculated and are listed in Table 2. Temocillin plasma protein-binding (%PPB) was high (mean ± SD: 78 ± 12%), seemed saturable at high drug concentrations and was only weakly correlated to plasma albumin levels (Figure S1). A clear trend was observed where patients with lower renal function (GFR) showed decreased drug clearance (Cl), extended half-lives ($T_{1/2}$) and increased plasma drug concentrations (C_{max}, C_{min}) and overall exposure (AUC). The patient population as a whole ($n=22$) appeared to achieve ≥35% *f*T > MIC for the target MIC value of 16 mg/L (median *f*T > MIC = 50%), yet interpatient %*f*T > MIC variability was very high (min–max range = 13%–99%). Stratification of the PK data based on patient renal function showed that the median %*f*T > MIC (range) was 26% (13%–38%), 34% (25%–47%) and 68% (38%–99%) for patients with no, mild and moderate RI, respectively.

Population PK model building and validation

We then constructed a population PK model to describe temocillin plasma concentration-over-time profiles. A one-compartmental model that included the impact of GFR on CL (dOFV = –8.153) and non-linear temocillin protein-binding to describe unbound temocillin concentrations was found to best describe the patient data. Pharmacokinetic model building and evaluation are described in full detail in Results S1.

Table 2. Pharmacokinetic (PK) parameters of temocillin after administration of 2 g (IV) in non-intensive care unit (non-ICU) UTI patients with no ($n=5$), mild ($n=8$) or moderate ($n=9$) RI. All values represent median and ranges, which were estimated with NONMEM®

		Group		
PK parameter		1. No RI (GFR ≥ 90 mL/min)	2. Mild RI (GFR < 90–60 mL/min)	3. Moderate RI (GFR < 60–30 mL/min)
Total drug	AUC_{0-12h} (h.mg/L)	692 (537–946)	918 (512–1373)	1143 (666–1502)
	C_{max} (mg/L)	139.5 (93.6–192.72)	176 (86.2–286.5)	187.4 (128.5–240.5)
	C_{min} (mg/L)	33.3 (20.7–56.3)	26.7 (11.4–45.6)	36.0 (19.9–90.6)
	Cl (L/h)	2.89 (2.11–3.72)	2.18 (1.46–3.91)	1.75 (1.33–3.00)
	Vd (L)	15.6 (12.0–22.6)	13.8 (9.7–26.6)	14.0 (10.5–18.8)
	$t_{1/2}$ (h)	3.94 (2.65–5.19)	4.48 (3.28–5.06)	4.88 (4.17–9.76)
Unbound drug	$fAUC_{0-12h}$ (h.mg/L)	109 (68–176)	174 (82–269)	250 (151–588)
	fC_{max} (mg/L)	43.9 (20.3–50.2)	46.7 (15.6–105.1)	57.2 (39.2–113.5)
	fC_{min} (mg/L)	4.0 (0.5–5.1)	3.1 (0.9–5.7)	4.7 (2.5–12.0)
	*f*Cl (L/h)	18.4 (11.4–29.4)	11.5 (7.4–24.3)	8.0 (3.4–13.2)
	*f*Vd (L)	51.1 (41.9–90.4)	51.0 (21.5–137.3)	41.0 (20.4–61.3)
	$fT_{1/2}$ (h)	2.29 (1.42–3.11)	2.81 (1.67–3.91)	3.21 (2.39–5.19)

PK/PD analysis

Finally, we performed Monte Carlo simulations using the temocillin pop-PK model to explore PK/PD target attainment for different dose, MIC and GFR scenarios.

Figure 2 shows the temocillin %*f*T > MIC (median and 95% CI; target: ≥35% *f*T > MIC) for the 4 g/day and the 6 g/day dose, with the aim to determine the most appropriate standard dose. For GFR > 60 mL/min (i.e. patients with no or mild RI that should receive the standard dose), the 4 g/day temocillin dose does not result in sufficient exposure to cover the entire bacterial wild type for MIC = 1–16 mg/L. In contrast, the 6 g/day dose can achieve sufficient exposure for MIC up to 8 mg/L based on the lower 95%CI bound, and up to 16 mg/L based on the median value. Figure S2 shows %*f*T > MIC outcomes for all temocillin dose simulations.

Figure 3 shows the temocillin PTA (median; target: 90%PTA for 35% *f*T > MIC) in function of MIC, exploring doses from 1 to 8 g/day to propose optimized regimens based on renal function (GFR). For patients with normal renal function (GFR = 90 mL/min) or mild RI (GFR = 60 mL/min), the 6 g/day dose achieves 90% PTA for MICs up to 8 mg/L, but not for 16 mg/L (8 g/day is required for this). For patients with moderate RI (GFR = 30 mL/min), the 4 g/day achieves 90% PTA for MICs up to 8 mg/L, but not for 16 mg/L (6 g/day is required for this). For patients with severe RI (GFR = 10 mL/min), the 2 g/day achieves 90% PTA for MICs up to 8 mg/L, but not for 16 mg/L (4 g/day is required for this). The vast majority of clinical isolates in our study (~ 80%) had MIC values in the 1–8 mg/L range (grey vertical bars), in line with the EUCAST MIC distribution for the bacterial wild type (white vertical bars). Table S2 provides an overview with all median PTA values, indicating the lowest dose that can achieve 90% PTA for a given GFR and MIC value. Figure S3 shows the PTA outcomes for all temocillin dose simulations including 95% CIs.

Discussion

This study is the first to evaluate the plasma PK and PK/PD of the standard temocillin dose (4 g/day, 2 g q12h) in non-critically ill cUTI patients. Our findings suggest that (i) the standard dose should be increased from 4 to 6 g/day (2 g q8h) for patients with no or mild RI, in line with recent EUCAST recommendations, and (ii) the 4 g/day dose is appropriate for patients with moderate RI.

First, regarding the standard dose, we found that temocillin plasma PK in our non-critically ill cUTI patients was overall much more comparable to that of critically ill patients, rather than to that of healthy volunteers (Figure S4). For patients with no RI and mild RI, we found *f*Cmax values of 43.9 and 46.7 mg/L and $fCmin_{12h}$ values of 4.0 and 3.1 mg/L, respectively. These concentrations are close, but slightly lower, than those reported by reported in critically ill patients by De Jongh[17] (4 g/day: *f*Cmax = 50.3 mg/L, $fCmin_{12h}$ = ~ 5 mg/L) and Laterre[18] (6 g/day: *f*Cmax = 64 mg/L and $fCmin_{8h}$ = 16 mg/L). However, the values we obtained for key PK parameters, including Vd (~ 14 L), half-life ($T_{1/2}$ ~ 4.4 h) and protein binding (%PPB ~ 78%), were near-identical to those calculated by De Jongh. This finding was relatively unexpected, as temocillin is a highly protein-bound, hydrophilic drug[25] and critically ill patients often show hypoalbuminemia (decreasing %PPB) and capillary leak (increasing Vd).[26] The comparable PK profiles may be explained by the fact that some of our patients, although not on the ICU, were still severely ill (SOFA-scores up to 3), suffered from low plasma albumin levels (<35 g/L) or showed systemic inflammation (CRP values > 300 mg/L) (Table 1 and Table S1). The outcomes of our PK/PD simulations were also similar to those reported earlier for critically ill patients. Based on the lower 95% CI bound for the computed %*f*T > MIC values (Figure 2), a dose of 4 g/day achieves sufficient exposure to cover MICs up to 8 mg/L (i.e. De Jongh[17]), but 6 g/day is needed for MIC = 16 mg/L (i.e. Laterre[18]) for the 'typical' patient in our population (median GFR = 70 mg/L). However, to obtain 90% PTA for the 35% *f*T > MIC target for MIC = 16 mg/L, an off-label dose as high as 8 g/day would be required (Figure 3). A more clinically feasible alternative to 8 g/day via intermittent infusion might be the administration of 4–6 g/day via continuous infusion, as this approach has been shown to achieve stable unbound plasma concentrations > 16 mg/L for

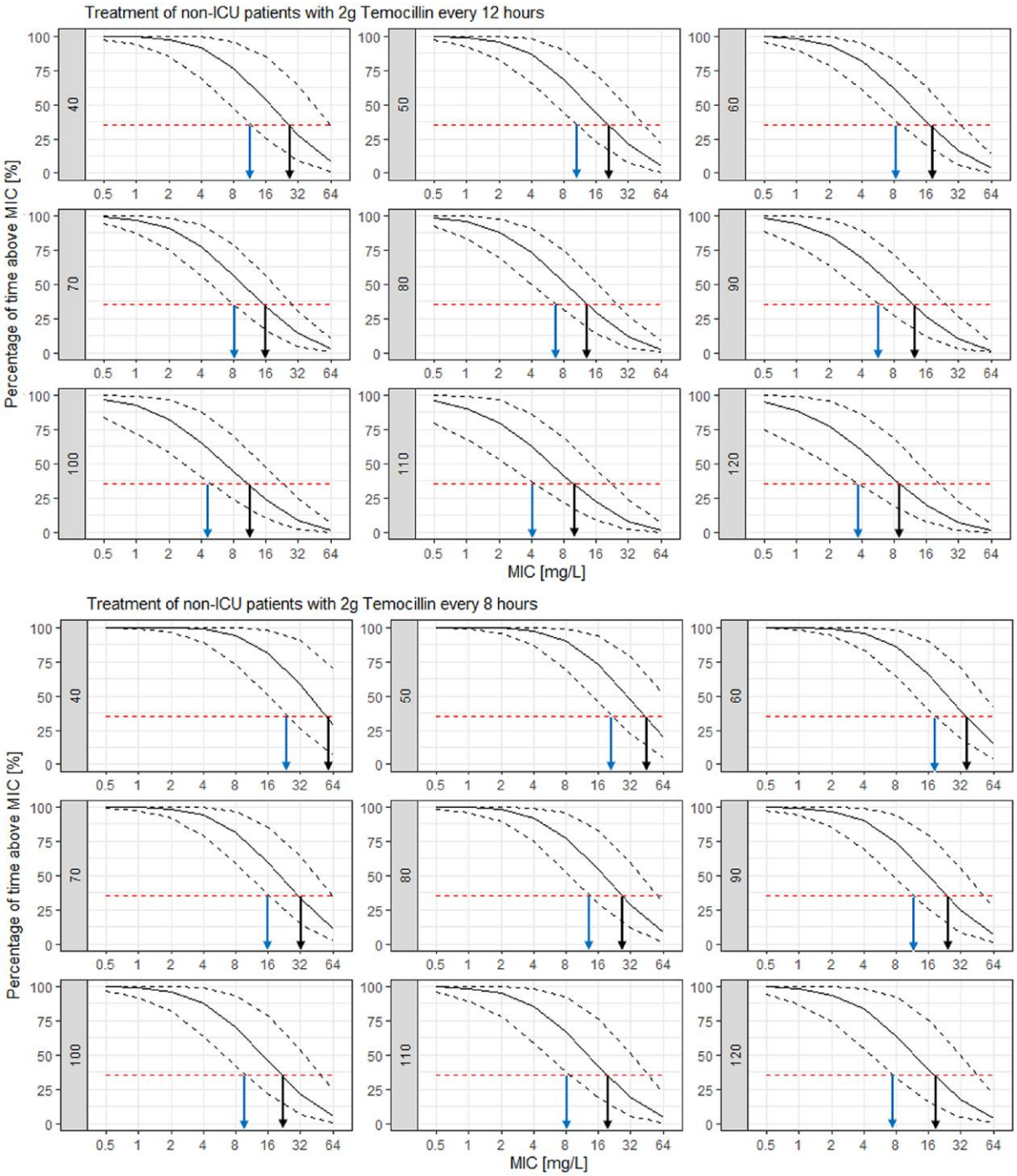

Figure 2. Temocillin %*f*T > MIC outcomes based on Monte Carlo simulations (solid line = median, dotted lines 95% confidence interval, CI) for the standard 4 g/day (top panel) and high 6 g/day dose (bottom panel) for different renal functions (grey boxes: GFR value for the range 40–120 mL/min). The model is based on the PK data from 22 non-critically ill cUTI patients treated with 4 g/day temocillin. The *x*-axis shows the MIC range used for the simulation and the *y*-axis the percentage of the time during which unbound plasma drug concentrations remain above the corresponding MIC (%*f*T > MIC). The horizontal line represents the target value of 35% *f*T > MIC (i.e. the PK/PD target EUCAST previously used to set breakpoints and associated doses based on critically ill patient PK data[16]). The highest MIC at which the %*f*T > MIC can obtain the target value is shown by vertical arrows (left arrow: lower 95% CI bound; right arrow: median). The data show that for GFR ≥ 60 mL/min (i.e. the standard dose population with no/mild RI), the 4 g/day temocillin dose results in sufficient exposure to cover MICs up to 4–8 mg/L based on the lower 95% CI and MICs up to 8–16 mg/L based on the median %*f*T > MIC. In contrast, the 6 g/day dose results in sufficient exposure to cover MICs up to 8–16 mg/L based on the lower 95% CI and MICs up to 16–32 mg/L based on the median %*f*T > MIC. This indicates that the temocillin 4 g/day standard dose fails to cover the entire bacterial wild type (MIC = 1–16 mg/L) and higher doses might be needed for PK/PD target attainment. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

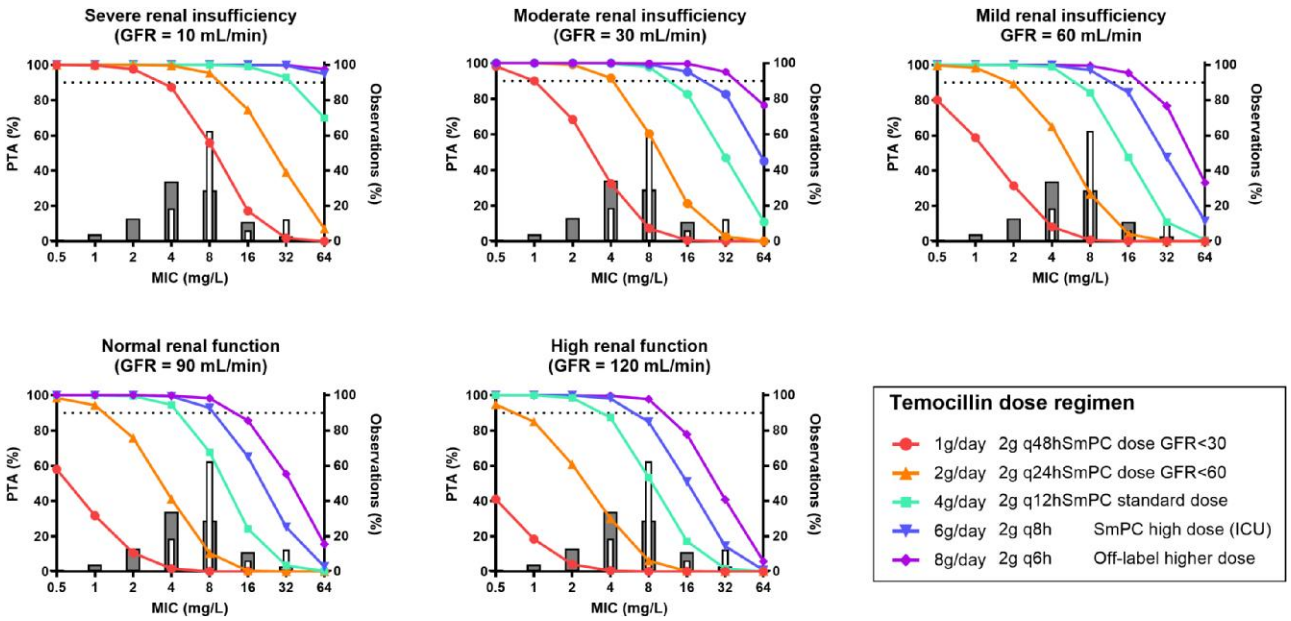

Figure 3. Probability of target attainment (%PTA) in function of minimal inhibitory concentration (MIC) for different hypothetical temocillin doses (1–8 g/day). Dose simulation results are shown for 1000 hypothetical patients with various degrees of RI based on GFR. The horizontal dotted line represents the 90% PTA for the PK/PD target of 35% %*f*T > MIC. The vertical bars show the EUCAST MIC wild-type distribution for *Enterobacterales* (grey bars) and the MIC values for the clinical isolates in this study (white bars). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

prolonged durations.[18] However, the clinical outcomes do not support the need for such high doses. All of our patients who suffered from confirmed Enterobacterial infections ($n=18/22$) were successfully cured with 4 g/day temocillin, albeit often in combination with other antibiotics (Table S1). This was remarkable, considering almost all patients with normal renal function were clearly underdosed (i.e. *f*T > MIC < 35%) and that some individuals were infected with pathogens resistant to temocillin (i.e. MIC >16 mg/L). Overall, temocillin shows surprisingly high efficacy in cUTI despite its suboptimal PK/PD profile, in particular for higher MICs. Increased drug exposure in the urinary tract, the primary site of infection, might contribute to these favourable outcomes. However, as plasma concentrations are much lower, urine levels alone fail to fully explain the high efficacy in our cUTI patients with concurrent bloodstream infections and urosepsis ($n=10/22$ in our population).

Second, regarding dose adaption in patients with RI, we confirm the clear and profound impact of renal function on temocillin PK. Indeed, compared to our patients with healthy kidney function (GFR ≥ 90 mL/min), those with moderate RI (GFR 60–30 mL/min) showed extended half-lives ($T_{1/2}=3.9$ versus 4.9 h) and double the plasma exposure for both total (AUC = 692 versus 1143 mg.h/L) and unbound drug (*f*AUC = 109 versus 250 mg.h/L). Boelaert *et al.* previously reported an extension of $T_{1/2}$ up to 10 h and 3-fold higher AUC values in RI patients,[19,20] but these studies also included individuals with kidney failure. We showed that the 4 g/day dose resulted in 68% *f*T > 16 mg/L in patients with moderate RI (Figure 1) and that 98% and 83% PTA were obtained for MIC = 8 and 16 mg/L, respectively, for GFR = 30 mL/min (Figure 3). No signs of toxicity were reported in our patients with moderate RI treated with 4 g/day temocillin, even though this is double the current 2 g/day SmPC-recommended dose (which showed unacceptably low PTA in our dose simulations). Thus, 4 g/day temocillin might be a safe dose to attain PK/PD targets associated with improved clinical outcomes in cUTI patients with moderate RI. Because a significant portion of patients seeking cUTI treatment in the hospital comprises elderly individuals with moderately decreased kidney function (i.e. almost half of our study population, $n=9/22$), the standard temocillin dose may remain relevant in many clinical scenarios. Finally, our dose simulations indicate that 2 g/day temocillin, rather than the 1 g/day SmpC dose, would be required to reach PK/PD targets in patients with severe RI. However, as we did not enroll severe RI patients in the current study, these results should be interpreted cautiously (extrapolation). In Table 3, we provide an overview of our new temocillin dose recommendations, based on a pragmatic approach considering both PK/PD and efficacy data.

Our study suffers from several limitations, which also present opportunities for future research. First, the sample size was relatively small ($n=22$), particularly for patients with normal kidney function ($n=5$). However, our results advocate for a dose increase from 4 to 6 g/day for any patient with GFR > 60 mL/min ($n=13$). Moreover, those with healthy renal function would likely benefit most from this dose escalation because they suffer from the lowest drug exposure. Second, we only measured temocillin concentrations in plasma and not in urine, which may have helped to understand infection site PK/PD in cUTI. Third, we only had access to renal function estimates based on GFR and not creatinine clearance (CrCL), the parameter mentioned in the SmpC to adapt dosing based on renal function. We therefore did not evaluate whether GFR or CrCL performed best as a covariate in our population PK model. Moreover, the model lacks external validation with independent clinical datasets, although this is a common limitation in small-scale PK studies, including previous

Table 3. Overview of the proposed temocillin dose adaptation scheme for non-critically ill cUTI patients based on renal function. We suggest increasing temocillin doses used in routine clinical care, as our study results indicate that the current SmPC doses fail to reach the conventional PK/PD target for β-lactams in non-critically ill patients (≥ 35% *f*T > MIC)

Degree of RI			SmPC dose (Belgium)		Dose to achieve 90% PTA for MIC = 4 mg/L		Dose to achieve 90% PTA for MIC = 8 mg/L		Dose to achieve 90% PTA for MIC = 16 mg/L		Proposed doses	
no	Severity	GFR (mL/min)	Daily	Regimen	Daily	Regimen	Daily	Regimen	Daily	Regimen	Daily	Regimen
1	None	>90	4g	2 g q12h	6g	2 g q8h	8g	2 g q6h	>8g	—	6g	2 g q8h
2	Mild	60–89	4g	2 g q12h	4g	2 g q12h	6g	2 g q8h	>8g	—	6g	2 g q8h
3	Moderate	30–59	2g	1 g q12h	4g	2 g q12h	4g	2 g q12h	>8g	—	4g	2 g q12h
4	Severe	<30	1g	1 g q24h	2g	1 g q12h	4g	2 g q12h	>8g	—	2g	2 g q24h
5	End-stage	<15	1g	1 g q24h 2 g q48h 3 g q48h	2g	2 g q24h	2g	2 g q24h	8g	2 g q6h	2g	2 g q24h

temocillin PK studies.[18,27] Fourth, we could not establish a direct link between temocillin exposure/dose and clinical outcomes, because we only evaluated a single dose (4 g/day) and the frequent co-administration of other antibiotics alongside temocillin biases the interpretation of efficacy results. Finally, clinical validation of the proposed temocillin dosing adaptation scheme is needed in terms of pharmacological target attainment, safety and clinical outcomes. This work is currently underway in the TEMORENAL study (EudraCT number: 2021-005741-32).

To conclude, our study indicates that the standard temocillin dose may need to be increased from 4 to 6 g/day to treat non-critically ill cUTI patients with no or mild RI. This is in line with recent EUCAST recommendations. For patients with moderate RI, who experience higher exposure due to reduced renal drug clearance, 4 g/day temocillin remains appropriate.

Acknowledgements

This work was presented in part at the 32nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in Lisbon in April 2022.

Funding

This study was carried out as part of our routine work and did not receive specific funding.

Transparency declarations

G.-J.W. is supported by a BElgian WAllonia REsearcher (BEWARE) postdoctoral fellowship between the Université catholique de Louvain and Eumedica Pharmaceuticals, the registration holder of temocillin (no 2010067). The company was not involved in the design, execution, analysis or interpretation of this study and its findings. P.N.P. was an employee of the *Université catholique de Louvain*. M.C., E.C., L.G. and S.V. are employees of AZ Delta. F.V.B. is Research Director of the Fonds de la Recherche Scientifique (F.R.S.-FNRS). All other authors: none to declare.

Supplementary data

Figures S1 to S4 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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Pharmacokinetics and pharmacological target attainment of standard temocillin dosing in non-critically ill patients with complicated urinary tract infections

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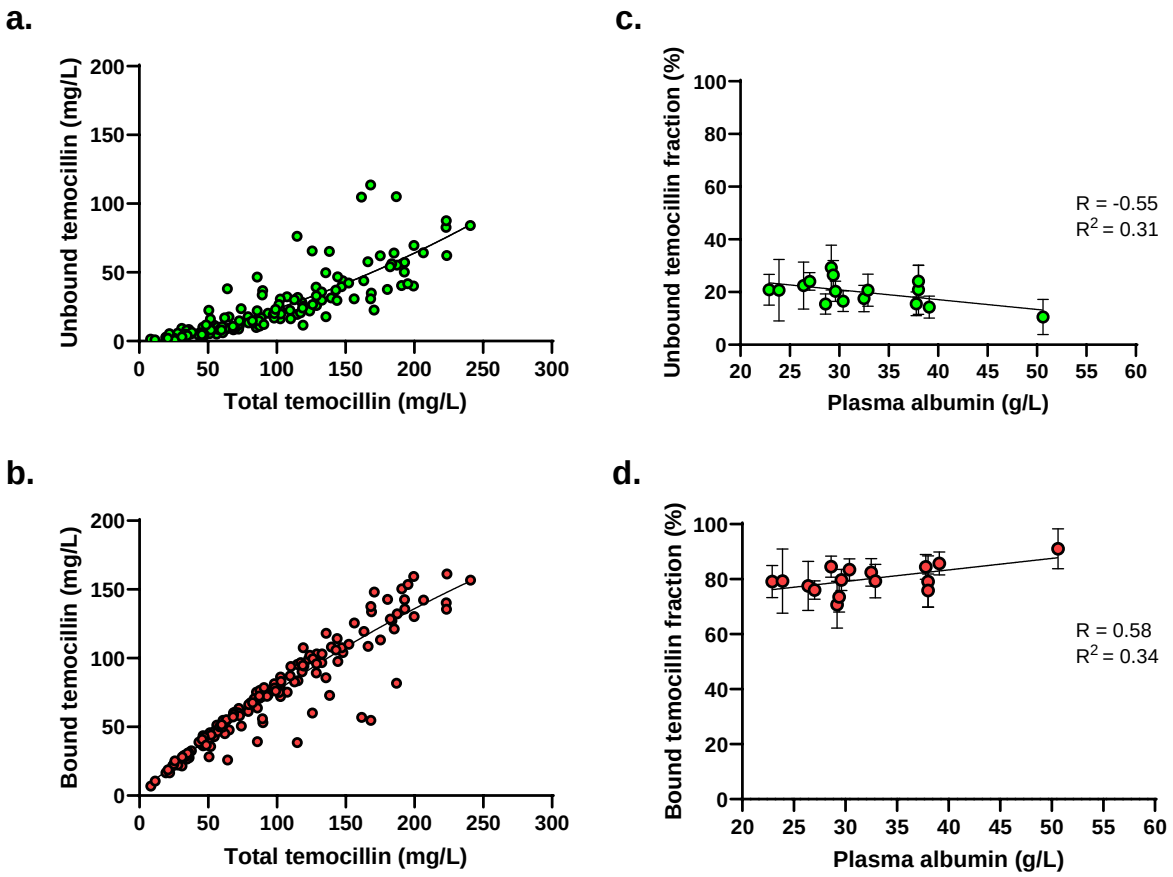
Supplementary material

Table S1. Characteristics and temocillin treatment details for the individual patients enrolled in this study (n=22). All patients were non-critically ill, presented with cUTI and received temocillin at 4g/day (2g q12h, IV). SOFA-score: Sequential Organ Failure Assessment score. CCI: Charlson Comorbidity Index. TURP: Transurethral resection of the prostate. (-): no causative pathogen identified and MIC value unavailable. ND: not determined. NA: data not available.

Grp	n°	SOFA-score	CCI	UTI type specification	Causal organism	Temocillin MIC (mg/L)	GFR (mL/min)	%fT>MIC for target MIC = 16 mg/L	Temocillin therapy duration (days)	Total therapy duration (days)	Other antimicrobial agents used before/during/after temocillin therapy	Clinical cure
1	1	0	0	pyelonephritis	*S. epidermidis*	ND	≥ 90	32%	3	7	During temocillin: switch to vancomycin (*S. epidermidis* infection)	No
	2	0	9	pyelonephritis	*E. coli*	8	≥ 90	38%	14	14	None	Yes
	3	0	1	urosepsis, pyelonephritis	*K. pneumoniae*	≤ 4	≥ 90	21%	4	14	After temocillin: oral ciprofloxacin	Yes
	4	0	0	pyelonephritis	*E. coli*	8	≥ 90	13%	3	13	After temocillin: oral ciprofloxacin	Yes
	5	0	7	suprapubic catheter-associated	-	-	≥ 90	25%	8	8	None	Yes
2	6	0	6	prostatitis	*C. glabrata*	ND	70	25%	10	21	Before temocillin: flucloxacillin + ciprofloxacin for 5 days. During temocillin: single dose amikacin.	No
	7	0	4	recurrent UTI	*K. pneumoniae*	≤ 4	65	38%	17	17	Before temocillin: poly-antibiotic use (recurring UTI)	Yes
	8	0	7	urosepsis	*E. coli*	32	73	33%	3	3	During temocillin: empirical fosfomycin on day 1	Yes
	9	0	5	urosepsis	*E. coli*	8	83	33%	10	11	During temocillin: empirical ceftriaxone on day 1	Yes
	10	0	0	prostatitis	*E. coli*	8	89	34%	3	21	After temocillin: oral ciprofloxacin	Yes
	11	2	8	ureteral stenting-associated	-	-	69	36%	3	8	After temocillin co-trimethoprim + vancomycin	Yes
	12	0	4	fever after TURP*	-	-	86	47%	6	16	After temocillin: oral ciprofloxacin	Yes
	13	0	5	urosepsis	*E. coli*	8	74	33%	7	7	Before temocillin: flucloxacillin. During temocillin: ciprofloxacin on day 1	Yes
3	14	0	6	urosepsis	*E. coli*	>32	58	73%	5	6	During temocillin: empirical amoxicillin-clavulanic acid on day 1	Yes
	15	3	9	urosepsis, prostatitis	*E. coli*	8	55	46%	3	14	After temocillin: oral ciprofloxacin	Yes
	16	2	6	urosepsis	*E. cloacae*	8	34	38%	3	14	During temocillin: clindamycin	Yes

											(concurrent skin infection). After temocillin: oral ciprofloxacin + clindamycin	
	17	1	11	unspecified	*K. pneumoniae + E. faecalis*	8 (*K. pneumoniae*)	49	99%	8	8	None	Yes
	18	1	4	urosepsis	-	-	40	58%	3	3	After temocillin: oral ciprofloxacin	Yes
	19	1	5	urosepsis	*E. coli*	16	40	46%	4	10	After temocillin: oral amoxicillin-clavulanic acid	Yes
	20	0	4	unspecified	*E. coli + S. agalactiae*	8 (*E. coli*)	56	89%	6	6	None	Yes
	21	0	4	NA	*E. coli*	≤ 4	38	96%	NA	NA	NA	Yes
	22	0	4	urosepsis	*E. cloacae*	8	56	66%	4	9	After temocillin: oral ciprofloxacin	Yes

Figure S1. Temocillin protein binding in plasma of non-critically ill cUTI patients. Figures a and b show, respectively, the unbound and the protein-bound temocillin concentrations plotted versus total temocillin concentrations. Data is obtained from all temocillin concentrations from all patients (n=22). The results indicate saturable protein binding of temocillin at higher plasma drug concentrations. Figure c and d show, respectively, the unbound, free fraction (%FF) and the protein-bound temocillin faction (%PPB) versus plasma albumin levels. Data is shown for patients for whom plasma albumin levels were available (n=16). %FF was calculated as free plasma concentrations/total plasma concentrations x100% and shown as mean ± SD for each patient (based on individual concentration-over-time profiles, 7 time points). %PPB was calculated as 100% - %FF. The results show a reverse correlation between %FF and plasma albumin levels, although the correlation was considered weak based on the Pearson correlation coefficient (R^2 = 0.31). Overall temocillin protein binding in plasma in our overall patient population (n=22) was high and relatively variable (mean ± SD = 78 ± 12%).



Results S1: Pharmacokinetic model building and evaluation.

S1.1. Overview

The pharmacokinetic model-building process was performed with NONMEM® (version 7.5.0, ICON plc, Dublin, Ireland) using first-order conditional estimation with interaction. Model selection for nested models was guided using the likelihood ratio test (alpha=0.05, df=1, dOFV=3.84) and the Akaike Information criterion (AIC) for non-nested models (lower value indicates better model fit). For the structural model, a one- and two-compartment approach with a combined additive and proportional error model was tested. A one-compartment model was chosen which provided a lower AIC compared to the two compartment model (dAIC= −0.624). Three approaches were investigated to model the free concentrations using molar concentrations:

(i) a constant free fraction (fu) of the total plasma concentration, or

(ii) a non-linear protein binding model:

$$C_{total} = C_{free} + \frac{N_P \cdot C_P \cdot C_{free}}{K_D + C_{free}} \quad (1)$$

rearranged for C_{free}:

$$C_{free} = 0.5 \cdot \left((C_{total} - B_{max} - K_D) + \sqrt{((C_{total} - B_{max} - K_D)^2 + 4 \cdot K_D \cdot C_{total})}\right) \quad (2)$$

with C_{total} representing the total temocillin plasma concentration, B_{max} representing the maximum concentration of the bound drug, and K_D representing the dissociation constant of the ceftriaxone-protein complex, modelled with molar concentrations.

(iii) a non-linear protein binding model assessing protein concentrations as covariate

$$C_{free} = 0.5 \cdot \left((C_{total} - N_P \cdot C_P - K_D) + \sqrt{((C_{total} - N_P \cdot C_P - K_D)^2 + 4 \cdot K_D \cdot C_{total})}\right) \quad (3)$$

With N_P representing the number of binding sites per plasma protein, C_P representing the concentration of the plasma protein (here: albumin)

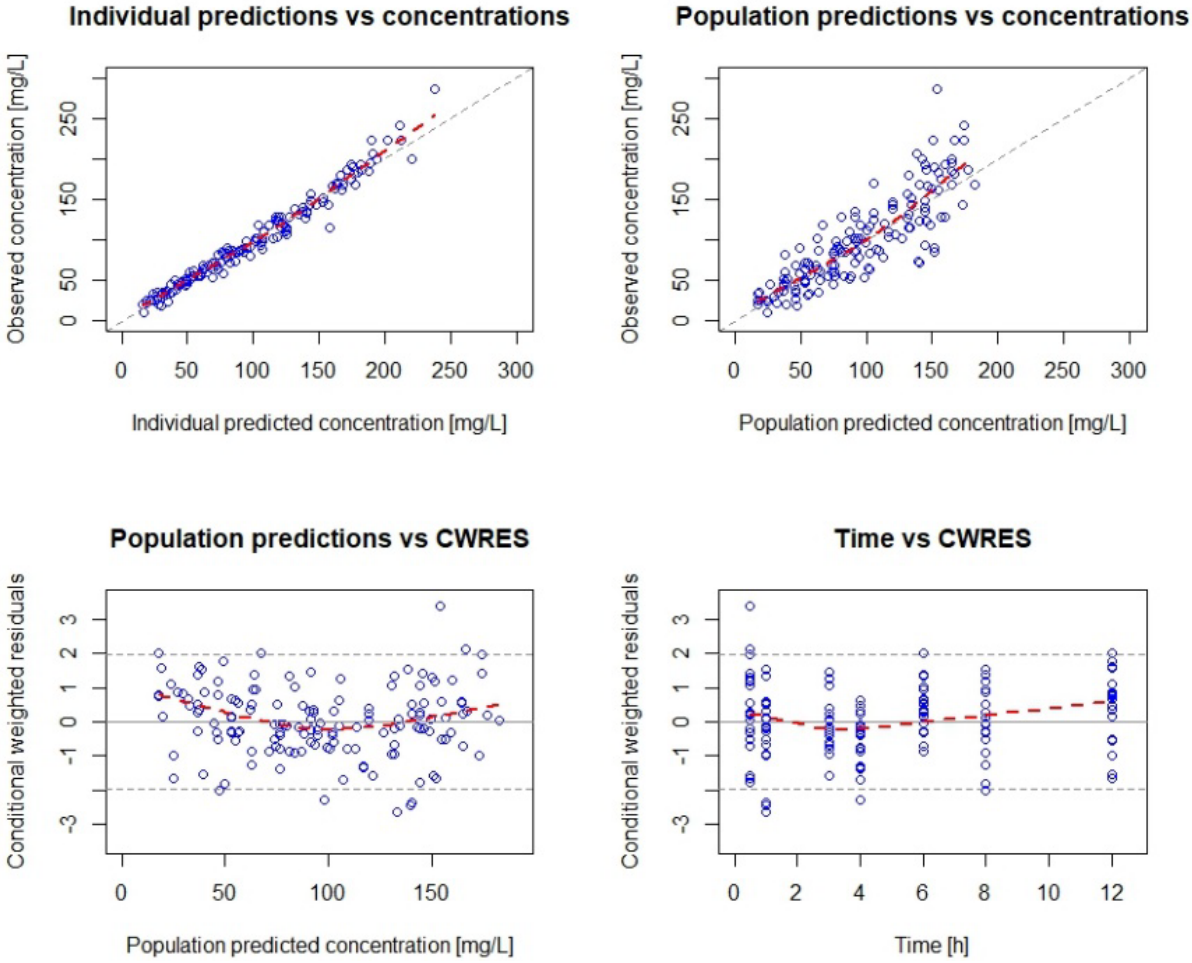
Model (ii) was superior over model (i) (dAIC: −126.1) and model (iii) was inferior to model (ii) (dAIC: +238.9).

Interindividual variability assuming lognormal distribution was found significant for clearance, volume of distribution, N_P and K_D.

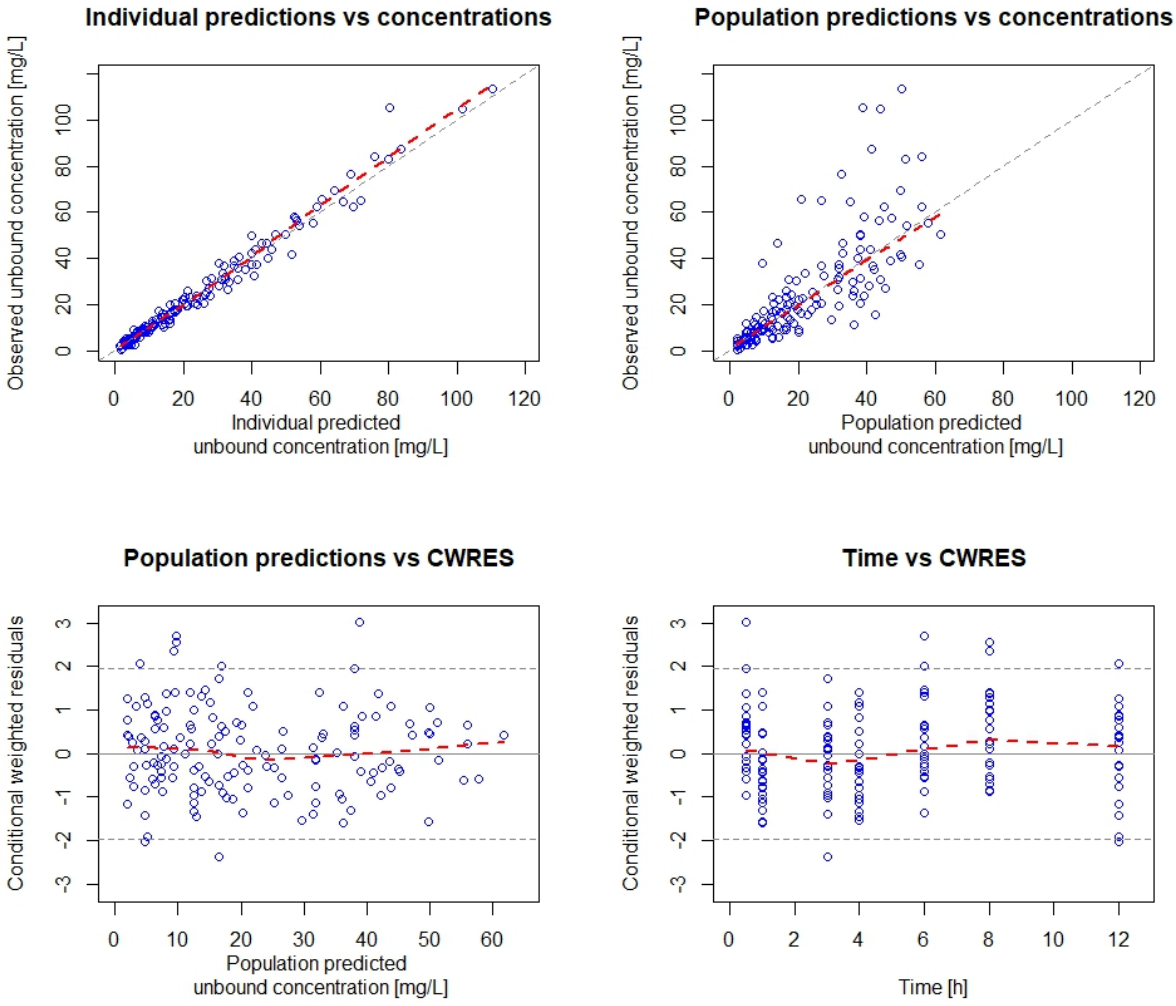
Covariates were evaluated based on physiological plausibility and graphical exploration of empirical Bayesian estimates of both individual clearance and volume of distribution plotted against the following covariates (age, height, sex, total protein, albumin and C-reactive protein plasma concentrations). Based on this preselection, glomerular filtration rate was tested as a covariate on clearance and body weight was tested on volume of distribution. While inclusion of the effect of GFR on clearance significantly improved the model (dOFV= −8.153), body weight on the volume of distribution was not found significant (dOFV: +0.002). Goodness-of-fit plots and visual predictive checks indicated a good predictive performance of the model. Parameter uncertainty was determined using the log-likelihood profiling-based sampling-importance resampling procedure. Broeker *et al.* [1] showed that the LLP-SIR seems to be the most accurate

method to estimate parameter uncertainty in small datasets, hence we decided to use it. Bootstraps tend to provide inaccurate results in small datasets. The advantage of this method lies in its two-step approach. The log-likelihood profiling creates a proposal distribution for the sampling importance resampling method. Anyhow, as it´s common practice we performed a bootstrap analysis as well. See results below.

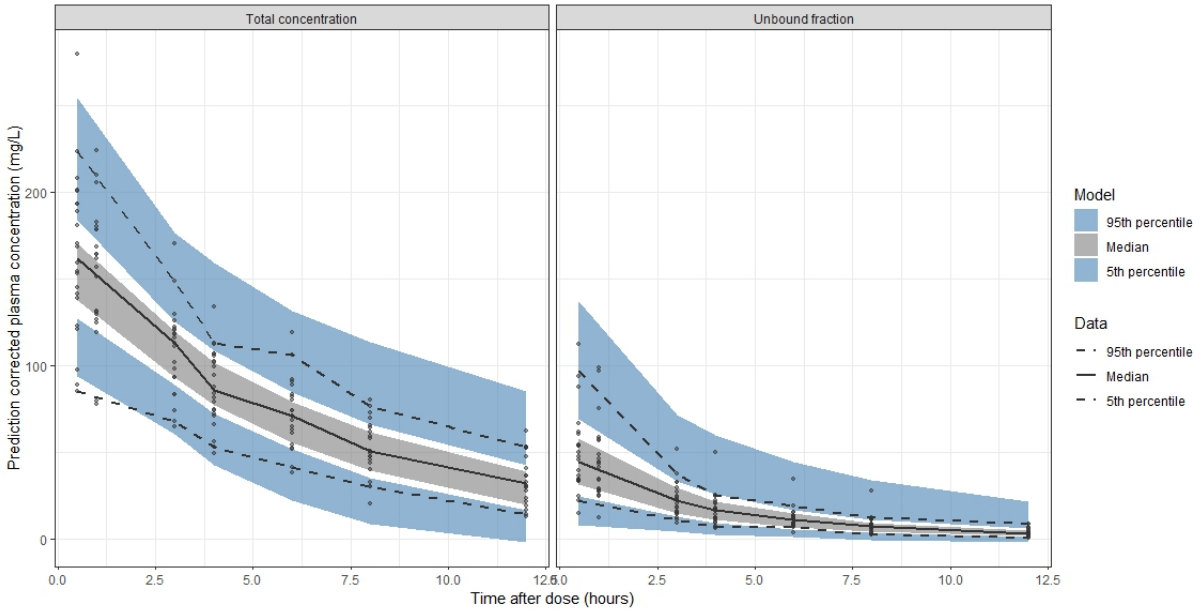
S1.2.: Goodness of fit plots regarding the total concentration of temocillin. *CWRES,* conditional weighted residuals. Dashed blue lines show the cut-off for |CWRES|>1.96. Dashed red lines show trends within the data and were calculated with the lowest weighted regression function (LOWESS).



S1.3.: Goodness of fit plots regarding the unbound concentration of temocillin. *CWRES,* conditional weighted residuals. Dashed blue lines show the cut-off for |CWRES|>1.96. Dashed red lines show trends within the data and were calculated with the lowest weighted regression function (LOWESS).



S1.4: Prediction-corrected visual predictive check (pcVPC) plots of the total and free concentrations. The median observed (solid black line), 5th and 95th percentiles of the observations (dashed black line), and corresponding 90% prediction intervals for the predicted percentiles (blue respective grey band) are shown.



S1.5: Pharmacokinetic parameter estimates of the final model with corresponding 95% CI calculated with LLP-SIR

Parameter	Population mean estimate	LLP-SIR 95% CI	Bootstrap 95% CI
Clearance (CL) [L/h]	2.29	2.28 - 2.31	2.00 - 2.58
Volume of distribution (V) [L]	14.9	14.9 - 15.0	12.8 - 17.0
Bmax [mg/L]	155.9	154.9 - 156.9	124.2 - 187.8
KD	18.4	12.4 - 25.8	11.4 - 24.4
GFR effect on Clearance (GFR_CL)*	0.569	0.553 - 0.585	0.262 - 0.876
BSV CL	0.069	0.067 - 0.071	0.035 - 0.102
BSV V	0.079	0.077 - 0.081	0.033 - 0.125
BSV Bmax	0.076	0.074 - 0.079	0.007 - 0.146
BSV KD	0.225	0.212 - 0.237	0.027 - 0.423
Prop. RUV (total concentration)	0.084	0.083 - 0.085	0.053 - 0.114
Add. RUV (total concentration) [mg/L]	5.23	5.16 - 5.30	3.12 - 7.35
Prop. RUV (free fraction)	0.131	0.129 - 0.132	0.098 - 0.164
Add. RUV (free fraction) [mg/L]	1.23	1.21 - 1.25	0.78 - 1.67

Bmax, maximum concentration of bound drug, BSV, between-subject variability (ω^2), CI, confidence interval, GFR, glomerular filtration rate, KD, dissociation constant, RUV, residual unexplained variability, TVCL, typical value of clearance

* $TVCL = CL \cdot ((GFR_i/GFR_{mean})^{GFR\_CL})$

S1.6: To further investigate the influence of renal function on reaching the PKPD target, simulations were made. 13 patients with CKD-EPI from 1 mL/min to 120 mL/min were created to cover to whole spectrum of renal functions. For every dosing regimen (2 g temocillin every 6, 8, 12, 24 or 48 h via short infusion) the same patient was simulated 1000 times. For MIC values of 0.5, 1, 2, 4, 8, 16, 32 and 64 mg/L, it was tested if the probability of target attainment (35% for the unbound plasma concentration being above MIC) was reached in over 90% of the simulations. The protein binding was simulated based on the developed PK model. Confidence intervals of the PTA were calculated according to Colin et al.[2]

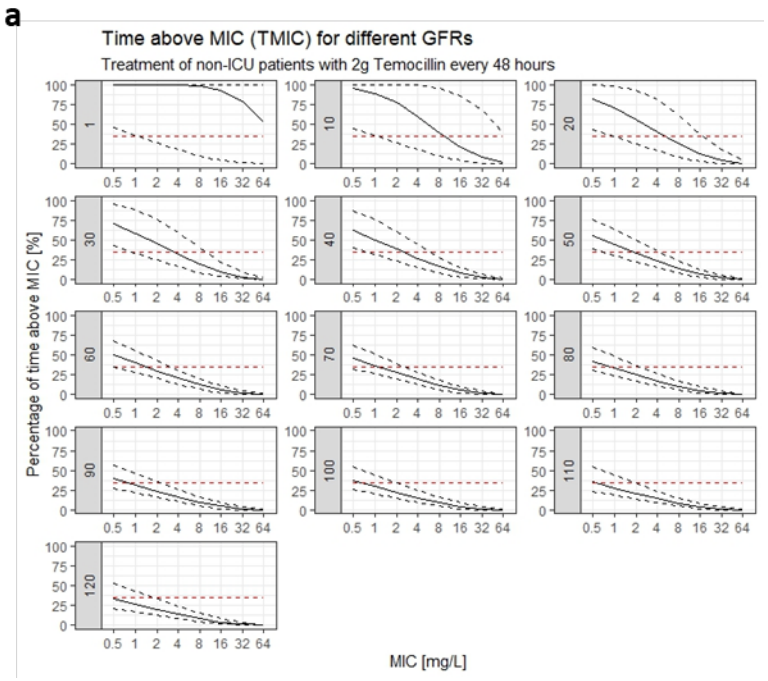
S1.7: Model code

```
$PROBLEM PK model
;; 1. Based on:
;; 2. Description: TEMODELTA model 1 CMP, COMB ERROR, IIV on CL, V, NP_UF, KD_UF, GFR_CL
;; x1. Author: julian.ermtraud
$INPUT X ID TIME DV EVID AMT RATE WT AGE HEIGHT PROT ALBU CRP GFR SEX FLAG SS II
;----------------------------------
$DATA temodelta_dataset.csv IGNORE=@
;----------------------------------
$SUBROUTINES ADVAN13 TOL=9
;----------------------------------
$MODEL NCOMPARTMENTS=1
;----------------------------------
$PK
TVCL = THETA(5) * ((GFR/67)**THETA(9))
CL = TVCL * EXP(ETA(1))
TVV = THETA(6)
V = TVV * EXP(ETA(2))
NP_UF = THETA(7) * EXP(ETA(3))
KD_UF = THETA(8) * EXP(ETA(4))
S1 = V
KE = CL/V
;----------------------------------
$DES
CTOTAL = A(1)/V
DADT(1) =  -KE*A(1)
CU_UF = 0.5*((CTOTAL - NP_UF - KD_UF) + SQRT((CTOTAL - NP_UF - KD_UF)**2 + 4 * KD_UF * CTOTAL))
;----------------------------------
```

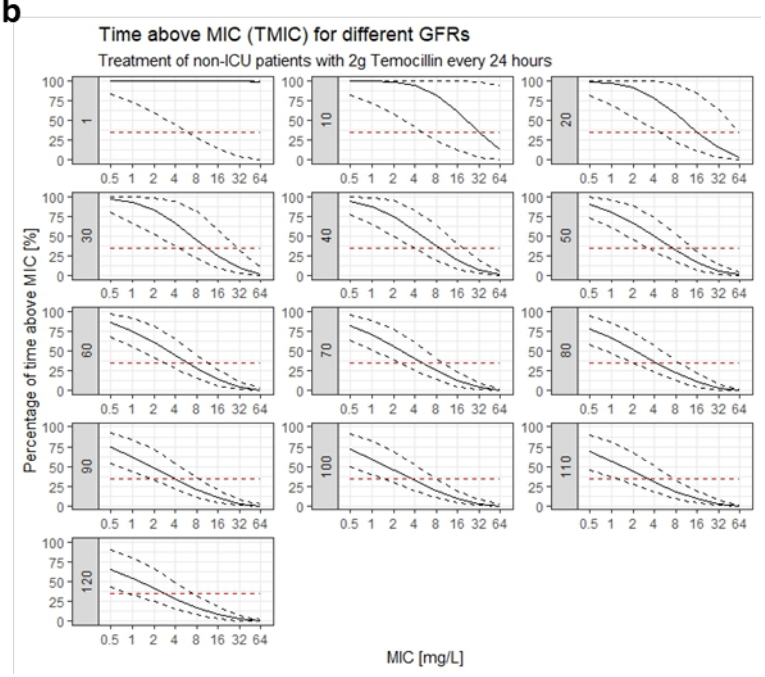
```
$THETA
(0, 0.0837) ;1_exp_error_total
(0, 5.23) ;2_add_error_total (check if scale makes sense!)
(0, 0.131) ;3_exp_error_free
(0, 1.23) ;4_add_error_free
(0, 2.29) ;5_CL
(0, 14.9) ;6_V
(0, 156) ;7_NP_UF
(0, 17.9) ;8_KD_UF
(0, 0.569) ;9_GFR_CL

$OMEGA
 0.0686 ; 1_IIV_CL
 0.0788 ; 2_IIV_V
 0.0763 ; 3_IIV_NP_UF
 0.225 ; IIV_KD_UF
;----------------------------------
$SIGMA
 1 FIX  ; 1_residual variability
;----------------------------------
$ERROR
IF (FLAG.EQ.1) THEN ;Plasma data
IPRED = A(1)/V
W1 = SQRT((IPRED*THETA(1))**2+THETA(2)**2)
Y = IPRED + W1*EPS(1)
IRES = DV-IPRED
IWRES = IRES/W1
ENDIF
IF (FLAG.EQ.2) THEN ;free Plasma data
```

```
CTOT = A(1)/V

IPRED = 0.5*((CTOT - NP_UF - KD_UF)+SQRT((CTOT - NP_UF - KD_UF)**2 + 4 * KD_UF * CTOT))

W1 = SQRT((IPRED*THETA(3))**2+THETA(4)**2)

Y = IPRED + W1*EPS(1)

IRES = DV-IPRED

IWRES = IRES/W1

ENDIF

;----------------------------------

$EST METHOD=1 INTERACTION

MAXEVAL=9999 SIG=3 PRINT=1 NOABORT

;----------------------------------

$COV PRINT=E MATRIX=S

;----------------------------------

$TABLE ID TIME DV EVID IPRED PRED IWRES CWRES NPDE MDV FLAG SS II ONEHEADER NOPRINT NOAPPEND FILE=sdtab3001

$TABLE ID CL V ETA1 ETA2 ETA3 ETA4 FIRSTONLY ONEHEADER NOPRINT NOAPPEND FILE=patab3001

$TABLE ID WT AGE HEIGHT PROT ALBU CRP GFR FIRSTONLY ONEHEADER NOPRINT NOAPPEND FILE=cotab3001

$TABLE ID SEX FIRSTONLY ONEHEADER NOPRINT NOAPPEND FILE=catab3001
```

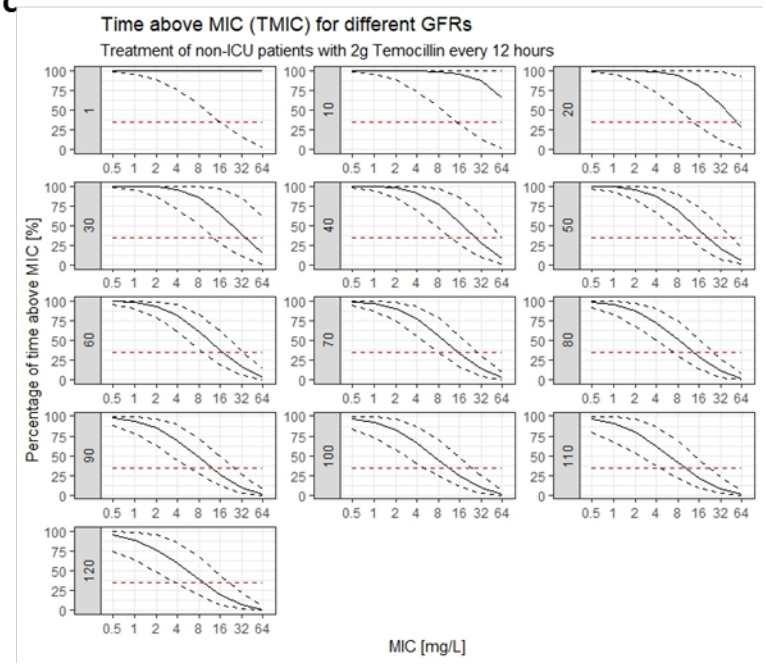
Figure S2. Temocillin %*f*T>MIC outcomes based on Monte Carlo simulations (solid line = median, dotted lines 95% confidence interval, CI) for various hypothetical doses based on the unitary 2g dose given every q48h (1g/day, figure a), to 24h (2g/day, figure b), to 12h (4g/day, figure c), to 8h (6g/day, figure d) and 6h (8g/day, figure e). The value in the grey bar within the boxes presents the chosen GFR value (range = 1-120 mL/min). The model is based on the PK data from 22 non-critically ill cUTI patients treated with 4g/day temocillin. The x-axis shows the MIC range used for the simulation and the y-axis the percentage of the time during which unbound plasma drug concentrations remain above the corresponding MIC (%*f*T>MIC). The purple horizontal line represents the target value of 35% *f*T>MIC (i.e. the PK/PD target EUCAST previously used to set breakpoints and associated doses based on critically ill patient PK data).



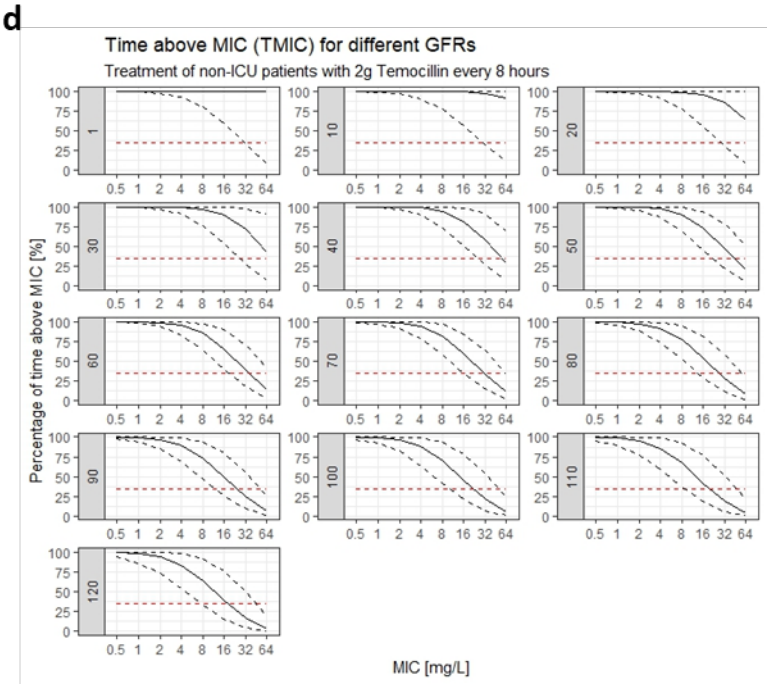
b


Time above MIC (TMIC) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 24 hours
Percentage of time above MIC [%]
MIC [mg/L]
1
10
20
30
40
50
60
70
80
90
100
110
120

c


Time above MIC (TMIC) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 12 hours
Percentage of time above MIC [%]
MIC [mg/L]
1
10
20
30
40
50
60
70
80
90
100
110
120

d


Time above MIC (TMIC) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 8 hours
Percentage of time above MIC [%]
MIC [mg/L]
1
10
20
30
40
50
60
70
80
90
100
110
120
0.5 1 2 4 8 16 32 64
0 25 50 75 100

e

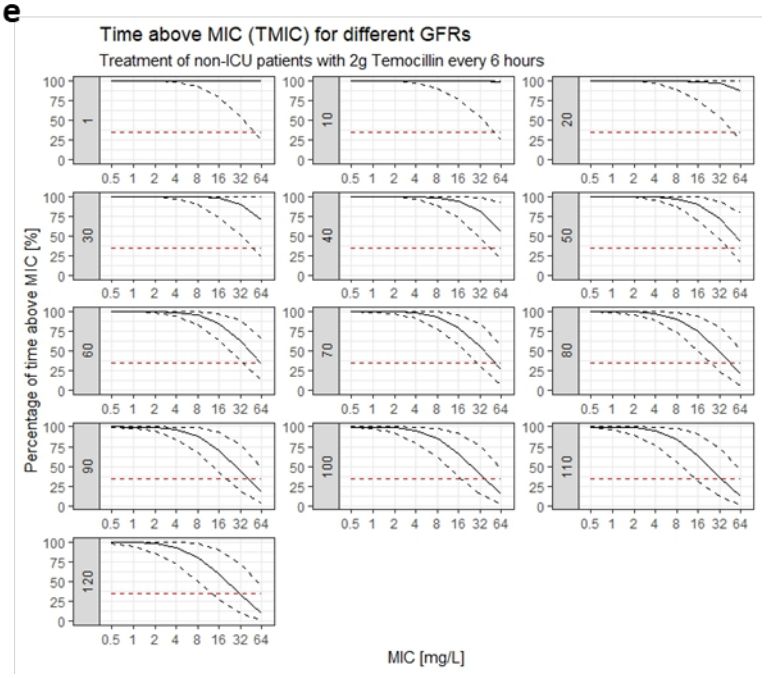

Time above MIC (TMIC) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 6 hours
Percentage of time above MIC [%]
MIC [mg/L]
1
10
20
30
40
50
60
70
80
90
100
110
120
0.5 1 2 4 8 16 32 64
0 25 50 75 100

Table S2. Probability of target attainment (PTA) for a PK/PD target of ≥ 35% *f*T>MIC (non-critically ill patients) for a range of simulated temocillin doses (1-8g/day) in patients with variable target minimal inhibitory concentrations (MICs) and glomerular filtration rates (GFRs). The green shaded areas indicate PTA ≥90%, whereas the red shaded areas show PTA <90%. The blue shaded area shows the lowest dose that is capable of achieving 90% PTA for a given GFR and MIC.

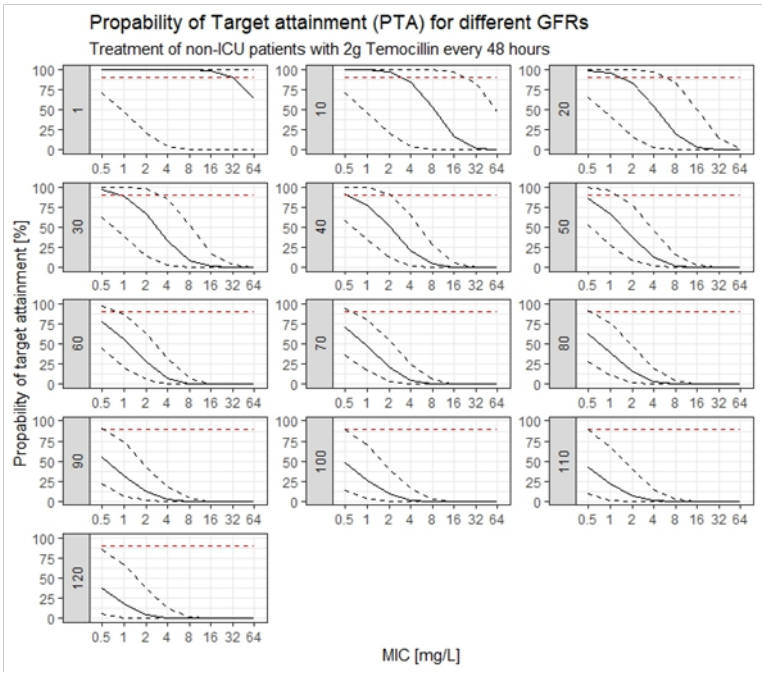
Target MIC (mg/L)	GFR (mL/min)	Temocillin doses				
		2g q48h (= 1g/day)	2g q24h (= 2g/day)	2g q12h (= 4g/day)	2g q8h (=6g/day)	2g q6h (= 8 g/day)
0.5	1	100.0	100.0	100.0	100.0	100.0
	10	100.0	100.0	100.0	100.0	100.0
	20	99.6	100.0	100.0	100.0	100.0
	30	98.2	100.0	100.0	100.0	100.0
	40	93.7	99.9	100.0	100.0	100.0
	50	88.5	100.0	100.0	100.0	100.0
	60	80.1	99.6	100.0	100.0	100.0
	70	71.9	99.8	100.0	100.0	100.0
	80	63.5	99.2	100.0	100.0	100.0
	90	58	98.5	100.0	100.0	100.0
	100	52.7	97.3	100.0	100.0	100.0
	110	45.3	97	100.0	100.0	100.0
	120	41	94.8	100.0	100.0	100.0
1	1	100.0	100.0	100.0	100.0	100.0
	10	99.7	100.0	100.0	100.0	100.0
	20	97.7	100.0	100.0	100.0	100.0
	30	90.0	100.0	100.0	100.0	100.0
	40	79.3	99.7	100.0	100.0	100.0
	50	69.5	99.3	99.9	100.0	100.0
	60	58.7	98.4	100.0	100.0	100.0
	70	49.0	96.8	100.0	100.0	100.0
	80	38.4	94.2	100.0	100.0	100.0
	90	31.7	94.3	99.9	100.0	100.0
	100	29.7	90.5	100.0	100.0	100.0
	110	23.5	88.4	99.9	100.0	100.0
	120	18.4	85.0	100.0	100.0	100.0
2	1	100.0	100.0	100.0	100.0	100.0
	10	97.6	100.0	100.0	100.0	100.0
	20	87.0	99.7	100.0	100.0	100.0
	30	68.4	99.2	100.0	100.0	100.0
	40	53.2	97.0	99.9	100.0	100.0
	50	37.8	93.8	99.9	100.0	100.0
	60	31.4	89.3	99.8	100.0	100.0
	70	21.7	86.4	99.8	100.0	100.0
	80	14.8	81.2	99.8	100.0	100.0
	90	10.6	75.8	99.5	100.0	100.0
	100	9.7	69.8	99.3	100.0	100.0
	110	6.9	65.3	98.7	99.9	100.0
	120	4.1	60.8	98.5	100.0	99.9

4	1	100.0	100.0	100.0	100.0	100.0
	10	87.3	99.6	100.0	100.0	100.0
	20	54.4	96.8	99.9	100.0	100.0
	30	32.4	91.6	99.9	100.0	100.0
	40	18.8	82.0	99.5	100.0	100.0
	50	11.0	72.5	98.4	99.6	100.0
	60	8.2	65.0	98.9	99.8	100.0
	70	3.6	55.1	96.6	99.7	100.0
	80	2.9	48.7	95.5	99.5	100.0
	90	1.6	41.1	94.6	99.4	99.8
	100	1.2	35.3	92.5	99.0	99.9
	110	0.8	32.4	88.5	98.0	99.8
	120	0.5	30.1	87.4	98.1	99.7
8	1	100.0	100.0	100.0	100.0	100.0
	10	55.8	95.4	100.0	100.0	100.0
	20	16.6	80.3	99.2	100.0	100.0
	30	7.3	60.4	97.8	99.3	99.9
	40	2.0	46.0	92.8	99.1	100.0
	50	0.4	34.3	89.3	98.2	99.7
	60	0.7	26.8	84.2	97.0	99.5
	70	0.1	19.3	80.1	95.7	99.9
	80	0.1	15.2	73.6	94.9	99.5
	90	0.0	10.4	67.7	92.8	98.3
	100	0.0	6.9	62.6	90.4	97.8
	110	0.0	5.9	57.8	85.8	97.6
	120	0.0	6.1	53.3	84.9	97.8
16	1	98.8	100.0	100.0	100.0	100.0
	10	17.1	74.6	99.1	100.0	100.0
	20	2.4	43.3	92.8	99.5	99.9
	30	0.6	21.2	82.6	95.2	99.7
	40	0.0	11.7	68.8	93.2	98.8
	50	0.0	6.9	61.9	89.1	96.5
	60	0.0	4.1	47.6	84.3	95.5
	70	0.0	1.6	40.8	77.7	92.4
	80	0.0	1.1	35.2	71.3	90.1
	90	0.0	0.4	24.2	65.1	85.6
	100	0.0	0.3	22.2	60.9	84
	110	0.0	0.1	19.6	55.3	81.9
	120	0.0	0.2	17.2	50.9	77.8

32	1	91.2	99.6	100.0	99.9	100.0
	10	1.7	39.1	92.9	99.7	99.9
	20	0.2	8.6	69.9	94.4	97.7
	30	0.0	2.7	46.9	82.6	95.1
	40	0.0	0.4	28.8	68.7	90.1
	50	0.0	0.7	21	57.8	81.7
	60	0.0	0.0	10.9	47.5	76.8
	70	0.0	0.0	10	38.8	69.7
	80	0.0	0.0	6.2	31.6	61.8
	90	0.0	0.0	3.4	25.2	55.3
	100	0.0	0.0	2.5	19.4	48.5
	110	0.0	0.0	2.5	18.3	42.2
	120	0.0	0.0	1.6	14.4	40.8
64	1	63.3	97.7	99.6	99.8	100.0
	10	0.0	7	69.9	94.8	97.6
	20	0.0	0.5	29.6	71.8	89.3
	30	0.0	0.1	10.9	45	76.4
	40	0.0	0.0	3.6	29	61.1
	50	0.0	0.0	1.2	16.3	47.2
	60	0.0	0.0	0.8	11.3	33.2
	70	0.0	0.0	0.4	7.9	25.4
	80	0.0	0.0	0.3	4.1	20.7
	90	0.0	0.0	0.2	2.7	15.5
	100	0.0	0.0	0.0	1.1	12
	110	0.0	0.0	0.1	1.3	8.6
	120	0.0	0.0	0.0	0.8	5.8

Figure S3. Temocillin probability of target attainment (PTA) outcomes for the 35% *f*T>MIC target based on Monte Carlo simulations (solid line = median, dotted lines 95% confidence interval, CI) for various hypothetical doses based on the unitary 2g dose when administered every q48h (1g/day, figure a), to 24h (2g/day, figure b), to 12h (4g/day, figure c), to 8h (6g/day, figure d) and 6h (8g/day, figure e). The value in the grey bar within the boxes presents the chosen GFR value (range = 1-120 mL/min). The model is based on the PK data from 22 non-critically ill cUTI patients treated with 4g/day temocillin. The x-axis shows the MIC range used for the simulation and the y-axis the percentage of the time during which unbound plasma drug concentrations remain above the corresponding MIC (%*f*T>MIC). The purple horizontal line represents the target value of 90% PTA.

a



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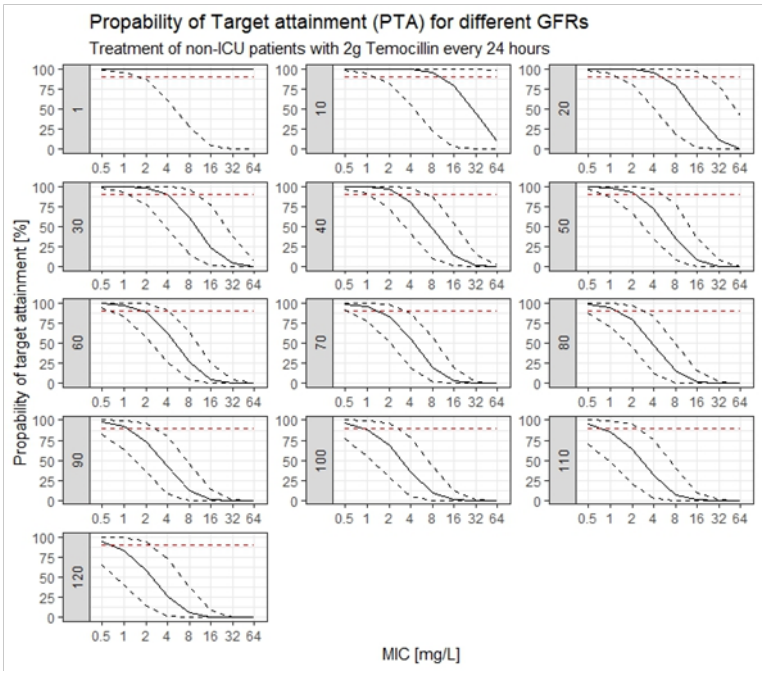
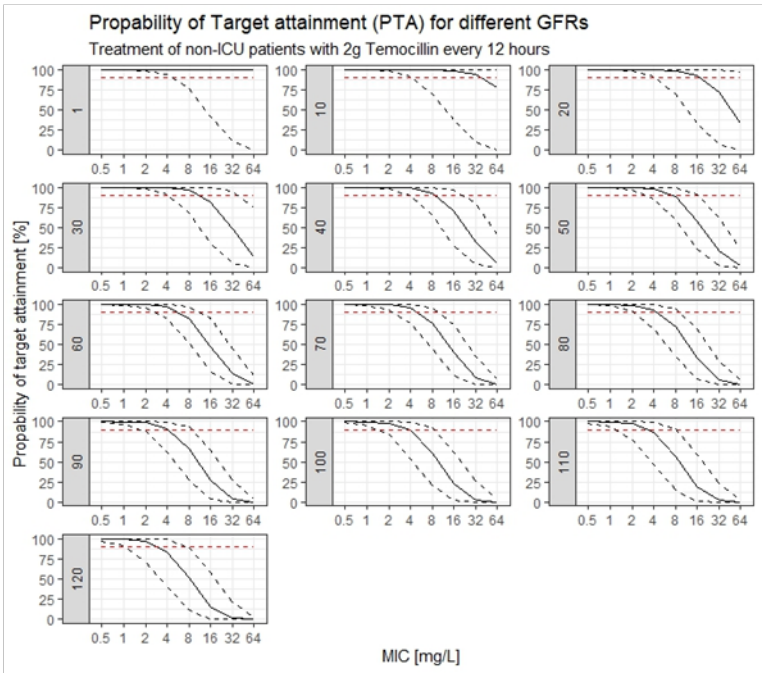
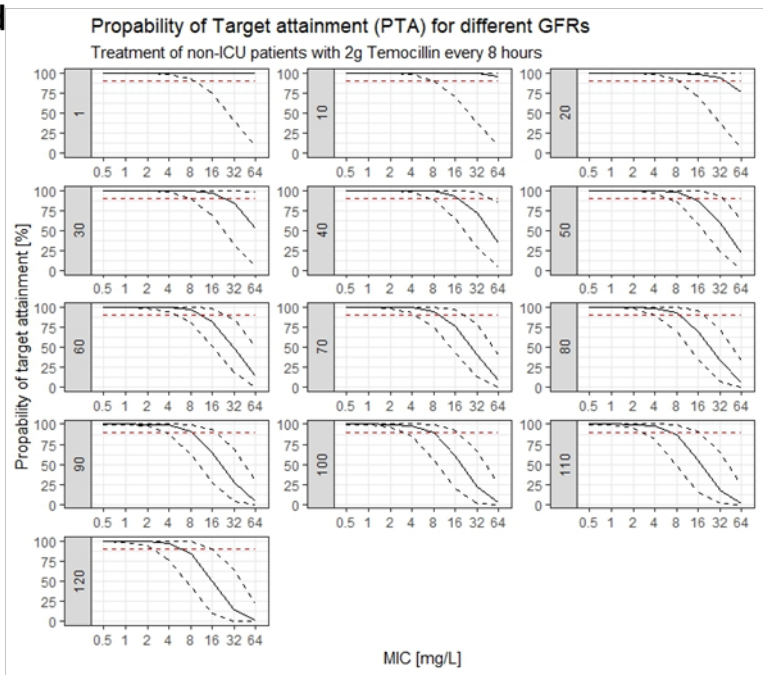

Propability of Target attainment (PTA) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 24 hours
Propability of target attainment [%]
MIC [mg/L]

c


Propability of Target attainment (PTA) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 12 hours
Propability of target attainment [%]
MIC [mg/L]

d


Propability of Target attainment (PTA) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 8 hours
Propability of target attainment [%]
MIC [mg/L]
1
10
20
30
40
50
60
70
80
90
100
110
120
0.5 1 2 4 8 16 32 64
0 25 50 75 100

e

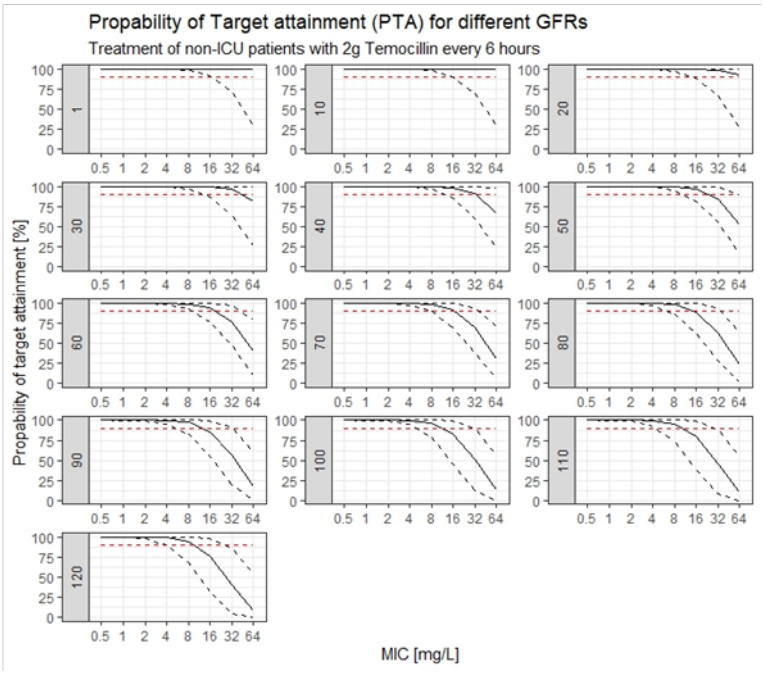
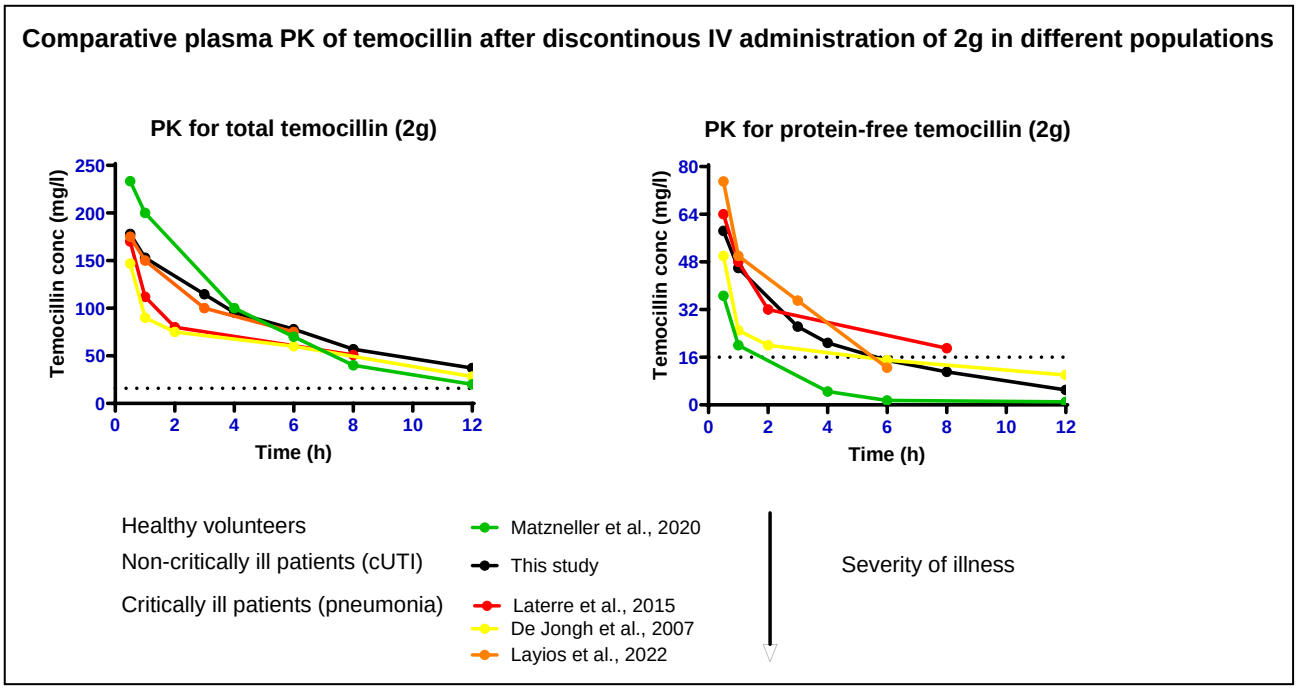

Propability of Target attainment (PTA) for different GFRs
Treatment of non-ICU patients with 2g Temocillin every 6 hours
Propability of target attainment [%]
MIC [mg/L]
1
10
20
30
40
50
60
70
80
90
100
110
120
0.5 1 2 4 8 16 32 64
0 25 50 75 100

Figure S4. Comparative plasma concentration-over-time profiles for total (left) and free (right) temocillin following administration of 2g via discontinuous infusion in different patient populations[3-6], based on published literature data and the results from this study (non-critically ill cUTI patients, n=22). The horizontal dotted line represents the MIC value = 16 mg/L, the EUCAST breakpoint for *Enterobacterales*.



References to supplementary material

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