**01909**

# Population pharmacokinetics and dosing simulation of the β-lactam temocillin in liver-transplanted pediatric patients

*05. New antibacterial agents, PK/PD & Stewardship*

5b. Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring

**Likely attendance**

Onsite

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## Background

Temocillin, a carbapenem-sparing β-lactam antibiotic, is useful for the empirical treatment or prophylaxis of Gram-negative bacterial infections in liver-transplanted children. Here, we characterize the total and unbound plasma pharmacokinetics (PK) of temocillin in this population, to propose optimized and personalized dosing regimens based on patient characteristics.

## Methods

Patients aged 6-36 months received 25 mg/kg/12h (standard dose) or 25 mg/kg/8h (high dose) temocillin intravenously. Blood samples were collected after the 4th and 8th doses and temocillin concentrations in plasma were measured via a validated LC-MS/MS method. Clinical safety was monitored. Non-compartmental and population PK analyses were performed, together with Monte-Carlo simulations. Probability of target attainment (PTA) calculations were based on a PK/PD target of >40% fT>MIC (% time of the dosing interval with unbound drug concentrations above the minimal inhibitory concentration).

## Results

For 25 mg/kg/12h, Cmax and Cmin were 108 ± 22 and 8 ± 4 mg/L (total concentrations), and 38 ± 16 and 2 ± 1 mg/L (unbound concentrations), respectively. For 25 mg/kg/8h, Cmax was similar, but Cmin was increased to 22 ± 8 and 5 ± 3 mg/L for total and unbound concentrations, respectively. Temocillin PK was best described by a two-compartment model with first-order elimination, with body weight and glomerular filtration rate (GFR) as significant covariates. Monte-Carlo simulations suggested that PTA was achieved in 90% of the population for (a) MICs <8 mg/L, GFR ≤120 mL/min or weight ≥11 kg with 25 mg/kg/12h, (b) MICs <16 mg/L, GFR ≤30 mL/min or weight ≥13 kg with 25 mg/kg/8h and (c) for more elevated MICs or GFR, or lower weight, with higher simulated doses. No safety concerns were reported at the tested dose levels.

## Conclusions

The 25 mg/kg temocillin standard dose appears appropriate in specific clinical scenarios, but the dosing interval may need to be reduced from 12 to 8 hours in patients with lower body weight, increased renal function or infections caused by less susceptible bacteria. Simulations showed that higher, off-label doses (> 25 mg/kg/8h) could further improve PK/PD target attainment, yet caution is warranted as their clinical safety remains unknown.

Figure 1

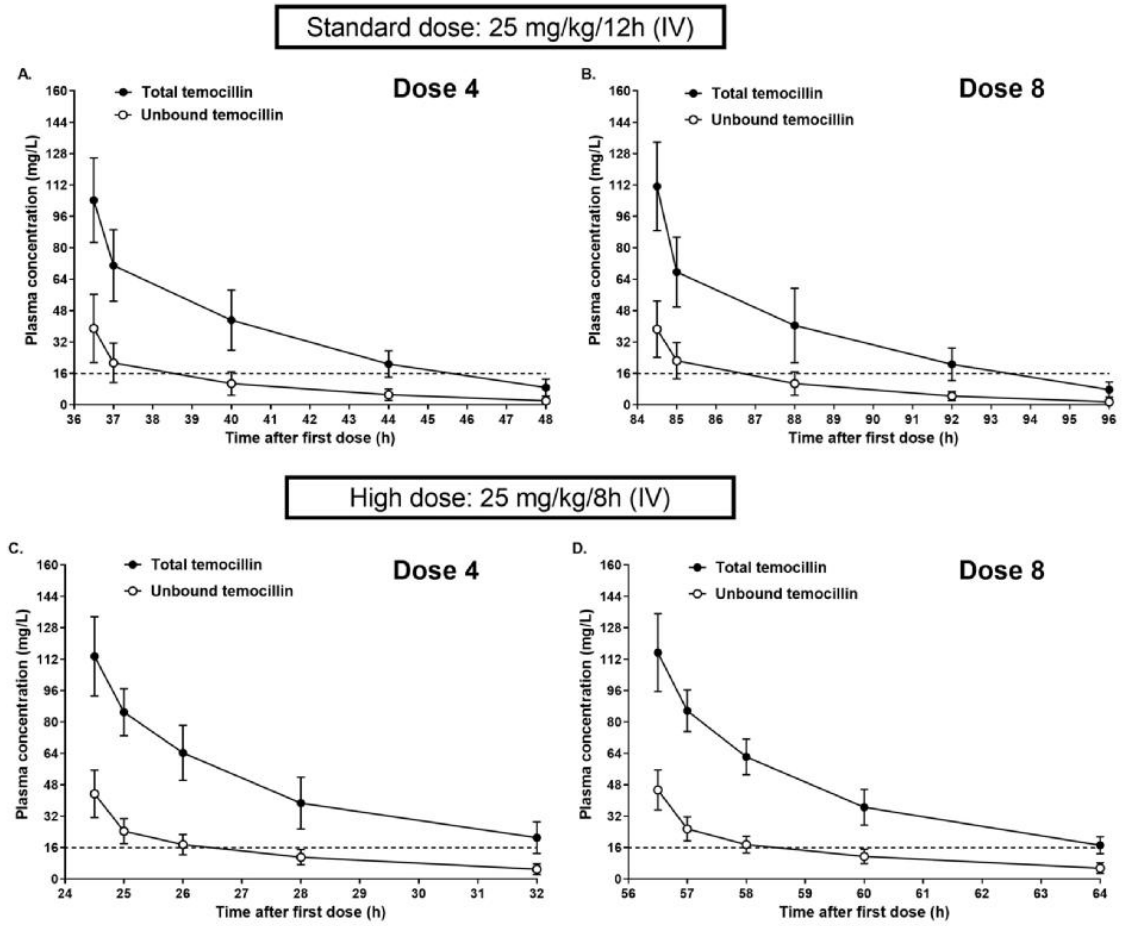


**Figure 1:** Plasma concentration-time profiles of total and unbound temocillin following multiple intravenous administrations. A: standard dose (25mg/kg/12h), dose 4 (n=14), B: standard dose (25mg/kg/12h), dose 8 (n=12), C: high dose (25 mg/kg/8h), dose 4 (n=14) and D: high dose (25 mg/kg/8h), dose 8 (n=11). The horizontal dashed line represents the pharmacodynamic target (minimal inhibitory concentration (MIC) against Enterobacterales = 16 mg/l, EUCAST susceptibility breakpoint). Data are shown as mean ± SD

Figure 2

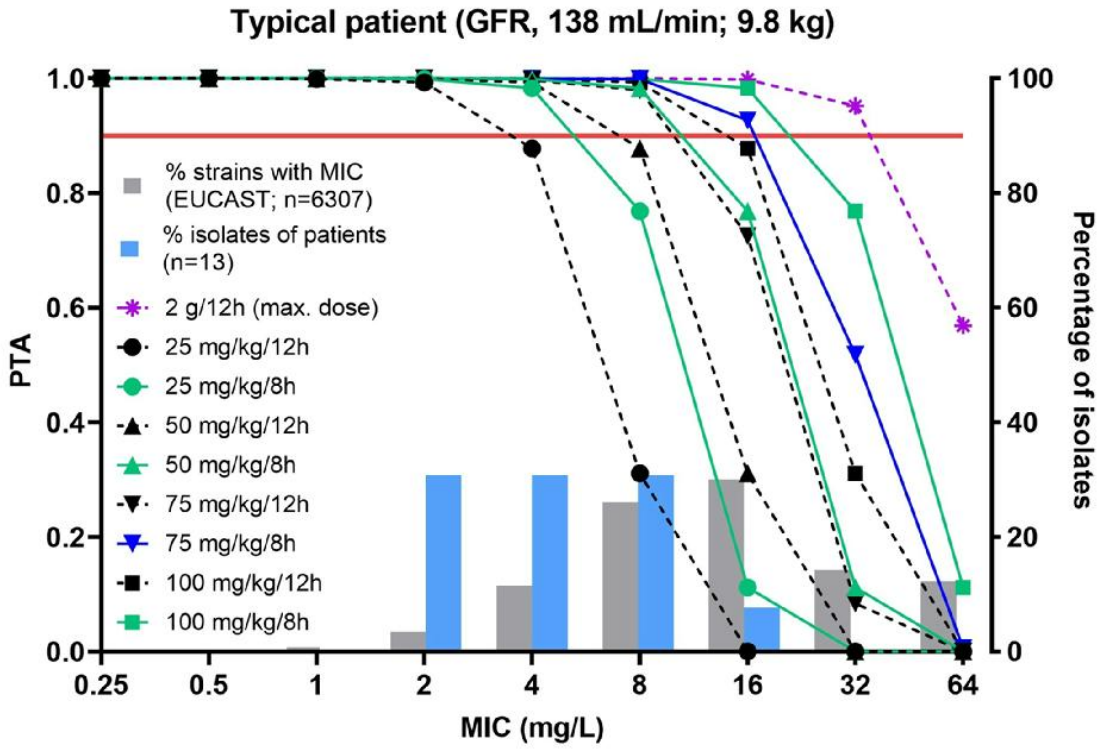


**Figure 2:** Monte Carlo simulations and PTA analysis for the clinically tested doses (25mg/kg/12 or 8h), theoretical higher doses (50mg/kg, 75mg/kg and 100mg/kg/12 or 8 h) and the maximum dose listed in the Summary of Product Characteristics (2g/12h) for a typical pediatric patient (body weight: 9.8 kg; GFR: 138mL/min). Red dotted line: PTA of 90%; dose in blue: lowest for which a PTA of 90% is reached for an MIC of 16 mg/L (EUCAST susceptibility breakpoint for temocillin). Blue and grey histograms: MIC distribution of the E. coli and K. pneumoniae isolates observed in this study and reported by EUCAST, respectively.

Table 1

**Table 1:** Probability of target attainment (PTA)[a] for various temocillin dosing regimens against bacteria with MICs of 4 or 8 or 16 mg/L according to (i) the GFR, and (ii) the body weight values.

| Target MIC (mg/L) | GFR (mL/min) | Body weight (kg) | Temocillin doses: Studied 25mg /kg/12h | Studied 25mg /kg/8h | Studied 50mg /kg/12h | Simulated 50mg /kg/8h | Simulated 75mg /kg/12 h | Simulated 75mg /kg/8h | Simulated 100mg /kg/12h | Simulated 100 mg /kg/ 8h |
|---|---|---|---|---|---|---|---|---|---|---|
| 4mg/L | (i) target attainments (%) according to the GFR | | | | | | | | | |
| | 30 | 9.8 | 94 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 60 | 9.8 | 93 | 99 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 90 | 9.8 | 93 | 99 | 99 | 100 | 100 | 100 | 100 | 100 |
| | 120 | 9.8 | 91 | 99 | 99 | 100 | 100 | 100 | 100 | 100 |
| | **138** | **9.8** | **88** | **98** | **99** | **100** | **100** | **100** | **100** | **100** |
| | 150 | 9.8 | 83 | 98 | 99 | 100 | 100 | 100 | 100 | 100 |
| | 180 | 9.8 | 77 | 97 | 99 | 100 | 100 | 100 | 100 | 100 |
| | 210 | 9.8 | 71 | 96 | 98 | 100 | 100 | 100 | 100 | 100 |
| | 250 | 9.8 | 56 | 93 | 98 | 100 | 100 | 100 | 100 | 100 |
| | (ii) target attainments (%) according to the body weight | | | | | | | | | |
| | 138 | 6 | 27 | 77 | 81 | 97 | 95 | 100 | 98 | 100 |
| | 138 | 8 | 71 | 94 | 97 | 100 | 99 | 99 | 100 | 100 |
| | **138** | **9.8** | **88** | **98** | **99** | **100** | **100** | **100** | **100** | **100** |
| | 138 | 11 | 93 | 99 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 138 | 13 | 98 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | 138 | 15 | 99 | 100 | 100 | 100 | 100 | 100 | 100 | n.a. |
| | 138 | 17 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | n.a. |
| | 138 | 20 | 100 | 100 | 100 | 100 | 100 | n.a. | 100 | n.a. |
| 8 mg/L | (i) target attainments (%) according to the GFR | | | | | | | | | |
| | 30 | 9.8 | 78 | 91 | 94 | 100 | 99 | 100 | 100 | 100 |
| | 60 | 9.8 | 70 | 88 | 93 | 99 | 99 | 100 | 100 | 100 |
| | 90 | 9.8 | 52 | 88 | 93 | 99 | 98 | 100 | 100 | 100 |
| | 120 | 9.8 | 41 | 79 | 91 | 99 | 98 | 100 | 99 | 100 |
| | **138** | **9.8** | **31** | **77** | **88** | **98** | **98** | **100** | **99** | **100** |
| | 150 | 9.8 | 25 | 75 | 83 | 98 | 98 | 100 | 99 | 100 |
| | 180 | 9.8 | 14 | 69 | 77 | 97 | 96 | 99 | 99 | 100 |
| | 210 | 9.8 | 9 | 61 | 71 | 96 | 95 | 100 | 98 | 100 |
| | 250 | 9.8 | 5 | 47 | 56 | 93 | 87 | 98 | 98 | 100 |
| | (ii) target attainments (%) according to the body weight | | | | | | | | | |
| | 138 | 6 | 0 | 17 | 27 | 77 | 63 | 93 | 81 | 97 |
| | 138 | 8 | 10 | 57 | 71 | 94 | 62 | 99 | 97 | 100 |
| | **138** | **9.8** | **31** | **77** | **88** | **98** | **98** | **100** | **99** | **100** |
| | 138 | 11 | 47 | 82 | 93 | 99 | 99 | 100 | 100 | 100 |
| | 138 | 13 | 70 | 90 | 98 | 100 | 100 | 100 | 100 | 100 |
| | 138 | 15 | 81 | 97 | 100 | 100 | 100 | 100 | 100 | n.a. |
| | 138 | 17 | 86 | 99 | 100 | 100 | 100 | 100 | 100 | n.a. |
| | 138 | 20 | 93 | 100 | 100 | 100 | 100 | n.a. | 100 | n.a. |
| 16 mg/L | (i) target attainments (%) according to the GFR | | | | | | | | | |
| | 30 | 9.8 | 44 | 68 | 78 | 91 | 91 | 97 | 94 | 100 |
| | 60 | 9.8 | 26 | 48 | 70 | 88 | 88 | 95 | 93 | 99 |
| | 90 | 9.8 | 4 | 35 | 52 | 88 | 86 | 94 | 93 | 99 |
| | 120 | 9.8 | 0 | 19 | 41 | 79 | 76 | 93 | 91 | 99 |
| | **138** | **9.8** | **0** | **11** | **31** | **77** | **73** | **93** | **88** | **98** |
| | 150 | 9.8 | 0 | 7 | 25 | 75 | 69 | 91 | 83 | 98 |
| | 180 | 9.8 | 0 | 3 | 14 | 69 | 57 | 85 | 77 | 97 |
| | 210 | 9.8 | 0 | 1 | 9 | 61 | 43 | 82 | 71 | 96 |
| | 250 | 9.8 | 0 | 1 | 5 | 47 | 34 | 79 | 56 | 93 |
| | (ii) target attainments (%) according to the body weight | | | | | | | | | |
| | 138 | 6 | 0 | 0 | 0 | 17 | 10 | 60 | 27 | 77 |
| | 138 | 8 | 0 | 1 | 10 | 57 | 43 | 82 | 71 | 94 |
| | **138** | **9.8** | **0** | **11** | **31** | **77** | **73** | **93** | **88** | **98** |
| | 138 | 11 | 0 | 21 | 47 | 82 | 81 | 96 | 93 | 99 |
| | 138 | 13 | 0 | 43 | 70 | 89 | 91 | 99 | 98 | 100 |
| | 138 | 15 | 15 | 60 | 81 | 97 | 97 | 100 | 100 | n.a. |
| | 138 | 17 | 27 | 74 | 86 | 99 | 99 | 100 | 100 | n.a. |
| | 138 | 20 | 47 | 82 | 93 | 100 | 100 | n.a.[b] | 100 | n.a. |

[a] PTA > 90%: green background or blue background (lowest dose reaching 90%); PTA < 90%: red background, considering MIC, GFR and body weight. Bold values: data for a typical paediatric patient (median values of GFR and body weight for the studied population). [b] n.a. not applicable (would exceed the maximum paediatric daily dose (4g/day)).

**Keyword 1**
PK/PD, pharmacology and TDM
**Keyword 2**
Paediatric ID

**Keyword 3**
β-lactam antibiotics

*Conflicts of interest*

**Do you have any conflicts of interest to declare?**
Yes
Personal grants/research supports