Dosing optimization of amoxicillin in children treated for Lyme disease

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Introduction:

- **Amoxicillin** is prescribed to **children** for the treatment of **erythema migrans (EM)**, stage I of Lyme disease.
- The currently recommended oral dose is **50 mg/kg/day divided into three doses** (t.i.d), with a maximum total daily dose of 1500 mg.
- For other infections such as pneumonia or otitis media, amoxicillin can be given **twice daily** (b.i.d), but there is **no evidence that such a regimen is adequate to treat Lyme disease.**

Objective:

To verify whether a dose of 50 mg/kg/day given b.i.d provides an amoxicillin exposure coverage comparable to that observed under the currently recommended t.i.d dosing schedule in children, using a model-based simulation approach.

Methods:

- **Model-based simulations** on 15000 virtual children (bodyweight range: 4-80 kg and renal function assumed to be normal) receiving 50 mg/kg/day given t.i.d (i.e., 16.67 mg/kg per dose) and b.i.d (i.e., 25 mg/kg per dose) using the software package NONMEM® and a previously published population pharmacokinetic (popPK) model for adults adapted to children[1]. **Other dosage regimens** were also tested: 30 to 50 mg/kg (with a 5 mg/kg step) b.i.d.
- Two common **therapeutic targets**, based on the percentage of time the unbound concentration remains over the minimal inhibitory concentration (ft>MIC), were selected: **40% and 50% ft>MIC.** As the **MICs** for *Borrelia burgdorferi sensu latu* are not clearly defined, different values from literature were tested **(0.06, 0.25, 1, 2 and 4 mg/L)** [2,3].
- The probability of target attainment (**PTA**) was used to compare both dosage regimens and considered **acceptable if it remain above 50% for each MIC.**

Results:

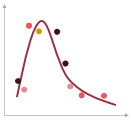
Adult PopPK model description[1]

- Population used:

A total of 155 hospitalized adults
Median age = 72 (range: 16, 93) years
Median body weight = 70 (range: 30, 140) kg

- PopPK model:

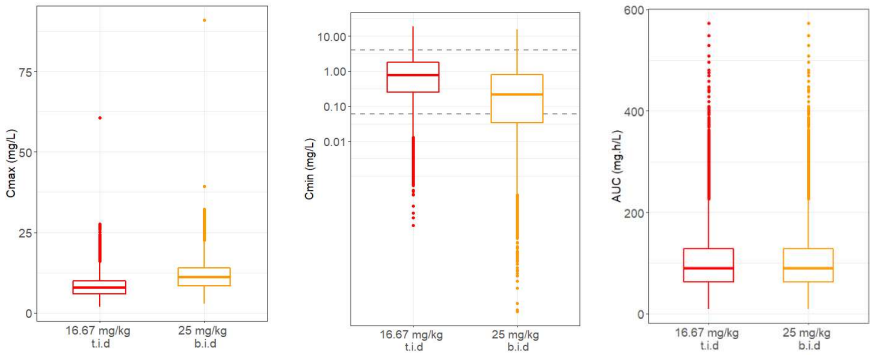
One-compartment model with first-order absorption and elimination.
Bioavailability fixed to 80% according to the literature values.



- Extrapolation to pediatric population:

An allometric effect of body weight on apparent clearance and volume of distribution was assumed to bridge the popPK model built on adult data to children.

Figure 1. Distribution of PK parameters obtained under 50 mg/kg/day given t.i.d (red) or b.i.d (yellow)



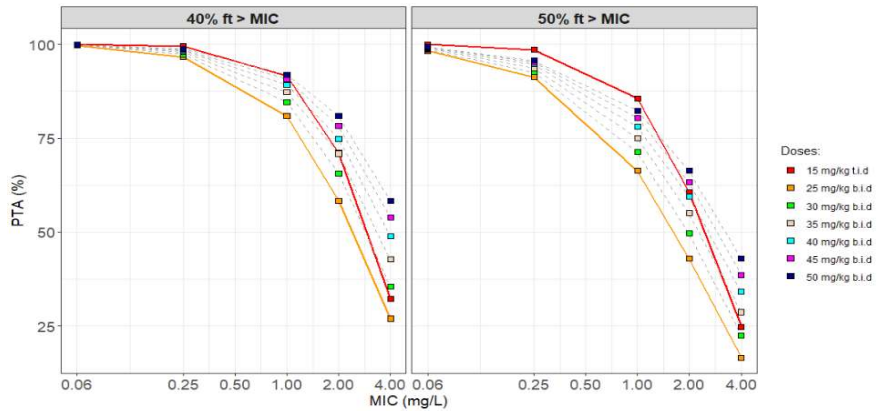
The dotted lines represent the range of the studied MICs. Cmax: maximum concentrations, Cmin: minimum concentrations, AUC: daily area under the curve

Table 1. Comparison of PTAs obtained under 50 mg/kg/day given t.i.d or b.i.d

MIC (mg/L)	PTA (%) 16.67 mg/kg t.i.d	PTA (%) 25 mg/kg b.i.d	Difference between both dosage regimens (%)
Target: 40% ft > MIC			
0.06	100	100	0.3
0.25	97	100	2.9
1	92	81	11.8
2	71	58	17.9
4	32	27	16.3
Target: 50% ft > MIC			
0.06	100	98	1.7
0.25	99	91	7.4
1	86	66	22.4
2	61	43	29.3
4	25	17	33.1

Green cells represent PTAs >50%. MIC: minimum inhibitory concentration, PTA: probability of target attainment

Figure 2. PTAs obtained under standard and alternative dosage regimens as a function of MICs



The solid lines represent the PTA obtained under current recommended daily dose (i.e. 50 mg/kg/day) given t.i.d (in red) and b.i.d (in yellow) for different MICs tested. The grey dashed lines correspond to PTAs obtained under alternative b.i.d dosage regimens: 30, 35, 40, 45 and 50 mg/kg. MIC: minimum inhibitory concentration, PTA: probability of target attainment

Conclusions:

Our model-based simulations suggest that bactericidal activity of amoxicillin might be achieved for the treatment of EM in the majority of children treated with 25 mg/kg b.i.d assuming a MIC between 0.06 mg/L and 1 mg/L for *Borrelia burgdorferi sensu latu*. **This regimen might be preferred in children to simplify treatment and enhance adherence.** For MIC=2 mg/L and a therapeutic target of 50% ft>MIC, a slightly higher dose of 30 mg/kg b.i.d should be considered to satisfy the PTA acceptability criteria. Additional clinical studies are warranted to further evaluate and optimize pediatric amoxicillin dosing in the treatment of EM infections with higher MICs.

1. Smit C et al. *Steering Away from Current Amoxicillin Dose Reductions in Hospitalized Patients with Impaired Kidney Function to Avoid Subtherapeutic Drug Exposure.* 2022.
2. Veinović G et al. *In vitro efficacy of antibiotics against different Borrelia isolates.* 2021.
3. Hunfeld K-P et al. *Antimicrobial susceptibility of Borrelia burgdorferi sensu lato: What we know, what we don't know, and what we need to know.* 2006.

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