

Adequacy of oral versus intravenous amoxicillin exposure in neonates at risk for sepsis: a pooled population pharmacokinetic study

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INTRODUCTION

The use of oral antibiotics in neonates is limited due to the lack of evidence on adequate exposure and pharmacokinetics (PK). Adequate antibiotic exposure ensures bacteriostatic effects, whereas suboptimal dosing induces antibiotic resistance and side effects.

Amoxicillin/clavulanic acid covers most causative pathogens of early-onset neonatal sepsis. Oral amoxicillin is already used in Low and Middle Income Countries in simplified regimens. However, data on absorption and target attainment are lacking and hamper broad implementation of oral amoxicillin in neonatal care.

AIMS

- Describe amoxicillin PK in neonates, including absorption and bioavailability.
- Evaluate target attainment and provide dosing guidelines for oral and intravenous (IV) amoxicillin in neonates.

METHODS

- Three datasets with oral and IV amoxicillin plasma concentrations were pooled (RAIN Study, SATT Trial, MUMC).
- A one-compartmental NONMEM population PK model with inter-individual variation on clearance was developed to quantify amoxicillin exposure.
- Monte Carlo simulations were performed to determine target attainment and dosage recommendations for both oral and IV amoxicillin.

RESULTS

- Amoxicillin pharmacokinetics can be described by a one-compartmental model with *a priori* allometric scaling on clearance and distribution volume.
- Interindividual variation on clearance was reduced by adding gestational age and postnatal age as a covariate.
- Mean clearance at a postnatal age of 5 days was 2.6-fold and 4.7-fold higher in case of a gestational age of 34 weeks and 40 weeks, compared with 30 weeks.
- A twice daily dosing regimen is sufficient for oral amoxicillin treatment.

CONCLUSION

- Dosing guidelines for amoxicillin can be optimized with personalized recommendations based on postnatal age and gestational age
- Current oral/intravenous dosing regimens lead to adequate exposure and may even be reduced.

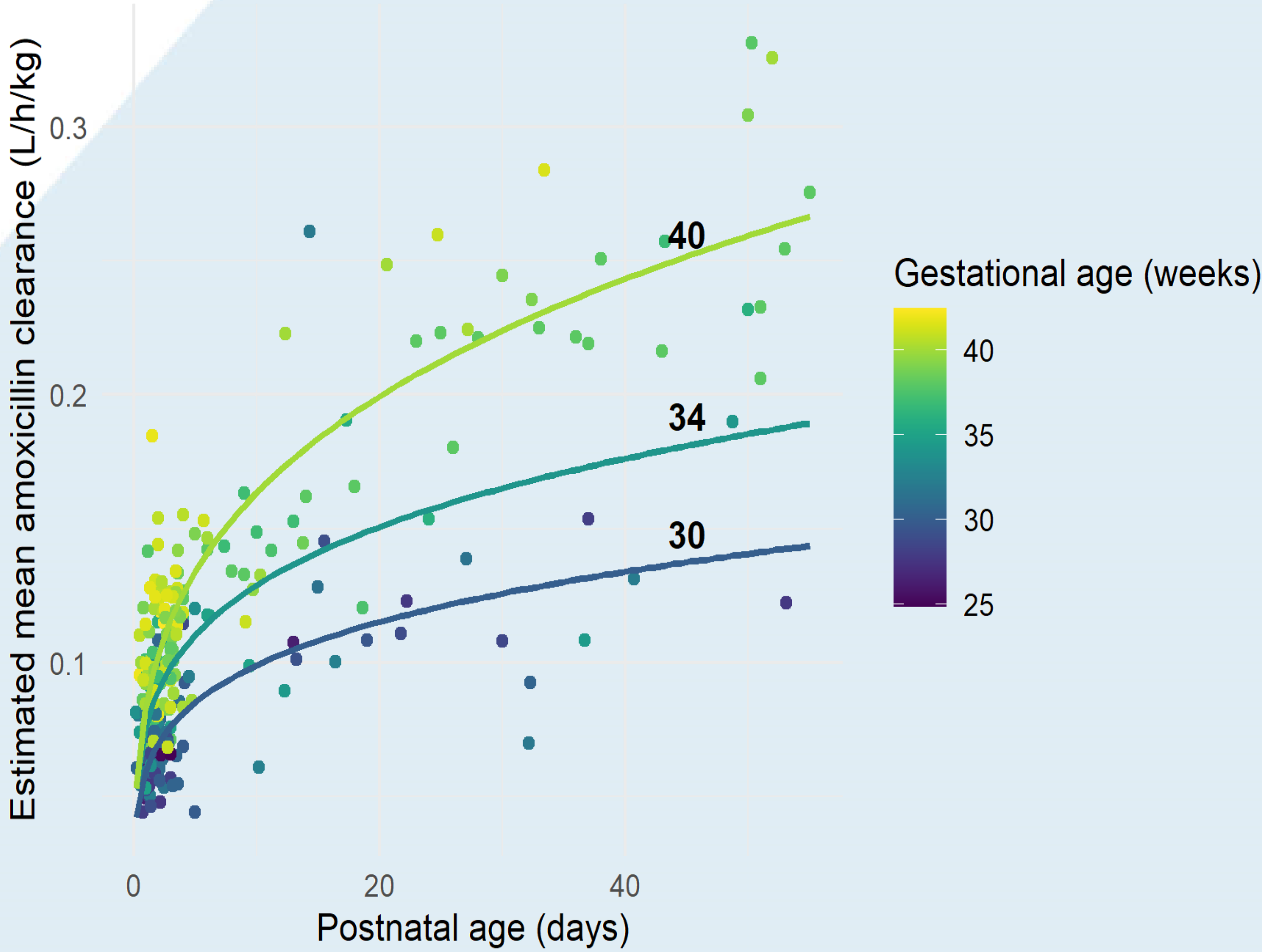


Figure 1: Impact of PNA and GA on amoxicillin clearance.

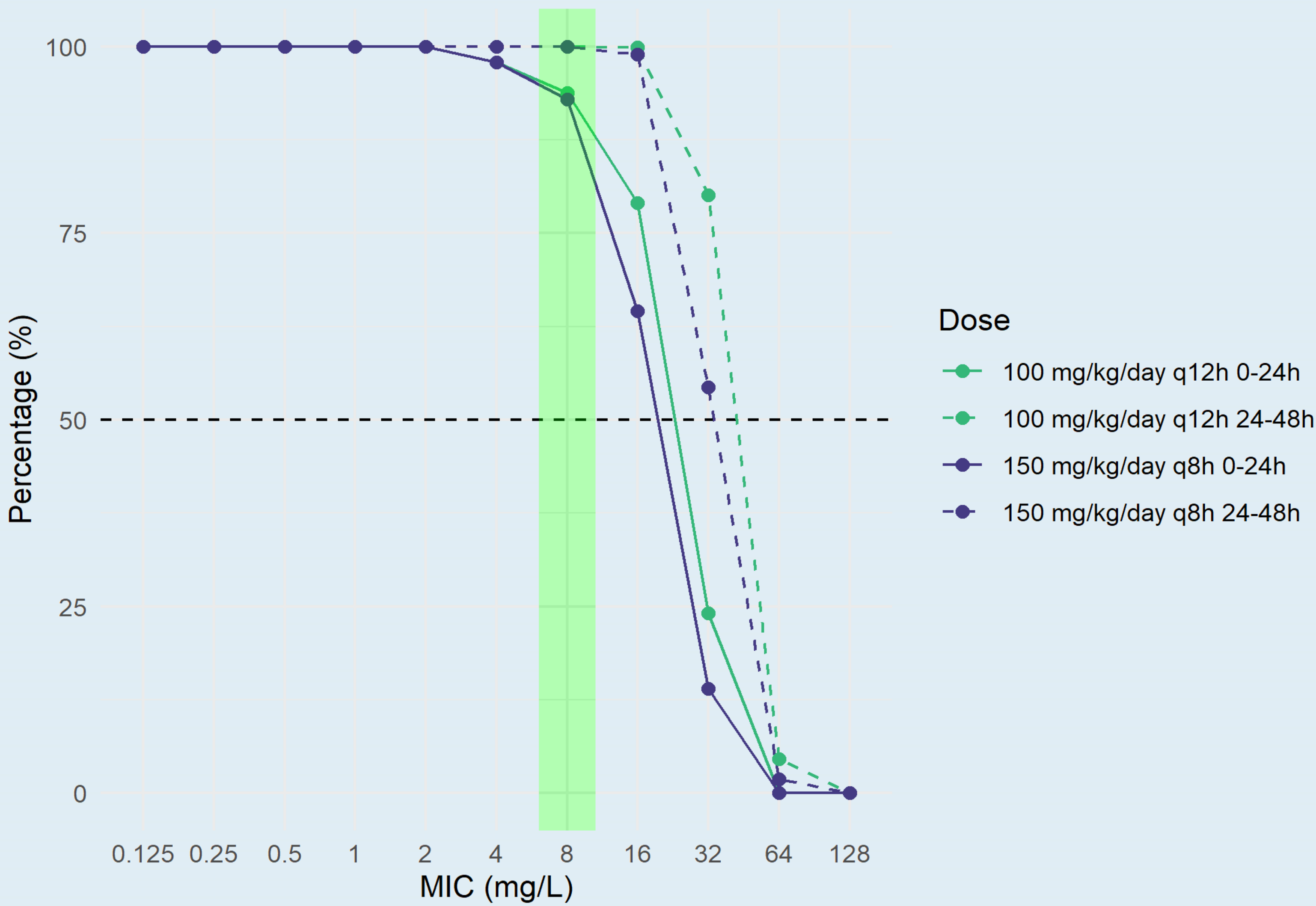


Figure 2: Percentage (%) of target attainment (fT>MIC = 8 mg/L) for intravenous amoxicillin.

		Postnatal age (days)	
		0 – 7	7 – 28
Gestational age (weeks)	34 – 37	50 mg/kg q12h	50 mg/kg q12h
	37 – 41	50 mg/kg q12h	60 mg/kg q12h

Table I: Oral amoxicillin dosage recommendations. q12h: Two times daily.