Minimization of a utility function for optimizing the dosing frequency of amoxicillin administration in neonates according to a fixed PK/PD index

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OBJECTIVE

Optimize *a priori* amoxicillin dosing regimen by individualizing dosing frequency of 50 mg/kg dose in neonates according to weight cut-offs (CO) with the aim to:

- achieve antibiotic exposure to concentrations above the minimum inhibitory concentration (MIC) during the entire dosing interval (100%T>MIC)
- while avoiding drug administered in excess and prolonged time below the MIC

METHOD

Individual exposure was simulated from a popPK model using ARPEC patient's demographic characteristics. Identification of optimal individualized dosing strategies via minimization of a **utility function**. **Dosing interval τ** and **weight CO** were the parameters to be **optimized**. The utility function implemented in NONMEM[1] allows quantification of

1. the risk associated with the deviation from the treatment target (PK/PD index:**100%T>MIC**) i.e. aiming to achieve drug concentrations above the MIC for the entire dosing interval (**efficacy**)

$$Y_1 = [\ln(\mathbf{100\%}\boldsymbol{T > MIC}) - \ln(\%T > MIC)_{individual}]^2$$

2. to minimize the time that neonates are exposed to concentrations below the MIC (**regrowth**) i.e. for > **4 hours** per dosing interval

$$Y_2 = [\mathbf{4} - (Time < MIC)_{individual}]^2$$

3. to **minimize** the amount administered in excess (AIE) (**adverse events**)

$$AIE = \left(\frac{1}{\tau} - \frac{1}{\tau_{dose}}\right) \Big/ \frac{1}{\tau_{dose}}$$

τ : estimated dosing interval

τ_{dose} : dosing interval resulting in 100%T> MIC for each individual

$$Y_3 = [0 - (AIE)_{individual}]^2$$

The utility function to minimize is

$$Y = Y_1 + Y_2 + Y_3 + \varepsilon$$

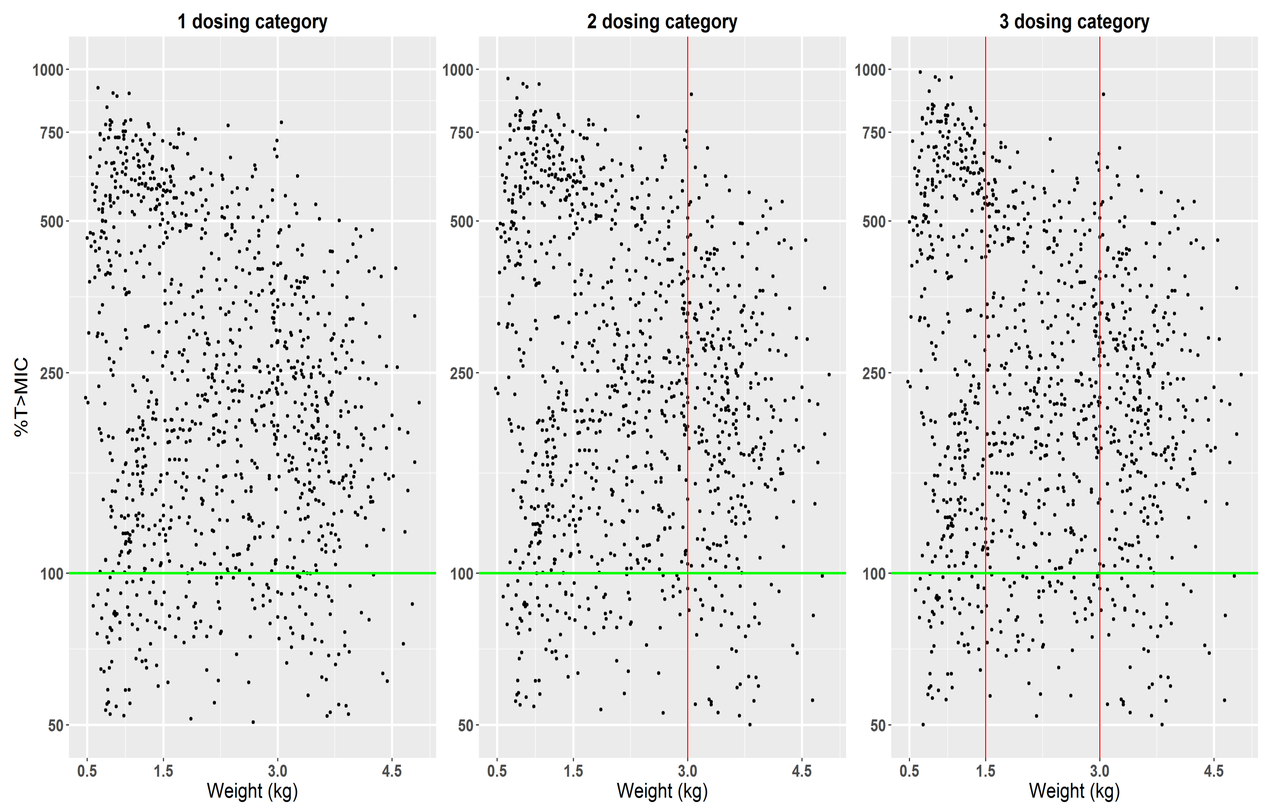
Estimation of weight CO was a stepwise search in which the COs were restricted to take value multiples of 0.5 kg.

Single dose administered was fixed to 50 mg/kg, the non-species related breakpoint for amoxicillin resistance of 8 mg/L was used for the MIC[2].

RESULTS

For a fixed dose of 50 mg/kg, optimum weight COs were 3 kg for 2 categories, and 1.5 kg and 3 kg for 3 categories. However, the difference in estimated dosing interval per weight subgroup was small for both 2 or 3 dosing categories (table):

Fixed dose 50 mg/kg			
2 dosing categories		3 dosing categories	
Weight (kg)	Dosing interval (hrs)	Weight (kg)	Dosing interval (hrs)
< 3	16.4	< 1.5	18.5
≥ 3	15.3	1.5 - 3	16.2
		≥ 3	15.8



This suggests that amoxicillin exposure might be optimal without neonatal dosing categories based on weight cut-offs when using 50 mg/kg as a fixed dose.

Driven by efficacy endpoints and for clinical implementation, a 12h interval appears to be the most convenient. In terms of efficacy, 50 mg/kg every 12h results in 93% of patients reaching 100%T>MIC and 1.5% being > 4h below the MIC after the first dose

CONCLUSION

- The method facilitate dose decision based on quantitative rational drug dosing using a combined utility function. This is particularly valuable in the dynamic neonatal population which exhibits highly correlated weight and age values.
- It was applied to body weight but it can be extended to other demographic factors that may be clinically relevant and facilitate implementation during routine clinical care.

Limitation: the PK model used for simulations requires validation

References:

(1) Viberg A et al. J Clin Pharmacol. 2008 Nov;48(11):1270-81.

(2) EUCAST. Clinical breakpoints. http://www.eucast.org/clinical_breakpoints/ (2017-02-20)

ARPEC data are used under the kind permission of Prof. Herman Goossens and Ms Ann Versporten , University of Antwerp, and the ARPEC project group