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BRIEF REPORT

Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs

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Abstract The defined daily dose (DDD) as defined by the World Health Organization (WHO) has been the most frequently used unit of measurement to measure antibiotic use. However, measuring antibiotic use in paediatrics is a problem as the WHO DDD methodology is not applicable in children (aged >1 month) due to the large variation in body weight within this population. Based on the narrow range of body weights in the neonatal population, we therefore aimed to develop a set of neonatal DDDs for antibiotics. Eight well-respected (inter)national sources for dosage recommendations of antibiotics in children and neonates were consulted for the assumed maintenance dose of the ten most frequently used antibiotics in neonatal intensive care units in its main indication for neonates. A set of neonatal DDDs for ten commonly used antibiotics in neonates based on an assumed neonatal weight of 2 kg was proposed. Primarily in children DDDs are not applicable to quantify antibiotic use since there is large variation in body weight. In the neonatal population, however, based on its narrow range of body weights and when access to patient level data is not available, neonatal DDDs can be used as a unit of measurement.

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Detailed quantitative and qualitative knowledge of antibiotic use is essential to implement strategies for reducing overuse, underuse and misuse of antibiotics in order to address the threat posed by resistant microorganisms. Antibiotic use in hospitals can be quantified using several methods. The defined daily dose (DDD) as assigned by the World Health Organization (WHO) has been the most commonly used unit of measurement to quantify (e.g. as the number of DDDs used per 100 hospital days) in various settings and is particularly recommended to compare drug use between (international) settings, and has it shown its value for this purpose [1, 2]. The DDD is the assumed average maintenance dose per day for a drug in its main indication for adults and is commonly expressed with a certain population size denominator such as patient days, bed days, admission days, inhabitant days. The popularity of the DDD mainly originates from its general applicability and its advantage that comparison of the amount of drug use between different (international) settings and between different drugs based on grouped dispensing data is possible without requiring utilization data on the individual patient level. The main disadvantage is that the DDD neither reflects the recommended, nor the actual prescribed daily dosage (PDD) for individual patients or specific patient populations [3–7]. Hence, in an ideal situation, the actual consumption of antibiotics should be measured at the level of the individual patient and subsequently aggregated over patient groups and settings. This gives more precise estimates but more importantly also allows study of associations on an individual patient level between patient characteristics, setting characteristics (e.g. antibi-

otic policy), antibiotic use and clinically relevant outcomes, including antibiotic resistance [4].

One of the other main shortcomings of the DDD methodology is its applicability in paediatrics. In an editorial commentary, Monnet concluded that in addition to the revision of WHO DDD, more research is needed to address other problems, such as the difficulty in measuring antibiotic use in children in those hospitals where data at patient level are not available [5]. Problems arise because dosing of antibiotics in children is based on body weight. Therefore, in order to calculate a paediatric DDD, an average body weight for the paediatric population needs to be assumed. However, in our opinion, this methodology is questionable as there is a large variation in body weight within the paediatric population. This view is supported by the WHO International Working Group for Drug Statistics Methodology's publication 'Guidelines for ATC classification and DDD assignment' [8]. In this, the WHO states that it is impossible to define paediatric DDDs because dose recommendations for use in children vary according to age and body weight (and setting). Furthermore, many drugs used in paediatrics are not even approved for such use and dosing information is not available. In response to the WHOs negative comments about paediatric DDDs, several alternative measurement systems for antibiotic use in children have been proposed, e.g. an estimation of antibiotic exposure by controlling for patient weight and amount of wasted drug [9, 10].

Nevertheless, regarding the issue on variation in body weight, one should distinguish children (>1 month of age) from neonates (<1 month of age) as the variation in body weight in children (mean body weight at age 1 month is 4.2 kg [11]; mean body weight at age 17 years is 60 kg [12]) is larger compared to the neonatal population (mean body weight 2.1 kg ± 1.0, based on own data). Consequently, in our view the disadvantage of the DDD methodology in paediatrics is more relevant for children than for neonates. Therefore, we aimed to devise a set of neonatal DDDs for antibiotics. We consulted eight well-respected (inter)national sources for dosage recommendations of antibiotics in children and neonates for the assumed maintenance dose of the ten most frequently used antibiotics in NICUs in its main indication for neonates (i.e. neonatal sepsis) (Table 1) [13]. Considering these antibiotics we did not find discrepancies in the dosage recommendations between the various evaluated sources. In addition, this overview of assumed maintenance dosages was evaluated and approved by two external experts: a hospital pharmacist and a paediatrician-infectious disease specialist. As a result, we propose a set of neonatal DDDs for commonly used antibiotics in neonates based on an assumed neonatal weight of 2 kg (Table 1). Regarding these proposed neonatal DDDs, one should, however, take into account the general limitations of the DDD but also limitations specific

Table 1 Overview neonatal defined daily doses (DDDs) top ten antibiotics neonatal intensive care units (NICUs)

Name of antibiotic	Maintenance dose in mg/kg/day in its main indication for neonates [Reference]										Assumed maintenance dose in mg/kg/day in its main indication for neonates	Neonatal DDD (g) (assumed average body weight of 2 kg)	Adult DDD[a] (g) (assumed body weight of 70 kg)	Factor (adult vs neonatal DDD)
	[16]	[17]	[18]	[12]	[11]	[19]	[20]	[21]						
Ampicillin	n.a.	100	100	100	100–200	100–200	100	200	100			0.2	2	10
Amoxicillin	75–100	n.a.	n.a.	n.a.	100–150	n.a.	n.a.	n.a.	100			0.2	1	5
Amoxicillin and enzyme inhibitor	100	n.a.	n.a.	n.a.	90	n.a.	n.a.	n.a.	100			0.2	3	15
Flucloxacillin	100	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	100			0.2	2	10
Ceftazidime	150	150	150	150	75	150	150	150	150			0.3	4	13
Cefotaxime	150	150	150–200	150–200	75–100	150–200	150–200	150	150			0.3	4	13
Meropenem	60	60	60	60	60	60	60	60	60			0.12	2	17
Erythromycin	30	n.a.	n.a.	30	50	n.a.	n.a.	n.a.	30			0.06	1	17
Gentamicin	4	5	5	5	4	5	5	5	4			0.008	0.24	30
Vancomycin	30	30	30	30–60	45	30–60	30	30	30			0.06	2	33

n.a. not available

[a] Established by WHO in 2005

to this patient group such as the policy on handling of waste of unused antibiotics in a NICU setting. After all, waste of unused antibiotics would not reflect a real estimate of neonatal DDDs.

Obviously, our proposed neonatal DDDs do not alter the fact that there is a lack of data on antibiotic use on the individual patient level. Yet, with the increasing use of computerised medical information systems it will be considerably easier to get access to data on the level of the individual patient, such as days of therapy (DOT). DOT is not influenced by discrepancies between the DDD and the PDD, by changes in the WHO assigned DDD and is independent of age- and weight-related differences in dosage [7, 14]. A major disadvantage of this parameter is, however, that currently such detailed data on the individual patient level are not readily available. Moreover, if one would like to link data on antibiotic use to resistance, preferably both units of measurement, DOT (*in*dependent of dosage) and DDD (dependent of dosage), should be used, since it is unidentified which of these measurement methods is most predictive of resistance [7]. A recent study has shown that repeated and/or prolonged antibiotic use in neonates resulted in an increase of hospital-acquired, antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and multidrug-resistant Gram-negative rods [15].

In conclusion, in order to quantify antibiotic use, the DDD methodology is not applicable in the paediatric population, mainly in children aged between 1 month and 18 years, due to the large variation in body weight within this population. Although, in the neonatal population, until patient level data are widely available and based on its narrow range of body weights, we suggest, illustrated by the example of antibiotics, that the neonatal DDD (nDDD) is a good alternative unit of measurement, both in research and for benchmarking purposes.

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