Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs

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To cite this version:
T. B. Y. Liem, E. R. Heerdink, A. C. G. Egberts, C. M. A. Rademaker. Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs. European Journal of Clinical Microbiology and Infectious Diseases, Springer Verlag, 2010, 29 (10), pp.1301-1303. <10.1007/s10096-010-0990-3>. <hal-00601515>
Title: Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs

Article Type: Brief Report

Keywords: antibiotic use; Defined Daily Dose (DDD); neonates

Abstract: Purpose
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), because 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.

Methods
Eight well-respected (inter)national sources for dosage recommendations of antibiotics in children and neonates were consulted for the assumed maintenance dose of the 10 most frequently used antibiotics in neonatal intensive care units in its main indication for neonates.

Results
A set of neonatal DDDs for ten commonly used antibiotics in neonates based on an assumed neonatal weight of 2 kg was proposed.

Conclusions
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 unit of measurement.
Dear Dr Van Belkum,

Thank you very much for the comments on our manuscript, which helped us to improve our manuscript.

We are very pleased that our manuscript is considered interesting and that we have been given the opportunity to revise the document.

We highlighted all changes in yellow in the revised manuscript and mentioned the referring line numbers in our answers to you.

We have carefully studied the comments and included a point by point summary of our response on the comments (see below).

Answer to the comments of the reviewer:

**Major remarks**

1. The reliability of the proposal of DDDs can be improved considerably by including more details about the exact proposed dose given by each of the eight 'well-respected' sources and by adding this information to table 1.

We added the exact proposed dosages of the ten antibiotics given by each of the eight reference sources to table 1.

2. You mentioned to present DDDs for 'the 10 most frequently used antibiotics in NICUs'. What sources did you use to identify these 10 antibiotics? Did you also include international sources?

For the selection of the 10 most frequently used antibiotics in neonates, we used data of our study as recently published in the Journal of Antimicrobial Chemotherapy (Liem et al. J. Antimicrob. Chemother. 2010; 65: 1270-1275; doi:10.1093/jac/dkq107) in which we showed the variation in antibiotic use in all ten tertiary care neonatal intensive care units in the Netherlands. In addition, we also included data of international studies on the antibiotic use in NICUs for this selection of 10 antibiotics, such as:

- Du W, Warrier I, Tutag L, V, Salari V, Ostrea E, Aranda JV. Changing patterns of drug utilization in a neonatal intensive care population. Am J Perinatol 2006; 23(5):279-285.
- Gortner L. Drug utilisation in preterm and term neonates. Pharmacoeconomics 1993; 4(6):437-445.
- Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J 2005; 24(9):766-773.
- Lesko SM, Epstein MF, Mitchell AA. Recent patterns of drug use in newborn intensive care. J Pediatr 1990; 116(6):985-990.
- Warrier I, Du W, Natarajan G, Salari V, Aranda J. Patterns of drug utilization in a neonatal intensive care unit. J Clin Pharmacol 2006; 46(4):449-455.
Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. Pediatrics 2006; 117(6):1979-1987.

The ‘Instructions for authors’, however, don’t permit us to add all these articles to the reference list, as a maximum of 10 references is allowed for a ‘Brief report’.

3. In your report, you motivated why you developed DDDs for neonates. As long as comparisons are geographically limited to one country however, other methods to approach the volume of consumed antibiotics can be used. You forgot however to mention that the use of DDDs is particularly recommended for international comparisons.

We agree with the reviewer’s comment that the use of DDDs is mainly recommended for international comparisons. Therefore, we rephrased lines 61-62 and 67 in our revised manuscript.

4. You mentioned the link between antibiotic use and resistance. I am wondering however if a relationship between neonatal antibiotic use and resistance has been demonstrated, as yet. If so, references need to be added. If not, please speak about resistance in a more generalized way, clearly stating that there is still a lack of knowledge in this field.

There certainly have been studies showing a relationship between antibiotic use and resistance in neonates. Therefore, we added some information (including a reference) regarding this issue in lines 129-133 in our revised manuscript.

Editing remarks

1. I do not know if form requirements exist for the publication of a Brief Report in the journal. It looks rather strange however, that on the one hand a well-structured abstract was added to your report and that on the other hand, the body of the report lacks any structure.

Although we submitted our manuscript as a ‘Brief Report’, the ‘Instructions for authors’ of the European Journal of Clinical Microbiology and Infectious Diseases stated that we are obliged to submit a structured abstract of 150 to 250 words which should be divided into the following sections: Purpose (stating the main purposes and research question), Methods, Results, Conclusions.

2. The complete references of the ‘well-respected’ sources should be added to the reference list with only reference numbers in table 1.

We added the complete references of the eight reference sources to the reference list of our revised manuscript. As a consequence we exceed the maximum of 10 references as stated for a ‘Brief report’.
Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs

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Abstract

Purpose
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), because 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.

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Conclusions
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 unit of measurement.
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 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 to study associations on an individual patient level between patient characteristics, setting characteristics (e.g. antibiotic 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 WHO’s 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: 4.2 kg [11]; mean body weight at age of 17 years: 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 10 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 found 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 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 (independent 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-18 years, because 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.
Acknowledgments

We thank dr. J. Zwaveling, hospital pharmacist, and dr. T.F.W. Wolfs, paediatrician-infectious disease specialist, for evaluating and approving the overview of assumed maintenance dosages of antibiotics in neonates.
## Table 1. Overview neonatal DDDs top 10 antibiotics NICUs

| Name of antibiotic | Maintenance dose in mg/kg/day in its main indication for neonates | Assumed maintenance dose in mg/kg/day in its main indication for neonates | Neonatal DDD (assumed average body weight of 2 kg) | Adult DDD (WHO 2005) (g) (assumed body weight of 70 kg) | Factor (adult vs neonatal DDD) |
|--------------------|---------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------|------------------------------------------------------|-----------------------------|
| Ampicillin         | n.a. 100 100 100 100 100-200 100-200 100 200 100 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
Reference List

[1] Natsch S, Hekster YA, de JR, Heerdink ER, Herings RM, Van Der Meer JW. Application of the ATC/DDD methodology to monitor antibiotic drug use. Eur J Clin Microbiol Infect Dis 1998; 17: 20-24.

[2] World Health Organization. Guidelines for ATC Classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health: 2002.

[3] Berrington A. Antimicrobial prescribing in hospitals: be careful what you measure. J Antimicrob Chemother 2010; 65: 163-168.

[4] De With K, Maier L, Steib-Bauert M, Kern P, Kern WV. Trends in antibiotic use at a university hospital: defined or prescribed daily doses? Patient days or admissions as denominator? Infection 2006; 34: 91-94.

[5] Monnet DL. Measuring antimicrobial use: the way forward. Clin Infect Dis 2007; 44: 671-673.

[6] Muller A, Monnet DL, Talon D, Henon T, Bertrand X. Discrepancies between prescribed daily doses and WHO defined daily doses of antibacterials at a university hospital. Br J Clin Pharmacol 2006; 61: 585-591.

[7] Polk RE, Fox C, Mahoney A, Letcavage J, MacDougall C. Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. Clin Infect Dis 2007; 44: 664-670.

[8] WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2009. Oslo: 2008.

[9] Antachopoulos C. Development of a paediatric daily defined dose system for the measurement of antibiotic consumption in paediatric units. In. 2004.

[10] Bennet R, Eriksson M, Fant H. Estimating exposure to antimicrobial agents in a pediatric hospital ward, controlling for patient weight and waste of unused drug [abstract K-1413]. In Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology: 2006: 345.

[11] Paediatric Formulary Committee. BNF for children 2009. London: BMJ Group, RPS Publishing and RCPCH Publications; 2009.

[12] Taketomo CK, Hodding JH, Kraus DM. Pediatric Dosage Handbook, 15th ed. Hudson, Ohio: Lexi-Comp; 2008.

[13] Liem TB, Krediet TG, Fleer A, Egberts TC, Rademaker CM. Variation in antibiotic use in neonatal intensive care units in the Netherlands. J Antimicrob Chemother 2010.
[14] Pakyz AL, Gurgle HE, Ibrahim OM, Oinonen MJ, Polk RE. Trends in antibacterial use in hospitalized pediatric patients in United States academic health centers. Infect Control Hosp Epidemiol 2009; 30: 600-603.

[15] Bizzarro MJ, Gallagher PG. Antibiotic-resistant organisms in the neonatal intensive care unit. Semin Perinatol 2007; 31: 26-32.

[16] Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (NKFK), Het Kinderformularium. www.kinderformularium.nl. In. 2010.

[17] Sáez-Llorens X, McCracken Jr GH. Clinical pharmacology of antibacterial agents. In: Remington JS, Klein JO, Wilson CB, Baker CJ (eds.), Infectious Diseases of the Fetus and the Newborn Infant., 6th ed ed. Elsevier Saunders; 2006: 1223-1267.

[18] James LP, Abdel-Rahman S, Farrar HC, Jacobs RF. Antimicrobial agents. In: Long SS, Pickering LK, Prober CG (eds.), Principles and practices of pediatric infectious diseases., 2e ed. ed. Churchill Livingstone; 2003: 1458-1510.

[19] Rennels MB, Frenck RW, Baker CJ, Long SS, Baltimore, McMillan JA. Red Book. Elk Grove Village: American Academy of Pediatrics; 2006.

[20] Michelow IC, McCracken Jr.GH. Antimicrobial Therapeutic Agents. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL (eds.), Textbook of Pediatric Infectious Diseases, 5th ed. Elsevier Saunders; 2004: 2987-3029.

[21] Bradley JS, Nelson JD. Nelson's Pocket Book of Pediatric Antimicrobial Therapy, 7th ed. Elk Grove Village: 2009.