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Antimicrobial defined daily dose adjusted by weight: A proposal for antibiotic consumption measurement in children



Dosis diaria definida ajustada por peso: una propuesta para la medición de consumo antimicrobiano en pediatría

Dear Editor,

We read with great interest the article “Antimicrobial defined daily dose adjusted by weight: a proposal for antibiotic consumption measurement in children” by Montecatine-Alonso et al. The authors provide novel data to formulate and establish a measurement that better reflects the actual use of antibiotics in hospitalized children.¹ Quantifying antimicrobial use (AU) is essential in antimicrobial stewardship (AS) since it allows both the measurement of the impact of the program and benchmarking. Currently, an optimal standardized metric of antimicrobial consumption is lacking, especially for the pediatric population. Days of Therapy (DOT) has become the preferred measurement in children and adults, while Defined Daily Dose (DDD) is listed as an alternative option in recent guidelines and publications.^{2–5} The simultaneous use of at least two metrics to express AU has also been recommended in order to make up for the drawbacks of each one.⁶

Aiming to define suitable DDD for children, the authors retrospectively collected the age and sex of 45,575 pediatric patients admitted to 10 Spanish hospitals during a 12-month period and also the most frequently used weight-based doses of 29 antibiotics and 4 antifungals. The mean WHO weight for age was then used to estimate DDD for the children. Although the authors acknowledge the main limitations of their study, we would like to further comment on the methodological approach and data interpretation in the current validation phase of the proposed tool.

Firstly, the rate of AU in the included patients was unknown. The AU rate may vary between age ranges, but also between different centers and physicians, according to the reason for admission, the duration of hospital stay, and the individual medical history. Also, even if a 12-month study period may be of reasonable length for the purpose of the study, it should be borne in mind that it only partly avoids the potential impact of seasonality (e.g. the number and severity of infants admitted due to bronchiolitis could change significantly from one year to another).

In addition to the potential deviation of the estimated median age, the calculation of a unique value may oversimplify the high variability of children's weight, precluding the comparison between centers admitting children with different age or weight ranges. In accordance with Porta et al.,⁷ the authors suggest the use of weight bands to calculate weight-adjusted DDD to allow easier benchmarking. Moreover, to improve the validity of the weight estimation method, data on the actual weight of the study cohort

and how these agree with WHO or Spanish reference weight charts would be of great value.

Accurate details on antimicrobial inclusion and exclusion criteria are lacking and it is unclear why some of them were left out, such as voriconazole and the most frequently used antivirals. When surveying the most frequently prescribed doses, the need for consensus could obviate not only variations in patients' complexity among different centers, but also not so uncommon dosages (e.g. the oral use of amoxicillin at 80 mg/kg/day). Finally, the discrepancy in the most frequently prescribed doses in nearly one quarter of cases may be higher in daily clinical practice than what is reflected in a questionnaire under study conditions.

Currently, DOT remains the metric of choice in all age ranges despite its limitations. We believe that efforts should be made into obtaining the most precise AU data (antimicrobial administration and/or prescription data *versus* purchasing or dispensing data), and improving the homogenization of denominators (days-present *versus* patient-days) and reliable estimations (patient-days calculation based on calendar days *versus* passages of midnight).^{6,8} Likewise, finding complementary tools to overcome the limitations of DOT such as the potential to favor the use of less antimicrobials even when these are of broader spectrum is mandatory.⁹

The large number of patients and participating centers and a 1-year study period are remarkable strengths of the present study. We believe that this work and future ones could significantly contribute to improving the quantification of AU in children, providing a novel metric complementary to DOT. The proposed DDD adjusted by weight needs internal and external validation. Also, the use of weight bands and focus on a specific age range with more homogeneous weights, such as the neonatal age, should be considered.¹⁰

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In reply to: “Antimicrobial defined daily dose adjusted by weight: A proposal for antibiotic consumption measurement in children”



En respuesta a: “Dosis diaria definida ajustada por peso: una propuesta para la medición de consumo antimicrobiano en pediatría”

Dear Editor,

We thank the authors of the letter¹ (AOL) for their interest in our manuscript.² They have correctly pointed out the importance of quantifying antimicrobial use (AU) for antimicrobial stewardship programs (ASP), recalling the lack of an optimal standardized metric for paediatric patients while reviewing current recommendations on approved metrics: Days of Therapy (DOT) and Daily Defined Dose (DDD). Further comments on the methods and the results interpretation in our article has been made.² We agree with their comments, which correctly summarized some of the challenges we have faced and mentioned in the manuscript and would like to further elaborate on some of the points stated.

We agree that the AU rate may possess different sources of variability that may not have been fully covered through the time period selected. The chosen 12-month period (which importantly includes the winter season) focused on setting up the methodology for the proposed metric, however validation will require an extended period.

We also agree that age and weight variability between different cohorts hampers the comparison between centres and benchmarking. As suggested in our manuscript, and supported by the AOL with additional references, weight-adjusted DDD would require the use of weight bands,³ which our group is in the process to establish for the validation phase. Dose based metrics with agreed doses for standardization indeed could obviate dose variability, however a harmonized set-up value is necessary to allow benchmarking and comparison.⁴ Aggregate metrics for ASP tackles patient's complexity and dose variability in real life practice by the distribution of cases through periods of time, although this may not be exact in all situations and interpretation of data deviation is required.⁴

Admittedly, antimicrobial inclusion and exclusion criteria are lacking in our methodology. Antibiotics were included based on available data between centres. Voriconazole (not widely used in all included hospitals) and antiviral drugs (data was not systematically recorded by all participants) were not included. Great efforts were made (Delphi methodology) in order to homogenize antibiotic doses. Nevertheless, and not surprisingly, discrepancies were

observed and are possibly more pronounced in non-study conditions as it is frequently observed in clinical settings.

The AOL state that DOT remains the metric of choice for all ages based on recommendations and guidelines from the United States of America (USA).^{5,6} It must be noted, that DOT is the measure recommended by the Center for Diseases Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA),^{5,6} therefore hospitals in the USA have adapted to report their results using this metric. The IDSA guideline recommendation for using DOT in preference to DDD has a weak recommendation and low-quality evidence level, nonetheless recognizing the advantage of DOT in children due to weight-based dosing.⁵ However, DOT also possess limitations for its use in children and require patient level antibiotic use data which may not be available in all settings.^{4–7}

The referenced study by Stanić Benić et al., gives a global approach to the issue, reviewing different settings by different professionals to identify inpatient quantity metrics (IQM) for AU.⁸ Their consensus procedure resulted in a set of 12 IQMs where DDD and DOT based metrics were included among others.⁸ One of the IQM proposed was to preferably express AU in at least two metrics simultaneously,⁸ as AOL suggest to overcome the disadvantages of individual metrics and get further information to correctly interpret AU data.

As mentioned in the manuscript, we agree that DDD has important disadvantages for monitoring AU in children and that DOT remains as the currently recommended option when available. Considering all this, we feel that our proposed metric, when refined and validated, may serve as a complementary option for DOT. Efforts should be directed not only to improve process metrics in our opinion, but also to develop impact metrics for paediatric ASP that would correlate with clinical outcomes and evaluate not only quantity but quality of AU.^{6,9,10} The quest for the best AU metric in children continues, and further data and investigation is needed.

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Conflicts of interest

None to declare.

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