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Letters to the Editor

Biomarkers: Another help tool to predict bacteriemia in the emergency department☆

Biomarcadores: otra herramienta de ayuda para predecir bacteriemia en el servicio de urgencias

Dear Editor,

We read with interest the review entitled "Microbiological diagnosis of bacteraemia and fungaemia: blood cultures and molecular methods" by Guna Serrano et al.[1] An excellent article in which it is underlined that the detection of bacteraemia and fungaemia is a priority for the clinical microbiology department due to its significant diagnostic and prognostic relevance. The importance of adequate blood culture collection prior to antibiotic treatment for patients with sepsis[2] is also highlighted, which may determine their progress and mortality.[3] Furthermore, the authors state "nowadays, we cannot discuss the diagnosis of sepsis without taking into consideration the detection of biomarkers".[1]

In this context, bearing in mind that around 60% of sepsis cases are diagnosed in hospital emergency departments (HED)[2] and that the vast majority of blood cultures, which are sent to the microbiology department for processing, are obtained in these departments,[4] we would like to highlight the importance of correctly suspecting and predicting the existence of bacteraemia in the HED for the patient. The new sepsis definitions (as well as the traditional ones) have limitations as they are not very specific,[4] hence why there are disputes and different proposals regarding the inclusion of other criteria for diagnosing infection, sepsis and/or bacteraemia.[5] In recent years, different reviews have been published which propose different criteria to optimise the indications for blood culture collection, as well as to improve their efficacy (increasing the number of positive blood cultures), effectiveness (reducing the number of contaminated blood cultures) and efficiency (cost of collection and processing, improving the adequacy and timeliness of antibiotic treatment, decision to discharge or admit).[6] Thus, finding an applicable and genuinely useful predictive model for bacteraemia has become the objective of many authors combining different clinical, epidemiological and analytical variables, among which biomarkers such as procalcitonin (PCT), which increases the predictive performance of these models and is available in the vast majority of HEDs throughout Spain, currently stand out.[4,7]

At our centre, since the implementation years ago of "code sepsis" (CS), we use directed triage (where from the initial patient assessment, laboratory tests for lactate and PCT are carried out, and, in case of suspicious findings, blood cultures are performed).[8] We also follow the recommendations of Julián-Jiménez et al.,[7] in which blood culture collection is indicated if the PCT concentration is >1 ng/ml. In this regard, we created a retrospective study in relation to the two conditions that result in the highest number of cases of sepsis and bacteraemia in HEDs: urinary tract infections (UTIs) and pneumonia. In this study, we have proven, in the second half of 2017 on adult patients aged ≥18 years, that PCT, which is usually available in HEDs, is the biomarker with the best prognostic performance for bacteraemia (better than C-reactive protein). A total of 346 patients were included, from whom blood cultures were taken (125 cases of pneumonia of which 18 [14.4%] had bacteraemia, and 221 cases of UTIs of which 25 [11.31%] had bacteraemia), with a mean age of 56 ± 24 and 54% of whom were female. To predict the existence of bacteraemia, PCT obtained the greatest area under the Receiver Operating Characteristic curve (AUC-ROC) of 0.94 (95% CI: 0.91–0.98; $p < 0.001$) and, with a cut-off point of ≥0.95 ng/ml, a sensitivity of 98%, a specificity of 94%, a positive predictive value of 84% and a negative predictive value of 98% were obtained. Meanwhile, CRP (mg/l) obtained a predictive performance with an AUC-ROC of 0.652 ($p = 0.28$). The mean values when comparing PCT in patients with pneumonia and UTIs with/without bacteraemia were 9.26 ± 16.42 vs. 0.36 ± 0.38 ng/ml; $p < 0.001$. As a conclusion to our study and experience, and in line with the recommendations of other authors, we can safely say that PCT is of use and provides great diagnostic performance for the prediction of bacteraemia in HEDs, improving both blood culture indications and results. It also helps us to get urgent decisions, such as the timely and adequate administration of antibiotics, and the decision to admit the patient and in the most appropriate place, right.

Therefore, as Guna Serrano et al. state in their article, we consider it relevant and necessary to include biomarkers as support tools in the assessment and confirmation of patients with sepsis, as well as to confirm suspected bacteraemia in the HED.[4,9]

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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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