Med Intensiva. 2020;44(5):265–266

medicina intensiva

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EDITORIAL

Adequate antibiotic monitoring to improve what needs to be improved

Monitorización adecuada de antibióticos para mejorar lo que necesita mejorarse

R. Amaya-Villar

Jefa de Servicio, UGC Cuidados Intensivos, Hospital Universitario Virgen del Rocío, Avda. Manuel Siurot s/n, Sevilla 41013, Spain

The World Health Organization (WHO) defines that patients receive appropriate medications to their clinical needs if they are prescribed in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. These general principles are obviously applicable to antimicrobial use in general and to the administration of antimicrobials in the critical care setting. Many parameters of importance for optimal quality of antimicrobial therapy have already been defined. Maximal efficacy of the treatment should be combined with minimal toxicity at the lowest cost. Quality of antimicrobial drug use is dependent on knowledge of many aspects of infectious diseases and patient characteristics.[1]

Inappropriate use of antimicrobial drugs is the major determinant of antimicrobial resistance development increasing the costs of care, morbidity and mortality. Critically ill patients are especially complex suffering profound pathophysiological changes that can affect PK/PD properties of antibiotics.[2]

Institutional programs aiming at reducing the inappropriate use of antibiotics have been launched worldwide. These activities require accurate comparators of antibiotic consumption to benchmark antimicrobial drug use. The three more common metrics for measuring aggregate antimicrobial use are the defined daily dose (DDD), the prescribed daily doses (PDD), and the days of therapy (DOT).[3]

The DDD is the measure endorsed by the WHO, and nowadays, the metric most widely used for comparisons of antibiotic use in primary care and in hospitals. The consensus document of the Spanish programs for optimizing the use of antibiotics (PROA) in hospitals recommends DDD as the basic meter for monitoring antibiotic consumption considering DOT and DDP as metrics of excellence.[4]

However, many studies have documented that DDD does not accurately reflect the antibiotic consumption and the quality of antibiotic prescription. One of the major drawbacks of DDD measurement is that it underestimates antibiotic consumption when the WHO-consigned DDD is greater than the administered dose as occurs in patients with renal insufficiency or in pediatric populations. Conversely, DDD overestimates antibiotic consumption when reference DDD is lower than the administered dose as occurs very frequently in the critical care setting.

In this issue, the study by Vallès et al.[5] has documented that DDD misjudges antibiotic use in adult critically ill patients overestimating the utilization of the majority of antibacterial and antifungal drugs. Previous studies have shown discordant measurements between DDD and DOT.[6–8] The measurement of DOT favors those situations where broad spectrum monotherapy is used, independently of the dosages administered. DOT punishes the use of combination therapy including those with narrow spectrum antimicrobials. DOT is more difficult to measure requiring patient-level antibiotic use data, but it has been demon-

E-mail address: ramayavillar@gmail.com

strated to be a superior measurement methodology than DDD.[9]

These differences may be even greater in burns or neurocritical care units.[7] Severe burn injury results in a complex physiological derangement that significantly alters drug PK/PD. Burns patients require higher and more frequent dosing to reach and maintain therapeutic levels. Similarly, antibiotic doses are higher for central nervous system (CNS) infections than for other infections in order to achieve therapeutic levels in the CNS.

Nowadays, high doses of antimicrobials are used appropriately in the ICUs. The advent of therapeutic drug monitoring has revealed that up to 50% of critically ill patients have suboptimal antibiotic plasma concentrations (beta lactam, aminoglycosides, etc.), especially those with augmented renal clearance or high volume of distribution.[10] The dramatic increase in bacterial resistance is the other factor that forces clinicians to increase antibiotic dosing to prevent therapeutic failure and death. Therefore, in this scenario, DDD will not accurately reflect the quality of antibiotic prescription punishing hospital with routine use of TDM or those with outbreaks or endemics of multi-drug resistant bacteria.

In the study by Vallès and colleagues,[5] discrepancies between DDDs and DOTs were major (>25%) in nine antibiotics and in three antifungals. It is true that in 2019, WHO has modified the DDD of several critical antibiotics to bring DDD closer to the usual dose of antibiotics.[11] This modification affects only to four of the antimicrobials including in the list of ''major differences'' (amoxicillin–clavulanic, cefepime, ciprofloxacin, and meropenem) and none of the antifungals. Moreover, these updated DDD are still lower than the doses used in many critically ill patients. As examples, 3 g a day of meropenem may be clearly insufficient in hyperdynamic critically ill patients as occurs with de new DDD of ampicillin (6 g a day) for the treatment of a bacteremia caused by *Enterococcus faecalis*.

The study by Vallès et al.[5] is not absent of some limitations. It is a single center study so their findings cannot be extrapolated to other Units with different levels of complexity. However, its compelling data should be taken into account to consider DOT as the standard measurement to monitor antibiotic use in the critical care setting. In fact, the new Infectious Diseases Society of America (IDSA) antibiotic stewardship guidelines suggests the use of DOT over the DDD for antibiotic consumption monitoring.[12]

There is room for improvement in antibiotic prescriptions in all hospitals and obviously in the ICUs. However, validated antibiotic use data are needed to provide correct feedback to clinicians. The DOT method should be also used to carry out national and international comparisons among different Units. In critical care units, DOT, undoubtfully with its limitations, reflects more appropriately the quality of antibiotic prescription and ecological antibiotic pressure.

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