Med Intensiva. 2018;42(5):263–265

medicina intensiva

www.elsevier.es/medintensiva

EDITORIAL

Antimicrobial stewardship program in critical care medicine: What is going on? Who gives more?

Programas de optimización antibiótica en medicina crítica. ¿Qué está ocurriendo? ¿Quién da más?

R. Zaragoza Crespo[a,*], A.C. Cercos LLetí[b]

[a] *Intensive Care Unit, PROA TEAM, Hospital Universitario Dr. Peset, Valencia, Spain*
[b] *Pharmacy Department, PROA TEAM, Hospital Universitario Dr. Peset, Valencia, Spain*

It goes without saying that prompt, appropriate and adequate empirical antimicrobial therapy is life-saving, specially in Intensive Care unit (ICU) setting. Given the prevalence of antimicrobial resistance often results in use of very broad-spectrum agents in critically ill patients, even when risk factors for resistance are not present, many times for treatment of colonization or contamination or treatment of non-infectious or viral infections, or too-long or too-broad treatments. On the other hand early decisions to shift to directed therapy or cessation of therapy could reduce antibiotic exposure significantly. Consequently it leads to reductions in resistance and less cost. Controlling resistance selection within the ICU without any doubt has also an important impact in the whole hospital. For these reasons ICU is a unique and high-stakes setting for antimicrobial use that presents distinct challenges for antimicrobial stewardship programs (ASP).[1]

ASP include a set of activities intended to optimize the antimicrobial treatment, ensuring the best clinical outcome for the patient but avoiding where possible the development of antimicrobial resistance. The latter objective is largely based on the elimination of all those unfair treatments and on the replacement of broad-spectrum drugs when possible, reduction of time of antibiotic exposure and the elimination or decrease of adverse events and interactions associated with the use of antimicrobials. Antimicrobial de-escalation (ADE) of antimicrobial therapy, the cornerstone of ASP, is a strategy proposed to allow for the rational use of broad spectrum antimicrobial therapy as the empiric treatment for infections and minimize the overall exposure to these agents including the duration of the therapy.[1,2]

However, its implementation in ICU has an added difficulty due to patient severity, high multi-drug resistant microorganisms (MDRM) prevalence and pharmacokinetic-pharmacodynamic particularities. Some studies have been performed in ICU outside and inside our frontiers. Elligsen et al.[3] achieved a 23% reduction in consumption of antimicrobials and also a positive ecological effect related to an improvement in sensitivity to meropenem. Furthermore Rimaway et al.[4] in addition to a reduction in broad-spectrum antibiotics consumption, achieved a diminution in the days of mechanical ventilation and length of stay in the unit. In Spain, Garnacho et al.[5] carried out

DOI of original article: http://dx.doi.org/10.1016/j.medin.2017.07.002
* Corresponding author.
E-mail address: zaragoza_raf@gva.es (R. Zaragoza Crespo).

a prospective observational study enrolling 712 patients admitted to an unique ICU with severe sepsis or septic shock. ADE was applied in 34.9% of the patients. By multivariate analysis, factors independently associated with in-hospital mortality were septic shock, SOFA score the day of culture results, and inadequate empirical antimicrobial therapy, whereas ADE was a protective factor. A subanalysis in patients with adequate empirical therapy reconfirmed ADE as a protective factor.

A recent systematic review of the literature,[2] including 2 randomized controlled trials and 12 cohorts studies of ADE in critical care setting, showed a lack of uniform definition of ADE and a clear relationship between this approach with patients with broad-spectrum and/or appropriate antimicrobial therapy, when more agents have been used, in the case of absence of multidrug-resistant pathogens and lower or improving severity scores. ADE did not reduce the total duration of antimicrobial treatment costs or length of stay. Although the pooled estimate shows a protective effect of ADE on mortality, there was too much bias to retain this result as evidence for a direct beneficial effect due to the relationship with lower severity index. None of the studies included in this analysis were designed to investigate the effect of ADE on antimicrobial resistance.

Following the aim of optimizing antimicrobials use in Spanish hospitals, in 2012 several scientific societies produced an ASP consensus document.[6] Efforts have been made also in the field of antifungal agents in ICU based on Delphi methodology[7] and educational programs.[8] Since then, more and more centres in Spain have developed ASP (PROA in Spain) including in majority of the cases an intensivist in the PROA team.

In this issue, Ruiz et al.[9] from Hospital Universitario y Politécnico la Fe de Valencia, one of the pioneers of ASP in our country, have evaluated the experience of an ASP in an intensive care unit (ICU). Antimicrobial consumption, antimicrobial related costs, MDRM prevalence, nosocomial infections incidence, ICU length of stay, and ICU mortality rates were compared prospectively before and after one-year intervention. ASP was associated with a significant decrease in the prescription of antimicrobials. Total antimicrobial DDD/100 patient-days consumption was reduced from 380.6 to 295.2 and subsequently overall antimicrobial spending was reduced by €119,636. Neither MDRM isolation and nosocomial infections per 100 patient-days nor length of stay and mortality rates change after the intervention period.

As far as we concern, this is the first study in Spain describing the global results of an ASP in ICU. The benefits achieved in terms of reduction of cost must be considered as a highlight in this program. The report of adverse events associated with antimicrobial use is also remarkable as well as the high rate of acceptation of the suggestions made by PROA team inside ICU (91.5%). However, the authors have not been able to evaluate some of the indicators recommended to assess the appropriateness of antimicrobial treatment as days of treatment (DOT) and percentage of appropriate empirical treatment, these pitfalls reinforces the efficacy of an audit and feedback design in this kind of studies. Furthermore, we should note the great difficulty of achieving an effect on hospital stay or mortality due to the multitude of factors that influence the prognosis of critically ill patients as other authors suggest.[10]

As previously we have commented, some studies[3,4] have demonstrated an association of ASP with a reduction in the emergence of MDRM. Although ASP did not achieve a global significant decrease of total MDRM colonization rate in this study, a significantly reduction in MDR *K. pneumoniae* colonization was noted, more probably related with the control of an outbreak that the own effect of ASP.

To sum up, in concordance with Ruiz et al., the summarized data described in the literature further support the implementation of an ASP programme in critical care units, lead by an intensivist working in an interdisciplinary way with PROA team inside and outside the ICU. We support its implementation although there are not enough scientific evidence to show a positive impact of ASP on the evolution of critically patients and their ecological environment. A randomized trial is required to assess the effect of the ADE strategy on the bacterial ecosystem, on MDR carriage, and on patient outcomes specially in critically setting.

Funds

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgement

None.

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