

## Extended infusion of cephalosporins, penicillins and carbapenems: a cost-effective point-of-view and critical appraisal of Surviving Sepsis Campaign guidelines

## Infusão prolongada de cefalosporinas, penicilinas e carbapenêmicos: uma avaliação crítica, do ponto de vista econômico, das diretrizes da Surviving Sepsis Campaign

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**ABSTRACT | NARRATIVE/ INTRODUCTION.** In the last edition of the Surviving Sepsis Campaign guidelines - SSC guidelines - recommendations regarding the optimization of antibiotics pharmacokinetics and pharmacodynamics (PK/PD) were made. Among these, the use of extended infusion of beta-lactams (penicillins, cephalosporins and carbapenems), are proposed to improve clinical and microbiological outcomes. However, according to the authors, studies of the economic implications of extended infusion - cost-effectiveness studies - are needed for these recommendations. **CAVEATS.** Sepsis represents a huge economic burden around the world due to the need for hospital and ICU beds, qualified staff and therapies for the treatment of the pathology, whereas it is known that antibiotics are the mainstay therapy. The basic research question for cost-effectiveness studies is to understand the superiority of a new and more expensive intervention over the "standard" therapy and, then, the implications of this in a health system and time perspective. However, extended infusion of antibiotics has shown a benefit in clinical outcomes and its use can reduce direct costs since is less expensive than the standard approach, considering that smaller amounts of the antibiotic are needed to reach the same PK/PD and clinical effect. Moreover, additional costs to do an extended infusion would not be significant, and more effective therapy could also reduce the indirect economic burden on the health systems. Therefore, it is beyond the scope of cost-effectiveness analyses, and should be incorporated by health systems.

**KEYWORDS:** Cost Analysis. Sepsis. Antibiotics.

**RESUMO | NARRATIVA/ INTRODUÇÃO.** Na última edição das diretrizes da Surviving Sepsis Campaign - diretrizes do SSC - foram feitas recomendações sobre a otimização da farmacocinética e farmacodinâmica dos antibióticos (PK/PD). Dentre estes, o uso de infusão prolongada de beta-lactâmicos (penicilinas, cefalosporinas e carbapenêmicos), são propostas para melhorar os resultados clínicos e microbiológicos. No entanto, segundo os autores, são necessários estudos sobre as implicações econômicas da infusão prolongada - estudos de custo-efetividade - para essas recomendações. **RESSALVAS.** A sepse representa um enorme ônus econômico em todo o mundo devido à necessidade de leitos hospitalares e de UTI, equipe qualificada e terapias para o tratamento da patologia, sabendo-se que os antibióticos são a terapia principal. A questão básica de pesquisa para estudos de custo-efetividade é entender a superioridade de uma intervenção nova e mais cara sobre a terapia "padrão" e, então, as implicações disso em uma perspectiva de sistema de saúde e de tempo. No entanto, a infusão prolongada de antibióticos mostrou benefício nos resultados clínicos e seu uso pode reduzir os custos diretos, uma vez que é menos dispendioso do que a abordagem padrão, considerando que são necessárias quantidades menores do antibiótico para atingir o mesmo PK/PD e efeito clínico. Além disso, os custos adicionais para fazer uma infusão prolongada não seriam significativos, e uma terapia mais eficaz também poderia reduzir o ônus econômico indireto para os sistemas de saúde. Portanto, está além do escopo das análises de custo-efetividade e deve ser incorporada pelos sistemas de saúde.

**PALAVRAS-CHAVE:** Análise de Custos. Sepse. Antibióticos.

## Narrative

In the last edition of Surviving Sepsis Campaign guidelines – SSC guidelines <sup>1</sup>, the importance was reinforced about measures to optimize the pharmacokinetics and pharmacodynamics (PK/PD) of antibiotics in treatment of sepsis, however caveats were made in the sense of the costs of trained medical staff and protocols for adequate monitoring of changes in antibiotics delivery. Thus, according to the authors, studies of the economic implications of these measures – cost-effectiveness studies – are needed for these recommendations. Among these PK/PD approaches, extended infusions for beta-lactams (penicillins, cephalosporins and carbapenems) are recommended to increase the fraction of time above the minimum inhibitory concentration (Ft%>MIC) and in this way to improve clinical and microbiological cure, as well as suppression of resistance and bactericidal effect.<sup>1,2</sup>

## Caveats

Cost-effectiveness studies are very interesting mainly from a health systems perspective. After clinical trials and studies of efficacy/effectiveness along steps to evaluate and to incorporate an intervention, the cost-effectiveness of the intervention, availability and disposition of resources is the final question to answer.<sup>3</sup>

Sepsis represents an important health problem today, with high mortality rates in several countries, especially in less developed countries.<sup>1</sup> In Brazil, in-hospital mortality from sepsis reaches 50% in some states, representing a high cost to health systems due to the need for hospital and ICU beds, qualified staff and therapies for the treatment of the pathology, as well as for the rehabilitation of patients, and indirect costs mainly due a reduction in the period of time able to work between patients.<sup>4,5</sup>

It is known that antibiotics are the mainstay therapy for sepsis patients.<sup>1</sup> The costs with carbapenems alone in 2015 in Brazil, for example, when around 19 daily doses of carbapenems were dispensed for every 1000 individuals in this year (about 4 million doses in total)<sup>6</sup>, were approximately R\$40 to R\$80 million, excluding other related costs.<sup>7</sup>

In this sense, since the economic burden of sepsis is high, is it necessary cost-effectiveness studies to implement PK/PD optimization measures, specifically extended infusion of beta-lactams? The basic research question for these studies starts with understanding the superiority of a new and more expensive intervention over the "standard" and, then, the implications of this in a health system and time perspective.<sup>8</sup>

The use of beta-lactams in extended infusion is recommended by the sepsis management guidelines, motivated by studies that showed a benefit in clinical outcomes, including a possible reduction in mortality.<sup>1,2</sup> However, despite the superiority this intervention is not more expensive in terms of antibiotic costs. Instead, the extended infusion of these antimicrobials is naturally cheaper than the standard intervention (normal infusion), as smaller amounts of antimicrobials are needed to reach the same Ft%>MIC.<sup>9,10</sup> For example, when using piperacillin-tazobactam in a conventional infusion regimen, 4.5 grams every 6 hours, over 30 minutes of infusion, we use a total of 18 grams of drug per day; while an extended infusion strategy, 4.5 grams every 8 hours, infused over 4 hours, results in a total of 13.5 grams of drug per day (25% savings).<sup>10</sup>

It is known that in critically ill patients, the effective concentration of the drug is constantly variable due to a number of factors, such as increased drug clearance, altered volumes of distribution, abnormal fluid balance and/or alterations in protein binding, often resulting in at infra-therapeutic antimicrobial levels.<sup>2</sup> However, even in septic patients, it is possible to reach, for example, an Ft%>MIC of 80% with meropenem as recommended in some scenarios to avoid emergence of resistant bacteria<sup>11</sup>, with 1 gram infusion over 4 hours in a greater percentage of cases than with 2 grams infusion over 1 hour, both for 8/8 hours.<sup>9</sup>

In terms of cost analysis, others costs, as suggested in the SSC guideline, such as software for monitoring beta-lactams, is not necessary, as is necessary for a good use of vancomycin, with periodic examinations.<sup>12</sup> The additional costs for extended infusions would be reserved mainly for the greatest need for trained teams, development of

care protocols and infusion pumps, topics that are easily resolved in the contemporary scenario, even in middle-income countries such as Brazil, especially with the advent of telemedicine, where access to groups of infectious disease specialists is carried out remotely in some hospitals.<sup>13</sup>

Finally, still in the analysis of costs, besides understanding the direct costs of the intervention and the way to measure them, it is important to evaluate the indirect costs and a more effective therapy for the management of sepsis can speed up the rehabilitation process of the individual, increasing the percentage of economically active individuals in population, as well decreasing the emergence of resistant bacteria can reduce future costs with hospital antibiotic regimens in the community.<sup>5</sup>

Thus, the extended infusion of beta-lactams seems to be a great measure to optimize the management of sepsis, improving bactericidal effectiveness, thus morbidity and mortality related to sepsis as well reduce direct and indirect costs compared to standard therapy (common infusion). Therefor is beyond the scope of cost-effectiveness analyses and should be incorporated by health systems.

#### Author's contribution

Decker SRR, Marzzani LE, Ferreira PR contributed with critical intellectual content. Decker SRR, Marzzani LE, Ferreira PR wrote the manuscript. All authors reviewed and approved the final version of the paper.

#### Conflicts of interest

No financial, legal or political conflicts involving third parties (government, corporations and private foundations, etc.) have been declared for any aspect of the submitted work (including, but not limited to grants and funding, advisory board participation, study design, preparation of manuscript, statistical analysis, etc.).

#### Indexers

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