

Practical approach by main clinical syndromes

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Practical Decalogue in the management of sepsis

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ABSTRACT

Sepsis is a complex entity where there are still many controversies regarding diagnosis and therapeutic management. The present article pretends to review the recently published in relation to these disagreements and contains a proposal of practical approach to the infected patient.

Decálogo práctico en el manejo de la sepsis

RESUMEN

La sepsis es una entidad compleja donde existen aún múltiples controversias en cuanto al diagnóstico y el manejo terapéutico. El presente artículo pretende hacer una revisión de lo publicado recientemente en relación con estas polémicas y ofrece una propuesta de aproximación práctica al paciente infectado.

INTRODUCTION

Sepsis is an increasingly frequent entity with high morbidity and mortality [1]. One of the main characteristics is that initial decisions can condition the patient's prognosis. Therefore, we must be clear about what to do and when to do it. For this reason, there are numerous published guidelines that address this complex syndrome. However, and despite the attempt to standardize the care, there are still many controversies in both diagnostic and prognostic or therapeutic aspects, key issues that we will review next.

DIAGNOSIS

The diagnosis of sepsis requires first of all the presence of infection, which is not always easy to determine. Klein Klouwenberg et al [2] showed that among patients admitted to the Intensive Care Unit (ICU) for sepsis, 13% did not present an infectious disease and in the 30% it was only possible. The study concludes that the diagnosis of sepsis at admission corresponds poorly with the final diagnosis. Other studies carried out on necropsies have shown in patients admitted to the ICU that the clinical and anatomopathological diagnoses do not match with certain frequency, with type I errors being the most frequent. These errors are characterized because if it had knowledge of the true diagnosis, the therapeutic attitude would have changed. The discrepancy between the clinical diagnosis and that of the necropsy occurs in both senses. That is, patients diagnosed clinically for an infectious process did not present it at necropsy and infection was demonstrated in patients without this clinical diagnosis [3].

The complex physiopathology of the septic syndrome may justify the difficulties in establishing the clinical diagnosis (table 1) [4]. Another aspect that makes it difficult is the progressive increase in the age of the attended population, and the fact that this one more frequently presents important comorbidity or immunosuppression, aspects that make that the clinical and analytical manifestations of our patients are often atypical [5].

RISK STRATIFICATION

As a result of the publication of the definitions of Sepsis-3, an important controversy about the effectiveness of quick sequential organ failure assessment (qSOFA) as a screening tool to detect patients with suspected sepsis has been established in the literature. In the last year, new studies have been published that evaluate the prognostic accuracy of the qSOFA and other scales such as the National Early Warning

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Table 1 Signs in sepsis and mimics

	Sepsis	Other etiologies
Tissue damage	Production of pro and anti-inflammatories	Injuries, hypoxia, ischemia, toxins
Hemodynamic effects (initial stages)	Decrease in peripheral resistances, with increased cardiac output and tachycardia	Distributive shock: anaphylaxis, pancreatitis, spinal cord injuries
Hemodynamic effects (late stages)	Increase in peripheral resistances, decrease in cardiac output, colder peripheral limbs with poor capillary refill time	Hipovolemic shock
Laboratory data	Leucocytosis with left deviation	Physiological stress Systemic inflammation
	Coagulopathy	
	C reactive protein	
	Procalcitonin	
Fever	Lactic	Problems in the elderly, immunosuppressed, and patients with biological therapies.
	Cardinal sign of infection Related to cytokines in the hipothalamus	

Adapted from Long B, et al. *J Emerg Med.* 2017;52:34-42

Score (NEWS) or Systemic Inflammatory Response Syndrome (SIRS) in the initial evaluation of the patient with suspected infection [6]. Several systematic reviews and meta-analyses have recently been published. Serafim et al [7] show that the prognostic accuracy is greater for the qSOFA while SIRS shows a better sensitivity for infection diagnosis. So, they advocate a combination of both and not to establish an exclusive competition between them.

In the meta-analysis of Fernando SM et al [8] it is striking that among the 38 studies evaluated, the sensitivity and specificity of qSOFA ranges from 0.98-0.12 and 0.19-0.96, respectively. Likewise, the sensitivity and specificity of SIRS ranges from 0.99-0.51 and from 0.05-0.68, respectively. This shows that probably the populations studied are very heterogeneous or that the clinical stage of the infection is different, because otherwise the dispersion of the reported results can not be explained. Another meta-analysis and systematic review of the literature shows that Early Warning Score (EWS) are not sufficiently accurate to rule in or rule out mortality in patients with sepsis, based on the evidence available, which is generally poor quality [9].

Last, other remarkable study is the one that evaluates the qSOFA depending on the source of infection, showing that an area under the curve (AUC) of 0.841 in urinary tract infection vs. 0.722 in the respiratory track infections ($p < 0,001$), showing the influence that can have the site of infection in their prognostic accuracy [10].

The problem to establish the prognosis is given because the infection is a dynamic process and in the studies the variables are measured on a one-time. Probably the best strategy will be determined by the monitoring of these scales, observing their deterioration in the first hours in order to identify the patient with high risk of poor outcome [11].

TREATMENT

Multiple articles show that complying with the 3-hour bundles (measuring lactate, taking blood cultures and administering antibiotics) leads to a reduction in mortality in patients with sepsis or septic shock. A more rapid completion of a 3-hour bundle of sepsis care and quick administration of antibiotics, but not quick completion of an initial bolus of intravenous fluids, were associated with lower risk-adjusted in-hospital mortality [12].

However, studies that assess adherence to these recommendations show that only 25% of physicians achieve this goal. Among patients with severe sepsis or septic shock receiving antimicrobials in the emergency department, door-to-antimicrobial times varied five-fold among treating physicians. Given the association between antimicrobial delay and mortality, interventions to reduce physician variation in antimicrobial initiation are likely indicated [13].

Studies show that Emergency Department crowding was significantly associated with lower compliance with the entire resuscitation bundle and decreased likelihood of the timely implementation of the bundle elements [14]. The structured care by a code for the patient with sepsis has led in multiple publications to a significant reduction in the mortality [15].

However, even in this, there is controversy. SSC guidelines affirm that administration of antimicrobials should begin as soon as possible after sepsis identification and within the first hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence). However, the IDSA, fearing that this will lead to overprescription of antibiotics in uninfected population or the overuse of broad spectrum antimicrobials, and considering that this recommendation is supported only by observational studies, recommends that in patients with

sepsis (without shock), is better to completed studies in order to determine if infection is the responsible of the patient's clinical manifestations, and once it is confirmed start antibiotic treatment as soon as possible [16].

Finally, SSC guidelines suggest that in septic shock, combined treatment with 2 antimicrobials, both active against the microorganism, may be useful. It is recommended to continue until the clinical improvement or resolution of the infection, independently of the microbiological results of susceptibility. The IDSA, on the contrary, states that there are no solid data to support these recommendations. The evidence would support the empirical use of two active agents against Gram-negative bacilli for the empirical treatment in septic shock in order to increase the chances of administering at least one active agent, but once the susceptibility is known available data suggest that there is no evidence to support the treatment continuation with two agents [16].

A recent Spanish study corroborates that there is no difference, once the susceptibility is known, between maintaining biotherapy or establishing monotherapy with the active agent [17]. However, it is important to note that this study excludes neutropenic patients and infection by *Pseudomonas* spp, where future studies are required.

DECALOGUE

The discrepancy in the results showed by the different studies that address the problem of sepsis is given because they try to label different profile patients with the same definitions and therapeutic attitudes. Sepsis is an heterogeneous syndrome secondary to different etiologies and with a wide range of severity. The clinical presentation, the prognosis and the therapeutic approach will depend on the source of infection, the immunological situation of the host, age, comorbidity, and timing. Two patients can meet the definition of septic shock by requiring inotropes or having high lactic acid, but nevertheless have different age, comorbidity or site of infection. All these factors can conditioned the therapeutic approach or the outcome of the episode.

Kalil et al. [18] make a recommendation of approaching the infected patient based on 4 points: identify the site of the infection, source control, evaluate the immunological status of the host and establish whether it is in shock or not. The site of infection can conditionate the etiology and, therefore, the selection of the antimicrobial treatment. But it also has connotations in the prognosis since it is known that certain sources of infection, such as respiratory or abdominal, have higher mortality than others such as urinary tract infection [19]. The source control has been shown to be essential in improving the patient's prognosis and poor control is associated with increased mortality [20]. The immunological situation can condition the mortality and the etiology of the process. Therefore, it is necessary to know if the patient has a solid organ or hematopoietic cells transplant, cancer, chemotherapy, immunotherapy, HIV with less than 250 CD4, takes immunosup-

pressive medication or biological therapy, or receives chronic corticosteroid treatment [21]. Finally, the shock situation must be evaluated since it conditions a higher mortality. To the contribution of Kalil et al [18] we thought that the consideration of comorbidity should be added, since this will be related to higher mortality and have therapeutic implications. It is known that a Charlson index greater than 2 leads to an 10% excess of in-hospital mortality [22].

CONCLUSION

The approach based on the 5 previous points is valid to decide the therapeutic attitude. Severity stratification should be based not only on risk scores, which have a modest AUC around 0.75, but should be supported by biomarkers such as lactate or proadrenomodulin. Procalcitonin can be helpful in diagnosing infection.

In any case, when faced with an infection, cultures must be taken, antibiotics must be prescribed and the source control must be established, attitudes that must be completed as soon as possible regardless of the severity. Risk stratification is useful in establishing priorities.

Regarding the timing of antibiotic administration, in relation to the dispute between SSC and IDSA, we comment that both agree in what attitude must be follow against the shock. Regarding sepsis, we must consider that this definitions means that the patient has failure of at least two organs, and therefore it has an increase mortality of 10%. In this context, considering the risk-benefit evaluation, we think that early antibiotic administration must be done, especially considering that we are speaking of an initial moment where there can be great uncertainty both diagnostic and prognostic. We do not think that the administration of a single dose of antibiotic could condicionate a risk of serious adverse event on the patient or a significant modification on the ecosystem.

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