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## Sepsis, a public health problem: Clinical aspects and problems in the identification



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### Epidemiology >>

Sepsis is a very common syndrome. In Spain, there are estimated to be more than 40,000 cases of severe sepsis each year. In general, studies report a mortality rate of around 12% for sepsis and around 45% for septic shock. The incidence and mortality are higher in elderly patients or those with comorbidities, especially in those with diabetes, neoplastic illnesses, chronic liver disease, chronic kidney failure or who receive immunosuppressant treatments. The importance of sepsis will be even higher in the years to come, as its incidence is increasing and it is expected that this trend will continue over time. Over the last 20 years, it has increased at a rate of 8.7% annually. According to an epidemiological study carried out in more than sixty Spanish emergency services, where the overall infectious disease prevalence was 14%, the most frequent localisations were respiratory infection (3.2%) followed by urinary tract infection (2.1%).

### Etiopathology >>

We understand infection to be the invasion of normally sterile tissue by microorganisms, while bacteraemia is the presence of viable bacteria in the blood. The pathophysiology of sepsis is complex and includes factors dependent on the host and the causative microorganism. Mortality will depend on these factors and on the treatment introduced in terms of the type of treatment and prescription period.



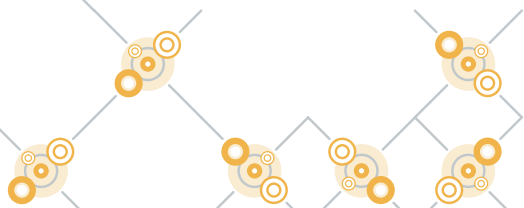
In very simple terms, we can say that sepsis is the result of the activation of a cascade of inflammatory reactions and the imbalance of the anti-inflammatory response, also involving clotting and fibrinolysis processes. This inflammation is characterised by the loss of integrity of the vascular endothelium, capillary leakage, oedema, microthrombosis, accumulation of leukocytes and, as a result, cellular and tissue ischaemia. The reduction of the tissue perfusion of oxygen, direct tissue damage and alteration of mitochondrial respiration causes failure of the cell, tissue, organ and, finally, the system. Ultimately, these factors cause a loss of homeostasis; the loss of the existing balance between inflammatory and anti-inflammatory factors, between coagulation and fibrinolysis, which causes organ dysfunction and can cause death.

In recent years, much progress has been made in the physiological knowledge of the septic phenomenon and this has led to the better characterisation of the mechanisms and mediators responsible for its evolution. However, the reason remains unclear as to why, in reaction to the same infection, some patients develop sepsis or septic shock while others do not. The reasons why two patients with septic shock have different prognoses are unknown, in spite of similar levels of care, with race and gender possibly having an influence on the evolution. The prognosis of an infectious illness depends mainly on three variables which interact with each other to give a final result of cure or death in each patient: the magnitude or initial severity of the acute insult (rarely predictable or modifiable); the efficiency and specific nature of the treatment administered and the degree of functional reserve and “susceptibility” of the patient that can be classified as “constitutional” factors.

The search for individual factors that predispose sepsis in a reaction to infection is very interesting. In recent years, the susceptibility to infection and other diseases has been analysed through the study of genetic polymorphisms of the different molecules involved in any phase of the inflammatory response (recognition, amplification and effecting response). This is due to the fact that natural born children of parents who have died of infection have, in turn, a greater risk of dying from an infectious process than children adopted by those who had died from their infections, revealing the role of heredity in the susceptibility to the infectious process.

The prevalence of sepsis due to Gram-negative microorganisms (mainly enterobacteria) and Gram-positive pathogens (especially streptococci and staphylococci) is similar, each of these two groups of bacteria causing 25% of sepsis cases, and a combination of both causing another 15%, approximately. The sepsis of fungal etiology is responsible for 5 to 10% of cases. Viral infections, and even tuberculosis or parasitic infections, can appear as sepsis or septic shock, although very infrequently. In a third of cases, the microorganism causing the infection cannot be identified.

Some clinical settings are a predisposing factor for the onset of Gram-positive or Gram-negative sepsis. Therefore, intravenous drug use, being a carrier of an endovascular device or the previous use of broad-spectrum antibiotics against Gram-negatives, may lead to the onset of Gram-positive sepsis. Oncohaematological processes or severe neutropenia, on the other hand, are risk factors for infection by Gram-negative bacteria.



## Definition of sepsis >>

The new definitions establish that sepsis is a potentially life-threatening organ dysfunction caused by an abnormal response of the host to the infection. In this regard, the importance of the non-homeopathic host response to the infection, the potential lethality, which considerably exceeds that of an infection, and the need for urgent identification are emphasised. The importance of including “organ dysfunction that threatens life” in the definition is consistent with the pathophysiology that underlies the syndrome: cellular defects, physiological and biochemical abnormalities within the specific organ systems.

Similarly, septic shock is defined as a subset of patients with sepsis in which the abnormalities of the cellular and circulatory metabolism are deep enough to substantially increase mortality. These patients, when diagnosed with sepsis, have an increase in mortality of 10%, while for those who experience septic shock, this increase is 40%. Finally, note the definition of Multiple Organ Dysfunction Syndrome (MODS) as the ongoing presence of the altered function of several organs, with the need for sustained therapeutic intervention.

## Diagnostic tools >>

These definitions consider that the clinical and analytical criteria that best identify the organ dysfunction condition are those contained in the SOFA score (Sepsis-related Organ Failure Assessment) (Table 1).

**Table 1. SOFA Score (Sepsis-related Organ Failure Assessment)**

	0	1	2	3	4
<b>Respiration<sup>a</sup></b> PaO <sub>2</sub> /FIO <sub>2</sub> (mmHg) or SaO <sub>2</sub> /FIO <sub>2</sub>	>400	<400 221-301	<300 142-220	<200 67-141	<100 <67
<b>Cogulation</b> Platelets 10 <sup>3</sup> /mm <sup>3</sup>	>150	<150	<100	<50	<20
<b>Liver</b> Billirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
<b>Cardiovascular<sup>b</sup></b> Arterial pressure	MAP ≥70 mmHg	PAM <70 mmHg	Dopamine at <5 or dobutamine at any dose	Dopamine at dose of 5.1-15 or Epinephrine at ≤0.1 or Norepinephrine at ≤0.1	Dopamine at dose of >15 or Epinephrine >0.1 or Norepinephrine at >0.1
<b>Central Nervous System</b> Glasgow Scale	15	13-14	10-12	6-9	<6
<b>Renal</b> Creatinine (mg/dL) or urinary flow (mL/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 <500	>5.0 <200

<sup>a</sup> PaO<sub>2</sub>: arterial oxygen pressure; FIO<sub>2</sub>: fraction of inspired oxygen; SaO<sub>2</sub>, arterial peripheral oxygen saturation; MAP, mean arterial pressure; <sup>a</sup>PaO<sub>2</sub>/FIO<sub>2</sub> is a preferred measurement, but if it is not available, we use SaO<sub>2</sub>/FIO<sub>2</sub>;

<sup>b</sup> Vasoactive drugs administered for at least 1 hour (dopamine and norepinephrine as ug/kg/min) to maintain the MAP above 65 mmHg.



Organ dysfunction (in sepsis) is identified by demonstrating a modification of 2 or more points in the SOFA score with respect to the baseline situation as a consequence of an infection. It is assumed that patients normally present a SOFA score of zero, unless there is an acute or chronic organ dysfunction prior to the commencement of the infection. A SOFA score of 2 shows an overall mortality risk of approximately 10% in the general population with a suspected infection.

With the aim of developing a simple sepsis surveillance, the term “quick SOFA” (qSOFA) is defined which includes a score of 13 or less on the Glasgow scale, a systolic blood pressure equal to or less than 100 mm of Hg and a respiratory rate of 22 or more per minute. Patients with 2 or 3 of these variables must be suspected of having sepsis.

Septic shock refers to the situation in which the patient requires vasopressors to maintain mean arterial pressure above 65 mm of Hg and have a blood lactate level  $> 2$  mmol/L (18 mg/dL) despite adequate volume replacement.

## Difficulties in the identification »

Diagnosis of sepsis first of all requires the presence of infection, which is never simple. There are studies which highlight this difficulty, demonstrating that among patients admitted to the Intensive Care Unit (ICU) for sepsis, 13% did not show an infectious process and confirmation of an infection possible in only 30%. The study concludes that the sepsis diagnosis on admission corresponds poorly with the final diagnosis. Other studies carried out on post-mortems showed that, in patients admitted to ICU, there was a certain frequency where the clinical and anatomopathological diagnoses did not correspond, with type I errors being the most frequent. These errors are characteristic because having had knowledge of the true diagnosis, the diagnostic or therapeutic attitude would have changed. The discrepancy between the clinical diagnosis and post-mortem diagnosis was two way, in that patients clinically diagnosed with an infectious process did not present it in the post-mortem, as well as patients not diagnosed with infection showing infection in the post-mortem.

The complicated pathophysiology of the septic syndrome can justify the difficulties for establishing the clinical diagnosis. Another aspect that gets in the way is the progressive increase in the age of the population, and the fact that this more and more commonly presents important comorbidity or immunosuppression. These aspects often make the clinical and analytical signs of our patients become more atypical, which hinders early detection of these illnesses and situations. Furthermore, the infection is a dynamic process and in these studies the variables are measured at a certain time, therefore the results may not be comparable to all evolutionary stages.

Following the publication of the Sepsis-3 definitions, a significant controversy was established in the literature concerning the effectiveness of the qSOFA as a screening tool for detecting patients suspected of sepsis. In recent years, new studies have been published which assess the prognostic accuracy of the qSOFA and other scores such as NEWS (National Early Warning Score) (Table 2) or systemic inflammatory response syndrome (SIRS) in the initial assessment of the patient with suspected infection. Systematic reviews and meta-analysis have recently been published which show that the prognostic accuracy is greater for the qSOFA, while the infection diagnosis is greater for SIRS, which calls for a combination of both and not the establishment of an exclusive competition between them.





In a recent meta-analysis, it is noteworthy that among the 38 studies evaluated, the sensitivity and specificity of the qSOFA ranges from 0.98–0.12 and from 0.19–0.96, respectively. Equally, the sensitivity and specificity of the SIRS ranges from 0.99–0.51 and from 0.05–0.68, respectively. This underlines that the populations studied are very heterogeneous or that the evolutionary moment of the infection is different, because otherwise the dispersion of the results reported cannot be explained.

For this reason, the best strategy will probably be determined by the monitoring of several of these scores, observing their deterioration in the first few hours and thus identify the patient at risk of poor results. The use of various diagnostic strategies for identifying the patient at high risk can increase the degree of detection, which is fundamental to applying the specific treatment as soon as possible.

**Table 2. NEWS scale (National Early Warning Score)**

Physiological parameters	3	2	1	0	1	2	3
Respiratory rate	≤ 8		9-11	12-20		21-24	≥ 25
Oxygen saturation	≤ 91	92-93	94-95	≥ 96			
Supplemental oxygen	35.0	Si		No			
Temperature	≤ 35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	
Systolic blood pressure	≤ 90	91-100	101-110	111-219			≥ 220
Heart rate	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Level of consciousness				A			V, D, I

A: alert; V: Voice, P: Pain, U: Unresponsive

The problem with the use of several tools for identifying patients with sepsis is that the commonly used scores are difficult to perform at the patient's bedside (tables 1 and 2) and even more in an area where there is high demand for medical care such as emergency rooms. For this reason, the use of automatic electronic warning systems has been implemented in recent years, combining clinical and analytical variables. These systems can automatically calculate the patient's risk and give a warning to the attending doctor for the early assessment of the patient at risk. However, it will ultimately be the doctor who will determine if we are facing a true case or a false positive depending on the clinical context. These electronic tools increase the number of patients identified, which improves the start times of the specific treatment, thereby increasing a patient's chances of survival.

In this context, the introduction of an objective element, such as the biomarker, improves, facilitates and promotes the decision-making process. The use of biomarkers is increasingly useful and important for the doctor because it improves the diagnostic approach, facilitates a rational use of complementary tests, improves the empirical prescription of antibiotics and promotes better capacity to decide on issues regarding admission, intensive care or surgery. A biomarker is a measurable and reproducible indicator of a biological state or condition. They are indicators that a process is normal or pathological. Ideally, the biomarker should:

1. **Establish a rapid diagnosis** (even before the signs and symptoms of an infection manifest and prior to the microbiological results).
2. **Quantify the severity and stratify the risk.**
3. **Monitor evolution** of the bacterial infection and its response to treatment so that it can serve as a guide for its use (e.g. indication, cessation or change of the antibiotic).





For the correct interpretation of the biomarker result, we must consider both its purpose and the factors that can modify the values: the characteristics of the patient, the clinical situation, the focus of infection, the microorganism and the previous intake of antibiotic. The evolution time of the symptomatology or onset of the infection must likewise be assessed with the biomarker's own kinetics.

## Importance of early identification >>

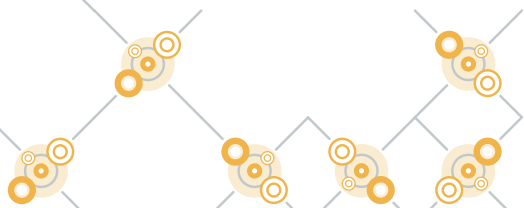
Its importance lies in the fact that the completion of the initial therapeutic measures in the first 3 hours after the identification of patients, can reduce their risk of in-hospital death by up to 40%. The treatment priorities of patients with sepsis or septic shock are as follows:

- > Taking cultures.
- > The immediate onset of adequate empirical antibiotic therapy.
- > Focus control, if necessary, by means other than pharmacological.
- > The early onset of resuscitation and life support that corrects physiological abnormalities such as arterial hypotension or hypoxemia.

The delay in the establishment of antimicrobial therapy is one of the modifiable parameters that is most closely associated with mortality. Its early establishment is essential to achieve better clinical results in terms of survival. Each hour of delay in antibiotic administration after the onset of hypotension is associated with a 7.6% decrease in survival, with the detection to antibiotic time factor being the predictor of risk most strongly associated with the patient's vital prognosis. The recommendation of early antibiotic administration was initially based on the result of retrospective studies, with the limitations that this implies. However, considering the similar result obtained in observational studies and the risk/benefit ratio for patients with serious infections, it should be recommended that antibiotic treatment be administered early in patients with sepsis or septic shock, always within the first to third hour after the detection of the clinical situation.

If the infected site is suitable for further treatment, in addition to antibiotic therapy, it must be performed within the first 12 hours (except where peripancreatic necrosis is the site, when we must wait for the lesions to be defined) and the least aggressive treatment procedure should be performed amongst those considered possible treatments (e.g. percutaneous drainage is better than open surgery). These procedures include drainage of abscesses, debridement of skin lesions or the removal of catheters that might be the site of infection.

The "initial resuscitation" group of procedures must be carried out within the first 6 hours after the suspicion of sepsis, this being essential to its start when providing outpatient and inpatient emergency services. The utility of initial resuscitation is currently being questioned based on the objectives set by the Rivers study after the publication of three clinical trials in which there were no statistically significant differences in patients who followed the Rivers protocol or standard care procedures that are less strict. However, it should be noted that the "standard care procedures" of these clinical trials guaranteed adequate volume replacement and the administration of antibiotics showed no differences between the different protocols. For this reason, we should not interpret "standard care procedures" to mean "doing whatever you want". What we could conclude is that if standard care procedures guarantee good





resuscitation, starting vasoactive amines in those who do not respond to volume to achieve minimum average blood pressure and adequate use of antibiotics, the setting of very strict objectives as per the Rivers study (including measuring SvcO<sub>2</sub> or blood pressure invasively) does not improve results. This would make it easier for patients to be quickly treated without requiring complex monitoring measures at least in these first six hours.

In summary, the measures indicated in the international protocols that are to be established immediately are:

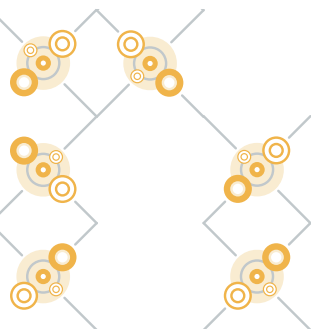
- |          |  |
|----------|--|
| <b>1</b> | Serum lactate measurement  |
| <b>2</b> | Obtaining blood cultures before starting antibiotic treatment  |
| <b>3</b> | Early start of antibiotic treatment  |
| <b>4</b> | In the presence of hypotension or lactate $\geq 2$ mmol/L:<br>A Start resuscitation with 30 mL/kg of crystalloids<br>B Consider using vasopressors to treat hypotension during and after resuscitation with fluids |





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