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REVIEW

TAXONOMY OF THE UPDATED DEFINITION AND STAGING CRITERIA OF BACTERIAL SEPSIS

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Abstract. Sepsis can be easily defined as an exaggerated inflammatory response to a pathogen's aggression. Due to its severity that caused increased rates of mortality, research entities mobilised impressive human and material resources in order to reach and establish rapid and safe diagnostic methods. By setting a rapid diagnosis, the proper etiologic treatment can be applied thus lowering complications and severity occurring in a sepsis case. Recently, at the Third International Consensus Definitions for Sepsis and Septic Shock held in February 2016, new scores and criteria were established in order to define and stage sepsis as accurately as possible. The new approach excludes the classical terms of systemic inflammatory response syndrome (SIRS) and includes new criteria, grounded by the PIRO concept, enabling a correct evaluation of intensive care patients, which also asses the host's susceptibility, infection degree, response and affected organs. The objective of this study is to present the new definitions and staging criteria for bacterial sepsis and their benefitst.

Keywords: sepis, PIRO, staging, definition

Introduction

Sepsis represents the exaggerated inflammatory response to a pathogen's aggression. It is a severe affection, with high mortality rates and frequent complications that requires prolonged hospital stay and complex treatment. The diagnostic and therapy methods are thus in permanent evolution.

A pathogenic microorganism or a potentially pathogen's invasion in a tissue, liquid or normally sterile cavities that triggers a pathological process is known as infection. Once abnormal bacteria are detected by the organism- defence mechanisms are activated, but when they are overcharged they can evolve into a septic stage:

- Systemic inflammatory response syndrome (SIRS)
- Sepsis
- Severe Sepsis
- Septic shock
- Multiple organ dysfunction syndrome (MODS)

SIRS - Systemic inflammatory response syndrome corresponds to an unspecified inflammatory process that can be set off by numberless aggression causes such as: a localized and generalised infection, a traumatism, a burn, etc. They produce important lesions and determine homeostasis disruptions.[20, 29]

Septic shock occurs as acute circulatory failure characterized by persistent hypotension associated to tissue hypoperfusion and organ failure. At this stage the patient is unresponsive to intravenous fluids. [4,19]

In severe sepsis, alongside the specific bacterial infections, organic dysfunction can also appear: respiratory dysfunctions (hipoxia), hypotension, neurologic, haemotologic, gastrointestinal, liver dysfunctions and/or tissue hypoperfusion signs, metabolic disorders. [12]

The last sepsis stage, also known as the most severe one is *Multiple organ dysfunction syndrome* **(MODS)** that, in most cases, leads to death. At this point, multiple organic dysfunctions impede the body to maintain homeostasis without an emergency medical intervention. [21, 26]

Overview of the new criteria released by the Third International Consensus Definitions for Sepsis and Septic Shock.

Recently at the Third International Consensus Definitions for Sepsis and Septic Shock held in February 2016, specialists established new criteria in terms of definitions and scores. Thus, the new sepsis definition no longer includes the terms „**SIRS**" and „severe sepsis" the remaining terms being sepsis and septic shock.

Several studies showed that SIRS occurs frequently in hospitalised patients and is detected in benign conditions linked or not to an infection, hence its lack of specificity only for the sepsis diagnosis. [36]

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As specialists considered that a share of SIRs symptoms, namely fever or leukocytosis represents inflammatory responses of the host but not mortality indicators, a reconfiguration of sepsis' definition was imposed. [30]

In accordance to the new criteria, sepsis is defined as a life threatening condition triggered by the host's response to an infection. [35, 37, 38, 36]

Clinical criteria: organ dysfunction as an increase with 2 SOFA score points. (For patients with infections, increase by 2 SOFA score points determined a 10% death rate).[35, 37, 38, 36]

Sepsis is defined as a potentially lethal affection, caused by the host's immune response to an infection. Organ dysfunction can be identified by the SOFA score that has ≥ 2 points secondary to the infection. SOFA score can be considered zero in patients not known with organic dysfunction. [35]

A value of ≥2 SOFA score reflects an increase in the mortality rate with up to 10%, particularly in populations with suspicion for an infection. Even patients with minor organic dysfunctions can experience rapid health status deterioration this emphasizing the seriousness of organ dysfunctions and the need for rapid therapy implementation. [35]

Patients with suspicion of infection, who need more than three days of hospitalization in the Intensive Care Unit (ICU) can be rapidly identified using the rapid qSOFA score, namely the „HAT" acronym that meets 2 or more criteria from the following:

- Hypotension < 100 mmHg
- Mental health status impairment (SCG<15)
- Tachypnea with respiratory rate >/= 22/min [35, 37, 38, 36]

Septic shock is a complicated form of sepsis where metabolic or circulatory disorders are so important that they can substantially increase the death prognosis.

Clinical criteria: sepsis and persistent hypotension >/= 65 mmHg under vasopressor support and a blood lactate value >2 mmol/L. When these criteria are met the mortality rate increases up to 40% [35, 37, 38, 36]

However, how these criteria can be applied to the paediatric population is still debatable. [34]

Depending on the SOFA score and other clinical signs, sepsis or septic shock diagnostic can be established.

A cohort study conducted between 2010 and 2012 in USA in 12 clinical units in Pennsylvania on patients admitted on ICUs, emergency or surgical departments that were evaluated using SIRS criteria, SOFA score, LODS and qSOFA aimed at establishing the usefulness of the new sepsis criteria and definitions.

The main study conclusions revealed that in intensive care units, the predictive value of the SOFA score on mortality did not significantly differ from the LODS score but it was statistically superior to SIRS and qSOFA criteria, thus proving its utility in the clinical diagnosing of sepsis. For patients in other wards, the predictive value of mortality by qSOFA turned out statistically higher than SOFA and SIRS scores thus being considered a rapid diagnosis tool for sepsis [33].

PIRO evaluation system

Older definitions that staged patients as SIRS, sepsis, severe sepsis and septic shock failed doing so based on the severity degree. An effective assessment system should consider both the patient's medical history, risk factors, type of infection (nosocomial or community) as well as the host's type of response. Similar to the TNM (tumour, lymph nodes, metastases) staging, a system was created for the assessment of patients with sepsis-PIRO (predisposition, infection, response and organ dysfunction).

The patients are classified based on Predisposition, nature and spread of the Infection, nature and importance of the Host's Response and degree of Organ Dysfunction. Its efficacy resides firstly in the differentiation between morbidity caused by an infection or the host's response to an infection and secondly to the ability to evince the risk factors that can influence an unfavourable evolution independent from the infectious process.[1, 2]

Prognosis

A patients' medical history significantly influences sepsis' evolution and the therapeutic conduct elected by the clinician. In what concerns sepsis and its influence on the risk of premature death, predisposition is accentuated by genetic determinism.

Predisposition comprises several factors: age, sex, other clinical simultaneous clinical conditions, drug therapy administered at the same time with immunusupressors or antibiotics or even affiliation to a certain culture or religious confession.[1]

All these factors may impact the response to treatment or the patient's evolution. New genetic studies highlighted associated high risk factors for infections and increased rates of mortality.

The unique nucleotides' polymorphism, microsatellites and insertion/deletion polymorphisms represent genetic variation forms that define an individual's risk to develop sepsis, organ dysfunction or death. [5]. Most genetic traits associated with severe infections have been proven to be linked to malfunctions in the innate immune response.

For example, a genetic polymorphism as TNF2 allele may have as consequence a more aggressive inflammatory response to a pathogen's action. Hence, the mechanisms that on one hand lower the infectious risk can, on the other hand, exacerbate the risk of an excessive inflammatory and potentially harmful infection.

Gender based clinical studies revealed a greater predisposition in men to develop sepsis than women. [18, 32] Furthermore, conditions such as cirrhosis, diabetes or BPOC along with chronic immunosuppressant drugs may predispose to sepsis with unfavourable evolution. Immunosuppressive therapy increases the risk of infections and decreases the host's inflammatory response.

Further investigations are needed to establish which risk factor should be taken into consideration, which has a higher significance for the prognosis and if by knowing the specific sepsis risk factor the clinical evolution can have better outcomes.

Severe traumas, burns, deterioration of skin and mucosal barriers, obstructive lesions and several immunosuppressive agents may influence the risk for severe infections and septic shock. [8, 17] The degree to

which these elements and, possibly, other predisposing factors modify both the infection risk and the host's systemic response to invasive infections remains a topic in need of broader clinical investigation for the future.

Situations where patients develop sepsis that leads to systemic inflammation and invasive infections without any predisposing factor are quite rare.

Predisposition

The site, type and magnitude of an infection influence considerably the prognosis. Extended infections carry a higher mortality risk than localised infections. For example, stercoral peritonitis known for its extensive infectious potential is more severe with a more reserved prognosis than normal appendicitis.

Many times the infection site was associated with the occurrence of severe sepsis, thus demonstrating its role in a patient's clinical evolution. Patients who develop sepsis in: the lungs, gastro intestinal tract or the nervous central system (CNS) presented a higher rate of mortality compared to patients with skin or genitourinary sepsis. [3, 10, 22] It also appears that patients with bacteraemia display a more severe evolution than those who don't develop it, although, so far, this connection has not been established for all microorganisms or in all studies focusing on sepsis.[3, 10, 22]

Primary bacteraemia (especially the one caused by disseminated intravascular devices) has better prognosis than secondary bacteraemia (caused by abscess, collections). Furthermore, the quantitative value of pathogens present in the blood stream and tissue is, generally, higher in secondary bacteraemia than in primary ones. The share of microorganisms and their intrinsic virulence stand as determining factors for the evolution to severe, invasive infection. [6, 23] Virulent microorganism like *Staphylococcus aureus*, *Streptococcus pyogenes* and *Pseudomonas aeruginosa* have a higher rate of mortality than less pathogenic organisms such as coagulase-negative staphylococci. Obviously, the etiologic agent of sepsis cannot determine a patient's evolution as the host's response to an infection is equally important in identifying the rate of mortality by systemic infection.

Also, the host's response differs based on the pathogenic agent, especially its class (Gram positive or negative).[23]

An important feature of PIRO is that it relies on both the aetiological agent and the nature of the host's response within the pathogen-host interaction, occurring in severe infections.

Response

The host's inflammatory response to a systemic infection probably represents the most essential key to decoding severe sepsis and septic shock.

The complexity of the host's response and variations between patients, as response to the microbial aggression are major barriers to understanding the physiopathology of the septic shock.[8,14, 17]

Although both the humoral immune response and the cell response contribute to the occurrence of septic shock, the integration of these dissipated processes within a well defined and easily recognisable system turned out difficult. Multiple clinical and biological options are easy to identify, especially those that that have the ability to alter the host's response to an infection. Many of them are simple, with direct action. The patient's age, nutrition status, sex, genetics, a different but simultaneous infection can affect the host's immune response to invasive infections.[2, 11, 15, 18]

It is well known that some patients have an intense systemic immune response, frequently interpreted as an acute inflammation, induced by certain microbial agents. [14]

Modern therapies applied in sepsis target particularly the host's response rather than the infectious agent but the former continues to be difficult to quantify. Biological markers of the immune response for predicting severity include, among others, values of circulatory procalcitonin and IL-6. Until a new inflammation mediator is identified, epidemiological studies must focus on the hypothesis that the currently used markers can be useful in the staging process of septic patients. [7, 13, 24]

Distinguishing between a host's intense inflammatory response from an inadequate one can sometimes be challenging as sepsis itself can induce a relative immunosuppressive status.

However, applying the same immunomodulary treatment in patients with intense inflammatory response and in those with immunosupression, for the general term of sepsis shock can be perilous. Some of them might need immunostimulators in view of obtaining immune reconstruction, while others may very well benefit from anti-inflammatory treatment.[9, 14]

A better understanding of the host's immune response and development in genetics reserach, with the purpose of rapid and proper identification of the immune response to the microbial aggression can improve the way immediate treatment is initiated in septic patients, in the near future.

Organ dysfunction

By drawing a parallel with the TNM staging system, the presence of organ dysfunctions in sepsis can be compared with the presence of metastases in cancers. The severity of organ dysfunctions constitutes a determinant prognostic factor.

Modern assessment scores for multiple organ deficiency syndrome can be used to describe, qualitatively and quantitatively, the degree of organ dysfunction.

Organ dysfunctions represent late tissue sequelae that happen as a response to severe sepsis aggression thus becoming the essential survival determinant factor. It has been demonstrated, on a number of times that patients with multiple organ dysfunctions present a higher death rate than those with a single dysfunction or none at all, as a consequence of sepsis.[16, 25, 27, 28]

However, uncertainty revolves around the reason why some patients develop a particular organic dysfunction while others develop different ones, despite apparently similar stimuli released by sepsis. For example some patients develop coagulation abnormalities during early sepsis stages while others develop respiratory stress syndrome or kidney failure. [8] In addition to that, the pattern grounding organic dysfunctions in severe sepsis may vary from one patient to another and may provide data on the survival prognosis and treatment response.

Another key issue in research on sepsis concerns the effect some pre-existent conditions have on the risk of organic dysfunction occurrence but, most often, a cause-effect relationship between them can hardly be identified. Still, secondary organic dysfunctions can be easily differentiated from the primary ones.

What is certain is that the endothelial cells that constitute the tunica intima of the capillary beds in different organs express different answers to septic stimuli. This microcirculation heterogeneity can be responsible for some of the differences springing among organ dysfunctions, in patients with sepsis. [31]

Conclusions

The loss of rules and control of multiple organic dysfunctions in severe sepsis are definite interest areas for research, in view of understanding physiopathological mechanisms.

As already demonstrated, many of the elements that include predisposing factors to sepsis affect the host's response. Furthermore, various PIRO components may easily overlap. In some patients, one PIRO element can prevail while in other patients, equal contributions can be detected, as pertaining to each element that triggers the diseases' evolution and prognosis.

Decoding the complexity of the immune response to the challenge delivered by microbial aggression is incomplete and remains an important topic for biomedical research in the field f sepsis.

The main objective of PIRO pattern is to achieve the ability to distinguish between morbidity caused by the infection and morbidity linked to the infection response.

PIRO pattern was recommended as a developing model in the area of research but also as a pattern per se that can be used in its current state. Its implementation will definitely need a close examination of sepsis history and evolution, in order to delineate the cases with unfavourable prognosis as well as the probable therapeutic response of each sub-class.

Studies evinced that Systemic inflammatory response syndrome (SIRS) is present in almost all admitted patients and occurs in various benign conditions, associated or not to an infection. Hence due to the fact that SIRS was not sufficiently specific to sustain a sepsis diagnostic, the definition and diagnostic criteria for sepsis had to be reviewed and updated.

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