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## *Review article*

# **Systemic inflammatory response syndrome and sepsis – epidemiology, differentiation, diagnostics in in clinical practice**

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**Key words:** sepsis, systemic inflammatory response syndrome, SIRS, cytokines, procalcitonin, C-reactive protein

**Słowa kluczowe:** posocznica, zespół ogólnoustrojowej reakcji zapalnej, SIRS, cytokiny, prokalcytonina, białko C-reaktywne

## **SUMMARY**

Bacterial infection is an important factor causing morbidity and mortality in different populations. Every time exacerbation of infectious response (strength, time of symptom severity, time of progression) and whole cascade of inflammatory reaction is dependent on the efficiency of the organism's homeostasis. In many situations, especially in case of patients with a decrease level of immune system efficiency, we observe very dynamic intensification of infection and inflammation symptoms.

Every time the inflammatory response affect whole body functions and manifests itself in change of biochemical, hematological, and immunological parameters. Those changes are visible specially during systemic inflammatory response. SIRS (systematic inflammatory response syndrome) and sepsis with high levels of incidence and mortality from many years it is a the large diagnostic and therapeutic problem in clinical practice. Annual mortality caused by sepsis which reaches 30 and 50 deaths per 100 000 population, makes it classified as one of a top causes of death among patients under hospital care. Due to its dynamic nature of its course, it is necessary to thoroughly understand its course which may contribute to the search for more effective biochemical and hematological diagnostic markers which will allow to shorten the time of implementation of effective therapy and decrease mortality.

The aim of this study was to present the specificity of a SIRS and sepsis and to show its progression, complications and available tools and methods of its diagnosis in clinical practice.

## **Introduction**

Bacterial infection are an important medical factor causing morbidity and mortality in different populations, especially for people with low immunity and immunological deficits [1,2,3]. Even in countries with high medical services standards, generalized bacterial infections constitute a serious medical problem. This particularly applies to newborns as well as to the elderly and co-occurring immune disorders [3,4].

Symptoms such as elevated body temperature, increased heart rate, respiratory rate, and partial blood carbon dioxide, as well as the number of peripheral blood leukocytes and the proportion of immature (12,000 /  $\mu\text{l}$  adult or less than 4,000 /  $\mu\text{l}$  in adults and the percentage of immature leukocyte forms above 10%), may but not always constitute a criterion for making a diagnosis of sepsis [5,6,7].

Due to the specificity of the sepsis development, its symptoms and very quick progression it seems very important to search for markers allowing for a early diagnosis of the actual somatic disorder. The clinical course of the sepsis depends on the interaction between

the pathogen penetrating the human body and the defense reactions arising in response to the infection. The presence of the microorganism in physiologically sterile tissues and fluids induces an inflammatory cascade. As a result high release of the inflammatory mediators blood vessels dilate and damage of their endothelium is being observed. This situation leads to increased vascular permeability and fluid leakage. In addition, the formation of microthrombosis in arterial vessels is observed, which is caused by the contact of morphotic elements of peripheral blood with the endothelium, whose continuity is violated. All these processes lead to impairment of blood supply to organs manifested clinically in their dysfunction. Too late diagnosis of the SIRS (systemic inflammatory reaction) during the sepsis results in the development of septic shock and multiorgan damage syndrome, which reduces the chances of success of the implemented therapy and definitely worsens the patient's prognosis [8,9].

Diagnostic possibilities to confirm or exclude infection as a cause of deterioration of the patient's clinical condition, allow for a proper therapeutic decision and may have a positive effect on the results of the used treatment. Early exclusion of infection may contribute to a reduction in the number of situations in which antibiotics are used unnecessarily, which increases the risk of developing resistant strains of bacteria.

During sepsis and inflammation, both pro-inflammatory mediators (IL-1 $\beta$ , TNF- $\alpha$ ) and bacterial toxins (LPS - lipopolysaccharide, peptidoglycans) induce expression of the CALC-1 gene and CTmRNA in neuroendocrine cells of many organs: lungs, intestines, liver, pancreas, brain, kidney, adipocytes and peripheral blood cells (monocytes, lymphocytes and granulocytes) [10]. Expression can be attenuated by INF- $\gamma$ , which is secreted during the viral infection. INF- $\gamma$  blocks the activity of IL-1 and at the same time PCT synthesis, so during its viral infection its concentration is low [11, 12, 13]. The increase in procalcitonin concentration occurs very early after the bacterial toxins have been activated. The maximum level occurs between 6 and 8 hours after injection and lasts for at least 24 hours. This finding explains why PCT can be a good indicator for differentiating between bacterial and viral infections. Determination of PCT concentrations seems to be useful for detecting and monitoring the course of infection with bacterial, fungal, parasitic etiology, and thus allows early optimization of the implemented treatment methods depending on the clinical condition of the patient [14].

Therefore the aim of this work was to present the specificity of a SIRS and sepsis and to show its progression, complications and available tools and methods of its diagnosis in clinical practice, to reduce morbidity and mortality. This may translate into shortening the time of selection of treatment methods and increase a chances of success of the therapy.

## **Definition of sepsis**

A better clinically understanding of the essence of sepsis is possible only if it is precisely defined.

During last one hundred years there were many different attempts to define sepsis. Starting from “*host response to an infection*”, “*body response that makes the disease*” , “*form of blood poisoning*” [15,16,17] modern definition of sepsis changes during years [18].

Although all attempts there are still many limitations about the specific definitions of SIRS, sepsis and sepsis shock, but all presented always use a criteria as sepsis is a systematic inflammatory response occurring from bacterial systemic infection. For septic patients PIRO system (*Predisposition, Infection, Response and Organ dysfunction*) is being developed to assess the risk of patients with sepsis [19]. Generally in developed countries, sepsis occurs approximately not less than 1,8-2% of all hospitalized patients and from 6% to 30% of all patients hospitalized in intensive care unit [20]. Analyses of sepsis epidemiological reports in developed countries clearly indicates that the incidence of sepsis and severe sepsis is still increasing [21–24]. This may be associated to longer life time and long-term therapy of seriously ill patients that is associated with immunological deficits (cancers, immunological infectious diseases HIV and diabetes, etc.) [25]. In case of developing countries all incidences of sepsis, severe sepsis and septic shock are not statically described due to the fact that in many cases specific proper diagnosis is not made before death of the patients [26]. It is essential to state that patients dying as a result of infectious diseases inevitably die of sepsis and sepsis-related organ dysfunction, as a result of systematic inflammatory response for the infection. In this conclusions it is essential to state that patients dying as a result of infectious diseases die not only from the infection, but as a result of the host immune system response.

Increasing with age, the incidences of sepsis results from the occurrence of serious and intensifying general health disorders related to the aging process. Furthermore some research reveal that race, gender (males) and ethnicity (non-Caucasian) may be also associated with risk of sepsis [21,24,27,28].

### **Microbiological etiology of sepsis**

Precise description of sepsis causative organisms have evolved similar like definition of sepsis, over many years. Initially sepsis was fully associated with *Gram-negative bacteria* infections [24]. It resulted from the conclusions that sepsis is a human body response to endotoxins (which are mostly specific for Gram-negative bacteria) [30]. Nowadays it is known that sepsis occurs as a result of systematic inflammation so it may be associated with any bacteria (*Gram-negative, Gram-positive*) as well as from fungal and viral infections. Furthermore recent studies indicates that in the past 25years *Gram-positive* bacteria are one of the most common cause of sepsis in hospitalized patients [21]. Fungal associated sepsis (associated with exemple. *Candida albicans* colonization) is increasing to, because of very effective bacterial treatment, specially in hospital wards. Effective bactericidal therapy is promoting fungal infections to colonize new areas of human body [31,32].

Analyses of a sepsis etiology clearly indicates that most cases of sepsis, severe sepsis and septic shock are associated with respiratory infections which frequency affects nearly 50 percent of all sepsis cases [21,27,33]. On the further places there are ureter-derived, abdominal and nonspecific sources of septic infection. Observed during serve sepsis acute organ dysfunction is related to the source of infection, so in the cases of respiratory infection it is common that respiratory tract dysfunction is observed.

### **Medical diagnostics of sepsis**

Precise medical diagnostics of sepsis is still very difficult. This is due to the fact that septic symptoms are constantly highly variable and are non-specific – may indicate systematic illness. Specific etiology of sepsis (pathogens, health status, comorbidities, used medications, host susceptibility etc.) contributes to its parameters and the appropriate confirmatory investigations. On the other hand, there are few cases of sepsis where rapid diagnostic tests will easily identify the pathogen, so the diagnosis of which does not cause any difficulties, ex. *meningococcal sepsis* (no additional examination is needed) [35,36].

Most cases of sepsis are not fully recognized before start of treatment and there is need of early therapy and treatment, basing mostly on a clinical suspicion and the occurrence of an developing inflammatory process. Medical professionals have to recognizes during medical

diagnostic examination changes of specific – and non-specific inflammation parameters changes that can indicate that patients may be suffering from sepsis [35].

Some of recently described and used laboratory tests for diagnosing severe microbial disease are being presented in Table 1. In addition time of received results and its non-specificity lead to a situation in which making a diagnosis – sepsis or SIRS is time-consuming and not always fully unambiguous. This situation leads to a conclusion that in future high quality systematic analyses of used diagnostic tools is still needed. It may improve effectiveness of therapy and increase the survival of patients [35-40].

Table 1. Examples of usable markers for the sepsis diagnosis

<b>Usable markers for the sepsis diagnosis</b>	
<b>1. Peptides Monocyte/macrophage</b>	<ul style="list-style-type: none"> <li>• Tumour necrosis factor <math>\alpha</math> (TNF-<math>\alpha</math>)</li> <li>• Interleukins: 1<math>\alpha</math>, 1<math>\beta</math>, 6, 8, 10, 18</li> <li>• Macrophage migration inhibitory factor (MIF)</li> <li>• Soluble triggering receptor expressed on myeloid cells (sTREM-1)</li> <li>• High mobility group box protein 1 (HMGB-1)</li> </ul>
<b>2. Leucocyte products</b>	<ul style="list-style-type: none"> <li>• Soluble L-selectin (=CD62L)</li> <li>• Soluble P-selectin (=CD62P)</li> </ul>
<b>3. Endothelial cell products</b>	<ul style="list-style-type: none"> <li>• Soluble vascular cell adhesion molecule (sVCAM-1=CD106)</li> <li>• Soluble E-selectin (=CD62E)</li> </ul>
<b>4. Acute phase reactants</b>	<ul style="list-style-type: none"> <li>• C reactive protein</li> <li>• Ferritin</li> <li>• Lactoferrin</li> <li>• Neopterin</li> <li>• Procalcitonin</li> <li>• Serum amyloid A</li> </ul>
<b>5. Pathogens confirmation methods</b>	<ul style="list-style-type: none"> <li>• real-time quantitative broad-range PCR assays</li> </ul>

## Conclusions

Unfortunately, despite observed new diagnostic methods in medical practice and new bactericidal, antiviral and antifungal therapies incidence of sepsis are still very big medical problem specially for the patients hospitalized on intensive care units. The total number of people dying as result of sepsis, SIRS, severe sepsis and sepsis shock is still rising. In this fact, it is necessary to look for new methods of sepsis diagnostics and to confirm already used diagnostic criteria in order to shorten the time of therapy implementation and reduce the risk of mortality.

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