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Clinical guidelines for the diagnosis of sepsis in children

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Sepsis is the one of the leading mortality causes for children. A *timely diagnosis is essential for the successful treatment of sepsis. This article presents the analysis of recommendations for the diagnosis of systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock of* the *American Society of Thoracic Physicians Consensus Conference, Society of Critical Care Medicine (1992), International pediatricians Consensus Conference on sepsis (2005), Surviving Sepsis Campaign: International Guidelines for the Management of Severe Sepsis and Septic Shock: 2012, which was published in 2013. The current understanding of the physiology of systemic inflammation in sepsis and "sterile" inflammation is highlighted.*

Keywords: *systemic inflammatory response syndrome, sepsis, septic shock, children.*
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Introduction

In 1914, Schottmueller gave the definition of septicemia – “a state of microbial invasion from the entrance gate into the bloodstream, which causes symptoms of the disease". Over the next 100 years the definition underwent minor changes, but the international medical community is making great efforts to do clinical and laboratory verification of this diagnosis. Suffice it to say, more than 170 biological molecules are proposed as predictors of sepsis, but until now there hasn’t been a single indication with sufficient sensitivity and specificity. It should be noted that both the terms - sepsis and septicemia - mean clinical conditions associated with bacteremia. However, less than half of patients with clinical signs of sepsis have positive results of cultural microbiological tests. In addition, not all patients with confirmed bacteremia clinical picture of septic process are noted.

The interpretation of the concept of "sepsis" has been going on for decades. A significant move towards the understanding of the discussed problem was made in 1992 by The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) specialists. At a joint consensus conference, definitions for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock in adult patients were given for the first time (Fig. 1) [1].

Fig. 1. Systemic inflammatory response syndrome: manifests by at least two of these conditions

Синдром системного воспалительного ответа (минимум два из указанных состояний): ✓ **ЧСС** более 90 ударов в минуту; ✓ **Тахипноэ** - более 20 дыханий в минуту или $PaCO_2$ менее чем 32 mm Hg; ✓ **Лейкоцитоз** более 12,0 x 10^9/L или лейкопения менее 4,0 x 10^9/L, или более 10% палочкоядерных нейтрофилов. ✓ **Температура** выше чем 38°C или ниже чем 36°C; *Crit Care Med 1992 June 20(6): 864-74*	Systemic inflammatory response syndrome (two of these conditions minimum): • Heart Rate is more than 90 beats per minute; • Tachypnea – more than 20 breathes per minute or $PaCO_2$ less than 32 mm Hg; • Leukocytosis of more than 12.0 x 10^9/L, or more than 10% of band neutrophils • Body temperature higher than 38^0C or lower than 36^0C

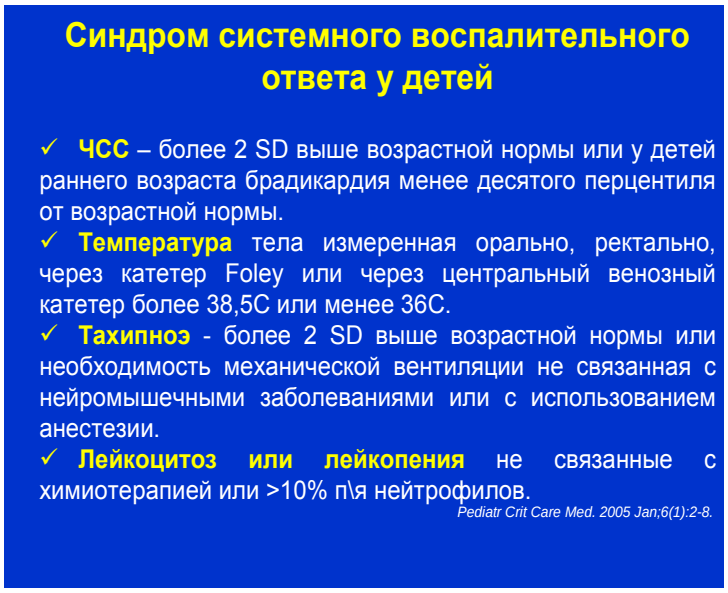
The definition for SIRS remains stable until now, the characteristics of sepsis has been changed; in addition, the International consensus conference of pediatricians on sepsis in 2005 (International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics), recommendations were made for the diagnosis of this syndrome in children (Fig. 2) [2]. It should be noted that these criteria have low specificity, in connection with which the members of the conciliation commission have recommended to interpret the presence of these symptoms in children strictly in the clinical context.

Sepsis and the systemic inflammatory response syndrome

Sepsis has been described as the systemic inflammatory response to the alleged or confirmed infection (by cultural, microscopic techniques, as well as by a polymerase chain reaction) or as a clinical syndrome pathogen, pathognomonic for infection. Severe sepsis - as well as sepsis with organ dysfunctions caused by hypoperfusion, and / or with an elevated serum lactate more than 4 mol/l; other manifestations included oliguria (less than 0.5 ml/kg per hour) and the disturbances of consciousness (fig. 3).

Alternatively, in the absence of the infection process and the presence of two or more SIRS criteria, it is recommended to diagnose systemic inflammatory response syndrome, in combination with SIRS with organ dysfunction - severe systemic inflammatory response syndrome (specific criteria for organ dysfunction in children are shown in fig. 4-7). The diagnosis of septic shock is defined as sepsis combined with hypotension after aggressive fluid replacement (40 ml/kg of crystalloids).

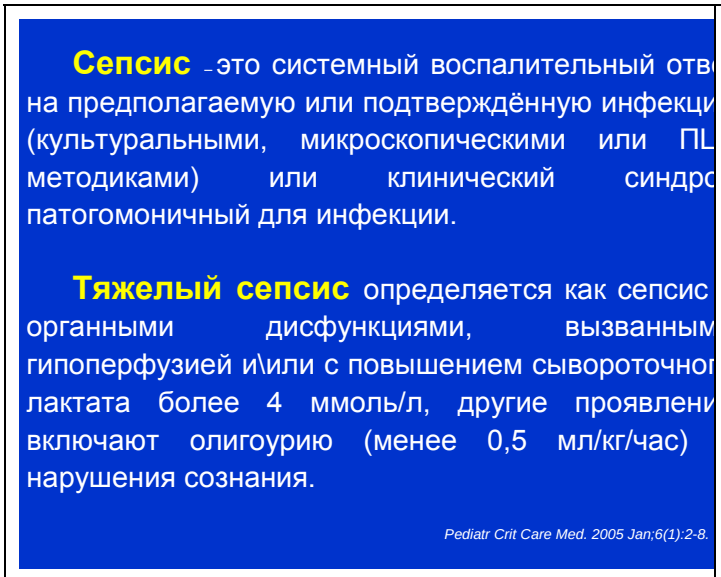
Fig. 2. The characteristics of children with systemic inflammatory response syndrome



Systemic inflammatory response syndrome in children

- Heart Rate is more than 2SD higher than the age norm; or bradycardia less than ten percent in younger children;
- Body temperature measured orally, rectally, by catheter Foley or by central venous catheter is higher than 38.5^{0}C or lower than 36^{0}C
- Tachypnea – more than 2SD higher than the age norm or the need for mechanical ventilation not associated with neuromuscular diseases or with anestesia;
- Leukocytosis or leukopenia not associated with chemotherapy or >10of band neutrophils

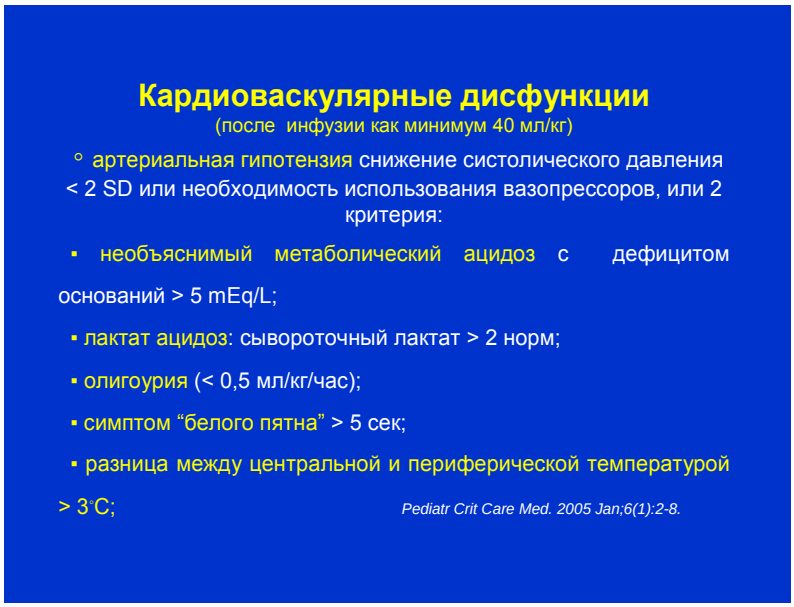
Fig. 3. Basic definitions



Sepsis is a systemic inflammatory response on a purposed or documented infection (by cultural, microscopic or PCR methods) or a clinical syndrome, pathognomonic for the infection.

Severe sepsis is defined as sepsis with organ dysfunctions caused by hypoperfusion and / or by the increase in serum lactate of more than 4 mol/l; other manifestations include oliguria (less than 0,5 ml/kg/h) and disturbances of consciousness.

Fig. 4. Cardiovascular dysfunctions



Cardiovascular dysfunctions (after infusion of at least 40 ml/kg)

arterial hypotension, decrease in systolic blood pressure < 2 SD or the need of use of vasopressors, or 2 criteria:

unexplained metabolic acidosis with a base deficit > 5 mEq/l;

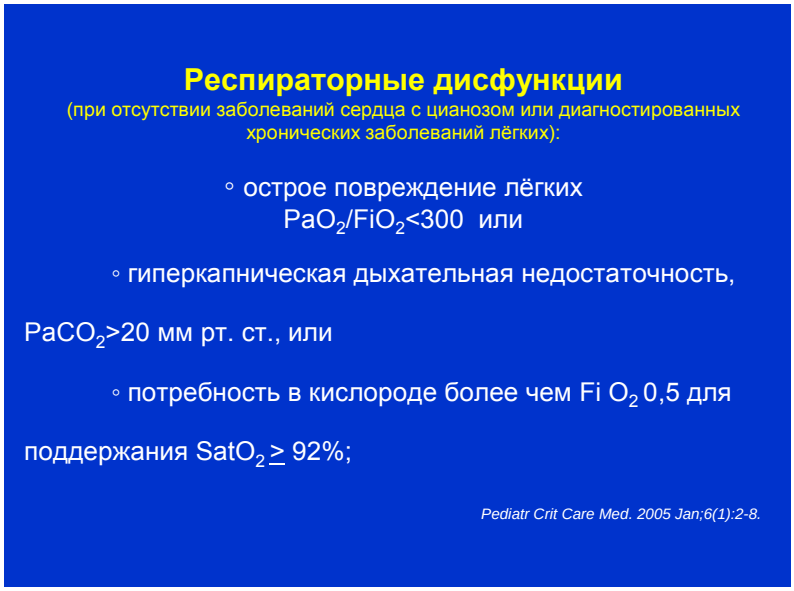
lactic acidosis: serum lactate > 2 norms;

oliguria (< 0.5 ml/kg/h);

"White spot" syndrome > 5s;

Difference between central and peripheral temperature is > 3°C

Fig. 5. Respiratory dysfunctions



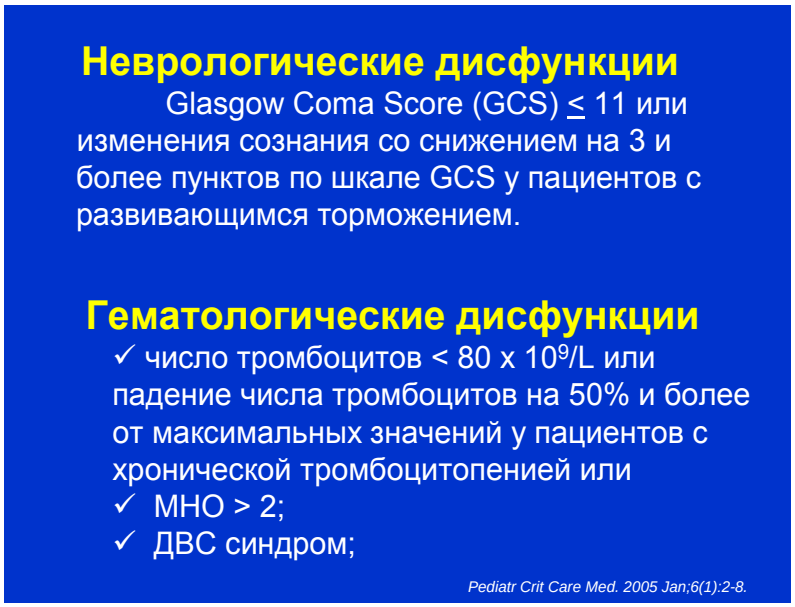
Respiratory dysfunctions (in the absence of heart diseases with cyanosis or diagnosed chronic lungs diseases)

acute lung injury PaO_2/FiO_2 <300 or

hypercapnic respiratory failure, $PaCO_2$<20 mmHg or

the need for oxygen more than Fi O_2 0.5 for maintaining $SatO_2$ ≥ 92%

Fig. 6. Neurological and hematological dysfunctions



Neurological dysfunctions

Glasgow Coma Score (GCS) ≤ 11 or more changes in consciousness by 3 and more points on GCS scale in patients with developing retardation

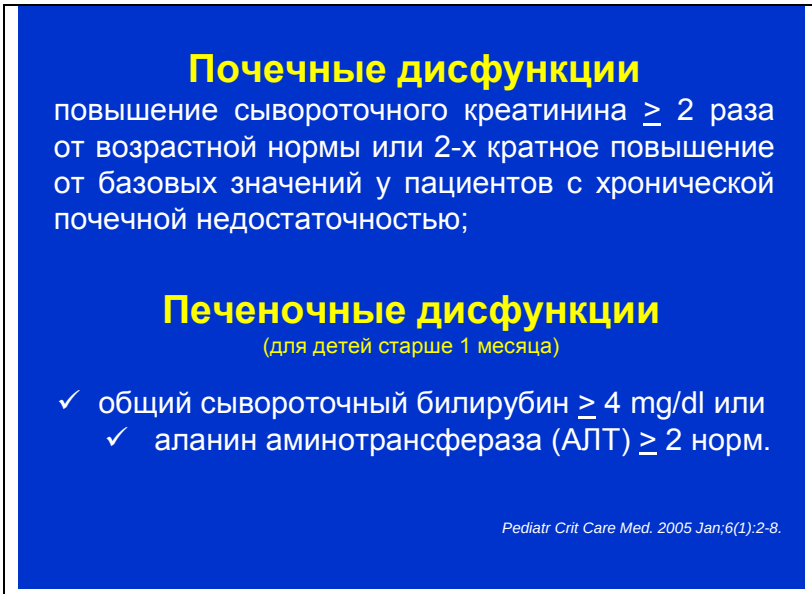
Hematological dysfunctions

Number of thrombocytes < $80x10^9$/L or reduction of the number of thrombocytes by 50% and more from maximal values in patients with chronic thrombocytopenia or

PT > 2

DIC syndrome

Fig. 7. Renal and hepatic dysfunction



Renal dysfunction

Increase in serum creatinine ≥ 2 times from the age norm or two-fold increase from base values in patients with chronic renal failure

Hepatic dysfunction (for children older than 1 year)

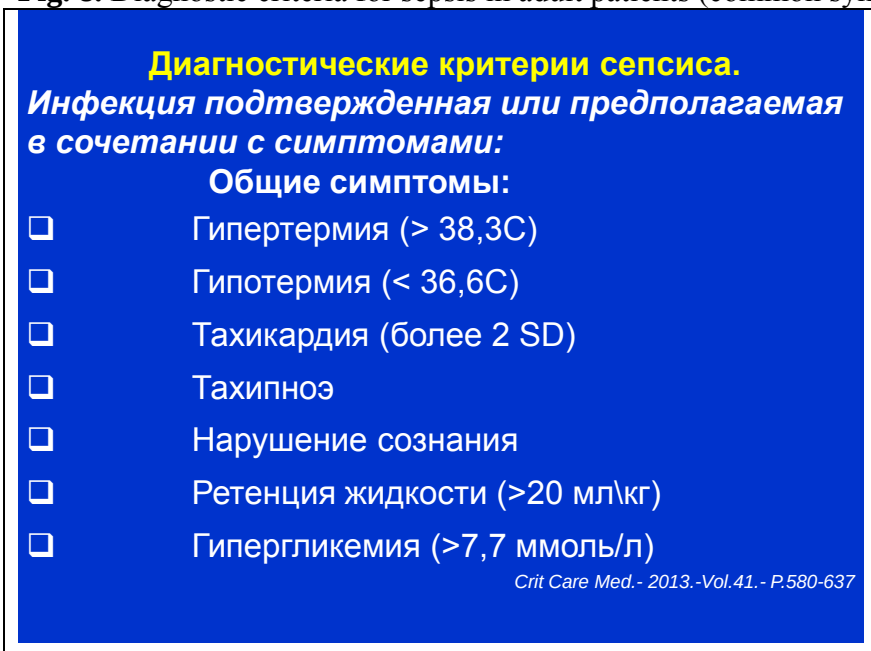
General serum bilirubin ≥ 4 mg/dl or

alanine aminotransferase (ALT) ≥ 2 norms.

Latest recommendations for the diagnosis of sepsis (Fig. 8), severe sepsis and septic shock were published in 2013 by the International Organization “Surviving Sepsis Campaign”

(Surviving Sepsis Campaign: International Guidelines for the Management of Severe Sepsis and Septic Shock: 2012) [3].

Fig. 8. Diagnostic criteria for sepsis in adult patients (common symptoms)



Diagnostic criteria of sepsis.
Purposed or documented infection combined with symptoms:
Common Symptoms:
Hyperthermia (> 38.3C)
Hypothermia (<36.6C)
Tachycardia (more than 2 SD)
Tachypnea
Disturbance of consciousness
Fluid retention (>20 ml/kg)
Hyperglycemia (>7.7 mol/l)

According to the presented recommendations, sepsis is defined as the presence (probable or documented) of infections with systemic manifestations of infection; severe sepsis – as sepsis in conjunction with organ dysfunction or tissue hypoperfusion, septic shock - as severe sepsis in combination with hypotension refractory to massive infusion therapy.

As shown in the data presented, the term "sepsis" has undergone minor changes, the most significant of which is the formal absence of the "systemic inflammatory response" definition, but by the content, this concept is present in the diagnostic criteria of sepsis (fig. 9, 10).

So what is the reason for the limited use of the concept of "systemic inflammatory response" in the diagnosis of sepsis? The answer is simple: the high sensitivity and low specificity. As an illustration, it is sufficient to provide data for European Studies on Sepsis Occurrence in Acutely ill Patients (SOAP), published in 2006: 93% of patients were admitted to the intensive care unit, and met the diagnostic criteria for SIRS [4]. SIRS can be diagnosed with different diseases of infectious nature: in severe trauma, pancreatitis, surgical interventions, reperfusion syndrome, etc.

Fig. 9. The diagnostic criteria for sepsis in adult patients (symptoms of inflammation, hemodynamic disorders, organ dysfunction)

Диагностические критерии сепсиса. **Симптомы воспаления:** Лейкоцитоз или лейкопения (<4,0x10^9/л) Левый сдвиг (>10% незрелых форм) Повышение СРБ и ПКТ (>2SD) **Гемодинамические показатели:** Артериальная гипотензия (<2SD) **Органные дисфункции:** Артериальная гипоксемия (Pao_2/Fio_2<300) Олигоурия Повышение креатиниа (>44,2 мкмоль/л) Гемокоагуляционные расстройства (МНО>1,5, аЧТВ>60 сек) Парез кишечника Тромбоцитопения (<100,0x10^9/л) Гипербилирубинемия (>70 мкмоль/л) *Crit Care Med.- 2013.-Vol.41.- P.580-637*	Diagnostic criteria of sepsis symptoms of inflammation: Leukocytosis or leukopenia (4,0x10^9/l) Left shift (>10% immature forms) Increase in CRP and PCT (>2SD) Hemodynamic indexes: arterial hypotension (<2SD) Organ dysfunctions: Arterial hypoxemia (PaO_2 / FiO_2 < 300) Oliguria Increase in creatinine (>44.2 mc mol/l) Hemocoagulation disorders (INR>1.5, aPTT>60s) Enteroplegia Thrombocytopenia (<100.0x10^9/l) Hyperbilirubinemia (>70 mc mol/l)

Fig. 10. Diagnostic criteria for sepsis in children

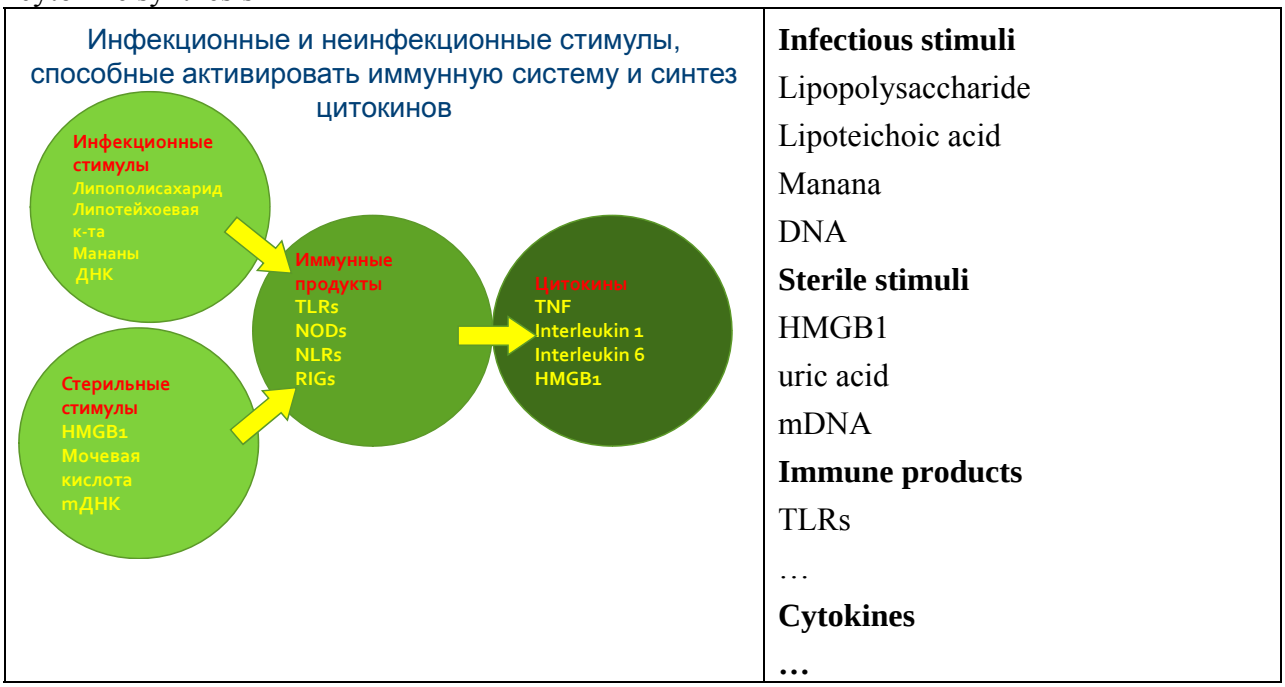
Диагностические критерии сепсиса у детей: Наличие инфекционного процесса с системными проявлениями воспаления в сочетании с: ✓ гипер- или гипотермией ✓ тахикардией + не менее одного из проявлений органных дисфункций: ✓ нарушенное сознание ✓ гипоксемия ✓ повышение сывороточного лактата ✓ вариабельный пульс. *Crit Care Med.- 2013.-Vol.41.- P.580-637*	Diagnostic criteria for sepsis in children Presence of infection process with systemic inflammation manifestations combined with: Hyper- or hypothermia Tachycardia + at least one of the organ dysfunction manifestations: Disturbed consciousness Hypoxemia Increase in serum lactate Variable pulse

Ehtiopatogenez of systemic inflammatory response

For a more precise definition of SIRS, we must answer the question, are there any differences in the nature of occurrence of SIRS with sepsis, and with sterile inflammation?

In recent years, it has been found that in terms of the molecular biology, the initial body's response to infection stimulus does not significantly differ from the response to the sterile inflammation that occurs in trauma, burns, and reperfusion syndrome, i.e., states, accompanied by a massive cellular necrosis (fig. 11). As an example, Toll-like receptors, NOD-like protein induced cellular responses, the totality of which implements the sepsis' phenotype. These receptors are activated by molecular structures such as lipopolysaccharide-endotoxin or lipoteichoic acid-exotoxin.

Fig. 11. Infectious and non-infectious stimuli capable of activating the immune system, and cytokine synthesis



Note: *DNA - deoxyribonucleic acid.*

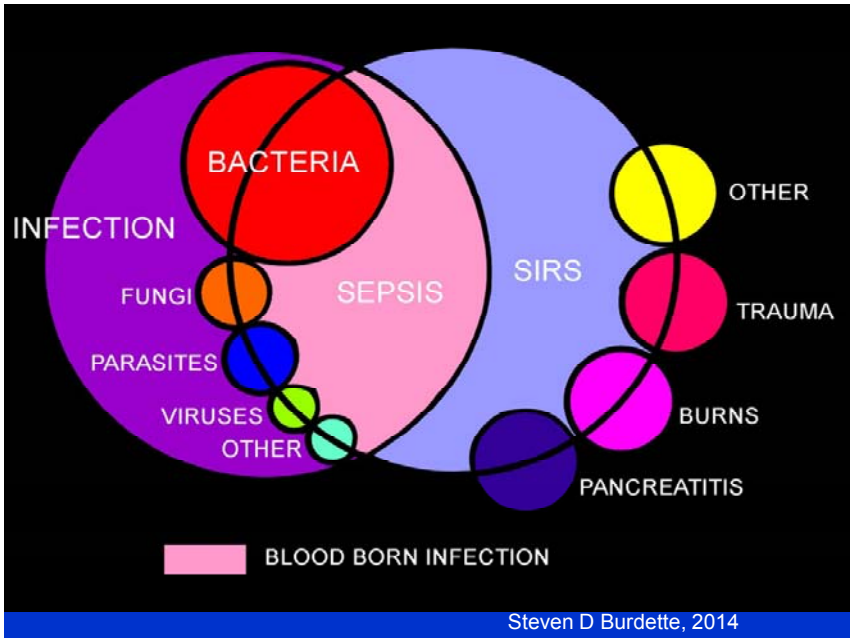
Innate immune system receptor activation ways are similar in recognizing microbial and non-microbial ligands pathologically present in the extracellular space. Thus, the HMGB1 protein (high-mobility group protein B1) is secreted by activated macrophages and monocytes as a cytokine mediator in infectious processes. But the HMGB1 protein can also be released in the necrosis of cells and tissues. After being released from the cells, the protein binds to the receptor of the innate immunity - Toll-like receptor 4, which leads to the secretion of cytokines by macrophages and mediates the damage of its own tissues. Thus, in the case of both infection and a sterile tissue necrosis, similar processes are implemented: inflammation, coagulopathy, isolation and the destruction of microorganisms, the recovery of tissues from a position of self-preservation of the organism. The interaction of innate and adaptive immunity is accompanied

by the eradication of a microbial invasion (in the case of sepsis) and / or the recovery of damaged tissue (in sepsis and sterile tissue damage) [5, 6].

To summarize, let's answer the previously set question: of course, sepsis differs from sterile inflammation, but not by the nature of the immune response or the type of organ dysfunction. It differs by the presence of an infectious process (fig. 12). In this sense, the tasks that have priority and the key to success in both the timely diagnosis and the treatment of sepsis, in terms of the prevention of progress of the disease from sepsis to severe sepsis and infectious shock, are:

- control of infectious invasion;
- timely detection of the source of infection;
- verification of the type of infectious agent;
- timely start of anti-infective therapy;
- maintaining the volemic status;
- adequate perfusion of organs and tissues.

Fig. 12 Causes of sepsis and sterile systemic inflammatory process



CONCLUSION

The results of the development of leading experts in the field of intensive therapy of sepsis in children and adults are presented in the article for the diagnosis of sepsis. Recommendations for the "Surviving Sepsis Campaign" International organization are based on the principles of evidence-based medicine, the important aspects of both the diagnosing and maintaining of patients with sepsis, severe sepsis and septic shock. Compliance with the above recommendations will lead to an increase in the survival of patients with this pathology.

Future prospects in context with the diagnosis of sepsis, differential diagnosis between SIRS of infectious and noninfectious etiologies which are related to improving clinical guidelines, and the development of scoring systems and multiplex diagnostic technology.

CONFLICT OF INTEREST

The author has indicated he has no financial support / conflict of interest relevant to this article to disclose.

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