

### The Course of Sepsis in Young Children

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#### ABSTRACT

Sepsis is a confirmed or suspected infection with the development of life-threatening multiple organ dysfunction (MOD) of the internal organs due to dysregulation of the body's response to infection.

#### *Etiology and pathogenesis*

Sepsis can be caused by bacterial, fungal, viral and parasitic pathogens, although the main thing is the reaction of the macroorganism due to dysregulation of the body's response to infection [1]. Bacteremia is not mandatory for the diagnosis of sepsis, and a positive culture occurs in only 30–50% of patients with SS [1]. In a recent population-based study, mortality in children with confirmed bacteremia was close to zero in the absence of organ dysfunction and increased to 17% in the presence of any organ dysfunction, supporting the distinction between "infection" and "sepsis", defined as infection with impaired organ function [2].

Sepsis has a complex pathogenesis and a diverse and non-specific clinical presentation affecting heterogeneous patient groups, so a simple and objective definition is not easy [3].

The pathophysiology of SS is not well understood, but it is thought to involve a complex interaction between the pathogen and host immune system. If the normal physiological response to localized infection includes activation of host defense mechanisms that results in an influx of activated neutrophils and monocytes, release of inflammatory mediators, local vasodilation, increased endothelial permeability, and activation of coagulation pathways, then in sepsis/septic shock these responses occur on a systemic scale, which leads to diffuse destruction of the endothelium, vascular permeability, vasodilation and thrombosis of the capillaries of target organs [4]. Gram-positive and Gram-negative bacteria induce a variety of pro-inflammatory mediators, including cytokines, which play a key role in initiating sepsis and shock [5]. The

exact mechanisms of cell damage and consequent organ dysfunction in patients with sepsis are also not fully understood. POD is associated with widespread damage to endothelial and parenchymal cells through the following proposed mechanisms:

- Hypoxic hypoxia - septic circulatory damage impairs tissue oxygenation, alters the metabolic regulation of oxygen delivery to tissues, and contributes to organ dysfunction.
- Direct cytotoxicity - endotoxin, TNF- $\alpha$  and NO can cause damage to mitochondrial electron transport, resulting in impaired energy metabolism. • Apoptosis (programmed cell death) - disruption of apoptosis plays a critical role in tissue damage in patients with sepsis.
- Immunosuppression. The interaction between pro-inflammatory and anti-inflammatory mediators can lead to an imbalance and an inflammatory response, immunodeficiency can predominate, or both can occur simultaneously [6].

### ***Clinical picture***

There is no typical clinical picture of sepsis. Symptoms vary depending on the age of the child and the location of the infectious focus. Usually, non-specific symptoms and signs are identified, especially in infants. Sepsis may initially present with non-specific, non-localized symptoms such as feeling very unwell at normal temperatures. If a child has signs or symptoms suggestive of a possible infection, regardless of temperature, the possibility of sepsis should be considered.

Although laboratory tests (eg, blood cultures, biomarkers) are useful in confirming the diagnosis, the diagnosis must first be established on the basis of clinical judgment. The diagnostic criteria of the international consensus guidelines are primarily considered as criteria for research aimed at facilitating informative research.

Research criteria and clinical assessment are not always consistent: up to one third of patients with clinical sepsis do not meet the diagnostic criteria of the studies. Anamnesis: change in mental state; decrease in functional ability; weakening of the immune system; or recent injury, surgery or invasive procedure, prescription of antibiotics.

### ***Clinical symptoms***

- Behavior [behavioral change, decreased activity, drowsiness, inability to wake up; lack of response to social cues (in newborns and infants), weak high-pitched or continuous crying (in newborns and infants)].
- Breathing (apnea, moaning, flaring of the alae, increased respiratory rate, new oxygen demand to maintain oxygen saturation).
- Circulation and hydration (decreased systolic blood pressure, decreased capillary refill time, increased heart rate, decreased diuresis).
- Skin (signs of infection; marbled or ashy appearance; cyanosis of the skin, lips, or tongue; skin rash that does not blanch when pressed).
- Other: cold hands or feet, decreased peripheral perfusion (increased capillary refill time more than 3 s), body temperature over 38.5 or under 36.0 °C, leukocytosis or leukopenia.

### ***Diagnosis of sepsis in children***

Early detection of sepsis is critical because early treatment—when sepsis is suspected but not yet confirmed—is associated with significant benefits in terms of short-term and long-term outcome. However, the identification of sepsis can be difficult because the clinical picture of sepsis can be

mild and nonspecific. Thus, thresholds for suspecting sepsis are important. The aim is to identify patients at risk of worsening with the possibility of developing sepsis before this occurs. Because time is critical in severe sepsis and SS, if sepsis is suspected on the basis of the clinical presentation, it is best to initiate sepsis testing and treatment, and continue until the diagnosis of sepsis is ruled out.

### ***Microbiological diagnosis of sepsis in children***

Currently, several observational studies have shown that the use of this tactic is associated with improved treatment outcomes [6-8]. Blood samples to determine the presence of bacteremia are obtained by puncture of peripheral veins in compliance with the rules of asepsis and antisepsis. Sampling from a vascular catheter is only permitted if a catheter-associated bloodstream infection is suspected or, as a last resort, if venipuncture is technically impossible. There is no advantage in using arterial blood for culture over venous blood. An important aspect for obtaining an optimal blood culture result is to take a sufficient volume of blood for analysis, as well as to use an approach that allows differentiating sample contamination from true bacteremia. The blood volume for culture should not exceed 4% of the BCC and is determined based on the patient's body weight [9].

In patients with greater body weight, the recommended total volume of the studied samples corresponds to that for adult patients - 40-60 ml. Optimal results in diagnosing bacteremia are obtained using standardized, prefabricated, enriched vials intended for use in children. In all cases, except for suspected anaerobic infection, aerobic blood culture vials should be used [3]. For one blood culture, it is recommended to use at least two vials, between which the sample taken is equally distributed. Single vial blood cultures should not be performed as this practice results in insufficient blood cultures and the danger of missing a significant number of bacteremia cases, as well as the impossibility of ruling out specimen contamination.

### ***Treatment of sepsis in children***

Initiation of antimicrobial therapy within 3 hours of the diagnosis of sepsis (within 1 hour for SS), despite the lack of strong evidence, may be considered as a recommended intervention in appropriate conditions. An important aspect is also the conduct of adequate clinical and laboratory diagnostics, which makes it possible to identify patients with sepsis in a short time and initiate a complex of intensive care for this condition. Their widespread and often irrational use contributed to the emergence and spread of resistance to carbapenems. Infections caused by carbapenem-resistant non-fermentative gram-negative bacteria, primarily *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are also a serious problem. The resistance of gram-negative bacteria to carbapenems is due to various mechanisms and their combinations, including impaired cell wall permeability, efflux, and enzymatic inactivation, in which the production of carbapenemases plays a key role. In accordance with the Ambler classification, 4 molecular classes of beta-lactamases are distinguished - serine (A, C, D) and metalloenzymes having a zinc atom in the active center (B). Enzymes of the AmpC type (molecular class C), characteristic of enterobacteria and *P. aeruginosa*, show predominantly the hydrolysis of cephalosporins.

Class A is represented by a number of enzymes of various substrate profiles, including ESBLs, which cause resistance of enterobacteria to all beta-lactam antibiotics, except for carbapenems, as well as KPC and GES carbapenemases, found in enterobacteria and *P. aeruginosa*. Class D includes carbapenemases of the OXA type, characteristic of members of the order Enterobacterales and acinetobacteria. Metallobetalactamases (IMP, VIM, NDM) are found predominantly in *P. aeruginosa* and enterobacteria, have a wide range of hydrolytic activity, including carbapenems, but they are inactive against monobactams. Identification of carbapenemase production makes carbapenem monotherapy inappropriate, even in the presence

of phenotypic sensitivity to them. With low MIC values ( $\leq 8 \mu\text{g} / \text{ml}$ ) for meropenem, in some cases it is possible to use combined regimens of therapy, including meropenem at maximum doses, amikacin, fosfomycin, tigecycline, polymyxins in various combinations). At high MICs of meropenem, combination therapy based on polymyxins can be considered.

Infusion therapy is a fundamental part of the treatment of patients with sepsis in the first hours after diagnosis. In SS, volume loading allows correction of hypovolemia due to capillary leak syndrome and vasodilation. Without maintaining adequate preload, cardiac output will decrease, resulting in impaired tissue perfusion.

### ***Extracorporeal Therapy***

Currently, for the treatment of patients with sepsis and SS, the possibility of using various methods of extracorporeal hemocorrection is being considered. It is possible to use plasma exchanges, RRT, sorption methods of extracorporeal hemocorrection. There is a pathogenetic rationale for these procedures in the treatment of patients with sepsis. Unfortunately, most of the data to date have been obtained from adult patients.

The main tasks of rehabilitation of patients with sepsis:

1. Prevention or reduction of the severity of violations of the functions of organs and systems of the body.
2. Prevention or reduction of the degree of disability and progression of the disease and the development of complications.
3. Elimination and correction of emotional and psychological disorders.
4. Reducing the severity of the disabling consequences of the disease, adaptation to everyday household physical activity.
5. Continue learning.

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