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Modern Diagnostics of Sepsis and Septic Shock in Children

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Abstract

Sepsis is still one of the leading causes of child mortality worldwide, despite advances in its diagnosis and treatment. Difficulties in recognizing the transition of a localized infectious-inflammatory process to a generalized one lead to a belated diagnosis and the beginning of therapy. Meanwhile, the earlier treatment is started, the higher the patients' chances of life. Early diagnosis of sepsis, which corresponds to modern ideas about this condition, is one of the main tasks for both scientists and practitioners. The aim of this review is to study modern recommendations for the diagnosis of sepsis and septic shock in children. The article reflects the epidemiology, etiological features, modern definitions, and methods of diagnosis of pediatric sepsis.

Introduction

Sepsis is one of the leading causes of child mortality worldwide, despite the progress made in its study over the past decades [1], [2]. In 2017, the World Health Organization named sepsis as one of the priority tasks of healthcare in the coming decade [3], [4]. Clinically, sepsis is a syndrome that complicates the course of severe out-of-hospital and in-hospital infections and leads, in turn, to life-threatening conditions such as septic shock and multiple organ failure [5]. The symptoms of sepsis are polymorphic and depend on many factors: The age of the child, its premorbid state, the infectious agent, the source of infection, and others. At present, sepsis is considered as a body regulation disorder of the normal protective response to infection and a serious role in its development is given to genetic factors [6], [7], [8], [9]. Thus, at this stage, it is difficult to predict whether a particular child will have an infectious disease with sepsis or not, and clinical polymorphism and the presence of the so-called "latent" course of sepsis create significant diagnostic difficulties. On the other hand, timely diagnosis of sepsis in children and, consequently, the earliest possible start of therapy is crucial for the prognosis of the disease. Delay of therapy even for 1 h leads to an increase in mortality [5], [10].

In accordance with the foregoing, the earliest possible diagnosis of the septic process in children is one of the main tasks for the clinician. Indeed, the sooner targeted treatment is started, which includes antibiotics and infusion therapy, the more chances there are to stop the development of sepsis [11].

It should be noted that in this article we did not aim to consider the features of sepsis in newborns since sepsis in this age group differs significantly from sepsis in children older than the neonatal period and adults and requires separate consideration [12].

Research Materials and Methods

Study of the literary sources collected in the databases of PubMed, ScienceDirect, Cochrane Library, and search depth 10 years, from 2009 to 2019 was conducted, all types of articles were studied, key words: Sepsis in children, pediatric sepsis, septic shock in children, sepsis diagnostics, sepsis recognition, and sepsis biomarkers. As a result of a thorough scientific search, 62 articles were selected that, in our opinion, are of the greatest interest according to the chosen topic.

Main Part

Epidemiology of sepsis

Assessing the global epidemiology of sepsis and septic shock in children presents certain difficulties related to economic and diagnostic factors. In recent years, several attempts have been made to estimate the worldwide incidence of pediatric sepsis. In 2014, the original study the sepsis prevalence, outcomes and therapies study was published, showing very interesting results. The study included 6925 children from 128 intensive care units (ICUs) from North America, Europe, Asia, Australia and New Zealand, South America, and Africa. The average incidence of severe sepsis was 8.2%, but it certainly varied from 6.2% in Europe to 23.1% in Africa. At the same time, the mortality rate from this pathology in all the studied countries was approximately the same and amounted to 23–24%. It is also interesting that the majority of patients (77%) were diagnosed with concomitant diseases, among which the most common were respiratory disorders. The most common foci of infection were the respiratory system (40%) and blood flow (19%) [1], [13], [14], [15].

A detailed review of 2019 showed the following results: In countries with a high level of economic development, the prevalence of severe sepsis ranged widely from 1.4% in Japan to 7.7% in the United States, the mortality rate from severe sepsis was 7–17%, from septic shock to 51%. In developing countries, the incidence of severe sepsis among children also varied from 1% to 25.9%, and the mortality rate was 12.3–34.6%. The authors attribute these significant fluctuations to various diagnostic criteria and economic factors [16], [17].

At present, there are no clear and unambiguous criteria for diagnosing sepsis in children in the Republic of Kazakhstan. The statistical collection of population health of the Republic of Kazakhstan contains the following data: The incidence of sepsis in children under 1 year was 7 children out of 1000 in 2016, 21 children out of 1000 in 2017, and the death rate from sepsis was registered only for neonatal sepsis and amounted to 3.88 per 10,000 children born alive [18].

It should also be noted that, according to research, most cases of sepsis occur before the age of 3 years, which can probably be associated with the anatomical and physiological characteristics of young children [11], [19], [20]. Children with chronic comorbidities had a higher mortality rate [21], [22].

Etiology of sepsis

Infectious agents that lead to septic complications in children differ from those in adults. Bacteria and viruses most often cause sepsis. For children older than the neonatal age is the most common causative agents are *Streptococcus*, *Staphylococcus*, *Meningococcus*, and *Pseudomonas*. *Streptococcus pneumoniae* most often leads to sepsis among toddlers and young children. It should also be noted the important role of *Haemophilus influenzae* in the development of sepsis in countries where there is no active vaccination against this infection. A special place is occupied by nosocomial and multi-resistant to antibacterial drugs microorganisms. Among hospital infections, Gram-negative bacteria – *Pseudomonas aeruginosa*, *Klebsiella* species, *E. coli, Acinetobacter* species, and *Salmonella* spp. – most often lead to sepsis. Catheter-associated sepsis is caused by coagulase-negative staphylococci [6], [19], [20], [23].

It is necessary to take into account the possibility of participation of other microorganisms in the development of sepsis – viruses and fungi. According to the literature, the prevalence of viral and mycotic septic complications in the child population is 2.9–5.3%. Among viral infections, influenza, parainfluenza, adenovirus infection, CMV infection, and herpes are most often complicated by sepsis [24], [25].

Fungal infections usually lead to septic complications in children with concomitant immunodeficiency and the need for invasive manipulations. Among the pathogens of mycosis, sepsis is most often caused by *Candida* species, *Candida albicans*, and *Aspergillus* species.

In patients with immunodeficiency disorders of various etiologies, sepsis may be caused by opportunistic microorganisms [25].

It should be noted that it is not always possible to identify the pathogen in the hemoculture. According to current data, the pathogen remains unknown in 30–75% of children with sepsis [25], [26].

Definitions of sepsis and septic shock in children

The active study of sepsis and its complications continues all over the world, and new data on pathophysiology, microbiology, and clinical disciplines are accumulating, which contributes to changing the current understanding of this condition. If earlier the leading role in the development of sepsis was given to an infectious agent, then gradually the pathological reaction of the macroorganism came to the fore, that is, a generalized inflammatory response combined with damage to various organs and systems. Thus, there was a fundamentally new understanding of sepsis, approaches to its diagnosis and treatment.

According to the original concept of the American College Consensus Conference of pulmonologists and Society of Critical Care Medicine ACCP/Society Critical Care Medicine (SCCM), 1991, basis of sepsis development was considered to be systemic inflammatory reaction syndrome in response

to infectious aggression. To diagnose sepsis, the criteria for systemic inflammatory response syndrome (SIRS) were developed, which clinicians have relied on for a long time in their work. However, it has now been established that the response of the human body to a microbial agent is a much more complex and multi-faceted process in which not only the immune system but also other organ systems are actively involved, as well as genetic characteristics, gender, age, race, concomitant conditions, and therapy [9], [27], [28], [29]. Due to these factors, the clinical picture of sepsis is characterized by pronounced polymorphism, which makes it very difficult to diagnose it early.

It should also be noted that the results of the conducted studies indicate a low specificity of SIRS criteria in the diagnosis of sepsis. SIRS develops in most patients of the ICU against a variety of conditions and, in principle, does not indicate the etiology of the disease. In addition, the existence of SIRS-negative sepsis has now been proven. In this case, sepsis develops without prior development of systemic inflammation, respectively, according to the ACCP/SCCM criteria, such children cannot be classified as patients with sepsis [30].

Thus, on the one hand, the concept of sepsis ACCP/SCCM was an important step toward studying the problem of sepsis and set a further direction for the search, on the other hand, it left a lot of questions.

In 2005, the results of the International Pediatric Sepsis Consensus Conference (IPSCC-2005) were published. Criteria for SIRS and definition of sepsis in children were developed based on criteria for adults, taking into account the anatomical and physiological characteristics of children of different age groups [31].

In 2016, new consensus definitions of sepsis and septic shock were published, called “The Third International Consensus on the definition of sepsis and septic shock “(Sepsis-3”),” authored by experts from the SCCM, European Society Intensive Care Medicine. According to new data, sepsis is considered as a dysregulation of the body response to the infectious process with the development of organ dysfunction. At the same time, the concept does not deny the participation of systemic inflammation in the septic process, but considers it as one of the possible variants of the body response to infection [9].

Modern diagnostics of sepsis and septic shock in children

There are several fundamentally important differences in the development of the body response to infection, which clearly distinguish between pediatric sepsis and adult sepsis. Age-related differences in the concentration and composition of hemoglobin, heart rate, stroke volume, blood pressure, pulmonary vascular resistance, systemic vascular resistance, metabolic rate, glycogen stores, and protein mass are the basis of many age-related differences in the body response to infection [32], [33], [34], [35]. Thus, the principles of sepsis diagnosis developed for adults are not suitable for children.

Modern diagnostics of sepsis, as well as its complications – septic shock and multiple organ failure – in children are based on the recommendations of IPSCC-2005 and “Sepsis-3” (Tables 1 and 2). Diagnostic measures can be divided into two groups: Clinical diagnostics and laboratory-instrumental methods. Despite the large number of different laboratory markers of systemic inflammation and sepsis, most researchers now agree that the priority belongs to clinical signs. This can be attributed to the lack of a universal marker that would be sensitive to all types of infection, detect sepsis, at the earliest stages, in different children and would be financially available in any clinic in the world. As mentioned above, sepsis is a condition characterized by clinical polymorphism, but it has certain pathophysiological stages of development that can be traced in the patient’s condition.

In accordance with the concept of IPSCC-2005, sepsis begins with a systemic inflammatory reaction, for the diagnosis of which certain criteria were proposed, adapted to children of different age groups.

Age groups of children with sepsis, IPSCC-2005 [31] (Table 3)

1. Early neonatal period (0–7 days)
2. Late neonatal period (8–28 days)
3. Infant age (29 days–1 year)
4. Preschool age (1–5 years)
5. School age (6–12 years)
6. Adolescence (13–18 years).

Systemic inflammation develops not only as a result of infection but also in other conditions (injuries, acute pancreatitis, in the postoperative period, etc.) since it is essentially a non-specific reaction of the body to damage [36], [37]. This reduces its diagnostic value in sepsis. In accordance with the concept “Sepsis-3”, the main manifestation of sepsis is organ dysfunction, which is recommended to determine in the ICU using the Pediatric Sequential Organic Failure Score (pSOFA) (Table 4).

The advantages of the scale include high specificity and sensitivity in relation to children in the ICU [38]. On the other hand, the scale is aimed at predicting the outcome of the disease, rather than diagnosing sepsis at the early stages of its development, when there are no pronounced signs of multiple organ failure; in addition, the scale requires daily biochemical studies, which is not always possible and not always safe for the patient, especially for young children. Thus, the search for a better tool for timely diagnosis of sepsis continues [39], [40].

At the same time, there is no doubt that the concept of multiple organ failure as a leading link in pathogenesis is an important step toward improving the management of sepsis in children and adults.

Septic shock in children

Septic shock in a child is considered as severe hemodynamic disorders that complicate the course of sepsis. It should be noted that the clinical manifestations of septic shock in children differ from those in adults due to age-related features of the circulatory system. It is important to remember that arterial hypotension in children of the 1st year of life appears only at the later stages of shock development. Focusing only on blood pressure, the doctor risks missing the development of septic shock. It is known that the main compensatory mechanism of hemodynamics in young children is an increase in heart rate, so tachycardia is one of the most significant signs in shock in a young child. Pathogenetic mechanisms of septic shock lead to a disorder of microhemodynamics, which can be seen clinically by evaluating the time of capillary filling. Disorder of microhemodynamics leads to tissue hypoxia, which manifests itself as a significant increase in the concentration of lactate in the blood plasma. Thus, the main signs indicating septic shock in a child should not be considered a decrease in blood pressure, but signs of impaired tissue perfusion and tachycardia – as an attempt by the body to compensate for hemodynamic disorders [31], [41].

Criteria for cardiovascular dysfunction (after infusion of at least 40 ml/kg), IPSCC-2005 [31]

- Arterial hypotension – decreased systolic pressure <2 SD or the need to use vasopressors, or 2 criteria
- Unexplained metabolic acidosis with base deficiency >5 mEq/L
- Lactate acidosis: Serum lactate >2 norms
- Oliguria (<0.5 ml/kg/h)
- Symptom of a “white spot” (a spot that appears when pressing your finger on the skin over the III-IV metatarsal bones of the patient lying on his back) >5 s
- Difference between central and peripheral temperature >3°C.

Specific diagnosis of sepsis and septic shock in children

Numerous laboratory biomarkers are used to clarify the diagnosis of sepsis and septic shock. Seroreactive protein (CRP) and procalcitonin (PCT) are the most commonly used in clinical practice. CRP is recommended to be used in combination with PCT; together they have shown high efficiency in recognizing severe bacterial infection in young children with long-term fever, as well as in neutropenia. Isolated use of CRP is not recommended [42].

According to research, PCT is a valuable diagnostic marker for sepsis caused by bacterial infection in children. It should be noted that the concentration of PCT may increase in non-infectious conditions, which limits its use [43].

Table 1: Definitions of sepsis in children, IPSSC-2005 [31]

SIRS
• The presence of at least two of the following four criteria, one of which is necessarily an abnormal temperature or number of white blood cells
• Central temperature > 38.5°C or < 36.0°C
• Tachycardia defined as a heart rate exceeding 2 square deviations from the age norm in the absence of external stimuli; for children less than 1 year – bradycardia defined as a heart rate < 10% in the absence of external stimuli; or unexplained hemodynamic depression lasting more than half an hour
• Respiration rate exceeding 2 square deviations from the age norm or the need for a ventilator in an acute process that is not associated with neuromuscular diseases or general anesthesia
• The number of white blood cells increased or decreased in comparison with the age norm, in the absence of chemotherapy, or immature neutrophils >10%
Infection
• Suspected or proven by detecting a pathogen in the internal environment, caused by any pathogen, or clinical syndromes associated with a high probability of infection
Sepsis
• SIRS in the presence of a proven or suspected infection
Severe sepsis
• Sepsis + one of the following: Cardiovascular organ dysfunction, acute respiratory distress syndrome, and two or more dysfunctions of other organs and systems
Septic shock
• Sepsis + cardiovascular organ dysfunction

Presepsin is an effective biochemical marker of sepsis, the mechanism of which is different from the mechanism of increasing CRP, PCT, and other markers. The level of presepsin increases quickly when the infection generalizes and also quickly shows a positive trend. According to a recent meta-analysis, presepsin showed high sensitivity and diagnostic accuracy in sepsis in children compared to CRP and PCT, but its specificity was lower. There was also a significant increase in presepsin concentration in children with suspected or registered catheter-associated infection compared to healthy children in the control group [44], [45], [46].

Table 2: Definitions of sepsis according to the concept “Sepsis-3” [9]

Definition	Sepsis is a life-threatening acute organ dysfunction that occurs as a result of a disorder of the regulation of the macroorganisms response to infection
Pathophysiological diagnostics	Disorder of the regulation of the macroorganisms response to infection is manifested by damage to its own tissues and organs
Criteria of sepsis	Suspected or documented infection in combination with acute organ dysfunction, the development of which is concluded on the index of the SOFA scale by 2 points or more from the base value
Septic shock	A clinical variant of the course of sepsis characterized by circulatory insufficiency, which is manifested by arterial hypotension, an increase in the level of lactate more than 2 mmol/l, despite adequate infusion, and requiring the administration of vasopressors to maintain normal blood pressure

The level of cytokines in the blood increases early in the infectious process, which allows them to be used as markers of systemic inflammation and sepsis. According to different authors, the concentration of IL-6 in serum in children with sepsis

Table 3: Systemic inflammatory reaction syndrome in children, IPSCC-2005 [31]

Age	Heart rate		RR	Leukocytes, *10^9/l	Systolic blood pressure, mm Hg
	Bradycardia	Tachycardia			
0 – 7 days	< 100	> 180	> 50	> 34000	< 65
8 – 28 days	< 100	> 180	> 40	> 19500 or < 5000	< 75
28 days–1 year	< 90	> 180	> 34	> 17500 or < 5000	< 100
1 – 5 years	-	> 140	> 22	> 15500 or < 6000	< 94
6 – 12 years	-	> 130	> 18	> 13500 or < 4500	< 105
13 – 18 years	-	> 110	> 14	> 11000 or < 4500	< 117

Table 4: Scale of diagnosis of multiple organ dysfunction in children with pSOFA sepsis [9]

No.	Criteria	Points				
		0	1	2	3	4
1	PaO_2/FiO_2 or	≥ 400	300 – 399	200 – 299	100 – 199 ALV	< 100 ALV
	SpO_2/FiO_2	≥ 292	264 – 291	221 – 263	148 – 220 ALV	< 148 ALV
2	Platelets	≥ 150	100 – 149	50 – 99	20 – 49	< 20
3	Bilirubin, mg/dL	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥ 12
4	Average blood pressure			Dopamine or dobutamine	Dopamine > 5 μg/kg/min or	Dopamine > 15 μg/kg/min or
	Less than 1 month	≥ 46	< 46	5 μg/kg/min	epinephrine, norepinephrine ≤0.1	epinephrine, norepinephrine
	1 – 11 months	≥ 55	< 55		μg/kg/min	>0.1 μg/kg/min
	1 – 2 years	≥ 60	< 60			
	2 – 5 years	≥ 62	< 62			
	5 – 12 years	≥ 65	< 65			
	12 – 18 years	≥ 67	< 67			
5	GCS	15	13 – 14	10 – 12	6 – 9	< 6
6	Creatinine, mg/dL					
	Less than 1 month	< 0.8	0.8 – 0.9	1.0 – 1.1	1.2 – 1.5	≥ 1.6
	1 – 11 months	< 0.3	0.3 – 0.4	0.5 – 0.7	0.8 – 1.1	≥ 1.2
	1 – 2 years	< 0.4	0.4 – 0.5	0.6 – 1.0	1.1 – 1.4	≥ 1.5
	2 – 5 years	< 0.6	0.6 – 0.8	0.9 – 1.5	1.6 – 2.2	≥ 2.3
	5 – 12 years	< 0.7	0.7 – 1.1	1.1 – 1.7	1.8 – 2.5	≥ 2.6
	12 – 18 years	< 1.0	1.0 – 1.6	1.7 – 2.8	2.9 – 4.1	≥ 4.2

differs significantly from its concentration in healthy children [25], [47].

Lactate is used to diagnose septic shock and evaluate its therapy, but evidence for its effectiveness in children is limited. Studies have shown that the concentration of lactate in blood plasma in children more than 4 mmol/l is associated with the development of multiple organ failure in the next 24 h, but in 4% of cases, multiple organ failure developed in children with a lactate level <4 mmol/l. Therefore, normal or slightly elevated levels of lactate in blood plasma do not exclude the development of severe sepsis and septic shock [48], [49].

Pentraxin 3 significantly increases in critically ill children, including those with sepsis, but there was no difference in the concentration of pentraxin 3 between critically ill children with sepsis and other diagnoses. Thus, pentraxin 3 is more of a marker of systemic inflammation than of sepsis [45].

In recent years, The Pediatric Sepsis Biomarker Risk Model (PERSEVERE, PERSEVERE II, and PERSEVERE-XP) biomarker panels based on patient genome studies have been developed to identify the risk of death in septic shock in children. PERSEVERE biomarkers are generally associated with inflammation and cellular damage, which makes it highly likely to identify the risk of deterioration in a particular child with septic shock [50], [51], [52].

There are also separate studies that prove the diagnostic effectiveness in pediatric sepsis of indicators of hemostasis, leuco formula, adapted to the age characteristics of the “shock index” [53], [54], [55], [56].

It should be noted that currently no set of biomarkers can reliably detect the presence of sepsis in a child, and PERSEVERE panels require special equipment and are aimed only at recognizing septic shock in ICU conditions, so the use of laboratory studies should always be based on the clinical picture [57], [58].

Conclusion

It should be noted that much has been done in the study of pediatric sepsis in recent years [59], [60]. In general, child mortality in the world has decreased significantly in recent years, including through the use of common methods of diagnosis and treatment confirmed by numerous studies [61]. The mainstreaming of modern diagnostic methods should significantly reduce the mortality from sepsis and its complications in children due to earlier and better recognition of this process.

Despite the undoubted success in the study of sepsis, there are still a number of urgent problems, especially typical for pediatrics. First, the SIRS cannot be the only basis for diagnosing sepsis. Second, diagnosis of sepsis using the pSOFA scale in children requires the presence of obvious organ dysfunction, which delays treatment. Third, the pSOFA scale, like other similar scales, was created to assess the severity of the patient’s condition and predict death, not to diagnose sepsis. The scale requires daily laboratory tests, which may not be available in real clinical settings and require frequent blood sampling, including in very young children.

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