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MODERN DEFINITIONS AND PRINCIPLES OF INTENSIVE THERAPY OF SEPSIS IN CHILDREN

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Abstract: The review of the literature is concerned with one of the current problems of modern intensive care - diagnosis of sepsis in children The review highlights the modern definition of sepsis and a critical analysis of publications on pediatric sepsis in recent years The advantages and disadvantages of the Sepsis-3 approach to pediatric intensive care are considered Special attention is paid to the possibilities of methods for early detection and assessment of the severity of organ dysfunction in children with infection through special pSOFA or PELOD-2 scales. It can guide clinicians to early-identify patients at high risk of developing sepsis and to predict adverse outcomes.

Keywords: sepsis, children, diagnosis, mortality, dysregulation, macroorganism, septic shock, bacteremia, clinical criteria, disability.

Introduction

Sepsis is a condition that is a combination of disorders that can differentially demonstrate pathobiological responses of the body to infection and have different risks of developing lethal outcome, including age-related risks. Therefore, it should be understood that both in recognizing sepsis and in treating it, children should not children should not be presented to clinicians as "septic little adults".

Sepsis is one of the leading causes of hospital mortality in children. Multicenter studies in pediatric sepsis in various countries using a prospective methodology in nearly 7,000 children (mean age 3 years) in 128 pediatric intensive care units intensive care units 26 different countries have shown that.

In a typical pediatric intensive care unit therapy, there should be, on average, at least one child with sepsis per 16 beds. 16 beds should have at least one child with sepsis. The overall mortality in pediatric intensive care unit therapy by region varied by geography: 21% in North America, 29% in Europe, 32% in Australia/NZ, 40% in Asia, 11% in South America, 40% in Africa. Significantly, among the survivors, one-fifth of the children after hospital discharge were found to have moderate functional disability.

Until recent years, pediatric sepsis, like in adults was defined as an infection in the presence of at least two signs of systemic inflammatory response syndrome (systemic inflammatory reaction syndrome) [34]. However, numerous studies in adults and children have demonstrated the low specificity of this approach and the not uncommon compensatory nature of SSRIS. In this regard, its most recent definition (Sepsis-3) emphasizes that sepsis differs from uncomplicated infection in the presence of Life-threatening organ dysfunction due to dysregulation of the macroorganism's response to the infection. The criteria for the occurrence of organic dysfunction has been suggested that an increase in the SOFA score by 2 points or more due to infection is a criterion for the onset of MI.

Septic shock is a sepsis with profound circulatory, cellular and metabolic disorders, the criteria for which are the need to use vasopressors to Arterial pressure ? 65 mmHg, lactate > 2 mmol/L, despite adequate intravenous infusion of solutions. The mortality rate in sepsis is approximately 10%, and in septic shock it is > 40%. The Pediatric Consensus Conference on Sepsis Consensus Conference (IPCSS 2005) [14], in describing sepsis, the basic 62 Bulletin of Anesthesiology and Critical Care Medicine, Vol. 15, No. 4, 2018 is based on a spectrum of increasing clinical Severe sepsis, systemic inflammatory reaction syndrome, septic shock. Can these recommendations be reconciled with the clinical criteria given in Sepsis-3?.

The key features that underlie the Sepsis-3 consensus are related to the differentiation of sepsis from non infectious diseases and infections that are not life-threatening for the patient [34]. Previous studies have shown that systemic inflammatory reaction syndrome criteria occur in 90% of children admitted with febrile fever, of which only 5% require transfer to the intensive care unit Intensive Care Unit (ICU), and more than two criteria are observed in 81.8% of the children admitted with infection.

A recent study [3] in children with bloodstream infection showed that the mortality rate in the presence of bacteremia and systemic inflammatory reaction syndrome without organic dysfunction was 1% and 17% in the presence of organic dysfunction . Hence, The abandonment of the systemic inflammatory reaction syndrome criteria and the switch to organic dysfunction assessment greatly increases the specificity and sensitivity of sepsis recognition in both adults and children. In addition, the use of systemic inflammatory reaction syndrome to discriminate between low and high severity disease in pediatric practice is not supported by recent data. L. G. Schlapbach et al. have convincingly demonstrated that organ dysfunction organs, rather than systemic inflammatory reaction syndrome, is a key element determining the risk of adverse outcome in a cohort children with infection [34].

However, the sepsis criteria in the Sepsis-3 consensus are proposed only for the adult population, especially Moreover, the SOFA scale has not been developed or adapted for the pediatric age group. Meanwhile, one of the key issues of the fight against sepsis is the earliest possible recognition, i.e., detection of infection and significant signs of organic dysfunction. Ideally, sepsis and Septic shock in children should be diagnosed by clinical signs: hypo- or hyperthermia, mental status changes, capillary filling, but these signs are also nonspecific, as are systemic inflammatory reaction syndrome.

Consequently, a number of studies have been conducted to to assess the validity in sepsis of pediatric severity scales. F. Leclerc et al. [23] in children with presumptive infection have found that has a high predictive power in on day 1 of admission to the ICU, the PEOLOD-2 scale of lethality and can be used as a as a diagnostic criterion for pediatric sepsis (Table 1). Recently, the most valid version of the age-adapted assessment pediatric SOFA system for children, the pSOFA [25] (Table 2). There have been two large studies [25, 34] using the using the pSOFA pediatric pSOFA scale and PELOD-2, the authors observed very high prognostic accuracy of these scales. For both scales. the cutoff point for predicted mortality was 8 points or more. These papers provide compelling evidence that the systemic inflammatory reaction syndrome is not necessary for the detection of pediatric sepsis. This finding is important because The use of the systemic inflammatory reaction syndrome criteria to define sepsis can be problematic. For example, most febrile children with bronchiolitis currently qualify as septic, despite the extremely low risk of death. Thus, the above studies have convincingly demonstrated that it is organic dysfunction not systemic inflammatory reaction syndrome, that is a key element indicating the development of The pSOFA or PELOD-2 scales can be used in clinical practice for this purpose. can be used in clinical practice. In a recent study by J.

L. Schlapbach et al. pointed out the feasibility of using for early diagnosis of sepsis not only pSOFA and PELOD-2, but also adapted age-specific qSOFA criteria to identify children at risk for sepsis [34].

In a clinical setting, it is extremely important to identify patients at risk of developing sepsis in order to initiate treatment before the onset of OA. However, this approach has not yet been validated for the pediatric population, and generally accepted pqSOFA-type criteria do not yet exist. At the same time, the limitations of the aforementioned assessment systems are also emphasized. In particular, it is noted that the PELOD-2 scale is calibrated on patients of the 2006-2007 sample. With somewhat different intensive care tactics sepsis as recommended by the Surviving Sepsis Campaign and a relatively low mortality rate (6%), and the pSOFA indicates that it is still in need of broader international validation. Nevertheless, it allows the diagnosis of respiratory and cardiovascular dysfunction in clinics with limited funding (based only hemoglobin oxygen saturation and, therefore, measuring only mean arterial pressure) [35, 36]. And already at the present time expert opinion tends to make the use of this scale more reasonable [19]. According to the results of our preliminary information significance of these scales in sepsis in children (42 children), the area under the ROC curve was relatively high and comparable (PELOD-2 - 0.73, pSOFA - 0.71). Unfortunately, the currently used criteria for measuring organ dysfunction and hence identification of sepsis are limited to institutions in countries with high levels of population income and investment in health care. At the same time, most cases of sepsis occurs in low- and middle-income. Ultimately, redefining the definition of pediatric sepsis will require, in addition to peer review, the involvement of clinical data reflecting the full range of information on pediatric sepsis in different regions of the of the world [34, 40].

Table 1. PELOD 2 scores

Dysfunction	Scores						
	0	1	2	3	4	5	6
Neurologic							
Glasgow Com Scale score*	≥ 11	5–10			3–4		
Pupillary response	Both react				Both fixed		
Cardiovascula							
Blood Lactate (mmol/l)		<5,0	5,0–10,9			≥11,0	
Average blood pressure (mm Hg) (months)							
0–<1	≥ 46		31–45	17–30			≤ 16
1–11	≥ 55		39–54	25–38			≤ 24
12–23	≥ 60		44–59	31–43			≤ 30
24–59	≥ 62		46–61	31–43			≤ 31
60–143	≥ 65		49–64	36–48			≤ 35
≥ 144	≥ 67		52–66	38–51			≤ 37
Renal, creatinine (µmol/L) (months)							
0–<1	≤ 69		≥ 70				
1–11	≤ 22		≥ 23				
12–23	≤ 34		≥ 35				
24–59	≤ 50		≥ 51				
60–143	≤ 58		≥ 59				
≥ 144	≤ 92		≥ 93				
Respiratory							
PaO_2/FiO_2	≥ 61		≤ 60				
PaCO2 (mm Hg).	≤ 58	59–94		≥ 95			
artificial lung ventilation	No			Yes			
Hematological							
Leucocytes ($\times 10^9$/л)		> 2		≤ 2			
Thrombocytes ($\times 10^9$/л)	≥ 142	77–141		≤ 76			
Probability of death = 1/(1+exp [−logit (mortality)]);							
Logit (mortality) = −6,61+0,47 × score by PELOD-2;							

In addition to scales, various biomarkers are widely used to diagnose infection and sepsis, various biomarkers are widely used. Among these, it is necessary to emphasize the usefulness The use of procalcitonin test and blood lactate levels, an increase in the initial level of of which in children correlates with increased mortality, and its subsequent decrease with recovery [15]. Thus, so far, existing data suggest that the benefit of the current terminology of OD (pSOFA or PELOD-2 scale) improves prognostic validity relative to the Sepsis 2005.It should be understood that the criteria for Sepsis-3 must be appropriately modified before they can be applied to children (Table 3).

It is important to emphasize the importance of this problem because the term "sepsis" is a universal definition, representing a combination of disorders that manifest in different ways and have different risks and outcomes depending on depending on age.

Intensive care. When identifying sepsis in children, the protocol [30] in 1 h recommends Providing intravenous access, starting the infusion, administration of antibiotics (prior to this, samples should be taken for microbiological testing) and, if necessary, initiation of vasoactive agents. It is advisable to follow generally accepted or local protocols, adherence to which in children leads to improved therapy outcomes [4]. In addition, adherence to the principles of recommendations early diagnosis and treatment of sepsis in children can improve the effectiveness of intensive therapy and leads to a reduction in mortality by more than 2-fold [31, 33].

Table 2. pSOFA score

Dysfunction	**Scores**				
Respiratory					
PaO_2/FiO_2	≥ 400	300–399	200–299	100–199	< 100
SpO_2/FiO_2	> 292	264–291	221–264	148–220	< 148
Cardiovascular **Mean. blood pressure (mm Hg) or vasopressors (μg · kg-1 · min-1)**					
0– < 1 month.	≥ 46	< 46	Dopamine < 5 μg · kg-1 · min-1 or dobutamine in any dosage	Dopamine > 5 μg · kg-1 · min-1 Adrenaline or noradrenaline ≤ 0.1 μg · kg-1 · min-1	Dopamine > 5 in-1
1–11 month	≥ 55	< 55			
12–23 month	≥ 60	< 60			
24–59 month	≥ 62	< 62			
60–143 month	≥ 65	< 65			
144–216 month	≥ 67	< 67			
≥ 216 month.	≥ 70	< 70			
Renal, creatinine (mg/dL)					
0– < 1 monthc.	< 0,8	0,8–0,9	1,0–1,1	1,2–1,5	≥ 1,6
1–11 month.	< 0,3	0,3–0,4	0,5–0,7	0,8–1,1	≥ 1,2
12–23 month.	< 0,4	0,4–0,5	0,6–1,0	1,1–1,4	≥ 1,5
24–59 month.	< 0,6	0,6–0,8	0,9–1,5	1,6–2,2	≥ 2,3
60–143 month	< 0,7	0,7–1,0	1,1–1,7	1,8–2,5	≥ 2,6
144–216 month	< 1,0	1,0–1,6	1,7–2,8	2,9–4,1	≥ 4,2
≥ 216 month.	< 1,2	1,2–1,9	2,0–3,4	3,5–4,9	≥ 5,
Hematological					
Thrombocytes ×10⁹/л	≥ 150	100–149	50–99	20–49	<
Renal					
Bilirubin (mg/dL)	< 1,2	1,2–1,9	2,0–5,9	6,0–11,9	2
Neurological					
The Glasgow Com Scale *	15	13–14	10–12	6–9	6

Table 3. Existing and proposed terms describing sepsis in children.

Definition	IPCSS 2005 [14]	Pediatric sepsis
approach	Expert consensus systemic inflammatory reaction syndrome Sepsis Severe sepsis Septic shock	Expert Consensus Sepsis Septic shock
Clinical criteria		
Definitions of clinical criteria		
Sepsis	SIRS, related to infection	Life-threatening organ dysfunction caused by Dysregulation of the response to infection
Severe sepsis	Sepsis with cardiovascular dysfunction or ARDS, or dysfunction of two or more other systems	no
Septic shock	Sepsis with cardiovascular dysfunction	Variations of sepsis when cardiovascular and metabolic disorders are associated with increased mortality
Clinical criteria additional to infection		
Sepsis	≥ 2 of the SIRS criteria	A combination of easily measured clinical variables that are valid for predicting mortality (pSOFA or PELOD-2 scale)
Severe sepsis	Cardiovascular dysfunction, ARDS, or Dysfunction of two or more other systems	no
Septic shock	Cardiovascular dysfunction	Sepsis with decreased perfusion or hypotension requiring vasopressor support ± Hyperlactatemia

It is well known that control of the focus of infection plays a fundamental role in the outcome of sepsis and timely adequate antibiotic therapy. The time of the first administration of antibiotics in children is of key importance, so that a delay with their use by 1 h is independently associated with increased mortality. Moreover, there is an increase not only in hospital mortality but also in delayed annual mortality increases [7]. Special attention is paid to early access to the vascular bed. In pediatric septic shock can be started with peripheral venous or intracranial access. It is generally recognized that Aggressive volemic reimbursement tactics with crystalloids and/or colloids is fundamental to the survival rate of children with septic shock [16].

Close monitoring is an essential component of infusion therapy. The primary utility of blood pressure (BP) monitoring in intensive care is to detect and respond to hypotension. If invasive arterial pressure is considered the gold standard for correctly detecting hypotension in adults, in children only a recent comparison of its informative value with noninvasive arterial pressure measurement, it was found that the latter, as as in adults, has a low predictive value, which may lead to excessive therapy [11].

In children arterial hypotension is the last hypovolemia: at a loss of 20% of circulating blood volume or more, normal BP can be maintained. If in adults arterial hypotension is one of the three necessary criteria of Septic shock , in children it develops only in the late stages of septic shock [1]. Therefore, adequate analysis of infusion therapy can be carried out on the basis of a set of indicators, including dynamic assessment of cardiac output, transthoracic Doppler or transpulmonary thermodilution and peripheral vascular resistance [22].

Rapid restoration of circulation, tissue perfusion, oxygen delivery by aggressive infusion therapy is the most important in the treatment of Septic shock [26], and fluid resuscitation with crystalloids and colloids should be started immediately [10]. If circulation is not restored after three boluses 20 ml/kg, vasopressor support should follow. In this

case, crystalloids are preferred because of their sufficient effectiveness, low cost and availability. Among crystalloids, balanced crystalloids have an undoubted advantage [13]. crystalloids have a clear advantage [13]. Among the colloids in sepsis albumin solutions are the drugs of choice [12]. Infusion therapy in children is more aggressive than in adults: the starting volemic reimbursement is started with the infusion of isotonic crystalloid solutions or albumin by bolus injection of 20 ml/kg for 5-10 min, and then within an hour another 40-60 ml/kg or more under monitoring [16].

However, the role of bolus resuscitation remains unclear [29, 32]. Two systemic reviews have found harmful effects of such therapy in children [18, 27]. M. Bregje et al. [7] found that in children with Septic shock, high fluid bolus volume in the first 2 hours was independently associated with prolonged stay in pediatric ICU and duration of artificial ventilation.

Table 4. Pediatric Glasgow Coma Score, Zh.B. Semenova score etc.

<table>
<tr><td>Opening of eyes</td><td colspan="2">Older than 1 year</td><td colspan="2">Under 1 year</td></tr>
<tr><td></td><td>4
3
2
1</td><td>Spontaneously
On the speech command
pain
No reaction</td><td colspan="2">Spontaneously
On the speech command
pain
no reaction</td></tr>
<tr><td>Best motor response</td><td>6
5
4
3
2
1</td><td>Execution of the command
Pain localization Flexion - pulling back Pathological flexion
(decerebral stiffness)
Flexion (decerebrating stiffness)
No response</td><td colspan="2">Pain localization Normal flexion Pathological flexion
(decertification stiffness)
Flexion (decerebrating stiffness)
No response</td></tr>
<tr><td></td><td colspan="2">Older than 5 year</td><td>2–5 year</td><td>0–23 month</td></tr>
<tr><td rowspan="3">Best speech response</td><td rowspan="3">5
4
3
2
1</td><td rowspan="3">Orientable and contactable
Incoherent speech confusion
Individual words in response to stimuli or spontaneously
Unintelligible sounds in response to stimuli or spontaneously
No response</td><td>Age-appropriate speech production</td><td>Humming, smiling, or showing displeasure</td></tr>
<tr><td>Incoherent speech confusion
Screaming and/or crying</td><td>Episodic crying, crying Continuous crying or wailing</td></tr>
<tr><td>Moaning</td><td>Moaning</td></tr>
</table>

Average fluid volumes at septic shock in deceased children were 32.9 ml/kg compared to 20 ml/kg in survivors [6]. As an alternative, slow volumetric infusion or early use of vasoactive drugs is suggested as an alternative [9]. At the same time, one should carefully watch closely for signs of fluid overload: increased respiratory work, the appearance of rales, galloping rhythm, hepatomegaly. Particularly careful monitoring of fluid overload should be performed in children with pneumonia. Adrenaline replaces dopamine as a first-line vasoactive drug [24]. Children quite often develop shock with vasoconstriction ("cold shock") in association with myocardial dysfunction, and low doses of epinephrine cause some vasodilatory effect. In classic vasodilatory shock ("warm shock") norepinephrine is the drug of choice. When the use of vasopressors is necessary, their administration should be started as soon as possible, within the first 60 min, even via intraosseous access.

Patients with low cardiac output and high vascular resistance (after infusion therapy with normal AP, cold extremities, delayed capillary filling, decreased diuresis) should

be dobutamine should be prescribed. If, after epinephrine and norepinephrine administration, children maintain normotensive low cardiac output and high vascular resistance, it may be indicated administration of phosphodiesterase inhibitors. In the case of extremely low vascular resistance, not relieved by norepinephrine, vasopressin may be used, although to date there is no substantiated evidence of its efficacy in children [31].

It is suggested that steroids should not be used in children with sepsis without at least minimal evidence of adrenal insufficiency. Therapy with water-soluble hydrocortisone at doses of 1-2 mg kg-1 day-1 bolus or as a continuous infusion may be used in children with catecholamine resistance and suspected adrenal insufficiency.

Conclusion

It is important to recognize sepsis as early as possible in children and newborns. The pSOFA or PELOD-2 scales can currently be used for this purpose. pSOFA or PELOD-2 scales. Intensive care is based on the early and rational administration of antibacterial drugs, infusion therapy with hemodynamic monitoring, If vasopressors are indicated, they should be started as early as possible. It is desirable to create local protocols based on the capabilities of the specific ICU and the characteristics of the patients.

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