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The problem of sepsis in children, the relevance of diagnosis and treatment

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Abstract

Background and aim. Despite medical advances and the rapid development of diagnostic and treatment methods, the problem of paediatric sepsis is still relevant. The problem of sepsis also remains relevant because of changing etiologic factors related to the introduction of new vaccines, the global antimicrobial resistance, and the rise of new resistant strains of microorganisms. The relevance of the sepsis problem is also related to the complicated early suspicion of sepsis, diagnosis, and emergency response. It is medically proven that the outcome of sepsis directly depends on early diagnosis and the proper treatment in the first hour. review aim is to analyse the sepsis problem in children and present the early diagnosis and treatment guidelines.

Materials and methods. The most recent scientific literature was reviewed on paediatric sepsis prevalence, early diagnosis and treatment.

Results. Sepsis is still one of the most common causes of death in children today. The definition of sepsis is still evolving, and it is difficult to accurately understand the epidemiologic situation and the changing aetiology of sepsis in children. The most important factor that can determine a good outcome is the early treatment of sepsis.

Conclusion. Sepsis in children remains one of the greatest burdens on healthcare systems worldwide. Much research is needed to better understand the problem of sepsis. A good outcome of the disease can only be expected if sepsis in children is diagnosed and treated in a timely manner.

Keywords: pediatric sepsis, sepsis early diagnostic, sepsis early management, paediatric sepsis outcomes.

1. Introduction

Sepsis is one of the main causes that cause the highest cost of re-hospitalization in all hospitals in the world, and it requires the most economical expenses in healthcare system. Therefore, the problem of sepsis is one of the primary priority to the World Health Organization (1). Sepsis in children can be caused by any infection of the body, but the majority of the identified pathogens are bacteria (2) Having reviewed the early clinical diagnosis of sepsis in children, it is clear that early recognition of sepsis in children is crucial and that it is important to know the criteria and signs of the systemic inflammatory syndrome that give rise to suspicion of sepsis (3,4). Currently, guidelines for the diagnosis and treatment of sepsis are still not widely applied, although only their timely application can improve the outcome of the disease (5,6). Sepsis in children is still a major health care systems problem despite advances in medical science. More research is needed to better understand sepsis in children and to provide even more accurate diagnostic and treatment guidelines. Early diagnosis and treatment remain a major challenge, and the high mortality rate means that the problem of sepsis is still relevant today.

2. Materials and methods

This literature review reflects on paediatric sepsis, which remains a major problem due its high mortality in children, and analyses the guidelines for early management.

3. Results - the problem of sepsis

3.1. Epidemiology

Because of the changing definition of sepsis and its difficult diagnosis, it is difficult to determine the exact number of annual cases – it is estimated that sepsis is affects approximately 47 to 50

million people worldwide each year (7). Worldwide, sepsis causes an average of 19 % of deaths in the population, most of which are children younger than 5 years (8). In the paediatric group, the mortality rate after sepsis diagnosis is 25 %, and worldwide, on average, about 8 million children die from sepsis each year (9–12). Among children, most deaths are neonates, infants, and children with chronic diseases. Sepsis mortality in children has declined not only because of improved diagnostics, but also because of vaccination, antibacterial treatment and better availability of health services (13). The spread of vaccines has not only reduced the number of sepsis cases in older children, but also changed the aetiology of sepsis in children.

3.2. Aetiology

Sepsis can be caused by practically any infection in the human body - the most commonly identified agents are bacteria and viruses, but fungi and parasites can also occur (2). In studying the aetiology of sepsis in children it was found that in nearly 43 % of cases of paediatric sepsis, the causative agents were not identified (14). In the study of neonates and infants up to 3 months of age, the most common disease-causing bacteria were found to be *Staphylococcus aureus*, group B *Streptococcus*, *Escherichia coli* and *Listeria*, and sometimes the *Herpes simplex virus* may be the cause of the disease (2,15,16). Sepsis in older children is usually caused by *Haemophilus influenzae*, *Neisseria meningitidis*, *Klebsiella* spp. and *Streptococcus pneumoniae* (2,15,17). In children with febrile neutropenia, the most common microorganisms are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aureus*, *Escherichia coli*, *Klebsiella* (18). The

most common cause of hospital-acquired sepsis is coagulase-negative staphylococci, gram-negative bacteria (18). The most commonly identified microorganisms causing community-acquired sepsis are bacteria - *N. meningitidis*, *S. pneumoniae* (19–21). Overall, the aetiology of sepsis in children is very diverse and variable, influenced by the age of the sick child, his comorbidities or existing chronic diseases, as well as vaccinations and excessive use of antibacterial drugs.

3.3. The definition of paediatric sepsis.

In recent decades, the concept of sepsis undergone major changes, mainly due to the increasing understanding of pathophysiologic processes that occur in the human body during infection. In 2002 the first sepsis guidelines for children were published, highlighting the differences between paediatric and neonatal sepsis and sepsis in adults. In 2005, the International Paediatric Sepsis Conference published definitions in paediatric systemic inflammatory response syndrome, sepsis, septic shock, and multiple organ dysfunction syndrome (3,4). In 2020 guideline on sepsis and septic shock in children were published, but to date the question remain whether the definition of sepsis in adults can be applied to children, and therefore the formal definition of paediatric sepsis has yet to be updated (2,16). In 2005, the International Paediatric Sepsis Definition Consensus Conference defined sepsis as a systemic inflammatory response syndrome, caused by an existing, confirmed or suspected infection based on clinical, laboratory, or imaging studies (4). The definitions currently used are not sufficient for early diagnosis; they are more relevant for research related in paediatric sepsis. But much more important than

the definition is to know and understand what the basic criteria for early diagnosis of sepsis are so that paediatricians can recognise this life-threatening condition as soon as possible.

3.4. The importance and possibilities of diagnosis on paediatric sepsis

Sepsis in children is one of the most common causes of death despite scientific advances in treatment, but only timely recognition can lead to a good outcome of the disease (18). Sepsis mortality in children ranges from 4 to 50 % in various literature sources - most of these deaths occur within the first 48 to 72 hours of treatment, so early diagnosis and treatment are paramount to good outcomes (22). Early recognition of sepsis in children is difficult because the disease begins non-specifically and progresses variably (5). Unlike adults, children have large physiologic reserves, so the child's condition can be compensated for at the onset of illness, is clinically silent, and later decompensates very rapidly. Therefore, early diagnosis of sepsis in children poses challenges (1).

3.5. Clinical diagnosis

Often, sepsis in children resembles a simple viral infection in the early phase of the disease, making it very difficult for physicians to diagnose the disease in time (23). The clinical manifestation of sepsis in children can vary widely- slowly progressive or sudden and dramatic (3). A thorough examination of a sick child should include recording of vital signs and evaluation of clinical signs important for suspicion of sepsis. If sepsis is at least minimally suspected, the patient should be constantly monitored (3,24). According to the criteria of systemic inflammatory response syndrome, body temperature, heart rate, state of

consciousness, oxygen saturation level, arterial blood pressure, and capillary refill time must be measured. It is also important to collect data on the patient's diuresis during the last 18 hours (25). Paediatric sepsis "red flags" described in the medical literature to raise suspicion of sepsis are altered body temperature ($> 38.3^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$), tachycardia, tachypnoea, changes in heart rate or capillary refill time, hyperglycaemia, purpura or pathesia below the nipple line, macular erythema anywhere on the body (3,16,26). After reviewing the early clinical diagnosis of sepsis in children, it is clear that early sepsis recognition in children is crucial. It is important to know the systemic inflammatory response syndrome criteria and signs that help to suspect sepsis. The authors emphasize the triad of clinical symptoms of sepsis that many patients present with: fever, tachycardia, and vasodilatation with altered consciousness or capillary refill time greater than 2 seconds (17,27).

3.6. Laboratory diagnosis

For a long time, complete blood count test was important for the early laboratory diagnosis of sepsis. However, leukocyte and neutrophil counts have low sensitivity or specificity for bacterial infection to determine the absolute neutrophil count can still be used to identify the bacterial infection in younger infants under 60 days of age with fever (6). Although these tests can confirm the suspicion of bacterial infection in febrile infants, they have little prognostic value in the diagnosis of paediatric sepsis (6). Acute phase C-reactive protein is the most common and oldest known sepsis marker (28). For early diagnosis of sepsis, it is important that CRP does not begin to rise until after 12 hours

and does not rise significantly until 20-72 hours after the onset of inflammation (29). Therefore, a procalcitonin test is currently recommended for the early diagnosis of sepsis, based on scientific evidence (6,16,29,30). C-reactive protein and procalcitonin not routine tests, the main indications for their performance are suspected severe bacterial infection or sepsis in febrile infants and young children when the source of infection is unclear - these markers have a high prognostic value in the diagnosis of sepsis (18,31). Blood culture is considered the gold standard sepsis diagnosis in children, but it has low specificity and sensitivity for pathogen identification (30). The result of blood culture is an extraordinary value for the choice of optimal antimicrobial therapy and the duration of its administration (6,23,30). Currently, early laboratory diagnosis of sepsis in children is increasingly supported by polymerase chain reaction (PCR). A blood culture usually is not informative. In neonatal population, PCR and blood cultures have been observed during the same period of the disease, the PCR test was positive in a higher percentage of patients, so this study shows the importance of PCR in early diagnosis of paediatric sepsis nowadays (32). Thus, the early diagnosis of sepsis in children is based on clinical symptoms suggestive of sepsis and the totality of laboratory markers - this is also shown by the systemic inflammatory response syndrome criteria. Clinical symptoms alone are not sufficient to confirm the diagnosis of sepsis, but the main laboratory markers of sepsis (C-reactive protein, procalcitonin, etc.) are performed only in the presence of a clinical manifestation of sepsis in children and then acquire the diagnostic value.

3.7. Early first-hour sepsis treatment in children

Research shows that early treatment of sepsis in children can significantly reduce mortality (6,33). Guidelines for early treatment of sepsis in children are not yet conclusive, but their use leads to better outcomes in the disease (5,34,35). It is known that the main goals of treatment in the first hour of sepsis in children are to ensure and manage airway, optimize oxygenation and ventilation, restore and maintain perfusion to organs as needed, ensure early empiric antibiotic therapy (3,17). The goal of the early treatment is to correct the child's vital signs and normalize the state of consciousness, shorten capillary refill time (<3 s), and ensure greater diuresis than 1 ml/kg/hour (3,5,16). In the first hour, begin treatment of sepsis in children with high-flow oxygen therapy via nasal cannulas or 100% oxygen delivery via mask, however, oxygen saturation should not exceed 97% to avoid adverse events, hyperoxygenation, and free radical formation (3,18). At the same time, an intravenous catheter or an intraosseous needle should be inserted within 5 minutes (3,36). After puncturing a vein or bone marrow, it is important to do a blood culture and perform the main laboratory tests: common blood count, c-reactive protein and procalcitonin, coagulation indicators, blood gas test, calcium and other electrolytes, glucose and lactate tests (3). Empiric antibiotic therapy should be initiated at the maximum recommended dose no later than 1 hour after clinical suspicion of sepsis (3,5,36). Antibiotic therapy should not be delayed because of obtaining a blood culture, but in any case, an attempt must be made to obtain a blood culture before the first antibiotic administration, because delayed antibiotic therapy is one of the

risk factors for organ dysfunction or the progression of the disease (5,37). Patients with suspected sepsis should be monitored continuously - body temperature taken at least every 30 minutes, arterial blood pressure and oxygen saturation should be measured every 15 as well as other vital signs (3). Fluid therapy should be administered to the patient within the first 5-10 minutes into a vein or bone with rapid crystalloid agents in boluses of 10-20 ml/kg for children (up to 1000 ml) and 10 ml/kg in neonates depending on the patient's weight; if necessary, the bolus may be repeated up to 60 ml/kg/hour (3,5). If the above first-hour management steps do not produce the expected results, a paediatric intensivist should be consulted immediately for advice and the administration of inotropic medications should also be considered. Only if the paediatric sepsis treatment guidelines are applied within the first hour (establishment of a blood culture, broad-spectrum antibacterial treatment, and administration of fluids as part of infusion therapy), the good outcome of disease can be expected to prevent the patient's death or long-term health consequences.

4. Conclusion

The problem of sepsis in children is still relevant due to its high incidence and mortality rate in children worldwide. Data on sepsis prevalence data are imprecise because there is no unified definition of sepsis in children. The aetiology of sepsis in children is very diverse and variable. Early diagnosis of sepsis in children is based on clinical symptoms, which are usually nonspecific to sepsis, and on a number of laboratory markers, such as C-reactive protein or procalcitonin. These markers are only valuable for diagnosis when the clinical manifestations

are characteristic of sepsis in children. Treatment protocols for the first hour of suspected sepsis help manage sepsis for a better outcome. The sepsis problem is multifactorial, but it is obvious that the most important thing for a good outcome of paediatric sepsis is the timely application of early diagnosis and treatment guidelines.

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