MULTIPLE ORGAN FAILURE IN THE PRACTICE OF PEDIATRIC RESUSCITATION: UPDATED PATHOPHYSIOLOGY AND PROGNOSIS

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https://doi.org/10.5281/zenodo.10275495

Abstract. *Multiple organ failure is a leading cause of admission to the intensive care units, characterized by a high case fatality rate and significant financial costs. Here we review the mechanisms of multiple organ failure in pediatric patients (triggers, concomitant diseases, release of danger- and pathogen-associated molecular patterns, bacterial translocation, epithelial, endothelial, or mitochondrial dysfunction, and inadequate immune response) and recent diagnostic and prognostic scales.*

Keywords: *children, multiple organ failure, systemic inflammatory response, pathophysiology, prognosis.*

The relevance of the problem of treating critical conditions in both adults and children there is no doubt due to the spread of aggressive surgical interventions, increasing the proportion of immunocompromised patients among intensive care patients, genetic defects, development of a care system for newborns with low and extremely low body weight [1,2,3]. Universal syndrome to deal with doctors of intensive care units (ICU), is multiple organ failure syndrome (MON) [4]. MODS is a combination of failure of two or more organs and systems that are observed either simultaneously or sequentially, requires prosthetics or complete replacement of the function of the affected organs, with the effects of mutual potentiation and a high probability of persistence and death [6,7,8]. The syndrome was first described in a series of articles Baue et al., who observed the sequential development of insufficiency of pulmonary function and further liver and kidney function, the development of this syndrome was characteristic on the third day after aggressive surgical operations and not related to shock. The autopsy revealed foci of inflammation in the organs and microcirculation disorders, but inflammatory changes were sterile, that is, they did not have a primary infectious beginning [8,9,10]. First descriptions multiple organ failure (MOF) in children in critical conditions appeared in the eighties of the 20th century; in the 90s, similar works were published regarding MODS in newborns [11,12].

In children, in a number of clinical studies there was multiple sequential organ dysfunction has been described, on average developing for the third or fourth day from the moment of admission to the hospital. The authors also highlight options for the development of early and late MODS. The clinical pathophysiology of MOF in children has been confirmed by numerous experimental studies [13,14,15,16]. Currently, MOF in children is one of the main causes of mortality in the ICU. Since sepsis is the leading cause of patient admission to the ICU, it is believed that sepsis-associated MOF is the most common form of critical illness complicating the course of the underlying disease in pediatrics [17,18]. Thus, in the case of development of sepsis-associated MODS, mortality increases by an order of magnitude compared to the group patients without MODS or with low scores on critical patient severity scales [19]. According to some authors, mortality in the group of children with MODS is expressed in numbers from 13 to 25% [20]. In addition, intensive therapy for MODS places a significant burden on

public health system that is expressed in an increase in the cost of therapy every patient. In the United States, the number of cases of MOF is 42,000 per year among all intensive care patients with a mortality rate of 10.3% [21]. Total hospital costs for treatments for MODS in children are approaching $1.7 billion per year In the USA, for caring for children with average hospital stay 74 days (patients with MOF requiring long-term organ function support methods) costs approach $75,000 per case [22,23].

A number of risk factors have been identified development of MODS in children, including severe hypoxemia at the time of admission to the ICU, cardiac arrest, shock, trauma, acute pancreatitis, acute leukemia, transplantation (as solid organ and stem cells), sepsis, the fact of prematurity and hypoalimentation. They all make their own contribution in the formation of PON, as evidenced by many studies [24,25]. Children are predisposed to the development of a systemic inflammatory response (SIR) and MOF in to a greater extent than adults, due to the imbalance of the mechanisms regulating inflammatory response, vulnerability of the hemostasis system and metabolic reactions, immaturity of the immune and endocrine systems, which predisposes to infection, which subsequently leads to the progression of multiple organ failure syndrome (SPON). The authors indicate that acute respiratory distress syndrome is a common cause of SIDS and MOF in children. (ARDS) – up to 70% of all cases of MODS, asphyxia – 45%, sepsis – 34% of cases [26,27]. The main pathogenetic factor of MODS – the body's response to massive damage tissues and/or infection, which has a greater influence on the outcome than the fact itself damage, defined as "inflammatory response syndrome." SVO is being considered at the moment as a key pathogenetic link in critical conditions associated with the development of multiple organ failure. In recent years, analytical articles have begun to appear in the literature emphasizing the low degree of sensitivity and specificity of SVO criteria for development critical conditions and the need to formulate new ideas about the nature and pathogenetic role of systemic inflammation. Systemic inflammatory response syndrome (SIRS) is initially diagnosed in the majority of children (70-80%) admitted to intensive care units, with progression SIRS in sepsis occurs in 15-30% and depends by age group: in younger children, the frequency of transition from SIRS to sepsis is higher, than in older children [21,28].

At the moment, the "danger hypothesis" prevails, which implies that damage to the host's own cells leads to the release of molecular patterns associated with the damage (DAMP), which, in turn, are capable of disrupt the cellular antigen-presenting response to exogenous antigens or pathogen-associated molecular patterns (PAMP). This hypothesis is supported by a number of studies conducted in the clinic: children who had manifestations of SVO and MOF had higher concentrations of circulating biomarkers PAMP, DAMP and cytokines, which is associated with the severity of MODS. Cytokine levels in such patients lead to dysfunction of the endothelium, apoptosis, realized in the form of ARDS, acute injury kidneys, liver dysfunction. Consequence of cytokinemia and impaired DAMP recognition is microangiopathy and micro thrombosis, mitochondrial autophagy (mitophagy), which looks like catabolism and immune suppression, as well as secondary immunodeficiency due to apoptosis of immune cells [29,30].

Reasons that determine the sequence and number of people involved in MODS organs and their contribution to the outcome in pediatric patients have not been fully determined. There is an opinion that the sequence mechanisms can be presented as follows [27]: Triggering factor(s): ischemia and reperfusion, trauma, oncology, pancreatitis, cardiopulmonary bypass.

Background pathology: congenital disorders metabolism, sepsis, autoimmune condition.

DAMP release.

Impaired metabolism of cytochrome P450.

Increased PAMP levels, including the likelihood of translocation of bacteria from the gastrointestinal microbiome's own pool tract.

Qi Release.

Epithelial dysfunction (example: ARDS).

Endothelial dysfunction (example: microvascular thrombosis and disseminated intravascular coagulation).

Mitochondrial dysfunction (example: catabolism, ICU-associated polyneuromyopathy, muscle weakness).

Dysfunction of immunological effector cells (example: impaired tissue resistance, wound wasting, apoptosis of immunological cells, persistence of immunosuppression, catabolism, wasting).

Initially, the idea of MODS and the gastrointestinal tract (GIT) as the “motor” of MODS was proposed in 1992 by Meakins et al. The idea assumed the presence of MOF without signs of primary infection and sepsis without a primary source of infection or when the primary the source of infection was completely sanitized. Components of this theory may be: elements of damage to the gastrointestinal tract epithelium, translocation intestinal microbiome and contamination gram-negative flora of the gastrointestinal tract with further movement of lipopolysaccharide (LPS) as the main endotoxin and participation in the implementation of the effects of PAMP. It is believed that in children all these mechanisms are implemented [26]. So, due to a systemic inflammatory response, the use of long-term parenteral nutrition, systemic ischemia and reperfusion, immaturity of the villous microcirculation system (especially in premature infants and children with systemic hypoxia) elements are observed apoptosis of intestinal epithelial cells, which is characterized by overexpression of Bcl2 [25]. Dense contacts of enterocytes are broken and damaged due to the activity of free radicals under conditions of ischemia and reperfusion, as well as use of infusion-transfusion therapy based on synthetic colloids. In addition, ruptures of tight junctions are realized based on the action of systemically released cytokines, which can be potentiated by sepsis and systemic hypoxia.

In children, dysfunction of the microbiome has also been described, which is determined by the use of active antibiotic therapy, creating conditions for ischemia and reperfusion intestines, disruption of the trophic function of the gastrointestinal epithelium [33]. Despite the rather large evidence base of experimental studies regarding the participation of the gastrointestinal tract in the genesis of MODS in children, clinical methods for assessing the translocation phenomenon (in particular, biochemical markers of permeability, markers of damage to tight junctions and glycocalyx of capillaries of the gastrointestinal vascular system, detection of LPS or its activity in the patient's blood serum) is clearly insufficient. Clinically, MOF consists of signs of dysfunction of two or more organs and organ systems [34].

Simple calculation of the number of affected organs and organ systems based on the presence or absence of organ failure does not allow identifying MOF on early stages, therefore, scoring the degree of dysfunction of the affected system is considered more informative. Severity rating MODS in pediatrics are associated with peculiarities of physiological parameters, which depend on the periods of childhood age, which must be taken into account when creating a tool for assessing the severity of MODS in children. PELOD (Paediatric Logistic Organ) scale

Dysfunction) is one of several most commonly used severity rating scales MODS in children.

The scale includes variables assessing organ dysfunctions of the central nervous system using the Glasgow Coma Scale, the circulatory system is assessed taking into account heart rate and level systolic blood pressure, recording parameters is made depending on age, the respiratory system is assessed based on the respiratory index (PaO2/FiO2) and partial pressure of carbon dioxide in arterial blood (PaCO2), kidney function is assessed based on the level of creatinine, liver function – based on the level of aspartate transaminase (AST) and prothrombin index (PTI), the blood system - based on the level of leukocytes and platelets. Scale PELOD overestimates the risk of adverse outcome, like scales used in adults. Assessment of the severity of MODS using the PELOD scale dynamically increases prognostic value. PRISM (The Pediatric Risk) scale of Mortality) uses level to evaluate systolic and diastolic blood pressure, heart rate and respiratory rate taking into account the child's age, respiratory index (PaO2/FiO2), partial pressure of carbon dioxide in the arterial blood (PaCO2), levels of glucose, potassium, calcium, bicarbonate, total bilirubin, ratio of prothrombin time to activated partial thrombin time, pupillary reactions and Glasgow Coma Scale. Modifications of the PRISM II and PRISM III scale are simplified versions of it. PRISM scale more suitable for assessing prognosis than for assessing the severity of MODS. While creating digital assessment of the severity of the condition in children in case of MODS, the physiological characteristics of this age group must be taken into account.

In particular, for each age period There are specific scales. For example, in newborns the PELOD scale has lower sensitivity than in children other age groups. Given the impossibility of predicting the exact prognosis of a given patient with MODS using only scale assessment, by many researchers attempts are being made to use various physiological and biochemical methods parameters as markers, which, along with assessment on the scale could clarify the forecast and choose the optimal ones for each specific case, treatment methods for MODS [2,13,34]. The most important drawback of all scales for assessing the severity of MODS is the lack of integration of biochemical and biological markers of MODS into composition of prognostic and diagnostic models, which is undoubtedly the rationale for further research.

Conclusion: The pathogenesis of MODS in children consists of the combined action of risk factors, initiating factor(s), implementation of DAMPs and PAMP, systemic inflammatory response and MODS, the mechanisms of which include epithelial dysfunction, endothelial dysfunction, mitochondrial dysfunction and disorders of immunological function.

Existing scales for assessing the severity of MODS and prognosis have undoubted clinical validity, but are not included in their the composition of the components of the PON mechanisms presented above, which makes it justified continuation of clinical attempts to integrate markers of biological origin as part of prediction and diagnostic scales.

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