https://doi.org/10.15360/1813-9779-2022-6-37-49

Pathogenesis, Prognosis and Outcomes of Multiple Organ Failure in Newborns (Review)

Alexander V. Golomidov[1]*, Evgeny V. Grigoriev[2], Vadim G. Moses[3], Kira B. Moses[1]

[1] S.V. Belyaeva Kuzbass Regional Clinical Hospital,
22 Oktyabrsky prospect, 650000 Kemerovo, Russia
[2] Research Institute for Complex Problems of Cardiovascular Diseases,
6 Sosnovy Boulevard, 650002 Kemerovo, Russia
[3] Kemerovo State University,
6 Krasnaya Str., 650000 Kemerovo, Russia

For citation: *Alexander V. Golomidov, Evgeny V. Grigoriev, Vadim G. Moses, Kira B. Moses.* Pathogenesis, Prognosis and Outcomes of Multiple Organ Failure in Newborns (Review). *Obshchaya Reanimatologiya = General Reanimatology.* 2022; 18 (6): 37–49. https://doi.org/10.15360/1813-9779-2022-6-37-49 [In Russ. and Engl.]

***Corresponding author:** Alexander V. Golomidov, golomidov.oritn@yandex.ru

Summary

Multiple organ failure (MOF) is the leading cause of neonatal mortality in intensive care units. The prevalence of MOF in newborns is currently unclear, since its incidence varies in asphyxia, sepsis, prematurity, and comorbidity, and depends on the level of development and funding of health care in different countries. Sepsis and acute respiratory distress syndrome prevail among the causes of MOF in this category of patients.

Aim of the review. To summarize the available literature data on the pathogenesis, therapeutic strategies and outcomes of MOF in newborns.

Material and methods. We searched PubMed, Scopus, Web of Science, and RSCI databases using the following keywords: «newborns, multiple organ failure, etiology, pathogenesis, premature, diagnosis, treatment, respiratory support, cardiotonic support», without language limitations. A total of 144 full-text sources were selected for analysis, 70% of which were published in the last five years and 50% were published in the last three years. Criteria for exclusion were low information value and outdated data.

Results. The prevalence of MOF in neonates is currently unclear. This could be due to common association of neonatal MOF (as well as the adult one) with various diseases; thus, its incidence is not the same for asphyxia, sepsis, prematurity, and comorbidities. There is no precise data on neonatal mortality in MOF, but according to some reports, it may be as high as 13–50%.

In newborns, MOF can be caused by two major causes, intrapartum/postnatal asphyxia and sepsis, but could also be influenced by other intranatal factors such as intrauterine infections and acute interruption of placental blood flow.

The key element in the pathogenesis of neonate MOF is cytokinemia, which triggers universal critical pathways. Attempts to identify different clinical trajectories of critical illness in various categories of patients have led to the discovery of MOF phenotypes with specific patterns of systemic inflammatory response. This scientific trend is very promising for the creation of new classes of drugs and individual therapeutic pathways in neonates with MOF of various etiologies.

The pSOFA scale is used to predict the outcome of neonatal MOF, however, the nSOFA scale has higher validity in premature infants with low birth weight.

Central nervous system damage is the major MOF-associated adverse outcome in newborns, with gestational age and the timing of treatment initiation being key factors affecting risk of MOF development in both full-term and premature infants.

Conclusion. The study of cellular messengers of inflammation, MOF phenotypes, mitochondrial insufficiency, and immunity in critically ill infants with MOF of various etiologies is a promising area of research. The pSOFA scale is suggested for predicting the outcome of MOF in full-term infants, while the nSOFA scale should be used in premature infants with low birth weight.

Keywords: multiple organ failure; newborns; critical illness phenotype

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Multiple organ failure (MOF) syndrome has been studied in all areas of contemporary health care, but the issue is particularly relevant for neonatology [1, 2]. The MOF is one of the leading causes of neonatal death in intensive care units (ICU) and carries a huge financial burden for the healthcare system and the parents, e.g., in the United States, the cost of treatment of these patients is estimated to be $20 billion annually [3].

The MOF syndrome is a relatively «new» complication, which appeared due to the evolution of critical care. Advances in transfusion medicine, respiratory support, adsorption methods of treatment, inotropic and fluid therapy made it possible to prolong the life of critically ill patients, which resulted in the

emergence of novel clinical patterns leading to identification of MOF. The earliest studies were focused on the study of MOF in adults, and only afterwards the issue came to attention of pediatric and neonatology specialists J. J. Skillman (1969), who described a new syndrome consisting of respiratory failure, hypotension, sepsis and jaundice in a patient with acute bleeding from a stress gastric ulcer, is considered the pioneer of MOF research [4]. Later in 1973, N. L. Tilney showed a stereotyped sequential organ involvement in patients with abdominal aortic aneurysm rupture [5]. The detailed description of MOF was given by A. E. Baue in 1975, who highlighted the sequential pattern of critical symptoms and showed the inevitable development of respiratory and hepatorenal failure during the first three days in a series of dead patients who have undergone extensive and aggressive surgical intervention [6]. The term «multiple organ failure» was first proposed by B. Eiseman in 1977, whereas definitions and pathogenesis of systemic inflammatory response in this condition were formulated by D. E. Fry (2012) [7]. The main focus of scientific research concerning MOF was first placed on both adults and children, but in the last decade began to shift towards the newborns. As a result, a lot of new data were obtained for this category of patients. Our review discusses the latest data on diagnosis, definition, etiology and pathogenesis of MOF syndrome in newborns, as well as the current ways of its management.

The aim of the review is to summarize the available literature data on the prevalence, pathogenesis, treatment and outcomes of MOF syndrome in newborns.

Material and Methods

The information was searched through PubMed, Scopus, Web of Science, and RSCI databases using the following keywords: newborns, multiple organ failure, etiology, pathogenesis, premature, diagnosis, treatment, respiratory support, cardiotonic support, with no language limitations. A total of 144 full-text sources were selected for analysis, 70% of which were published within the last five years and 50% within the last three years. The exclusion criteria were low relevance and outdated content.

Definitions of MOF in neonates

To summarize the available definitions of MOF, it can be defined as a severe nonspecific stress response characterized by failure of two or more organs and systems seen separately or sequentially, requiring partial or complete replacement of the function of the affected organs, with a mutual enhancement effect and a high likelihood of persistence and death [8–10].

Currently, there is no unified definition of neonatal MOF, so neonatologists use criteria accepted in pediatrics [11, 12]. The first set of criteria for pediatric MOF was proposed by J. D. Wilkinson in 1987 [13]. In 1996, the proposed criteria were modified by F. Proulx, who defined pediatric MOF as simultaneous dysfunction of at least two of seven organ systems including respiratory, cardiovascular, neurological, hematological, renal, hepatic and gastrointestinal ones [14]. In 2005, the International Pediatric Sepsis Consensus Conference developed and introduced into clinical practice a set of diagnostic criteria for MOF that includes dysfunction of two of the six organ systems [15, 16].

Prevalence of MOF in Newborns

No precise data of prevalence of MOF in the newborns are available to date. This could be due to various underlying diseases: similarly to adults, the frequency of MOF in neonates is different in asphyxia, sepsis, prematurity, and multiple comorbidities [17–19]. Thus, S. L. Weiss (2021) reports that the frequency of MOF in children with respiratory-associated asphyxia requiring mechanical ventilation can be as high as 73%. Development of MOF on day 1 of ventilation occurred in 63% of patients, while in others MOF was diagnosed on days 2–28 of ventilation [20]. In sepsis, the frequency of MOF varies from 19% to 68% [21, 22], In newborns who had fetal inflammatory response syndrome (FIRS), the frequency of MOF was 38.2% and even greater in premature infants [23]. The frequency and outcomes of MOF significantly vary depending on country income and healthcare expenditures. Thus, in high-income countries, the neonatal mortality rate from MOF due to intrapartum asphyxia is 10%, while in developing countries it is as high as 28% [24].

There is no exact data on neonatal mortality in MOF; only several reports show mortality in the range of 13–50% [25–27]. The wide variation in mortality rate of neonates is due to dependence of MOF on numerous factors including availability of health care resources, presence of malformations in the neonate, gestational age and weight at birth, mode of delivery, etc. [28–30]. Nevertheless, MOF is considered an independent factor of neonatal death, increasing the likelihood of an adverse outcome by 6-fold and more, whereas surviving children have a higher risk of developing organic and functional failure [31–33].

Etiology and Pathogenesis of Neonatal MOF

The pattern of causes of MOF in children and newborns differs from that in adults. The causes of pediatric MOF have been thoroughly analyzed in the J. S. Upperman (2017–2018) series «Specific etiologies associated with the multiple organ dysfunction syndrome in children» [34, 35]. Sepsis and acute respiratory distress syndrome (ARDS) are the

most frequent and studied causes of pediatric MOF. Sepsis is usually caused by respiratory infections (37%), bacteremia (25%), urinary tract infections, surgical conditions, brain disorders (12%), etc. In pediatric patients, the incidence and mortality of MOF is lower than in adults: the former averages 2–2.8 per 100,000 person-years, while the latter ranges from 18 to 27%. At the same time, in this age group MOF can also develop in organ transplantation, acute kidney injury, trauma, burns, etc.

In newborns, the etiology of MOF is distinct: as in children, it is most often initiated by two main causes which are intrapartum asphyxia and sepsis. However, MOF is often influenced by intrapartum factors, most often, intrauterine infections and acute placental circulation disorder [36–39]. This causes fetal inflammatory response syndrome, which worsens MOF in newborns who, in E. Jung's apt words (2020), have been «rescued by birth» [40]. Another mechanism of MOF, unique for newborns, is due to therapeutic hypothermia used to prevent brain damage in neonatal asphyxia, which does not occur in older children and adults [41, 42]. This procedure reduces the risk of death from asphyxia but increases the risk of MOF and adverse outcomes [43].

The pathogenesis of MOF in neonates is poorly understood, therefore, many ideas about its key events were extrapolated from older patients. At the same time, despite assumptions about the uniformity of the pathogenesis of MOF, there is evidence that immune system reactivity varies not only among neonates, children and adults, but also within the same age group. All this has prompted the study of critical illness phenotypes in different diseases and age groups.

The involvement of cellular messengers of inflammation was clearly shown in the experimental model of aseptic MOF developed by S. Steinberg (1989) when injection of combination of mineral oil and zymosan activated pathogen-associated molecular patterns (PAMPs) initiating inflammatory response to infectious agent, which in turn triggers cytokine-mediated epithelial, endothelial, mitochondrial, immune cellular and systemic organ dysfunction [44]. The universal endogenous protective factor in this model is the cytochrome-P450 system reducing inflammation, which has been demonstrated in «adult» and «child» models [45, 46]. The findings suggested that an imbalance between cellular messengers of inflammation and cytochrome-P450 metabolism is a key factor in the pathogenesis of MOF in all age groups. Experimental data were confirmed in clinical studies in critically ill children with different conditions. In such patients, a decrease in cytochrome-P450 activity was inversely correlated with the severity of cytokinemia and organ dysfunction, and increased levels of danger signals (PAMP, MAMP, DAMP, SAMP, TAMP) and cytokines initiating the cascade of systemic inflammatory reactions were observed in the blood [47–50].

Cytokinemia is the leading factor of self-injury in MOF in adults, children and newborns. It triggers the universal mechanisms of the critical condition including epithelial cell dysfunction and apoptosis, clinically presenting as ARDS, hepatobiliary dysfunction and/or acute renal tubular dysfunction; endothelial cell dysfunction and apoptosis, clinically presenting as thrombotic microangiopathy with loss of microvascular homeostasis; mitochondrial autophagy (mitophagy) and dysfunction manifested as catabolism, hibernation and impaired autonomy; immune cell dysfunction and apoptosis, clinically manifested as lymphoid organ depletion with ineffective pathogen removal and tissue regeneration [51–53].

In the last decade, antimicrobial peptides (AMPs), the molecules composed of 12–50 amino acid residues, exhibiting antimicrobial, antifungal and antiviral effects and potent chemoattractant activity, have been shown to impact pathogenesis of MOF. A 2017 meta-analysis revealed age-related patterns of AMPs involvement in the pathogenesis of MOF. Thus, in adults, severe sepsis was associated with impaired dynamic expression of cathelicidin and defensin, and in neonates, with that of hepcidin and presepsin [54, 55].

The search for new signaling pathways and inflammatory messengers opens up new possibilities in the prediction of MOF in neonatology. The most promising biomarkers of MOF are shown in Table 1.

The immune system plays a key role in the pathophysiology of neonatal MOF, but it is unclear when the immune system is suppressed and when it is overreactive. Activity of thymus gland and capability to generate immune responses are changing with age that impacts the complexity of the pathophysiology of MOF in different age groups [70, 71]. Attempts to identify different clinical trajectories of critical illness in various categories of patients led to the discovery of MOF phenotypes with specific systemic inflammatory response [72]. The phenotype of MOF refers to the pattern and timing of organ dysfunction that affect the risk of adverse outcome, are universal for a particular phenotype and can be seen in adults, children and neonates [73, 74]. For example, the NPMODS phenotype develops in 26% of children with sepsis and is accompanied by a high risk of death regardless of the presence of MOF at the time of seeking medical care [75]. However, the suitability of a concept to distinguish critical illness phenotypes in children is still a controversial issue, since the literature contains data questioning this scientific direction. In particular, M. M. Pollack (2020) in a study that included 681 patients, mean age 2.4 years, failed to identify the reported clinical trajectories of MOF in critically ill children [76].

Table 1. Promising inflammatory biomarkers in the prediction of MOF.

Inflammatory biomarker	Potential for use
Endocan (endothelial cell-specific molecule-1 or ESM-1)	The biomarker level correlates with the severity of sepsis, but its threshold level having high sensitivity and specificity is still to be determined [56].
Cluster of differentiation 64 (CD64)	It is expressed by inflammatory cells in response to bacterial infection and is not affected by transient neonatal tachypnea, ARDS or other noninfectious factors, usually occurring within the first 72 hours after birth. Its high values in premature infants and other infectious conditions often associated with MOF are a shortcoming [57, 58].
Differentiation molecule 11b (CD11b) cluster	The marker level increases within 5 minutes after exposure to an infectious agent, making it a more accurate biomarker in predicting MOF [59].
Pancreatic stone protein (PSP)	It belongs to the class of C-type lectins and is secreted by the pancreas in response to systemic stress and organ damage associated with critical illness. This biomarker has demonstrated 100% sensitivity and specificity in clinical studies with preterm and premature infants [60, 61].
Soluble intercellular adhesion molecule-1 (sICAM-1)	A protein factor used in the transport of neutrophils to the site of inflammation *in vivo* [62]. When endothelial cells are activated by cytokines, there is a rapid increase (within 1-6 hours) in the serum level of sICAM-1, which makes it a marker of systemic inflammation. Currently, there is debate about the usefulness of this marker for diagnosing EOS, as some authors have suggested sICAM-1 as a useful marker only in the first 4 days of life, while others have noted similar or even higher values in healthy neonates during the first 5 days after the birth [63, 64].
Progranulin	Autocrine growth factor of 593 amino acids, which regulates the TNF/TNFR signaling system, can predict sepsis and MOF in neonates after 34 weeks' gestation [65]
Neopterin	Biomarker of immune activity, which increases in the cell-mediated immune response [66].
Resistin (FIZZ3)	Cysteine-rich protein, which plays a controversial physiological role in obesity and insulin resistance and is elevated in systemic inflammatory response in neonates, children, and adults, but its diagnostic value remains to be known [67,68]
Presepsin (PSP)	The protein is the N-terminal fragment of the macrophage CD14 receptor. The mechanism for the production of PSP is associated with bacterial phagocytosis and cleavage of membrane-bound CD14 by lysosomal enzymes. PSP showed comparable performance with procalcitonin in predicting neonatal sepsis at threshold value of 706.5 pg/mL having a sensitivity of 85.7%, a specificity of 68.8%, a positive predictive value of 85.7%, and a negative predictive value of 68.8%. However, the performance of this biomarker in various age groups and in other causes of MOF remains unknown [69].

The study of MOF phenotypes in different illnesses could be potentially useful for revealing new treatment options for critically ill newborns. E. K. Stroup (2019) based on a study in 5,297 critically ill children identified 4 phenotypes that developed in the first 72 hours of disease and manifested as the following clinical and laboratory syndromes: 1) severe encephalopathy with moderate organ dysfunction; 2) moderate resolving hypoxemia; 3) severe persistent hypoxemia and shock; 4) persistent cytopenia, hepatobiliary dysfunction and shock [77]. These results were echoed by a larger cohort study by L. N. Sanchez-Pinto (2020), which conducted a six-year evaluation of 20827 children admitted to the ICU in critical condition [78]. Based on the most distinctive features of MOF (type of organ dysfunction, severity of disease and clinical trajectory of ICU stay on day 3), 4 main phenotypes were identified. They include Phenotype 1, manifesting as severe persistent encephalopathy (19.2%), Phenotype 2, manifesting as moderate resolving hypoxemia (34.5%), Phenotype 3, manifesting as severe persistent hypoxemia and shock (19.1%), and Phenotype 4, presenting as moderate persistent thrombocytopenia and shock (22.6%). The lowest mortality rate was registered in phenotype 2, while risk-adjusted mortality ratios (aHR) on day 28 of ICU stay for other phenotypes were as follows: phenotype 1, 3.0 (IQR, 2.1–4.3); phenotype 3, 2.8 (IQR, 2.0–4.1); phenotype 4, 1.8 (IQR, 1.2–2.6). The findings prove the feasibility of different therapeutic approaches to the management of critically ill children.

Each phenotype in SARS exhibits unique pathogenesis and therefore differs significantly from the others. Thus, in some cases there is an overreaction of the immune system, in others, on the contrary, its inhibition. As an example, the three most studied phenotypes of MOF in children can be discussed. The first of them is AHUS (atypical hemolytic-uremic syndrome), manifested by thrombocytopenia, low ADAMTS13 activity, acute kidney injury, extensive endotheliosis and systemic thrombotic microangiopathy [79–81]. The pathogenesis of this phenotype includes deficiency of genes involved in the synthesis of complement inhibitors and ADAMTS13, resulting in an overreactive immune response [82]. The disease is successfully treated with monoclonal antibodies (eculizumab) that block the terminal activity of human complement [83–89]. Another phenotype is caused by insufficiency of the Fas receptor-Fas ligand system [86, 87]. The hyperinflammation in

Table 2. Sequential Assessment of Organ Failure in Newborns (nSOFA) scale [110].

Respiratory score					
Points	0	2	4	6	8
Criteria	not intubated	intubated			
	$SpO_2/FiO_2 \geqslant$ 300 mm Hg	$SpO_2/FiO_2 <$ 300 mm Hg	$SpO_2/FiO_2 <$ 200 mm Hg	$SpO_2/FiO_2 <$ 150 mm Hg	$SpO_2/FiO_2 <$ 100 mm Hg
Cardiovascular score					
Points	0	1	2	3	4
Criteria	No inotropes, no systemic steroids	No inotropes, systemic steroid treatment	One inotrope, no systemic steroids	Al least two inotropes or one inotrope and systemic steroids	At least two inotropes and systemic steroids
Hematological score					
Points	0	1	2	3	
Критерии	Platelets $\geqslant 150\times10^9$/л	Platelets $100–149\times10^9$/л	Platelets $<100\times10^9$/л	Platelets $<50\times10^9$/л	

this phenotype is associated with the inability to undergo the activation-induced cell death. The latter is mediated by two molecular signals which are the Fas receptor (Fas, CD95) and Fas ligand (FasL, CD178) signaling pathway and the CTL/NK cell signaling pathway [88]. A defect in these signaling pathways triggers the process of immune overreaction and systemic self-damage [89]. Fas ligand known as «death factor» binds to Fas receptor and induces cell death. Mutations in Fas-FasL genes lead to FasL-mediated T-cell apoptosis and «immune escape mechanism», which is crucial for the pathophysiology of MOF, autoimmune lymphoproliferation and oncogenesis [90–92]. MOF in this phenotype can be easily reproduced experimentally in knockout mice with an inactivated gene located on chromosome 19 (in humans on chromosome 10) [93]. Another phenotype is manifested by the «immune paralysis» phenomenon [94, 95]. The child's immune response in critical illness is very dynamic, with systemic inflammation often accompanied by suppression of leukocyte count and function and clinically manifested by the compensatory anti-inflammatory response syndrome (CARS) [96]. Normally, it is a time-limited syndrome and prevents systemic inflammation, but when CARS is excessive, it is considered an acquired immunodeficiency, which can significantly compromise the patient's recovery [97]. The «immune paralysis» always associated with high mortality was reported in children and newborns with sepsis, viral infections, trauma and asphyxia [98–100]. External and intrinsic factors contributing to this phenomenon include family history, use of steroids, chemotherapy, and immunosuppressive medications [101, 102].

The role of mitochondrial failure in neonatal MOF has not been studied, but studies in children show promise for this research area. In addition to ATP production, mitochondria play important roles in cell homeostasis and intercellular interactions, including gene expression, inflammation, immune function, oxidative stress, calcium homeostasis, cell motility, heat production, hormone synthesis, and apoptosis [103, 104]. There is evidence proving the role of mitochondria in the pathogenesis of MOF. First, decreased mitochondrial oxygen consumption, low ATP levels, and mitochondrial gene suppression correlate with the severity of MOF and death [105]. Secondly, mitochondrial abnormalities in all vital organ systems have been reported in experimental models of sepsis and MOF [106, 107]. Finally, both spontaneous and pharmacological recovery of mitochondrial function improves critical illness survival. In particular, enhancing mitochondrial biogenesis to produce new mitochondria and mitophagy to remove defective mitochondria restores organ function and positively affects the outcome of MOF [108, 109].

Prediction of MOF Outcomes in Neonates

Several systems for predicting death in children with MOF hospitalized to ICU have now been proposed, but the best one suited for neonates remains unknown. In children, the prediction of death in MOF is based on the Pediatric Sequential Organ Failure Assessment (pSOFA) Scale [110], which is also valid for preterm infants (Table 2). The neonatal SOFA scale (nSOFA) has been proposed for low birth weight preterm infants, but its validation for different variants of MOF is still under development. In a study by James L Wynn (2020, 679 neonates), the nSOFA demonstrated high accuracy in preterm infants at 0, 6, and 12 hours (AUC 0.77 with 95% CI 0.62–0.92, P=0.001, AUC 0.78 with 95% CI 0.66–0.92, P<0.001 and AUC 0.93 with 95% CI 0.86–0.997, P<0.001) [111]. At the same time, the authors emphasize that nSOFA needs further development and inclusion of additional parameters to improve the accuracy of the prediction. The high validity of nSOFA has been repeatedly confirmed: the high discriminatory ability of the nSOFA scale (0.891) in sepsis-associated MOF has been reported by Russian and international researchers in large

populations, and the endpoint of patient death (9 points) was comparable in all studies [112, 113].

Basic Principles of Neonatal MOF Treatment

The treatment of neonatal MOF is based on the same principles as in adults, i. e., hemodynamic and respiratory support [114].

Considering the specifics of neonatal physiology, the main scientific research regarding hemodynamic support in MOF is focused on the most effective regimens and dosages of inotropic therapy. Today, dopamine, dobutamine and adrenaline remain the most studied drugs in neonatology, and dopamine remains the most frequently prescribed drug in neonates with MOF, even with low gestational age [115]. Meanwhile, their efficacy with respect to perfusion of organs and systems in neonatal MOF remains poorly documented [116], hence, other drugs with good clinical potential such as milrinone, norepinephrine, vasopressin, and levosimendan, have been introduced in neonatology.

Milrinone is a phosphodiesterase-3 inhibitor with positive inotropic, peripheral vasodilator and lusitropic effects [117]. In the last decade, milrinone has been prescribed in neonatology for the treatment of cardiopulmonary dysfunction in the context of pulmonary hypertension and low cardiac output in cardiovascular and respiratory anomalies, asphyxia, perioperative period during cardiac surgery and congenital diaphragmatic hernia [118]. At the same time, the authors of the Cochrane review (2015, 8 RCTs) emphasize the need for better quality studies, as the available data are insufficient to identify the advantages of milrinone compared to placebo, levosimendan or dobutamine with regard to mortality, duration of ICU stay, hospital stay, and ventilatory support [119].

Norepinephrine is an endogenous sympathomimetic amine that acts primarily on α-1 vascular and myocardial receptors with mild β-1 stimulation and minimal effect on β-2 adrenoreceptors. Because of this, norepinephrine is effective for constriction of peripheral vessels with minimal inotropic effect [120]. There is data on the use of norepinephrine in hypotensive preterm infants with refractory shock or low cardiac output, especially in severe septicemia, cardiac surgery or right ventricular «stress» [121]. In combination with dobutamine or milrinone, norepinephrine maintains vascular tone and can enhance coronary perfusion and support right ventricular myocardium in cases of asphyxia with severe pulmonary hypertension and right ventricular failure [122].

Vasopressin is a hypothalamic peptide hormone that increases vascular smooth muscle tone and peripheral resistance through V1A receptors, except in the pulmonary circulation, where the drug increases nitric oxide release, causing vasodilation [123]. Vasopressin is well established in the therapy of neonatal refractory shock, but further studies are needed to assess its efficacy, as a 2017 meta-analysis (8 RCTs, 224 patients) showed no impact of the drug on neonatal survival (RR=1.19; 95% CI: 0.71–2.00) [124]. Moreover, some studies have reported side effects of vasopressin that included significant hyponatremia, transient thrombocytopenia, liver and limb necrosis [125, 126]. Therefore, the use of vasopressin in the therapy of neonatal MOF requires further clarification.

Levosimendan is a cardiotonic agent that increases cardiac calcium sensitivity and has positive inotropic and vasodilatory effects, reducing pre- and postload for the heart [127]. Levosimendan is mainly used in neonates with heart failure and pulmonary hypertension [128]. Despite the promising use of levosimendan in neonates with MOF, there are currently no large studies of its effectiveness in this category of patients.

A high-potential area of respiratory support for neonates with MOF is the use of inhaled pulmonary vasodilators for severe hypoxemia due to neonatal respiratory failure. For this purpose, inhaled nitric oxide and prostacyclin (epoprostenol, iloprost, treprostinil) are used. Inhaled pulmonary vasodilators, in addition to their pulmonary vasodilatory effects, can potentially be employed to improve oxygenation, control local inflammation, and provide alveolar protection [129]. In a 2019 meta-analysis (9 RCTs, 856 patients), the use of nitric oxide in neonates with hypoxemia reduced neonatal mortality (OR 0.66, 95% CI: 0.57–0.77, P<0.00001) and the need for ECMO (OR 0.89, 95% CI: 0.50–0.71, P<0.00001) [130]. Nevertheless, currently there is still insufficient data on the efficacy and safety of nitric oxide in MOF, therefore its use is marked as «based on expert consensus» in the draft Russian guidelines for the treatment of pediatric sepsis [131]. Prostacyclin and its synthetic analogues, as well as milrinone and levosimendan may be cheaper alternatives to nitric oxide, but evaluation of their effectiveness and safety in neonatology is still under way.

The efferent therapies in neonatology have not been widely used and therefore are also in the process of investigation of their effectiveness. Several small retrospective studies of low quality showing promising results are available in the literature. Inclusion of adsorption technologies in standard therapy of MOF was associated with positive effects in 81% of neonates. These included an increase in the oxygenation index and a significant decrease in the dose of inotropic drugs after 6 hours, improvement of acid-base balance, creatinine and urea values after 12 hours, and an increase in urine output and stabilization of blood pressure after 24 hours. The incidence of complications was relatively low: thrombocytopenia was observed in 6 children, one patient had occlusive disorders [132].

The efficacy and appropriateness of ECMO in neonates with respiratory disease remain unclear today, since the literature data are quite contradictory. In a study of the effectiveness of ECMO in severe adenovirus pneumonia in 542 patients of different ages (adults, children and newborns), significantly higher mortality was observed in the neonates (OR 10.9; 95% CI=3.2–37.3; *P*<0.001) [133]. An independent factor of increasing survival rate during ECMO in critically ill neonates was absence of intraventricular hemorrhage and acute renal failure in patients [134]. Promising results were obtained with advanced ECMO technologies and creation of «artificial placenta» (extracorporeal life support, ECLS) for extremely premature infants, which is now in clinical trial phase [135].

Outcomes of Neonatal MOF

Multiple organ failure is associated with negative long-term outcomes for children and newborns [136–139].

A retrospective study by N. P. Pinto (2017) evaluated the functional status of 303 children during three years after MOF. The clinical trajectory of these children was as follows: cumulative mortality increased from 3.9% to 7.8% from discharge to 6 months later (*P*=0.08), and to 10.4% after 3 years (*P*=0.03); overall morbidity increased from 5.2% to 6.5% and 10.4%, respectively. The number of children with worsening functional status or death was comparable to that of patients who survived with no change in functional status (38% and 44%, respectively). The study showed that long-term functional status in children was associated with parameters characterizing MOF such as need for invasive therapy, ventilator use, number of days on ventilator, use of vasopressor therapy, and length of stay in the ICU [140].

Brain damage is the leading adverse outcome associated with MOF in newborns, with gestational age and timing of treatment initiation being the key factors influencing its risk in both full-term and premature infants [144]. In a retrospective cohort study of preterm infants who lived more than 7 days (2021, 3940 infants, 22–26 weeks) with MOF caused by sepsis, necrotizing enterocolitis, or bowel perforation, timely antibiotic therapy in all children reduced the risk of brain damage, but did not influence the risk of death [145]. Similar data were obtained in full-term infants [143].

According to E. Serebryakova (2017), the course and outcomes of MOF in newborns significantly depend on gestational age and birth weight, so these parameters can be considered predictors of adverse outcomes [144]. In contrast to full-term infants, very low birth weight and extremely low birth weight newborns had higher incidence of respiratory distress syndrome, a longer stay in the ICU, and a high frequency of severe brain damage, bronchopulmonary dysplasia, and retinopathy.

Conclusion

The issue of neonatal MOF is urgent, but insufficiently studied. The study of different critical illness phenotypes in full-term and premature infants is the most promising area of pathophysiology of MOF, which makes it possible to personalize therapeutic trajectories. The pSOFA scale for full-term infants and nSOFA scale for premature infants with low birth weight should be used to predict the outcomes of MOF. The treatment of neonatal MOF is based on the same principles as in adults, i. e., hemodynamic and respiratory support, while the use of several promising drugs such as milrinone, noradrenaline, vasopressin, levosimendan, and inhaled pulmonary vasodilators, could potentially improve the therapy outcome.

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Received 01.02.2022
Online First 09.11.2022