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Pneumonia Complicated by Multiple Organ Dysfunction Syndrome in Young Children (Literature Review)

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Abstract The article presents a literature review related to the problem of pneumonia in children complicated by multiple organ dysfunction syndrome. The incidence reaches 40% in newborns who are in the ICU on mechanical ventilation. The greatest risk of death from pneumonia in childhood occurs in the neonatal period, the frequency of which can vary from about 1 to 35%. The article highlights the mechanisms of predisposition and development of multiple organ dysfunction syndrome in children compared with adults, methods for evaluation the condition of sick children, clinical and diagnostic criteria. It is especially emphasized that the determination of the significance of immunological changes at MODS, their correct and timely diagnosis and targeted correction are an integral part of patients' management in the intensive care units, but, unfortunately, there are very little researches in this area of studies.

Keywords Neonatal pneumonia, Multiple organ dysfunction syndrome, Risk factors, Clinic, Diagnostic criteria

Pneumonia is the most urgent problem among respiratory diseases in pediatric practice, as the increase in morbidity and high mortality continues to grow, especially in countries with a low standard of living [1]. The greatest increase in pneumonia is observed in patients admitted to intensive care units [2]. According to literature sources, the incidence of pneumonia among full-term newborns is about 1%, and in premature infants this indicator reaches about 10%. The incidence reaches 40% in newborns who are in the ICU on a ventilator [3]. The greatest risk of death from pneumonia in childhood occurs in the neonatal period, the incidence of which can vary from about 1 to 35% depending on various factors such as race, gestational age, level of neonatal care received or socio-economic environment [4-5].

Like neonatal sepsis, pneumonia in newborns is early (early onset) – acquired in utero and late (late onset) – when infected in the postnatal period. Pneumonia which manifests itself in the first week of life is described as pneumonia with an early onset. Congenital pneumonia (CP), which occurs during the first day of life and is associated with prolonged premature rupture of fetal membranes, chorioamnionitis and perinatal maternal infections, is considered a variant of pneumonia with an early onset [1]. Pneumonia is also common in patients with early neonatal sepsis [6].

In case of nosocomial pneumonia, the main risk factors are mechanical ventilation of the lungs (with a duration in the ICU of more than 3 days) and a severe underlying disease of the patient, ineffective or insufficient antibiotic therapy, low gestational age, shock or limitation of the lung lobes mobility [7-8]. Pneumonia associated with artificial lung ventilation is usually bacterial. The bacteriological spectrum of neonatal pneumonia is largely similar to microorganisms in neonatal sepsis [9].

Artificial airways become colonized by pathogenic bacteria shortly after intubation or tracheostomy, and major pathogens include both gram-positive and gram-negative bacteria: S. aureus (including MRSA), P. Aeruginosa, and also types of Klebsiella и Enterobacter. Patients in the intensive care unit are at risk of infection with enterococci and group B streptococci. It is explained by the fact that prolonged ventilation and stay in the intensive care unit increases the risk of infection due to exposure to humidifiers and fan circuits, which have been proven to be an important source and environment for microorganisms. [10-11].

Due to mechanical ventilation, especially among very preterm newborns, the risk of bronchopulmonary dysplasia and the development of other neonatal diseases, including neurological complications, lung diseases, etc., increases. В дальнейшем, при лечении таких больных, увеличиваются как сроки госпитализации, так и медицинские затраты [12].

A.B. Mohamed et al. showed that preterm infants are more likely to develop ventilator associated pneumonia (VAP) than term infants (OR=2.66, 95% CI=1.39–5.09, PARP 42.64%). Besides, the main group (preterm infants) received enteral nutrition more often than the control group (OR = 5.59, 95% CI = 2.40-13.03, PARP 74.15%) which may increase the risk of colonization of the stomach with gram-negative microorganisms and consequently lead to an increase in the incidence of nosocomial pneumonia [13]. Blood transfusion (OR = 3.32, 95% CI = 2.25–4.88) and

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parenteral nutrition (OR = 2.30, 95% CI = 1.64–3.24) were also identified as risk factors. The authors associated this factor with the immunosuppressive effects of blood transfusion and parenteral nutrition, which were evident in preterm infants. In addition, dependent risk factors were found in this study: repeated intubation, tracheal intubation and bronchopulmonary dysplasia.

An important role in the development of congenital pneumonia is played by infectious and inflammatory diseases of the urinary and reproductive systems of the mother (pyelonephritis, chorioamnionitis, endometritis, etc.); gestational maturity of the fetus, the state of the surfactant system and the bronchopulmonary apparatus, malformations of the bronchial tree, intrauterine hypoxia, birth asphyxia, aspiration of meconium and amniotic fluid. R.L. Goldenberg et al. have revealed that 90% of births before 28 weeks of gestation are caused by intrauterine infection and inflammation [14].

Prematurity, respiratory distress syndrome (RDS), impaired cardiopulmonary adaptation, fetal hypoxia contribute to the development of the infectious process due to functional, morphological and immunological immaturity of lung tissue. The disease is developed as a result of hematogenic introduction of the pathogen in the last days or weeks of pregnancy or as a result of infection of the lungs when amniotic fluid enters them (infected with endometritis, chorioamnionitis, etc.), or at the aspiration of the infected contents of the birth canal. In all cases, bilateral lung lesion is detected (both alveoli and interstitium). These changes cause the occurrence of hypercapnia, hypoxemia, mixed acidosis and hypoxia after birth, deterioration of surfactant synthesis, which causes the appearance of atelectasis, parenchymal pulmonary edema, increased intrapulmonary pressure. As a result of progressive hypoxia, acidosis and microcirculation disorders, in view of the close functional and morphological relationship of the respiratory apparatus with the circulatory system in severe complicated forms of pneumonia in children, multiple organ dysfunction is developed very quickly (first cardiopulmonary, then - other organs) [15-17].

Newborns with pneumonia, the development of which is caused by infection during childbirth or post-natally, are characterized by signs of a systemic disease: depression syndrome, the appearance of tolerance to enteral nutrition, fever. Such respiratory disorders as tachypnea, bradypnea, "moaning" breathing, inflating of the wings of the nose, irregular breathing, the appearance of wheezing in the lungs during auscultation and weakening of breathing that occur in newborns can serve as the debut of the disease, and join later [18]. A severe form of congenital pneumonia may be accompanied by the development of shock and respiratory failure, requiring mechanical ventilation (ALV).

All the described clinical manifestations are nonspecific and can be observed in newborns against the background of other diseases of the respiratory system, as well as with other pathological conditions, in particular, with critical congenital heart defects, therefore, risk factors for the infectious process in a newborn, X-ray and laboratory examinations are of great importance in the diagnostics. Despite recent advances in management strategies, nonspecific clinical signs of newborns and an insufficient amount of early objective diagnostic evaluation contribute to delaying the start of treatment [1].

Congenital pneumonia has similar clinical manifestations with many diseases - respiratory distress syndrome (hyaline membrane disease), atelectasis, aspiration pneumonia, pneumothorax, pneumomediastinum, chylothorax, hypoplasia or lung infarction, cystic fibrosis, therefore, it is necessary to differentiate it from these pathologies when making a diagnosis [19]. It should be borne in mind that the majority of very preterm infants are born in serious condition and have signs of respiratory failure requiring respiratory therapy. The genesis of these disorders may have an infectious nature or be a consequence of the respiratory distress syndrome development against the background of pronounced morphofunctional immaturity of the lungs, which also determines a significant difficulty in making a differential diagnosis. It is also important to consider the presence of the following risk factors when making a diagnosis of congenital pneumonia: prematurity, prolonged anhydrous interval, premature rupture of membranes, invasive antenatal manipulations (amniocentesis, cordocentesis), the presence of amniotic fluid with an unpleasant odor, which may be associated with the development of both pneumonia and neonatal sepsis.

It is difficult to determine any disease in the absence of a so-called "gold standard" diagnostic test. The problems with defining a syndrome such as MODS are even more complicated, since its causal relationship is multifactorial, and the underlying etiopathology is not fully understood. Nevertheless, its study is supplemented by the clarification of definitions and diagnostic criteria with the appearance of new facts.

To date, a considerable number of scales used in pediatrics and neonatology which are used to determine organ dysfunction, severity of the condition and the effectiveness of the treatment have been developed [20-22]. However, they do not always accurately describe the dysfunction of a particular organ. It is impossible to accurately calculate the probability of outcome in a particular patient using currently existing MODS severity scales, despite the high sensitivity and specificity of the same scales in relation to large groups of patients. Scales often overestimate the probability of death in a particular patient and the actual mortality from MODS turns out to be lower than predicted based on the scales [23].

The first set of diagnostic criteria for MODS in children was proposed by Wilkinson and his colleagues in 1987. The list of scales was changed in 1996 by A. Proulx in which MODS was defined as simultaneous dysfunction of at least two organ systems. The considered organs and systems were respiratory, cardiovascular, neurological, hematological, renal, hepatic and gastrointestinal. Failure of each organ or dysfunction is determined by conformance to one or more criteria in each system. It is believed that all the organs of the non-survivors failed on the date of death.

In 2005, the International Consensus Conference on Pediatric Sepsis developed a new set of diagnostic criteria [Goldstein B, Giroir B, Randolph A., 2005; P.2-8]. This mode of MODS is defined as the simultaneous disruption of the function of two or more systems. Each organ failure or dysfunction is determined by compliance with one or more criteria of each organ system.

The Pediatric Logistic Organ Dysfunction (PELOD) scale and its modification PELOD-2 is one of several most commonly used scales for evaluating the severity of MODS in children [24-25], which helps to measure changes in organ dysfunction over time. Firstly, the daily PELOD evaluation, which shows deterioration or lack of improvement over time, is a strong prognostic factor of death. This information can be especially useful during the first four days of the patient's treatment course. Secondly, changes in the PELOD scale describe patterns and trajectories of multiple organ dysfunction over time. Such changes can also be used as a marker of the disease severity in clinical studies.

The scales of Clinical Risk Index for Infants (CRIB), Assessment of acute physiology of newborns (SNAP) and its modification, Multiple Organ dysfunction of newborns (NEOMOD) are used to evaluate the severity of the condition in newborns [26]. The Pediatric Risk of Mortality (PRISM) is used to estimate the level of systolic and diastolic blood pressure, heart rate and respiratory rate, taking into account the age of the child, respiratory index (PaO2/FiO2), partial pressure of carbon dioxide in arterial blood (RaSO2), glucose, potassium, calcium, bicarbonate, total bilirubin, the ratio of prothrombin time to activated partial thrombin time, pupillary reactions and the Glasgow coma scale. Modifications of the PRISM II and PRISM III scale are its simplified versions. The PRISM scale is more suitable for evaluating the prognosis than for estimating the severity of MODS [27-28].

Currently, the NEOMOD scale is most often used in newborns to quantify the severity of the condition and determine the prognosis. The scale evaluates the state of 7 systems: central nervous system, cardiovascular system, respiratory system, gastrointestinal tract, hemostasis system, urinary system, acid-base balance. The maximum possible number of points is 14 when evaluating on this scale. It is possible to evaluate the condition of newborns according to the NEOMOD scale from the first to the 28^{th} day of life. Also, this scale allows to estimate the severity of syndromes and the risk of deaths on a daily basis. It should be noted that with a NEOMOD score of 6 points, the mortality rate of patients reaches 30% (0-29%), while with 7 points it increases over 55% (57-100%) [29].

Chest x-ray is recommended as instrumental diagnostic methods for the pneumonia diagnosing. At the same time, there may be no specific signs of pneumonia on the X-ray in children with intrauterine pneumonia. It is also possible the presence of peribronchial seals, indicating the presence of bronchopneumonia [30]. Diffuse decrease in airiness or an air bronchogram is possible both with respiratory distress syndrome, sepsis, and congenital pneumonia. Alveolar lesion, infiltration sites, air bronchogram, the presence of pleural effusion is more typical for the bacterial process [31]. Although the differential diagnosis of bacterial and viral pneumonia is difficult only on the basis of the X-ray method of investigation.

In the last decade, the use of lung ultrasound has become widespread in various fields, not only to reduce radiation exposure, but also because of the wide range of diagnostic capabilities of this previously underestimated method, especially in neonatal intensive care units [32]. Ultrasound demonstrates high diagnostic accuracy for the diagnosis of pneumonia in full-term and premature newborns, as well as in children [33-34]. Typical signs are seals, which are usually larger than in bronchiolitis or respiratory distress syndrome, air bronchograms and pleural effusion [35-36]. Ultrasound screening of children with pneumonia most often reveals four clinical signs, including pulmonary consolidation, positive air bronchogram, abnormal pleural line and pleural effusion. J.H. Yan, N. Yu, Y.-H.Wang, Y.-B. Gao, L. Pan showed that the combined sensitivity, specificity and DOR for children with pneumonia diagnosed by ultrasound were 0.95 (95% CI: 0,94–0,96), 0,90 (95% CI: 0.87–0.92) and 137.49 (95% CI: 60.21) to 313.98), respectively [37].

It is recommended to conduct ECHO-CG, neurosonography (NSG), ultrasound examination of the abdominal cavity to clarify the diagnosis. Also, if there are deviations from the side of cardiac activity during arrhythmia, severe bradycardia or tachycardia, etc. electrocardiography (ECG) is recommended.

Non-invasive monitoring of key indicators is recommended, especially in newborns requiring respiratory therapy (heart rate, respiratory rate, blood pressure, $SatO_2$, body temperature, diuresis). Standard laboratory tests used for infection screening are recommended for diagnosing pneumonia in young children with MODS: complete blood count (CBC), absolute neutrophil count (ANC), ratio of immature/total neutrophils (I/T) и C-reactive protein (CRP) [38,6,39-40]. However, taking into account the nonspecific nature of these parameters, distinguishing pneumonia from non-infectious causes of respiratory distress, such as transient tachypnea in newborns (TTN) or respiratory distress syndrome (RDS), becomes a serious clinical problem [4,1]. Although blood cultures are the most useful diagnostic tests, the etiological agent cannot be identified in many cases.

Many researchers are trying to use various physiological and biochemical parameters as biomarkers, which, along with the assessment on the MODS severity scale, could clarify the prognosis and choose the optimal treatment methods in each case [22]. The levels of cytokines, procalcitonin, immune cell phenotype, heart rate variability, lactate level, oxygen status, number of normoblasts in peripheral blood, nucleotide sequences are studied as biomarkers [41,21,23,42].

Some studies have reported higher levels of CRP in serum, which is closely correlated with the progression of neonatal

pneumonia. CRP production is highly stimulated by tumor necrosis factor-α, interleukin-6 and interleukin-1β in response to infection or inflammatory conditions [43]. To be specific, a decrease in serum CRP levels may indicate a relief of the inflammatory process, whereas permanently elevated CRP levels or an initial decrease followed by an increase may indicate persistent inflammation and a poor prognosis. Therefore, CRP as a common biomarker of systemic inflammation may help clinicians to make difficult therapeutic decisions in neonatal pneumonia.

Mean platelet volume (MPV) is also used to diagnose neonatal pneumonia. MPV is a surrogate marker for platelet activation and is associated with neonatal infections and other inflammatory and infectious diseases [24,44]. The CRP/MPV ratio can be used in pediatrics as a marker for the differential diagnosis of bacterial and viral pneumonia, as well as for predicting complications.

Interleukin-6 (IL-6) is a pleiotropic proinflammatory cytokine produced by various cells in response to infection. IL-6 in the blood is an early sensitive marker of neonatal bacterial infection and one of the most studied cytokines in the diagnostics of infection in newborns [45]. Other authors suggest using IL-6 in saliva as a biomarker for the diagnosing late neonatal pneumonia in full-term newborns and have shown that the combination of IL-6 in saliva and the CRP/MPV ratio improved sensitivity and specificity up to 100% [46].

Conclusions

Summarizing the above mentioned, it must be said that today there are many different scientific papers in the world related to the problem of MODS, which characterize the mechanisms of development, etiological moments, methods of assessing the patient's condition and methods of correction. These researches have made a significant contribution to practical medicine in reducing lethal outcomes. Various positions for the management of patients with MODS have been developed. However, all of these clinic and diagnostic MODS positions represent descriptive and isolated criteria. This also applies to the development of pneumonia complicated by multiple organ dysfunction in young children.

To date, a considerable number of scales for evaluating functional disorders and the degree of multiple organ dysfunction have been created.

Also, the issue of immunology of critical conditions has acquired a pronounced pragmatic character for recent years. It became obvious that determining the significance of immunological shifts in MODS, their correct and timely diagnosis, and targeted correction are an integral part of the management of patients in intensive care units. But, unfortunately, very little studies have been done in this area. In this regard, in order to improve the methods of diagnostics and therapy, further researches in the field of development and introduction into clinical practice of an effective algorithm for early diagnosis are needed, based on which a decision on the adequate treatment of young children with multiple organ dysfunction at pneumonia will be made.

REFERENCES

[1] Nissen M.D. Congenital and neonatal pneumonia. Pediatr. Respir. Rev. 2007; 8: 195-203.

[2] Chernyakhovsky O.B., Abramova I.V., Polyanchikova O.L. Intrauterine infections in newborns, risk factors. In Russian. Russian Bulletin of Perinatology and Pediatrics. 2009; 1: 80-88.

[3] Neonatology - national. In Russian. Ed. N.N. Volodin. Moscow: GEOTAR-Media, 2008; 749.

[4] Huang F.K., Chen H.-L., Yang P.-H.ong, Lin H.-C. Bird's Eye View of a Neonatologist: Clinical Approach to Emergency Neonatal Infection. Pediatr. Neonatol. 2016; 57(3): 167-73.

[5] Rudan I., Boschi-Pinto C., Biloglav Z., Mulholland K., Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008; 86(5): 408-416.

[6] Hornik C.P., Benjamin D.K., Becker K.C. et al. Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr. Infect. Dis. J. 2012; 31: 799.

[7] Rudnov V.A., Zubarev A.S. Infections in intensive care units and intensive care units caused by Pseudomonas aeruginosa and Acinetobacter spp. Consilium medicum. In Russian. 2008; 10(1): 37-44.

[8] Pepin B.J., Lesslie D., Berg W., Spaulding A.B., Pokora T. ZAP-VAP: A Quality Improvement Initiative to Decrease Ventilator-Associated Pneumonia in the Neonatal Intensive Care Unit, 2012-2016. Adv. Neonatal. Care. 2019; 19(4): 253-261.

[9] Horowitz E.S., Sokolova E.A., Freind G.G. To the etiology of intrauterine pneumonia with a fatal outcome. In Russian. Medical almanac. 2013; 2: 110-112.

[10] Volyanyuk E.V., Safina A.I. Congenital pneumonia in premature newborns: features of etiology, diagnosis and treatment. In Russian. Practical medicine. 2011; 53: 55-59.

[11] Horowitz E.S., Sokolova E.A., Freind G.G. To the etiology of intrauterine pneumonia with a fatal outcome. In Russian. Medical almanac. 2013; 2: 110-112.

[12] Viscardi R.M. Perinatal inflammation and lung injury // Semin. Fetal Neonatal Med. 2012; 17(1): 30-35.

[13] Mohamed A.B., Yasser F.A., Ehab A.M., Mohamed R.B., Gahdaa E.A. Ventilator associated pneumonia in critically ill neonates admitted to neonatal intensive care unit, Zagazig University Hospitals. Iran J. Pediatr. 2011; 21(4): 418-424.

[14] Goldenberg R.L., Culhane J.F., Iams J.D., Romero R. Epidemiology and causes of preterm birth. Lancet. 2008; 371: 75-84.

[15] Alibekova M.B., Satvaldieva E.A., Babadzhanova Z.O., Rakhimova S.R., Nuralieva G.S. Features of the course and treatment of pneumonia complicated by acute heart failure in young children. In Russian. Bulletin of emergency medicine. 2013; 3: 254-255.

[16] Alimova Kh.P., Alibekova M.B. Multiple organ failure:

problems and modern methods of treatment. In Russian. Bulletin of emergency medicine. 2019; 12(1):75-79.

[17] Finer N.N., Carlo W.A., Walsh M.C. et al. Early CPAP versus surfactant in extremely preterm infants. N. Engl. J. Med. 2010; 362: 1970-9.

[18] Cooke R.J., Lucas A., Makrides M., Ziegler E. Postnatal growth and development in the preterm and small for gestational age infants. Importance of growth for health and development. Nestle Nutr. Inst. Workshop Ser Pediatr. Program. 2010; 65: 85-98.

[19] Santos R.P., Tristram D. A practical guide to the diagnosis, treatment, and prevention of neonatal infections. Pediatr. Clin. North. Am. 2015; 62(2): 491-508.

[20] Serebryakova E.N., Volosnikov D.K. Prognostic significance of the SNAPPE II, CRIB II, NEOMOD scales in relation to the risk of death in newborns with multiple organ failure syndrome. In Russian. Difficult patient. 2016: 14(8-9): 19. -21.

[21] Bestati N., Leteurtre S., Duhamel A. et al. Differences in organ dysfunctions between neonates and older children: a prospective, observational, multicenter study. Crit. Care. 2010; 14(6): 202.

[22] Vincent J.I., Zambon M. Why do patients who have acute lung injury/acute respiratory distress syndrome die from multiple organ dysfunction syndrome? Implications for management. Clin. Chest. Med. 2006; 27(4): 25-731.

[23] Mongardon N., Dyson A., Singer M. Is MOF an outcome parameter or a transient, adaptive state in critical illness? Curr. Opin. Crit. Care. 2009; 15(5): 431-436.

[24] Leteurte S. Duhamel A., Grandbastien B. et al. Daily estimation of the severity of multiple organ dysfunction syndrome in critically ill children. CMAJ. 2010; 182(11): 1181-1187.

[25] Leteurtre S., Duhamel A., Salleron J., Grandbastien B., Lacroix J., Leclerc F. PELOD-2. an update of the PEdiatric logistic organ dysfunction score. Crit Care Med. 2013; 41: 1761-1773.

[26] Janota J., Simak J., Stranak Z. et al. Critically ill newborns with multiple organ dysfunction: assessment by NEOMOD score in a tertiary NICU. Ir. J. Med. Sci. 2008; 177(1): 11-7.

[27] Costa G.A., Delgado A.F., Ferraro A. et al. Application of the pediatric risk of mortality (PRISM) score and determination of mortality risk factors in a tertiary pediatric intensive care unit. Clinics (Sao Paulo). 2010; 65(11): 1087-1092.

[28] Ruan L., Chen G. Y., Liu Z. et al. The combination of procalcitonin and C-reactive protein or presepsin alone improves the accuracy of diagnosis of neonatal sepsis: a meta-analysis and systematic review. Critical Care. 2018; 22(1): 316.

[29] Janota J., Stranák Z., Statecá B., Dohnalová A., Šípek A., Šimák J. Characterization of Multiple Organ Dysfunction Syndrome in Very Low Birthweight Infants: A New Sequential Scoring System. Shock.2001; 15(5): 348-52.

[30] Ng P.C. Diagnostic markers of infection in neonates. Arch. Dis. Child Fetal Neonatal Ed. 2004; 89(3): 229-235.

[31] Thomas D.B., Anderson J.C. Antenatal detection of fetal pleural affusion and neonatal management. Med J Aust. 1979: 2(8): 435-436.

[32] Raimondi F., Yousef N., Migliaro F., Capasso L., De Luca D. Point-of-care lung ultrasound in neonatology: Classification into descriptive and functional applications. Pediatr. Res. 2018; 20: 1-8.

[33] Hegazy L.M., Rezk A.R., Sakr H.M., Ahmed A.S. Comparison of Efficacy of LUS and CXR in the Diagnosis of Children Presenting with Respiratory Distress to Emergency Department. Indian J. Crit. Care Med. 2020; 24: 459-464.

[34] Tusor N., De Cunto A., Basma Y., Klein J.L., Meau-Petit V. Ventilator-associated pneumonia in neonates: The role of point of care lung ultrasound. Eur. J. Pediatr. 2021; 180: 137-146.

[35] Chen S.-W., Fu W., Liu J., Wang Y. Routine application of lung ultrasonography in the neonatal intensive care unit. Medicine. 2017; 96: 5826.

[36] Liu J., Liu F., Liu Y., Wang H.-W., Feng Z.-C. Lung Ultrasonography for the Diagnosis of Severe Neonatal Pneumonia. Chest. 2014; 146: 383-388.

[37] Yan J.H., Yu N., Wang Y.-H., Gao Y.-B., Pan L. Lung ultrasound vs chest radiography in the diagnosis of children pneumonia: Systematic evidence. Medicine (Baltimore). 2020; 99(50): 23671.

[38] Chiesa C., Natale F., Pascone R. et al. C reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period. Clin. Chim. Acta. 2011; 421: 1053-59.

[39] Rashwan N.I., Hassan M.H., Mohey El-Deen Z.M., Ahmed A.E.-A. Validity of biomarkers in screening for neonatal sepsis-a single center-hospital based study. Pediatr. Neonatol. 2019; 60(2): 149-155.

[40] Ruan L., Chen G. Y., Liu Z. et al. The combination of procalcitonin and C-reactive protein or presepsin alone improves the accuracy of diagnosis of neonatal sepsis: a meta-analysis and systematic review. Critical Care. 2018; 22(1): 316.

[41] Barie P.S., Hvdo LJ., Pieracci F.M. et al. Multiple organ dysfunction syndrome in critical surgical illness. Surg. Infect. (Larchmt). 2009; 10(5): 369-377.

[42] Von Dessauer B., Bongain J., Molina V. et al. Oxidative stress as a novel target in pediatric sepsis management. J. Crit. Care. 2011; 26(1): 103-107.

[43] Li X., Chen., Z. Correlation between serum levels of C-reactive protein and neonatal pneumonia. A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021; 100(20): 25977.

[44] Milas G.-P., Karageorgiou V., Bellos I. Mean platelet volume and neonatal sepsis: a systematic review and meta-analysis of diagnostic accuracy. J. Maternal-Fetal Neonatal Medicine. 2021; 4: 1-13.

[45] Cortés J.S., Losada P.X., Fernández L.X. et al. Interleukin-6 as a biomarker of early-onset neonatal sepsis. Am. J. Perinatol. 2021; 38(01): 338-346.

[46] Ali Y., Abdalla M.O., et al. Salivary Interleukin-6 and C-Reactive Protein/Mean Platelet Volume Ratio in the

Diagnosis of Late-Onset Neonatal Pneumonia. J. Immunol. Res. 2021; 2021: 8495889.

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