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Preventive strategies in the stages of formation and course of bronchopulmonary dysplasia

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Prevention of development of bronchopulmonary dysplasia (BPD) and possibility of preventing severe course of the disease are the first-priority areas of neonatal pulmonology. Use of modern medical technologies allows protecting a premature infant's respiratory system from as early as antenatal period of development. Use of the newest neonatal resuscitation protocols may prevent development of BPD. International experience and clinical data gathered by the authors demonstrate that seasonal palivizumab immune prevention of severe course of a respiratory syncytial viral infection in children with BPD results in rarer cases of hospitalization, resuscitation measures and fatal outcomes. The article presents modern preventive strategies used in this category of patients.

Keywords: respiratory distress syndrome, artificial pulmonary ventilation, surfactant replacement therapy, bronchopulmonary dysplasia, respiratory syncytial virus, palivizumab.

Bronchopulmonary dysplasia (BPD) is one of the multifactorial diseases, the development of which is to a certain extent affected by iatrogenic stimuli. Along with such BPD development risk factors as the mother's health condition, pregnancy failure and genetically determined peculiarities of fetal surfactant synthesis, toxic effect of oxygen, pulmonary barotrauma and volutrauma suffered in the process of resuscitation, insufficient caloric content in the diet and other issues of developmental care of premature infants contribute significantly to the disease's pathogenesis. Miscarriage prevention, development of antenatal fetal protection techniques and improvement of resuscitation techniques for premature infants may not only reduce severity of the disease, but also prevent development of bronchopulmonary dysplasia in neonatology. In the present stage obstetricians, resuscitators, neonatologists, pediatricians and pulmonologists have an extensive range of techniques based on high medical technologies and aimed at minimizing aggressive impact of intrauterine pathogens and resuscitation factors on children with respiratory distress syndrome (RDS) and capable of preventing severe exacerbations of the disease secondary to a viral infection in the children with bronchopulmonary dysplasia [1, 2].

The historically developed preventative orientation of the national pediatrics could not be more evident than in the management of the BPD risk group patients or the BPD patients. Bronchopulmonary dysplasia outcomes by three years of age largely depend on the application of the new high technology techniques in the follow-up of the patients with this disease starting from the antenatal period of life. The possibility of clinical recovery from BPD determines the need in using all the available preventative measures in order to reduce severity of the disease with the ultimate goal of improving quality of the child's life [3, 4].

Prevention of BPD development in small premature infants with very low (VLBW) or extremely low (ELBW) birth weight in the setting of intensive therapy of respiratory distress syndrome and/or intrauterine pneumonia must be conducted with due regard to all the pathogenetic mechanisms of the child's bronchopulmonary system's damage in the prenatal period of life, when the processes of alveologenesi and angiogenesis have not yet been completed.

This primarily refers to the aspiration to enhance pulmonary tissue maturation in neonates both by miscarriage prevention and antenatal steroid application in order to prevent development of respiratory distress syndrome in a child. It is widely known that glucocorticoids stimulate cell specialization and surfactant synthesis, increase the amount of type II alveolocytes and enhance function thereof [5]. In the developed countries, 92-97% women liable to premature delivery receive glucocorticoids antenatally; RDS and neonatal mortality rates are becoming significantly lower, especially among the neonates of 24-34 weeks of gestational age. A large prospective study conducted in Spain demonstrated decrease in the neonatal morbidity and BPD development rates after a completed antenatal glucocorticoid prevention course [6].

The early neonatal life of a child with RDS in the stage of resuscitation and intensive therapy is, without any doubt, crucial for BPD development prevention. The first important step in treating small premature infants, especially VLBW and ELBW infants, is adequate rendering of primary and resuscitation care at the labor ward, the key factors being hypothermia prevention and adjustment of respiratory therapy on the basis of the concept of "lung protection".

Hypothermia prevention decreases the risk of development and severity of RDS and thus prevents development of bronchopulmonary dysplasia or severe forms thereof. The algorithm of such prevention involves:

- thermal comfort at birth (air temperature of 26-28 °C at the labor ward);
- thermal care provision in the first 30 seconds of life (placement of a patient into a plastic bag without postnatal skin drying, thermal protection of head surface and minimal bag integrity damage in the course of manipulations);
- transportation of a neonate to the resuscitation unit in the bag placed in the transport incubator and continuous monitoring of body temperature and pulse oximetry indicators.

Respiratory therapy on the basis of the concept of "lung protection" involves:

- early application of artificial pulmonary ventilation (APV) with continuous positive airway pressure (CPAP) / positive end-expiratory pressure (PEEP). Buildup and maintenance of continuous positive airway pressure is an essential element of early stabilization of small premature infants regardless of whether the children are able to breathe spontaneously or are subject to APV. Continuous positive pressure contributes to buildup and maintenance of the functional residual lung capacity, prevents atelectasis and reduces the work of breathing;
- when APV is indicated, it is reasonable to perform "prolonged inflation of lungs" with the help of a manual or automatic lung ventilator with inspiration pressure delay before starting the traditional ventilation for the best possible spread of alveoli and development of the functional residual lung capacity;
- early (within the first 15 minutes of life) preventative administration of exogenous surfactant drugs. According to the methodological letter of the Ministry of Health and Social Development of Russia of 21.04.2010, "surfactant therapy at the labor ward is indicated for preventative purposes (before manifestation of the clinical symptoms of RDS) to the neonates born before the 27th gestational week and the neonates of 27-29 weeks of gestational age, whose mothers did not undertake the antenatal steroid RDS prevention course, and for therapeutic purposes to all the neonates born before the 32nd gestational week, who required tracheal intubation at the labor ward due to the development of respiratory disorders" [7];
- intratracheal bolus surfactant administration under the INSURE procedure (tracheal intubation, surfactant administration, extubation and conversion to CPAP) is aimed at minimizing the APV-associated pulmonary damage risks: it decreases APV, BPD and air leak syndrome rates;
- CPAP buildup (nasopharyngeal tube, binasal prongs, nasal mask) and administration of surfactant without intubation (SWI) with a thin endotracheal catheter immediately after birth in

spontaneously breathing small premature infants (22-26 weeks of gestational age). Multicenter trials demonstrated that the new method of surfactant administration was proposed in order to decrease the risk of lung damage, as even a short-term APV in the setting of surfactant administration under the INSURE procedure may result in complications. The proposed method consists in the combination of two efficient methods of RDS therapy: surfactant and nasal CPAP. The obtained results demonstrated decrease in BPD development and mortality rates, as well as in the rate of glucocorticoid use [8, 9]. Analysis of clinical studies of surfactant drugs demonstrated that these drugs of animal origin are efficient for RDS prevention and treatment. Correlation of clinical outcomes with certain surfactant drugs has not been proved [10].

When condition of a child with RDS is stabilized, a set of measures aimed at preventing bronchopulmonary dysplasia development is implemented at the resuscitation and intensive care unit. The primary stages in the present stage are described below.

Oxygenation control. Fluctuations of saturation level, hyperoxic and hypoxic peaks should be avoided at APV. The target saturation level is 91-95%. Upon 36 weeks of postconceptional age (PCA), the saturation level should be maintained at 94-95% if BPD has developed (in order to prevent development of *cor pulmonale* – pulmonary heart).

Fluid overload prevention. Body weight loss in the first 5 days of life must be 10-15%.

Early drug and surgical closure of the hemodynamically significant patent arterial duct (PAD). It is widely known that PAD rate is 10-20% in infants with VLBW and 25-70% in infants with ELBW. PAD diagnosis protocol involves sonographic screening of all patients of less than 30 weeks of gestational age in the first 48 hours of life. Sonography is performed upon such indications as systolic noise, mixed acidosis and infection manifestation. The main criteria of hemodynamic significance are:

- arterial duct diameter > 1.5 mm (body weight < 1,500 g);
- left-to-right blood shunting;
- retrograde blood flow in the postductal aorta $\geq$ 50% of antegrade blood flow.

Hemodynamically significant PAD may lead to the development of intraventricular hemorrhage, aggravates RDS severity, contributes to pulmonary hemorrhage and is a risk factor of development of necrotizing enterocolitis, circulatory failure, retinopathy, periventricular leukomalacia and BPD. Implementation of a conservative ibuprofen therapy course consisting in three intravenous injections with interval of 24 hours in doses of 10, 5 and 5 mg/kg contributed to considerable reduction in the number of operative interventions aimed at PAD clipping and the rate of development of BPD and severe forms thereof [11].

Systemic corticosteroids may be prescribed by a council of physicians. It is indicated to neonates with VLBW and ELBW of 7 days of age undergoing APV for more than 7 days (course dexamethasone dose – 0.89 mg/kg intravenously) [12]. If a hemodynamically significant PAD is revealed, the first measures to be undertaken must involve duct closure. Occurrence of an infectious process is a contraindication against dexamethasone prescription. Therapy efficacy is assessed in the 3rd day of therapy. Dexamethasone therapy should be terminated if no positive dynamics of APV parameters is observed. Possibility of another dexamethasone course is discussed if a child experiences a relapse or if the first course yielded no effect. Steroid therapy should not be prescribed to the children not undergoing APV. Inhaled steroids (budesonide) in a dose of 0.125-0.5 mg/day (in 2 administrations) may be prescribed; treatment duration is determined on an individual basis.

Caffeine prescription is indicated to all infants with ELBW and VLBW undergoing respiratory therapy from birth. Caffeine benzoate is prescribed intravenously in a dose of 20 mg/kg (loading dose) in the first day of life, 24 hours later – in a dose of 5 mg/kg per day (support dose); dosage should be corrected on the basis of tachycardia. Caffeine is completely withdrawn from the therapy when the patient reaches 34 weeks of PCA and features no apnea (in the event of completely enteral feeding, caffeine is administered *per os*) [13].

Diuretic therapy at developing BPD (from the 3rd week of life) may be prescribed by a council of physicians. Indications for prescription of diuretics are clinical and/or radiographic signs of

interstitial pulmonary edema in the setting of respiratory therapy (APV/CPAP), including moist rales in the lungs and increase in the symptoms of respiratory failure. If diuretics are used, electrolytic composition of blood must be monitored. The therapy involves use of furosemide (intravenously, 0.5-1 mg/kg OD-BID (used in the acute stage of pulmonary edema; long-term course is not recommended [14])) and spironolactone (1-4 mg/kg per day per os in (1-2 administrations), preferably in the afternoon; the course may be short and long (up to 4 weeks)) [15]. Furosemide and spironolactone may be used in a combination (in small doses).

Use of bronchodilators to terminate acute episodes of bronchial obstruction. 1 drop of inhalation solution Berodual (β 2-agonist + M-cholinolytic) per 1.5-2.0 ml of 0.9% NaCl (25 mcg of fenoterol hydrobromide and 12.5 mcg of ipratropium bromide per 1 kg of body weight) every 6-8 hours *in short courses* using a nebulizer may be prescribed *by a council of physicians* as nebulizer broncholytic therapy.

Nutritional support. Optimal caloric content of the diet by the end of the 2nd week of life for BPD prevention and therapy must be 130-140 kcal/kg (20% higher than the standard caloric content). A fortifier (such as Friso: 12 kcal/bag per 50 ml of milk) may be added to the breast milk used to feed infants with ELBW or VLBW to ensure its higher caloric content.

Use of vitamin A. Vitamin A (retinol) is the basis for growth and specialization of epithelial cells. It is generally considered that prescription of high retinol doses (at least 1,500-2,800 IU/kg of the child's body weight per day) reduces the BPD development rate in children with respiratory distress syndrome [16]. Use of vitamin A may be restricted if the parenteral form thereof is not available.

Along with the early preventive administration of exogenous surfactant, **surfactant replacement therapy**, which may be employed in all stages of managing premature infants with respiratory distress syndrome, also plays a significant role in preventing BPD development in the aforementioned patients. We have already mentioned the early therapeutic administration of surfactant drugs to all the neonates born before the 32nd gestational week, who required tracheal intubation at the labor ward due to the development of respiratory disorders [7]. However, endogenous surfactant deficit plays a significant role in pathogenesis of respiratory disorders in the later stages of development of small premature infants as well. Thus, foreign studies demonstrated that most premature infants with VLBW or ELBW undergoing APV for more than 7 days feature symptoms of surfactant dysfunction caused by degradation or deficit of surfactant-associated proteins (SP-B and SP-C) accompanied by respiratory failure [17, 18]. Secondary surfactant deficit plays a significant role in BPD development due to impaired respiratory mechanics and increased impact of barotrauma, toxic effect of oxygen and inflammatory alterations resulting in the increase in respiratory disorders in premature infants with RDS. On the basis of non-randomized studies dedicated to "late" use of surfactant drugs in neonates in the Russian Federation, a new method of BPD prevention for infants with VLBW or ELBW was proposed; it consists in daily administration of surfactant emulsion using nebulizer Aeroneb Pro five times per day, starting from the 8th respiratory support day [17, 19, 20].

Due to wide use of antenatal RDS prevention all over the world and preventative and therapeutic application of exogenous surfactant drugs, the classic BPF form described by W.H. Northway as far back as in 1967 [19] and consisting in pulmonary trauma caused by oxygen, pressure and volume and resulting in an inflammatory response, respiratory tract involvement, fibrosis and emphysema is observed far more rarely. The new BPD form specific to infants of less than 27-28 weeks of gestational age may develop despite sparing surfactant therapy and APV and without preliminary RDS. In that case oxygen dependence usually persists for a long time, whereas bronchoobstructive syndrome and pulmonary hypertension are only rarely observed.

Prevention of bronchopulmonary process exacerbations secondary to intercurrent diseases comes to the fore in the process of follow-up observation of children with BPD (especially with severe forms of BPD). Statistical data indicate that viral infections and virobacterial associations play a key role in the development of bronchopulmonary dysplasia exacerbations [22], which is why

prevention of BPD exacerbations after discharge from a neonatal inpatient hospital virtually means control over acute respiratory infections in risk group children.

We examined 80 children (35 girls and 45 boys) from 1 month to 2 years of age (average age – 11 months) with bronchopulmonary dysplasia within 2 epidemic seasons of respiratory diseases (November 2011 – March 2012 and November 2012 – March 2013). We performed virological analysis of nasopharyngeal swabs taken in this group of children monthly (when bronchopulmonary dysplasia was non-acute) (242 samples in total). In order to detect genetic material of respiratory syncytial, metapneumo-, boca-, adeno-, corona-, rhino- and parainfluenza viruses in real time, we used AmpliSens ARVI-screen-FL reagent kits (InterLabService, Russia) for polymerase chain reaction (PCR) on the Bio-Rad CFX96 system (USA). Positive PCR result was registered in 88 samples (36.4%). Respiratory syncytial virus was detected in 4 samples (4.5%), metapneumovirus – in 1 sample (1.1%), parainfluenza viruses – in 5 samples (5.7%), coronaviruses – in 7 samples (8.0%), rhinoviruses – in 41 samples (46.6%), adenoviruses – in 8 samples (9.1%), bocavirus – in 22 samples (25%) [23].

The obtained data indicate that more than 1/3 of children with non-acute bronchopulmonary dysplasia latently carry respiratory viruses. Most positive nasopharyngeal swabs of these patients feature rhino- and bocaviruses. Respiratory syncytial virus (RSV) was detected only in 5% of children with non-acute BPD. However, it is widely known that the severest exacerbations of the bronchopulmonary process in children with BPD are caused by RSV infection – severe bronchiolites accompanied by respiratory failure. It has been found that RSV may cause up to 70% of all lower respiratory tract infections in younger children [22]. RSV is the main cause of hospitalizations due to acute respiratory viral infections (ARVIs) during epidemic seasons in children under 1 year of age. Statistics of the World Health Organization indicates that at least 4 mn younger children die due to RSV infection every year all over the world [24]. RSV-associated respiratory diseases take the severest course in the premature infants born before the 35th gestational week in the setting of imperfect immune response and the respiratory system's morphofunctional immaturity [25]. Severe RSV infection risk group also includes children under 2 years of age with bronchopulmonary dysplasia and hemodynamically significant congenital heart diseases (CHDs). It is widely known that the risk of hospitalization due to severe course of RSV infection in the first 6 months of life is twice as high in premature infants, 3 times as high in children with CHDs and 13 times as high in children with BPD as in term infants without chronic cardiorespiratory pathologies [26, 27]. The children with BPD may be considered the group of high risk of severe RSV infection course for several reasons:

- major prematurity (most patients);
- immaturity of the child's immune system and insufficient protection with maternal antibodies due to preterm birth;
- damaging impact of aggressive resuscitation factors on immature bronchopulmonary system;
- development of chronic bronchopulmonary process and impairment of the distal respiratory tract segments [28].

It is in children with BPD that high rate of hospitalizations due to disease exacerbations (RSV-associated bronchiolites) often comes with the need in resuscitation measures and results in fatal outcomes. According to the Canadian authors, who observed 260 BPD patients, most children (80%) have to resort again to additional oxygenation in the setting of severe course of RSV infection; 1/3 (33%) require resuscitation measures; 3.5% die [29]. A clinical functional monitoring demonstrated that bronchopulmonary dysplasia exacerbation in children is the severest in the first 6 months of life; however, high risk of hospitalization persists until 2 years of age [30]. According to several foreign authors, almost all children under 2 years of age are affected by RSV [31].

Insignificant rate of latent RSV carriage among children with bronchopulmonary dysplasia may be an additional factor determining severer course of RSV-bronchiolitis in these patients. In case of long-term asymptomatic colonization in the upper respiratory tract's mucosa, some respiratory causative agents provide long-term active immunization of the child's body, preventing

development of a pathological process or reducing its severity in the event of contact with these infectious agents. It appears that such immunization does not take place in case of RSV. Moreover, long-lasting immune response does not develop even after an RSV infection; this results in frequent reinfections [32]. It is widely known that RSV is highly contagious and often causes outbreaks of acute respiratory diseases and lower respiratory tract infections at resuscitation units, neonatal pathology units, children's collectives and retirement homes. The rate of fatal outcomes among children in the event of nosocomial RSV infection outburst may be as high as 12% [33].

The epidemic situation concerning RSV required development of efficient preventative measures. The RSV infection vaccines that had already been developed appeared to be insufficiently efficient [34]. Passive immunization with palivizumab – one of the fundamentally new drugs – humanized monoclonal immunoglobulin G antibodies (in this case they were specific to RSV fusion protein (protein F) with marked neutralizing and inhibiting effect on RSV A and B strains) – proved to be efficient. Palivizumab molecule consists of human (95%) and murine (5%) sequences and belongs to the pharmacological class of immunoglobulins. This is the only known drug suitable for specific immune prevention of RSV infection among children.

Palivizumab has already been used all over the world for preventing severe course of RSV infection in risk group children for 15 years. Ca. half a million children from 50 countries have already received this drug. Palivizumab is a well-proven efficient prophylactic drug for younger children susceptible to severe course of RSV-associated bronchiolites. It was included in the National Recommendations on ARVI Prevention for the children with high risk of severe course of RSV infection. The drug was registered in the Russian Federation on February 16, 2010, under trademark "Synagis"; it is a lyophilisate for preparation of intravenously administered solutions marketed in 50 and 100 mg phials. Registration number – LSR-001053/10. The single dose of the drug is 15 mg/kg of a child's body weight; injections are made on a monthly basis throughout the epidemic season [35].

Results of the authors' own clinical functional data on the current (2013/2014) and 4 previous epidemic seasons correlate with the international experience of using palivizumab, confirm its safety and efficacy of using in the children susceptible to severe course of RSV infection [28]. 222 children from 15 days to 2 years of age have been vaccinated and continue undergoing passive immunization against RSV infection throughout these 5 seasons at the Scientific Center of Children's Health; most of them are children with bronchopulmonary dysplasia (174) and/or premature; 8 premature children have a hemodynamically significant congenital heart disease. No cases of the RSV-associated acute respiratory infections have been registered in this group of children.

Safety of palivizumab use in the children susceptible to severe course of RSV infection was confirmed by results of foreign multicenter studies, which included a large number of patients. We have not observed any drug-associated side effects, allergic symptoms or serious adverse events among our patients.

Analysis of the international experience of palivizumab use, results of the multicenter studies conducted in the Russian Federation in 2008-2010 and the authors' own clinical data determines the conclusion that the drug must be used in groups of high risk of severe course of RSV infection. Patients with bronchopulmonary dysplasia and/or hemodynamically significant congenital heart diseases and the premature infants born before or in the 35th gestational week must be protected against this infection in the age periods, most dangerous in terms of development of severe lower respiratory tract diseases or serious complications and the risk of death. Such a period for premature infants is the first 6 months of life, for children with BPD and CHD – the first 2 years of life. Immune prevention of RSV infection is especially crucial for children with BPD, as in this case the disease acquires a regressive course and, if no bronchopulmonary exacerbations occur, the chance of clinical recovery increases. Thus, use of palivizumab may be recommended to all the children susceptible to severe course of RSV infection, including children with BPD, from all the regions of the Russian Federation.

CONCLUSION

Almost half a century has passed since the term “bronchopulmonary dysplasia” was introduced to pediatric practice and since the disease was first described in 1967. Long-term clinical observations and scientific studies all over the world led to significant achievements in the research of development and course peculiarities of this disease. Improvement of neonatal resuscitation and methods of developmental care of the infants with VLBW or ELBW resulted in a new form of BPD, characterized by a milder course. Preventative strategies along with the modern medical technologies enable preventing development of BPD or its severe forms and exacerbations, make clinical recovery of some patients possible by 3 years of age and reduce the number of patients with chronic bronchopulmonary process or incapacitation as BPD consequences. The main outcome is the improvement in life quality of the patients with bronchopulmonary dysplasia.

The passive immunization is a preventive measure against exacerbation of bronchopulmonary dysplasia in the setting of severe form of BVD which influences positively on the course of the disease along with vaccination against respiratory causative agents (pneumococcus, Haemophilus influenzae) followed by favorable outcome of BVD and acceleration of psychomotor development of children [1, 36].

Therefore realization of current preventative strategies against bronchopulmonary dysplasia and its severe forms provides stable health condition of premature, rehabilitation of functional abilities and the improvement in life quality.

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