Research Article

Bronchopulmonary dysplasia at children, outstanding issues

Tatyana A. Li, Nurila A. Maltabarova

ABSTRACT

Aim: Bronchopulmonary dysplasia is one of the most significant pathologies, which affects life quality of preterm infants. More than 50 years, scientists from all over the world have shed light on most of the issues related to BPD. Despite these remarkable advances in the study of this issue, many knowledge gaps and blind spots still present in the comprehension of BPD and require more detailed study. **Materials and Method:** We had provided literature review of up to date information about BPD for clear understanding of unsolved issues. **Results and discussion:** Analysis of various literary sources has shown that today there is disparate information on many issues concerning BPD. A review of the world and local literature has shown that the available evidence base on the therapy of patients with BPD only affects the management of patients during the newborn stage and recommendations for the management of this category of patients at home. **Conclusion:** We had find lack of information about postneonatal period management and intensive care. BPD is still an actual issue for study.

KEY WORDS: Bronchopulmonary dysplasia, Extremely immaturity, Preterm newborns

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease that mostly affects premature newborns and infants.[1] Northway *et al*. described that BPD, in 1967, as an iatrogenic disease due to long-term artificial lung ventilation, had been defined as the presence of persistent respiratory signs and symptoms, the need for supplemental high concentration of oxygen to treat hypoxemia.[2] BPD is the leading cause of chronic lung disease in children.[3] Main causes of BPD these are lung tissue immaturity, mechanical ventilation, oxygen toxicity, infection and inflammation, and genetic predisposition. Mortality at children with severe BPD until 2 years old about 25%.[4]

MATERIALS AND METHODS

We had provided literature review of up to date information about BPD for clear understanding of unsolved issues.

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Website: jprsolutions.info | ISSN: 0975-7619

Definition

BPD definition was several times changed and transformed. Today it is characterized as a chronic lung disease of prematurity have often been used interchangeably to describe the condition post-treatment of premature infants for respiratory distress syndrome.[5] The earliest clinical definition of BPD was named as an oxygen requirement at 28 days with changes at X-ray examination. These were originally modified to include continuing need for oxygen therapy at 36 weeks corrected age of gestation. However, this definition inadequately addresses highly variable clinical practices as well as the wide range of disease, leading to further modification to include a severity assessment at 36 weeks gestational age.[6-8] The definition today takes into account oxygen supplementation duration, positive pressure ventilation requirements and age of gestation, also to oxygen dependency at 36 weeks postmenstrual age. This distinction has helped to identify that severity of BPD influences both pulmonary and neurodevelopmental outcomes as well as risk of mortality.[9] However, there are numerous limitations, as the system cannot adequately classify infants with respiratory problems (including trachea or bronchomalacia and/or reactive airway disease) and

Department of Emergency Medical Care and Anaesthesiology Reanimatology, JSC "Astana Medical University," Astana, Kazakhstan

***Corresponding author:** Li Tatyana Anatolyevna, Department of Emergency Medical Care and Anaesthesiology Reanimatology, JSC "Astana Medical University," Astana, Kazakhstan

Received on: 17-02-2018; Revised on: 23-03-2018; Accepted on: 28-05-2018

pulmonary vascular disease.[10] In 2001, the National Institute for Child Health and Human Development defined and classified BPD for gestational age and additional oxygen consumption. Infants A 32-month postmenstrual age with clinical manifestations of the disease requiring additional oxygen for 28 days of life and that were weaned for 36 days or at discharge was considered moderate BPD. Infants in need of 30% continuous oxygen at the age of 36 weeks after menstrual age or at discharge were considered moderate. Infants who remained at 30% oxygen and with a constant positive airway pressure were considered a serious form of the disease. For infants at 32 weeks of gestation, the identical oxygen demand was realized on the day of life 56.[11]

Another classification of "classical" and "old-fashioned" BPD has been described in populations of large preterm infants before the use of surfactant substitution therapy.[12] Classical BPD was characterized by pneumonia, respiratory tract trauma, secondary to interstitial and alveolar fluid overload, fibrosis of the lung parenchyma due to hyperinflation and development of the disease of small respiratory tract, smooth muscle hypertrophy, and oxidative stress.[13] With the increase in survival rates in newborns with a lower weight and newborn gestational age, a "new BPD" was detected and presented in the early stages of gestational development of the child before the alveolarization was completed. New BPD occurs in children with very low birth weight and is created because of the impact of antenatal infection. These patients usually have less inflammation and fibrosis, and only a moderate degree of supplemental oxygen or fan support may be required.[14]

Pathogenesis of BPD

Nature of this pathology still raises controversy among scientists. Pathological changes as a result of BPD complex multifactorial process in which various pre- and post-natal factors compromise normal development in the immature lung. BPD is caused due to an interaction between genetic and environmental factors (hyperoxia, invasive mechanical ventilation, and sepsis).[15] Immature lung tissue impacted by external factors: Infections, high concentration of oxygen, long time ventilation, barotrauma, volutrauma, or atelectrauma, which initiates an cascade of inflammation reaction involving cytokines. This activates the cell death pathways. Damage of immature lungs is followed by resolution of injury to close to normal lung architecture or repair and leads to fibrosis.[16]

Mechanical Trauma

BPD occurs almost exclusively in preterm infants that have received positive pressure ventilation suggesting that mechanical lung over-distension and alveolar stretch play a critical role in the pathogenesis of BPD. Ineffective pulmonary mechanics results in the need for ventilatory assistance at birth. The premature lung is often difficult to ventilate due to surfactant deficiency resulting in decreased compliance and challenges maintaining functional residual capacity.[17,18] Positive pressure and excess volume delivered through assisted ventilation can cause injury to the immature lung by further over-inflation of alveoli, leading to cellular injury, inflammation, and reactive oxygen species (ROS) generation, thereby potentially amplifying pre-existing injury associated with prenatal inflammation.[19]

Review which had been conducted by Lauren M. Davidson and Sara K. Berkelhamer in 2016, emphasized main points in pathogenesis such as:

Oxygen Toxicity

Supraphysiologic oxygen results in increased mitochondrial ROS generation with unique susceptibility to oxidative stress and alveolar cell injury in the developing lung, in part attributable to antioxidant deficiencies and immature defenses.[20] Supporting these concerns are clinical data suggesting that even brief exposure to supraphysiologic oxygen during resuscitation increases the risk of BPD,[21] and that prolonged evidence of oxidative stress can be identified in exhaled breath condensate of adolescents born preterm.[22]

Infection and Inflammation

While several clinical studies have reported an association between chorioamnionitis and BPD, a meta-analysis including 59 studies and over 15,000 infants suggested that limited association between chorioamnionitis and BPD existed when adjustments were made for gestational age.[23]

Growth Restriction

Studies have further identified that provision of optimal enteral feeding as compared to parenteral nutrition decreases risks of developing BPD.[8] Of interest is recent studies which demonstrate a decreased risk of BPD despite compromised growth with the exclusive use of breast milk.[24]

Genetics

While BPD results from cumulative exposures to both the pre- and post-natal factors noted above, there is a growing interest in the heritable contributions to the development of BPD. Rapid advances in genomics and proteomics suggest that regulators of susceptibility may eventually be identified, potentially allowing for targeted or individualized therapy to prevent and treat BPD.[25]

Epidemiology

Data on epidemiology of BPD in the world differ, due to the lack of common criteria of diagnosis, differences in the study population, levels of technical equipment, and hospital work intensity. On average, BPD develops in 30% of newborn children who need ventilation. In Germany, of 8,059 preterm infants with GV <32 weeks, 29% received additional oxygen,[26] in the United States, 20% of children with extremely low body weight (ELBW), and very low body mass.[27] In the UK among children with breastfeeding <26 weeks, the frequency of BPD was 50%.[28] According to a study conducted in Japan, which included 2,145 children with ONMT born in 2003, BPD was observed in 28-33% of children,[29] in Finland BPD was registered in 39% of 211 children with ELBW. Data on the frequency of BPD in the whole of the Russian Federation currently missing, available information concern the incidence of disease in individual centers different regions and it varies from 2.3% to 21.1%.[30] In general, the frequency of diagnosis of BPD for significantly exceed domestic may indicate a persistent hypo-diagnosis of the disease in the Russian Federation. The frequency of BPD is inversely proportional to gestational age and birth weight. At the present time, BPD occurs mainly in children less than 32 weeks of gestation.[31] Published research results demonstrate a significant reduction in mortality in children with BPD accounting for 4.1% in children of the first 3 months of life, 1.2–2.6% in infancy.[27]

Premature birth is still a major problem in obstetrics and neonatology, which accounts for the greater part of perinatal mortality and long-term neurological morbidity among newborns.[32] Andrews noted that about half of all preterm labor is the result of a spontaneous onset of premature birth and that about the third result from premature rupture of amniotic membranes. The remaining 20% of cases of premature birth are medically indicated for specific conditions of the mother or fetus. The frequency of clinically asymptomatic colonization of the chorioamnion and amniotic fluid increases with decrease in the period of pregnancy during childbirth. In one study, positive cultures of the chorioamnion were seen in 73% of women with spontaneous preterm births occurring before 30 weeks of pregnancy, and 83% of newborns weighing up to 1 kg. Colonizing bacteria initiate the inflammatory cascade and release of numerous cytokines, chemokines, prostaglandins, and other bioactive substances that can cause cervical ripening, premature birth, and rupture of the membrane.[33] This inflammatory response can also cause adverse neonatal outcomes such as neurological damage and cerebral palsy, necrotizing enterocolitis, and BPD.

Management of BPD

A management manual for patients with BPD, published, in 2016, in the journal Pediatrician, discusses some questions about the pharmacotherapy of patients with BPD after discharge from hospitals in the early period. They noted that there are no specific recommendations for prescribing drugs for the treatment of respiratory diseases. Each case should be considered individually, depending on the clinical manifestations, the need for oxygen therapy, as well as possible complications.[34] Indications for the use of inhaled bronchodilators - an acute episode of airway obstruction, which positively affects therapy.[35] Ipratropium bromide has a less pronounced bronchodilator effect, and today this drug is not indicated for patients with BPD.[36] With regard to the use of inhaled corticosteroids, there is insufficient evidence of their effect on the development of pulmonary tissue and airway obstruction, so this category of drugs should be administered with caution.[31,37] Diuretics are indicated for use in patients with hypoxemia and pulmonary edema, or in the case of severe lung disease with a violation of fluid homeostasis. Furosemide is the most widely used drug; however, the available actual base is not sufficient to recommend long-term use.[38] In connection with the potential risk of complications, furosemide is recommended for a short period of time.[7,39] Therapy of pulmonary hypertension includes the optimization of respiratory and nutritional status. Chronic and intermittent hypoxemia can worsen pulmonary hypertension. Therefore, the target saturation should be within 94% or 95%.[40] The use of pulmonary vasodilators is also not shown because of the lack of convincing data. The use of sildenafil in the treatment of pulmonary hypertension in patients with BPD was the most common.[41] The main goal of oxygen therapy for children with BPD at home is to minimize chronic or intermittent hypoxemia. Addition of additional oxygen positively influences weight gain,[42] reduces the phenomenon of respiratory insufficiency,[43] and reduces pulmonary hypertension.[44] Food support is to optimize growth and development. Methods and composition of enteral nutrition to this day are the subject of discussion. According to the analysis of foreign and domestic literature, it can be concluded that, despite certain achievements in studying the mechanisms of occurrence, course options, treatment and outcomes of BPD, there remains a significant range of questions of complex intensive therapy requiring further study.[39] In addition, there are currently no clear recommendations for the treatment of patients with BPD requiring intensive care. Specific recommendations on the preferred patterns and parameters of ventilation for patients with respiratory insufficiency of the 3rd class are

not present in the background of BPD. There are conflicting data on the tactics of managing young children with BPD, and the nuances of respiratory support are poorly understood.

RESULTS AND DISCUSSION

Analysis of various literary sources has shown that today there is disparate information on many issues concerning BPD. A review of the world and local literature has shown that the available evidence base on the therapy of patients with BPD only affects the management of patients during the newborn stage and recommendations for the management of this category of patients at home. We had find lack of information about postneonatal period management and intensive care. BPD is still an actual issue for study.

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Source of support: Nil; Conflict of interest: None Declared