ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 07, pp.5514-5521, July, 2019

DOI: https://doi.org/10.24941/ijcr.35915.07.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

PHARMACOTHERAPY OF BRONCHOPULMONARY DYSPLASIA: MODERNITY AND PERSPECTIVE

***Dr. Maria Vasilievna Kushnareva, Dr. Galina Mihailovna Dementyeva and Dr. Elena Solomonovna Keshishyan**

Yu. E. Veltishchev Research Clinical Institute of Pediatrics, N.I. Pirogov Russian National Research Medical University, Moscow, Russian

ARTICLE INFO

Article History:
Received 17th April, 2019
Received in revised form
20th May, 2019
Accepted 24th June, 2019
Published online 31st July, 2019

Key Words:

Bronchopulmonary Dysplasia, Pharmacotherapy, Clinical Action, Side Effect, Infants.

**Corresponding author:*
Maria Vasilievna Kushnareva

ABSTRACT

Bronchopulmonary dysplasia (BPD) is a common chronic lung disease in premature babies, especially those with very low body mass. Being a multifactorial disease, BPD requires complex pathogenetic, syndromnal, and symptomatic pharmacotherapy. In addition to oxygen therapy, it should include anti-inflammatory and antibacterial treatment, sparing prescription of glucocorticosteroids. It is also advisable to use antioxidants, proteinase inhibitors, drugs for the relief of apnea, diuretics. When prescribing pharmacotherapy, it is necessary to take into account the severity of the disease, the development of complications, the tolerance of drugs, the therapeutic response of the infant's body to treatment. However, the effect of treatment can vary from very good to extremely weak.

Citation: Dr. Maria Vasilievna Kushnareva, Dr. Galina Mihailovna Dementyeva and Dr. Elena Solomonovna Keshishyan, **2019.** "Pharmacotherapy of bronchopulmonary dysplasia: modernity and perspective", *International Journal of Current Research*, 11, (07), 5514-5521.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a common chronic lung disease in premature babies, especially those with very low body mass. According to the literature' source, the incidence of BPD among premature infants varies within widely limits: from 28 till 50% [13, 41, 58, 73, 76]. Treatment of BPD is a big problem and, unfortunately, is not always effective: up to 15% of children with this disease die within the first year of life [14, 82]. The disease occurs as a result of the damage of immature lung tissue under the influence of high concentrations of O_2, which is supplied under the high pressure during artificial lung ventilation (ALV) for respiratory distress syndrome (RDS). A significant contribution to the development of BPD is made by antenatal and postnatal infection, mainly ventilator-associated pneumonia (VAP). These factors lead to impaired alveolarization and vascularization in the respiratory tract of the infant [8, 9, 50]. Being a multifactorial disease, BPD requires complex pathogenetic, syndromal, symptomatic, antibacterial and anti-inflammatory pharmacotherapy [9, 26]. However, the effect of treatment can vary from very good to extremely weak [3, 12, 44]. In addition, the use of drugs can cause undesirable side effects that leads to disputes about the appropriateness of their assignment to infants [3, 14].

Aim: To prove the need of complex pharmacotherapy of BPD in premature infants and to share their own experience in the treatment of this disease.

Prevention of BPD: Prophylaxis of BPD is, first of all, prevention and treatment in preterm newborns with severe form of RDS, requiring the use of hardware ALV. Currently, clinics use several approaches to prevent the development of BPD. In obstetric practice, the prescribed glucocorticosteroids (GCS) for pregnant women is used earlier than a day before the birth. However, this method was not widely used because of the high probability of side effects on the woman's body and fetus [22]. One of the first methods of BPD preventing in newborns was the use of glucocorticosteroids [23]. Although this method has proved to be effective for the prevention of BPD in premature infants and it is widely used in neonatology [10, 23, 36, 51], however, the attitude to it in pediatricians is ambiguous [10, 32, 63]. Early postnatal prophylactic use of hydrocortisone and dexamethasone in neonates remains concern due to possible long-term adverse effects, in particular, the development of late sepsis, ulcerative necrotic enterocolitis, delay in the development of the nervous system [31, 32, 51, 74]. The study of Qin *et al.* (2017) is revealed that the administration of dexamethasone to extremely premature neonates (gestational age from 23 to 28 weeks) was associated with an increased risk of hospitalization in respiratory hospitals and deterioration of the neurological condition in the first year of life [56]. Dexamethasone is associated with altered neuronal maturation in deeply premature newborns, which may explain the adverse neurodevelopmental effects of postpartum GCS. The severity of neurological disorders grew with an increase in the dose of dexamethasone, but not postpartal age. [83]. Ji *et al.* based on a meta-analysis of 16 randomized controlled trials

found that early postpartum use of GCS for the prevention of BPD in preterm infants reduced the incidence of BPD at an adjusted gestational age of 36 weeks but there was an increased risk of hypertension and intestinal perforation [32]. Hitzert *et al.* (2014) for the prevention of BPD in premature infants with a risk of developing this disease, low doses of dexamethasone (the initial dose of 0.25 mg / kg / day) were administered. Neurologic functioning improved among surviving infants (15 out of 17), Moreover, most of them had normal neurology at the age of 12-36 months [30]. In prophylaxis with sol-cortef, there was no development of severe SDR, which required mechanical ventilatory equipment [23]. A study on the use of antenatal GCS with the observation of a large number of newborns with gestational age at birth less than 32 weeks showed a decrease in mortality and the development of major serious diseases in infants (SDR, BPD, sepsis, necrotizing enterocolitis, VAP) [20]. In connection with the possible undesirable consequences of the prophylactic use of systemic GCS at the risk of BPD developing in premature newborns, the expediency of using inhaled steroid medications, preferably dexamethasone [35, 51, 63]. It was shown in Bassler D et al (2015) study that the administration of inhaled budesonide in the first day of life in extremely premature infants the frequency of BPD formation is reduced in comparison with infants receiving a placebo [10]. According to Onland *et al.* (2017), at present, topical administration of inhaled GCS, which are prescribed at the age of 7 days and older, cannot be recommended as a safe alternative to systemic GCS to protect BPD. To apply the requirements, additional research is needed [47].

However, according to Shah (2017), based on methanalysis, early administration of inhaled GCS does not have advantages over systemic GCS [68]. The use of surfactant preparations in SDR allows for ventilation under less severe regimens, and reduces the frequency of interstitial emphysema. Using the drugs Exosurf neonatal and Kurosurf in premature newborns during the first day of life allowed to reduce the concentration of oxygen in the inhaled mixture, the magnitude of peak pressure, reduce the frequency of barotrauma, reduce the duration of mechanical ventilation (by 30%), increase the survival rate of newborns with SDR by half in comparison with infants who did not receive surfactant-substituting drugs [22, 23, 28]. The most effective is the use of surfactant preparations in newborn infants before the implementation of RDS clinical symptoms [28, 53]. However, there is the evidence of a positive clinical effect of surfactant use in infants who were on medical ventilator for 7 and more days. Thus, the "later" administration of surfactant improved breathing mechanics, reduced inflammatory changes in the respiratory tract, reduced the frequency and severity of barotrauma [61]. Based on a meta-analysis Rutkowska *et al.* (2018) consider that the use of CPAP and the early introduction of surfactant are the key preventive measures [60]. Currently, the search for effective measures to prevent BPD continues. Sakurai R et al (2018) conducted a study of the combined use of a PPAR-γ-agonist pioglitazone with a synthetic pulmonary surfactant (a surfactant protein B peptide mimic, B-YL) via a nebulizer on a one-day- old Sprague-Dawley rat pups with induced BPD (animals were exposed to either 21 or 95% O_2). The drugs accelerated the maturation of the lungs and prevented lung damage caused by neonatal hyperoxia [62]. To prevent the development of BPD in preterm infants with a birth weight less than 1500 g and SDR, the effective use of mucolytic ambroxol in the first 5 days of life [64]. He positive pharmacological effect of the drug, apparently, is caused to the induction of the synthesis of surfactant by the alveolocytes of the second type [85].

Oxygenotherapy: Treatment, as well as prevention of BPD, is based on limiting the toxic effect of oxygen on the respiratory organs, preventing barotrauma, preventing and treating infectious and inflammatory complications of the bronchopulmonary system, and they also include symptomatic and pathogenetic treatment, sufficient provision of energy needs in infants [22, 26, 52]. ALV is one of the main factors contributing to the development of BPD. However, the maintenance of optimal gaseous exchange in infants with RDS, as well as VAP, against the background of which BPD develops, is usually not possible without use of ALV for a long time [26, 35, 74, 76]. While conducting mechanical ventilation, it is necessary to strive to reduce the oxygen concentration in the inspired air and a decrease in pressure during inhalation as much as possible. It is important to prevent the development of hypoxemia, since low PaO_2 values cause a spasm of pulmonary vessels and the development of pulmonary hypertension. In arterial blood analysis acceptable rates are the following: pH > 7.25-7.4; $PaCO_2$ 45-55 mm Hg.; PaO_2 55-70 mm Hg. Minimum PIP is used under control of tidal volume (4-6 ml / kg). If possible, reduce the "tough" ventilation modes as quickly as possible and transfer infants from the ventilator ALV [2, 14, 21, 26, 86]. Oxygen is the main element of therapy in the stage of formed BPD. It is necessary to maintain SaO_2 in the range of 88 to 92%, and in the stage of an emerging or formed BPD SaO_2 should be at least 90% (90-95%), when conducting artificial oxygenation in the acute phase of respiratory disorders [14, 26, 50]. Currently, an early NCPAP is used in the delivery room in newborns with with extremely low body mass (ELBW) and very low body mass (VLBW) if they have regular spontaneous respiration and heart rate (CR) above 100 beats / min. [14, 22, 23, 26, 50]. When conducting mechanical ventilation in the neonatal period, it is also necessary to ensure optimal temperature conditions (t° of skin is 36.8°C). The vibration and percussion massage of the chest and the airways clearance should be performed (removal of sputum from the endotracheal tube as it accumulates) to improve bronchial drainage function. It is necessary to maintain a hemoglobin level of at least 140 g / l and hematocrit is above 40% to ensure sufficient oxygen transport function of the blood. According to indications it is possible to carry out red blood cell transfusions [14, 22, 23, 50].

Nutrition: It is necessary to provide adequate energy kalorazh equal to 120-150 kcal / kg / day due to increased metabolic needs for respiratory failure in newborns. Parenteral nutrition has to be used in extremely premature babies for a long time with the introduction of amino acids at the rate of 2-3 g of protein per kg of body weight per day and fat emulsions starting from 0.5 g / kg of fat to 3.0 g / kg / day. Weight gain in infants at 10-30 g / day (up to 1% of body weight) indicates sufficient caloric intake. The adapted preparations of amino acids (for example, aminogen infantes or others) are used in combination with a lipid emulsion (for example, lipovenosis, intralipid); vitamin preparations for carrying out parenteral nutrition [22, 23, 26, 43, 45, 46]. Enteral nutrition is used adapted infant formula - breast milk substitutes in accordance with the age of the infant, as well as breast milk. To enhance the nutritional value of breast milk, it can be enriched with breast milk fortifier [11, 15]. Mixtures based on highly hydrated whey protein and containing medium-chain

triglycerides and polyunsaturated fatty acids are also used. [11, 15, 32, 83, 52].

Pharmacotherapy

a). Antibiotic therapy: BPD is a serious complication of mechanical ventilation in 10-65% of premature babies [22]. Microorganisms - pathogens cause inflammation, damage and destruction of the tissues of the respiratory system [14, 23, 43, 50, 80]. In this regard, conducting timely and adequate antibiotic therapy, taking into account etiological factors, reduces the frequency of BPD and the formation of a severe form of this complication. [12, 22, 23, 26, 35, 36, 57]. The causative agents of VAP in premature newborns are most often aerobic and elective gram-negative microorganisms (Enterobacteriaceae, Pseudomonas aerugimosa, Stenotrophomonas maltophilia), and their associations with mycoplasmas (Mycomlasma hominis, Ureaplasma urealiticum). Broad-spectrum antibiotics are recommended (III-IV generation cephalosporins, carbapenems, aminoglycosides) and macrolides (erythromycin) [14, 22, 36, 87]. The causative agents of VAP can also be gram-positive bacteria, such as Staphylococcus aureus, Enterococcus spp., Streptococcus group B. Most often vancomycin or linezolid are used for treatment in these cases [39, 40]. A number of researchers also point at the significance of Ureaplasma urealiticum in the formation of BPD. The effectiveness of azithromycin, claritomycin and, to a lesser extent, erythromycin in the prevention and complex treatment of this disease has been shown [19, 27, 72, 89].

b). Intravenous immunoglobulins (IVIG)**:** Being on mechanical ventilator, IVIG showed good effectiveness in the complex treatment of premature infants with SDR, complicated and uncomplicated pneumonia. Previously, the use of IVIG from 2 days of life in infants on "hard" regimes of mechanical ventilation has reduced infectious complications and formation BPD by 2.5 times, the duration of respiratory support is 2 times lower (from 13.6 to 6.8 days), the duration of mechanical ventilation in "hard" regimes is 1.7 times less (from 6.3 to 3.7 days), mortality is 1.9 times decreased (from 22.8 to 12.5%). Sepsis did not develop in the treatment of IVIG in any infant, while in infants who did not receive immunotherapy, sepsis was diagnosed in 11.4%. VAP was not the cause of death in infants who received IVIG (deaths occurred as a result of progression of obstructive hydrocephalus, which developed against the background of massive intraventricular hemorrhages). The purpose of IVIG in the acute period of PN (on the 5–9th day of the disease) also showed a positive effect: the incidence rate in BPD reduced (from 45.6 to 27.6%), the outcome in sepsis decreased by 1.9 times (from 11.4 up to 6.4%), and mortality is 2 times diminished (22.8 to 10.6%) in comparison with infants who did not receive IVIG [77]. The good clinical effect of IVIG is associated not only with its direct antimicrobial activity, but also with its immunomodulatory effects like opsonin. So, there was an increase in the phagocytosis of blood neutrophils in infants after a course of IVIG, normalization of neutrophil enzyme activity (acid and alkaline phosphatase, myeloperoxidase, NADP-oxidase) and an increase in lysozyme levels in tracheobronchial aspirates [78].

c). Anti-inflammatory medication. An important pathogenetic role belongs to inflammationi the development of BPD. n recent years, the possibility of using indomethacin for the prevention and treatment of BPD has been discussed. However, the effectiveness of this drug in babies with BPD has not yet been clearly proven and additional studies are required [12, 36, 43, 57, 80].

d) Mucolytics. Effective use of mucolytic drugs (acetylcysteine, ambroxol) is enterally or by inhalation. You can use a 20% solution of acetylcysteine for inhalation at a dose of 0.5 ml per inhalation 2-3 times a day [23].

e) GCS infusions. GCS is prescribed to infants with emerging (or formed) BPD in order to reduce pulmonary inflammation, edema, and reduce the level of proteolytic enzymes. Various courses of corticosteroid therapy are applied in practice. Dexamethasone is currently preferred [10, 14, 22, 26, 74, 47]. Our studies have shown a pronounced anti-inflammatory effect of dexamethasone. The introduction of this hormone in a dose of 0.5 mg / kg body weight intravenously in premature infants with bronchopulmonary dysplasia was accompanied after an hour by a decrease in the increased activity of blood elastase and the total proteolytic activity of the tracheobronchial aspirates 1.4-6 times in comparison with baseline. Taking into account the detected dynamics of neutrophil elastase activity, alpha-1 proteinase inhibitor (alpha-1 PI) in the blood and inhibitory activity of the tracheobronchial aspirates, we administered dexamethasone in premature infants with SDR who are on ALV 2 times a day with 12 hours' interval at a dose of 0.5-1 mg / kg / day the first 3-4 days with a decrease of 0.1-0.2 mg / kg / day every week for 4 weeks. When bronchopulmonary dysplasia is developed, it is effective to administer hormonal preparations of glucocorticosteroids (dexamethasone) from the second week of life intravenously 2 times a day (2 days) at a dose of 0.5 mg / kg then 0.3 mg / kg (2 days) and 0.1 mg / kg (2 days). In severe BPD, the course is repeated [25]. An alternate scheme of dexamethasone 0.075 mg / kg per dose every 12 hours for 3 days is also recommended. Then 0.05 mg / kg per dose every 12 hours for 3 days. Further 0.025 mg / kg per dose every 12 hours for 2 days and 0.01 mg / kg per dose every 12 hours for 1-2 days intravenously slowly [14]. Contraindications to the use of dexamethasone is the development of sepsis in infants with bronchopulmonary dysplasia and the presence of hemorrhagic syndrome [14].

f) **Inhibitors of proteinases**. An imbalance of the leukocyte elastase system and its inhibitors makes a definite contribution to the development of BPD. Proteolysis activity with SDR and VAP increases, which accompanies infectious inflammation and leads to destruction of lung tissue. High activity of elastase disrupts alveolar development at high concentrations of O_2 (85%) and plays an important role in violation of elastogenesis [15, 37]. The use of hypoxic mixtures of oxygen causes oxidation of the alpha-1 proteinase inhibitor, reduces its activity and increases the activity of leukocyte elastase - a pro-inflammatory factor that causes both the beginning of the inflammatory process and its maintenance [15]. During complication of the respiratory distress syndrome severe pneumonia, anti-protease drugs (proteinase inhibitor) such as gordox (aprotinin) at a dose of 10 thousand kallikrein inactivating units (RIU)is recommended to use in the complex treatment intravenously drip for at least 10 days. According to our data, the use of gordox was accompanied by a significant increase in the activity of proteinase inhibitors in the tracheobronchial aspirates, the indices of which were zero before the treatment [22]. Correction of the system of elastase -

proteinase inhibitors is also carried out by contrycal (aprotinin). Optimal prevention and treatment of BPD is the appointment of contrycal to infants from the high risk group (SDR of type I and VAP) at a dose of 1000 antitrypsin units (ATrU) / kg per day intravenously in 10% glucose solution at a rate of not more than 5 ml / hour for 5 - 6 days. The dose of contrycal gradually reduced within three days until the complete abolition of the drug. After that a short course of dexamethasone at a dose of 0.5 mg / kg twice a day (1 day), then 0.3 mg / kg (1 day) and 0.1 mg / kg (1 day) from the beginning of the second week of life [88]. The use of contrycal followed by a three-day course of dexamethasone reduced the severity of VAP, the duration of VAP was for 8 days, the duration of antibacterial therapy was for 7 days, the hospital stay was for 19 days, as well as the number of complications such as sepsis and BPD [88]. Follow-up observation of 30 infants with BPD of varying severity was performed at the age of 3, 6 and 12 months of life. The diagnosis of BPD was withdrawn at the age of one year of life in 12 infants (40%, the percentage of small numbers is given for comparison). The severity of BPD by the same year remained the same as at the time of discharge from the clinic (1.5-2.5 months) in 18 infants (60%). The most favorable outcome was observed in infants who received contrycal and a short course of dexamethasone [88]. It is also possible to use contrycal and a long course of the GCS. Namely, (I option) dexamethasone is prescribed intravenously from 12 to 14 days of life for 13-14 days according to the following scheme: 0.5 mg/kg 3 days, 0.3 mg/kg 3 days, 0.2 mg/kg 3 days, 0.1 mg/kg 4-5 days. The second variant of long-term hormone therapy consists of two stages. At the first stage, dexamethasone is administered intravenously for an average of 9 days from the second week of life, and at the second stage, due to obstructive syndrome – inhalation GCS (as a suspension of budesonide - Pulmicort) at a dose of 0.125 mg 2-3 times a day for a week [88]. In the future, it is possible to use recombinant human elafin (elastase inhibitor), which can be considered as a therapeutic agent to prevent human lung damage caused by O2. In the experiment, elafin was administered by intratracheal instillation to newborn mice. These animals were exposed to 85% O_2. Elafin inhibited elastase and the TGF-β1 signal cascade. The drug softened the structural disintegration that developed in hyperoxia-affected lungs. Elafin prevented the degradation of elastin, the influx of neutrophils into the respiratory tract and cell apoptosis [29].

g. Diuretics. Diuretics occupy the seventh place among prescribed drugs in the neonatal intensive care unit. The use of diuretics is necessary to optimize renal function and improve respiratory status. Their purpose is accompanied by accelerated resorption of pulmonary fluid, improved urine output and prevents fluid retention in the body [33]. In order to reduce interstitial edema and pulmonary vascular resistance, diuretic drugs are prescribed, such as furosemide at a dose of 0.5-1 mg / kg / day intravenously or enterally 1-2 times a week, veroshpiron is in the dosage 1.5-2 mg / kg / day enterally for 1-1.5 weeks. [23]. It is also recommended to use higher doses of diuretics (enteral dose of furosemide can be increased up to 2 / mg / kg / day) (dose of veroshpiron can be increased by 2 times: 2-4 mg / kg / day.) [14]. The liquid load should be also limited to 140 ml / kg / day. It is necessary to monitor the water-electrolyte state and ultrasound of the kidneys during the entire period of diuretic treatment.

h). Relief of bronchial obstruction syndrome (BOS). The use of caffeine is most effective for the relief of broncho-obstructive syndrome. Caffeine stimulates the respiratory center, it reduces the need for ventilatory equipment and mechanical ventilation and lung damage, it also reduces the frequency of BPD and the duration of oxygen dependence, and it accelerates extubation [65]. The mechanism of action of caffeine to prevent apnea occurs, apparently, due to the Central inhibition of adenosine receptors [1]. It is recommended to prescribe caffeine - benzoate at the rate of 20 mg / kg (loading dose) and 5 mg / kg (maintenance dose) [23]. However, it is preferable to use caffeine citrate [66, 71]. Its efficiency, portability, wide therapeutic index have made it a preferred medication among methylxanthines. Its therapeutic use in premature apnea, mechanical ventilation and BPD has turned caffeine citrate into a "silver bullet" in neonatology [71]. According to some authors, the use of caffeine citrate is effective and safe in terms of intellectual, motor and behavioral development [66]. There are recommendations to prescribe caffeine to all newborns weighing less than 1250 g who are on a ventilator from the first day of life. Caffeine is canceled when an infant reaches 33-34 weeks of age and in the absence of apnea. However, treatment with caffeine may be accompanied by side effects: tachycardia, tachypnea, tremor, excitation, convulsions, vomiting seldom [14]. In addition to caffeine, methylxanthines (euphyillin, theophylline) can be used, which, along with the bronchodilating effect, stimulate the respiratory center, being soft diuretics, improve the contractility of skeletal muscles and diaphragm. When prescribing theophylline, it is necessary to take into account the fact that prematurity and BPD are factors that reduce the clearance of this drug, and aminophylline may cause excessive tachycardia [14, 24, 66].

i) Pulmonary hypertension with BPD. Both early screening diagnosis of pulmonary hypertension in infants and proper treatment of infants are relevant [84]. Management of infants and young children with pulmonary hypertension is a new area of Pediatrics. Combination therapy with a multidisciplinary approach (intensive treatment of lung diseases, prevention of hypoxemic episodes, optimal nutrition, treatment with pulmonary vasodilators, treatment of cardiovascular abnormalities) can improve outcomes for these babies [38]. The formation of pulmonary hypertension is due to the abnormal development of blood vessels and remodeling of the blood vessels of the lungs. This leads to a decrease in the cross-sectional area of pulmonary vasculature. According to some authors, the optimal treatment approach includes O_2 saturation (with oxygen) from 91 to 95%, inhalation of nitric oxide, sometimes in combination with sildenafil, prostacyclin or endothelin-receptor antagonists [4, 43, 59, 81]. Thus, inhalation NO was used in 51 premature infants with early pulmonary arterial hypertension in the first two weeks of life. Most children responded well to treatment. Mortality has decreased with the use of NO lo 8% vs 13.3% in controls without treatment [67].

j) Treatment of hypertension in infants with BPD. Violations of the regulation of systemic pressure have been established in infants with BPD. Arterial hypertension was identified as a complication of BPD, which confirms its importance as a comorbid disease. The role of endothelial dysfunction in increasing systemic pressure has been established. It has been shown in special studies that 38% of arterial hypertension manifested at the age of 5 months. The average duration of therapy was 7 months. In patients who did

not receive therapy, hypertension resolved independently during the first 2 years of life [48].

k). Inhalation therapy for bronchial obstruction syndrome (BOS). Inhalation therapy of BOS in infants can be carried out in the acute period of pneumonia after removal from the ventilator in the conditions of supplemental oxygen therapy in the form of a subsidy of 30-60% oxygen (tent or mask) in the couveuse or beds. Beta-adrenergic alupent or terbutaline can be used for inhalation [14, 23, 26]. Currently, most authors prefer alberterol (salbutamol), specific beta-adrenomimetic in the form of inhalations of 0.5% solution of 0.02-0.05 ml or enterally at 0.15 mg / kg every 8 hours [6, 14, 88]. The drug salbutamol-ventolin in the form of nebula and pulmicort (budesonide) in the form of suspensions for inhalation (0.5 mg/ml) is also used for infants. These drugs are sequentially administered in one session. The course of inhalation ranges from 3 to 12 days. An inhalation session is usually carried out once a day. Two inhalations of drugs are allowed per day. Pulmicort and salbutamol can be used effectively and independently [7, 22]. The use of beta-adrenomimetics can be complicated by an adverse reaction in the form of excessive tachycardia [14, 22]. Berodual (beta-agonist and m-cholinomimetic) showed good effect during the treatment of BOS in infants with BPD [14]. Currently, it is also proposed to replace the system GCS in the first week of life with the appointment of inhalation GCS, which are introduced together with the surfactant [24]. Early use of surfactant in the nasal nCPAP system reduces the need for mechanical ventilation, miminizes the use of surfactant, but slightly reduces the incidence of BPD [17]. Along with this positive effect, there is a low level of pneumothorax in infants [21]. Also indicate a good effect of the combined use of pulmonary surfactant with budesonide for the prevention of BPD in infants with very low body weight and gestational age at birth less than 32 weeks [49]. The use of minimal invasive surfactant therapy using nCPAP in the first week of life is a gentle, safe and effective treatment in premature infants. The method involves the introduction of surfactant by intrapharyngeal instillation, spraying, laryngeal mask and thin catheter. However, further research is needed to apply this method. However, further research is needed to apply this method, to determine the indications, the choice of infants for treatment, determine the optimal dose, duration of treatment, the need for sedation [21, 70].

l). Antioxidants. Complex pharmacotherapy of BPD includes also the use of antioxidants: vitamins A and C [9, 12, 14, 22, 23, 75]. Good efficacy of quercetin is shown in the experiment on newborn mice with induced BPD [46]. The use of mexidol is promising for the treatment of neonatal pathology, including BPD. The positive clinical and antioxidant effect of Mexidol has been shown earlier in newborns with hypoxic-ischemic damage of the Central nervous system [5, 42].

Cell therapy: In recent years, many studies have been actively conducted to research the possible use of stem cells [55, 74], as well as extracts of stem cell exosomes for the treatment of BPD [16]. Good results have been obtained in various biological models of BPD (mice, rats, etc.), which opens up encouraging opportunities for the application of these approaches to the treatment of this disease [54]. Aerosol stimulating vascular growth and alveolization was effective in an experimental study [18].

The first reports on the effectiveness of stem cell use in the clinic also appeared [34, 67, 68, 69]. However, there are still many research steps to study the effectiveness and safety of this type of treatment. In this regard, already known pharmacotherapy BPD will find its application for a long time [12, 34].

Conclusion

Given the multifactor and variability of the clinical course of BPD and its complications in infants, the treatment of the disease should be complex. In addition to oxygen therapy, it should include anti-inflammatory and antibacterial treatment, sparing prescription of GCS. It is also advisable to use antioxidants, proteinase inhibitors, drugs for the relief of apnea, diuretics. When prescribing pharmacotherapy, it is necessary to take into account the severity of the disease, the development of complications, the tolerance of drugs, the therapeutic response of the infant's body to treatment.

REFERENCES

1. Abu-Shaweesh JM, Martin RJ. Caffeine use in the neonatal intensive care unit. *Semin Fetal Neonatal Med.,* 2017 Oct;22;5::342-347. doi: 10.1016/j.siny.2017.07.011. Epub 2017 Aug 8.
2. Al-Hathlol K, Bin Saleem N, Khawaji M, Al Saif S, Abdelhakim I, Al-Hathlol B, Bazbouz E, Al Anzi Q, Al-Essa A. Early extubation failure in very low birth weight infants: Clinical outcomes and predictive factors. *J Neonatal Perinatal Med.,* 2017;10:2:163-169. doi: 10. 3233/NPM-171647.
3. Allen J, Zwerdling R, Ehrenkranz R. et al. American Thoracic Society. Statement on the care of the child with chronic long disease of infancy and childhood. Am J Respir Crit Care Med 2003; 168: 1723-1729.
4. Ambalavanan N, Mourani P. Pulmonary hypertension in bronchopulmonary dysplasia. *Birth Defects Res A Clin Mol Teratol.,* 2014; 100:3:240-6. doi: 10.1002/bdra.23241. Epub 2014 Mar
5. Askerova JM. Application of Mexidol in newborns with intrauterine growth retardation syndrome in the correction of hypoxic-ischemic lesions of the Central nervous system. Successes of modern natural science (Uspekhi sovremennogo estestvoznanija) 2011; 5: 50-52URL: (In Russ) http://natural-sciences.ru/ru/article/view?id=21457
6. Balashova ED, Dementieva GM, Kushnareva MV, Kuznetsova LK, Vitushko SA, Rksenov AN. Clinical efficacy of nebulizer therapy with salbutamol in combination with budesonide in the newborn with ventilator-associated pneumonia in the presence of bronchial obstructive syndrome. Rossiyskiy Vestnik Perinatologii i Pediatrii (Russian Bulletin of Perinatology and Pediatrics) 2008; 53:1:31-36 Rossiyskiy Vestnik Perinatologii i Pediatrii (Russian Bulletin of Perinatology and Pediatrics) 2008; 53:1:31-36. (In Russ).
7. Balashova ED, Dementieva GM, Keshishyan EU, Kushnareva MV, Marhulia HM. Frolova MI, Kuznetsova LK et al. Nebulizer therapy in neonotai infants with pneumonia complicated by bronchoobstructive syndrome. Rossiyskiy Vestnik Perinatologii I Pediatrii (Russian Bulletin of Perinatology and Pediatrics) 2012; 57:2:24-30. (In Russ).
8. Bancalari E, Claure N, Sosenco IRS. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition Semin Neomatol., 2003; 8: 63-71.
9. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med.,* 2007; 357: 1946-1955. https://www.ncbi.nlm.nih.gov/pubmed/30737034
10. Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau PH, Carnielli V. et al. NEUROSIS Trial Group. Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia.

N Engl J Med., 2015; 373: 16: 1497-506. doi: 10.1056/NEJMoa1501917.
11. Bhandari V. Postnatal inflammation in the pathogenesis of bronchopulmonary dysplasia. Birth Defects Res A Clin Mol Teratol. 2014; 100:3; 189-201. doi: 10.1002/bdra. 23220. Epub 2014 Feb 27. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4023567/
12. Bhandari V, Gruen JR, Jang KL, Göpel W, Hallman M, Lavoie PM. Genetics of bronchopulmonary dysplasia: When things do not match up, it is only the beginning. J Pediatr. 2019; Feb 5. pii: S0022-3476(19)30034-4. doi: 10.1016/j.jpeds.2019.01.014. [Epub ahead of print], PMID: 30737034 DOI: 10.1016/j.jpeds.2019.01.014
13. Bohin S., Field D. J The epidemiology of neonatal respiratory disease. Early Human Deevelopment 1994; 37: 73–90.
14. Bronchopulmonary dysplasia. Scientific and practical program. Moscow; Publishing house of the Russian respiratory society. 2012; 81. (In Rus).
15. Chakraborty M, McGreal EP, Williams A, Davies PL, Powell W, Abdulla S, Voitenok NN, Hogwood J, Gray E, Spiller B,Chambers RC, Kotecha S. Role of serine proteases in the regulation of interleukin-877 during the development of bronchopulmonary dysplasia in preterm ventilated infants. PLoS One. 2014 Dec 4;9:12:e114524. doi: 10.1371/journal.pone.0114524. eCollection 2014. https://www.ncbi.nlm.nih.gov/pubmed/25474412
16. Chaubey S, Thueson S, Ponnalagu D, Alam MA, Gheorghe CP, Aghai Z, Singh H, Bhandari V. Early gestational mesenchymal stem cell secretome attenuates experimental bronchopulmonary dysplasia in part via exosome-associated factor TSG-6. Stem Cell Res Ther. 2018 Jun 26;9:1::173. doi: 10.1186/s13287-018-0903-4. https://www.ncbi.nlm.nih.gov/pubmed/29941022
17. Celik M, Bulbul A, Uslu S, Dursun M, Guran O, Kıray Bas E, Arslan S, Zubarioglu U. A comparison of the effects of invasive mechanic ventilation/surfactant therapy and non-invasive nasal-continuous positive airway pressure in preterm newborns. J Matern Fetal Neonatal Med. 2017 Aug 31:1-7. doi: 10.1080/14767058.2017.1367380.
18. Chen Y, Gao S, Yan Y, Qian J, Chen H. Aerosolized deferoxamine administration in mouse model of bronchopulmonary dysplasia improve pulmonary development. Am J Transl Res. 2018; 10:1:325-332. eCollection 2018.https://www.ncbi.nlm.nih.gov/pubmed/29423017
19. Choi CW . Chorioamnionitis: Is a major player in the development of bronchopulmonary dysplasia? Korean J Pediatr 2017;60:7:203-207. doi: 10.3345/kjp.2017.60.7.203. Epub 2017 Jul 31.
20. Collaborative Study Group for Respiratory Distress Syndrome in Preterm Infants. Effect of antenatal corticosteroids therapy on the mortality and morbidity of small for gestational age infants born at 24-34 completed weeks: a retrospective multicenter stud]. [Article in Chinese; Abstract available in Chinese from the publisher]. Zhonghua Er Ke Za Zhi. 2017; 2;55:8:613-618. doi: 10.3760/cma.j.issn.0578-1310.2017.08.013.
21. Dargaville PA, Ali SKM, Jackson HD, Williams C, De Paoli AG. Impact of Minimally Invasive Surfactant Therapy in Preterm Infants at 29-32 Weeks Gestation. Neonatology. 2017 Sep 19;113(1):7-14. doi: 10.1159/000480066.
22. Dementieva GM. Bronchopulmonary dysplasia in newborns. In the book: "A guide to pharmacotherapy in pediatrics and pediatric surgery." Under the general editorship of AD Tsaregorodtsev and VA Tabolin; Volume 4 "Neonatology"; under the editorship of GM Dementieva and NN Volodin; Moscow; Medpraktika-M: 2004: 46-51. (In Rus).
23. Dementieva GM, Kushnareva MV, Ryumina II, Zhitova EP, Vetrova EV. Prevention and treatment of bronchopulmonary dysplasia in premature infants with a high degree of immaturity (manual for doctors). Ed. Ministry of health of the Russian Federation; Moscow; 2000: 12. (In Rus).
24. Doyle LW, Cheong JLY. Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia - Who might benefit Semin Fetal Neonatal Med. 2017;2:5::290-295. doi: 10.1016/j.siny.2017.07.003. Epub 2017 Jul 19.
25. Efimov M. S., Kushnareva, M. V., Zagashtokova A.Kh., Savelieva, R. G., Zhogin S. I. Effect of glucocorticosteroids on the activity of elastase - inhibitory system of blood and respiratory tract in premature infants with bronchopulmonary dysplasia. Questions of gynecology, obstetrics and Perinatology 2010; 9: 3: 42-46 (In Rus). http://www.phdynasty.ru/katalog/zhurnaly/voprosy-ginekologii-akusherstva-i-perinatologii/2010/tom-9-nomer-3/10180
26. Federal clinical guidelines for the management of children with bronchopulmonary dysplasia. Moscow, Publishing house of the Union of pediatricians of Russia. 2014: 31. (In Rus).
27. Gancia P, Delogu A, Pomero G. Ureaplasma and bronchopulmonary dysplasia. Early Hum Dev. 2014; Mar;90 Suppl 1:S39view/209/249-41. doi: 10.1016/S0378-3782(14)70013-1. https://www.ncbi.nlm.nih.gov/pubmed/24709455
28. Grebennikov VA, Milenin OB, Ryumina II. Respiratory distress syndrome in newborns. Replacement therapy with synthetic surfactant EXOSURF NEONATAL Moscow; Ed. “Bulletin of medicine", 1995: 136. (In Rus).
29. Han W, Li X, Zhang H, Yu B, Guo C, Deng C. Recombinant human elafin promotes alveologenesis in newborn mice exposed to chronic hyperoxia. Int J Biochem Cell Biol. 2017 ;92:173-182. doi: 10.1016/j.biocel.2017.08.004. https://www.ncbi.nlm.nih.gov/pubmed/28802561
30. Hitzert MM, Roescher AM, Bos AF. The quality of general movements after treatment with low-dose dexamethasone in preterm infants at risk of bronchopulmonary dysplasia. Neonatology. 2014;106; 3:222-8. doi: 10.1159/000362919. Epub 2014 Jul 5. https://www.ncbi.nlm.nih.gov/pubmed/ 25012880
31. Jain D, Bancalari E. Bronchopulmonary dysplasia: clinical perspective. Birth Defects Res A Clin Mol Teratol. 2014; 100: 3:134-44. doi: 10.1002/bdra.23229. Epub 2014 Feb 27.https://www.ncbi.nlm.nih.gov/pubmed/?term=Jain+D%2C+2014%2C++bronchopulmonary+dysplasia
32. Ji FJ, Yin Y, Xu J, Zhao LX, Zhou YJ, Zhu L. Early postnatal application of glucocorticoids for preventing bronchopulmonary dysplasia in preterm infants: a Meta analysis. Zhongguo Dang Dai Er Ke Za Zhi. 2017; 19: 6: 638-645. https://www.ncbi.nlm.nih.gov/pubmed/28606229
33. Johnson AK, Lynch N, Newberry D, Jnah AJ. Impact of Diuretic Therapy in the Treatment of Bronchopulmonary Dysplasia and Acute Kidney Injury in the Neonatal Population. Adv Neonatal Care. 2017 Oct;17;5:337-346. doi: 10.1097/ANC.0000000000000427.
34. Kang M, Thébaud B. Stem cell biology and regenerative medicine for neonatal lung diseases. Pediatr Res. 2018;83;1-2:291-297. Epub 2017 Oct 18. 2017 Oct 18. doi: 10.1038/pr.2017.232. https://www.pubfacts.com/detail/28922348/Stem-cell-biology-and-regenerative-medicine-for-neonatal-lung-diseases
35. Koch A, Kreutzer K, von Oldershausen G, Poets CF, Bassler D; NEuroSIS Trial Group. Inhaled Glucocorticoids and Pneumonia in Preterm Infants: Post Hoc Results from the NEuroSIS Trial. Trials. 2018; 19: 1: 178. doi: 10.1186/s13063-018-2505-y.
36. Kolls JK.Commentary: Understanding the Impact of Infection, Inflammation and Their Persistence in the Pathogenesis of Bronchopulmonary Dysplasia. Front Med (Lausanne). 2017 Mar 2;4:24. doi: 10.3389/fmed.2017.00024. eCollection 2017.
37. Kravtsova A. G., Kushnareva, M. V.. Efimov M. S., Dulenkov A. B., Chabaidze Zh.D. Activity of the elastase-inhibitor system for nosocomial pneumonia in premature infants on artificial ventilatie of the lungs. Questions of gynecology, obstetrics and Perinatology. 2005: 4: 5-6: 13-17. (In Rus).
38. Kumar VHS. Diagnostic Approach to Pulmonary Hypertension in Premature Neonates. Children (Basel). 2017 Aug 24;4(9). pii: E75. doi: 10.3390/children4090075.

39. Kushnareva M.V., Dementyeva G.M., Gerasimov A.Y. The clinical and microbiological efficacy of vancomycin in the combination treatment of newborns with ventilator-associated pneumonia caused by gram-positive cocci. Rossiyskiy Vestnik Perinatologii i Pediatrii (Russian Bulletin of Perinatology and Pediatrics). 2014;59:2::71-77. https://www.ped-perinatology.ru/jour/article/
40. Kushnareva M.V., Gerasimov A.Y., Dementieva G.M., Keshishian E.S., Okuneva T.S. Combination treatment for ventilator-associated pneumonia in neonatal infants. Rossiyskiy Vestnik Perinatologii i Pediatrii (Russian Bulletin of Perinatology and Pediatrics). 2016;61:2::92-99. (In Russ.) https://doi.org/10.21508/1027-4065-2016-61-2-92-99;
41. Kusuda S. Morbidity and mortality of infants with very low birth weight in Japan: center variation. Pediatrics 2006; 118:1130–1138.
42. Levitina E. V., Petrushina A. D. Pathogenetic substantiation of Mexidol application in treatment of hypoxic-ischemic encephalopathy in newborn children. Russian pediatric journal (Russkiyi pediatricheskiyi zhurnal) 2001; 6: 4-8. (In Russ).
43. Leroy S. Caumette E, Waddington C, Hébert A, Brant R, Lavoie PM. A Time-Based Analysis of Inflammation in Infants at Risk of Bronchopulmonary Dysplasia. J Pediatr. 2018 Jan;192:60-65.e1. doi: 10.1016/j.jpeds.2017.09.011. Epub 2017 Oct 31. https://www.ncbi.nlm.nih.gov/pubmed/29092751
44. Lyu C, Qu Y, Mu DZ. Research advances in immune tolerance of allogeneic cell transplantation in preterm infants Zhongguo Dang Dai Er Ke Za Zhi. 2018; 20: 4::338-340.[Article in Chinese]
45. Martin CR, Redshaw M. Establishing a coherent and replicable measurement model of the Edinburgh Postnatal Depression Scale. Psychiatry Res. 2018:264:182-191. doi: 10.1016/j.psychres.2018.03.062. Epub 2018 Mar 23. https://www.ncbi.nlm.nih.gov/pubmed/29649675
46. Maturu P, Wei-Liang Y, Androutsopoulos VP, Jiang W, Wang L, Tsatsakis AM, Couroucli XI Quercetin attenuates the hyperoxic lung injury in neonatal mice: Implications forBronchopulmonary dysplasia (BPD). Food Chem Toxicol. 2018; Apr;114:23-33. doi: 10.1016/j.fct.2018.02.026. Epub 2018 Feb 9. . https://www.ncbi.nlm.nih.gov/pubmed/29432836
47. Onland W, Offringa M, van Kaam A. Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2017; 24:8:CD002311. doi: 10.1002/14651858.CD0023 11.pub4
48. Ovsyannikov D.Y., Strutynskaya A.D., Karnaushkina M.A., M.G. Kantemirova M.G.. Arterial hypertension in children with bronchopulmonary dysplasia. Pediatria. 2017; 96: 1: 117–122 (In Rus). https://pediatriajournal.ru/files/upload/mags/356/2017_1_4830.pdf
49. Pan J, Chen MW, Ni WQ, Fang T, Zhang H, Chen Y, Pan JH. Clinical efficacy of pulmonary surfactant combined with budesonide for preventingbronchopulmonary dysplasia in very low birth weight infants**.** Zhongguo Dang Dai Er Ke Za Zhi. 2017; 19;2:137-141. [Article in Chinese]
50. Panchenko AS, Gaymolenko IN, Ignat'eva AV. Bronchopulmonary dysplasia in children: risk factors, immunological and biochemical markers. Pulmonology. 2015; 25: 1: 86-92. (In Rus). DOI:10.18093/0869-0189-2015-25-1-86-92. https://www.volgmed.ru/uploads/files/2013-4/18298-bronholyogochnaya_displaziya_u_detej_nauchno-prakticheskaya_programma_rro_raspm_2012_www_raspm_ru.pdf
51. Poets CF, Lorenz L. Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: current evidence. Arch Dis Child Fetal Neonatal Ed. 2018; 103: 3: F285-F291. doi: 10.1136/archdischild-2017-314264. Epub 2018 Jan 23.
52. Poindexter BB, Martin CR. Impact of Nutrition on Bronchopulmonary Dysplasia. Clin Perinatol. 2015; 42: 4::797-806. doi: 10.1016/j.clp.2015.08.007. Epub 2015 Oct 2. PMID: 26593079 DOI: 10.1016/j.clp.2015.08.007
53. Principles of management of newborns with respiratory distress syndrome. Guidelines. Ed. N. N. Volodin. Moscow; Medicina: 1997; 66. (In Rus). http://metodich.ru/vedenie-novorojdennih-s-respiratornim-distress-sindromom/index.html
54. Precision Medicine, CRISPR, and Genome Engineering: Moving from Association to Biology and Therapeutics - Editors: S.H.T sang**,** **(**Ed.) Tsang S.H. 2017: 178. Published by Springer International Publishing. https://www.springer.com/us/book/9783319639031#aboutBook available fromj 25.11.17 1
55. Progenitor and Stem Cell Technologies and Therapies. Anthony Atala (ed): Woodhead Publishing 2012: 483. https://play.google.com/store/books/details/Anthony_Atala_Perinatal_Stem_Cells?id=x-JgDwAAQBAJ
56. Qin G, Lo JW, Marlow N, Calvert SA, Greenough A, Peacock JL. Postnatal dexamethasone, respiratory and neuro developmental outcomes at two years in babies born extremely preterm. PLoS One. 2017; 19: 12:7: :e0181176. doi: 10.1371/journal.pone.0181176. eCollection 2017 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181176.
57. Reese J, Shelton EL, Slaughter JC, McNamara PJ. Prophylactic Indomethacin Revisited**.** J Pediatr. 2017 Jul; 186:11-14.e1. doi: 10.1016/j.jpeds.2017.03.036. Epub 2017 Apr 7.
58. Rennie JM, Roberton NR. A Manual of Neonatal Intensive Care. Oxford University Press, 2002; Ch. 12. Chronic lung disease.: 204–214.
59. Rossor T, Greenough A. Advances in paediatric pulmonary vascular disease associated with bronchopulmonary dysplasia. Expert Rev Respir Med. 2015; 9:1::35-43. doi: 10.1586/17476348.2015.986470. Epub 2014 Nov 26. https://www.ncbi.nlm.nih.gov/pubmed/25426585
60. Rutkowska M, Hożejowski R, Helwich E, Borszewska-Kornacka MK, Gadzinowski J. Severe bronchopulmonary dysplasia - incidence and predictive factors in a prospective, multicenter study in very preterm infants with respiratory distress syndrome. J Matern Fetal Neonatal Med. 2018; Jan 15:1-7. doi: 10.1080/14767058.2017.1422711. https://www.ncbi.nlm.nih.gov/pubmed/29295665,
61. Ryndin AYu, Antonov AG. Method of prevention of bronchopulmonary dysplasia in infants with very low and extremely low birth weight. The patent for the invention №2416388. It is registered in the State register of inventions of the Russian Federation on April 20, 2011. Priority of the invention 26 August 2009. (In Rus)
62. Sakurai R, Lee C, Shen H, Waring AJ, Walther FJ, Rehan VK. A Combination of the Aerosolized PPAR-γ Agonist Pioglitazone and a Synthetic Surfactant Protein B Peptide Mimic Prevents Hyperoxia-Induced Neonatal Lung Injury in Rats. Neonatology. 2018;113:4:296-304. doi: 10.1159/000486188. Epub 2018 Feb 9. https://www.ncbi.nlm.nih.gov/pubmed/?term=Sakurai+R+et+al+(2018)
63. Shinwell ES. Are inhaled steroids safe and effective for prevention or treatment of bronchopulmonary dysplasia? Acta Paediatr. 2018; 107:4:554-556. doi: 10.1111/apa.14180. Epub 2017 Dec 26.
64. Schmalisch G, Waner RR, Bohme B. Changes in pulmonary function in preterm infants recovering from RDS following early treatment with ambroxol: results of a randomized trial. Pediatr Pulmono. 1999; 27: 2: 104-112.
65. Schmidt B. Caffeine Therapy for Apnea of Prematurity. New Engl J Med 2006; 354: 2112-2121.
66. Schmidt B, Roberts RS, Anderson PJ, Asztalos EV, Costantini L, Davis PG. et al. Caffeine for Apnea of Prematurity (CAP) Trial Group. Academic Performance, Motor Function, and Behavior 11 Years After Neonatal Caffeine Citrate Therapy for Apnea of Prematurity: An 11-Year Follow-up of the CAP Randomized Clinical Trial. JAMA Pediatr. 2017;171:6::564-572. doi: 10.1001/jamapediatrics.2017.0238.
67. Seth SA, Soraisham AS, Harabor A. Risk factors and outcomes of early pulmonary hypertension in preterm infants. J Matern Fetal Neonatal Med. 2017 Aug 21:1-6. doi: 10.1080/14767058.2017.1365129
68. Shah SS, Ohlsson A, Halliday HL, Shah VS. Inhaled versus systemic corticosteroids for preventing bronchopulmonary dysplasia in ventilated very low birth weight preterm neonates.

Cochrane Database Syst Rev. 2017; Oct 17;10:CD002058. doi: 10.1002/14651858.CD002058.pub3. [Epub ahead of print]
69. Simones AA, Beisang D, Panoskaltsis-Mortari A, Roberts KD Panoskaltsis-Mortari a mesenchymal stem cells in the pathogenesis and treatment of bronchopulmonary dysplasia: a clinical review. Pediatr Res. 2018 Jan;83(1-2):308-317. doi: 10.1038/pr.2017.237. Epub 2017 Oct 25. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5895100/
70. Shim GH. Update of minimally invasive surfactant therapy. Korean J Pediatr. 2017; 60:9:273-281. doi: 10.3345/kjp.2017.60.9.273. Epub 2017 Sep 21.
71. Shrestha B, Jawa G. Caffeine citrate - Is it a silver bullet in neonatology? Pediatr Neonatol. 2017;58:5:391-397. doi: 10.1016/j.pedneo.2016.10.003. Epub 2017 Mar 27.
72. Silwedel C, Speer CP, Glaser K. Ureaplasma-associated prenatal, perinatal, and neonatal morbidities. Expert Rev Clin Immunol. 2017;13:1:1073-1087. doi: 10.1080/1744666X.2017.1381559. Epub 2017 Sep 23.
73. Stelmashuck TV, Matysina NB, Belkina AV, Leonova IV. Analysis of perinatal pathology in preterm very low birth weight. Practical Pediatrics (Voprosi prakticheskoji pediatrii). 2010; 5 (Suppl. 1): 79. (In Rus)
74. Strueby L, Thébaud B. Advances in bronchopulmonary dysplasia. Expert Rev Respir Med. 2014; 8: 3: 327-38. doi: 10.1586/17476348.2014.899907. Epub 2014 Mar 26. https://www.ncbi.nlm.nih.gov/pubmed/24666156
75. Strueby L, Thébaud B. Novel therapeutics for bronchopulmonary dysplasia. Curr Opin Pediatr. 2018; 30:3:378-383. doi: 10.1097/MOP.0000000000000613. https://www.ncbi.nlm.nih.gov/pubmed/29465463
76. Thomas W., Speer CO. Universitats-Kinderklinik Wurzberg. Bronchopulmonale Dysplasie Fruehgeborener Epidemiologie, Pathogenese und Therapie. Monatsschrift Kinderheilkd;2005: 153: 211–219.
77. Vetrova E.V., Kushnareva M.V., Kubrin A.V. The effect of standard preparations of immunoglobulins for intravenous administration on the phagocytic activity of blood neutrophils in premature newborns with IUVL-associated pneumonia. Vestnik pediatoricheskoy farmakologii i nutritsiologii. 2007: 4: 3: 51-57 (Bulletin of Pediatric Pharmacology and Nutriciology. 2007: 4: 3: 51-57). (In Russ).
78. Vetrova E.V., Kushnareva M.V., Kubrin A.V. Local immunity of the respiratory tract and correction of immunoglobulin disorders for intravenous administration in premature newborns with ventilator-associated pneumonia. Vestnik pediatoricheskoy farmakologii i nutritsiologii. 2007: 4:4: 5 (Bulletin of Pediatric Pharmacology and Nutriciology. 2007: 4: 4: 5. (In Russ).
79. Volodin NN, Degtyareva MV, Kushnareva MV, Vetrova EV. In the book .: Pharmacotheraphy of childhood. Guide for doctors. " Edited by AD Tsaregorodtsev, Izd. Medical information agency. Moscow; 2010: 18-30. (In Russ) http://patrick-book.ru/farmakoterapiya_detskih_bolezney_ru, https://www.mmbook.ru/index.php?plugin=jklibs&file=UGhhcm1ha290ZXJhcGl5YS1kZXRza2l4LWJvbGV6bmV5LnBkZg==Qchnm&download=1
80. Wang C, Jiang ZD. Brainstem auditory abnormality in extremely premature babies and the impact of neonatal bronchopulmonary dysplasia. Acta Obstet Gynecol Scand. 2018;97:5:545-551. doi: 10.1111/aogs.13312. Epub 2018 Feb 23. https://www.ncbi.nlm.nih.gov/pubmed/29381192
81. Wardle AJ, Connolly GM, Stonier T, Tulloh R. Sildenafil in bronchopulmonary dysplasia: safe to use? Arch Dis Child Fetal Neonatal Ed. 2015 Jul;100(4):F369. doi: 10.1136/archdischild-2015-308164. Epub 2015 Feb 25. https://www.ncbi.nlm.nih.gov/pubmed/25716676
82. Wauer .R. Morbidität und Mortalität in der Neugeborenen- und Säuglingsperiode — Grundlagen für die molekulare Epidemiologie in der Neonatologieю. In: Molekularmedicziniche Grundlagen von fetalen und neonatalen Erkrankungen. Editors: Ganten D, Ruckpaul K, Wauer RR., (Hrag.) Shpringer-Verlag, Heidenberg. 2005; 72: 49-80.
83. Wilson-Costello D, Walsh MC, Langer JC, Guillet R, Laptook AR, Stoll BJ et al. Impact of postnatal corticosteroid use on neurodevelopment at 18 to 22 months' adjusted age: effects of dose, timing, and risk of bronchopulmonary dysplasia in extremely low birth weight infants. Pediatrics 2009; 123: e430–e437 doi:10.1542/peds.2008-1928
84. Youn Y, Moon CJ, Lee JY, Lee C, Sung IK**.** Timing of surgical ligation and morbidities in very low birth weight infants. 2017 Apr;96(14):e6557. doi: 10.1097/MD.0000000000006557.
85. Yu Q, Lian JM, Li JQ. Efficacy of intravenous or atomizing ambroxol for prevention of respiratory distress syndrome in preterm infants. ZhongguoDangDaiErKeZaZhi: 2006; 8: 4: 301-303.
86. Zagashtokova AH, Kushnareva MV, Efimov MS, Kravtsova AG. Activity of the elastase-inhibitor system in infectious and non-infectious lung pathology in premature infants with extremely low body weight. Questions of gynecology, obstetrics and perinatology. Voprosy ginekologii, akusherstva i perinatologii (Questions of gynecology, obstetrics and perinatology) 2009;8:6:58-61. http://www.phdynasty.ru/katalog/zhurnaly/voprosy-ginekologii-akusherstva-i-perinatologii/2009/tom-8-nomer-6/10690
87. Zagashtokova A.Kh., Efimov M.S., Kushnareva M.V. The etiological structure of nosocomial pneumonia complicated by bursonchopulmonary dysplasia in premature infants with extremely low body weight. Materials of reports of the VIII Russian Congress "Modern technologies in pediatrics and pediatric surgery". Moscow, 2009: 156 (In Russ).
88. Zagashtokova A.Kh.The Influence of corticosteroids and kontrikal on proteolytic activity and its inhibitors in bronchopulmonary dysplasia in preterm infant". Thesis abstract of candidate of medical Sciences, Moscow, 2010: 25. (In Rus). http://medical-diss.com/medicina/vliyanie-glyukokortikosteroidov-i-kontrikala-na-aktivnost-proteoliza-i-ego-ingibitorov-pri-bronholegochnoy-displazii-u-ne#ixzz5qFcGHpsM; http://medical-diss.com/medicina/ vliyanie-glyukokortikosteroidov-i-kontrikala-na-aktivnost-proteoliza-i-ego-ingibitorov-pri-bronholegochnoy-displazii-u-ne
89. Zheng XD, Li D, Yang DH, Xiang X, Mei H, Pu JR. et al. Association of Ureaplasma urealyticum colonization with development ofbronchopulmonary dysplasia: a systemic review and meta-analysis. J Huazhong Univ Sci Technolog Med Sci. 2014 Apr;34(2):265-9. doi: 10.1007/s11596-014-1269-1. Epub 2014 Apr 8. https://www.ncbi.nlm.nih.gov/pubmed/24710943

****