



Turkish Neonatal Society guideline on prevention and management of bronchopulmonary dysplasia

Türk Neonatoloji Derneği bronkopulmoner displazi korunma ve izlem rehberi

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Abstract

Scientific and technological advances in perinatology and neonatology have led to an increased rate of survival and decreased incidences of various neonatal morbidities. However, the incidence of bronchopulmonary dysplasia has remained almost the same for years in very-low-birth-weight preterm infants. Although bronchopulmonary dysplasia is the leading cause of chronic respiratory morbidity in small preterms, no substantial improvement has been achieved in prevention and treatment strategies to date. Currently, postnatal very-low-dose corticosteroids, caffeine, and vitamin A seem to be the drugs of choice, and stem cell therapy appears to be the most promising treatment modality for the future. In this guideline, which was prepared by the Turkish Neonatal Society, recent evidence-based recommendations for the prevention and treatment of bronchopulmonary dysplasia are summarized.

Keywords: Bronchopulmonary dysplasia, guideline, prevention, treatment

Öz

Neonatoloji ve perinatoloji alanındaki bilimsel ve teknolojik gelişmeler çok düşük doğum ağırlıklı prematüre bebeklerde sağkalımı arttırmış ve birçok yenidoğan hastalığının sıklığını azaltmış olmasına rağmen bronkopulmoner displazi sıklığında önemli bir değişim olmamıştır. Bronkopulmoner displazi günümüzde prematüre bebeklerde görülen en önemli kronik solunumsal morbiditedir ve ne yazık ki son 20 yılda korunma ve tedavi yaklaşımlarında önemli bir gelişme olmamıştır. Günümüzde bronkopulmoner displazi korunma ve tedavisinde doğum sonrası çok düşük doz yeni steroid ilaç tedavileri, kafein ve vitamin A ön planda olmakla birlikte gelecekte kök hücre tedavileri önem kazanacak gibi görünmektedir. Türk Neonatoloji Derneği tarafından hazırlanan bu rehber ile ülkemizde yenidoğan sağlığı ile uğraşan hekimlerin bronkopulmoner displazi konusunda güncel ve kanıta dayalı bilimsel veriler eşliğinde, standart tanı, korunma ve tedavi yaklaşımlarında bulunmalarını, etkisiz ya da olumsuz yaklaşımlardan kaçınmalarını sağlamak amaçlanmıştır.

Anahtar sözcükler: Bronkopulmoner displazi, korunma, rehber, tedavi

Introduction

A significant reduction has been observed in the prevalences of sepsis, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) in preterm infants born with a low gestational age due to many novel medical approaches pertinent to preterm infant care. However, nearly no reduction in the prevalence of bronchopulmonary dysplasia (BPD) has been observed. Currently, the fact that the chance of survival of preterm babies born with gradually decreasing

gestational ages has increased with these novel approaches has rendered BPD an unavoidable morbidity considering the disease pathogenesis.

Bronchopulmonary dysplasia was defined by Northway et al. (1) for the first time 50 years ago, and in that period, it was perceived as a chronic lung disease characterized by fibrosis of relatively older preterm babies who were mostly intubated due to respiratory distress syndrome (RDS) and received conventional ventilation support.

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Currently, it is considered as a 'new' condition reflecting an arrest of the pulmonary alveolar and vascular development of relatively smaller preterms born at earlier gestational weeks.

In accordance with the currently valid definition, the diagnosis of BPD is made in the postmenstrual (PM) 36th week. 'Treatment' is a concept that can only be used after the diagnosis of a disease is made. In fact, many approaches, which are in question for bronchopulmonary dysplasia, carry the potential to reduce the risk of BPD and the disease severity when applied before the PM 36th week, which is the diagnosis time. Therefore, there is a requirement for a guideline for practices that would provide prevention rather than treatment.

Subjects with BPD who have mild and moderate clinical severity according to the current definition are not serious enough to require respiratory support after discharge and respiratory system morbidities do not create a significant long-term follow-up problem. Accordingly, scientific research and new BPD guidelines to be developed should better focus on preterm babies who are candidates for severe-fatal BPD.

There are some special national problems related to BPD in Turkey. The most significant ones are as follows:

- Widespread use of assisted reproduction techniques, adolescent pregnancies (child brides) and encouragement to have multiple children make it difficult to maintain the principle of prevention of preterm deliveries.
- There is no consensus on antenatal steroid treatment and the application frequency varies.
- The possibility of chorioamnionitis is being ignored in preterm deliveries and the diagnosis and treatment protocols show variance.
- The quality and number of the teams in charge of stabilization of small preterm babies in the delivery room and their medical approaches vary tremendously.
- Most small preterm babies who carry a risk for bronchopulmonary dysplasia still exit the delivery room as intubated and receive intubated mechanical ventilation (MV) support in NICUs as a first-line therapy. Intubated MV support is being applied for very long periods in some centers.
- Surfactant preparations are being administered with different doses, numbers, and positions.
- The diagnosis of pulmonary hypertension, which may accompany BPD, may be overlooked.
- Follow-up of preterm babies after discharge is inadequate and respiratory support and nutrition at home

and special vaccination requirements do not yet depend on standard protocols.

Our first national guideline related with BDP was published in 2014 on the website of the Turkish Neonatal Society (TNS). In 2017, which was the 50th year of the definition of BDP, important meta-analyses and systematic reviews related with the definition, pathogenesis, prevention and treatment of BPD, which had been modified in these 50 years, were published.

The title of the updated 2018 BPD guideline was changed to "Guideline for Prevention and Management of Bronchopulmonary Dysplasia" and its content was updated after reviewing national and international randomized controlled studies, systematic reviews and meta-analyses published until the end of December 2017 considering those that could provide an evidence level of at least 1++ and 1+ and a recommendation level of A and B. In addition, it was attempted to avoid repetition in the content considering the recommendations in the other management, treatment, and follow-up guidelines published by the TNS in the last two years in which BPD was addressed as a subtitle. Accordingly, "Follow-up after Discharge" recommendations were not included in the 2018 BPD Guideline, because the 'TNS Guideline for Approach and Follow-up in High-risk Babies' (2018) includes the principles of home follow-up of preterm babies with BPD.

The objective of this guideline is to form a common and standard consensus based on current and evidence-based medical scientific data in order to prevent BPD in preterm babies who are followed-up in NICUs and carry a special risk for BPD in our country.

1. Definition

The classic definition and diagnostic criteria of BPD as specified by Northway WH Jr in 1967 have been updated by various researchers in the last 50 years (1). After the years in which BDP was defined for the first time, preterm babies born with very low gestational ages started to survive with the introduction of various clinical applications including mainly surfactant treatment for RDS, and more gentler and non-invasive respiratory support methods, and chronic respiratory failure observed in these babies was defined as 'new BPD' (2). The pathophysiology of BPD was changed with this definition and has been understood better over time.

The definition and classification of new BPD seems to be appropriate mainly for BPD epidemiology, but it car-

Table 1. Classification of bronchopulmonary dysplasia

	Gestational age <32 weeks	Gestational age ≥32 weeks
Time of assessment	Postmenstrual 36 th week or at the time of discharge (whichever is earlier)	>28 th day - <56 th day or at the time of discharge (whichever is earlier)
Mild BPD	≥21% O ₂ requirement for at least 28 days + absence of additional O ₂ requirement at the PM 36 th week or at the time of discharge (whichever is earlier)	≥21% O ₂ requirement for at least 28 days + absence of additional O ₂ requirement at the postnatal 56 th day or at the time of discharge (whichever is earlier)
Moderate BPD	Presence of additional O ₂ requirement (<30%) at the PM 36 th week or at the time of discharge (whichever is earlier)	Presence of additional O ₂ requirement (<30%) at the postnatal 56 th day or at the time of discharge (whichever is earlier)
Severe BPD	Presence of O ₂ requirement (≥30%) and/or positive pressure (PBV or nCPAP) requirement at the PM 36 th week or at the time of discharge (whichever is earlier)	Presence of O ₂ requirement (≥30%) and/or positive pressure (PBV or nCPAP) requirement at the postnatal 56 th day or at the time of discharge (whichever is earlier)

BPD: bronchopulmonary dysplasia; nCPAP: nasal continuous positive airway pressure; PBV: positive pressure ventilation; PM: postmenstrual

ries some problems. This definition does not objectively reflect the degree of exposure of the lungs to injury and repair processes and cannot specify preterms who are candidates for 'severe (serious-fatal) BPD before the PM 36th week while they are still in the prevention/treatment window. On the other hand, it leads to a diagnosis of BPD in preterms who require oxygen because of other reasons including apnea of prematurity without lung parenchyma problems in the PM 36th week. The current widespread use of high-flow nasal cannula (HFNC), also leads to difficulties in the diagnosis. For example, a preterm baby receiving 21% O₂ with a flow rate of 4 L/min in the PM 36th week is not diagnosed as having BPD, whereas another baby receiving 100% O₂ with a flow rate of 0.1 L/min is diagnosed as having severe BPD (3). Application of Walsh's 'room air challenge test,' which is recommended for use at the time of diagnosis, is not found to be practical (4). Studies for definition and classification that are based on a more sensitive clinical evaluation and could give more objective information about the condition of the lungs, and thus would enable to specify the target patient group as early as possible, are continuing (5, 6).

The specific definition that we recommended in the 2014 guideline was not included in this guideline because it is far from answering the above-mentioned questions and may lead to confusion in practice.

It is recommended that the BPD definition and classification recommended by Jobe AH. and Bancalari E. in the 2001 National Institutes of Health (NIH) Workshop

should also be used in our country until a more sensitive and valid clinical definition gains acceptance (2).

According to this definition, BPD is defined at the PM 36th week for preterms born before 32 weeks of gestation and on the postnatal 28th day for preterms born at or after 32 weeks of gestation, or at the time of discharge whichever occurs earlier, regardless of the clinical severity of respiratory failure due to RDS or other reasons in the first days of life, as demonstrated in Table 1.

2. Prevention

2.1. Prenatal period

Development of BPD is related with multiple factors occurring in the prenatal, perinatal, and postnatal period. Specifying the main risk factors and markers that could predict preterm babies who will develop significant respiratory morbidities in the postnatal period and be diagnosed as having BPD in the PM 36th week is currently one of the most challenging research topics. The objective of most of these ongoing studies is to find out the target patient group which will benefit the most from specific treatment options early in the postnatal period.

In two different prospective, longitudinal studies published in 2017, low gestational age at birth, male sex, and intubation in the delivery room, as well as maternal factors including smoking during pregnancy, hypertension, and intrauterine growth retardation were found to be correlated with a diagnosis of BPD in the PM 36th week (2, 7).

Table 2. Recommendations for approaches related with the prenatal period and the delivery room

- It is recommended that mothers of preterm babies should be encouraged not to smoke and consume tobacco during their subsequent pregnancies and antitobacco advocacy should be promoted during hospitalization in neonatal intensive care units and during follow-up after discharge.
- See "TNS Guideline for Respiratory Distress Syndrome and surfactant Treatment (2018)" for recommendations related with prenatal care, decision for place of delivery and antenatal steroid administration.
- See "TNS Guideline for Respiratory Distress Syndrome and surfactant Treatment (2018)" and "TNS Guideline for Delivery Room management (2016)" for recommendations related with stabilization, monitoring and management of oxygenation, heat control, placental transfusion and noninvasive respiratory support of small preterm babies in delivery room.

TNS: Turkish Neonatal Society

Smoking during pregnancy causes a two-fold increased risk for development of BPD and respiratory morbidities after preterm delivery in the long-term follow-up.

Association between chorioamnionitis and BPD, which was included in the 2014 BPD Guideline, could not be demonstrated clearly in subsequent studies. Appropriate management of gestational hypertension and intrauterine growth restriction (IUGR), as well as diagnosis and management of chorioamnionitis are involved in the field of obstetricians rather than neonatologists.

Prevention of preterm deliveries is a recommendation that is difficult to realize, especially when the conditions specified for our country are considered (8, 9). RDS developing as a result of delivery in early gestational weeks and therapeutic approaches directed to RDS lead to a process that could result in BPD.

2.2. Approach in the delivery room

It is known that lung injury resulting in BPD in small preterm babies with extremely low birth weight/gestational week is initiated with exposure to the first positive-pressure ventilation applied in the delivery room with a large tidal volume and very high oxygen concentration, even in room air as compared with fetal life. The lungs of small preterm babies are very immature in terms of structure and function. The lungs are vulnerable to injury because they lack surfactant, they are filled with fluid and are not protected by a secure thoracic wall. If spontaneous respiration is present in the delivery room in small preterm babies, application of early nasal-continuous positive airway pressure (CPAP) with measurable positive end expiratory pressure (PEEP) (5-8 cm H₂O), which is initiated with low O₂ concentration (21-30%), is recommended (10, 11). In this way, it is attempted to enable a physiologic functional residual capacity and oxygenation with minimal barotrauma, volutrauma, atelectrauma, and surfactant inactivation.

It is known that placental transfusion realized by delayed cord clamping or cord milking during delivery enhances stabilization of the preterm babies in the delivery room (12).

Recommendations related with the prenatal period and delivery room approaches are shown in Table 2.

2.3. Postnatal period

2.3.1. Respiratory support

2.3.1.1. Noninvasive (nasal) respiratory support

Lung injury that occurs during respiratory support applied after delivery has one of the most important roles in the development of BPD. Therefore, providing adequate gas enhance with the least respiratory support possible is the main strategy in the prevention of BPD. This is best accomplished using noninvasive respiratory support.

The noninvasive methods that can be used for respiratory support in respiratory failure occurring in the first days of life in preterm babies include nPAP and nasal intermittent positive pressure ventilation (NIPPV). In recent years, use of heated humidified high-flow nasal cannula (HHHFNC) is also being tried.

2.3.1.1.a. Nasal Continuous Positive Airway Pressure (nCPAP)

Results of large randomized controlled studies and systematic reviews/meta-analyses of these studies recommend routine use of nCPAP to minimize lung damage and decrease the possibility of BPD in preterm babies (11, 13-16). Even nCPAP alone causes a significant reduction in the frequency of BPD and BPD/mortality and decreases the need for MV and surfactant when compared with MV with intubation with or without administration of surfactant (11). In a meta-analysis in which all non-invasive approaches of respiratory support were compared, it was shown that the most positive result in terms of preven-

tion of BPD was achieved with less invasive surfactant administration (LISA). Here, LISA does not describe a method of administration of surfactant alone. After respiratory support is initiated with nCPAP, administration of surfactant via a thin catheter under continuing nCPAP is defined as LISA (13).

In randomized studies that considered reduction of BDP as the primary outcome, bubble CPAP (bCPAP) seems to be the most efficient nCPAP method among all nCPAP methods (17). It is recommended that short bi-nasal prongs should be used as an interface for nCPAP applications (18).

In our country and across the world, nCPAP applications are still lacking a standard setting protocol relevant initiation and weaning. Criteria for nCPAP failure are not described well. Various, and usually inappropriate devices, circuits and interfaces are utilized with a view to apply nCPAP. Therefore, it is recommended that, optimal requirements for nCPAP applications should be met starting from the first minutes following delivery (16).

2.3.1.1.b. Nasal Intermittent Positive Pressure Ventilation (NIPPV)

NIPPV is a non-invasive method of respiratory support performed by adding an adjustable and measurable peak inspiration pressure (PIP) onto PEEP performed by nasal CPAP with an adjustable and measurable rate, either synchronized or not synchronized with the patient's spontaneous breathing. In the first multi-center, controlled, randomized trial with a large patient group in which the efficacy of NIPPV in reducing the risk of BPD was investigated, it could not be demonstrated that NIPPV was more effective compared with nCPAP (19). The reason that no difference could be found between the two methods was the fact that two-level nCPAP (BiPAP) was applied in a significant portion of the patient group in the NIPPV arm and the maximum upper pressure that could be applied by BiPAP was 8-10 cm H₂O.

The results of a systematic review and meta-analysis that examined many controlled randomized studies conducted after 2013 and published in 2016 showed that NIPPV reduced BPD and BPD/mortality to a greater extent compared with nCPAP (13). In the Cochrane meta-analysis of 2016, NIPPV was not shown to have a more positive effect on BPD compared with nCPAP, but it was reported to more efficiently decrease the need for intubation and MV in preterm babies developing RDS (20). It is not yet known if synchronization has an additional contribution in NIPPV applications.

2.3.1.1.c. Heated Humidified High Flow Nasal Cannula (HHHFNC)

The interface used for HHHFNC is totally different from the interfaces used for nCPAP and does not usually cause a nasal injury. For that reason, HHHFNC has become a more and more popular mode of non-invasive respiratory support in NICUs during the last 10 years. It is used both for primary respiratory support and to augment extubation success in preterm newborns.

Most randomized, controlled trials that compared HHHFNC with nCPAP as the method of primary respiratory support were conducted with preterm babies with a gestational age of ≥ 28 weeks (21-23). In addition to these trials, a retrospective study that investigated the clinical data of more than 2500 preterm babies with extremely low birth weight (ELBW) demonstrated that use of HHHFNC instead of nCPAP in primary respiratory support increased the frequency of BPD or mortality and the hospitalization period (24).

HHHFNC is not recommended for the primary respiratory support in preterm infants with a gestational age of < 28 weeks. Recommendations for non-invasive respiratory support are shown in Table 3.

2.3.1.2. Invasive respiratory support (mechanical ventilation via an endotracheal tube)

The primary lung protective strategy is to avoid intubation and to provide non-invasive respiratory support in preterm infants with RDS. However, it becomes mandatory to perform intubation and initiate mechanical ventilation in some preterms with insufficient spontaneous breathing effort during non-invasive respiratory support.

In recent years, tidal volume-targeted synchronized ventilation is commonly being preferred because both insufficient volume and overdistention of the immature alveoli during conventional ventilation leads to lung damage. The Cochrane meta-analysis published in 2017 reported that tidal volume-targeted modes decreased the frequency of BPD/mortality, pneumothorax, hypocarbia, and IVH, and the duration of MV compared with pressure-controlled ventilation modes (25).

Controlled randomized studies that compare high-frequency oscillation ventilation (HFOV) with conventional ventilation as a primary respiratory support report contradictory results in terms of BPD. The inconsistency of high-frequency ventilation trials may be related to differences in the selection of patients, devices, and settings. Nevertheless, the Cochrane meta-analysis showed that

Table 3. Recommendations for noninvasive (nasal) respiratory support

- nCPAP should go into routine use for initial respiratory support beginning from the delivery room in small preterms who are candidates for pulmonary injury.
- FiO₂ and PEEP should be administered by using a T-piece resuscitator and adjusted carefully in the delivery room. nCPAP support should be initiated with a FiO₂ value of 21-30% and a PEEP value of 5 mm H₂O. FiO₂ should be gradually increased according to the targeted O₂ levels by monitoring oxygen saturation and PEEP should be gradually increased up to 8 cm H₂O in preterm infants at risk for BPD.
- It would be appropriate to define “nCPAP failure” with more liberal criteria to avoid intubation in the process after delivery room in small preterms. A FiO₂ of ≥40% and a PEEP value of ≥7 cm H₂O may be considered failure criteria.
- Presence of teams educated and experienced in the issues of placing interfaces and appropriate positioning of patients is essential to increase the success of nCPAP application in neonatal intensive care units.
- Although NIPPV appeared to be more efficient compared to nCPAP in terms of preventing BPD in a substantially strong meta-analysis, there is still insufficient evidence to recommend preferring NIPPV before nCPAP as the primary respiratory support in small preterm babies who are candidates for BPD.
- Respiratory support should be initiated with nCPAP beginning from the delivery room, LISA should be applied with early rescue approach when indication emerges and NIPPV should be tried before intubation, if PEEP exceeds 7 cm H₂O and FiO₂ requirement exceeds 40%, spontaneous respiration is insufficient or respiratory acidosis develops.
- Use of HHHFNC for primary respiratory support is not recommended in small preterm babies who are candidates for BPD.

BPD: bronchopulmonary dysplasia; HHHFNC: heated humidified high-flow nasal cannula; nCPAP: nasal continuous positive airway pressure; NIPPV: nasal intermittent positive pressure ventilation; PEEP: positive end-expiratory pressure

Table 4. Recommendations for invasive respiratory support (mechanical ventilation with intubation)

- If intubation is required, “tidal volume targeted synchronized ventilation” is recommended.
- HFOV may be tried as a rescue approach in babies who cannot be ventilated with tidal volume targeted synchronized ventilation.
- Hypocarbica and hypercarbica whould be avoided during mechanical ventilation.
- The duration of mechanical ventilation should be kept as short as possible and noninvasive respiratory support is recommended inorder to increase extubation success.

HFOV: high frequency oscillation ventilation

HFOV as the primary respiratory support in preterm babies with acute respiratory failure decreased the frequency of BPD, albeit to a small extent, when compared with conventional ventilation (26).

High MV settings augment lung damage by creating overdistention of the alveoli. In order to prevent a rapid increase in settings during MV, permissive hypercarbica has been recommended for many years. However, a multicenter, large, randomized, controlled trial published in 2015 showed that permissive hypercarbica did not decrease BPD in preterm babies with a birth weight of 400-1000 g and a gestational week between 23 and 28 weeks (27). Therefore, acceptance of permissive hypercarbica approach as a lung protective strategy should be approached with caution, a pCO₂ level of 45-60 mm Hg should be targeted during MV, and both hypo- and hypercarbica should be avoided.

The relationship between mechanical ventilation and

BPD is well known. Extubation should be tried as soon as possible in preterm babies who have been intubated, and shortening the duration of MV should be targeted with weaning protocols. All non-invasive methods of respiratory support increase the success of extubation (28). Recommendations are given in Table 4.

2.3.2. Surfactant treatment

In the Trial of Late Surfactant (TOLSURF) study, it was shown that administration of multiple doses of surfactant (up to five doses in total with intervals of 1-3 days) did not decrease BPD in the PM 36-40th weeks in preterm babies with a gestational age of ≤28 weeks who were still receiving inhalation nitric oxide (iNO) in addition to invasive MV support between the 7th and 14th days (29). Recommendations are given in Table 5.

2.3.3. Oxygen support and oxygenation targets

There are prospective, randomized, controlled studies

Table 5. Recommendation for surfactant treatment

- See "TNS Guideline for Respiratory Distress Syndrome and Surfactant Treatment (2018)" for surfactant treatment in the first days following delivery.
- It is recommended that recurrent multiple doses of surfactant treatment should be avoided during hospitalization in NICU except for repeated doses, which may be given with indications, defined in the acute period and for early rescue treatment recommended by "TNS Guideline for Respiratory Distress Syndrome and Surfactant Treatment (2018)".

TNS: Turkish Neonatal Society

with a high level of evidence, which investigate the level of oxygen saturation that should be maintained from delivery to the PM 36th week in preterm infants with a gestational age of <28 week as long as additional oxygen requirement continues (30-33). These large-scale studies, which compare the oxygen saturation targets between 85-89% and 90-95%, as well as the NeoProM meta-analysis, showed that there was no reduction in BPD and ROP, besides the mortality was higher in the low target oxygen saturation group (34). Recommendation:

- It is recommended that the target oxygen saturation range should be kept between 90% and 94% with alarm limits of 89-95% in preterm babies requiring additional oxygen.

2.3.4. Patent ductus arteriosus (PDA) management

Hemodynamically significant PDA (hsPDA) increases pulmonary blood flow and edema through left to right shunt, which will augment the lung injury and may lead to increased need for MV. "The Turkish Neonatal Society Guideline for the Approach to PDA in Preterm Babies (2016)" recommends that PDA should be screened with echocardiography in the first 72 hours in VLBW babies with a gestational age of <28 weeks, and hsPDA should be treated with non-steroidal antiinflammatory drugs (NSAIDs).

A study that supported this recommendation in terms of BPD, and three important studies and a meta-analysis that did not support this recommendation were published in 2017. In a single-centered, prospective cohort of VLBW babies with a gestational age of <28 weeks, it was reported that BPD and BPD/mortality in the PM 36th week were observed less frequently in subjects who were born before 2011 and received prophylactic indomethacin (PINDO) on the first day of life compared with subjects who did not receive PINDO (35). However, a larger, multi-center, retrospective cohort that included approximately 8000 preterm babies showed that early indomethacin treatment did not affect the frequency of BPD (36). In a single-center, retrospective cohort from Korea, it was reported that the BPD frequency was lower in the group in

which PDA was not treated and left for spontaneous closure (37). When the records of 61 500 preterm babies with a gestational age between 23 and 30 weeks hospitalized in 280 NICUs between 2006 and 2015 in the United States of America were examined, it was specified that the BPD frequency remained stable at around 20%, although a statistically significant reduction in the frequencies of NSAID treatment and surgical closure for PDA was observed over the years (38). Finally, a large meta-analysis including 12 000 preterm babies with a gestational age of <28 weeks followed up in a total of 25 NICUs between 2006 and 2013 showed that treatment or lack of treatment for PDA had no impact on moderate-severe BPD (39). Recommendation:

- "The Turkish Neonatal Society Guideline for Approach to PDA in Preterm Babies (2016)" recommendations should be taken into consideration until this guideline is updated because the presence of hsPDA, time period of exposure to hsPDA and treatment of hsPDA do not seem to be solely and directly effective in the development of BPD.

2.3.5. Fluid treatment and nutrition

Recommendation:

- See "The Turkish Neonatal Society Guideline for Fluid and Electrolyte Balance in Newborns (2016)", Fluid and Electrolyte Balance in Special Conditions, Bronchopulmonary Dysplasia and "The Turkish Neonatal Society Guideline for Nutrition of Preterm and Sick Term Babies (2018)"

2.3.6. Management of pulmonary hypertension

Pulmonary hypertension (PH) accompanies the development of BPD with a frequency of 20-25% in preterm babies. Presence of pulmonary hypertension is related with the severity of BPD and negative prognosis. The European Pediatric Pulmonary Vascular Diseases Network and the American Pediatric Pulmonary Hypertension Network (PPHNet) have published two compatible international guidelines for the management of pulmonary hypertension in preterm infants, respectively in 2016 and 2017 (40, 41).

Table 6. Recommendations for management of pulmonary hypertension

- Echocardiographic assessment in the PM 36th week is recommended 1) if there is severe hypoxic respiratory failure suggesting persistent fetal circulation despite all necessary medical treatment given in the first week of life, 2) if MV requirement still persists on the 7th day of life, 3) if MV is needed especially for recurrent hypoxic episodes in any period of hospitalization for preterm infants.
- 1. Pulmonary veins, shunts and anatomical structure, 2. Ventricular sizes, systolic and diastolic functions, 3. Systolic and diastolic position of the interventricular septum, 4. Trikuspid and pulmonary valve regurgitation rates should be evaluated on echocardiography, 5. Systemic blood pressure should be measured simultaneously.
- If a diagnosis of PH has been made with echocardiography, basal BNP and NT-pro-BNP levels should be considered. These parameters do not substitute for echocardiography and angiography for primary diagnosis, but are helpful in clinical follow-up.
- Gastroesophageal reflux, aspiration, pulmonary arterial or pulmonary venous stenosis, left ventricular diastolic dysfunction and presence of aortopulmonary collateral should be excluded before PH specific treatment is initiated.
- Cardiac catheterization and angiography should be planned in patients in whom a decision can not be made with echocardiography.
- Oxygen support, which will keep oxygen saturation in the range of 92%-95% should be enabled in patients with BPD who have been diagnosed with PH.
- iNO should be administered for acute PH episodes and discontinued after stabilization. Initiation of "sildenafil" while discontinuing iNO enhances discontinuation of iNO.
- PH specific treatment options should be carefully reviewed and efficacy and side effects should be closely monitored in patients with very high pulmonary vascular resistance with left heart disease or right ventricular hypertrophy/dysfunction without pulmonary valve stenosis.
- The following drugs are recommended as treatment options: Sildenafil, Bosentan (inhaled), iloprost (IV), Epoprostenol (IV or SC), Treprostinil (IV), Milrinon.

BPD: bronchopulmonary dysplasia; BNP: brain natriuretic peptide; IV: intravenous; iNO: inhaled nitric oxide; MV: mechanical ventilation; PH: pulmonary hypertension

Our recommendations related with the management of PH in BPD were established in accordance with these guidelines, and are shown in Table 6.

2.3.7. Drug therapies

2.3.7.1. Methylxanthines (caffeine)

Methylxanthines are used in the treatment of apnea of prematurity as an evidence-based practice (42). It was found that caffeine decreased the frequency of BPD and PDA requiring treatment, as well as neurodevelopmental impairment at the 18th month in preterm babies. Although it was also demonstrated that this positive effect disappeared at the age of five years, use of caffeine in small preterm babies became prevalent (43, 44). There is no meta-analysis that indicates that caffeine citrate treatment decreases the frequency of BPD in preterm babies. Although caffeine citrate appears to be effective in the prevention of BPD, the mechanisms of action are not exactly known.

2.3.7.2. Postnatal steroid treatment

Corticosteroids are the most commonly used drugs in BPD candidates and in patients with BPD, and they are being studied intensively; however, there is still no stan-

dard guideline for the use of these drugs. Despite the well-known long-term negative adverse effects of this group of drugs on the nervous system and lung, they are the most efficient drugs known for extubation of preterm babies who cannot be separated from MV because of lung injury. Although there are some uncertainties related with their use, systematic reviews and meta-analyses in addition to many important prospective, randomized, controlled studies published in the last 3-4 years have elucidated the issue to some extent.

Corticosteroids are generally administered systemically by the parenteral or enteral route or locally by inhalation. Whatever route is used, efficiency and adverse effects should always be taken into consideration when deciding to use these drugs.

2.3.7.2.a. Systemic steroid treatment

2.3.7.2.a.1. Early (first seven days) systemic steroid treatment

A Cochrane meta-analysis evaluated 20 prospective, randomized controlled studies related with use of systemic dexamethasone in the first seven days of life and nine

prospective, randomized controlled studies related with use of systemic hydrocortisone in the first seven days of life (45). Early systemic dexamethasone treatment facilitates extubation, shortens the duration of MV and decreases BPD. Its use is not recommended because of its short-term adverse effects including mainly gastrointestinal perforation and long-term adverse effects, mainly including cerebral palsy (46).

The patient numbers in studies related with early systemic hydrocortisone had not been sufficient to enable any recommendation before the multi-center, prospective, double-blind, randomized, controlled clinical trial (PREMILOC) conducted by Baud et al. (47) was published in 2016., PREMILOC trial included more than 500 preterm babies with a gestational age of 24-27 weeks. Hope emerged in the issue of using early low-dose systemic hydrocortisone because parenteral systemic hydrocortisone at a dose of 2x0.5 mg/kg/day for seven days after the first 24 hours and at a dose of 1x0.5 mg/kg/day for the consecutive three days reduced BPD and BPD/mortality at the PM 36th week without leading to any significant acute adverse effects and neurodevelopmental outcomes at the adjusted 22nd month in the PREMILOC trial. However, more clinical studies are still needed to recommend its use.

2.3.7.2.a.2. Delayed (>7 days) systemic steroid treatment

Dexamethasone was used in almost all randomized, controlled studies related with delayed systemic corticosteroid treatment. Two large, prospective, randomized, controlled studies using delayed systemic hydrocortisone are continuing (SToP-BPD and ClinicalTrials.gov. NCT013533137).

Although use of delayed systemic dexamethasone decreases the frequency of BPD, BPD/mortality and need for treatment for PDA at the PM 36th week, it leads to hyperglycemia, hypertension, and hypertrophic cardiomyopathy (48, 49). Its long-term neurodevelopmental adverse effects are not negative unlike early treatment (46).

There is still no study that could suggest a decision for the cumulative dose to be used, duration of use, and when to begin use after the seventh day (50).

2.3.7.2.b. Inhaled corticosteroid treatment

Two separate Cochrane meta-analyses related with early and delayed inhaled corticosteroid treatment were published in 2017, though they did not present evidence-based and qualified information. A qualified, prospective, randomized, controlled clinical study related with early inhaled corticosteroid treatment that was included in the

meta-analyses and had the strength to change outcomes was published in 2015, and an independent meta-analysis related with early inhaled corticosteroid treatment dominated by this study was published in 2016 (51-54).

2.3.7.2.b.1. Early inhaled corticosteroid treatment

In the study conducted by Bassler et al. (53), inhaled budesonide given at a dose of 2x400 micrograms in the first 14 days of life and at a dose of 2x200 micrograms from the 14th day to the PM 32nd week significantly decreased BPD and BPD/mortality. The reduction in BPD/mortality was found to be more significant in one third of patients who were not intubated and received non-invasive respiratory support. No difference in terms of complications during administration was found between the study and control groups.

With inclusion of the study of Bassler et al., both Cochrane and Shinwell meta-analyses results were altered showing a positive effect of early corticosteroid treatment in reducing BPD (51, 54).

2.3.7.2.b.2. Delayed inhaled corticosteroid treatment

Use of delayed inhaled corticosteroids is not recommended because they have not been found to have any effect on the frequency of BPD and BPD/mortality.

2.3.7.3. Vitamin A

Vitamin A is needed for the normal growth and repair of the lungs and the integrity of the respiratory system. In addition, it is a strong antioxidant. In preterm babies, vitamin A stores and the levels of the vitamin A transport carrier protein, retinol-binding protein (RBP), are decreased. This condition has been associated with the risk of development of BPD. In many randomized, controlled studies, the effects of vitamin A use above the routine doses on BPD, other morbidities, and mortality risk have been examined in preterm babies. In the final Cochrane meta-analysis, it was shown to reduce BPD, albeit to a small extent, without leading to early or delayed adverse effects (55).

Administration of vitamin A is difficult because it is performed by the intramuscular route. Oral vitamin A is not recommended because of weak absorption and low RBP levels. Studies for appropriate enteral administration are ongoing (56).

2.3.7.4. Inhaled nitric oxide (iNO)

Endothelial nitric oxide is essential for alveolar and vascular development and its deficiency may lead to BPD. Use of iNO to prevent BPD has been the subject of many studies, but the results of these studies are contradic-

Table 7. Recommendations for drug therapy

- Use of caffeine citrate is recommended beginning from the first day after delivery up to the PM 36th week in preterm babies with a birth weight of <1250 g, and a gestational age of <28 weeks who carry a risk for BPD:
Caffeine citrate loading dose: 20 mg/kg, IV 30 min. infusion
Caffeine citrate maintenance dose: 5-10 mg/kg/day, IV slow push or oral (24 hours after the loading dose)
- Early systemic corticosteroid treatment is not recommended to prevent BPD.
- Delayed systemic dexamethasone treatment may be given for extubation at the lowest cumulative dose and with the shortest duration possible considering acute severe side effects in preterm babies who are candidates for "severe" BPD and have been dependent on ventilator with a FiO₂ of >40% for at least 2 weeks with a very low probability of extubation and in whom conditions including delayed neonatal sepsis, PDA and IVH have been excluded.
- If the patient has not been able to be extubated on the 72nd hour of systemic dexamethasone treatment, discontinuation of the drug is recommended.
- Although sufficient evidence related with long-term safety of inhaled corticosteroids is absent, use of early inhaled "budenoside" may be recommended to decrease the frequency of BPD in preterm babies with a gestational age of <28 weeks.
- Use of delayed inhaled corticosteroids is not recommended, because it has not been found to have any effect on the frequency of BPD and BPD/mortality.
- Vitamin A is recommended to be administered intramuscularly in preterm babies with a birth weight of <1000 g beginning from delivery three days a week for four weeks at a dose of 5000 IU.
- Use of iNO is not recommended to prevent BPD except for treatment of confirmed BPD related PH.
- Use of macrolid antibiotic (azithromycin) is recommended in preterm babies who are candidates for BPD and in whom presence of "ureaplasma" has been demonstrated in the respiratory tract by microbiologic methods.
- Routine use of diuretics, bronchodilators and anti-reflux drugs which are used commonly is not recommended to prevent BPD in preterm babies who are candidates for BPD except for specific indications in symptomatic patients.

BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus; PH: pulmonary hypertension.

tory. In a Cochrane systematic review, it was shown that iNO treatment had no effect in terms of preventing BPD (57). In the recommendation of the American Pediatric Academy related with iNO treatment in preterm babies, it was emphasized that high-dose (>20 ppm) iNO treatment in the postnatal 2nd week enabled a small reduction in the rate of BPD in a single-center study, but this study needed to be supported by further studies (58).

2.3.7.5. Antioxidants

Routine use of superoxide dismutase (SOD), N-acetyl cysteine, vitamin E, and vitamin C, which are antioxidant drugs, is not recommended in preterm babies because they do not prevent the development of BPD.

2.3.7.6. Macrolide antibiotics

Use of macrolide antibiotics in the prevention of BPD has come to the forefront because colonization of the airway with ureaplasma has been associated with the development of BPD (59). In a meta-analysis, azithromycin treatment was found to be efficient in decreasing the frequency of BPD (60). A large randomized controlled study related with its long-term safety, appropriate dose, and pharmacokinetics is continuing (ClinicalTrials.gov: NCT01778634).

2.3.7.7. Diuretics, bronchodilators, anti-reflux drugs

Routine use of diuretics, bronchodilators, and anti-reflux drugs, which are commonly used, is not recommended to prevent BPD in preterm babies other than for indications in symptomatic patients. Most of the drugs in this group are potentially harmful (61).

Drug therapy recommendations are shown in Table 7.

2.3.7.8. Promising therapies for the future

2.3.7.8.a. Inositol

Inositol is a phospholipid that has a critical role in fetal and neonatal life, and it improves pulmonary functions by increasing surfactant synthesis and secretion. It has been shown that production of phosphatidylinositol, which is a surfactant phospholipid in type II pneumocytes, is dependent on extracellular inositol concentration and inositol support increases surfactant maturation (62).

In a phase 3 study, it was shown that administration of inositol at a dose of 80 mg/kg/day by the intravenous or enteral route for 10 weeks provided a sufficient serum level without development of any adverse effects (63).

In a Cochrane meta-analysis published in 2015, it was reported that inositol caused a reduction in many early neonatal morbidities including BPD and was a promising drug with referral to five randomized controlled studies, four of which were completed and one of which was continuing (64).

2.3.7.8.b. Clara cell protein (rHCC10)

Clara cell protein is a protein molecule secreted by the non-ciliated epithelium in the respiratory tract with immunomodulator and antiinflammatory characteristics. Its positive effect was demonstrated in many animal studies and a small pilot study. A large randomized controlled study related with its safety and efficacy is continuing (65).

2.3.7.8.c. Stem cell treatment

The results of the preclinical studies related with mesenchymal stem cell applications to prevent bronchopulmonary dysplasia, which have been continuing for more than 10 years, are encouraging (66). There is a single Phase 1 clinical study with favorable results that has been published, and there are numerous ongoing studies registered in Clinical.Trials.gov (67).

Although many issues related with the time of administration, the dose and the route of administration are controversial, it appears that stem cells will be the essential tool for the prevention and treatment of BPD in the future (68, 69).

2.3.7.8.d. Intratracheal administration of budesonide adsorbed on surfactant

There is one randomized controlled clinical trial related with intratracheal administration of budesonide at a dose of 0.25 mg/kg adsorbed on surfactant at a dose of 100 mg/kg with eight-hour intervals until FiO_2 requirement is less than 30% in 265 VLBW preterms with respiratory distress syndrome who required a FiO_2 above 50% (70). Although the results of the study were encouraging in terms of BPD, its long-term results have not been published. There is still insufficient evidence to make a recommendation for this issue.

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