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NARRATIVE REVIEW

Bronchopulmonary dysplasia: preventive measures and therapeutic approach until discharge from the neonatal unit

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Abstract

Bronchopulmonary dysplasia (BPD) is the most common long-term respiratory morbidity affecting very preterm infants and has a negative impact on future lung function and quality of life. BPD management during a neonatal intensive care unit (NICU) stay is mainly based on a set of preventive measures. Despite improvements in pharmacological and non-pharmacological research, only a few therapeutic measures available are supported by high-quality evidence. This review essentially focuses on preventive and therapeutic options for preterm neonates at risk of, or with established, BPD, during their NICU stay.

Keywords: Bronchopulmonary dysplasia. Preterm infant. Prevention. Treatment.

Displasia broncopulmonar: medidas preventivas e abordagem terapêutica antes da alta da unidade de neonatologia

Resumo

A displasia broncopulmonar (DBP) é a morbidade respiratória a longo prazo mais comum em recém-nascidos de grande prematuridade e tem um impacto negativo na função pulmonar e na qualidade de vida futura. A abordagem terapêutica da DBP durante a permanência na unidade de cuidados intensivos neonatais (UCIN) baseia-se essencialmente na adoção de um conjunto de medidas preventivas. Apesar dos avanços na investigação de novos agentes farmacológicos e medidas não farmacológicas, apenas algumas das medidas terapêuticas disponíveis são apoiadas por evidências de alta qualidade. Esta revisão aborda as medidas preventivas e terapêuticas a utilizar em recém-nascidos pré-termo em risco de desenvolver ou com DBP estabelecida, durante sua permanência na UCIN.

Palavras-chave: Displasia broncopulmonar. Prevenção. Tratamento. Recém-nascido pré-termo.

Keypoints

What is known

– Management of bronchopulmonary dysplasia is based on a set of preventive and therapeutic measures.

What is added

– This review brings together preventive and therapeutic measures to be used in BPD.

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Introduction

Bronchopulmonary dysplasia (BPD) is the most common long-term respiratory morbidity affecting preterm infants, and the risk of its occurrence is inversely proportional to the gestational age at birth[1,2].

The technical and scientific advances that have taken place in the area of neonatology in recent decades have paved the way for the survival of more and more infants with very low gestational ages, even though the prevalence of BPD has not decreased, affecting up to 45% of infants born below 29 gestational weeks[2,3]. However, these scientific advances have modified the phenotype of the disease, leading to the emergence of a "new" BPD, as opposed to the "old" BPD, previously called chronic lung disease of prematurity[4].

BPD is the result of abnormal pulmonary alveolarization, vascularization, and airway development, in which several prenatal, perinatal and postnatal factors act simultaneously and in sequence, which translates into chronic dependence on supplemental oxygen[5]. Today, we know that BPD is not merely a lung disease, but a systemic condition with lifelong implications for adult health and quality of life[6,7]. The pathophysiology of BPD is complex and is beyond the scope of this article[8-22]. The strongest risk factors for BPD are prematurity and low birth weight[1]. BPD risk factors, beyond variation in practices at the neonatal intensive care unit (NICU), are listed in table 1[9-11].

This article focuses, essentially, on preventive and therapeutic measures that are currently recommended for preterm neonates at risk of, or with established, BPD, during their NICU stay. This article does not address aspects related to the treatment and follow-up of patients with BPD after discharge from the NICU.

Table 1. Risk factors for bronchopulmonary dysplasia[9-11]

Antenatal	Lower socioeconomic status Lower maternal education Lower gestational age Male gender White race Fetal growth restriction Maternal smoking Multiple gestations Oligohydramnios Family history of atopic disease Chorioamnionitis Preeclampsia Pre-existing hypertensive disorders Gestational diabetes Maternal obesity Absence of antenatal steroids
Perinatal	C-section Hyperoxia High inflation pressures Intubation in the delivery room Respiratory tract colonization with *Ureaplasma parvum* and *Ureaplasma urealyticum*
Postnatal	Severity of acute respiratory distress syndrome Surfactant administration Apnea Hyperoxia Mechanical ventilation Prolonged patency of the ductus arteriosus Excessive fluids administration Ventricular dysfunction Intracardiac shunts Sepsis Inflammation Air leaks or pulmonary interstitial emphysema Pulmonary hypertension Systemic and pulmonary infections Prematurity-related comorbidities Nutritional deficits Extrauterine growth restriction Vitamin A deficiency

BPD definition and diagnostic criteria

BPD was first described in 1967 by Northway, in moderately preterm infants in the pre-surfactant era, when supplemental oxygen was the primary therapy for severe respiratory distress syndrome (RDS) and mortality was over 50%[23]. In 1988, Shennan defined BPD as the requirement for supplemental oxygen at 36 weeks post-menstrual age, based on a positive predictive value of 63% for abnormal pulmonary outcomes at two years of age[24]. In 2001, the *Eunice Kennedy Shriver-National Institute of Child Health and Human Development* (NICHHD) workshop developed a more comprehensive definition for BPD, made after 28 cumulative days of supplemental oxygen; with severity based on oxygen use at 36 weeks post-menstrual age, with a scale of mild (room air), moderate (< 30% supplemental oxygen), and severe (> 30% supplemental oxygen or positive pressure) (Table 2)[25]. In 2004, Walsh et al.[26] added a 'physiological' test to the NICHHD workshop definition to assess the need for supplemental oxygen at 36 weeks post-menstrual age; infants were classified as having BPD if oxygen saturation fell to values of < 90% within 60 minutes of a room air challenge test. In 2018, the NICHHD workshop provided a review of the BPD definition, that removed the requirement for 28 days of oxygen therapy prior to 36 weeks post-menstrual age, but added a requirement for radiographic confirmation of parenchymal lung disease and used a severity grading of

Table 2. The 2001 and 2018 definitions of bronchopulmonary dysplasia from the National Institute of Child Health and Human Development[25,27]

Gestational age	< 32 weeks	≥ 32 weeks
Time points of assessment	36 weeks PMA or discharge to home, whichever comes first	> 28 d but < 56 d postnatal age or discharge to home, whichever comes first
Treatment with oxygen > 21% for at least 28 days PLUS		
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need* for < 30% oxygen at 36 weeks PMA or discharge, whichever comes first	Need* for < 30% oxygen at 56 days postnatal age or discharge, whichever comes first
Severe BPD	Need* for ≥ 30% oxygen and/or positive pressure (PPV or N-CPAP), at 36 weeks PMA or discharge, whichever comes first	Need* for ≥ 30% oxygen and/or positive pressure (PPV or N-CPAP), at 56 days postnatal age or discharge, whichever comes first

2018 - Eunice Kennedy National Institute of Child Health and Human Development suggested refinements to the definition of BPD					
A premature infant (< 32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks PMA requires 1 of the following FiO_2 ranges/oxygen levels/O_2 concentrations for ≥ 3 consecutive days to maintain arterial oxygen saturation in the 90%-95% range.					
Grades	**Invasive IPPV***	**N-CPAP, NIPPV, or nasal cannula ≥ 3 L/min**	**Nasal cannula flow of 1- < 3 L/min**	**Hood O_2**	**Nasal cannula flow of < 1 L/min**
I	-	21	22-29	22-29	22-70
II	21	22-29	≥ 30	≥ 30	70
III	> 21	≥ 30			
III (A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (e.g., necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc.). *Excluding infants ventilated for primary airway disease or central respiratory control conditions. Values are percents.				

*A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range. BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) are considered common to the broad description of BPD and have not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen > 21% and/or positive pressure for non-respiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen > 21% means that the infant received oxygen > 21% for more than 12 h on that day. Treatment with oxygen > 21% and/or positive pressure at 36 weeks PMA, or at 56 d postnatal age or discharge, should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and following 36 weeks PMA, 56 d postnatal age, or discharge.
BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; IPPV: intermittent positive-pressure ventilation; NCPAP: nasal continuous positive airway pressure; NIPPV: non-invasive positive pressure ventilation; PMA: post-menstrual age; PPV: positive-pressure ventilation.

I-III that incorporated newer modes of non-invasive ventilation[27]. This NICHHD 2018 definition needs to be validated in a large neonatal population. Since then, other definitions have been proposed: in 2017, Isayama et al.[28] proposed the use of oxygen and/or respiratory support as a better indicator of chronic respiratory insufficiency compared to just oxygen, and that assessment at term-equivalent age (40 weeks post-menstrual age) increases the predictive value; in 2019, Svedenkrans et al.[29] proposed the modification of a 'physiological test' that uses the simultaneous measurement of FiO_2 and peripheral saturation to calculate the rightward shift of the oxyhemoglobin dissociation curve at any given point in time; in 2019, Jensen et al.[30] proposed a modification of NICHHD workshop definition, which uses positive pressure instead of supplemental oxygen to classify BPD severity at 36 weeks post-menstrual age. The scale is: no

BPD (no support), grade 1 (nasal cannula ≤ 2 L/min), grade 2 (nasal cannula > 2 L/min or non-invasive positive airway pressure), and grade 3 (invasive mechanical ventilation).

If a BPD diagnosis, or definition, can predict pulmonary outcomes in childhood, how those long-term pulmonary outcomes should be defined remains a challenge for neonatologists and pediatric pulmonologists, and new definitions will, very likely, emerge in the future.

BPD prevention and treatment

BPD is not limited to the perinatal period. Affected infants will not only have respiratory morbidities in their childhood and adult life, (decreased lung function, increased incidence of emphysema, higher risk of wheezing) but also present decreased right ventricular function, increased cardiovascular risk, and a higher incidence of arterial hypertension in adolescence and adulthood[31-34]. BPD is also associated with retinopathy of prematurity and neurological morbidities like developmental delay and cerebral palsy[35,36]. Some studies have suggested that BPD is an independent risk factor for poor neurodevelopmental outcomes, even in the absence of definite brain injuries, such as intraventricular hemorrhage or hypoxic ischemic encephalopathy[37,38]. For example, motor functions, cognitive development, and academic progress are worse in preterm infants with BPD than in those without it[39], and strategies to protect the lungs might also be neuroprotective.

Every measure should be taken to minimize the abnormal development of the lung after birth, as well as its impact on the well-being, development, and growth of the very premature child. In this way, BPD "treatment" is, to start with, based on prevention.

Preventive measures include adequate pregnancy follow-up, prevention of preterm delivery and intrauterine infection, reducing exposure to ventilation using an endotracheal tube, and measures to avoid or minimize long-term lung and brain damage[39].

Antenatal care and delivery room stabilization

Measures that can be taken in the antenatal period that also aim to promote pulmonary development are similar to those recommended for the prevention of RDS in preterm infants (Table 3)[40].

Extremely low gestational age preterm infants should be delivered in tertiary centres[41]. Antibiotics can delay preterm delivery and reduce neonatal morbidity in cases of prenatal pre-labor rupture of membranes (PPROM); co-amoxiclav should be avoided in women due to the increased risk of neonatal necrotizing enterocolitis[42]. Tocolytic drugs are recommended for delaying birth, permitting safe *in utero* transfer to a tertiary center, and giving prenatal corticosteroids time to take effect[43]. Given the neuroprotective beneficial effects of magnesium sulphate on reducing cerebral palsy at two years of age, this should be given to women at risk of preterm birth[44].

Antenatal corticosteroids have been shown to promote lung maturation and prevent RDS in a preterm neonate[45]. Since 1995, antenatal corticosteroids have been recommended for impending preterm birth below 34 weeks of gestation[46]. Some observational studies suggest that antenatal corticosteroids, together with other active management practices, reduce mortality at gestations as low as 22 weeks[47]. When given before elective Caesarean section up to 39 weeks, they reduce the risk of admission to NICU, although there is currently insufficient data to draw any firm conclusions[48]. Optimal treatment up to the delivery interval is more than 24 hours and less than seven days after starting steroid treatment; after 14 days, the benefits are reduced. Advanced labor should not be a reason to refrain from therapy with corticosteroids since the beneficial effects of the first dose start within a few hours. The same applies to magnesium sulphate[49]. The WHO recommends that a single repeat course of steroids between 24 and 34 weeks of gestation may be considered if preterm birth does not occur within seven days after the initial course and there is a high risk of preterm birth in the next seven days[50]. According to Asztalos E.V. et al.[51], a repeat course given after 32 weeks' gestation does not seem to improve outcome. The most common regimens include betamethasone and dexamethasone in a total dose of 24 mg (four doses of dexamethasone 6 mg IM 12 hours apart or two doses of betamethasone 12 mg IM 24 hours apart)[50].

The attitudes in the delivery room should be to support the transition; however, the guidelines of the *European Resuscitation Council*[52] should be followed whenever a resuscitation is needed. Body temperature should be maintained with a polyethylene bag and radiant warmer, and it is feasible to provide advanced resuscitation with the umbilical cord intact since fully-equipped mobile trolleys have been developed in order to allow bedside resuscitation with an intact cord[53]. Delayed (60 seconds) cord clamping is advised[54]. Umbilical cord milking may be an alternative to delayed cord clamping in emergency situations, but

Table 3. Summary of recommendations, from the *European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2022 Update*[40]

Prenatal care	– Mothers at high risk of preterm birth < 28-30 weeks' gestation should be transferred to perinatal centers with experience in RDS management – In women with a singleton pregnancy and a short cervix in mid-pregnancy or previous preterm birth, vaginal progesterone treatment should be used to increase gestational age at delivery and reduce perinatal mortality and morbidity – In women with symptoms of preterm labor, cervical length and accurate biomarker measurements should be considered to prevent unnecessary use of tocolytic drugs and/or antenatal steroids – Clinicians should offer a single course of prenatal corticosteroids to all women at risk of preterm delivery from when pregnancy is considered potentially viable up to 34 weeks' gestation, ideally at least 24 h before birth – A single repeat course of steroids may be given in threatened preterm birth before 32 weeks' gestation if the first course was administered at least 1-2 weeks earlier – Neuroprotector magnesium sulphate (MgSO4) should be administered to women in imminent labor before 32 weeks' gestation – In women with symptoms of preterm labor, cervical length and fibronectin measurements should be considered to prevent unnecessary use of tocolytic drugs and/or antenatal steroids – Clinicians should consider short-term use of tocolytic drugs in very preterm pregnancies to allow completion of a course of corticosteroids and/or in utero transfer to a perinatal center
Delivery room stabilisation	– If clinical condition allows, delay clamping the umbilical cord for at least 60s, to promote placento-fetal transfusion. When not feasible, consider umbilical cord milking in infants with gestational age > 28 weeks – Use a T-piece device, rather than bag and mask – In spontaneously breathing babies, stabilize with CPAP. If apneic or bradycardic, start mask ventilation/ inflations, at initial CPAP pressures of 6-8 cm H2O and PIP 20-25 cm H_2O; do not use sustained inflations as there is no long-term benefit – Oxygen for resuscitation should be controlled using a blender; use an initial FiO_2 of 0.30 for babies < 28 weeks' gestation, 0.21-0.30 for those 28-31 weeks, and 0.21 for 32 weeks' gestation and above; FiO_2 adjustments up or down should be guided by pulse oximetry; aim for SpO_2 of 80% or more (and heart rate over 100/min) by 5 minutes of age – Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs; babies who require intubation for stabilization should be given surfactant – Plastic bags or occlusive wrapping under radiant warmers and humidified gas should be used during stabilization in the delivery suite for babies < 32 weeks' gestation to reduce the risk of hypothermia; hyperthermia should also be avoided
Surfactant	– If babies < 30 weeks of gestation require intubation for stabilization, they should be given an animal-derived surfactant preparation; babies with RDS needing treatment should be given an animal-derived surfactant preparation – A policy of early rescue surfactant should be standard, but there are occasions when surfactant should be given in the delivery suite, such as when intubation is needed for stabilization – Babies with RDS should be given rescue surfactant early in the course of the disease; a suggested protocol would be to treat babies who are worsening when FiO_2 > 0.30 on CPAP pressure of at least 6 cm H_2O, or if lung ultrasound suggests surfactant need – Poractant alfa at an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or 100 mg/kg of beractant for rescue therapy – LISA is the preferred mode of surfactant administration for spontaneously breathing babies on CPAP, provided that clinicians are experienced with this technique – Laryngeal mask surfactant may be used for more mature infants > 1.0 kg – A second and occasionally a third dose of surfactant should be given if there is ongoing evidence of RDS, such as persistent high oxygen requirement and other problems have been excluded
Oxygen beyond stabilization	– In preterm babies receiving oxygen, the saturation (SpO_2) target should be between 90 and 94% – Alarm limits should be set to 89 and 95% – Protocols for screening and treating preterm babies for ROP should be in place
Non-invasive respiratory support	– CPAP or (s) NIPPV should be started from birth in all babies at risk of RDS, such as those < 30 weeks' gestation who do not need intubation for stabilization – The system delivering CPAP is of little importance; however, the interface should be short binasal prongs or mask with a starting pressure of about 6-8 cm H_2O; positive end-expiratory pressure (PEEP) can then be individualized depending on clinical condition, oxygenation, and perfusion; ability to escalate to NIPPV will reduce the need for invasive mechanical ventilation in some infants – CPAP with early rescue surfactant is considered optimal management for babies with RDS – BIPAP devices confer no advantages over CPAP alone. Synchronized NIPPV, if delivered through a ventilator, can reduce the need for ventilation or reduce the need for re-ventilation following extubation and may reduce BPD – HFNC can be used as an alternative to CPAP for some babies with the advantage of less nasal trauma, provided the center has access to CPAP or NIPPV for those failing this mode

(*Continues*)

Table 3. Summary of recommendations, from the *European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2022 Update*[40] (*continued*)

Invasive MV strategies	– After stabilization, MV should be used in babies with RDS when other methods of respiratory support have failed; duration of MV should be minimized – Lung protective modes such as volume target ventilation or high-frequency oscillation ventilation should be the first choice for babies with RDS who require MV – When weaning from MV, it is reasonable to tolerate a modest degree of hypercarbia provided the pH remains above 7.22; avoid pCO_2 < 4.7 kPa (35 mmHg) when on MV to reduce brain injury – INO in preterm babies should be limited to a therapeutic trial for those in whom there is documented pulmonary hypertension with severe respiratory distress and stopped if there is no response – Caffeine (20 mg/kg loading, 5-10 mg/kg maintenance) should be used to facilitate weaning from MV; early caffeine should be considered for babies at high risk of needing MV, such as those on non-invasive respiratory support – A short tapering course of low dose dexamethasone should be considered to facilitate extubation in babies who remain on MV after 1-2 weeks – Inhaled budesonide can be considered for infants at very high risk of BPD – Opioids should be used selectively when indicated by clinical judgment and evaluation of pain indicators; the routine use of morphine or midazolam infusions in ventilated preterm infants is not recommended
Monitoring and supportive care	– Core temperature should be maintained between 36.5 and 37.5°C at all times – Most babies should be started on intravenous fluids of 70-80 mL/kg/day in a humidified incubator, although some very immature babies may need more; fluids must be tailored individually according to serum sodium levels, urine output, and weight loss – Parenteral nutrition should be started from birth; amino acids 1.5-2 g/kg/day should be started from day one and quickly built up to 2.5-3.5 g/kg/day; lipids 1-2 g/kg/day should be started from day one and built up to a maximum of 4.0 g/kg/day as tolerated – Enteral feeding with mother's milk should be started from the first day if the baby is hemodynamically stable – In infants with RDS, antibiotics should be used judiciously and stopped early when sepsis is ruled out
Managing blood pressure and perfusion	– Treatment of hypotension is recommended when it is confirmed by evidence of poor tissue perfusion such as oliguria, acidosis, and poor capillary refill rather than purely on numerical values; treatment will depend on the cause – If a decision is made to attempt therapeutic closure of the PDA, then indomethacin, ibuprofen, or paracetamol can be used with a similar efficacy; paracetamol is preferred when there is thrombocytopenia or concerns about renal function – Hemoglobin (Hb) concentration should be maintained within acceptable limits; Hb thresholds for infants with severe cardiopulmonary disease are 12 g/dL (HCT 36%), 11 g/dL (HCT 30%) for those who are oxygen dependent, and 7 g/dL (HCT 25%) for stable infants beyond 2 weeks of age
Miscellaneous	– Surfactant can be used for RDS complicated by congenital pneumonia – Surfactant therapy can be used to improve oxygenation following pulmonary hemorrhage – Surfactant therapy can be used to improve oxygenation following meconium aspiration syndrome

BIPAP: bi-level positive airway pressure; CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; GA: gestational age; HFNC: high flow nasal cannula; HTC: hematocrit; INO: inhaled nitric oxide; LISA: less invasive surfactant administration; MV: mechanical ventilation; NIPPV: nasal intermittent positive pressure ventilation; PDA: patent ductus arteriosus; PIP: peak inspiratory pressure; RDS: respiratory distress syndrome; SpO_2: peripheral saturation of oxygen.

should not be used in preterm infants below 28 weeks of gestational age because of an increased risk of intraventricular hemorrhage[55]. Oxygen for resuscitation should be controlled using a blender, using an initial FiO_2 of 0.30 for babies of < 28 weeks' gestation, 0.21-0.30 for those at 28-31 weeks, and 0.21 for 32 weeks› gestation and above[40]. Babies breathing spontaneously should be started on nasal continuous positive airway pressure (NCPAP) rather than intubated in the delivery room to reduce the risk of BPD[56]. Recent data does not support the routine use of sustained inflations at birth and it does not reduce the risk of BPD[57,58]. Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs[40].

Early respiratory support

Data from randomized controlled trials and meta-analyses support the early initiation of NCPAP for preterm neonates at risk of BPD[56,59-61]. Nasal bi-level CPAP (or biphasic CPAP or SiPAP) and nasal intermittent positive pressure (NIPPV) have been shown to reduce the need for intubation when compared to NCPAP, although they are not associated with a reduced risk for BPD[62]. Nasal bi-level CPAP uses delta pressures of 3-6 cmH_2O above positive end expiratory pressure (PEEP) and is not as effective as NIPPV given by a ventilator device in reducing hypercarbia[63]. A subgroup analysis of a large multicenter randomized controlled trial comparing outcomes of infants on NIPPV versus bi-level NCPAP

did not show a significant difference in the composite outcome of BPD or BPD/death, but morbidity was higher in the bi-level NCPAP group[63].

A recent meta-analysis of eight trials involving 463 patients, showed that nasal high-frequency oscillatory ventilation (NHFOV) significantly improved CO_2 clearance and reduced the need for intubation compared to NCPAP/bi-level CPAP[64].

NIV-NAVA (non-invasive neurally-adjusted ventilatory assist) detects the electrical activity of the diaphragm and is able to synchronize non-invasive ventilation with the patients' inspiratory efforts, allowing for a decrease in the work of breathing. According to a study by Yagui A.C. et al., in infants with respiratory distress after birth, no differences in treatment failures were observed between NIV-NAVA and NCPAP[65]. Other small, randomized controlled trials have shown that NIV-NAVA is as effective as NCPAP in preventing extubation failure, but large trials studying the outcome of BPD in extremely preterm infants are needed before NIV-NAVA can be routinely recommended[66].

High-flow nasal cannula has become popular but showed similar results when compared to NCPAP in relation to the risk of BPD, air leak syndrome, and nasal injury[67].

Invasive mechanical ventilation

If intubation cannot be avoided and invasive mechanical ventilation has to be started, strategies using volume-targeted ventilation are advised[68]. One meta-analysis by Klingenberger C. et al. demonstrated that infants ventilated using volume-targeted ventilation compared to traditional pressure-limited ventilation (PLV) modes had lower rates of death or BPD, pneumothoraces, hypocarbia, severe cranial ultrasound pathologies, and shorter durations of ventilation compared to infants ventilated using PLV modes[69].

Today, there are no strong recommendations for the primary use of high-frequency oscillatory ventilation (HFOV) in preterm infants, to prevent BPD. A systematic review and meta-analysis of ten randomized controlled trials, with the primary outcomes being death or BPD at 36 weeks' postmenstrual age, death or severe adverse neurological event, or any of these outcomes, did not support the use of HFOV on the basis of gestational age, birthweight for gestation, initial lung disease severity, or exposure to antenatal corticosteroids[70].

The requirement of invasive mechanical ventilation at day seven of life is associated with an increased risk for BPD. The general advice is to wean during the first week of life and attempt extubation if settings are low[67]. In invasively ventilated preterm infants, the total number of ventilation days is more predictive of BPD than the number of courses of invasive ventilation[71].

Permissive hypercarbia is a reasonable strategy to allow a moderate increase in $PaCO_2$ during weaning, provided the pH is acceptable[40].

Surfactant

Surfactant administration in the course of neonatal RDS is an important measure that improves lung compliance and helps to reduce ventilator settings, ventilator days, and supplemental oxygen requirements, while also facilitating extubation, thus reducing the risk of BPD[72].

Less-invasive surfactant therapies (LIST) use surfactant instillation through a thin tracheal catheter in spontaneously breathing infants, rather than administering surfactant through an endotracheal tube (InSurE technique). A systematic review and meta-analysis by Rigo V. et al. revealed that LIST strategies decrease the risks of BPD, of death or BPD, and of NCPAP failure compared to strategies where surfactant is administered through an endotracheal tube[73]. Specialized catheters designed for this method, known as less-invasive surfactant administration (LISA), are now commercially available. There is a better chance of achieving success when LISA is used without sedation. With the increased use of antenatal steroids and early initiation of NCPAP, outcomes are best if surfactant is reserved for infants showing clinical signs of RDS (early rescue administration)[40]. Poractant alfa, at an initial dose of 200 mg/kg, is associated with increased survival when compared with 100 mg/kg of beractant or 100 mg/kg of poractant alfa[74]. Third-generation synthetic surfactants containing proteins B and C have been shown to be promising[72]. Surfactant combined with budesonide significantly reduces BPD, but studies with long-term follow-up are needed before this can be routinely used[75].

Use of supplemental oxygen

The supplemental fraction of inspired oxygen (FiO_2) to be used in the delivery room and during the neonatal period has been the subject of several studies. At present, there is no doubt that continuous peripheral saturation of oxygen (SpO_2) monitoring should be started promptly after birth. Supplemental oxygen should be titrated in order to achieve a SpO_2 of over 80% by five minutes of life, because there is evidence of poorer outcomes where

this is not achieved[76]. Recommendations from the *European Resuscitation Council – guidelines 2021*[52] are for starting in room air at 32 weeks' gestation or more, 21-30% inspired oxygen at 28-31 weeks' gestation, and 30% inspired oxygen at < 28 weeks' gestation[77].

Although oxygen use is an unresolved issue, today for infants requiring supplemental oxygen after transition, most authors recommend the use of saturation targets within the 90-95% range[9,68].

Caffeine

The Caffeine for Apnea of Prematurity (CAP) trial showed that caffeine administration significantly reduced BPD in infants with a very low birth weight, as well as neurodisability at 18 months of age, and improved lung function at 11 years old[78-80]. The standard regimen includes a loading dose of 20 mg/kg of caffeine citrate, followed by 5-10 mg/kg/day; when started within the first two days of life, it appears to lead to a lower risk of BPD. Caffeine is used until drug therapy for apnea of prematurity is no longer needed. The optimal dosage and timing of initiation remain unknown[68]. The most positive effect on the lungs of preterm infants may derive from a reduced need for invasive mechanical ventilation[68].

Postnatal steroids

Dexamethasone reduces both the duration of mechanical ventilation and BPD. When used during the first week of life, dexamethasone increases the risk of neurodevelopment impairment and cerebral palsy; after the first week of life, the neurological effects are secondary to the risks of poor pulmonary outcomes[68]. A low-dose course of dexamethasone (0.89 mg/kg over 10 days) to invasively-ventilated preterm infants, after the first week of life, increases the likelihood of extubation, although it does not reduce BPD[81], and has a weak association with long-term morbidity[82].

Hydrocortisone treatment (4 mg per kilogram of body weight per day tapered over a period of 10 days) starting on postnatal day 14 to 28 did not result in substantially higher survival without moderate or severe BPD. Survival without moderate or severe neurodevelopmental impairment did not differ substantially between the BPD and the placebo groups[83].

In the PREMILOC trial, in extremely preterm infants, the rate of survival without BPD at 36 weeks of postmenstrual age was significantly increased by prophylactic low-dose hydrocortisone administered during the first ten postnatal days (1 mg/kg of hydrocortisone hemisuccinate per day, divided into two doses, for seven days, followed by one dose of 0.5 mg/kg per day for three days)[84]. In this study, hydrocortisone was not associated with a statistically significant difference in neurodevelopment at two years of age[85].

The STOP-BPD study group assessed the effect of hydrocortisone initiated between seven and 14 days after birth on death or BPD in mechanically-ventilated very preterm infants and found that hydrocortisone did not improve the composite outcome of death or BPD at 36 weeks' postmenstrual age. The authors concluded that these findings do not support the use of hydrocortisone for this indication[86].

Early use of inhaled budesonide is not recommended to prevent BPD, since its use was associated with an increase in mortality[87]. A meta-analysis of 17 trials of early- or late-inhaled corticosteroids showed a significant reduction in BPD without any increase in mortality, offering reassurance that inhaled corticosteroids can be added to current management of developing BPD in preterm infants[88,89]. Although promising, uncertainty about the optimal dose persists and this intervention needs to be tested further in larger, multicenter trials.

A systematic review and network meta-analysis assessed 14 corticosteroid regimens used to prevent BPD in preterm neonates with a gestational age of 32 weeks or younger and for whom a corticosteroid regimen was initiated within four weeks of postnatal age: moderately early-initiated, low cumulative dose of systemic dexamethasone (MoLdDX); moderately early-initiated, medium cumulative dose of systemic dexamethasone (MoMdDX); moderately early-initiated, high cumulative dose of systemic dexamethasone (MoHdDX); late-initiated, low cumulative dose of systemic dexamethasone (LaLdDX); late-initiated, medium cumulative dose of systemic dexamethasone (LaMdDX); late-initiated, high cumulative dose of systemic dexamethasone (LaHdDX); early-initiated systemic hydrocortisone (EHC); late-initiated systemic hydrocortisone (LHC); early-initiated inhaled budesonide (EIBUD); early-initiated inhaled beclomethasone (EIBEC); early-initiated inhaled fluticasone (EIFLUT); late-initiated inhaled budesonide (LIBUD); late-initiated inhaled beclomethasone (LIBEC); and intratracheal budesonide (ITBUD). A total of 62 studies involving 5,559 neonates (mean gestational age of 26 weeks) were included. The results of this study suggested that MoMdDX, a moderately early-initiated (8-14 days), medium cumulative dose (2-4 mg/kg), short course (< 8 days) of systemic dexamethasone might be the most appropriate regimen for preventing the risk of BPD or mortality at 36 weeks, with low-quality evidence. In view of the observed low

confidence in the evidence, the successful outcome and safety of this regimen need to be confirmed by an adequately-powered multicentric randomized controlled trial[90].

Late systemic corticosteroids have been reserved for infants who cannot be weaned from mechanical ventilation. The role of late systemic corticosteroids for infants who are not intubated is unclear and needs further investigation. Longer-term follow-up into late childhood is vital for assessing important outcomes that cannot be assessed in early childhood, such as the effects of late systemic corticosteroid treatment on higher-order neurological functions, including cognitive function, executive function, academic performance, behavior, mental health, motor function, and lung function. Further, randomized controlled trials of late systemic corticosteroids should include longer-term survival free from neurodevelopmental disability as the primary outcome[91].

Diuretic therapy

Preterm infants with evolving or established BPD may develop chronic, mild pulmonary edema. Diuretics have been used "off label" to prevent or treat BPD. Diuretic therapy with furosemide is associated with several adverse consequences, such as reduced weight gain, electrolyte losses, metabolic bone disease, and nephrocalcinosis[68]. Loop diuretics and thiazides are still used in preterm infants on high-level respiratory support and should be used judiciously and limited to those that show clinical improvement[9,68,92].

The association of the potassium-sparing diuretic spironolactone with hydrochlorothiazide was associated with modest improvements in respiratory support requirements, but significant electrolyte abnormalities and a slowing down in weight gain[93].

Due to the side effects and the absence of benefits, diuretics became not recommended for routine chronic use. Sporadic use may be considered in preterm infants with pulmonary edema and worsening respiratory status[94].

Inhaled bronchodilators

Muscular bronchial hyper-responsiveness is increased in infants with BPD but there is no evidence that the use of bronchodilators reduces BPD or mortality. Bronchodilators include beta-agonists (isoproterenol, salbutamol, levalbuterol, and terbutaline), anticholinergics (atropine and ipratropium), and methylxanthines (theophylline, aminophylline, and caffeine). Bronchodilators are now reserved for symptomatic severe BPD with asthma-like symptoms[68,94].

Fluid restriction and patent ductus arteriosus treatment

A high fluid intake during the first week of life may cause pulmonary edema and increase the risk of BPD[72].

Persistent patent ductus arteriosus (PDA) has been historically associated with the development of BPD. Mandatory closure versus a non-intervention approach for PDA gave rise to conflicting results. More studies are needed to assess the benefits and risks of non-intervention for hemodynamically significant PDA[9].

Nutritional strategies

Adequate nutrition will promote lung repair and growth. A low caloric intake during the first weeks of life is associated with BPD development[95].

Infants with early or developing BPD should be fed with human milk, preferably with fortified fresh maternal milk[68]. Ideally, infants with BPD should receive a fluid intake of no more than 135-150 ml/kg/day and an energy intake of 120-150 kcal/kg/day[96,97]. Providing high energy in a low volume remains a challenge and is the main cause of growth restriction in these infants. They need a nutritional strategy that encompasses early aggressive parenteral nutrition and the initiation of concentrated feedings of energy and nutrients. The order of priority is fortified mother's own milk, followed by fortified donor milk, and preterm enriched formulas[68]. Specialized nutritional strategies may be needed to overcome difficulties that are common in BPD infants, such as gastroesophageal reflux and poorly coordinated feeding[96]. Table 4 summarizes a practical nutritional approach to use in infants at risk of, or with, BPD[96,97].

Vitamin A

Preterm infants treated with intramuscular vitamin A were shown to have a lower risk of BPD at 36 weeks of gestational age; nevertheless, vitamin A did not reduce mortality, duration of mechanical ventilation, or length of hospital stay, and it did not improve neurodevelopmental outcomes at 18-22 months of age. Also, intramuscular administration is painful and must be repeated several times (i.e., 5000 U i.m. three times/week for a total of 12 doses) and has been associated with an increased risk of sepsis[98-100].

Enteral water-soluble vitamin A (5000 IU/day) started within 24 hours of introducing feeds and continued until 34 weeks' postmenstrual age improved plasma retinol

Table 4. Nutritional approach in infants at risk of, or with, established BPD[96,97]

Preventive nutritional approach in infants at high risk of BPD	
Avoid excessive fluid intake	In the first postnatal day: 80-100 mL/kg/day After the first postnatal week: 135-150 mL/kg/day
Provide adequate incubator humidity	In the first postnatal week: 60-70%
Maintain adequate temperature	Abdominal skin: 36.0-36.5°C Inspired air temperature (hood, CPAP, or ventilator): 34.0-41.0°C, relative humidity of 100%
Optimize early parenteral energy intake	In the first postnatal week: 80-100 kcal/kg/day After the first postnatal week: 120-150 kcal/kg/day
Optimize early parenteral amino acid intake	Start with 1.5-2 g/kg/day after birth Increase to 3.5 g/kg/day from the first 48-72 postnatal hours
Optimize early parenteral fat intake	Start with 1.0-2.0 g/kg/day within the first postnatal day Increase by 0.5-1.0 g/kg/day up to a maximum of 4.0 g/kg/day at 72-96 postnatal hours
Provide adequate intravenous glucose	Limit the rate to 12 mg/kg/min (ideal limit: 8.3 mg/kg/min)
Optimize early parenteral calcium (Ca) and phosphorus (P) intake	In the first postnatal week: parenteral Ca 32-80 mg/kg/day and P 31-62 mg/kg/day After the first postnatal week: parenteral Ca 100-140 mg/kg/day and P 77-108 mg/kg/day Parenteral Ca/P ratio: 1.3 (mass) or 1 (molar)
Provide adequate intravenous lipid soluble vitamins	Vitamin A (retinol) 227-455 µg/kg/day or 700-1500 IU/kg/day Vitamin E (α-tocopherol) 2.8-3.5 IU/kg/day
Provide adequate intravenous trace elements	Particularly zinc 400-500 µg/kg/day
Initiate early enteral feeding	Initiate minimal enteral feeding (12-24 mL/kg/day) prior to 3rd postnatal day Use preferably mother's own milk or donor human milk as second choice
Nutritional management in infants with established BPD	
Fluid restriction	Less than 150 mL/kg/day Ideally, up to 135 mL/kg/day
Optimize enteral energy intake	Ideally, 120-150 kcal/kg/day
Optimize enteral amino acid intake	< 1000g body weight: 4.0-4.5 g/kg/day 1000-1800g body weight: 3.5-4.0 g/kg/day
Optimize enteral lipid intake	Total lipid intake 4.8-6.6 g/kg/day Arachidonic acid 12-30 mg/kg/day Docosahexaenoic acid 18-42 mg/kg/day
Optimize enteral calcium and phosphate intake	Ca 120-140 mg/kg/day; 150-220 mg/kg/day P 60-90 mg/kg/day; 75-140 mg/kg/day Ca/P ratio: 2 (mass)
Optimize sodium intake if diuretics are used	Provide sodium supplement to maintain serum Na>135 mEq/L
Optimize enteral vitamin A intake	400-1000 µg/kg/day or 1320-3300 IU/kg/day
Optimize enteral vitamin E (α-tocopherol) intake	2.2-11 mg/kg/day
Supplemental iron	4 mg/kg/day, from 4-8 postnatal weeks up to 12 months of life

levels in extremely preterm infants but did not reduce the severity of BPD[101].

Pulmonary vasodilators

Pulmonary hypertension often complicates severe forms of BPD and increases mortality. Pulmonary hypertension should be looked for in moderate/severe forms at 36 weeks of post-menstrual age, or during aggravating BPD. The pulmonary hypertension results from a structural component (fixed component) caused by abnormal development of pulmonary vessels, and an increased vascular resistance (reactive component)[94]. This reactive component can be treated with

Table 5. Summary of BPD management *(adapted from ref[68,96,97,104])*

Evolving BPD (> 1 postnatal week until 36 weeks post-menstrual age)	
Dexamethasone	A low-dose course of dexamethasone (0.89 mg/Kg over 10 days) to invasively ventilated preterm infants, after the first week of life, increases the likelihood of extubation
Methylxantines	Maintain caffeine (started within the first 3 days of life) until apneas are no longer present
Ventilation	Avoid endotracheal tube ventilation, encourage non-invasive support Blood gas targets: pH 7.25-7.35; PaO_2 50-70 mmHg; $PaCO_2$ 50-60 mmHg
Nutrition (see table 5)	Fluid intake: 135-150 mL/kg/day Energy intake: 120-150 kcal/kg/day Enteral feeding: the order of priority is fortified mother's own milk, followed by fortified donor milk, and preterm enriched formulas
Diuretics	May improve respiratory mechanics and facilitate weaning of ventilatory support; continue only if there is a clear response
Inhaled corticosteroids	Can be used to improve symptoms
Established BPD (> 36 weeks post-menstrual age)	
Ventilatory strategy	Hood oxygen, low-flow nasal cannula, high-flow nasal cannula, NIPPV, NCPAP, invasive IPPV Ventilatory settings in severe BPD: tidal volume 8-12ml/kg; PIP needed to deliver tidal volume may vary between 30-40 mmHg; inspiratory time: 0.4-0.8 s; frequency: 20-30/sec; PEEP: 6-10 cmH2O Target SpO_2: 90-95%; if PH $\geq$ 95% Target blood gases: pH > 7.22; PaO_2 50-70 mmHg; $PaCO_2$ 45-60 mmHg Tracheostomy: no consensus when to perform; for infants still requiring mechanical ventilation at 90-100 days of life who failed several (> 5-7) attempts at extubation, a tracheostomy should be considered
Oxygen targets	After 40 weeks of postmenstrual age and the maturation of retinal vascularity (documented by ophthalmology), oxygen output should be sufficient to maintain a peripheral oxygen saturation (SpO_2) - $\geq$ 93%. In patients with documented pulmonary hypertension or poor weight gain a SpO_2 recommended is $\geq$ 95%
Echocardiographic screening for pulmonary hypertension	About 25% of infants with moderate or severe BPD have echocardiographic evidence of pulmonary hypertension Supplemental oxygen should be supplied when target oxygen saturations are > 95% for infants with proven pulmonary hypertension INO may be considered in individual cases of BPD during acute pulmonary hypertension crisis Analgesia and sedation should be used before procedures to avoid pulmonary hypertension crisis Sildenafil may be used to treat BPD-associated pulmonary hypertension in selected cases, after consultation with a pediatric cardiologist; bosentan is often used as a second-line therapy, after sildenafil
Diuretics	Diuretic therapy in preterm infants remains controversial, given its negative impact on growth and the risk for metabolic bone disease. Treatment with hydrochlorothiazide and spironolactone may be considered in infants with severe BPD. However, indications and duration of diuretic treatment should be discussed in a multidisciplinary team, involving cardiologists, neonatologists, pulmonologists, and nutritionists. Consider allowing infant to outgrow dose
Bronchodilators	May improve symptoms in subpopulations of affected infants
Inhaled corticosteroids	May improve symptoms in subpopulations of affected infants
Nutrition	Fluid restriction: less than 150 mL/kg/day, ideally, up to 135 mL/kg/day Optimize enteral energy intake: ideally, 120-150 kcal/kg/day
Immunization	Before discharge, start prophylaxis against respiratory syncitial virus infection during winter season

BPD: bronchopulmonary dysplasia; INO: inhaled nitric oxide; IPPV: intermittent positive pressure ventilation; NCPAP: nasal continuous positive airway pressure; NIPPV: nasal intermittent positive pressure ventilation; PEEP: positive end expiratory pressure; PH: pulmonary hypertension; PIP: peak inspiratory pressure; SpO_2: peripheral oxygen saturation.

pulmonary vasodilators including inhaled nitric oxide (iNO), sildenafil, and bosentan. Although iNO is not recommended for routine use for either BPD prophylaxis or BPD-associated pulmonary hypertension, its use may be considered in individual cases of BPD during acute pulmonary hypertension crisis[94].

Only two drugs have so far been approved by the regulatory European Medicines Agency (EMA) for

pediatric patients with pulmonary arterial hypertension, which is sildenafil (body weight ≥ 8 kg and > one year old) and bosentan (age > one year), and only bosentan has been approved by the Food and Drug Administration (FDA) for chronic use in children > three years of age. However, both sildenafil and bosentan are frequently used for acute and long-term treatment of infants with BPD-associated pulmonary hypertension. In the absence of randomized clinical trial data, use of pulmonary hypertension targeted medications in infants is based on expert opinion and experience, underlining the necessity of comprehensive evaluation in expert centers according to current international recommendations. Sildenafil, a selective phosphodiesterase-5 (PDE-5) inhibitor, prolongs smooth muscle relaxation, and its use has been increasing over time. Sildenafil may be used to treat BPD-associated pulmonary hypertension in selected cases, after consulting with a pediatric cardiologist[94]. Bosentan, a non-selective competitive antagonist of ET-1 receptor reverses entothelin-mediated smooth muscle constriction and is often used as a second-line therapy, after sildenafil, in severe BPD with pulmonary hypertension[94].

Macrolides

Respiratory tract colonization with the genital mycoplasma species Ureaplasma parvum and Ureaplasma urealyticum in preterm infants is a known risk factor for BPD. Specific virulence factors, pathogen-host interactions, and variability in genetic susceptibility contribute to chronic infection, inflammation, and altered lung development[102].

Macrolides inhibit neutrophil chemotaxis, tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 and consequently exert an anti-inflammatory action[94]. Studies with erythromycin did not show a decrease in either the incidence or severity of BPD in preterm infants[94]. Azithromycin showed inconsistent results and was associated with a reduction in BPD in some studies and, like erythromycin, is associated with development of hypertrophic pyloric stenosis. While azithromycin may decrease the incidence of BPD, there is insufficient evidence regarding dosage, duration, and timing of therapy, and its routine prophylactic use for BPD prevention in preterm infants is not recommended[94]. The AZTEC trial (ISRCTN11650227) aims to assess the effect of azithromycin on BPD and is ongoing[103]. The role of clarithromycin has not yet been established[94].

Future directions

Mesenchymal stromal cells (MSC) facilitate healing in injury sites and may prove to be useful against BPD, but they are still in the experimental phase[94]. Recombinant human erythropoietin (rhEPO) was shown to reduce BPD in some retrospective studies. However, a meta-analysis consisting of 17 trials, and the PENUT (Preterm Erythropoetin Neuroprotection) trial showed no significant benefit[94]. rhEpo in combination with MSC has not yet been studied in humans. Docosahexaenoic acid (DHA), clara cell protein, superoxide dismutase (SOD), pentoxifylline, citrulline, and inositol are experimental therapies and safety and efficacy still need to be established[94].

Table 5 summarizes BPD management according to current evidence and knowledge.

Conclusions

BPD is a complex and multifactorial lung disease of the preterm neonate. The lack of an objective definition makes it difficult to evaluate new treatments. Despite improvements in treatment research, only a few treatments available are supported by high-quality evidence. Several, promising, novel therapies are under study and may change the course of the disease in the future.

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Conflicts of interest

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