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Review

Bronchopulmonary dysplasia: the more we learn, the less we know

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Abstract

Bronchopulmonary dysplasia (BPD) is a chronic lung disease typical of preterm infants. It is associated with high morbidity and risk of short- and long-term mortality. Despite improvements in perinatal care, its incidence has remained relatively constant: it occurs in 40-45% of infants born before the 29th week of gestation.

Current definitions of this disease show several limitations, and this could be linked, in particular, to its multifactorial pathogenesis. Today, BPD occurs more commonly in extremely preterm infants, and it is characterized by a milder but longer course, mainly due to the extreme immaturity of the lungs at birth, with arrested maturation in the canalicular or early saccular stage, interruption of alveolarization, altered and dysregulated microvascular development, high pulmonary vascular resistance, and abnormal vascular reactivity.

The pathogenesis of BPD is multifactorial: prolonged exposure to high oxygen levels, the lung damage caused by mechanical ventilation, the inflammatory state and, last but not least, the epigenetic/genetic risk factors. Further investigations concerning BPD pathogenesis showed that extremely preterm birth is associated with significative dysbiosis in airway microbiome.

In the future, metabolomics, thanks to its ability to identify instant variations of metabolites possibly related to disorders, could help to recognize those associated with BPD and its pathways alterations.

Keywords

Bronchopulmonary dysplasia, chronic lung disease, embryogenesis and lung, epigenetics, physiopathology, perinatal and postnatal factors.

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Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease typical of preterm infants. It is associated with high morbidity and short- and long-term mortality risk. Despite improvements in perinatal care, its incidence has remained relatively constant: it occurs in 40-45% of infants born before the 29th week of gestation [1].

Current definitions of this disease show several limitations, and this could be linked, in particular, to its multifactorial pathogenesis. Because of the high variability in BPD clinical presentation, most old definitions are now considered obsolete. Moreover, the broad spectrum of definitions has led to the need for uniform diagnostic criteria among neonatologists and a wide variability in its incidence among different centers. According to the 2001 National Institutes of Health Consensus Conference, BPD can be diagnosed in infants born before 32 gestational weeks who require supplemental oxygen for the first 28 days of life. Mild, moderate, or severe form is then assessed based on the amount of supplemental oxygen and modality of respiratory support at 36 weeks. In infants born after 32 weeks of gestation, severity is evaluated on the 56th day. However, this definition still has some shortcomings: first of all, it is difficult to standardize appropriate oxygen saturation limits for preterm infants in the various centers; secondly, it tends to classify a chronic disease based on oxygen exposure in a specific moment, not considering the multitude of factors that can influence saturation (e.g., altitude or ventilation modes, the presence of airway obstruction, the administration of some drugs like diuretics, steroids and pulmonary vasodilators) [2].

BPD was first described by Northway et al. as a chronic condition regarding preterm infants who developed severe respiratory insufficiency as a consequence of exposure to high pressures of oxygen and ventilation [3]. Today, BPD occurs more commonly in extremely preterm infants, and it is characterized by a milder but longer course, mainly due to the extreme immaturity of the lungs at birth, with arrested maturation in the canalicular or early saccular stage, interruption of alveolarization, altered and dysregulated microvascular development, high pulmonary vascular resistance, and abnormal vascular reactivity [4].

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) held a workshop on BPD in October 2016. On this occasion, a new definition of BPD was proposed to consider the most recent non-invasive ventilation (NIV) modalities (that had been excluded in the previous definitions) and a severity-based classification. It has been proposed to use the terms "grade I, II and III" because "mild, moderate and severe" may be interpreted differently by each clinician. Furthermore, Higgins et al. suggest moving the timepoint to 36 weeks to make the diagnosis of BPD possible for many currently excluded patients. The new ventilation strategies, such as low flows providing 100% oxygen or high flows with 21% oxygen, make some children not classifiable according to standard definitions [5].

The pathogenesis of BPD is multifactorial: prolonged exposure to high oxygen levels, lung damage caused by mechanical ventilation, the inflammatory state and, last but not least, the epigenetic/genetic risk factor. Epigenetic mechanisms, such as DNA methylation, histone modification and microRNA (miRNA or miR) expression, control the phenotypic programming by determining physiologic responses while contributing to the development of diseases, including BPD [6].

Prematurity, ventilatory support and other iatrogenic factors contribute to abnormal lung development and pulmonary vascular remodeling, thus leading to pulmonary hypertension (PH) and right ventricle failure. Approximately 25% of children born before 32 weeks of gestation with a moderate to severe BPD develop PH. The specific etiology in at-risk children remains unclear. Sallmon et al. suggest that early inflammation plays a relevant role, but more specific risk factors still need to be analyzed. In this work, infants born at 23-25 weeks of gestation were considered at risk of developing BPD-related PH, almost exclusively in case of moderate to severe BPD. At 3 months, 44% of these infants presented PH signs, and after 12 months of age, 18% still showed echocardiographic features of PH that required continuation of pharmacologic

treatment. Although therapeutic options for PH have improved in the last decades, they remain limited, and their use is not usually approved in preterm infants. In addition to supportive care, more patients with BPD receive a PH-targeted therapy (off-label in most cases). The study supports the hypothesis that the targeted therapy is safe even in premature newborns and can improve echocardiographic parameters at 12 months [7].

Moreover, further investigations concerning BPD pathogenesis showed that extremely preterm birth is associated with significant dysbiosis in the airway microbiome. Indeed, patients with BPD show an abundance of *Proteobacteria* and *Firmicutes* and a decrease in *Lactobacilli*. This would also correlate with BPD progression [8].

BPD can therefore be considered the result of a series of developmental dysregulations, including abnormalities in alveolar development and angiogenesis. However, its molecular pathway still needs to be precised. Thus, thanks to its ability to identify instant variations of metabolites possibly related to disorders, metabolomics could help recognize those associated with BPD and its pathways alterations [9].

The accurate identification of at-risk children may be helpful, both for the prognosis and for the potential new therapeutic strategies. A reliable biomarker should have the capacity to be detected in the first stages of the disease to permit early treatment and to avoid or at least minimize its damaging effects. Using "omics" technologies, researchers have studied markers like SPOCK2, vascular endothelial growth factor (VEGF) -624C > G, VEGF -460T > C, specific mast cells markers, miR-219 pathway, miR-152, miR-30a-3p, miR-133b, miR-206, miR-7, lactate, taurine, trimethylamine-N-oxide, gluconate, myoinositol and modifications in the lipid profile of surfactant [10].

Embryogenesis and histological properties of the immature lung

The development of the pulmonary vascular system is a highly complex process in which the expression of multiple transcription and growth factors regulates the different development stages. The normal development of the lung can be disrupted at different levels and stages, playing a pivotal role in the pathogenesis of several neonatal pulmonary vascular diseases, including BPD. To clarify the pathogenetic processes of BPD, the comprehension of the developing lung response to insult and its repair mechanisms is fundamental.

The stages of lung development are presented in **Fig. 1**.

Lung development starts with the appearance of the lung bud, which is divided into two lungs. At the 34th day of gestation, in the human embryo, every pulmonary bud is already perfused by a pulmonary artery. Lung development comprehends five different stages (embryonic, pseudoglandular, canalicular, saccular and alveolar). The alveolar stage, characterized by the gas exchange surface development, starts at the 36th gestational week and continues after birth and until the third year of life.

Pulmonary vascular development is closely related to airway development and is governed by two main mechanisms: vasculogenesis and angiogenesis. Vasculogenesis is the process through which the angioblasts differentiate themselves and create *de novo* blood vessels. During angiogenesis, new blood vessels are made by direct extension of pre-existing vessels. VEGF is a crucial regulator of pulmonary vascular development, together with the transforming growth factor beta (TGF-β) [11]. It is noteworthy that promising future therapies, such as the use of mesenchymal stem cells and extracellular vesicles, would bring histological improvements in BPD animal models, probably thanks to the paracrine effects of humoral factors like interleukin (IL)-6 and IL-8, VEGF, collagen, and elastin [12].

The fetal lung is created around the 3rd to 6th gestational week from the endodermic cells of the primitive anterior gut. During the embryonal period, the respiratory system draft emerges from the ventral region of the anterior endoderm of the anterior gut and separates itself from the esophagus. During the pseudoglandular stage, the lung buds proliferate and invade the splanchnic mesenchyme through branching morphogenesis to create the airway. In the saccular stage, epithelial cells covering the airway undergo differentiation and produce cuboid pre-alveolar AT2 and squamous AT1 cells. During the transition from the saccular to the alveolar stage, the acinus structures expand and create peripheral sacculi and alveoli. The lung turns from a glandular-like tissue to an alveolar structure where gas exchange can occur. During the third trimester (28th-40th gestational week), peripheral sacculi undergo a septation process: in this way, through the increase in the number of alveoli and the expansion of the gas-exchange surface, there is a further division of airway spaces. The peripheral lung epithelial cells mature into alveolar type 1 (AT1) and alveolar type 2

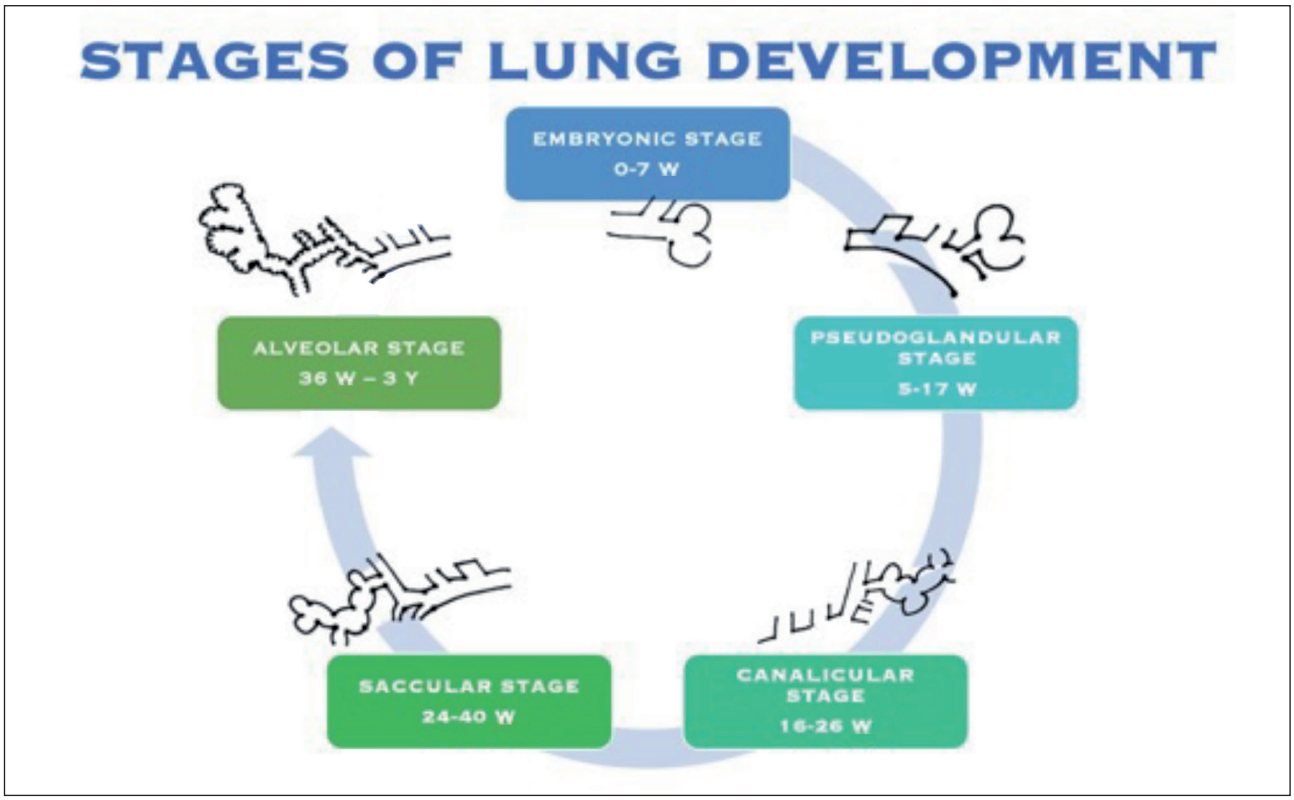

Figure 1. The stages of lung development: embryonic, pseudoglandular, canalicular, saccular and alveolar stage. W: weeks.

(AT2) cells. AT2 cells produce surfactant, a complex mix of phospholipids and surfactant proteins whose synthesis depends on AT2 cells' differentiation [13].

From a histopathological point of view, BPD is characterized by a reduction in arterial structures [14]. However, the platelet endothelial cells adhesion molecule (PECAM)-1, which is used to evaluate microvascular growth, is reduced in infants who require a short assistance period with ventilation, while, on the contrary, it is increased after prolonged ventilation. This suggests a reduction in endothelial proliferation, followed by a rapid proliferative response. The dysmorphic pulmonary vascular growth in BPD may not necessarily result simply from the reduction in the number of endothelial cells. Ventilation induces a significative expansion of pulmonary micro-vessels, but the scarcity of branches could reduce gas exchange efficiency in the parenchyma [15]. The damage during the vulnerable saccular or early alveolar stage results in an arrest of alveolarization, accompanied by fibrosis of the surrounding alveolar mesenchyme [16].

Premature infants of 22-23 gestational weeks begin ventilation in the canalicular-saccular stage of lung development well before morphogenesis and alveolar differentiation is completed. The lack of surfactant due to incomplete differentiation of AT2 cells causes respiratory distress syndrome (RDS). Histologically, very preterm babies' lungs consist of uniformly aligned air spaces covered by cuboid epithelial cells. As the lung matures, this epithelial lining becomes progressively thinner until, as it happens in full-term infants, alveoli are composed of a thin layer of squamous cells that resembles the adults' lungs. The relative number of cuboid cells gradually decreases while the squamous type increases. At least partially, survival in the extrauterine environment depends on this factor [14].

BPD is characterized by the interruption of alveolarization and microvascular development, resulting in inadequate gas exchange. Since most patients survive, few biopsy studies exist. The respiratory system is studied using imaging techniques showing different and heterogenous pictures. This suggests that BPD may result from multiple pre- and postnatal exposures, which could interrupt specific developmental pathways and promote injuries [17].

Moreover, patients with BPD have a higher risk of developing chronic obstructive bronchopneumopathy because of the persistence of emphysematous areas, bronchial wall thickening and interstitial opacities even in adulthood [12].

Supplemental oxygen, positive-pressure ventilation and postnatal sepsis determine pulmonary inflammation. However, proinflammatory cascades are complex, and all the clinical attempts to contrast these mechanisms, such as antioxidants and inflammation modulators, have been useless for BPD treatment in neonates. The only exception has been represented by corticosteroids, which would reduce the incidence of BPD when given immediately after birth and prevent the progression of lung damage if administered during the first weeks of life.

Knowledge of the interactions between lung development, injuries and repairs is necessary to develop an effective treatment.

Bronchopulmonary dysplasia and epigenetics

Epigenetics studies heritable gene expression changes triggered by mechanisms other than the expressed DNA sequence. Some environment-induced epigenetic DNA alterations can block cellular development, thus leading to changes in gene expression. In the context of lung cells, these mechanisms can modify pulmonary structure and function, but they can also allow the epigenome to drive the gene expression response to future damage and pulmonary repair. Both direct and epigenetic effects can modify the alveolar and capillary development by increasing vascular permeability and inflammatory responses, thus promoting the development of BPD. Epigenetic alterations may be partially responsible for the subsequent development of PH and increased susceptibility to respiratory tract infections [18].

The epigenetic mechanisms are complex: alterations affecting locus NOS3 in pulmonary endothelial artery cells in a mouse model appear to be associated with a pathological expression pattern of endothelial nitric oxide synthase (eNOS) following oxygen exposure. Furthermore, NOS3 mRNA levels increase in pulmonary artery cells after neonatal exposure to oxygen in newborn mice.

Some studies have reported an increase in global DNA methylation levels in human cells in the case of short-term oxygen treatment, while long-term treatment has the opposite effect. Recent researches suggest the involvement of the methylation of genes of the TGF-β pathway in the reaction of lung tissue to hyperoxia: it seems that the oxygen excess could trigger hypermethylation of the path, with the subsequent apoptosis stimulation. This, in turn, can lead to modifications in lung morphogenesis with altered branching and alveolarization. However, further experiments are necessary to clarify the precise mechanisms of the epigenetic influence of hyperoxia on lung tissue and their contribution to BPD development [19].

DNA methylation, histone modifications and miRNA expression play a significant role in regulating gene expression, especially in the lung tissue to environmental signals. To determine the impact of epigenetic programming on lung development and BPD, epigenetic modifications help directly associate factors and transcriptional machinery to the correct position in genes. These modifications could include DNA methylation, histone acetylation and the production of miRNA. DNA methylation is one of the main understood characteristics of epigenetic programming [18].

DNA methylation

DNA methylation is a reversible modification of DNA. It results from adding a methyl group to cytosines in nucleic acids. Neonatal lungs start their formation 4 weeks after conception and continue developing after birth. DNA methylation is crucial and plays a vital role in cell differentiation.

In human embryonic lung cells, methylation of CpG islands has been frequently found in the proximal promoter regions of tumor protein p53 binding protein 2 (TP53BP2) and apoptotic protease activating factor-1 (Apaf-1) [18].

It has been demonstrated that the methylation of CpG island in the promoter region VEGF-A of fetal distal lung epithelial cells during the pseudo-glandular/canalicular stage has an essential role in the vascular growth of the cardiopulmonary system.

Genes regulated by DNA methylation are also involved in inflammation. The analysis of these mechanisms can contribute to understanding how DNA methylation is related to normal and impaired lung development [20].

Histone acetylation

Histone modifications also play a relevant role in the epigenetics of lung development. Gene expression patterns can be controlled by a complex combination of histone acetylation and deacetylation [21].

MicroRNA

MiRNA is a class of small non-codifying RNA that inhibits gene expression by promoting mRNA

degradation or interrupting translation. Current studies require further analyses but support the crucial role of miRNA in lung development and suggest crosstalk between epigenetic mechanisms.

Dicer is an essential protein for miRNA elaboration. It is expressed in the lung epithelium and the developing mesoderm. Its defect can determine severe branching and epithelial structure defects, leading to perinatal death.

During the embryonic phase, miR-142-3p is upregulated in the embryonic lung mesenchyme, and its inhibition leads to ectopic expression and differentiation of para-bronchial smooth muscle cells' progenitors in the embryonic mouse lung. Likewise, it has been discovered that miR-326 has an essential role in distal epithelium development and interruption of branching patterns and mesenchymal integrity in the embryonic lung.

During the pseudoglandular stage, down-regulation of miR-17, miR-20a, and miR-106b would cause significant branching defects in embryonic lung epithelia. MiR-449a has an essential role in the middle stages of pulmonary development. MiR-26a is highly expressed in the mouse fetal lung, and its knockout promotes the formation of dilated lumens and aerated regions during the alveolar structure maturation in canalicular and saccular stages. MiR-127 is highly represented in the advanced stage of fetal lung development. MiR-17-92 can be downregulated by histone acetylation, thus promoting the diffusion of AT1 cells. MiR-539 and miR-590 inhibition would remarkably reduce alveolar development and lung compliance [18].

Prenatal, perinatal and postnatal factors

Timeline of BPD is presented in **Fig. 2**.

Prenatal factors

Although the close correlation between *in-utero* exposure to possible harmful agents and the subsequent development of BPD is known, most pathogenetic causes act in the postnatal period [22-24].

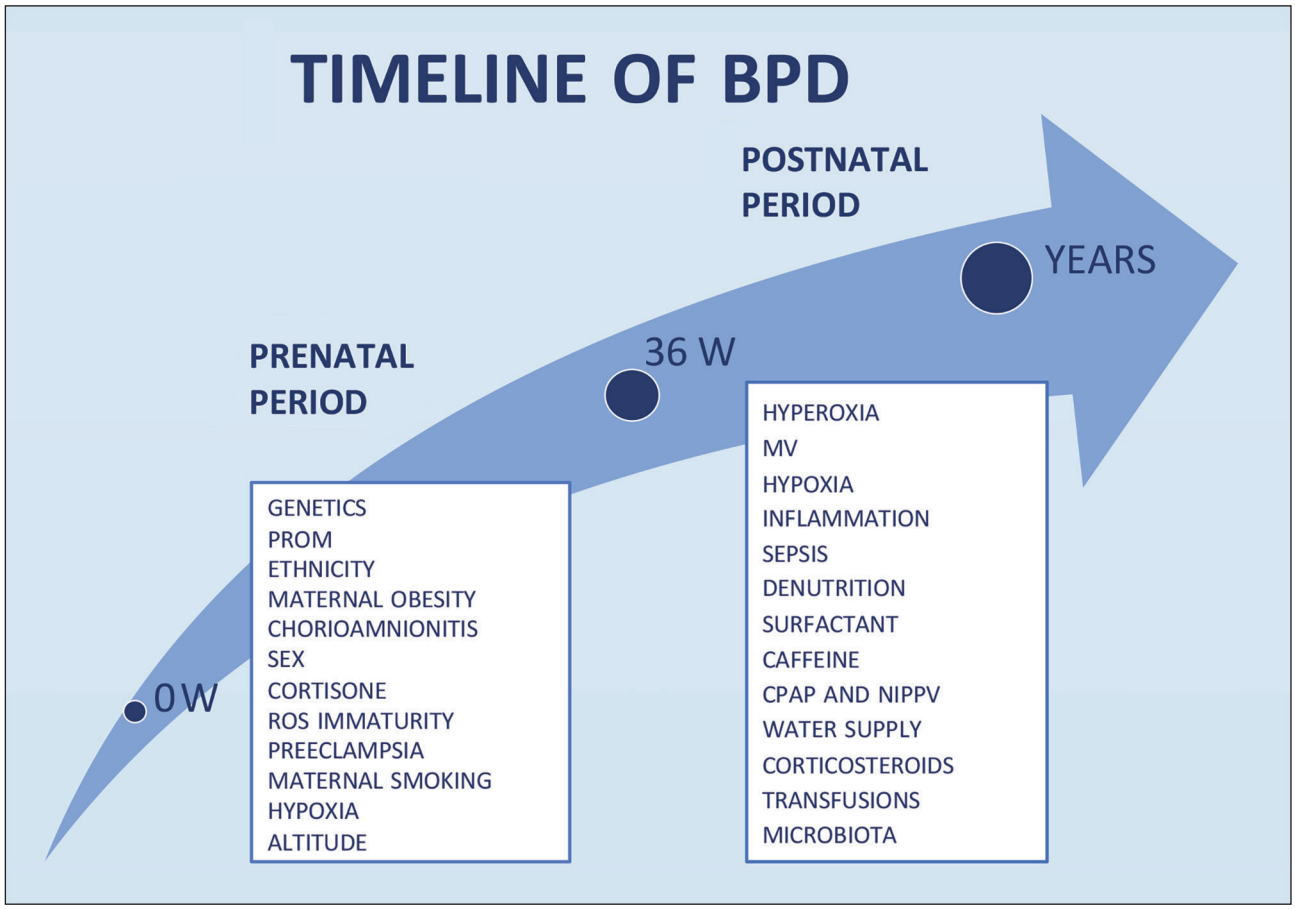

Figure 2. Timeline of bronchopulmonary dysplasia (BPD).
BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; MV: mechanical ventilation; NIPPV: nasal intermittent positive pressure ventilation; PROM: premature rupture of membranes; ROS: reactive oxygen species; W: weeks.

The main predictor for the development of BPD is gestational age at birth: all neonates born extremely premature must be considered at risk due to the anomalies that occurred during pregnancy [25]. However, many other factors can contribute to BPD occurrence: intrauterine growth restriction (IUGR) [26], postnatal extrauterine growth restriction (EUGR), and inflammation have all been proposed as crucial elements in the pathogenesis [27]. What makes the analysis of the epidemiology and pathophysiology of BPD even more complex is that some very premature infants initially have almost normal lung function and later progress towards early respiratory failure. On the contrary, there are infants with early severe respiratory failure who respond poorly to treatment with exogenous surfactant and require a very high concentration of supplemental oxygen and ventilatory support to regain good lung function in a few weeks. These two extreme patterns of respiratory function indicate that some very premature lungs are exceptionally sensible to injury and do not heal, while others are pretty resistant, with good insult response and effective recovery. As already mentioned, this is probably linked to different phenotypes of lung immaturity caused by different genetic backgrounds and influenced by prenatal and early postnatal exposures [14].

Today, most premature newborns survive thanks to prenatal corticosteroids, surfactants, advanced techniques of neonatal assistance and efficient respiratory support devices.

Therefore, BPD characteristics have constantly been evolving in the last 50 years [28]. According to some studies, *in-utero* exposure to stressing factors and genetic susceptibility have increased BPD incidence [29-32]. Each element modifies the lung response to external insults [14].

Genetic susceptibility

It is hypothesized that the variability of DNA gene sequences, particularly in genes involved in lung development, inflammation, and lesion repair, may contribute to BPD pathogenesis by acting on an altered protein function. The analysis of preterm twins' cohorts suggests that heritable factors have a significant role in the risk of BPD [33].

Studies in siblings and twins suggest a high concordance of BPD with shared genetic inheritance [34-37]. Potential modifier genes may include asthma-related genes, genes encoding for surfactants, inflammatory cytokines, and growth factors [38, 39]. It has been demonstrated that the ATP binding cassette family member A3 (ABCA3) has a critical role in surfactant metabolism, with its loss-of-function mutations on both alleles causing severe lung diseases. The hypothesis is that combining heterozygosity (due to loss or reduced function) of the ABCA3 allele and prematurity can lead to severe perinatal lung disease [32, 40].

Premature rupture of membranes

The premature rupture of membranes (PROM) more than a week before delivery has been associated with a tripled risk of BPD. Newborns who lately develop BPD have often been exposed to a long-lasting rupture of membranes; they are more frequently small for gestational age, have lower Apgar scores and require resuscitation at birth. All these aspects suggest that, during fetal life, infants with BPD have already been exposed to factors that cause pulmonary lesions and that "triggered" inflammation [27].

Ethnicity

Ryan et al. recruited a cohort of 835 premature infants, among which 765 survived to the 36th week. Data regarding the development of BPD were available for 707 of these babies. African-American children (105/274, 38%) were significantly less predisposed to developing BPD than Caucasian children (193/433, 45%). The authors concluded that considering the same gestational age, BPD was more common in the Caucasian population. Some recent studies suggest that this finding could be linked to faster lung maturation and surfactant production [41].

A similar situation is that of Japan, which had the lowest mortality but the highest incidence rate of retinopathy of prematurity (ROP) [14]. In this nation, from 2003 to 2016, BPD incidence has increased, while hospital mortality has decreased among extremely premature infants. Of 19,370 infants, 2,244 (11.6%) died by week 36 of post-menstrual age. The mortality rate dropped from 19% in 2003 to 8% in 2016. Among the 17,126 survivors, BPD occurred in 7,792 infants (45.5%), rising from 41.4% in 2003 to 52% in 2016. Advanced assistance in the Neonatal Intensive Care Unit (NICU) reduced mortality but was accompanied by an increase in BPD survivors.

Furthermore, Nakashima et al. showed that the combined incidence of BPD and death increased, especially in infants at 24-27 weeks of gestational

age. Despite the shorter duration of invasive ventilation over time, the increased incidence of BPD suggests that differences in patient population or other management strategies influence the development of the disease. Other individual risk factors include chorioamnionitis (CA), low birth weight, low gestational age, and treated patent ductus arteriosus, and all increased over the study period [42, 43].

Chorioamnionitis and inflammation

Inflammation is the common pathway that causes lung injury. Prenatal insults often precede postnatal inflammatory insults. More than 50% of pregnancies ending in very preterm births (< 28 weeks) have histologic evidence of CA, i.e., inflammation of fetal membranes, maternal decidua, and often of amniotic fluid [44]. It is the leading cause of preterm birth.

The fetal systemic response to inflammation is associated with BPD, intraventricular hemorrhage, cystic periventricular leukomalacia, and cerebral palsy [45].

Moreover, infants who have suffered inflammatory lesions of the placenta show high blood concentrations of cytokines (IL-1b, IL-6, TNF-a), chemokines (IL-8, mip-1b, Rantes, i-tac), adhesion molecules (icam-1, icam-3, and e-selectin), matrix metalloproteinases (mmp-1, mmp-9), VEGF, which correlate with an increased risk of BPD [45]. Finally, the severity of the disease is directly proportional to the severity of CA.

This infection is often associated with *U. Urealyticum*, but other vaginal commensals and pathogens have also been identified [46]. Studies conducted in multiple animal models have demonstrated that fetal breathing exposes the fetal lung to infections and/or inflammation of the amniotic fluid, causing lung inflammation and often a fetal inflammatory response. *U. urealyticum* colonization of the respiratory tract, which can begin *in utero* and be exacerbated postnatally, is a potential risk factor. PROM may be the initiation route for the invasion of the fetal respiratory tract [32]. CA is common among women with PROM [27, 47, 48].

Newborns whose pregnancy was complicated by CA show high blood levels of the protein soluble FMS-like tyrosine kinase 1 (sFlt-1), reducing VEGF signaling and stopping angiogenesis. Wallace et al. have hypothesized that fetal exposure to increased levels of sFlt-1, an endogenous inhibitor of VEGF, may contribute to pulmonary vascular damage, reduce alveolarization and increase the risk of PH in experimental models of preeclampsia and CA. Wallace and his research group have also found that prenatal and postnatal treatment with anti-sFlt-1 mAb, a monoclonal antibody, has preserved pulmonary growth and improved the indicators of right ventricular hypertrophy (RVH) in mouse models. These data support that early intervention that lower sFlt-1 levels, such as the use of anti-sFlt-1 mAb therapy, may provide a new strategy and therapeutic window for BPD prevention in preterm infants who are considered at risk because of prenatal stress exposure [49].

Sex

A prevalence of BPD has been observed in male newborns [14, 50, 51]. This is probably linked to weak circulating fetal androgens, which inhibit the production of phospholipids in the surfactant [52]. Several studies have established that male infants present an increased risk of BPD compared to females of similar gestational age and birth weight [53-56]. In the EPICure study, male survivors were more than twice as likely to develop BPD than female infants [57]. Among very low birth weight (VLBW) newborns enrolled in the NICHD study on inhaled nitric oxide, the risk of developing BPD or death was almost 5 times greater for boys than for girls [55, 57].

Corticosteroids

The role of corticosteroids in BPD prevention is still a matter of debate. At this point, it is well established that inflammation is the leading cause of the development of a BPD phenotype. Some authors claim that corticosteroids reduce its incidence if administered immediately after birth and prevent its progression if issued in the first weeks of life [14]. However, subsequent studies highlight the possibility that prenatal corticosteroids may not affect the risk of developing BPD [27]. Indeed, Elimian et al. compared 125 newborns who required 12 mg/dose of betamethasone before delivery with 104 other infants who were not given any antenatal corticosteroids therapy. The result has shown that gestational age at birth and the newborn's weight were lower in the group that received prenatal corticosteroids. Reduced need for postnatal vasopressors, intraventricular hemorrhage, and death in preterm infants have been

noticed in neonates who received a single dose of betamethasone. In conclusion, this study did not reveal any significative differences between the two groups regarding the clinical and histological incidence of CA, Apgar score, the need for postnatal surfactant, RDS and BPD, necrotizing enterocolitis (NEC), ROP and neonatal sepsis [58].

Antioxidant system immaturity

Preterm infants' antioxidant system is extremely immature compared to full-term newborns. At birth, the activity of superoxide dismutase (SOD), erythrocyte catalase (CAT) and erythrocyte cytosolic glutathione peroxidase is very low in preterm babies. They also have low levels of non-enzymatic antioxidants such as vitamins A, C and E [59-62]. Due to their highly reactive nature, reactive oxygen species (ROS) can react with various intracellular proteins and alter their structure and function. Normal perfusion and part of the placenta are essential for the fetus, as the placenta is ultimately responsible for providing oxygen and nutrients. A reduction in placental perfusion and placental hypoxia are associated with preeclampsia and IUGR. It has been demonstrated that ROS are elevated while antioxidant levels are reduced in the bloodstream of mothers experiencing preeclampsia [11, 63-65].

Preeclampsia

Relevant clinical studies have demonstrated that an abnormal placental vascular structure and its histologically documented hypoperfusion are associated with IUGR and the subsequent development of BPD and PH [14, 66, 67]. Being born small for gestational age doubles the risk of BPD and is closely related to uteroplacental insufficiency [68], which, in turn, is linked to inflammatory or vascular disorders like preeclampsia [27]. The association between IUGR and increased risk of BPD is probably indirectly connected to the development of preeclampsia during pregnancy [69, 70]. Hansen et al. have noticed a strong positive association between fetal exposure to preeclampsia and the subsequent development of BPD [71]. The authors have enrolled 107 mother-infant dyads. The causes of delivery included preeclampsia (n = 29; 27.1%), preterm delivery (n = 35; 32.7%), PROM (n = 29; 27.1%), cervical insufficiency (n = 10; 9.4%) and placental abruption (n = 4; 3.7%). 27 (25.2%) of these newborns developed BPD. The likelihood of developing BPD was significantly higher in neonates born from pregnancies complicated by preeclampsia than those born from pregnancies complicated by other causes or preterm birth. The bivariate odds ratio (OR) in the relationship between preeclampsia and BPD was 2.96 (95% CI = 1.17 to 7.51; p = 0.01). This indicates that preeclampsia is associated with an almost 3-fold increase in the likelihood of developing BPD.

The relationship between preeclampsia and increased risk of BPD can be explained as follows: the umbilical cord blood of infants born to mothers with preeclampsia contains relatively high levels of sFlt-1 and relatively low levels of VEGF. Since airway development parallels vascular growth, the anti-angiogenic environment of preeclampsia could cause impaired fetal and neonatal airway development. This is an example of a maternal condition that directly affects fetal development and alters long-term outcomes [49].

Maternal obesity

It is increasingly evident that maternal obesity affects fetal programming. The fetal lung development and the consequent risk of adverse respiratory outcomes at birth and in adulthood are influenced by several factors in the intrauterine environment of an obese mother. Maternal obesity determines PROM, placenta previa, placental abruption, congenital anomalies, stillbirth, macrosomia, fetal growth restriction, preterm birth, and cesarean section. This, in turn, is often related to an increased risk of neonatal respiratory problems, including RDS, apnea of prematurity, chronic lung disease, the need for ventilatory support, and prolonged hospital stays [72-75]. Circulating adipokines in maternal blood impair fetal lung development and surfactant production [76].

Maternal smoking

Fetal exposure to maternal smoking can contribute to the onset of early lung lesions during development and BPD, especially in VLBW infants [32, 77]. Intrauterine exposure to carcinogens in tobacco smoke and the associated effects, including IUGR, are important risk factors for respiratory morbidity in childhood. The main impact on the fetal lung is enlarged airspaces, reduction of the alveolar surface, altered airway function and a 16% decrease in lung weight. Tobacco smoke also induces epigenetic alterations in tumor suppressor

genes. Maternal and fetal glutathione S-transferase levels are reduced, and this deficiency leads to airway hyperreactivity experienced by many children with BPD. Finally, exposure to tobacco smoke reduces the action of PPAR-gamma [78] during lung development through histone alterations, blocking lung development, as it regulates both alveolar formation and surfactant synthesis [45].

Hypoxia

During the final stage of development (alveolarization), secondary septation breaks down the ducts into alveolar sacs. At the same time, the extension of capillary beds occurs through angiogenesis to facilitate gas exchange [79, 80]. The fact that the lung completes its maturation in the postnatal period makes it particularly vulnerable to external and environmental factors [81]. Canalization and the formation of alveolar sacs go together with the shape of the alveolar-capillary bed. Growth factors like VEGF, regulated by hypoxia and other signals, recruit capillaries distributed around the basal epithelial membrane, thus facilitating epithelial-endothelial interactions. The interruption of normal pulmonary vascular development can represent a critical moment in BPD pathogenesis. Chronic and intermittent hypoxia [82-84] compromise alveolarization and lung development in murine models [14].

Altitude

In women who carry pregnancy at high altitudes, exposure to hypoxia can negatively influence fetal oxygen intake and hinder its development. Preeclampsia is more common at high altitudes than at low altitudes. Moreover, preeclampsia is critical for reducing birth weight and IUGR in neonates at high altitudes. Therefore, the incidence of BPD is increased at high altitudes. Exposure of preterm infants to a hypoxic environment has been hypothesized to cause lung injury at a critical stage of development [11].

Perinatal and postnatal factors

After birth, preterm babies are exposed to several factors that can interrupt lung development and alter pulmonary repair and vascularization mechanisms. These patients are particularly susceptible to oxidative stress and factors such as resuscitation, oxygen exposure, surfactant, sepsis, mechanical ventilation, and patent ductus arteriosus. These factors altogether interfere with the formation of both the alveolar and vascular lung, thus resulting in a global developmental arrest [85].

Hyperoxia

Newborns, especially those born prematurely, are vulnerable to oxygen toxicity because of their inadequate levels of antioxidant enzymes that cannot protect tissues like the developing lung from oxidative damage [86]. Endothelial and AT2 cells are extremely susceptible to this type of damage. The activation of transcription factors by oxidative stress leads to surfactant inactivation, cell dysfunction and reduced cell survival. The risk of developing BPD is directly related to cumulative exposure to supplemental oxygen during the first 2 weeks of life. In animal models, hyperoxia induces pulmonary damage characterized by increased lung permeability, death of endothelial and epithelial cells and inadequate alveolarization. The use of high fractions of inspired oxygen (FiO_2) for the resuscitation of preterm newborns, in association with the underlying surfactant deficiency, chest wall instability and weak respiratory muscles, is related to greater production of ROS. The FiO_2 level at which oxidative stress occurs in the preterm newborn is not perfectly known, even though it probably depends on gestational age [62, 87].

Mechanical ventilation

The lung of premature infants is in the canalicular or saccular stage and is not ready for adequate gas exchange. For this reason, at birth, mechanical ventilation and the use of high oxygen concentration are required. The main factors contributing to immature lung damage are ventilation-induced barotrauma and volutrauma, oxygen toxicity and inflammation [4, 88].

Mechanical ventilation directly damages the neonatal lung because of overdistension and determines alterations in angiogenesis-related factors: VEGF-1, its receptor fit-1, angiopoietin-1 and its receptor Tie2 are downregulated. At the same time, the endoglin of the co-receptor of TGF-β is upregulated in the lungs of infants who underwent mechanical ventilation. The imbalance of angiogenic factors probably contributes to dysmorphic angiogenesis and to an altered alveolarization that can be frequently observed in lungs that have been

mechanically ventilated. At discharge, infants with tracheobronchomalacia and BPD are more likely to be mechanically ventilated (OR 1.37; IC 95%, 1.01-1.87; p= 0.045) and have more extended hospital stays (118 ± 93 days vs. 105 ± 83 days; p = 0.02) compared to patients with BPD but without tracheobronchomalacia [89].

The number of days during which the patient has been subjected to positive pressure provided via the endotracheal tube is predictive of long-term adverse pulmonary outcomes. Current evidence supports the need for weaning from mechanical ventilation during the first week of life. Using non-invasive respiratory support has become a fundamental strategy for preventing this disease. Some studies have demonstrated a significant decrease in BPD incidence or death with early nasal continuous positive airway pressure (nCPAP) compared to mechanical ventilation [90]. If invasive mechanical ventilation cannot be avoided, volume-guaranteed ventilation should be strongly considered [91-93].

Hypoxia

In addition to hyperoxia exposure and the need for supplemental oxygen, premature infants are exposed to chronic or intermittent hypoxia. Generalized pulmonary vasoconstriction occurs, resulting in increased pulmonary vascular resistance and, subsequently, the development of PH. When hypoxic vasoconstriction is sustained, it produces a global remodeling of the pulmonary vascular bed and leads to right heart failure. It has been demonstrated that postnatal exposure to hypoxia impairs alveolarization, determining alveolar simplification. Since airway development and maturation are closely related, altered alveolarization also compromises vascular growth in the alveolar wall [11, 94]. The only clear recommendation is continuous SpO_2 monitoring immediately after birth and the use of supplemental oxygen to achieve SpO_2 levels > 80% within 5 minutes after birth with saturation targets between 90-95% [91, 95].

Inflammation

Postnatal exposure to intermittent hypoxia and hyperoxia induces oxidative stress. As a result of the direct cell damage, DNA oxidation, cytokines induction and recruitment of neutrophils and macrophages in the lung, oxidative stress induces pulmonary inflammation. Moreover, also mechanical ventilation triggers an inflammation state. The infiltration of inflammatory cells into the immature lung and the ROS release damage endothelial and epithelial cells [11, 96, 97].

Sepsis

Postnatal sepsis is associated with a nearly 3 times higher probability of BPD and death and could be attributed to the effects of systemic inflammation and proinflammatory cytokines. Preterm newborns are more susceptible to infections because of the immunologic system immaturity. Infection and inflammation contribute to the interruption of the physiologic lung development, and their role in BPD pathogenesis is the increase in the concentration of proinflammatory and chemotactic factors. This is also associated with complement activation, increased vascular permeability, loss of proteins and neutrophils' mobilization in the interstitial and alveolar compartments. ROS release by activated neutrophils also contributes to lung damage [98]. Immature humoral and adaptive immunity increases the risk of frequent and severe viral respiratory infections during the first 2 years of life that worsen an already compromised pulmonary structure [12].

Nutrition

Poor postnatal growth is common in infants with BPD and can result from insufficient nutrition, higher energy consumption and adverse effects of therapies. Animal models suggest that undernutrition could be associated with reduced lung growth and may increase the risk of BPD regardless of the severity of the early respiratory failure. The use of breast milk has been associated with a reduction in BPD incidence. Therefore, an adequate nutritional strategy could prevent its development [98]. The premature child requires parenteral and eventually enteral nutritional support for postnatal growth. However, many nutrients transferred during the third trimester are fundamental for both endogenous and exogenous antioxidant function. For example, selenium is an essential trace element with a well-documented relevance for human health and diseases [98]. A *Cochrane* review has suggested that low plasmatic selenium levels may be associated with increased prematurity complications, including BPD, in days of oxygen dependence and the risk of long-term respiratory adverse outcomes [99]. A prospective study has analyzed the dose-dependent effect

of breast milk administered during NICU hospitalization on the risk of BPD and associated costs in VLBW infants. The results reveal a 9.5% reduction in the risk of developing BPD for every 10% increase in enteral feeding with breast milk from birth up to 36 weeks of gestational age. This would result in a 63% reduction in the likelihood of developing BPD with nutrition based 100% on breast milk compared to a breast milk-free diet [100]. Schanler et al., in their randomized study conducted on preterm patients fed with breast milk supplemented with formula or donor human milk, have demonstrated a reduced incidence of BPD in the group that received donor human milk supplementation [101].

A recent prospective cohort study conducted on German VLBW children has shown that children who received exclusively formula milk had a 2.6-fold increase in BPD development compared to those who received exclusively human milk [102]. Another recent retrospective study has revealed that an exclusive human milk diet fortified with a human milk-based fortifier has reduced BPD incidence compared to a diet based on human milk integrated with bovine products [103].

Multiple direct and indirect mechanisms support the role of human milk in reducing the risk of BPD in VLBW newborns. Their immature lungs are exposed to oxidative stress, inflammation, and inadequate nutrition. Breastfeeding, especially if fresh milk is used, can provide nutritional and bioactive components that contrast oxidative stress, inflammation, and nutritional deficiencies [104-106]. Furthermore, breast milk can also indirectly affect the risk of BPD by reducing NEC and sepsis incidence, both morbidities linked to the subsequent development of BPD [107, 108].

Surfactant

Using exogenous surfactant reduces mortality and severity of RDS, but it does not reduce BPD incidence. The minimally invasive modalities of surfactant administration, like the "Less Invasive Surfactant Administration" (LISA), can reduce the incidence of death and BPD [90]. Some meta-analyses indicate that the LISA minimizes the necessity of mechanical ventilation and that it reduces BPD incidence. In a study, LISA has been demonstrated to be more effective than the single CPAP or the intubate-surfactant-extubate (INSURE) for surfactant administration. However, data regarding the follow-up of children who received LISA treatment are still limited [109]. In the first randomized controlled follow-up study conducted on preterm newborns treated with LISA, any differences in weight, length or head circumference were noticed compared to the control groups at the corrected age of 2. Moreover, psychomotor development and mental scales were similar. This study underlines the safety of this new and less invasive approach [110].

Caffeine

The early start of caffeine therapy, within the first 3 days of life, has a considerable impact on BPD prevention and the reduction of long-term neurological outcomes [91] through different mechanisms [13, 111]. The tools responsible for BPD prevention with caffeine therapy include reduced airway exposure to positive pressure and supplemental oxygen and possible direct biochemical effects that mitigate inflammatory lung damage and improve alveolarization and pulmonary angiogenesis.

These benefits are supported by large-scale randomized controlled trials [112]. Data from preclinical studies indicate that its effects may also result from this drug's antioxidant and anti-inflammatory properties [113-115]. The optimal dosage and the perfect time to start therapy still need to be established [91].

Caffeine safety and efficacy to improve long-term respiratory health and neurodevelopment support the routine administration of caffeine in most VLBW newborns admitted to the hospital. However, BPD rates remain high, and some infants develop BPD despite caffeine use. Consequently, it is necessary to optimize basic treatment strategies [116].

Continuous positive airway pressure and nasal intermittent positive pressure ventilation

Several meta-analyses support the start of CPAP in the delivery room in newborns at risk of BPD. These studies underline a small but significant reduction in BPD outcomes for children exposed to CPAP compared to intubated children treated with surfactant. The probability of CPAP failure is higher in immature infants [117-120].

Any CPAP modalities have demonstrated to be superior to others by now. Data from a meta-analysis have highlighted that bubble CPAP show reduced failure rates. However, using bubble

CPAP is not associated with a reduced risk of BPD [121].

Nasal intermittent positive pressure ventilation (NIPPV) determines short increases in pressure and promotes breathing and stability by recruiting collapsed alveoli. Pressure increases can be synchronized with the baby's efforts (SNIPPV) or not synchronized. Compared with nCPAP, the early use of NIPPV is associated with a reduced need for intubation in preterm infants. However, this effect is not significantly associated with a reduced risk of BPD [91, 122-124].

Water intake

Infants with BPD may have difficulties eliminating excess fluids, which can build up in the lungs, thus determining breathing difficulties. Appropriate management to achieve hydroelectrolyte balance in these patients is essential. Nowadays, newborns at risk of developing BPD are smaller and more immature. For this reason, many questions remain unanswered. It is the case of the management of sodium supplementation, parenteral nutrition versus enteral nutrition, and what is the best breast milk fortification strategy [5]. It is known that hydroelectrolytic alterations in the postnatal period can contribute to disease development. In extremely preterm infants, because of renal immaturity, there may be a contraction of diuresis which can cause fluid overload, with impaired gas exchange in the respiratory tract and a possible need for mechanical ventilation [125-127]. In the NICU of Montreal Children's Hospital, between 2015 and 2018, the association between the fluid balance in the first 10 days after birth and mortality due to BPD among neonates of < 29 weeks of gestational age has been investigated. The study found that fluid retention during the early postnatal period, associated with low serum sodium concentration and reduced weight loss, would be linked to a higher chance of BPD-related death. According to the authors, close monitoring of hydric balance during the first 10 days of life, with particular attention to the first 5 days, may increase BPD-free survival [128].

Talking about therapy, furosemide determines various adverse effects, including failure to thrive, loss of electrolytes, and nephrocalcinosis. For this reason, diuretics should be carefully administered in preterm infants, and their use should be limited to those patients who show clinical improvement [91].

Postnatal corticosteroids

Since inflammation contributes to the development of BPD and corticosteroids inhibit proinflammatory signals and promote anti-inflammatory pathways, several studies have tried to demonstrate the efficacy of these drugs in the context of BPD.

Regarding BPD incidence in VLBW newborns, corticosteroids can acutely reduce ventilatory and oxygen needs, but any long-term benefit has not been demonstrated. An increased risk of brain damage and reduced growth have been reported [98]. Moreover, Watterberg et al. have shown that the treatment with hydrocortisone from the 14th to the 28th day of life has not determined a substantial increase in survival without moderate or severe BPD compared to placebo. Survival without neurologic development compromission was not significantly different between the two groups [129]. Furthermore, Yeh et al. have compared the administration of surfactant mixed with budesonide and surfactant alone in VLBW newborns with severe RDS. The intratracheal administration of surfactant/budesonide has significantly reduced the incidence of BPD or death compared to the surfactant alone, without immediate adverse effects (42% vs. 66%) [98].

In 2022, the American Academy of Pediatrics published a review that analyzed the most recent literature to guide the use of corticosteroids in the postnatal period in preterm infants. However, evidence remains insufficient to recommend the routine use of corticosteroids and neonatologists should base their decision on their clinical judgment and on the balance between disease risk and potential adverse effects of the treatment. The review affirms that postnatal corticosteroids may increase survival rate in patients with BPD, but they also imply significant short- and long-term risks. When administered during the first week of life, low-dose hydrocortisone can prevent BPD or death in newborns with birth weight < 1 kg exposed to CA. Low-dose dexamethasone given after the first week of life can improve outcomes in preterm infants who require respiratory support without severe BPD. Inhaled corticosteroids do not seem to offer any advantages compared to systemic corticosteroids, and they can be associated with an increased risk of mortality. Corticosteroids can be more effective if directly administered in the lung with the surfactant as a vehicle, but long-term data are lacking.

Therefore, the routine use of corticosteroids in the postnatal period is not recommended. The decision to use them to prevent or to treat BPD should be individualized, and it is recommended to prefer low doses for a short and predefined period. High-dose corticosteroids are not recommended to prevent or treat BPD in preterm infants. Finally, indomethacin must not be used concomitantly with corticosteroids [130].

Despite several studies, the appropriate formulation, time of administration, dose, and duration of glucocorticoid treatment in these patients have yet to be established. Therefore, they should not be used to prevent BPD. Further studies must verify their potential role in improving severe respiratory diseases [131].

Various pharmacometabolomic studies are helping to understand the mechanisms of steroid response in patients with BPD. This would help identify and confirm the metabolic changes associated with the answer to these drugs in this group of patients [132].

Transfusions

Fetal hemoglobin (HbF) is prevalent in newborns. Usually, its proportion gradually decreases with the concomitant production of adult hemoglobin. This process is typically completed within the first 25 weeks after birth. The decrease in HbF levels during the first postnatal week is associated with the development of BPD in the very preterm newborn. On the contrary, maintaining a higher percentage of HbF could be protective against BPD development [133].

Pulmonary microbiota

The lung microbiome changes during the first weeks of postnatal life, and the growth of the gut microbiome, in association with other conditions, contributes to BPD development. There is an association between the gut microbiome's development and the lung, called the gut-lung axis. Intestinal dysbiosis is one of the causes of NEC. If this dysbiotic process also occurs in the lung, it could trigger the inflammatory process underlying BPD. Commensal bacteria may explain this in the lungs: if these bacteria are eliminated or altered by conditions like transplacental infections or CA, an abnormal inflammatory response may happen, thus responsible for BPD pathogenesis [8]. Therefore, the gut-lung axis represents the linkage between gut microbiota and pulmonary diseases. This relationship is well explained in the context of conditions regarding these two organs.

In preterm babies, NEC is the most severe gastrointestinal complication. Similarly, BPD is the most severe lung complication. They both determine significant systemic morbidity. If altered, gut-lung axis physiologic mechanisms contribute to increasing the risk of BPD in preterm infants with NEC. NEC defines a concomitant inflammation of the pulmonary system, with a higher risk of developing BPD. Several molecular and cellular mechanisms are mediated by this effect, linked to the immunologic system dysregulation [134]. The pulmonary microbiota composition depends on different aspects, including the inhalation of micro-organisms, microbial clearance and local conditions like nutrition and temperature [135, 136]. The microbiota interacts with the host through the secretion of metabolites identified by the immune system and provides information regarding metabolic status [137-140].

Metabolomic profiling continues to develop as a powerful tool for hypothesis generation and studying biological mechanisms that may influence drug response [132].

Conclusions

Research regarding BPD is constantly growing. Despite recent progress, BPD still represents a challenge for future research. The precise mechanism that leads to the onset and development of this disease is not fully understood, especially in pathological processes caused by intrauterine hypoxia in the different stages of lung development.

Most preterm newborns and patients with BPD do not achieve the expected potential lung function and have a higher risk of developing the chronic obstructive pulmonary disease (COPD) in adulthood. Creating a structured and standardized follow-up is essential to improve assistance and prevent respiratory morbidity [12].

A better understanding of the environmental influence on fetal and neonatal lung development will be decisive in establishing preventive strategies and reducing or preventing lung disease development. The early identification of children at the highest risk of developing BPD can allow a targeted approach to reducing the severity of the disease and its complications. Adequate therapy for BPD prevention and treatment remains an essential

challenge for neonatologists. It may be only with the omics sciences and their various investigative possibilities in the context of the complex human organism, that we will be able to understand the peculiarities of this disease. Therefore, several studies are still necessary: the more we learn, the less we know.

Declaration of interest

The Authors declare that there is no conflict of interest.

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