Review

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Review

Noninvasive Monitoring Strategies for Bronchopulmonary Dysplasia or Post-Prematurity Respiratory Disease: Current Challenges and Future Prospects

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Abstract: Definitions of bronchopulmonary dysplasia (BPD) or post-prematurity respiratory disease (PPRD) aim to stratify the risk of mortality and morbidity, with an emphasis on long-term respiratory outcomes. There is no univocal classification of BPD, due to its complex multifactorial nature and the substantial heterogeneity of clinical presentation. Currently, there is no definitive cure available for extremely premature very-low-birth-weight infants with BPD, and challenges in finding targeted preventive therapies persist. However, innovative stem cells-based postnatal therapies targeting BPD-free survival are emerging, which are likely to be offered in the first few days of life to higher-risk subpopulations of premature infants. Hence the need for easy-to-use noninvasive tools for a standardized, precise and reliable BPD assessment at a very early stage, to support clinical decision-making and to predict the response to treatment. In this non-systematic review, we present an overview of strategies for monitoring preterm infants with early and evolving BPD-PPRD, and make some remarks on future prospects, with a focus on near-infrared spectroscopy (NIRS).

Keywords: bronchopulmonary dysplasia; post-prematurity respiratory disease; preterm infants; noninvasive monitoring; lung oxygenation; near-infrared spectroscopy

1. Introduction

Bronchopulmonary dysplasia (BPD) lacks an objective, comprehensive, and unambiguous definition, due to its complex multifactorial nature and the substantial heterogeneity of clinical presentation [1]. The most widely used operational definitions of BPD, or post-prematurity respiratory disease (PPRD), aim to stratify the risk of mortality and morbidity, with an emphasis on respiratory outcomes [1]. Therefore, the classification of this chronic lung disease requires a compromise between early definition and accurate prediction of long-term outcomes [1].

Both the definitions and phenotypes of BPD have evolved over the past 50 years [2–10]. Advances in obstetric and neonatal medicine, such as routine application of antenatal steroids, exogenous surfactant replacement therapy, and gentler mechanical ventilation strategies, have led to improved survival of extremely premature infants, and there is a growing trend towards offering initial life support to infants born at lower perceived levels of viability [11]. Therefore, BPD pathophysiology has dramatically changed in the "post-surfactant era": there are less severe lung injuries caused by volutrauma, barotrauma, and oxygen toxicity, but very immature lungs are affected during the early stages of development [12]. "New BPD" is the result of underdevelopment or dysregulated lung developmental trajectory, with incidents occurring in the saccular stage or

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earlier, resulting in alveolar simplification and disrupted angiogenesis [12–14]. Not surprisingly, BPD-PPRD is classified on the basis of clinical evidence of functional impairment at a time when the physiological development of the human lung should be characterized by the onset of the last stage, or alveolar stage [14]. In fact, the modality of respiratory support required at 36 weeks postmenstrual age (PMA) is predictive of long-term outcomes [1,5–9]. To improve the accuracy of prognosis, moving the time of assessment to 40 weeks PMA is a discussion topic [10]. In contrast, there is a demand for objective, precise and reliable, noninvasive methods to predict the diagnosis and classify the severity of evolving BPD at a very early stage [15].

It must be considered that, during infancy and adulthood, even immature lungs of very-to-extremely preterm (less than 32 weeks gestational age) and very-low-birth-weight (VLBW, <1500 g birth weight) infants who do not fit the classification criteria of BPD-PPRD may exhibit characteristic abnormalities in lung structure and function [16]. Prematurity itself carries a higher risk of chronic lung disease in infancy, with a phenotype similar to chronic obstructive pulmonary disease (COPD) later in life, hence the increasing attention to regular monitoring and early management of respiratory symptoms and comorbidities in these children and adolescents beyond the neonatal period [17,18].

The neonatal care of infants with BPD does not have a definitive available cure and challenges persist in finding targeted preventive therapies. Actually, the most effective strategy is to optimize obstetric-gynecological care and avoid extreme preterm delivery [1]. However, emerging stem cells-based postnatal treatments, such as intratracheal administration of extracellular vesicles (EVs or exosomes) derived from cultured human umbilical cord mesenchymal stromal cells (MSCs) to prevent BPD, are being investigated (EVENEW clinical trial). Pending applicable large-scale results, a future is beginning to emerge in which innovative treatments aimed at BPD-free survival will be offered in the first few days of life to all extremely premature infants or to subpopulations at higher-risk. Hence the need for multimodal risk prediction tools for early noninvasive detection of BPD, to improve and standardize assessment methods, and to support clinical decision-making. Furthermore, early predictors of response to treatment with noninvasive methods are required.

In this non-systematic review, we present an overview of strategies for noninvasive monitoring of infants with bronchopulmonary dysplasia or post-prematurity respiratory disease and make some remarks on future prospects.

2. Risk Prediction Models

2.1. Risk Prediction Early After Birth

Clinical and demographic data can support postnatal clinical decision-making and personalized monitoring strategies early after birth. Recently, a logistic regression risk prediction model and a risk scoring tool were derived from a systematic review and meta-analysis of statistically significant risk factors for BPD [19]. Risk factors were divided into 3 categories (antenatal factors, intrapartum factors, and postpartum factors) and 24 different risk factors were selected for analysis [19]. The meta-analysis showed that the pooled effects of 19 risk factors were significant, as follows: chorioamnionitis, gestational age, birth weight, sex, SGA, 5 minutes Apgar score, delivery room intubation, neonatal asphyxia, IMV, days on IMV, IMV >7 days, postnatal steroids, surfactant, patent ductus arteriosus, RDS, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, pulmonary air leak [19]. Five risk factors were not included in the subsequent analyses, as follows: maternal hypertensive disorders, antenatal steroids, premature rupture of membrane, caesarean section, retinopathy of prematurity [19]. Nine risk factors were included in this prediction model: chorioamnionitis (OR = 3.56, 95% CI [2.49, 5.11]); gestational age per 1 week increase (OR = 0.64, 95% CI [0.62, 0.67]); birth weight per 100 g increase (OR = 0.78, 95% CI [0.76, 0.80]); sex - male (OR = 1.46, 95% CI [1.39, 1.54]); SGA (OR = 4.78, 95% CI [3.88, 5.88]); 5 minutes Apgar score per 1 point increase (OR = 0.71, 95% CI [0.64, 0.78]); delivery room intubation (OR = 2.77, 95% CI [2.27, 3.39]); need for surfactant replacement therapy (OR = 3.59, 95% CI [2.90,4.45]); respiratory distress syndrome (OR = 5.08, 95% CI [4.06, 6.35]) [19]. A BPD risk prediction scoring tool for preterm infants was derived and 4 risk groups were stratified according to risk score in a Chinese validation cohort (total 767 infants,

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of which 185 were BPD infants) [19]. The risk groups were defined as follows according to prevalence rates: Low Risk (0.5%), Low-intermediate Risk (5.5%), High-intermediate Risk (67.0%), High Risk (94.7%) [19].

This study provided and validated an easy-to-use and low-cost BPD risk-scoring tool [19]. Despite several limitations, similar tools could play an important role to early identify and stratify preterm infants at higher-risk.

2.2. Antenatal Risk Prediction

Chorioamnionitis status and the recognition of placental inflammatory pathways (acute and chronic inflammation) and vascular pathways (maternal and foetal vascular disease) are predictive of BPD [20]. There is growing interest in models for predicting histologic chorioamnionitis and adverse outcomes in preterm infants [21]. As a matter of fact, BPD already develops in utero, and antenatal interventions should be investigated for pregnant women with a higher risk of chorioamnionitis. Placental inflammatory and vascular pathways may also be associated with response to postnatal therapies [20].

3. Biofluid Biomarkers

Currently, no biomarker-based diagnostic strategies are available, but various biomarkers and "omic" signatures (genomics and epigenetics, metabolomics, proteomics, microbiomics…) specific to BPD are being studied [22]. Researchers and clinicians are becoming more interested in comprehensive endotypic assessments and noninvasive monitoring techniques that contribute to early prediction of BPD development in premature infants [15].

Biofluid biomarkers have been studied mainly using umbilical cord blood, urine, and tracheal aspirate or bronchoalveolar lavage fluid samples. A review was recently published in a journal of the European Respiratory Society [15].

Inflammatory markers have also been studied in exhaled breath condensates: higher end-tidal carbon monoxide (ETCO) on DOL 14, higher fractional exhaled nitric oxide (FeNO), and higher exhaled nitric oxide (eNO) have a significant association with BPD [15].

"Omic" biomarkers of BPD include: genomics and epigenetics (higher vascular endothelial growth factor VEGF-634G>CG alleles, lower miRNA-876-3p in tracheal aspirate), proteomics (higher chitinase-3-like protein-1, matrix metalloproteinase-9 MMP9 in urine), microbiomics (lower Firmicutes and Staphylococcus, and higher Proteobacteria, Ureaplasma, and Stenotrophomonas in tracheal aspirate), metabolomics (numerous biomarkers in various specimens; note that the metabolome is also affected by the metabolic activity of the airway microbiome) [15].

4. Chest Imaging

5.1. Chest Radiograph

Since Northway 1967 definition, radiographic studies have been essential for identifying BPD [3]. Among chest imaging modalities, plain radiography is the primary line and the most studied in early and developing BPD, due to its wide availability in neonatal intensive care units (NICUs) and the low dose of ionizing radiation used [1].

Several abnormalities of chest X-ray (CXR) have been clearly associated with prolonged oxygen requirement, including the two radiographic patterns of "cystic BPD" (with "bubbly" alterations), and "leaky lung syndrome" (with "hazy-to-opaque lungs") [23]. The interstitial pneumonia pattern on DOL 7 and several scoring systems applied to CXR in the first week of life were found to correlate with the diagnosis of BPD [24,25]. Even earlier, on DOL 3, an elevated chest radiographic thoracic area (CRTA) measurement is a sign of hyperinflation and has been associated with air trapping, which likely reflects ventilation inhomogeneity and, in combination with lung function (lower functional residual capacity), might be a better predictor of BPD than certain clinical data [26].

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5.2. Lung Ultrasound

Newer than CXR, lung ultrasound (LUS) is widely used in NICUs for diagnostics, monitoring, prognostics, and prevention. It is accessible at the bedside, it can be done immediately and serially (point of care ultrasound or POCUS), and does not involve ionizing radiation [27].

VLBW infants with BPD have greater consolidations and pleural line anomalies than those without BPD [27]. In VLBW infants, a semi-quantitative LUS score has shown potential for predicting moderate-to-severe BPD [28,29]. VLBW infants without BPD have LUS scores that increase during the first week of life and decrease thereafter, whereas among VLBW infants with BPD, LUS scores remain elevated until 36 weeks PMA (substantially higher LUS score at admission, on DOL 7, on DOL 28, and at 36 weeks PMA). Notably, LUS scores can predict BPD diagnosis at 1-2 weeks of life and can predict BPD severity at 4 weeks of life (according to NIH 2001 and Jensen 2019 definitions) [30].

Additionally, LUS scores could be early predictors of treatment response. Failure to improve LUS scores with diuretic therapy (2 days after diuretic administration) was associated with worse respiratory outcomes [31].

5.3. Chest Computed Tomography Scan

Other chest imaging modalities, particularly computed tomography (CT), have been studied in infants and children with BPD, but there are several limitations to their use for early and evolving BPD, largely due to the ionizing radiation exposure in infants who may be radiosensitive throughout development [1]. However, as low-dose CT protocols progress, neonatal lung imaging with CT will become increasingly common.

Several qualitative, semi-quantitative, and quantitative CT scoring systems have been proposed to predict the severity of long-term respiratory outcome in BPD [32]. Typical CT abnormalities include bronchial wall thickening and bronchiectasis, hyperaeration or emphysematous areas and bullae, multifocal interstitial and subpleural opacities, fibrosis, and mosaic lung attenuation. Automatic or semiautomatic methods are being studied to quantify alveolar structure with chest CT scans [33].

5.4. Chest Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) protocols are emerging as new techniques in respiratory imaging, the impact of which is likely to be most significant in the long-term outpatient management of infants and children with severe BPD-PPRD. Ultrashort echo-time (UTE) MRI is the most studied technique [17,18].

5. Lung Function

Structural abnormalities such as alveolar simplicity, decreased number of alveoli and enlarged alveoli are the major pathophysiological basis for impaired lung function [34]. Pulmonary function tests (tidal flow-volume loops, raised volume rapid thoracic compression technique, functional residual capacity by plethysmography or multiple breath washout) have been proposed to further investigate the diagnosis of BPD and validate the proposed definitions [1]. However, they are not yet integrated into routine neonatal medicine, due to the need for specialized skills and equipment, and there is no consensus on the early lung function assessment that best predicts the development of BPD [1,35].

Preterm birth and VLBW status have been consistently associated with reduced lung capacity, lower lung compliance, increased airway obstruction and lung resistance, impaired gas exchange, and premature decline in respiratory function [34]. Pulmonary function abnormalities in preterm newborns that early predict BPD development include: lower functional residual capacity (FRC), lower compliance (Crs), and higher resistance (Rrs) on DOL 3 and 14; higher effective airway resistance per kilogram (Reff·kg−1), lower tidal volume per kilogram (TV·kg−1), lower functional residual capacity (FRC), lower ratio of time to peak tidal expiratory flow to total expiratory time (%

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T-PF), and lower ratio of volume to peak tidal expiratory flow to total expiratory volume (% V-PF) on DOL 7, 14 and 28 [15,36].

Serial measurements of lung function (spirometry, forced oscillation technique and impulse oscillometry, interrupter technique, multiple breath washout, plethysmography, and other advanced pulmonary function tests), lung diffusion testing (diffusion lung capacity for carbon monoxide or DLCO), polysomnography (sleep study), and assessment of respiratory morbidity should be part of the post-discharge follow-up of preschool and school-age children and adolescents with BPD [17,18,37].

6. Physiological Tests

Attempts at a "physiological definition" of bronchopulmonary dysplasia were initiated in 2003 by Walsh, who proposed a technique to standardize the assessment of BPD using a timed room-air challenge in selected infants [38]. BPD was defined at 36 weeks PMA for very preterm infants who required positive pressure ventilation (PPV) or fraction of inspired oxygen (FiO2) ≥0.3 to maintain pulse oximeter oxygen saturation (SpO2) at a range of 90-95% [7,38]. Most of the remaining infants, who mostly required oxygen supplementation with a low-flow nasal cannula (NC) 1-2 l/minute, were considered eligible for an oxygen reduction test (ORT) [7,38]. Those who maintained SpO2 ≥90% for 30 minutes while breathing FiO2 0.21 were classified as "no BPD" in Walsh 2004 "physiological definition" [7,38].

Recently, a modified physiological test for BPD has been proposed, which includes transcutaneous PCO2 (TcPCO2) monitoring [39]. After 28 days of life (DOL) and at 36 weeks PMA, infants on CPAP and/or on oxygen supplementation with nasal cannula and FiO2 ≤0.30 at rest, with SpO2 between 90 and 96%, were considered eligible to undergo the modified physiological test, and underwent a timed stepwise reduction of CPAP and/or FiO2 to room air. During the test, the infants were monitored continuously, and test failure was defined as the occurrence of any of the following events: SpO2 between 80 and 89% for 5 minutes with TcPO2 <50 mmHg, or SpO2 <80% for 1 minute, or apnea (cessation of breathing for >20 s) and/or bradycardia (heart rate <80 beats per minute for >10 s) [39].

There are no standard criteria for weaning preterm infants from CPAP and/or supplemental oxygen, so physiological testing represents not only an effort to standardize the diagnosis of BPD, but also a clinical tool for weaning respiratory support [1,7,38,39]. However, these are delayed tests, dedicated to infants who require low levels of respiratory support. Similar approaches to investigate the response of the respiratory system under stressful conditions in a standardized way could also be useful in the early days of life. Routine pulse oximetry, polysomnography (sleep study), hypoxia testing, and blood gas analysis are other techniques for monitoring and studying lung pathophysiology [40]. New tools for continuous pulmonary monitoring and oxygenation indices could be integrated into future multimodal assessments.

7. Lung Oxygenation by Near-Infrared Spectroscopy in Preterm Infants

Near-infrared spectroscopy (NIRS) is examined below as a possible tool for noninvasive, continuous lung monitoring of extremely preterm VLBW infants.

NIRS has been applied in various research and clinical care settings. In current neonatal care, continuous NIRS monitoring is applied to assess cerebral oxygenation and, to a lesser extent, renal, hepatic, and splanchnic oxygenation. Reference values for regional cerebral oxygen saturation have been published, and continuous NIRS monitoring of cerebral blood flow in preterm infants is an integral part of multiparametric brain monitoring. NIRS is being studied to assess its feasibility as a multi-organ monitoring tool in routine neonatal care and to evaluate its role in clinical decision making [41–47]. Local protocols and standard operating procedures are also needed for common use and better interpretation of available data and trends in new continuous monitoring techniques.

NIRS light penetration depth (1.0-1.5 cm) is adequate to assess lung parenchyma in preterm infants [48]. However, this application has been poorly investigated and data on normal values are lacking. Pulmonary oximetry by NIRS is expected to depend on pulmonary blood flow, as the

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bronchial circulation is estimated to receive only 1% of the left ventricular output. In a single-center study conducted in China, a population of 26 preterm infants (<32 weeks gestational age) underwent pulmonary NIRS monitoring, and lung rSO2 was positively correlated with both partial pressure of arterial oxygen (PaO2) and arterial oxygen saturation (SaO2) [49]. Pulse oxygen saturation (SpO2) was also positively correlated with PaO2 and SaO2, but interestingly, no significant correlation was found between rSO2 and SpO2 [49]. Hyperoxemia was defined as PaO2>100 mmHg, while hypoxemia was defined as PaO2<80 mmHg. Lung rSO2 could be used better than SpO2 to predict both hyperoxemia and hypoxemia [49]. In conclusion, NIRS objectively reflected changes in oxygenation in lung tissue [49].

In preclinical research, oxygenation in the target tissue measured by NIRS has been shown to detect the effects of hypoxia earlier than pulse oximetry in the Yucatan miniature pig. A NIRS sensor may be used as an earlier detector of oxygen saturation changes in the routine clinical setting compared with the standard pulse oximeter [50].

In a single-center prospective observational proof-of-concept study conducted in Florence, Italy, a cohort of 20 preterm infants with moderate respiratory distress syndrome (RDS) underwent continuous pulmonary NIRS monitoring, and lung rSO2 was found to have significant correlations with other oxygenation indices and with RDS severity [51].

It can be hypothesized that continuous pulmonary NIRS monitoring of lung oxygenation in preterm infants with evolving BPD is significantly different from reference values and, possibly, it is predictive of the diagnosis and severity of BPD. Good quality studies are needed to support this new noninvasive continuous monitoring strategy.

8. Conclusions

Noninvasive monitoring strategies for extremely preterm VLBW infants (risk stratification based on clinical and demographic data, biofluid biomarkers and "omic" signatures, chest imaging scores, lung function parameters, individual performance in physiological tests, and new noninvasive, continuous pulmonary monitoring strategies) should be integrated into easy-to-use risk-scoring tools for objective, precise and reliable BPD diagnosis at a very early stage, and as early predictors of response to treatment.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, T.Z., F.M. and A.B.; methodology, T.Z., F.M. and A.B.; validation, T.Z., F.M. and A.B.; writing—original draft preparation, T.Z.; writing—review and editing, T.Z., F.M. and A.B. All authors have read and agreed to the published version of the manuscript.

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Appendix A. Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a noninvasive optical sensing technique applied to the near-infrared light spectrum (λ ~700-950 nm). By measuring the variation of near-infrared (NIR) photons travelling between a NIR light source and a NIR detector, the optical properties of a biological tissue can be studied (modified Beer-Lambert law). Human tissues exhibit relatively low absorption in the NIR range, so they are assumed to be relatively transparent to NIR photons. Instead, there are chromophores whose absorption varies depending on the state of oxygenation, including oxyhemoglobin (O2Hb) and deoxyhemoglobin (HHb).

Commercially available NIRS monitors have specific neonatal-sized sensors which consist of a NIR light source and a NIR detector. As NIR light diffuses into the tissue being analyzed, it interacts with hemoglobin in 4 different ways: absorption, reflection, scattering, and transmission. Over the time frame of a typical NIRS recording, reflection, transmission, and scattering can be assumed to be constant. The only variable optical factor is absorption, which changes according to the degree of

oxygen saturation of hemoglobin. Therefore, the percentage of saturated hemoglobin in a target tissue can be investigated by NIRS [52].

Unlike pulse oximetry (SpO2), NIRS measurements are not pulse synchronized. Therefore, SpO2 is limited to the arterial hemoglobin source, i.e., the saturation of arterial oxygen (SpO2~SaO2), while NIR light interrogates intravascular oxygenated/deoxygenated hemoglobin in the arterial, venous, and capillary beds, providing a composite measure. Regional saturation of oxygen (rSO2) allows a direct, synthesized measurement of several variables of perfusion and oxygenation in the target tissue (rSO2~StO2). The contribution to rSO2 from venous, arterial and capillary beds varies in a ratio of approximately 75:20:5 (this ratio has been validated for the brain only, although it has been extrapolated to other human tissues).

Most of the contributions to StO2 come from the venous bed, i.e., the saturation of venous oxygen (SvO2). If venous hemoglobin saturation is approximated by regional oximetry (SvO2~rSO2) and SpO2~SaO2, NIRS and pulse oximetry together can add information on fractional tissue oxygen extraction (FTOE). FTOE=(SaO2–SvO2)/SaO2; estimated FTOE=(SpO2–rSO2)/SpO2. During continuous monitoring, in most cases the trend of actual FTOE can be approximated to the trend of estimated FTOE, although the absolute value is inaccurate. An increase in estimated FTOE suggests an increase in the oxygen extraction by the tissue due to higher oxygen consumption than oxygen delivery, while a decrease in FTOE suggests lower oxygen utilization than oxygen supply [53].

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