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Refining the Definition of BPD: Characterization of Intercurrent Episodes

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ABSTRACT

Background: The main definitions of bronchopulmonary dysplasia (BPD), proposed by Jobe-Bancalari, Shennan et al., and Walsh et al., focus on oxygen (O_2)-need and ventilatory support for the first weeks of life and at 36 weeks of post-menstrual age (PMA). Oxygen need at 36 weeks of PMA is sometimes due to intercurrent episodes (IEs) other than BPD. The aim of this retrospective study was to characterize IEs and determine their impact on BPD in preterm infants born at < 32 weeks of gestation.

Methods: O_2-dependence for > 28 days and at 36 weeks of PMA (±10 days) was analyzed. We classified each infant according to the three BPD definitions. Patients requiring O_2 or ventilator support at 36 weeks of PMA, with no need for O_2 in the first 28 days of life, were qualified for having IEs if their O_2/ventilator dependence (at 36 weeks) had a limited duration and/or could be ascribed to a known condition. Then, the contribution of IEs to the BPD rate was evaluated.

Results: Out of 1,210 patients, the BPD infants were 431 (35.6%), 169 (14.0%), and 186 (15.4%) according to Jobe-Bancalari, Shennan et al., and Walsh et al., respectively. Twenty-eight patients had IEs (16.6% of those on O_2 at 36 weeks of PMA) indicating a mild BPD overestimation (P=0.065).

Conclusion: We proposed a definition of IEs and found that IEs could lead to a potential BPD overestimation. Further research is needed to find out if patients with IE, similarly to infants with BPD, are prone to childhood complications and need preventive measures.

Keywords: Bronchopulmonary dysplasia, Chronic lung disease, Diagnosis, Infant, Oxygen, Premature

Introduction

Bronchopulmonary dysplasia (BPD) is one of the most important complications of prematurity, affecting about 30% of extremely low birth weight infants (particularly those born small for gestational age [GA]) (1-5). Three of the most frequently used definitions have been outlined by 1) Jobe-Bancalari, (6) 2) Shennan et al., (7) and 3) Walsh et al. (5) The severity of BPD has been recognized as a risk factor for later pulmonary morbidity, neurodevelopmental impairment, and health resource utilization (6, 7). Moreover, recent data showed that even infants without BPD experience a spectrum of oxygen diffusion impairment (at 36 weeks of post-menstrual age [PMA]) that is inversely associated with GA at birth (8).

The evaluation of early patterns of lung disease is important in order to predict the risk of BPD (3). According to Jobe-Bancalari, infants presenting O_2-dependence for at least 28 days after birth are then classified as mild, moderate, or severe BPD according to their respiratory support at 36 weeks of PMA (6). According to Shennan et al., BPD occurs in case of O_2-dependence at 36 weeks of PMA (7). A physiologic test combining oxygen and ventilator support reduction with an assessment of oxygen saturation has been advocated by Walsh et al. to standardize the definition of BPD (5).

Nevertheless, in clinical practice, it is recognized that some infants need O_2 at 36 weeks of PMA for reasons other than BPD (i.e., sepsis). These situations are called intercurrent episodes (IEs). To date, no study has focused on IEs in

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preterm infants at 36 weeks of PMA. Our aim was to characterize IEs and determine their impact on BPD incidence.

Methods

This was a retrospective single-center study, involving 1,412 consecutive admissions of preterm infants ($24^{0/7}$ to $31^{6/7}$ weeks of gestation) born within 2004 and 2017. The exclusion criteria were death before 36 weeks of PMA, major malformations, and admission after 48 h of life. The clinical characteristics of the patients were recorded according to the predefined criteria, as specified below. The O_2-dependence for > 28 days (before 36 weeks of PMA) and at 36 weeks of PMA (±10 days) was analyzed using a Matlab-based dedicated software (version R2016a, Mathworks, Natick, USA).

We classified each infant according to the three BPD definitions (5-7). Furthermore, we characterized what we called IEs. The patients requiring O_2 or ventilator support at 36 weeks of PMA, with no need for O_2 in the first 28 days of life, were qualified for IE if their O_2/ventilator dependence had a limited duration (arbitrarily chosen as <10 days) and/or could be ascribed to a known condition (i.e., sepsis, aspiration pneumonia, and acute fluid retention). The IEs definition was arbitrarily chosen to highlight that it was a transient condition.

We analyzed our electronic database to report possible causes of IEs, including sepsis (defined as positive blood culture or laboratoristic signs of infection, such as increased serum C-reactive protein, leukocytosis/leukopenia, and thrombocytosis/thrombocytopenia), aspiration pneumonia (based on the anamnesis and chest X-ray appearance), and excessive (>23 g/kg/day) weight gain combined with edema. The definitions were predetermined and did not change throughout the study period. Then, the contribution of IEs to the BPD rate was evaluated.

The data were presented as median with range, frequencies, and percentages as appropriate. Group differences were evaluated by the Chi-square test for categorical variables. The significance level was set at $P < 0.05$. Statistical analyses were performed using SPSS software (version 23.0; SPSS Inc., Chicago, Illinois, USA). The Institutional Review Board of Ospedali Riuniti Ancona Hospital in Italy approved the study.

Results

A total of 1,412 infants of < 32 weeks of gestation were born in the study period out of whom 1,210 subjects were analyzed (138 infants died before 36 weeks of PMA; 29 infants had major malformations; 35 infants had late admissions). The demographic and clinical characteristics of the patients are shown in Table 1. A total of 431 (35.6%; 273 mild, 143 moderate, and 15 severe subjects), 169 (14.0%), and 186 (15.4%) BPD infants were investigated according to the definitions outlined by Jobe-Bancalari, Shennan et al., and Walsh et al. (Figure 1).

A total of 1,393,970 hourly fraction of inspired oxygen data points were studied. Twenty-eight patients had IEs accounted for 16.6% of O_2-

Table 1. Demographic and clinical characteristics of patients

Characteristic	Frequency
Gestational age (week), median (IQR)	29^{+6} (27^{+6}-30^{+6})
Birth weight (g), median (IQR)	1190 (925-1480)
Antenatal steroids n (%)	1,040 (86.0)
Multiple births n (%)	313 (25.9)
Male gender n (%)	626 (51.7)
Early-onset sepsis n (%)	54 (4.5)
Late-onset sepsis n (%)	127 (10.5)
Surfactant therapy n (%)	614 (50.7)
Patent ductus arteriosus n (%)	488 (40.3)
Small for gestational age (birth weight <-2 standard deviation score) n (%)	50 (4.1)

IQR: Interquartile range

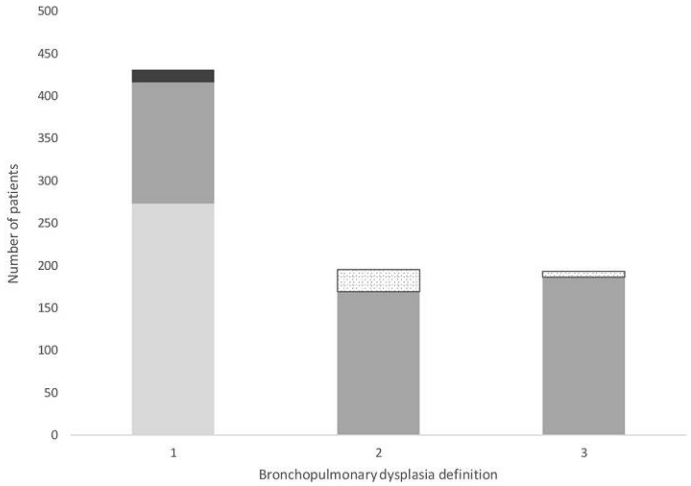

Figure 1. Number of patients with bronchopulmonary dysplasia (BPD) and intercurrent episodes (IEs); BPD definitions: 1) Jobe-Bancalari (i.e., mild, moderate, and severe BPD from bottom to top); 2) Shennan et al.; 3) physiologic definition; IEs: upper boxes in columns 2 and 3

dependent patients at 36 weeks of PMA. If IEs were separated from BPD (defined according to Shennan et al. and Walsh et al.), the BPD infants would have decreased from 169 to 143 (-15.4%; P=0.065) and 186 to 179 (-3.8%; P=0.367) as demonstrated by the Chi-square test. Regarding the definition of Jobe-Bancalari, moderate/severe BPD remained unchanged, as no infant with IEs was qualified for having moderate/severe BPD according to that definition.

The underlying causes of IEs could be explained in most cases (i.e., acute fluid retention [n=10], infection [n=8], and aspiration pneumonia [n=4]), whereas no clear explanation was found in other patients. Furthermore, 26/169 (15.4%) and 18/186 (9.7%) BPD infants diagnosed according to Shennan et al. and Walsh et al. did not need oxygen in the first 28 days, respectively; therefore, they were not qualified for BPD according to the definition by Jobe-Bancalari.

Discussion

In this study, we characterized IEs and found that 16.6% of O_2-dependent patients at 36 weeks of PMA had IEs. We would like to investigate the definition of IEs and its potential relevance to long-term respiratory health. The BPD definition proposed by Jobe-Bancalari is based on the fact that oxygen requirement for > 28 days and at 36 weeks of PMA is predictive of rehospitalization for respiratory causes and use of pulmonary medications after discharge. The authors warned against the fact that BPD should not reflect an acute event, but the definition of IEs remained elusive (6).

The definition of Shennan et al. focuses on oxygen requirement at 36 weeks of PMA as a predictor of poor pulmonary and neurosensory outcomes (7). The physiologic definition of BPD significantly reduced the variability among centers (5). This definition also correlated with pulmonary morbidity and health resource utilization and considered an oxygen saturation threshold for BPD diagnosis (5). Nevertheless, IEs are considered neither by Shennan et al. nor by the physiologic definition. In our study, patients with IE were improperly classified as having BPD if the definitions of Shennan et al. and Walsh et al. were adopted, even if this difference was not statistically significant due to the relatively small population.

We speculate that IEs should not probably be classified as BPD because IEs are likely to depend on transient conditions (e.g., infection, aspiration pneumonia, and acute fluid retention), whereas BPD is a persistent condition associated with subsequent lung impairment (9-12). It is possible that infants with IEs, compared to those with BPD, might not be prone to subsequent childhood complications and probably should not receive preventive measures, such as palivizumab prophylaxis (associated with potential adverse events and costs) (13). However, further studies with adequate longitudinal follow-up are needed in order to confirm this speculation. Another interesting finding of this study was that new BPD, characterized by lung deterioration after the first weeks of life, could be diagnosed using the definitions proposed by Shennan et al. and Walsh et al., but not by the criteria proposed by Jobe-Bancalari.

The strengths of this study included a highly

reproducible analysis of computed oxygen-dependence using the same algorithm in all patients and blinding of the performing investigator (PM) to the patients' characteristics. The limitations were associated with the retrospective design and relatively long period of the study. However, the local neonatal practice did not significantly change throughout the study period. For example, oxygen saturation targets were well defined (14), early caffeine administration was performed, and ventilator modes and settings were the same.

It is required to carry out further larger studies to confirm our findings and assess the long-term outcome of infants with IEs. An important limitation of the current study was the lack of follow-up data preventing us from drawing conclusions about the long-term consequences of IEs.

Conclusion

In conclusion, we proposed a definition of IEs and showed that in our setting, IEs may affect the true rate of BPD.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Author's Contributions

SN and VPC contributed to the conception and design of this study. SN and PM performed the statistical analysis and drafted the manuscript. VPC critically reviewed the manuscript and supervised the whole study process. All the authors read and approved the final manuscript.

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