Is bronchopulmonary dysplasia in adult age a novel COPD endotype?

Luca Bonadies [1], Alberto Papi[2] and Eugenio Baraldi[1]

[1]Neonatal Intensive Care Unit, Department of Woman's and Child's Health, University Hospital of Padova, University of Padova, Padova, Italy. [2]Respiratory Medicine Unit, University of Ferrara, University Hospital S. Anna, Ferrara, Italy.

Corresponding author: Eugenio Baraldi (eugenio.baraldi@unipd.it)

Shareable abstract (@ERSpublications)
Bronchopulmonary dysplasia is a chronic respiratory disease involving inflammation that occurs in childhood and may continue into adult age. BPD can be considered the earliest and longest lasting obstructive lung disease in humans. https://bit.ly/3O8TIe0

Cite this article as: Bonadies L, Papi A, Baraldi E. Is bronchopulmonary dysplasia in adult age a novel COPD endotype? *Eur Respir J* 2022; 60: 2200984 [DOI: 10.1183/13993003.00984-2022].

Received: 12 May 2022
Accepted: 7 June 2022

Preterm birth has a worldwide prevalence of nearly 11%. Due to advances in neonatal care, more than 95% of preterm infants in developed countries now survive into adulthood [1] (>10 million per year worldwide). However, improved early survival has been accompanied by long-term health risks [2].

Bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity, is the most common respiratory complication of preterm birth, affecting about 45% of preterm infants born weighing less than 1500 g [1]. This new entity was first described 55 years ago by Northway *et al.* [3]. BPD patients have a disruption in lung architecture and function associated with increased respiratory symptoms across the life span, including risk of hospitalisation for respiratory illness [4], wheezing disorders and prescriptions of asthma medications [5]. Several studies have been published on the lung function of BPD survivors, documenting an airflow limitation that is persistent over time [6], through adult age [7] and extended to the sixth decade of life [8]. BPD pathogenesis is still not completely understood and little evidence is available about the underlying airway pathobiology and the long-term outcomes [9]. The available data indicates that BPD begins as an alveolar disease [6] and evolves and persists mainly as an obstructive lung disease, somehow resembling the lung function and evolution of COPD [10]. The underlying mechanism is poorly evaluated; one of the hypotheses involves dysanaptic airway growth, which suggests that a rapid alveolar growth during infancy is not accompanied by concomitant airway development [11].

It is important to note that former very preterm infants not diagnosed with BPD are also likely to experience a trajectory of low lung performance throughout life [12, 13].

Moreover, BPD is a systemic clinical condition beyond the impairment of the respiratory system: from the first years of life subjects with BPD are more prone to neurodevelopmental, cardiovascular and growth abnormalities. Recent evidence shows the early development of several comorbidities in the adult age, such as ischaemic heart disease, metabolic syndrome and early mortality, configuring a new scenario of noncommunicable diseases of prematurity [14–17]. For these reasons it has been suggested that preterm birth should now be recognised as a chronic condition across the life course [2].

BPD prevention is consequently one of the main targets of neonatologists. Many strategies have been implemented through the years, not always with positive results [1, 18]. The preventive goal is now experiencing a new optimistic wave, related to the promising results obtained with breakthrough therapies such as mesenchymal stem cells and their secretome (extracellular vesicles) capable of regenerative and anti-inflammatory properties in preclinical studies when used in the first days of life [18–20].

However, to date an increasing number of extremely preterm infants survives prematurity, develops BPD [1] and experiences its sequelae, without any evidence-based treatment to stop or mitigate the evolution of the disease [21].

In this issue of the *European Respiratory Journal*, Um-Bergström *et al.* [22] address the unexplored field of airway inflammation in former preterm young adults with and without BPD. 22 subjects were evaluated with bronchoscopy and bronchoalveolar lavage (BAL) as part of the examinations planned in the LUNAPRE cohort [16], and airway inflammation was evaluated analysing the T-cell subsets in BAL with flow cytometry. This aspect is of critical importance in understanding the pathogenetic evolution underlying the reduced lung function of these subjects and possibly to spot new therapeutic options. They found that former BPD subjects, at a mean age of 19.6 years, had an increased presence of CD8-positive cells and a concomitant reduction of CD4-positive cells in BAL compared to healthy controls.

First of all, these data indicate a mobilisation of CD8-positive cells, which can be a driver of altered lung function trajectories over time, suggesting that BPD is also an active disease with inflammatory processes of the airway during adolescence, in contrast with the previous concept of established structural damage. Similar pathobiological findings have been described in bronchial biopsies of BPD adolescents, showing the presence of airway inflammation characterised by a higher proportion of CD8-positive T-cells and absence of eosinophils [23]. This evidence suggests that young adults with former BPD have a T-cell pattern in the airways resembling features of COPD. In addition, they also found a correlation between these cellular levels and forced expiratory volume in 1 s (FEV_1) or the FEV_1 to forced vital capacity (FVC) ratio, together with normal values of exhaled nitric oxide, reduced diffusing capacity of the lung for carbon monoxide and the positive response to methacholine challenge test [22]. Unfortunately, a group of young COPD subjects [24] was not included in the study, to allow a direct comparison.

The COPD inflammatory process, with elevated $CD8^+$ and reduced CD4/CD8 ratio [25, 26], is associated with airway obstruction and supported by remodelling and structural derangements of the airways and of the lung parenchyma [27–29]. A similar pattern in an already pathological lung of a former preterm subject may easily result in a worsening lung function.

An interesting finding of the study from the Karolinska Institute [22] is that former preterm subjects without BPD show an inflammatory pattern similar to that found in BPD subjects, with a percentage of $CD3^+CD4^+$ T-cells and a CD4/CD8 ratio correlating positively with FEV_1 while $CD3^+CD8^+$ T-cells were negatively related to both FEV_1 and FEV_1/FVC. These observations support a new mindset that former very preterm infants, independently from a diagnosis of BPD, have some degree of lung abnormalities [13], recalling those typical of COPD.

COPD is the third leading cause of death globally with a prevalence of 10% in subjects aged 30–79 years [30]. While for long time the disease was solely related to tobacco smoking, it is now widely recognised that COPD is not just one single entity, but rather a complex and heterogeneous condition that results from different causes and it has been proposed to modify the taxonomy and use the plural term “chronic obstructive pulmonary diseases” (COPDs) [31]. Recent evidence showed that COPD can also be the end result of processes that begin early in life (or *in utero*) with varying lung function trajectories [31]. Indeed, the current definitions of COPD acknowledge that airway and/or alveolar abnormalities that characterise COPD are influenced by host factors, including abnormal lung development [24]. Former BPD subjects can meet this definition, and could represent the paradigm of the long-term effect of a perinatal insult on lung development that determines chronic respiratory symptoms with a structurally altered respiratory system and consequent impaired lung function and accelerated decline.

Survivors of BPD are often labelled with a diagnosis of asthma during their childhood and empirically treated with inhaled corticosteroids. However, the pathophysiological pathways of BPD and asthma are quite different [22, 32]. Exhaled nitric oxide fraction, an indirect marker of eosinophilic airway inflammation in asthmatic patients [33], is normal to reduced in preterm and BPD patients [32]. Treatment of BPD subjects with inhaled steroids did not show significant improvements in randomised controlled trials and cross-over trials [34]. A recent study using a combination of inhaled corticosteroids with long-acting β2-agonists improved spirometry in preterm-born children with low lung function [35], but with doubtful clinical relevance. The therapeutic management of BPD patients is a bow without arrows and recent European Respiratory Society and American Thoracic Society guidelines were not able to formulate strong suggestions for their pharmacological management [21, 34]. The results of Um-Bergström *et al.* [22] confirm doubts about the appropriateness of treatment with inhaled

corticosteroids for these patients and hypothesises the need for different therapeutic strategies, such as new drugs used to target CD8 inflammation [36] or modulators of cytokine levels [37].

In conclusion, BPD can be considered the earliest and longest lasting obstructive lung disease in humans. It is a disease orphaned of an effective preventive strategy and treatment, and studies like the one reported by Um-Bergström *et al.* [22] have revealed new aspects of the disease. The similarities in pathology findings with COPD and the correlations with lung function impairment makes BPD in adult age a possible new COPD-like endotype. Pharmacological trials to prevent the evolution of this chronic lung condition and to treat its symptoms are urgently needed. The potential benefit could be expanded beyond BPD subjects to many preterm infants with extremely low birth weight. In parallel, the awareness of the increasing burden of this condition needs to be shared with chest physicians and general practitioners, and prematurity should be always thoroughly investigated in the diagnostic process of chronic respiratory conditions.

Conflict of interest: L. Bonadies has nothing to declare. A. Papi reports grants from Chiesi, AstraZeneca, GSK, BI, Pfizer, Teva and Sanofi; consulting fees from Chiesi, AstraZeneca, GSK, Novartis, Sanofi, Iqvia, Avillion and Elpen Pharmaceuticals; honoraria from Chiesi, AstraZeneca, GSK, BI, Menarini, Novartis, Zambon, Mundipharma, Teva, Sanofi, Edmond Pharma, Iqvia, MSD, Avillion and Elpen Pharmaceuticals; all of the above were not related to this specific work. E. Baraldi reports consulting fees from AstraZeneca, Sanofi and Exobiologics outside the submitted work.

References

1 Stoll BJ, Hansen NI, Bell EF, *et al.* Trends in care practices, morbidity, and mortality of extremely preterm Neonates, 1993–2012. *JAMA* 2015; 314: 1039–1051.
2 Crump C. Adult mortality after preterm birth – time to translate findings into clinical practice. *JAMA Netw Open* 2021; 4: e2033361.
3 Northway WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. *N Engl J Med* 1967; 276: 357–368.
4 Walter EC, Ehlenbach WJ, Hotchkin DL, *et al.* Low birth weight and respiratory disease in adulthood: a population-based case-control study. *Am J Respir Crit Care Med* 2009; 180: 176–180.
5 Been JV, Lugtenberg MJ, Smets E, *et al.* Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med* 2014; 11: e1001596.
6 Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007; 357: 1946–1955.
7 Moschino L, Stocchero M, Filippone M, *et al.* Longitudinal assessment of lung function in survivors of bronchopulmonary dysplasia from birth to adulthood the Padova BPD study. *Am J Respir Crit Care Med* 2018; 198: 134–137.
8 Bui DS, Perret JL, Walters EH, *et al.* Association between very to moderate preterm births, lung function deficits, and COPD at age 53 years: analysis of a prospective cohort study. *Lancet Respir Med* 2022; 10: 478–484.
9 Coalson JJ. Pathology of bronchopulmonary dysplasia. *Semin Perinatol* 2006; 30: 179–184.
10 McGrath-Morrow SA, Collaco JM. Bronchopulmonary dysplasia: what are its links to COPD? *Ther Adv Respir Dis* 2019; 13: 1753466619892492.
11 Ioan I, Gemble A, Hamon I, *et al.* Expiratory flow – vital capacity: airway – lung dysanapsis in 7 year olds born very preterm? *Front Physiol* 2018; 9: 650.
12 Bårdsen T, Røksund OD, Benestad MR, *et al.* Tracking of lung function from 10 to 35 years after being born extremely preterm or with extremely low birth weight. *Thorax* 2022; 77: 790–798.
13 Jobe AH, Bancalari E. An all-inclusive perspective on bronchopulmonary dysplasia. *J Pediatr* 2021; 234: 257–259.
14 Markopoulou P, Papanikolaou E, Analytis A, *et al.* Preterm birth as a risk factor for metabolic syndrome and cardiovascular disease in adult life: a systematic review and meta-analysis. *J Pediatr* 2019; 210: 69–80.e5.
15 Crump C, Howell EA, Stroustrup A, *et al.* Association of preterm birth with risk of ischemic heart disease in adulthood. *JAMA Pediatr* 2019; 173: 736–743.
16 Abman SH, Collaco JM, Shepherd EG, *et al.* Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr* 2017; 181: 12–28.
17 Baraldi E, Galderisi A. Noncommunicable diseases of prematurity: time for a new mindset? *J Pediatr* 2021; 237: 319–320.
18 Bonadies L, Zaramella P, Porzionato A, *et al.* Present and future of bronchopulmonary dysplasia. *J Clin Med* 2020; 9: 1539.
19 Lithopoulos MA, Strueby L, O'Reilly M, *et al.* Pulmonary and neurologic effects of mesenchymal stromal cell extracellular vesicles in a multifactorial lung injury model. *Am J Respir Crit Care Med* 2022; 205: 1186–1201.
20 Chang YS, Ahn SY, Yoo HS, *et al.* Mesenchymal stem cells for bronchopulmonary dysplasia: phase 1 dose-escalation clinical trial. *J Pediatr* 2014; 164: 966–972.e6.

21 Duijts L, van Meel ER, Moschino L, *et al.* European Respiratory Society guideline on long-term management of children with bronchopulmonary dysplasia. *Eur Respir J* 2020; 55: 1900788.
22 Um-Bergström P, Pourbazargan M, Brundin B, *et al.* Increased cytotoxic T-cells in the airways of adults with former bronchopulmonary dysplasia. *Eur Respir J* 2022; 60: 2102531.
23 Galderisi A, Calabrese F, Fortarezza F, *et al.* Airway histopathology of adolescent survivors of bronchopulmonary dysplasia. *J Pediatr* 2019; 211: 215–218.
24 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2022 Report). Date last accessed: 12 May 2022. https://goldcopd.org/wp-content/uploads/2021/12/GOLD-REPORT-2022-v1.1-22Nov2021_WMV.pdf
25 Kemeny DM, Vyas B, Vukmanovic-Stejic M, *et al.* $CD8^+$ T cell subsets and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: S33–S37.
26 Tzanakis N, Chrysofakis G, Tsoumakidou M, *et al.* Induced sputum CD8+ T-lymphocyte subpopulations in chronic obstructive pulmonary disease. *Respir Med* 2004; 98: 57–65.
27 Caramori G, Casolari P, Barczyk A, *et al.* COPD immunopathology. *Semin Immunopathol* 2016; 38: 497–515.
28 Barnes PJ. Cellular and molecular mechanisms of chronic obstructive pulmonary disease. *Clin Chest Med* 2014; 35: 71–86.
29 Wang Y, Xu J, Meng Y, *et al.* Role of inflammatory cells in airway remodeling in COPD. *Int J COPD* 2018; 13: 3341–3348.
30 Singh D, Agusti A, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019; 53: 1900164.
31 Celli BR, Agustí A. COPD: time to improve its taxonomy? *ERJ Open Res* 2018; 4: 00132-2017.
32 Baraldi E, Bonetto G, Zacchello F, *et al.* Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. *Am J Respir Crit Care Med* 2005; 171: 68–72.
33 Course CW, Kotecha S, Kotecha SJ. Fractional exhaled nitric oxide in preterm-born subjects: a systematic review and meta-analysis. *Pediatr Pulmonol* 2019; 54: 595–601.
34 Cristea AI, Baker CD, Allen J, *et al.* Outpatient respiratory management of infants, children, and adolescents with post-prematurity respiratory disease an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2021; 204: E115–E133.
35 Goulden N, Cousins M, Hart K, *et al.* Inhaled corticosteroids alone and in combination with long-acting β2 receptor agonists to treat reduced lung function in preterm-born children: a randomized clinical trial. *JAMA Pediatr* 2021; 176: 133–141.
36 Clement M, Pearson JA, Gras S, *et al.* Targeted suppression of autoreactive CD8+ T-cell activation using blocking anti-CD8 antibodies. *Sci Rep* 2016; 6: 35332.
37 Schmidt ME, Varga SM. Cytokines and CD8 T cell immunity during respiratory syncytial virus infection. *Cytokine* 2020; 133: 154481.