Targeting Treatable Traits across the Lifespan in Preterm-Born Individuals with Chronic Lung Disease of Prematurity

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In recent decades, the survival of extremely preterm infants (<28 weeks' gestation) has steadily increased, with a parallel burden of medium- and long-term related conditions leading to a growing population of individuals reaching midadulthood bearing a risk for multiple chronic morbidities, with substantial lifetime healthcare costs (1, 2).

Bronchopulmonary dysplasia (BPD) is the most known chronic respiratory complication of preterm birth, traditionally diagnosed using operational definitions such as respiratory support at 36 weeks of postmenstrual age. BPD affects almost half of infants born at less than 28 weeks of postmenstrual age and with birth weight less than 1,500 g (3). However, recent evidence shows that altered trajectories of lung function are observed in a broader population regardless of a BPD diagnosis (4, 5), leading to the broader definition of chronic lung disease of prematurity (CLDP). CLDP originates from a global arrest in alveolar and pulmonary vascular development, compounded by aberrant response to antenatal and postnatal injuries such as chorioamnionitis, intrauterine growth restriction, mechanical ventilation, and oxygen (Figure 1A) (3, 5). Mechanisms that hinder lung recovery are partly understood, but the altered lung remodeling to incoming noxae, such as recurrent infections, persisting inflammation, and poor nutrition may lead to interstitial fibrosis, increased arteriolar muscular thickness, and the developmental dysanapsis, an unbalanced growth of the alveolar lung component not appropriately matched by airway development (6). Historically considered a disease of infancy, CLDP may persist throughout the lifespan of preterm-born subjects, thus representing the earliest and most prolonged chronic respiratory disease in humans (7) (Figure 1A). The Global Initiative for Chronic Obstructive Lung Disease new etiotypes taxonomy recognizes preterm birth as a risk factor to the development of a chronic obstructive pulmonary disease (COPD) endophenotype (8). Therefore, as for COPD and other respiratory diseases we suggest the treatable traits (TTs) (9) strategy as a new approach for the management of these subjects (Figure 1B).

Lack of Holistic Care

There is insufficient awareness of the long-term impact of extremely preterm birth and CLDP, underrecognition of their lifelong consequences, and challenges in effective management, which during adulthood is fragmented among general practitioners and specialists (10). Notably, no recommendations have been developed for managing CLDP in adult patients (11).

CLDP can mimic traits of other respiratory conditions, such as asthma and COPD, and its management remains heterogeneous (11). This is likely due to multiple phenotypes of CLDP (obstructive-reversible or obstructive-fixed, restrictive pattern or mixed, dysanaptic airway growth, preserved ratio of impaired spirometry), stemming from a variable predominance and interplay of disease components (parenchymal disease, pulmonary hypertension, large airway disease), as reflected by the heterogeneity of the imaging findings among adults with CLDP (5, 6, 12) (Figure 1).

CLDP is invariably associated with other long-term morbidities, collectively imposing a significant multifaceted burden (Figure 1). The most prominent concerns pertain to the cardiovascular and neurodevelopmental domains. A significant proportion of subjects born extremely preterm carry pulmonary hypertension beyond the neonatal period (13). Systemic hypertension is also common, resulting from the impaired glomerulogenesis of prematurity (14). CLDP is often linked to traits of metabolic syndrome, including an elevated risk of diabetes. These factors combined may explain the worrisome risk of death and ischemic cardiac disease at early ages for these individuals (15). Preterm birth also interrupts normal brain development, with possible wide-ranging effects, in terms of late cognitive and executive function

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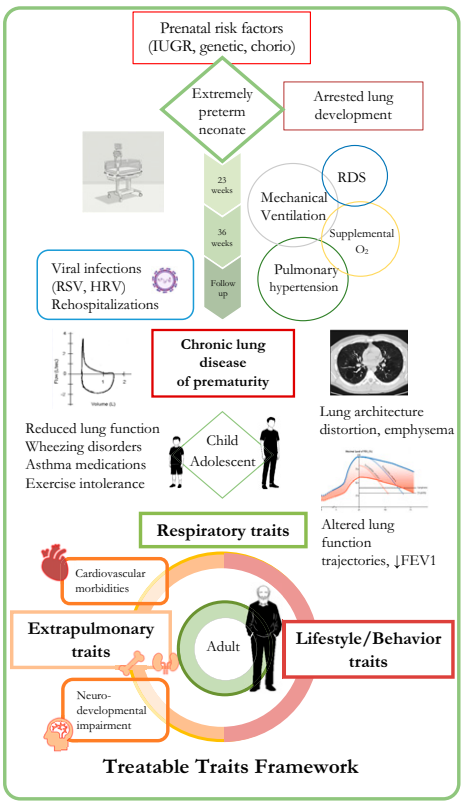

B

Respiratory treatable traits		Possible trait markers	Evaluation	(Future) Management options
Neonatal age	Poor alveolarization and reduced vascular development	Chest X-Ray, Lung US, Echocardiography BPD outcome estimator	NICU	Regenerative medicine, Extracellular vesicles, IGF1
	Lung inflammation	-omic biomarkers, IL-6, IL-8, TNF-α	NICU	Avoid MV, NIV, Postnatal steroids
Older ages	Reversible/fixed airflow limitation, pPRISm phenotype, dysanspsis	Forced Oscillatory Technique, Spirometry with bronchodilator responsiveness.	From childhood	Pharmacotherapy (SABA, LABA, ICS) Pulmonary rehabilitation
	Inflammation: a. Eosinophilic b. Neutrophilic c. T-cell	a. FeNO, eosinophilia, IgE b. Neutrophil count in sputum/BAL c. $CD8^+$, CD4/CD8 ratio in sputum/ BAL EBC, bronchoscopy/airway byopsies	All ages	a. Pharmacotherapy (ICS, LABA, CS…) b. Macrolides, smoking cessation
	Emphysema Airway mucus plugs	Spirometry, DLCO Chest CT	All ages	Smoking cessation, regenerative medicine
Extrapulmonary treatable traits				
Cardiovascular: a. Pulmonary Hypertension b. Cardiac dysfunction c. Exercise intolerance		ECG Cardiac Imaging (US, MRI) Cardiac Catheterization Cardiopulmonary exercise test	All ages	Pharmacotherapy (e.g. vasodilators) rehabilitation, nutritional support
Kidney: systemic hypertension		Arterial Blood Pressure monitoring Renal function biomarkers	All ages	Avoid nephrotoxins Pharmacotherapy
Neurological/ Neurodevelopmental		Imaging (brain US, MRI) EEG Developmental screening tests	From infancy	Antiepileptic drugs Neuromodulation Developmental therapy
Endocrine/metabolic		Fasting glucose/HbA1c, TSH, LDL/Cholesterol DEXA	From adolescence	Pharmacotherapy Lifestyle interventions
Nutritional/Somatic growth		Auxological parameters, Blood vitamins and micronutrients dosage	From infancy	Nutritional interventions and supplements
Lifestyle treatable traits				
Smoking, vaping		Patient-reported Exhaled CO Urinary cotinine	From adolescence/ adulthood	Parental counseling Nicotine replacement Media campaigns
Air Pollution (indoor and outdoor)		Air quality monitoring, triggered exacerbations	All ages	Relocation, air filters
Vaccination and infection prophylaxis		Surveillance data	All ages	Immunization (RSV, S. Pneumoniae) Advice on daycare attendance Immunostimulants
Adherence to treatment/ Suboptimal inhaler technique		Direct observation Prescription rate Patient feedback	All ages	Education Written instructions App-based notifications
Family and social support, Quality of Life		Quality of life questionnaires	All ages	Psychological and mental health support strategies

Figure 1. (*A*) Origins of chronic lung disease of prematurity (CLDP) and its evolution toward a treatable trait (TTs)-approachable respiratory disease across the lifespan. (*B*) Brief list of potential respiratory, extrapulmonary, and lifestyle TTs to consider in patients with CLDP, with potential markers and treatments to be explored and the suggested age for the initial screening. This list serves as an exploratory summary of the current evidence, to be expanded as future assessments and insights emerge (2–4, 6, 7, 11, 13, 15). BPD = bronchopulmonary dysplasia; chorio = chorioamnionitis; CS = corticosteroid; CT = computed tomography; DEXA = dual-energy X-ray absorptiometry; EBC = exhaled breath condensate; FE_{NO} = fractional exhaled nitric oxide; HbA1c = glycated Hb; HRV = human rhinovirus; ICS = inhaled corticosteroids; IGF1 = insulin-like growth factor 1; IUGR = intrauterine growth restriction; LABA = long-acting β-agonist; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; MV = mechanical ventilation; NIV = noninvasive ventilation; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome; RSV = respiratory syncytial virus; SABA = short-acting β-agonist; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; US = ultrasound. Adapted by permission from Reference 7.

impairment, neuropsychological, and behavioral deficits. In this context, the individual genetics and the superimposition of behavioral and environmental traits (e.g., smoking, pollution) could shape different trajectories of CLDP and related morbidities, either exacerbating or mitigating certain traits. Providing holistic and timely care for CLDP and its comorbidities might be the model of care to support healthy aging in survivors of preterm birth.

A New Proposal: Reframing CLDP Management through the TT Model

A tailored strategy has shown promising results for adult chronic airway diseases (e.g., asthma, COPD). The TTs concept represents a step toward precision medicine in chronic airway diseases management (9). It reflects a mindset shift from disease labels to assessing and treating patients on the basis of their clinical presentations (phenotypes) and pathobiological mechanisms (endotypes). In this context, a TT can be defined as a "therapeutic target identified by phenotype or endotype, through validated biomarker(s)." Three key domains have been described: pulmonary, extrapulmonary (comorbidities), and lifestyle/behavioral (9) (Figure 1).

By its very nature, the TTs approach could be applied to any patient with chronic airway diseases with multiple comorbidities and phenotypic heterogeneity; however, to our knowledge, it has not been applied to CLDP, which shares these characteristics with the previously TTs-approached diseases.

A multidimensional model has been used to describe prematurity-associated lung disease. This model suggests tailoring the follow-up of CLDP survivors, by identifying modifiable factors driving their progression of disease and, ultimately, optimizing their long-term outcomes (2). However, there is no robust evidence for existing treatments in improving trajectories of subjects with established CLDP, highlighting the need for new interventional options.

In this context, we propose to investigate the potential of the TTs to identify prematurity-related endotypes and phenotypes, inform clinical practice, and guide research and progress in evidence-based medicine for the benefit of preterm-born individuals with CLDP (Figure 1B).

Future Needs for TTs of CLDP and Other Morbidities

Several key questions emerge in implementing the TTs concept to CLDP and

prematurity-related morbidities: *1*) Which traits are associated with major long-term health outcomes? *2*) Is this framework effective in obtaining meaningful health outcomes? How to prioritize research efforts? *3*) How can clinicians identify and characterize the different phenotypes and endotypes early throughout lung development? and *4*) Which individuals warrant a follow-up during adolescence and adulthood and at what intervals?

A step in the process would be understanding the effect of the traits with validated identification markers and treatments on symptoms, disease progression, and prognosis. Acknowledging the impact of preterm birth on a patient's perceived quality of life, and caregiver wellness, engaging patients and families could help identify key traits and implement effective lifestyle changes.

How to best integrate the TTs approach into clinical practice will depend on the framework of TTs characterizing each patient, the effectiveness/availability of treatments, and the synergistic effect of treating multiple traits simultaneously. Some traits now lack effective interventions (Figure 1). Although not immediately actionable, they may serve as important indicators for further research into novel biological mechanistic pathways. The TTs framework will be easily adaptable as new evidence emerges, and will foster greater awareness, among pediatric and adult healthcare providers, of CLDP's often underrecognized multisystem complications, possibly driving the development of new treatments. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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