**Management of prematurity-associated lung disease from infancy through to adulthood**

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**Key Points:**

**Take home messages**

- Acknowledge prematurity-associated lung disease from infancy through to adulthood
- For preterm born children and adults, general and expert respiratory physicians are encouraged to phenotype PLD, for example based on lung function measures or imaging, which help identifying personalised 'treatable traits' leading to optimal management strategies
- Vaccination and immunisation, which are key to minimize early-life viral infections and prevent related hospitalisations in PLD are highly recommended; vaccination strategies for adults with PLD should be similar as for adults with COPD or other chronic respiratory diseases
- Consider inhaled corticosteroids, with or without long-acting beta-agonists or long-acting muscarinic antagonists, which may be effective in the treatment of PLD. A treatment trial of 2-3 months, particularly for specific spirometry phenotypes, such as POLD and pDysanapsis, and in patients with elevated $FE_{NO}$ levels, could be pursued.
- It is recommended to monitor for extra-pulmonary traits and optimise their treatment with special attention to central airways pathology, pulmonary vascular disease, feeding difficulties, gastro-esophageal reflux disease, impaired growth/weight and neurodevelopmental disabilities
- Promoting and offering support for a healthy lifestyle including physical activity and avoidance of adverse exposures is necessary
- Monitoring and follow up of all patients born preterm is recommended. Intensity and frequency of monitoring and duration of follow up depend on gestational age at birth and PLD, but assessment of symptoms, growth, blood pressure and lung function is minimally needed
- For children and adults with the most severe phenotype of PLD, it is imperative to establish adequate follow up programs, from infancy into adulthood; the composition of the multidisciplinary team depends on gestational age at birth and PLD, but except for the patient and family, the team should minimally include a neonatologist and/or pediatrician and a dedicated nurse/nurse practitioner.

**Recommendations for future research**

- Formulation of, and agreement on a definition of prematurity-associated lung disease covering the life course periods
- Although many studies have examined pathophysiological processes in the lungs during the neonatal period, there is still limited information on the underlying mechanisms of PLD in childhood and adulthood; future studies should aim to better understand these processes in order to identify distinct endotypes and uncover potential new therapeutic targets
- Studies on phenotype guided treatment are needed to identify which patients with PLD will benefit from repurposed existing drugs or new drugs, for example, the use of trained immunity based vaccines, monoclonal antibodies targeting specific proinflammatory cytokines, or anti-oxidants
- Tools to identify patients at the highest risk for adverse respiratory and non-respiratory outcomes are essential for selecting those who require the most intensive follow-up by a multidisciplinary team; early-life lung function tests, imaging, and biomarkers are crucial to detect these high-risk patients as early as possible and enable timely intervention

**ABSTRACT**

Preterm birth has lifelong pulmonary consequences, with many survivors developing prematurity-associated lung disease (PLD). This third review in the series summarises current evidence for treatment and monitoring of PLD and its phenotypes. Preventive strategies, including maternal and infant vaccination to reduce early-life viral exposures, are emerging as key interventions. Pharmacological approaches such as inhaled corticosteroids, alone or combined with long-acting bronchodilators, show potential benefits in childhood, although evidence on phenotype-specific responses remains limited. Management should also address extra-pulmonary traits, including central airway abnormalities, cardiovascular sequelae, gastro-oesophageal reflux, impaired growth, neurodevelopmental disabilities, reduced exercise capacity, and environmental exposures. We discuss monitoring tools for early identification and longitudinal assessment of PLD, evaluation of treatment response, and recommendations for structured follow-up from infancy into adulthood, suitable for both general and specialist respiratory clinicians. Finally, opportunities for repurposing existing drugs and developing new therapies for PLD in children and adults are highlighted.

## INTRODUCTION

Being born preterm has lifelong pulmonary and extra-pulmonary consequences.[1] However, the evidence base for the management of lung disease associated with preterm birth is very limited, as was evidenced by the two guidelines from the European Respiratory Society (ERS) in 2020 and the American Thoracic Society (ATS) in 2021.[2,3] Nevertheless, several treatable traits are often present (Table 1). Encouragingly, significant progress has since been made by the development of the concept of prematurity-associated lung disease (PLD) and its associated phenotypes as discussed by Cousins et al[4] and Course *et al* (first article of this series), and results from two randomised controlled treatment trials.[5,6] PLD is considered to reflect a continuous trend of pulmonary conditions across the life span determined by being born preterm and to which suboptimal fetal airway and lung development, with our without additional postnatal circumstances, has a significant role. The most favorable end of the spectrum comprises those being born late preterm (34 to 37 weeks of gestation) or even born early term having no overt respiratory symptoms but may having lower lung function measures in later life[7]. The extreme end of the spectrum, comprises those being born extreme preterm (<28 weeks of gestational age) having high supplementary oxygen need and/or positive pressure or ventilation support from the neonatal period into infancy (commonly described as bronchopulmonary dysplasia or BPD) including neonatal and early infant risk factors or specific clinical phenotypes having high risks of later life respiratory morbidity and mortality[8]. Identifying endotypes, phenotypes and/or treatable traits, which may vary across the life course as shown for lung function trajectories (second article of this series), may help to better understand, monitor and treat individuals with PLD. Recently, objective phenotypes based on lung function measures have been proposed including PRISm (%FEV1 < LLN and FEV1 /FVC ≥ LLN) and POLD (%FEV1 and FEV1 /FVC < LLN). Individuals with POLD had the greatest ventilation abnormalities measured with hyperpolarised MRI and impairment in exercise capacity). For adults, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recently proposed the etiotype COPD due to abnormal lung development (COPD-D), which is suggested to consists 50% of COPD

patients[9,10]. New terms as ‘pre-COPD’ and ‘PRISm’ were also proposed acknowledging the role of abnormal lung development and evidence for optimal management strategies in adults is lacking.

Following the first and second articles of this series proposing the PLD concept and its phenotypes, and lung function trajectories across the life span for preterm born subjects, respectively, this review from the series focuses on the current evidence available for treatment and monitoring strategies for PLD including a proposal for practical management from infancy to adulthood with the potential to be used by general and expert respiratory health care physicians caring for both children and adults as well as suggesting the way forward for the management of the recently described concept of PLD and its phenotypes.

## SEARCH STRATEGY AND SELECTION CRITERIA

In order to identify studies on management of PLD including daycare and therapeutic interventions with bronchodilators and corticosteroids as well as monitoring of PLD, we used our previous search terms from our ERS Task Force report in Embase, Medline Ovid, Cochrane Central Registry of Trials, and Web of Science Core Collection from July 2018 to December 2024[2]. In addition, we extended the search terms from the first paper in this series in Embase, Medline and Web of Knowledge from 1960’s to December 2024, but specifically included search terms for treatment including bronchodilators and corticosteroids.[2,3] We included, wherever possible, meta-analyses and systematic reviews of randomised trials, randomised trials, retrospective or prospective cohort studies, and additionally included articles that were considered important based on expert opinion. Conference abstracts were omitted. Articles published in English were included. References are provided in the relevant paragraphs of the main text.

## CURRENT AVAILABLE TREATMENT FOR PLD

The evidence base for the treatment of PLD after discharge of preterm-born infants from the neonatal unit up to adulthood is somewhat limited. Whilst many traits such as lung growth are less amenable to treatment, there are many traits which, as outlined in Table 1, are potentially treatable as discussed below.

**Respiratory support and supplemental oxygen**

Hypoxia - whether sustained or intermittent - is associated with the development of pulmonary hypertension, growth failure and poor neurodevelopmental outcomes.[11] In infants with more severe disease, discharge home on respiratory support may be needed to ensure adequate oxygenation, growth and development. Domiciliary oxygen programs are well established for infants who have prolonged need for supplemental oxygen home respiratory support may vary from low flow oxygen to noninvasive ventilation and to invasive ventilation via tracheostomy. Recent data suggest that up to 8.7% of children with BPD received a tracheostomy, however, this percentage obviously depends on settings, local guidelines and resources[12-14]. Main risk factors for home respiratory support using invasive ventilation via tracheostomy are extreme preterm birth, intrauterine growth retardation, tracheobronchomalacia, and male sex. Several randomised controlled trials have examined optimal oxygen saturation targets for extremely preterm infants (<28 weeks of gestation) during the first few weeks of life, but since lower targets are associated with increased death, most centres now aim for oxygen saturations of 92-95% during the early neonatal period. However, the optimal oxygen range for infants with prolonged oxygen requirements including those with established bronchopulmonary dysplasia (BPD) is lacking[15]. As a result, suggested targets are expert guided with the ERS guideline on BPD suggesting a minimum $SpO_2$ threshold of 90%, while the ATS guideline for PLD suggests a higher threshold of 93%.[2,3] Caution, however, is needed to avoid hyperoxia which can result in adverse outcomes.[16] Results of two ongoing randomised controlled trials examining oxygen saturation targets in children with established BPD and prolonged need of oxygen are eagerly awaited.[17,18] In adults, only general rather than specific recommendations for

supplemental oxygen and ventilatory support for individuals with PLD or having clinical symptoms of PLD (or more specified etiotype of COPD) are available.

**Childcare and vaccinations**

Recent (multi-centre registry) studies showed that very preterm born children with or without BPD who attended daycare or had 3 or more siblings have an up to 7·4-fold risk of acute respiratory infections, emergency department visits, systemic steroid use, activity limitation, troubled breathing or use of rescue medication.[19-21] These risks are greatest during the first year of life. Given the evidence of high exposure to viruses, especially during infancy, individualised advice to parents or guardians on daycare attendance, therefore, seems most sensible for infants with PLD especially during the first year of life and taking into account local childcare facilities, parental leave regulations and parental wishes.

Immunisations are of great importance including routine vaccinations against pneumococcus, diphtheria, pertussis, tetanus, hepatitis B and *haemophilus influenza* type b, often commencing during the neonatal stay. Vaccinations for seasonal viral infections, including influenza vaccination (with second dose depending on age), should be considered, particularly for those with a more severe form of PLD and their caregivers.[22] Maternal pertussis and influenza vaccinations during pregnancy have recently been introduced and may reduce the risk of preterm birth.[23] Maternal pertussis vaccination may also prevent pertussis in infants and slightly reduces upper respiratory infections, while maternal influenza vaccination is up to 56% efficacious against PCR-confirmed influenza in infants.[24,25] We speculate that beneficial effects in infants with PLD are more prominent. For several decades, selected at risk preterm-born infants have received monthly palivizumab, passive anti-RSV antibodies, during the winter season. Since RSV remains a great burden in both preterm- and term-born infants, many countries have started introduction of the newer passive anti-RSV antibody, nirsevimab, which, due to its long half-life, only requires a single injection.[26,27] The results have, thus far, been impressive in countries which have introduced

nirsevimab.[28] Additionally, many countries have introduced maternal RSV vaccination from 28 weeks of pregnancy to protect the infant after birth, especially as RSV causes severe disease during the first few months of life and showed a 50% reduction in RSV disease in infants.[29] Advice on preventing virus infections and vaccination strategies for adults previously born preterm with PLD should be similar as for adults with COPD or other chronic respiratory diseases.

**Inhaled corticosteroids and long-acting beta$_2$-agonist**

Preterm born infants who die from BPD in infancy have extension of smooth muscle into the peripheral airways when compared to preterm born infants who die from non-respiratory causes.[30] Whether this smooth muscle extension resolves or progresses to myofibroblast differentiation resulting in fixed airway disease unresponsive to bronchodilators is unclear. A previous systematic review included 22 studies with all studies, except one, assessing responses to only single doses of a variety of bronchodilators administered via a variety of devices.[31] In general, 30% of preterm-born individuals have bronchodilator reversibility in childhood and young adulthood[31-37], but longer-term effects on airway obstruction or respiratory symptoms is lacking. A study from the nineties showed an improvement of percent predicted $FEV_1$ of 5·8% in their BPD group (n=12) and 1·4% (n=17) after two weeks of terbutaline.[38] Similarly, until recently, only two previous studies from the pre-/peri-surfactant era have assessed if inhaled corticosteroids improve lung function in school-aged preterm-born children with significant airway disease. A double blind, placebo controlled, crossover study assessed beclomethasone (200 µg twice daily) for four weeks in 15 children aged 8 years with low birthweight showing minimal improvement in lung function.[39] Another study assessed budesonide (0·8 mg/m$^2$/day for one month followed by 0·4 mg/m$^2$/days for three months) showing improved diurnal variation but no differences for spirometry.[40] Despite these two studies showing lack of clear benefits from inhaled corticosteroids, several data linkage studies reveal significant use of both inhaled steroids and bronchodilators for PLD in clinical practice.[41] Recently, two randomised, double-blind, placebo-controlled trials

assessing inhalers in school aged children have been published. The first using twice daily one puff of 125 mcg fluticasone propionate for 12 weeks, compared with a placebo, in 170 children (born <32 weeks of gestation) showed an overall increase of 0·3 Z-score (~4% percentage predicted) for $FEV_1$ and 0·41 Z-score for $FEV_1$/FVC.[6] Those with a positive pre-treatment bronchodilator test responded greater to inhaled corticosteroids. 23% from the corticosteroid group had >0·5 Z-score (6% percent predicted $FEV_1$) increase in $FEV_1$, suggesting that a subgroup of children may benefit from this treatment. However, improvements far greater than 6% in percent predicted FEV would be required for any significant clinical benefit. The second trial studied children (7-12 years old, born at ≤34 weeks of gestation) who had percent predicted $FEV_1$ of ≤85%, administering two puffs of fluticasone propionate 50 µg alone or in combination with salmeterol 25 µg or placebo for 12 weeks resulting in 7·7% and 7·8% improvement for percent predicted $FEV_1$ and $FEF_{25\%-75\%}$ , respectively, after inhaled corticosteroids, and 14·1% and 19·5% for percent predicted $FEV_1$ and $FEF_{25\%-75\%}$ with combined treatment.[5] Whilst these studies were small, they were powered for their respective outcomes. Long-acting $beta_2$-agonist monotherapy has not been assessed due to safety concerns in both children and adults if used alone.[42,43] However, what remains unknown is if such treatment is disease modifying leading to long-term improvement in both symptoms and lung function. The next steps are to target treatment to the specific phenotypes of PLD especially POLD and pDysanapsis which appear to have greater bronchodilator response and greater $FE_{NO}$ than the pPRISm and preterm and term control groups [4]. However given the small numbers available from any individual cohort such studies are likely to require coordination by multinational collaborations, for example the PELICAN initiative.[44] Data specifically targeting adults with PLD or subjects with clinical symptoms of PLD (or more specified etiotype of COPD) as primary outcome are also lacking. GOLD provides more general recommendations, rather than focusing on etiotypes of COPD, and proposes treatment based on treatable treats (dyspnea, occurrence of exacerbations), which may be identified by phenotypes or endotypes through biomarkers and suggests either a short or long-acting bronchodilator, a long acting beta2 adrenergic agonist (LABA) and long-

acting muscarinic antagonists (LAMA) combination, or a LABA, LAMA, and inhaled corticosteroid combination if blood eosinophils are ≥300 cells/μl[9]. Until additional new evidence is available, it would be reasonable for school aged children to administer combined inhaled corticosteroids and LABA for 12 weeks with formal assessment of effect and continued only if clinical or physiological improvement is observed.

**Other pulmonary management**

Lung volume reduction surgery is considered in adults with COPD having extensive emphysema but should only be considered on an individual case-basis in preterm-born children with severe lung disease often secondary to prematurity including those who had BPD in infancy or (non-congenital) abnormalities on chest CT imaging.

**MANAGEMENT OF EXTRAPULMONARY TRAITS**

Risk of extrapulmonary conditions due to being born preterm is often present due to a complex interplay of multiple organ systems and may stem from the immaturity of multiple organ systems at birth or as a consequence of, or interaction with interventional treatment.

**Central and obstructive upper airway conditions**

Occurrence and prolonged duration of central dysregulated breathing or persistent apneoa, intermittent desaturation, or bradycardia are most frequently observed in infants born extreme (90%), very preterm (50-70%) or moderate (10-20%) preterm, as are sleep disorders (e.g. obstructive sleep-disordered breathing) and some may even persist in childhood.[45,46] Polysomnography is the gold standard for diagnosis but is not always feasible. Therefore, 24-hour nocturnal oximetry, and less preferable sleep questionnaires, have been used to identify the at-risk child.[3] Prolonged caffeine, adenotonsillectomy, CPAP or BiPAP are potential treatments conditional on the final diagnosis.

Retrospective studies using laryngoscopy or chest imaging show that (very) preterm born infants have a 3-fold risk of severe laryngomalacia and 43-49% have broncho- and/or mild-to-moderate tracheomalacia.[47,48] The latter conditions frequently lead to management change such as PEEP titration, placing of a trachea cannula, bethanechol or ipratropium bromide nebulisations with airway clearance techniques or a surgical intervention with aortopexy in extreme cases.[48] The pathogenesis remains not fully clear but likely involves structural abnormalities to the cartilage, neuromuscular dysfunction, and gastroesophageal reflux.

Incidence of (left) vocal cord paralysis after patent ductus arteriosus ligation or post-intubation shown by laryngoscopy varies widely (1-50%) but should be considered if stridor, tachypnoea, feeding difficulties or at later ages, even in adulthood, hoarseness, voice-related symptoms and increased respiratory symptoms with increasing exercise load occur.[49] Resolution or compensating with resolution of symptoms may occur, but sometimes vocal fold injection or laryngeal reinnervation are needed.[50]

Acquired laryngotracheal stenosis, including subglottic stenosis, can occur after prolonged endotracheal ventilation, for which serial intralesional triamcinolone acetonide injections, temporal trachea cannula placement and, in severe cases, laryngotracheal reconstruction or a cricotracheal resection surgery in specialised centres may be required.[51]

In adults, sleep apneoa and probably tracheomalacia are commonly present among those with COPD, but prevalences and related treatment of acquired vocal cord paralysis and laryngotracheal stenosis, which are specific potential co-morbidities in preterm born adults, are currently unknown.

**Management of non-respiratory co-morbidities**

Cardiovascular sequelae such as patent ductus arteriosus or pulmonary hypertension are mostly present among infants born extremely preterm. Initial symptoms are often present during the neonatal care period but there should be awareness of vascular and cardiac dysfunction in later life, specifically among those with severely impaired pulmonary function. Recent studies have revealed associations with increased cardiovascular risk factors, reduced cardiac function, higher rates of ischaemic heart disease and heart failure in later life. Intermittent cardiovascular imaging, particularly under physiological stress, should, therefore, be implemented in patient management strategies.[52-54]

Gastro-oesophageal reflux disease (GORD), unsafe swallowing and feeding difficulties due to dis-coordinated swallowing, poor endurance or performance of sucking, swallowing dysfunction, or poor swallow-breath coordination are often present and can lead to aspiration and respiratory problems. Numerous studies have observed that both underweight and overweight, and adverse body composition affect lung function and respiratory symptoms throughout life.[55,56] Therefore, optimising nutrition and growth especially in the early years, when rate of lung development and growth is steep and lung function still needs to reach its maximum peak, remains an urgent need. Also in preterm-born adults awareness is needed for GORD and metabolic syndrome, and additionally for osteoporosis, anemia or polycythemia, and frailty.[9]

PLD, especially among those born at lower gestations including those who had BPD in infancy, is strongly associated with neurodevelopmental disabilities.[57] Developmental, muscular and coordination disorders, behavioral difficulties, and lower IQ score may affect risk of GORD and aspiration, reduced airway clearance possibilities, and reduced exercise affecting optimal respiratory health.

**Management and prevention of behavioral or risk factor traits**

Systematic reviews and meta-analyses indicate reduced maximal exercise capacity in individuals born (very) preterm or with very low birth weight, although the effect sizes are generally small.[58-60] Findings of physical activity in patients with PLD are somewhat conflicting with some studies reporting lower levels of physical activity, while others have not. Nevertheless, stimulating regular moderate-vigorous physical activity is of great importance to enhance exercise capacity and also foster social interactions and reduce the risk of cardio-metabolic diseases in the long-term. Few small studies have investigated the effect of exercise programs. One study showed that a 4-week exercise program improves maximal oxygen consumption ($VO_2$ max) and another that a 12-week tailored exercise program (30–45 min high-intensity interval training twice weekly) modestly improves cardio-pulmonary fitness ($VO_2$ peak load and peak ventilation) and walked distance in 6 minutes. Additional recommendations on caloric intake and a healthy diet, and specifically semi-structured consultations with a psychologist and physician to discuss baseline results and potential barriers to physical activity improve both patient-reported and parent-reported quality of life significantly across all domains.[61-63] Importantly, in a study combining data from four birth cohorts in an accelerated longitudinal cohort design, increased physical activity during early childhood (4-7 years of age) and greater BMI z-scores at 4 years were associated with improved lung function ($FEV_1$).[64] Therefore, decreased exercise capacity associated with PLD has the potential for improvement but robust specific programs need to be developed.[65]

Last, to prevent further insults to the lung, maternal and any household or personal tobacco smoking as well as ambient pollution exposure should be strongly dissuaded at all ages. Although studies on adults with specifically PLD or COPD-D are lacking, advice in relation to smoking, physical activity, and pulmonary rehabilitation should be in line with general recommendations for COPD.

**MONITORING OF PLD**

PLD is associated with many lifelong health issues, emphasising the importance of early identification, early intervention, ongoing monitoring, and supportive care throughout childhood and into adulthood. Therefore, monitoring should be used (a) to identify PLD and its phenotypes as early as possible, (b) for longitudinal assessment of lung disease, and (c) to assess response to treatment.

**Lung function**

Lung function, especially spirometry, has been the mainstay of assessment of lung function in preterm-born children and young adults, mainly in research studies, to confirm the significant deficits in children with PLD. It can also be used to identify the different spirometry phenotypes, especially as each is likely to require different treatment and be associated with different outcomes. However, spirometry is only possible from the age of five or six years and onwards as it requires specific participant manoeuvres, although, as discussed below, much earlier diagnosis of PLD is required especially if disease modifying interventions are to be developed and instituted. Lung function in preterm born individuals with, but also without, PLD tends to track alongside that of term borns throughout life, albeit at significantly lower levels. Extreme preterm birth at <28 weeks' gestation, especially if associated with the diagnosis of BPD in infancy, and those with intrauterine growth restriction (IUGR), are significant risk factors for the lowest lung function later in life[1,55]. Importantly, airway obstruction may worsen over time, at least, in some individuals.[66-68] Taken together, there are compelling reasons to monitor lung function, most conveniently by spirometry together with assessment of bronchodilator response.[2,4] Firstly, spirometry can be used to identify if the subject has PLD. Furthermore, it can be extended to assess which spirometry phenotype the subject has and also assess response to a bronchodilator.[4] Secondly, spirometry permits longitudinal assessment of progression of the underlying lung disease in individual subjects from childhood to adulthood. Thirdly, for epidemiological purposes, different lung function phenotypes may be associated with specific longer term outcomes.

Although spirometry is feasible from 5-6 years of age onwards, clearly the optimal window to identify lung disease is at much earlier age, preferably in the neonatal period or in infancy, so that identification of PLD together with the different phenotypes, longitudinal assessment and intervention can commence at a far earlier age than is currently possible.[69-71] In this regard, oscillometry and multiple breath washout (MBW) tests are promising tools as they do not rely on participant cooperation.[72-74] Several studies of preschool children, school children and adolescents using oscillometry have reported impaired impedance, higher resistance and more negative reactance especially of the peripheral airways.[75-79] Whilst these techniques have the potential for introduction into clinical practice, several challenges remain for example technical comparability between devices or availability of reference ranges as well as relationships between oscillometry in early life and spirometry measurements in later life.

Similarly, tidal breathing flow volume loops, the time to peak expiratory flow/ expiratory time ($T_{PEF}/T_E$) can be measured, as an indicator of airway obstruction. In a small study of preterm-born children, $T_{PEF}/T_E$ in infancy correlated with $FEF_{25\%-75\%}$ Z-score at school age, while LCI and FRC as assessed with MBW in infancy, did not.[80] However, in another study in infants born moderate to late preterm, $T_{PEF}/T_E$ did not predict lung function nor respiratory symptoms at age 6 years.[81]

The hypoxic challenge test (HCT) was developed to assess flight fitness for children with respiratory diseases but it is also feasible in preterm-born preschool children to assesses both the condition of the respiratory and pulmonary vascular systems.[82] Infants with BPD often fail the HCT with postnatal corticosteroids, respiratory support at NICU discharge, pulmonary hypertension, and tracheostomy being risk factors for a failed test.[82] It is unknown, if HCT has any prognostic value for future respiratory health.

Fractional exhaled nitric Oxide ($FE_{NO}$), an exhaled biomarker indicating eosinophilic airway inflammation, has been used for monitoring treatment responses in asthma but the $FE_{NO}$ has

not shown to be increased in preterm-born subjects including those who had BPD in infancy.[83] However, recent data has shown that $FE_{NO}$ is increased in the POLD phenotype of PLD and to an extent in the pDysanapsis phenotype but not in the pPRISm phenotype or preterm and term controls.[4] Interesting, $FE_{NO}$ was decreased in both the randomised controlled trials described above, if the active arm included inhaled corticosteroids, suggesting that an inflammatory element is present in some children who have PLD. It also implies that $FE_{NO}$ may be a useful biomarker in monitoring treatment response to inhaled corticosteroids, at least, in specific groups.[5,6] Importantly, whether some of these children have eosinophilic inflammation measured by biomarkers as exhaled $FE_{NO}$ and blood eosinophils, and what the impact is on outcomes or how this is present in adults with COPD-D/young COPD, is an area which has not received much attention thus far.

To summarise, identification of PLD and its phenotypes as early as possible remains the ultimate goal. Currently, spirometry is the only optimal option from 5 – 6 years onwards but oscillometry provides a potential opportunity for much earlier identification of PLD, especially in the neonatal, infancy, and preschool periods. Development of biomarkers such as inflammatory markers or markers of oxidative stress to ideally identify PLD from an early age would be ideal but will require far greater understanding of the underlying mechanistic processes which lead to the development of PLD and its different phenotypes. Furthermore, the current range of interventions are somewhat limited and most used without any critically evaluated evidence.

**Lung imaging**

Structural lung abnormalities can be assessed with imaging techniques such as computer tomography (CT) and magnetic resonance imaging (MRI), including research techniques such as hyperpolarised $^{129}$Xenon MRI scanning. Key abnormalities noted in subjects with PLD, especially those who had BPD in infancy, include hypodense areas such as emphysema, bullae and cysts, and hyperdense areas including atelectasis, consolidations,

linear and triangular subpleural opacities, bronchial wall thickening and architectural distortion.[84-86] Hyperpolarised $^{129}$Xenon MRI scanning has provided evidence of abnormal lung growth and regional ventilation abnormalities especially in the POLD phenotype of PLD but not in the pPRISm phenotype.[87,88]

Routine chest imaging is not recommended and should be confined to selected cases such as subjects with significant symptoms or exercise capacity limitation in subjects with PLD, especially those with POLD, as well as those with significant symptoms unresponsiveness to treatment to identify impaired lung parenchyma and lower airways, tracheobronchomalacia (TBM), subglottic stenosis, (left) vocal cord palsy, and pulmonary vascular disease. For identifying PLD associated pulmonary vascular diseases, echocardiography and cardiac catheterisation remain the gold standard but chest CT using contrast has been used to identify pulmonary vein stenosis, and cardiac MRI can provide additional information on cardiac anatomy, cardiac function and pulmonary blood flow. Last, imaging is increasing useful in understanding the underlying structural disease process and to delineate the various phenotypes and structural changes associated with phenotype. MRI is the preferred modality given the lack of ionizing radiation, but newer CT techniques requiring lower radiation doses remain relevant.

**PRACTICAL FOLLOW UP STRATEGY FOR PLD FROM INFANCY TO ADULTHOOD**

We can no longer ignore the significant respiratory disease that affects survivors of preterm birth from infancy up to adulthood. Whilst multidisciplinary follow up programmes have been developed for preterm-born infants who are discharged home on supplemental oxygen, follow up for other groups of infants at risk of developing PLD, including those who are born extremely preterm but do not develop BPD and those who are born late or moderately preterm, are generally very poor in most countries including high income countries. It is, therefore, imperative to establish adequate follow up programmes for this at risk populations,

which should range from infancy cared largely by neonatologists to paediatric pulmonologists, and formal transition to adult pulmonologists.

As PLD is associated with adverse outcomes involving multiple systems including the cardiac, central nervous and growth systems, especially in extremely preterm born infants, a multidisciplinary team is essential to manage individuals at the highest risk of developing PLD, to detect PLD as early as possible and to optimise respiratory and associated non-respiratory health[89]. Between countries, and even within countries, there is considerable variation in practice in treatment and monitoring strategies for patients with PLD.[3,90] These differences are partly due to lack of robust evidence-based therapies and differences in resources. Figure 1 suggests potential members of a multidisciplinary team as currently included in many largely high income countries[91]. Evidence has shown that a comprehensive follow up program for infants with BPD, starting during the neonatal stay and closely involving the families, can lower readmission rates and improve neurodevelopmental outcomes.[92] The frequency and intensity of monitoring of subjects with PLD will depend on factors such as gestational age, presence of IUGR, BPD diagnosis, severity of PLD or PLD phenotypes, need for home oxygen, associated co-morbidities, and social status.[93] There is a need for comprehensive evidence-based protocols but few currently exists. To start the process of developing such programmes, we have adapted the recently introduced programme to follow up infants with severe BPD through adulthood at Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands, to a multidisciplinary program during the life course for preterm born infants with or without PLD discharged from the neonatal unit, up to adulthood (Tables 2 and 3). Since neonatologists often follow up their graduates generally up to the age of two to five years, formal hand over to paediatric pulmonologists, or earlier involvement for those with severe symptoms or lung structure abnormalities, and then formally to pulmonologists managing adults when the individuals with PLD reach 16 – 18 years of age, is lacking but is essential.

There is limited evidence for effective transitional care programmes from childhood to adulthood for PLD . Gaps which need to be addressed include inadequate training, lack of knowledge on long-term outcomes and poor communication among and between healthcare providers and professionals, lack of appropriate general physician, paediatrician, paediatric respiratory and adult respiratory services, deficits of targeted financial support, and poor research on long-term prognosis and outcomes for PLD in preterm born children and especially adults born preterm. Careful designing of a structured, personalised care programs should help to optimally transition patients from childhood to adulthood with the ultimate aim to improve lung health to prevent hospital admissions, reduce potential drug toxicity, and improve health-related quality of life, parental/self-management skills, disease-related knowledge, clinical attendance rates and satisfaction rates. We appreciate the burden such enhanced follow up programmes for preterm born children and adults will place on health care services throughout the world but the economic burden of established respiratory and associated conditions in the longer term is far greater. Thus, we believe these suggestions will start the debate of how to optimally follow up and manage preterm born individuals, especially in those patients with PLD at the severe end of the spectrum.

## FUTURE

### Potential drug therapies

Given the concerns of overlap between PLD and COPD and other respiratory diseases, therapies for those respiratory conditions can potentially have a role in PLD and possibly instituted much earlier in life. For example, one recent study reported a higher proportion of $CD8^+$ T-cells and lower proportion of $CD4^+$ T-cells in the airways of young adults with BPD, findings which are similar to those noted in COPD.[94,95] Similar findings have recently reported altered β-oxidation of fatty acids and glutathione metabolism in children with the POLD phenotype of PLD, also suggesting overlap with COPD.[96] For PLD patients with such 'COPD-like' endotypes, it would be reasonable to speculate that treatments used in COPD maybe relevant, especially if instituted early and if disease modifying properties are present.

In COPD, LAMA are widely used as first-line treatment[97], thus its evaluation in PLD especially for POLD, which is most likely to have overlap with COPD, is not unreasonable.

Studies have not shown benefits of using leukotriene receptor antagonists in preterm-born infants early in life but their evaluation in older subjects with PLD after discharge from the neonatal intensive care unit is lacking.[98,99] Caution, however, is required due their association with potential neuropsychiatric adverse events.[100]

Azithromycin has potent antibacterial, anti-inflammatory, and immunomodulating properties and has been successfully used in cystic fibrosis and COPD.[101] For example, azithromycin reduced rhinovirus replication and increased interferon response in patients with cystic fibrosis.[102] Whether azithromycin has a role to play in subjects with PLD is not certain. The trial listed on clinicaltrials.gov to evaluate if azithromycin *versus* placebo given to preterm-born infants with PLD during two respiratory syncytial virus (RSV) seasons decreases unscheduled visits seems to have recruited 60 of the anticipated 92. Findings appears not to show any benefits for unscheduled visits for respiratory symptoms (21/30 *vs.* 16/30) but may have for emergency room visits (15/30 *vs.* 6/30).[103] However, caution is needed, given global concerns of bacterial resistance by its widespread use but also because prophylactic use in the early neonatal period, targeting both pulmonary inflammation and *Ureaplasma* spp., which is strongly associated with development of BPD, was not successful.[104] More robust evidence is, therefore, required before azithromycin becomes routinely used for infants with PLD in infancy and beyond. As with many of the (potential) interventions mentioned, additional attention will be required of the optimal primary outcomes to assess success of any intervention given the limited number of objective measures currently available to assess lung function, especially in infants and pre-school children.

**Repurposing existing drugs**

In COPD, newer anti-inflammatory therapies are emerging, targeting inhibition of recruitment and activation of inflammatory cells.[105] Some have been tested in animal models to prevent development of BPD, such as PDE4-inhibitors with the reverse outcome[106], but have not been tested in animal models of established PLD. Activation of the p38 MAPK pathway leads to increased production of several cytokines and chemokines, especially IL-1β and IL-8[107,108], which is also noted to be increased in the development of BPD.[109-111] Inhibition of IL-33, a stimulator of epithelial and endothelial cells in the lungs to release IL-6 and IL-8, is now being tested in clinical phase 3 trials with COPD and asthma subjects[105] and may provide potential for treatment for PLD, especially, as COPD is now considered an important longer term outcome of PLD. Targeting specific proinflammatory cytokines with monoclonal antibodies, as against Th2 pathways in asthma, has potential to treat PLD but the underlying mechanisms of the specific phenotypes of PLD need careful evaluation before such treatments can be instituted in subjects with PLD.

**Development of new drugs**

In order to develop targeted therapies for the different phenotypes of PLD, there is an urgent need to understand the underlying mechanisms, i.e. endotype associated with each phenotype, and extending the work into both children and adults[112]. Studies especially in adults (given ethical issues in children) with PLD will permit the acquisition of more relevant samples such as bronchoalveolar lavage[94]. There is some evidence that oxidative stress plays a role in the pathogenesis of BPD during the neonatal period, but also thereafter.[113-116] A cohort study in 34 adolescents who had BPD in infancy reported increased 8-isoprostane in exhaled breath condensates when compared with 19 preterm-born children without BPD and 34 term-born controls.[114] More recent data also suggests an active oxidant process occurring in children who have the POLD variant of PLD.[96] Therefore, it can be postulated that anti-oxidants such as vitamins E and C, glutathione and antioxidant enzymes such as glutathione peroxidase, super-oxide dismutase and catalase may be potential therapeutic

options to treat PLD. However, to date no studies have evaluated anti-oxidants in the treatment of established PLD.[117]

During the neonatal period dysbiosis of the microbiome has been reported in preterm-born infants[118] and decreased bacterial diversity was observed in 19 year olds with BPD.[119] Whether probiotics with their antimicrobial and immunomodulatory properties can improve the gut-lung axis and hence reduce the severity of evolving PLD is currently unknown.[120,121] Similarly, trained immunity based vaccines (TiBV) have shown promise in reducing viral respiratory tract infections and wheezing episodes in largely term-born infants and young children.[122-124] Two studies of moderately (PROTEA) and extremely preterm (BALLOON) infants are ongoing to determine if newer bacterial lysates or inactivated bacteria, respectively, that target trained immunity can decrease recurrent respiratory tract infections after discharge from the neonatal unit.[125,126]

## CONCLUDING REMARKS

Despite clear evidence of higher rates of lung disease after preterm birth, the evidence base for its identification, follow up, and management including therapeutic interventions as well as understanding of the underlying mechanisms especially of individual phenotypes is embarrassingly limited, as summarized in Table 4. We have described the current options which can be introduced into follow up programmes as long as robust responses to each individual intervention is carefully evaluated. We have suggested future directions including the need for better evidence to manage this vulnerable group of subjects from infancy well into adulthood.

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SK, LD and MP conceptualised the article. LD composed the first draft with all authors contributing to the final draft. LD and SJK conducted the two systematic reviews for the review. The final manuscript was reviewed by all authors.

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Tables and figure are presented as separate Word or PowerPoint files.