Editorial Commentary

Evolving treatment for prematurity-associated lung disease

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Preterm birth remains a major world-wide health problem (1). Whilst mortality is decreasing especially at the immature gestations, it is apparent that survivors are at increased risk of life-long morbidity including from adverse respiratory outcomes. Our recently updated systematic review demonstrated that, despite advances in neonatal care over the last thirty years, lung function impairments are significant in preterm-born children, adolescents and adults including in those with and without the neonatal lung disease bronchopulmonary dysplasia [BPD, also known as chronic lung disease (CLD) of prematurity] (2). Notably, deficits in lung function are also observed in late preterm-born children who traditionally have not been considered as being at risk of long-term respiratory morbidity (3). The recent guidelines for management of BPD after discharge from the neonatal unit from both the American Thoracic Society (ATS) (4) and European Respiratory Society (ERS) (5) acknowledged the paucity of evidence to guide the long-term, post-discharge management of individuals with a neonatal history of BPD, highlighting the need for studies to assess treatment of prematurity-associated lung disease (PLD).

The Respiratory Health Outcomes in Neonates (RHiNO) study has recently demonstrated that there are multiple spirometry phenotypes of PLD, including both fixed and reversible prematurity-associated obstructive lung disease (POLD), prematurity-associated preserved ratio with impaired spirometry (pPRISm) and dysanaptic spirometry patterns, which are differentially associated with early- and current-life factors, including BPD (6). There is increasing concern that PLD may predispose an individual to the premature development of chronic obstructive pulmonary disease (COPD) in early adulthood (7,8), with implications for quality of life and life expectancy if lung function deficits continue to track into adulthood. Whilst much research focus has concentrated on the mechanism of respiratory morbidity in those with a history of BPD (9,10), it is increasingly apparent that there is a population of preterm-born subjects who develop PLD despite not having had a diagnosis of BPD in the neonatal period (3,11), with impaired spirometry, altered respiratory mechanics and reduced gas diffusion capacity (12). Furthermore, other early life risk factors such as gestational immaturity and intrauterine growth restriction are also strongly associated with later adverse respiratory outcomes (13). Many children with PLD are often given a diagnostic label of asthma (14). However, the mechanisms underlying PLD are likely to be different to those observed in classical asthma which is often predominated by eosinophilic airway inflammation (15) and are only now beginning to be investigated (16-18). Until recently, there have been two previous studies examining inhaled therapies in the management of children with PLD, both studying participants from the pre-/peri-surfactant era (*Table 1*). Chan *et al.* performed a double-

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Table 1 Summary of evidence from trials using corticosteroids inhaled in preterm-born children

Study (author, year)	Country	Inhaled therapies investigated (drug, dose, duration)	Active (n)	Placebo (n)	Results
Chan *et al.* 1993	United Kingdom	Beclomethasone dipropionate, 200 µg twice daily	15	15	Mean FEV_1 1.3 litres post treatment in beclomethasone group, 1.25 litres in placebo group
Pelkonen *et al.* 2001	Finland	Budesonide, 0.8 mg/m^2/day for 1 month followed by 0.4 mg/m^2/day for 3 months	18	N/A	%pred FEV_1 74% pre- and post-treatment (P=0.50). Significant improvement in PEFR diurnal variation (P=0.02)
RHiNO (Goulden *et al.* 2022)	United Kingdom	Fluticasone propionate, 100 µg twice daily for 12 weeks	20	14	%pred FEV_1 increased 7.7% (95% CI: –0.3% to 15.7%, P=0.16). Mean FE_{NO} reduced from 29.8 to 15.8 ppb
		Fluticasone propionate 100 µg and Salmeterol xinafoate 50 µg, twice daily for 12 weeks	19	14	%pred FEV_1 increased 14.1% (95% CI: 7.3% to 21.0%, P=0.002). Mean FE_{NO} reduced from 25.2 to 15.9 ppb
PICSI (Urs *et al.* 2023)	Australia	Fluticasone propionate, 125 µg twice daily for 12 weeks	87	83	0.30 (95% CI: 0.15, 0.45) improvement in FEV_1 z-score. Reduced FEV_1 bronchodilator response: –2.21 (95% CI: –4.68, –0.26) z-score. Mean FE_{NO} reduced from 15.2 to 10.5 ppb (P<0.05)

FEV_1, forced expiratory volume in one second; N/A, not applicable; %pred, percentage predicted; PEFR, peak expiratory flow rate; CI, confidence interval; FE_{NO}, fractional exhaled nitric oxide; ppb, parts per billion.

blind, placebo-controlled cross-over study of fifteen low birth weight children, aged eight years who were born with a mean gestational age of 30.5 weeks. All were born before the routine use of exogenous pulmonary surfactant replacement. The children received twice daily 200 µg of inhaled beclomethasone dipropionate for four weeks or placebo in a cross-over study. There was no significant effect on peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1) or airway hyper-responsiveness following treatment (19). In the other study occurring during introduction of exogenous surfactant treatment, Pelkonen *et al.* studied eighteen children (median gestation at birth of 28 weeks and median of age 10.1 years) who had evidence of reversibility of airway obstruction as assessed by response to short-acting β_2-agonists. These children received inhaled budesonide (0.8 mg/m^2/day for 1 month followed by 0.4 mg/m^2/day for 3 months) over a four-month period. No significant difference was noted for percent predicted FEV_1 (median 74% before and after treatment). However, PEFR diurnal variability improved suggesting decreased bronchial lability after treatment (20).

Whilst these two studies did not show an effect of inhaled corticosteroids on lung function in those with PLD, whether these results are applicable to the contemporary, more extremely preterm-born modern population is uncertain. The Australian conducted Preterm Inhaled Corticosteroid Intervention (PICSI) study (21) (*Table 1*) is, therefore, a welcome addition to the literature. The group enrolled 170 children born at <32 week's gestation and aged 6–12 years old, regardless of their initial lung function status, into a randomised, double-blinded placebo-controlled trial. Children received either twice daily inhaled fluticasone propionate 125 µg or placebo for 12 weeks, undergoing spirometry, oscillometry, bronchodilator response and fractional exhaled nitric oxide (FE_{NO}) testing before and after treatment with a revised primary outcome of improvement in z-score of FEV_1 of 0.5 or greater after treatment. A third of participants had a neonatal diagnosis of BPD. Baseline lung function was comparable between the two treatment groups; 82% of participants completed the trial (83% of placebo group, 80.5% of treatment group), with drop out largely due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus pandemic. Those lost to follow-up were younger and had higher rate of BPD. The intention-to-treat analysis showed 0.30 [95% confidence interval (CI): 0.15–0.45] improvement in FEV_1 z-score in the inhaled corticosteroids group, equating to approximately 4% improvement in percent predicted FEV_1, when compared to the placebo group. Significant improvement in FEV_1/forced vital capacity (FVC) ratio and decreased FE_{NO} was also noted. 23% of the inhaled corticosteroid group improved their FEV_1 z-score by 0.5 or greater (judged as clinically significant improvement). A positive baseline response to inhaled bronchodilators,

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as well as number of days of supplementary oxygen in the neonatal period, were significantly associated with treatment response.

The PICSI trial demonstrated modest improvement in lung function for preterm-born children following a 12-week course of inhaled corticosteroids when compared with placebo, although an improvement of 0.3 z-score for FEV_1, equivalent of 4% percent predicted FEV_1, is unlikely to be clinically significant. However, 23% showed a more clinically beneficial improvement in FEV_1 z-score of ≥0.5 (equivalent to approximately 6% percent predicted FEV_1). The characteristics of these 23% was not reported but these data suggest a significant subgroup that may benefit from such treatment. It has previously been shown that FE_{NO} is not increased in PLD (15), but in the PICSI study, mean FE_{NO} decreased in the inhaled corticosteroid group from 15.2 to 10.5 ppb suggesting an effect on an inflammatory pathway in the lungs of children born preterm.

Whilst the results for PICSI are comparable to those reported by Chan and Pelkonen, there are suggestions that subgroups may benefit from such treatment. Atopy has not been shown to be increased in preterm-born populations who have lung disease in childhood (22). An alternative, poorly investigated intervention is the effect of long-acting bronchodilators on children who have PLD. The role of long-acting bronchodilators in PLD associated with preterm birth has been less well evaluated, with most studies assessing response to administration of single doses of short-acting β_2-agonists (23). The RHiNO study published their results prior to the PICSI study, assessing the effects of inhaled corticosteroids alone and in combination with long-acting β_2-agonist (LABA) against placebo in preterm-born children who had significant deficits in their percent predicted FEV_1 (24). RHiNO screened over 550 children, aged 7–12 years, who were born at ≤34 week's gestation (together with 200 term-matched controls) from the United Kingdom. Preterm-born children with documented clinically significant lung function impairment (defined as percent predicted FEV_1 of ≤85%) were enrolled into a randomised, placebo-controlled trial assessing if 12-week treatment with twice daily inhaled corticosteroid (100 µg fluticasone propionate) alone, or in combination with a LABA (50 µg salmeterol xinafoate) improved percent precited FEV_1 by 12% or more when compared to placebo. The study was powered to include 53 children. From 53 children who were enrolled, 48 completed the treatment protocol. Overall, compared to placebo, inhaled corticosteroids increased percentage predicted FEV_1 by 7.7% (95% CI: –0.3%, 15.7%; P=0.16 when compared to placebo). Importantly, combination inhaler therapy of inhaled corticosteroids and LABA significantly improved percent predicted FEV_1 by 14.1% (95% CI: 7.3%, 21.0%; P=0.002, when compared to placebo). Interestingly, participants who had not received inhaled corticosteroids previously had a significant 10.2% (95% CI: 3.8%, 16.5%; P=0.03) improvement in percent predicted FEV_1 with combination inhaled therapy when compared to inhaled corticosteroids alone, and 17.2% (95% CI: 10.2%, 24.2%; P≤0.001) improvement when compared to placebo. In this steroid naïve group, participants had similar improvement of 7.0% (95% CI: –0.9%, 15.0%; P=0.26) using inhaled corticosteroids when compared to the placebo group. As with the PICSI trial, there was significant decrease in FE_{NO} in both treatment groups including inhaled corticosteroids, suggesting that this may be a target for intervention in subgroups of children with PLD. Whether this represents a sub-group of preterm-born individuals with "classical" (atopic) asthma, or whether there is some overlap in the underlying biochemical mechanisms between asthma and PLD will require further evaluation.

Whilst it is well documented that preterm-born subjects generally respond well to short-acting β_2-agonists, including those with and without a neonatal diagnosis of BPD (12,23), the Pelkonen study assessed two-week course of daily terbutaline administration. Although they did not report post-treatment lung function, they suggested improved diurnal variation of PEFR (20). Monotherapy with LABAs in children with asthma has been linked with an increased risk of asthma exacerbation/hospitalisation and asthma-related deaths across several studies thus should be avoided (25). There have also been concerns in adult populations that long-term use of LABAs as monotherapy is associated with increased risk of significant cardiovascular events, including arrhythmia and myocardial infarction, with the stimulation of cardiac β_2-adrenoceptors, increasing inotropic and chronotropic responses (26). Until safety data is established in the paediatric population, the use of LABAs alone should be avoided until safety concerns are addressed.

Due to lack of evidence, the ATS (4) and ERS (5) guidelines were largely based on expert opinion, highlighting the paucity of evidence for treatments for PLD. Both the PICSI and RHiNO trials have demonstrated that the use of inhaled corticosteroids have modest improvements in spirometry after 12 weeks of treatment. Encouragingly, the RHiNO study convincingly demonstrated clinically significant improvements in spirometry above that of

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inhaled corticosteroids alone when used in combination with LABA. Until additional evidence becomes available, it is reasonable to institute a trial period of combined inhaled corticosteroid and LABA therapy for 12 weeks in a preterm-born child with significant PLD, but with objective assessment of lung function before and after treatment to assess response and deciding whether to continue or stop the treatment. Future work should further identify mechanisms underlying PLD-related phenotypes, including both those with and without BPD, to identify those children most likely to benefit from current therapies, and aid development of novel treatments. Longitudinal assessment of respiratory function will be required to determine whether these short-term changes in spirometry values are maintained over the longer-term.

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