ERS International Congress 2021: highlights from the Paediatric Assembly

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Shareable abstract (@ERSpublications)
Highlights from the Paediatrics Assembly at #ERSCongress 2021 https://bit.ly/3FaFgNt

Cite this article as: Ardura-Garcia C, Abellan A, Cuevas-Ocaña S, *et al*. ERS International Congress 2021: highlights from the Paediatric Assembly. *ERJ Open Res* 2022; 8: 00643-2021 [DOI: 10.1183/23120541.00643-2021].

Received: 16 Nov 2021
Accepted: 2 Jan 2022

Abstract

In this review, Early Career Members of the European Respiratory Society (ERS) and the Chairs of the ERS Assembly 7: Paediatrics present the highlights in paediatric respiratory medicine from the ERS International Congress 2021. The eight scientific Groups of this Assembly cover respiratory physiology and sleep, asthma and allergy, cystic fibrosis (CF), respiratory infection and immunology, neonatology and intensive care, respiratory epidemiology, bronchology, and lung and airway development. We here describe new developments in lung function testing and sleep-disordered breathing diagnosis, early life exposures affecting pulmonary function in children and effect of COVID-19 on sleep and lung function. In paediatric asthma, we present the important role of the exposome in asthma development, and how biologics can provide better outcomes. We discuss new methods to assess distal airways in children with CF, as some details remain blind when using the lung clearance index. Moreover, we summarise the new ERS guidelines for bronchiectasis management in children and adolescents. We present interventions to reduce morbidity and monitor pulmonary function in newborns at risk of bronchopulmonary dysplasia and long-term chronic respiratory morbidity of this disease. In respiratory epidemiology, we characterise primary ciliary dyskinesia, identify early life determinants of respiratory health and describe the effect of COVID-19 preventive measures on respiratory symptoms. Also, we describe the epidemiology of interstitial lung diseases, possible consequences of tracheomalacia and a classification of diffuse alveolar haemorrhage in children. Finally, we highlight that the characterisation of genes and pathways involved in the development of a disease is essential to identify new biomarkers and therapeutic targets.

Introduction

The Paediatric Assembly (Assembly 7) reviewed recent research advances in the paediatric respiratory field presented by leading experts and Early Career Members at the European Respiratory Society (ERS) International Congress 2021. Assembly 7 members presented 249 abstracts in oral and e-poster sessions and organised several symposia, including two clinical guidelines sessions. The Paediatrics Assembly content is very diverse as it covers the whole field of paediatric respiratory diseases, from very rare diseases such as childhood interstitial disease, to extremely common diseases such as asthma. Additionally, many diseases in adulthood have their origin in childhood, and environmental factors such as air pollution and climate change have a disproportionate effect on children. We are proud that the Paediatrics Assembly was able to compose a high-quality programme for paediatricians and other health care professionals.

We here review the paediatric highlights from the 2021 virtual congress, summarised by Assembly 7 Early Career Members and Chairs of the eight Groups that form the Assembly. For each Group, the Chair selected the most relevant session. The sessions are presented in order of the Group's numbers.

Group 7.1: paediatric respiratory physiology and sleep

Several themes have emerged from this year's session on paediatric physiology and sleep research, including new developments in lung function testing and sleep-disordered breathing diagnosis, and the effect of early life exposures and COVID-19 on lung function.

Earlier studies showed that prematurity, low birthweight and maternal abuse of nicotine have an adverse effect on children's lung function [1]. Salem Mahmoud *et al.* [2] examined the association of low birthweight and impaired lung function in monochorionic-diamniotic twins with selective fetal growth restriction (FGR). Nineteen twin pairs (aged 8–29 years) were included with mean birthweight difference of 29% and a mean gestational age of 33.5 weeks. Mean z-score for FEV_1 was 0.61 and for FVC 0.56, and both were lower in twins with FGR compared to those without. Gudmundsdóttir *et al.* [3] investigated the influence of mid-pregnancy physical activity (PA) on lung function of 3-month-olds. Tidal flow volume measurements of 814 infants were compared with self-reported PA. The ratio time to peak tidal expiratory flow to expiratory time (tPTEF/tE) as a continuum was not significantly associated with maternal PA. However, infants of inactive mothers compared with active mothers had higher odds of having a lower lung function by tPTEF/tE <0.25.

Bains *et al.* [4] evaluated the tidal flow–volume (TFV) loops of 93 3-month-olds to investigate differences in awake and sleeping state. A higher ratio of tPTEF/tE, the corresponding volume ratio and respiratory rate, but similar tidal volume were observed during awake compared to the sleeping state, suggesting separate normative values may be required.

Fouzas *et al.* [5] examined the characteristics of FEV_1 fluctuations in children with controlled asthma who were treated with inhaled corticosteroids (ICS). They compared FEV_1 recordings (for 3 months) of 31 participants with controlled asthma with recordings of 68 healthy controls. Children with controlled asthma had normal FEV_1 values with correlated long-range fluctuations unrelated to age. A retrospective study determined the relationship between forced expiratory time (FET) and airway obstruction in 2623 children. FET was highly related to central airway obstruction (FEV_1/FVC) [6].

Impulse oscillometry (IOS), a noninvasive modality of testing lung function, measures airway impedance (resistance and reactance). However, no standards have been set for IOS [7]. Park *et al.* [8] compared IOS to conventional pulmonary function test (PFT) in 75 patients with neuromuscular disorders with a mean age of 20 years. PFT showed restrictive lung function in all participants. Lung volumes by PFT and resistance by IOS decreased by age. Higher lung volumes were correlated with higher resistances.

Two studies investigated the effect of COVID-19 and lockdown in children. Schlegtendal *et al.* [9] compared lung functions of 73 children after an average of 2.6 months following COVID-19 infection to 45 controls. Respiratory symptoms following COVID-19 were reported in 11%. There were no significant differences in the lung function. Only two patients with persistent respiratory symptoms showed abnormal lung function. Another study conducted a global survey to assess the sleep habits of children before and during the COVID-19 lockdown and analysed 845 questionnaires (ages 3–17 years). Lockdown was associated with later bedtime and wake time in children but this shift did not change the sleep duration in half of the children, with the 14–17-year-old group having the lowest rate of no change (28%) [10].

Nocturnal pulse oximetry (NOx) can be used to screen for obstructive sleep apnoea (OSA) [11]. Fouzas *et al.* [12] analysed advanced signals and indices that may accurately diagnose OSA for 45 children (aged

2–10 years). They suggested that cumulative desaturation area, variability of S_{pO_2}, and heart rate could improve the diagnostic ability of NOx.

In conclusion, mid-pregnancy physical inactivity and low birthweight may be associated with impaired lung function in children. IOS may be a useful technique to evaluate lung function in children with neuromuscular disease. COVID-19 seems to have no significant impact on lung function nor lockdown on sleep duration in children. Nocturnal pulse oximetry could be improved with the use of cumulative desaturation area, variability of S_{pO_2}, and heart rate to diagnose OSA.

Group 7.2: paediatric asthma and allergy

The session on "Advances in childhood asthma: biologics, biomarkers and infections" included eight oral presentations and focused on recent advances in the use of biologics and biomarkers in childhood asthma research.

The session started with two presentations around asthma in adolescents. Oyenuga *et al.* [13] presented data about asthma diagnosis and asthma control in children aged 12–14 years old in Sub-Saharan Africa. Indeed, there is only scarce available data around asthma control and impact on quality of life for Sub-Saharan adolescents [14]. Interestingly, they showed that 62% of the adolescent participants had severe symptoms and 81% of them had no doctor-confirmed diagnosis of asthma, while 37% of them had objective markers of asthma. A predictive approach was attempted by Amaral *et al.* [15], who performed latent class analysis on clinical data from 162 adolescents with asthma. The aim was to identify distinct clusters of disease progression. What they showed was that the cluster of adolescents who presented the highest number of exacerbations and associated hospital visits were the ones who had poorly controlled asthma at recruitment stage.

The session continued with data around use of biologics in children with asthma. Data presented from the Phase III Voyage study showed that the daily use of dupilumab [16], compared to placebo, was associated with a reduced number of asthma exacerbations and improved lung function, but not with improved asthma control, in children aged 6–11 years with allergic asthma ($p<0.05$ and $p<0.001$) [17]. Carraro *et al.* [18] focused on identifying urinary markers of response to omalizumab treatment and showed that histidine, the precursor of histamine, emerged as a sensitive marker that helped to identify response to omalizumab.

Fayon *et al.* [19] received the award for the best abstract of the Paediatric Assembly. This study aimed to identify clusters of preschool children with recurrent wheeze who are at higher risk of developing asthma based on bronchial remodelling features [20]. They performed fibre optic bronchoscopy in 56 preschool children with persistent wheeze and identified histological parameters that were stronger predictors of asthma development. These parameters included the reticular basement membrane (RBM) thickness and epithelial cell shedding [19]. Validation of these predictors in a larger sample is anticipated.

The last part of the session focused on data around asthma prevention. Hose *et al.* [21, 22] applied latent class analysis to systematically assess feeding patterns and to relate these to asthma risk at school age. This data-driven approach identified a pattern of increased meat consumption, conferring a risk for asthma diagnosis at 6 years. The possible underlying mechanism could involve gut microbial imbalance triggering immune dysfunction but is yet to be determined. Da Silva Sena *et al.* [23] aimed to investigate the associations between rhinovirus (RV)-induced bronchiolitis in infancy and lung inhomogeneities at preschool age using multiple breath nitrogen washout (MBW). Their cohort of 103 infants showed that hospitalisation with RV-positive bronchiolitis was associated with the highest risk for abnormal lung clearance index (LCI) at preschool age. Following on this association, Makrinioti *et al.* [24] presented data from a meta-analysis demonstrating that the associations between RV-bronchiolitis and preschool wheeze and asthma development are stronger than those for respiratory syncytial virus (RSV)-induced bronchiolitis. Future studies with further data around allergic sensitisation could help identify whether RV-bronchiolitis infants may be a specific group for intervention studies for asthma prevention.

In summary, data presented showed that the exposome (viruses, diet) plays an important role in asthma development and biologics can provide better outcomes in childhood asthma management. Assessment of control is important, as poor asthma control is associated with higher number of exacerbations.

Group 7.3: monitoring of lung disease and CFTR function in paediatric cystic fibrosis

This session focused on current and new methods to assess cystic fibrosis transmembrane conductance regulator (CFTR) function and lung disease in children with cystic fibrosis (CF).

Sandvik *et al.* [25, 26] examined MBW outcomes using EXHALYZER-D®-SPIROWARE® recordings of resident nitrogen (N_2) or sulphur hexafluoride (SF_6) in a cohort of 45 infants and toddlers with CF and 57 healthy controls. The use of SF_6MBW, regarded as gold standard for MBW [27], was recommended, as it provided less pronounced inter-test and between occasion differences for LCI than N_2MBW. Dumas *et al.* [28] used a cohort of 17 preschool children with CF [29] and 13 healthy controls to analyse S_{conc} and S_{acin} indices of MBW demonstrating 79% met acceptability criteria, similar to previously reported, in preschool children [30].

Longitudinal SF_6MBW assessments by Sandvik *et al.* [31] in 2–45-month-olds with CF and healthy controls detected a higher LCI in the CF than the control group, with 64% of children with CF showing intermittent lung function impairment and a LCI increase of 0.22 units/year associated with an overall worsening. This highlights the importance of early therapeutic intervention and regular SF_6MBW assessments during the early stages of CF. Oestreich *et al.* [32] also examined the evolution of LCI in healthy and CF cohorts by measuring SF_6MBW at 6 weeks and 1 year of age. Despite similar lung function at 6 weeks of age, LCI significantly deteriorated over the first year of life in infants with CF [33]. The association found between LCI at 6 weeks and LCI at 1 year highlights the importance of targeting prevention strategies for patients at risk from their first months of life. Perrem *et al.* [34] presented another LCI-focused prospective observational study in a cohort of 98 school-age children with CF and 48 healthy controls [35] over 2 years; 19% and 37% of the CF visits showed an LCI change relative to the last visit in the range of ±15% and ±10% threshold, respectively. Changes associated with additional clinical factors, *e.g.* FEV_1, were much higher in the CF group, 78% at ±15% and 72% at ±10% threshold [34]. Thus, a change in LCI in the range of 10–15% can be considered clinically meaningful and could be used to guide clinical decision-making. Frauchiger *et al.* [36] also longitudinally assessed LCI in 74 children with CF (4–18 years old) and 19 healthy controls over a 7-year period, reporting 9% coefficient variation at population level, but 15% relative change in healthy and 23% in CF at individual level. Thus, applying individual limits might be an appropriate approach to define minimal clinically important differences for routine clinical surveillance.

Willers *et al.* [37] evaluated lung functionality, using label-free functional matrix-pencil magnetic resonance imaging (MP-MRI) that allows for simultaneous ventilation and perfusion measurements, in 37 children with CF (4–17 years old) over 1 year. Although changes in LCI moderately correlated with changes in ventilation and perfusion defect, they did not correlate with change in structural pathology, highlighting the potential of MP-MRI to assess lung areas that are blind to LCI measurements. Interestingly, Lv *et al.* [38] presented the Thirona-developed Automated AA-LungQ method to analyse changes in small airways in a completely automated way. The AA-LungQ method showed high sensitivity in detection of progressive widening and thickening of small airways in 111 chest CT scans of 57 children with CF at 2-year intervals. Finally, Grosse-Onnebrink *et al.* [39] proposed using air–liquid interface cultures of respiratory epithelia derived from patient nasal brushings as an *in vitro* model to assess personalised treatment responses based on transepithelial conductance measurements by the Ussing chamber system.

Overall, we need to define clinically relevant thresholds for LCI changes. Despite the high sensitivity of LCI, some details remain LCI blind, especially in more distal airways. Further studies on S_{conc} and S_{acin} indices might help uncover silent disease by LCI, but currently CT scans are highly recommended to gain information on distal lung structures and any structural changes.

Group 7.4: ERS clinical practice guidelines for managing children and adolescents with bronchiectasis

Early diagnosis of bronchiectasis is crucial not just for therapeutic management but also for the family finally receiving this diagnosis after years of uncertainty. The task force for the management of paediatric bronchiectasis aimed to identify evidence-based management strategies for investigation and treatment. This session summarises the main findings and recommendations of the task force's resulting report [40].

Zena Powell shared the story of her 14-year-old son, who was described as a "wheezy baby" with years of recurring exacerbation cycles of the lower airways before he was diagnosed with bronchiectasis at the age of 8. In 2018, she joined the task force to form the management guidelines that she describes as a starting point, not just the end. Parents can take these guidelines to their consultant, who receives a basis to start the parents on the journey of bronchiectasis management [40].

Andrew Bush presented the overall clinical approach. Protracted bacterial bronchitis (PBB) leads to reversible followed by irreversible airway dilatations. The diagnosis and adequate treatment of PBB are

crucial before irreversible airway dilatations develop. For an improved bronchiectasis diagnosis, the guidelines recommend performing a chest CT scan and applying a ⩾0.8 broncho-arterial ratio instead of the 1.0 cut-off for adults. Investigations such as sweat test and immune function testing are necessary in every child with bronchiectasis to diagnose possible underlying causes. Exacerbations in bronchiectasis belong to the top three factors affecting a child's quality of life (QoL) according to a European Lung Foundation survey [41].

For treatment options, the guidelines recommend regular airway clearance techniques (ACT), as an individualised therapy performed by a paediatric trained respiratory physiotherapist, although no data are available on optimal ACT nor frequency [42]. Keith Grimwood further described the need to identify those who would benefit from hyperosmolar therapies while rhDNAse is advised against. Antibiotics are considered the standard of care for treating exacerbations, although there has only been one randomised controlled trial (RCT) [43]. The choice and route of antibiotics are based on airway cultures, history of hypersensitivity reactions to the antibiotic and the severity of the exacerbation. Recommendations for long-term macrolides to reduce exacerbations are based on three RCTs [44]. Findings of halving exacerbation frequency are consistent with RCTs in adults and children with primary ciliary dyskinesia. The guidelines formulate a conditional recommendation to eradicate *Pseudomonas aeruginosa* upon detection, based on the association between *P. aeruginosa* and deteriorating clinical status. Because no data are available, no preferred regimen is formulated. There is only low-quality evidence and lack of efficacy for the use of asthma-based medications; they should not be used unless there are clear signs of underlying asthma. The guidelines recommend surgical resection of the affected lung lobe only if maximal therapies have failed and QoL is substantially impaired. Lobectomy should only be conducted by an expert surgeon at a specialised centre after assessment by a skilled interdisciplinary team [40].

Finally, Angela Zacharasiewicz described the practical approach with case presentations. She highlighted the need to ask important questions about cough quality, clinical signs and other symptoms, because they might uncover red flags. These include timing, tendency, triggers and sound. Other symptoms to enquire about are failure to thrive, weight loss, fever, night sweat, hypoxia, chest pain, dyspnoea at rest or with exercise or tachypnoea. On clinical exam signs of chronic illness, neurodevelopmental abnormalities and pathological auscultation should be noted.

This session on the management guidelines for bronchiectasis in children and adolescents highlighted the involvement of parents and caretakers early on, from listening carefully to their symptom description to practical implementation of the guidelines they helped to develop. With the treatment plan, parents should receive an explanation of the disease pattern in lay terms.

Group 7.5: respiratory disorders in neonatal and paediatric intensive care

This session included presentations on interventions to reduce morbidity and monitor pulmonary function in newborn infants who are at risk of developing bronchopulmonary dysplasia (BPD) and long-term chronic respiratory morbidity in childhood and beyond [45].

Volumetric capnography is a novel noninvasive technique which can inform on ventilation inhomogeneity, although it is technically difficult in preterm infants due to anatomical characteristics and technical limitations [46]. Williams *et al.* [47] described this technique to be feasible during the resuscitation of mechanically ventilated prematurely born infants. Yet immediately following surfactant administration ventilation inhomogeneity increased (25.9 mmHg ml^{-1} *versus* 17.2 mmHg ml^{-1}), probably due to partial small airway obstruction caused by the presence of liquid surfactant in the small airways. Novel techniques of surfactant delivery in preterm infants are being developed. Use of high-flow nasal cannula (HFNC) oxygen during less invasive surfactant administration to preterm infants is one such method. This practice was deemed effective in reducing the rates of mechanical ventilation, with 56.6% of infants not requiring the use of premedication [48].

Upper airway compliance was described by Bizzotto *et al.* [49] to contribute to carbon dioxide removal during noninvasive high frequency oscillatory ventilation (nHFOV) and be maximal at 10 Hz. This dependence upon oscillatory frequency suggests tailoring of nHFOV could help optimise its effectiveness. Delivery of effective fraction of inspired oxygen (F_{iO_2}) is also important for oxygen-dependent infants supported by HFNC. Bertzouanis *et al.* [50] showed that when minute ventilation is high at 1200 mL·min^{-1} (compared to 400 mL·min^{-1}) and the flow rate set at less than 5 L·min^{-1}, the F_{iO_2} that is effectively delivered diverges from the target oxygen level that is set. Such observations may be useful when considering weaning of HFNC in those preterm infants who remain oxygen-dependent.

In prematurely born infants who require initial invasive respiratory support, accurate prediction of extubation success is a challenge. Surface diaphragmatic electromyography is a novel technique to measure electrical activity of the diaphragm. Arattu-Thodika *et al.* [51] used this method during a spontaneous breathing trial (SBT) in mechanically ventilated infants and found that an increase in electrical activity of the diaphragm during the SBT was 71.4% sensitive and 85.7% specific in predicting extubation failure. Neurally adjusted ventilatory assist (NAVA) also monitors diaphragmatic activity and can be used as both an invasive and a noninvasive mode of ventilation for preterm infants with evolving/established BPD. Shetty *et al.* [52] described how NAVA effectively reduced the duration of respiratory support and the length of hospital stay when compared to conventional modes of ventilation (112 *versus* 140 days).

Lung function trajectories, as measured by respiratory reactance (X_{rs}) in preterm infants born earlier than 32 weeks of gestation, may also aid in guiding ventilatory support with positive end-expiratory pressure (PEEP). Infants with BPD supported with high PEEP at 1 week of life had reduced X_{rs} suggestive of pulmonary overdistension. At 36 weeks postmenstrual age, however, an increase in X_{rs} in response to high PEEP was thought to be suggestive of peripheral small airway collapse [53]. Airway function post puberty was reported to be better in infants born earlier than 29 weeks of gestation to multiple pregnancies rather than singleton pregnancies (FEV_1 –1.11 *versus* –0.50) [54]. Moreover, Luchnikova *et al.* [55] described how infants born to mothers with severe bronchial asthma who required systemic glucocorticoids during pregnancy were more likely to be exposed to intrauterine infection and to be born prematurely (38.5% *versus* 11.7%). When considering exposure to antenatal corticosteroids and the effect by gender, female infants showed a greater beneficial response when considering the outcome of death before discharge compared to male infants (OR 1.81 *versus* 1.36) [56].

The novel techniques and respiratory modalities presented hold promise for improvement in the care of prematurely born infants. Greater understanding of the pathophysiology underlying specific diseases, combined with newer modes of non-invasive ventilatory support, may allow for reducing long-term pulmonary morbidity.

Group 7.6: paediatric respiratory epidemiology

Current research highlighted the importance of characterisation, causes and consequences of various paediatric respiratory diseases. Goutaki *et al.* [57] characterised the prevalence and severity of respiratory symptoms among patients in the Swiss Primary Ciliary Dyskinesia (PCD) Registry through a FOLLOW-PCD based questionnaire, and concluded that repeated standardised clinical data will allow improved characterisation of PCD phenotypes, disease course and prognosis [58]. Rumman *et al.* [59] showed how collaborations can facilitate PCD diagnosis in resource-limited settings among children participating in a large Palestinian PCD cohort, and identified nasal nitric oxide and targeted genetic testing to be useful diagnostic tools in local and resource-limited settings.

Early life is a critical period of airway and lung development and especially relevant in terms of long-term effects on respiratory health. Decrue *et al.* [60] observed among 254 preterm and 517 term infants of the Basel-Bern Infant Lung Development cohort [61] that higher particulate matter of less than 10 µm during the second trimester of pregnancy was associated with lower lung function and higher oxidative stress shortly after birth. Participants exposed to low-to-moderate air pollution levels and the effects observed were stronger among preterm infants [60]. Abellan *et al.* [62] applied unique exposome approaches among 5624 mother–child pairs from the Generation R birth cohort [62]. They showed that living during pregnancy in more polluted, noisier, with less green and blue spaces, and more urbanised neighbourhoods may contribute to lower lung function at 10 years of age and increased odds of wheezing during childhood [63]. Talaei *et al.* [64] used principal component analysis on food frequency questionnaire data, and identified processed, traditional and health-conscious dietary patterns at age 7 years. The health-conscious pattern was associated with higher lung function, and the processed pattern was with lower lung function at 15 years of age. Koch *et al.* [65] identified four lung function growth trajectories (low, average, high and catch-up) using repeated lung function data from the INfancia y Medio Ambiente (INMA) birth cohort [66]. They described a catch-up trajectory [67] that identified children with low lung function early in childhood that catch up to average levels by age 10 years. Maternal age and paediatric allergic diseases were associated with lower odds of belonging to the high lung function growth trajectory, and maternal allergic diseases with lower odds of the catch-up trajectory. Children's higher physical activity and greater changes in BMI between 4 and 7 years of age were associated with the catch-up lung function growth trajectory.

This year, emphasis was on the effects of COVID-19 preventive measures on children's respiratory health. Ardura-Garcia *et al.* [68] showed that among 253 children seen in a respiratory outpatient clinic from the Swiss Paediatric Airway cohort [69], preventive measures reduced the reported respiratory infections,

symptoms and medication use, but did not find differences in asthma exacerbation rates that required unscheduled medical care. School closure restrictions did not further reduce any respiratory outcome occurrence. Ghirardo *et al.* [70] found that COVID-19 preventive measures in Italy did not delay the onset of bronchiolitis season in infants, but were related to lower number of hospitalisations, shorter hospitalization stays, lower oxygen supplementation and lower admissions to ICU, which is suggestive of a less severe disease course. Mallet *et al.* [71] measured oxygen saturation and capillary blood gas after exercise testing in children with exercise-induced symptoms while wearing face masks, and concluded that there was no evidence of abnormal gas exchange.

In conclusion, characterisation of PCD, identifying early life determinants and COVID-19 preventive measures on respiratory health are crucial for understanding and optimizing respiratory health in children.

Group 7.7: paediatric bronchology

Several topics arose from this year's presentations in the field of paediatric bronchology; among others the incidence and prevalence of interstitial lung diseases, possible consequences of tracheomalacia and a classification of diffuse alveolar haemorrhage (DAH) in children.

Torrent-Vernetta *et al.* [72] analysed the incidence and prevalence of paediatric interstitial lung disease (chILD) in Spain during 2018–19. They found an average incidence of 8.18 cases/million/year and an average prevalence of 46.39 cases/million, which was higher compared to the UK, Ireland, Germany and Australasia. The authors believe these differences are due to greater understanding and increased awareness of chiLD. Regarding age groups, the researchers found that children younger than 1 year of age have the highest prevalence of interstitial lung diseases while there is a heterogenous distribution of age groups according to different types of disorders: some were more prevalent in children from 0 to 2 years while others peaked in children from 2 to 18 years.

Ring *et al.* [73] collected 93 cases of DAH in children with a mean age of 4.2 years at debut of symptoms and 5.5 years at diagnosis, in an international, cross-sectional study. The most frequent underlying causes for DAH were idiopathic pulmonary hemosiderosis (44%), systemic disease (21%), immune-allergic disease (2%), autoinflammatory disease (4%), unspecified (13%) or other condition (15%). Children most frequently presented with anaemia (59%) or haemoptysis (42%), cough and dyspnoea were found in 37% and 35%, respectively, and 19% suffered from fatigue. Immunosuppressants were most administered, above all a combination of glucocorticoids with hydroxychloroquine, azathioprine, or both. Nine patients (10%) died. The authors intend to form a large, prospective multicentre study to standardise clinical care and test new treatment strategies based on their results.

Bloise *et al.* [74] proposed tidal breath (TB) analysis as a new diagnostic method in children with stridor. They evaluated the shape of the airflow signal using TB analysis in five children with stridor at first evaluation (T0) and in three infants after 3 months (T1). As demonstrated in figure 1, they discovered an

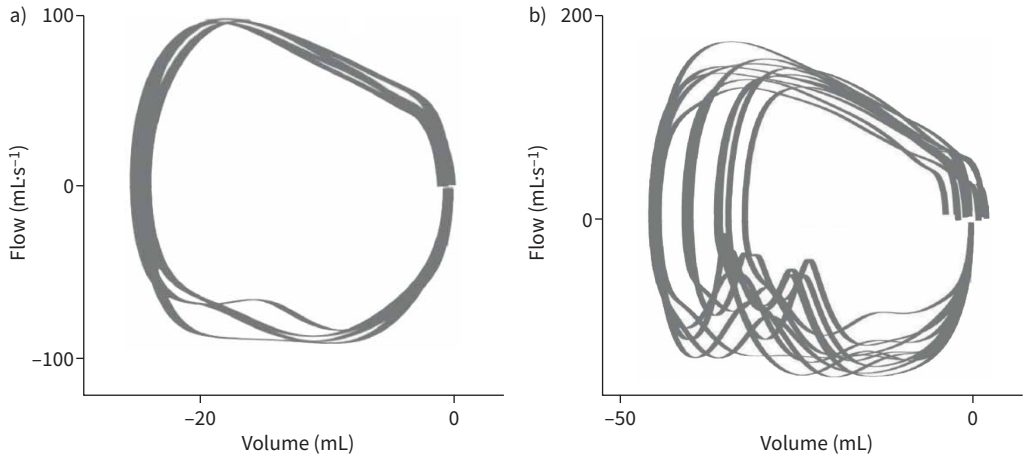

FIGURE 1 a) Typical tidal breath flow–volume (TB-FV) loop in a healthy child and b) TB-FV loop in children with inspiratory stridor. Figure modified from Bloise *et al.* [74].

abnormal morphological pattern of TB flow–volume loops at T0. Additionally, they observed lower peak inspiratory flow and longer inspiratory time compared to healthy children. At T1, tidal volume had increased and respiratory rate and ratio of inspiratory time to expiratory time had decreased. The authors conclude that TB analysis could be an important noninvasive tool in the management of laryngomalacia.

A case-control study performed by Thomas *et al.* [75] assessed the risk of bronchiectasis in children with tracheomalacia. The research team retrospectively evaluated high-resolution computed tomography (c-HRCT) for bronchiectasis and flexible bronchoscopies for tracheomalacia. They conducted both examinations in 45 cases with bronchiectasis and 90 controls without bronchiectasis under the age of 18 years within 4 weeks of time interval. After adjustment for age differences, they revealed an increased risk of developing bronchiectasis in children with tracheomalacia as defined by the ERS (adjusted odds ratio 20.2 (95% CI 2.3–174.2)) compared to controls. They concluded that children with tracheomalacia should be monitored for chronic wet cough and, if present, investigated for bronchiectasis.

In conclusion, we learned of a higher incidence and prevalence of chiLD in Spain than previously reported; we introduced a large case collection of children with DAH, describing clinical characteristics and underlying pathologies; a TB analysis technique was proposed for noninvasive management of laryngomalacia; and we identified tracheomalacia as a risk factor for bronchiectasis.

Group 7.8: lung and airway developmental biology

The session "Mechanistic pathways in chronic and new lung diseases" overviewed current studies that aim to unravel novel mechanisms of COPD, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH), primary ciliary dyskinesia (PCD), asthma, and the pulmonary sequelae of preterm birth.

Starting with the mesenchyme in COPD, Bekker *et al.* [76] identified 774 proteins differentially regulated in lung fibroblasts from COPD patients, using proteomic analyses, where HNRNPA2B1, FHL1, TUBA1C and HNRNPA1 represented novel candidate disease mediators or biomarkers that warranted functional follow-up studies. Turning to infections in COPD patients, Brake *et al.* [77] documented increased abundance of the SARS-CoV-2 entry- and co-receptors ACE2, TMPRSS2 and FURIN in type II pneumocytes, small airway epithelium and alveolar macrophages in smokers and in COPD patients, raising the possibility of increased susceptibility of those individuals to severe SARS-CoV-2 infection. Remaining with smokers, Paschalaki *et al.* [78] revealed that endothelial colony forming cells (ECFCs) from smokers and COPD patients exhibited increased expression of both senescence and DNA damage response markers, and that inhalation of corticosteroids reduced the senescence and interferon-γ-inducible-protein 10 in ECFC from COPD patients, thus suggesting a novel protective mechanism of corticosteroids. The vasculature in smokers was not neglected, and Bhattarai *et al.* [79] reported decreased arterial density and increased arterial wall thickness of vessels in smokers and mild-to-moderate COPD patients, indicative of early onset of PH. The increased arterial wall thickness in the COPD smoker group affected FEV_1/FVC, which was reversed by smoking cessation. Finally, with pulmonary malignancies in mind, Cerón Pisa *et al.* [80] documented that microRNA (miR)-34c-5p expression could differentiate COPD patients with and without lung cancer, and that miR-200c-3p and miR-449c-5p expression was increased in the COPD patients. These preliminary data highlight the potential utility of miRs as biomarkers in COPD.

Considering diffuse parenchymal lung disease, Gaikwad *et al.* [81] performed a comprehensive quantitative analysis of structural changes to the pulmonary vasculature in IPF patients, where intimal thickness was highest in the arterial diameter range of 200–399 μm and >600 to <1000 μm in IPF patients, whilst medial and adventitial thickness was significantly increased across all arterial diameter ranges in IPF patients.

Turning to the airways, Pérez García *et al.* [82] documented lower salivary microbiome diversity and more abundant *Rothia* spp. in asthma patients. Moving on to viral infections in the airways, Gay *et al.* [83] presented a transcriptional response to respiratory syncytial virus (RSV) in primary bronchial epithelial cells from asthmatic patients, where increased numbers of ciliated cells and decreased numbers of basal cells were noted in asthmatic patients after RSV infection. Thus, the response to RSV infection is altered in asthma, with reduced inflammatory response and a shift in cell-type composition after infection. Remaining with the airways, Hjeij *et al.* [84] revealed that DNAH5, DNAH11, CCDC40, CCNO and DNAI1 were the most frequent mutated genes in PCD patients.

Finally, the impact of prematurity on rabbit lung development was studied by Storti *et al.* [85], using histological and transcriptomic analyses in a preterm rabbit model, where radial alveolar count (RAC) progressively increased, whilst septal thickness and medial thickness of pulmonary arteries progressively

decreased over the course of lung development. Transcriptomic analysis suggested that cell cycle, epithelial morphogenesis and vascular endothelial growth factor signalling were more prominent in foetal samples, whilst immune system-related pathways were activated after birth.

In conclusion, this session highlighted that the characterisation of genes and pathways involved in the development of a disease is essential to identify new biomarkers and therapeutic targets.

Concluding remarks

This comprehensive summary is only a glimpse of the high-quality research presented during the 2021 virtual ERS Congress Paediatric sessions. We highlighted key advances in the paediatric respiratory field, with the aim of helping researchers and clinicians keep up to date with the latest and most relevant research. These research advances are also of vital importance for patients and their families, as they may reduce the time to diagnosis and improve their quality of life with more effective and targeted treatments. We encourage interested readers to participate in the ERS International Congress 2022 that will take place in Barcelona, Spain and online, to meet experts in the field and be exposed to the latest paediatric respiratory research first-hand.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: C. Ardura-Garcia is supported by the Swiss National Science Foundation (grant number 32003B_162820), support for attending meetings from the ERS, and is the Early Career Member Representative of the Paediatrics Assembly of the European Respiratory Society (ERS). S. Cuevas-Ocaña has received support for attending meetings from the ERS. M. Slaats received funding from Chiesi Pharmaceutical S.p.a. for his PhD studies. R.E. Morty has received grants or contracts from Deutsche Forschungsgemeinschaft, the Max Planck Society, Universitätsklinikum Heidelberg, and Bundesministerium für Bildung und Forschung; honoraria as the Editor-in-Chief of the *American Journal of Physiology – Lung Cellular and Molecular Physiology*; has a role as director of the International Graduate Programme, Molecular Biology and Medicine of the Lung, coordinator of the German Center for Lung Research Academy, Vice-Chair of the Gordon Conference of Lung Injury, Development, and Repair 2021, Chair of the Group 07.08 of the ERS, Chair of the Dept of Translational Pulmonology at the University Hospital Heidelberg. A. Moeller has received consulting fees from Vertex Inc., lecture fees from Vertex Inc. and Vifor Inc., has participated in the advisory board for Vertex Inc., and is the Secretary of the ERS Paediatric Assembly. M.W. Pijnenburg has received grants or contracts from Lung Foundation Netherlands and the Netherlands Organisation for Health Research and Development, consultation fees from Sanofi, honoraria as a speaker from Abbvie and Novartis, and support for attending meetings from the ERS. All other authors have nothing to disclose.

Support statement: C. Ardura-Garcia is supported by the Swiss National Science Foundation (grant number 32003B_162820). M. Storti is supported by Chiesi Pharmaceutical S.p.a.

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