



ERS International Congress 2022: highlights from the Paediatrics Assembly

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Abstract

This review has been prepared by the Early Career Members and Chairs of the European Respiratory Society (ERS) Assembly 7: Paediatrics. We here summarise the highlights of the advances in paediatric respiratory research presented at the ERS International Congress 2022. The eight scientific groups of this Assembly cover a wide range of research areas, including 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 developmental biology. Specifically, we report on abstracts presented at the congress on the effect of high altitude on sleep, sleep disorders, the hypoxic challenge test, and measurements of ventilation inhomogeneity. We discuss prevention of preschool wheeze and asthma, and new asthma medications. In children with CF, we describe how to monitor the effect of CF transmembrane conductance regulator modulator therapy. We present respiratory manifestations and chronic lung disease associated with common variable immunodeficiency. Furthermore, we discuss how to monitor respiratory function in neonatal and paediatric intensive care units. In respiratory epidemiology, we present the latest news from population-based and clinical cohort studies. We also focus on innovative and interventional procedures for the paediatric airway, such as cryotherapy.

Finally, we stress the importance of better understanding the molecular mechanisms underlying normal and abnormal lung development.

Introduction

The Paediatrics Assembly (Assembly 7) organised nine outstanding sessions at the 2022 European Respiratory Society (ERS) International Congress, including scientific symposia, clinical cases sessions, a skills lab on paediatric lung function and sleep measurements, and a postgraduate course on paediatric respiratory diseases (November 2022). Assembly 7 Early Career Members and leading experts presented 288 abstracts in oral and poster sessions. The Paediatrics Assembly sessions covered a wide range of the latest advances in paediatric respiratory research: from basic science, such as insight into the developing lung, to management, for example in rare diseases; and from diagnostics, such as lung function, to treatment, such as treatment with antibiotics. The final result was a very diverse programme of high interest to paediatricians as well as to adult physicians and allied healthcare professionals.

We here present the major paediatrics highlights from the 2022 congress. The Chairs of the eight groups that form the Assembly selected the sessions, which were summarised by Assembly 7 Early Career Members. The sessions are presented in order of the group numbers.

Group 7.1: paediatric respiratory physiology and sleep

The oral session “New respiratory physiological tests and home assessment of sleep disturbed breathing in children” included seven oral presentations. Several themes emerged from this session, including impact of altitude on physiology, outpatient access to diagnostic tests and improving assessment of ventilation indices in children.

Living at high altitude is a risk factor for sleep apnoea in adults [1]. GRIMM *et al.* [2] evaluated the prevalence of sleep apnoea in children living at high altitude compared to low altitude. This study included 37 healthy children living at high altitude (3250 m) and 41 healthy children at low altitude (760 m). The age range was 7–14 years. Whilst the mean saturation on nocturnal pulse oximetry was lower in the highlanders, no obstructive sleep apnoea was noted. Paediatric sleep questionnaire score (range 0 to 1 with increasing symptoms) was higher in the highlanders, suggesting the nocturnal hypoxemia and subtle sleep-related breathing disturbances may have clinical relevance.

Flying guidelines focus on the impact of altitude on hypoxia in primary lung disorders [3]. However, there is limited data on children with neuromuscular or hypoventilation disorders. RILEY *et al.* [4] assessed the response to low ambient oxygen (15%) using a hypoxic challenge test (HCT) in 20 children requiring nocturnal ventilatory support (10 with neuromuscular disease and 10 with congenital central hypoventilation): 13 out of 20 patients needed supplemental oxygen, and 11 out of 13 had normal saturations using their usual ventilator without supplemental oxygen. Transcutaneous carbon dioxide (P_{tCO_2}) remained within normal range for all patients. This highlights the use of HCT to plan air travel for children with failure of breathing drive, muscle failure or neuromuscular diseases.

A hot topic in sleep is developing methods to improve access to tests for diagnosing sleep disorders [5]. An in-laboratory polysomnography is considered the gold standard test for diagnosing sleep disordered breathing [6]. However, it is expensive, requires skilled inpatient laboratories and involves long waiting times. NATARAJAN *et al.* [7] described a high rate of technical adequacy and clinical utility of home cardiorespiratory sleep studies (including effort, flow, saturation, electrocardiography and video). They performed a retrospective data service evaluation of 50 studies in children. The adequacy of each study component was scored using the study report narrative. Most (96%) studies provided clinically relevant information and 36% of children were diagnosed with a breathing disorder. Electrocardiography scored most accurate (85.7%), nasal thermistor the least (32.7%) in the home testing. Another study, by SINHA *et al.* [8], evaluated leg fixation (LF) versus ear lobe fixation (ELF) of P_{tCO_2} monitoring during inpatient and outpatient sleep studies. P_{tCO_2} and capillary blood gas (arterial carbon dioxide tension (P_{aCO_2})) were compared for inpatient studies. 807 sleep studies were included. The measurement of LF was more successful than ELF. However, ELF was more accurate (mean difference between P_{tCO_2} and P_{aCO_2} was -0.5 kPa (95% CI $-2.21, 1.25$) in LF versus 0.0 kPa (95% CI $-2.01, 2.07$) in ELF).

ARIGLIANI *et al.* [9] investigated the impact of different versions of Spiroware (v3.3.1 versus v3.1.6) on interpretation of nitrogen multiple breath washout (MBW) in 35 children with sickle cell anaemia (SCA) and 31 controls. The upper limit of normal (ULN) for lung clearance index (LCI) was lower in both groups using Spiroware v3.3.1. Fewer SCA children had $\text{LCI} > \text{ULN}$ using the new software, highlighting the importance of knowing which version you use in your clinic as this influences normal values.

Volumetric capnography (Vcap) is a simpler alternative to MBW. Novel capnographic inhomogeneity indices (CII) detect ventilation inhomogeneity better than classical VCap indices in patients with cystic fibrosis (CF) [10], but their performance is unknown in infants. Kentgens and colleagues compared CII and Vcap in 248 tidal breathing files of 46 CF, 128 preterm and 74 term-born infants. CII were highest in CF followed by term-born and preterm, suggesting that CII have the potential to detect different underlying pathological processes. CII correlated with classical VCap indices but showed lower variability.

Take-home messages

- Nocturnal hypoxemia during sleep and subtle sleep-related breathing disturbances may have clinical relevance in children living at high altitude.
- It is important to use a HCT before a flight in children with neuromuscular or hypoventilation disorders.
- Electrocardiography and ear lobe fixation of $P_{t\text{CO}_2}$ scored the most accurate in outpatient sleep studies.
- Novel capnographic inhomogeneity indices have the potential to detect ventilation inhomogeneity in children with an underlying lung disease.

Group 7.2: paediatric asthma and allergy

One of the highlights for the paediatric asthma and allergy group was the Hot Topic session “Moving to prevention of preschool wheeze and asthma: almost there?” which included four presentations from experts in the field and focused on new insights of prediction and prevention of preschool wheeze and asthma.

David Cousins (Leicester, UK) started with a talk on “Immune system functions and reaction to infection and inflammation”, demonstrating the heterogeneous immune responses in infections in asthma, with the better understood type-2 immune responses and less well explored non-type-2 responses. Regarding these considerations, he presented a phase 2a placebo-controlled trial of risankizumab in severe asthma, where patients who took this anti-IL-23 medication had more frequent exacerbations and earlier time to first exacerbation compared to placebo [11]. On the contrary, tezepelumab showed an improved lung function and decreased rate of exacerbations in adults and adolescents with severe, uncontrolled asthma [12]. Tepelezumab is an inhibitor of thymic stromal lymphopoietin, a type 2 cytokine with a supposed central role in triggering and maintaining asthma.

Sejal Saglani (London, UK) presented “factors and mechanisms of preschool wheezing” with wheezing during infections, due to aeroallergen sensitisation (eosinophilia) and airway dysbiosis (neutrophilia). These types do not exist independent from each other, rather they interact with each other. Regarding risk factors, Saglani mentioned a significant correlation between presence of atopy and *Moraxella catarrhalis* infection, as well as with bacterial dysbiosis in the non-atopic group. Furthermore, rhinovirus seems to play a critical role as a contributing risk factor for preschool wheezing [13, 14]. In conclusion, future therapy strategies might contain inhaled steroids and targeted antibiotics, as well as bacterial lysates and certain vaccines.

Susanna Esposito (Parma, Italy) focused on “paediatric trials using bacterial lysates”. A 2012 Cochrane review on immunostimulants for respiratory tract infection prevention in children, showed that only the lysate named OM-85 showed a significant reduction of the total number of acute respiratory tract infections [15]. The results of the randomised, placebo-controlled, double-blinded phase IV trial on OM-85 showed a significant reduction of respiratory tract infections, acute otitis media and antibiotic prescription in comparison to placebo [16]. The benefits were detectable already after three months of therapy. In a further study regarding the efficacy and tolerability of influenza vaccine in combination with OM-85 [17] a significant advantage of the combined prevention could be detected compared to the single prevention arm. This finding was additionally supported by the recently online published expert consensus on the role of OM-85 in the management of recurrent respiratory infections [18].

Finally, Erika von Mutius (Munich, Germany) presented “Asthma Prevention in 2022”. First, she showed a study by MACKAY *et al.* [19] discussing how legislative smoking bans in Scotland in 2006 resulted in a 18% reduction of admission rates for asthma, independent of age, sex, urban or rural residence or socioeconomic status. Furthermore, a review from FRAZER *et al.* [20] showed that seven out of twelve studies reported a significant reduction of asthma hospitalisations after smoking bans. Other important modifiable risk factors which should be reduced for asthma prevention are indoor dampness and mould, obesity, air pollution and low physical activity [21–23].

Take-home messages

- New emerging therapeutic options for severe asthma are based on the heterogeneous immune responses in infections in asthma.

- Contributing risk factors for preschool wheezing: *Moraxella catarrhalis* and atopy, bacterial dysbiosis and rhinovirus infections.
- Bacterial lysate OM-85 may reduce the number of recurrent respiratory infections in children.
- Smoking is one of the most important modifiable risk factors regarding asthma prevention.

Group 7.3: paediatric cystic fibrosis

The oral session “Monitoring the effect of therapy with CF transmembrane conductance regulator (CFTR) modulator” included 10 oral presentations covering the current challenges in comprehensively monitoring patients with CF after the introduction of CFTR modulator treatment. These challenges are to establish easily applicable but sensitive diagnostic tools to follow-up mild courses of disease, and to investigate long-term effects of the CFTR modulator therapy. Relationships between different approaches of measuring lung function (*e.g.* lung function tests *versus* functional and structural imaging of the lung) were of particular interest.

Regarding outcomes of lung function parameters, LUCCA *et al.* [24] found that LCI and forced expiratory volume in 1 s (FEV₁) significantly improved after elxacaftor-tezacaftor-ivacaftor (ETI) treatment independently of baseline values and even in patients with a less severe course of disease at therapy start. Moreover, volume of trapped gas (VTG) expressed as percent of forced vital capacity (VTG/FVC%) significantly improved after ETI therapy start, as DUMAS *et al.* [25] reported. Relative changes in VTG/FVC% strongly correlated to relative changes in ventilation defects on functional magnetic resonance imaging (MRI) (phase resolved functional lung MRI and hyperpolarised 129Xe MRI) [25]. Further projects presented indicated that MRI is a suitable tool to monitor treatment effects of CFTR modulators: According to PENNATI *et al.* [26], low ventilation volume based on expiratory–inspiratory differences in MRI signal intensity significantly improved upon ETI. Besides, STREIBEL *et al.* [27] used functional matrix-pencil decomposition MRI, which allows calculating quantitative ventilation and perfusion maps of the lung, and common structural MRI to assess therapy effects. Their data showed a significant improvement of lung ventilation and perfusion and of structural lung pathologies (Eichinger score) upon ETI [27]. Also, NG *et al.* [28] demonstrated in a feasibility study that it is possible to apply even long MRI protocols targeting ETI treatment effects (assessing lung, gut and liver function) without sedation or anaesthetics in children younger than 12 years. KRIVEC *et al.* [29], however, took another approach and used lung ultrasound: they found a significant decrease of subpleural alveolar consolidations upon ETI reflecting better small airway clearance and consequently better distal lung aeration.

Further aspects to be considered regarding CFTR modulator therapy effects are respiratory immunity and airway colonisation. Neeland and colleagues determined key immune signatures of early life lung disease by observing significant differential gene expression in the alveolar macrophage population of children with CF compared to healthy controls, including genes associated with lung inflammation and fibrosis [30]. Changes after CFTR modulator therapy will have to be investigated in future studies. In addition, SEIDL *et al.* [31] observed differences in exhaled breath profiles between patients with CF and healthy controls, but CFTR modulator therapy did not normalise breath profiles.

Interestingly, first results on long-term effects of CFTR modulator therapy in real-world settings are now available. HIGGINS *et al.* [32] presented interim results of US and UK cohorts after an average therapy exposure to ivacaftor of 5.2 and 3.7 years showing significant long term benefits: reductions in pulmonary exacerbations, increases in weight and other nutritional parameters, decreases in hospitalisations, pancreatic enzyme supplement use and *Pseudomonas aeruginosa* prevalence. In accordance, MUILWIJK *et al.* [33] observed a significant improvement of percent predicted FEV₁ decline in children and adults and of body mass index z-score decline in children in a follow-up over 3 years after initiation of dual CFTR modulator therapy (lumacaftor/ivacaftor and tezacaftor/ivacaftor). However, although intravenous antibiotic use was significantly reduced in the first year of lumacaftor/ivacaftor and tezacaftor/ivacaftor treatment, this increased again in subsequent years [33].

Take-home messages

- Improvements in lung function upon CFTR modulator therapy were observed using different lung function tests as well as structural and functional imaging techniques.
- Patient benefits upon CFTR modulator therapy were sustained over a longer treatment period. Future follow-up studies may reveal additional aspects of the long-term effects.
- Further prospective studies will help to determine which combination of examination methods and outcome parameters are most suitable to monitor effects of CFTR modulator therapy in patients with CF.

Group 7.4: paediatric respiratory infection and immunology

Primary immunodeficiencies often present with severe or recurrent lower airway infections. Common variable immunodeficiency (CVID) is the most frequent and clinically significant primary antibody deficiency. Recurrent bacterial infections, usually of a sinopulmonary origin, are the hallmark feature of this disorder. Known complications include gastrointestinal tract involvement and increased risk for autoimmunity and lymphoproliferative disorders. Symptoms of CVID can occur at any age, with a peak in early childhood, late adolescence and young adulthood. The symposium “Lung involvement in common variable immunodeficiency: from diagnosis to lung transplantation” provided an overview of recent developments in the pathogenesis and diagnosis of CVID as well as CVID-lung management. It included four presentations from experts in the field.

Pere Soler-Palacín (Barcelona, Spain) emphasised the importance of detailed evaluation of patients with CVID phenotype before establishing a definitive diagnosis and before start of treatment. CVID diagnosis is challenging given its clinical, genetic and immunologic heterogeneity [34]. The immune defect common to all patients is loss of B-cell function, either intrinsic to B-cells or because of insufficient help from other cells for antibody production [35]. As no single clinical feature or laboratory test can establish the diagnosis, the European Society for Immunodeficiencies has established clinical criteria for a probable diagnosis of CVID [36]. Exclusion of other primary antibody deficiencies and secondary causes of hypogammaglobulinemia is an important part of the diagnosis [37]. In addition, 10–20% of patients with identified causative mutations are removed from the broad umbrella diagnosis of CVID and are reclassified as having a CVID-like disorder [38, 39].

Moving to prevention and treatment of infections in patients with CVID, David M. Lowe (London, UK) highlighted the management of acute and chronic respiratory tract infections. Despite routinely prescribed immunoglobulin (Ig) replacement, patients with CVID exhibit higher markers of inflammation and dysbiosis in their airways compared to healthy controls [40]. Antibiotics are often prescribed [41]. However, studies suggest that antibiotic treatment could be better targeted, as viral infections are common and illnesses dominated by upper respiratory tract symptoms respond poorly to antibiotics [41]. For patients with chronic or recurrent infections that do not respond to Ig replacement therapy alone, the addition of long-term antibiotic prophylaxis is a therapeutic strategy recommended by many experts [34, 35]. Nevertheless, there is no evidence that it has a beneficial effect on long-term pulmonary function [42].

Chronic lung disease in patients with CVID results from the sequelae of recurrent acute infections and immune dysregulation. Hence, two distinct patterns of chronic lung disease develop – bronchiectasis and interstitial lung disease [43]. Granulomatous–lymphocytic interstitial lung disease (GLILD), presented by Elisabetta Renzoni (London, UK), is a rare, potentially severe pulmonary complication of CVID, associated with increased mortality. It occurs in approximately 10–30% of patients and is rare in children. There is a lack of standardisation for diagnosis, monitoring and treatment of GLILD [43]. Consensus was reached that Ig optimisation and oral corticosteroids as first-line treatment are to be given in patients with lung function deterioration [44].

Last, Michael Perch (Chicago, IL, USA) addressed possible contraindications to referral for lung transplant and challenges in post-transplant follow-up. As in all patients with end-stage lung disease, the primary goal of lung transplantation in patients with CVID is to provide survival benefit [45]. Limited data are available regarding outcome after lung transplantation for patients with CVID end stage lung disease, especially for children. Case series show frequent postoperative infections and complications, deeming lung transplant in children high risk and a final resort [46].

Take-home messages

- CVID is the most frequent and clinically significant primary antibody deficiency.
- Respiratory manifestations of CVID are frequent and responsible for much of the associated morbidity and mortality.
- Recurrent infections and immune dysregulation of the respiratory tract contribute to the development of chronic lung disease such as bronchiectasis and interstitial lung disease.

Group 7.5: respiratory disorders in neonatal and paediatric intensive care

One of the conference highlights for members of this group was David Tingay’s (Melbourne, Australia) plenary talk on “Respiratory function monitoring in neonatal and paediatric intensive care units”. Monitoring respiratory function in these intensive care settings is vital as both the immature preterm lung, and developing paediatric lungs, are in a constant state of dynamic change. Respiratory function monitoring can be used for diagnostic purposes, to guide and optimise care, and to provide clinicians with

an understanding of complex pathophysiological processes [47]. We here summarise the crucial points from his talk.

Lung mechanics can be monitored extensively by ventilatory graphics and describe the dynamic interplay between pressure, flow and volume. Indeed, in neonates, lung protective ventilation can be continuously adapted to disease states by close monitoring of pulmonary pressure–volume curves [48, 49]. Furthermore, outcomes can be improved secondary to reduced patient–ventilator asynchrony and appropriate tidal volume monitoring in those requiring invasive ventilation [50]. Novel techniques such as automated oxygen control systems were reported to improve time spent within target oxygen saturations in the intensive care settings, with large trials reporting on the long-term outcomes being recommended [51]. Lung ultrasound is becoming much more widely available and accessible, and can be used as a diagnostic tool, to guide respiratory support, and predict outcomes [52, 53]. Electrical impedance tomography is an up-and-coming non-invasive method used to define pulmonary physiology and describe regional lung aeration and mechanics, and to guide the titration of positive end-expiratory pressure [54, 55]. Additionally, the forced oscillation technique or respiratory oscillometry can be used to provide an assessment of respiratory reactance and resistance, and can be applied during intubation and spontaneous breathing, to identify the requirement for surfactant therapy and predict preterm respiratory outcomes [56, 57].

As with all approaches, the limitations of current respiratory function monitoring may exclude global utility within paediatric and neonatal intensive care – such as the large variability of non-uniform lung diseases being cared for, the increasing use of non-invasive ventilation and a higher proportion of extremely low birthweight infants surviving. As discussed, there are many options available for clinicians to monitor respiratory function in neonatal and paediatric intensive care; however, there is a need for large interventional trials to determine the ability of such measures to improve outcomes – and indeed this is a promising and exciting area to explore.

Take-home messages

- Validated lung ultrasound scoring systems can be utilised to assess the transition of newborn infants at birth.
- Novel techniques of electrical impedance tomography and respiratory oscillometry can assess heterogeneity of ventilation and assist clinicians in tailoring ventilator setting and pharmacological treatment, respectively.
- Monitoring respiratory oscillatory mechanics can lead to improved outcomes in critically unwell infants and children.

Group 7.6: paediatric respiratory epidemiology

The oral session on “Latest news from paediatric population-based and clinical cohort studies” included eight oral presentations, which covered a broad range of topics addressed in cohort studies. Three presentations addressed early life factors with two focusing on maternal exposures during pregnancy. Here we summarise the studies presented.

Three presentations addressed early life factors with two focusing on maternal exposures during pregnancy. RUSCONI *et al.* [58] analysed data from 5997 children from the Italian NINFEA birth cohort (Nascita e Infanzia: gli Effetti dell’Ambiente – Birth and Childhood: effects of the environment) and found some evidence of association for self-reported pesticide use during pregnancy and residential proximity to fruit tree cultivations, with infant wheezing [58, 59]. DELVERT *et al.* [60] identified five allergic and respiratory profiles (*i.e.* asymptomatic, wheezing without asthma, asthma only, allergies without asthma and multiallergic) by applying latent class analysis to data on allergic and respiratory symptoms obtained from the French Longitudinal Study of Children cohort [61]. Maternal diet quality during pregnancy was not associated with any of the profiles. High fish consumption was associated with a higher probability of being in the allergies without asthma profile [60]. KOTCHA *et al.* [62] investigated the association between early life factors and lung function deficit associated with preterm birth in the Respiratory Health Outcomes in Neonates study. Bronchopulmonary dysplasia (BPD) was associated with low lung function at age 7–12 years only in the univariable analysis, in contrast to gestation and intra uterine growth restriction which remained associated with low lung function in the multivariable analysis [62, 63].

Two other presentations stayed on the topic of lung function. GRENVILLE *et al.* [64] studied the association between FEV₁ and FVC at age 8 and cognitive ability at ages 8 and 15 in 6644 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) [65]. After adjusting for potential confounders, only reduced FVC was associated with lower cognitive ability at both ages, with the effect attenuating with age [64]. VALACH *et al.* [66] outlined the potential of respiratory impedance as a diagnostic tool, especially

in children, as it is manoeuvre independent. Hence, they created reference values for respiratory impedance using measurements from 981 healthy 6–17-year-olds from the Austrian LEAD (Lung heart social body) cohort [67]. The availability of reference values may now help to integrate respiratory impedance in respiratory diagnostics [66].

The effects of coronavirus disease 2019 (COVID-19) were also addressed. ABELLAN *et al.* [68] assessed paediatric asthma incidence trends from 2010 to 2021, using data from a primary care records database in Catalonia [69]. Asthma incidence was higher in young children, in males until the age of 15 years, and among the most deprived. They also observed a small decrease in new asthma diagnosis in the years before the COVID-19 pandemic followed by a steep decrease of 37% following the pandemic. This trend should be confirmed after monitoring for a longer period of time [68]. BYAMUNGU *et al.* [70] analysed data of 82 children with PCR-confirmed SARS-CoV-2 from a high HIV burden region in South Africa. Of those, 45% required critical care and 17% died. Age <1 year and comorbidities such as HIV were important predictors of critical care need and in-hospital mortality from COVID-19. Such factors should therefore be considered in triage, allocation of intensive care resources and rapid referral.

GOUTAKI *et al.* [71] received the award for the best abstract in the Paediatrics Assembly for the largest study characterising otologic disease in patients with primary ciliary dyskinesia (PCD). Data from the ear-nose-throat (ENT) prospective international cohort of patients with PCD (EPIC-PCD) [72] showed that ear problems evolved with age and became more chronic. Hearing impairment was common but not always accurately perceived by patients. These findings highlight the need for regular ENT evaluation with audiometry [71].

Take-home messages

- Paediatric cohorts allow the study of different respiratory health factors as outcomes or as predictors of other conditions.
- Acquired knowledge can help inform targeted interventions to improve paediatric health.

Group 7.7: paediatric bronchology

Both sessions, “Paediatric respiratory diseases” (state-of-the-art) and “New insights into diagnostic and experimental paediatric pulmonology” (oral presentation), had a special focus on innovative and interventional procedures in paediatric bronchology. Here we summarise the studies presented at both sessions.

SCHRAMM *et al.* [73] presented a new study on cryotherapy in children. They demonstrated that cryotherapy is feasible and safe for the indications of biopsy, foreign body removal and restoration of airway patency. However, other interventional techniques, such as stent implantation, were discussed. Of particular interest were results of biodegradable stents. These stents are mainly used in children with tracheobronchomalacia and show successful results within the first three months. Subsequently, however, the material polydioxanone (PDO) begins to decay, which can lead to fragmentation and thus represents a potential complication [74].

For better understanding GIMENO DIAZ DE ATAURI *et al.* [75] investigated the possible effects of PDO stents on the trachea of 21 healthy mice. In three time points during the first 3 months, macro- and microscopical changes of the trachea were analysed based on the number of stents. Only mild macroscopic mucosal inflammation has been observed at the end of the clinical assessment, without any airway obstruction nor increase in the collagen matrix. In conclusion, the biodegradable stents seemed to be well tolerated in a mouse model, however they have not been able to increase the cartilaginous support of the trachea during a long follow-up period.

Among others, PCD represented a further thematic focus. ROEHMEL *et al.* [76] reported the results of LCI in preschoolers with PCD and CF as compared to healthy controls. They found that LCI is a feasible tool in this age group, and it is higher in PCD children than controls but comparable to children with CF, suggesting that the respiratory involvement might start very early in both groups. The role of nitric oxide (NO) synthesis, in particular decreased nasal NO (nNO) in PCD patients, has been investigated by SCHLEGTENDAL *et al.* [77]. They found that in patients with chronic lung disease (PCD and CF), sputum arginase activity and asymmetric dimethylarginine is increased, but only in patients with PCD the NO metabolites are reduced, what could explain the low nNO in these patients.

EMIRALIOĞLU *et al.* [78] studied the correlation between lung function decline and clinical and radiological scoring (Brody Score) in a group of patients with PCD. Their results suggest that there is a low grade

negative correlation between total bronchiectasis scores and the FEV₁, and that the increase in the hyperinflation score was correlated to the FEV₁ decline.

Finally, the alveolar capillary membrane function in patients with PCD, CF, childhood interstitial lung disease (chILD), BPD and Fontan circulation was investigated by RING *et al.* [79] using both lung diffusing capacity for nitric oxide (D_{LNO}) and lung diffusing capacity for carbon monoxide (D_{LCO}). D_{LNO} was below normal in more than half of patients with chILD and Fontan but also with PCD. D_{LNO} is considered an interesting supplement to D_{LCO} in pulmonary function testing, and reduced value has been found in children with PCD and chILD, suggesting early alveolar damage.

Take-home message

- Paediatric interventional techniques will become a challenge in diagnostics and therapy in the future, which implies that new training opportunities have to be developed.

Group 7.8: lung and airway developmental biology

BPD is one of the primary complications encountered in premature infants [80], and those infants that require oxygen supplementation are at particular risk for this chronic lung disease which may result in poor lung development. To understand the molecular mechanisms and identify new potential management strategies, knowledge must be acquired to understand how the lungs develop early in life. The lungs of very low birthweight infants with BPD are characterised by fewer, larger alveoli [81]. Lung development occurs partly postnatally, with pulmonary angiogenesis being essential for alveoli formation [82]. The ERS Mini-Symposium titled “Deconstructing the developing lung at the single cell level to determine phenotypes and cell-specific targets of BPD” focused on the molecular mechanisms of lung development and the impact of early-life injury on lung development. It included four presentations from experts in the field.

Using advanced mouse models and “-omics” techniques, Cristina Alvira (Stanford, NY, USA) presented novel (unpublished) data on the molecular mechanisms of late lung development and the effect of injury such as hyperoxia on lung endothelial subtypes. She documented that the transcriptome of pulmonary epithelial cells is unique compared to adult counterparts. The developing lung contains a transient transcriptionally distinct arterial endothelial cell subtype. Furthermore, hyperoxia alters endothelial cell subtypes and induces unique gene signatures in specific epithelial cell subtypes. Surprisingly, it was found that hyperoxia selectively induces proliferation of venous endothelial cells.

Miguel Alejandro Alcázar (Cologne, Germany) addressed intercellular communication in the alveolar niche. Different cell types comprise the alveolar niche, but cross-talk between those cells (such as immune cells, stem cells and fibroblasts) is critical for lung development. Focusing on immune cells, hyperoxia was revealed to activate macrophage-derived IL-6 signalling in newborn mice, thus inhibiting lung growth [83]. This might be an interesting pharmaceutical target, since blocking IL-6 *trans* signalling was protective in terms of impaired epithelial cell function, activation of myofibroblasts, arrest of alveolarisation and reduced lung function. When focusing on alveolar type 2 (AT2) progenitor cells, the transcription factor Krüppel like factor 4 (Klf4) seems to play an important role in influencing alveolarisation and AT2 differentiation through the Netrin-1–Unc5h2–Klf4 axis [84].

S. Elizabeth Taglauer (Boston, MA, USA) provided insight into lung development early in life from a placental biologist perspective. Antenatal conditions such as pre-eclampsia and chorioamnionitis may adversely impact the pulmonary development niche through the foetal exposure to inflammatory and/or antiangiogenic mediators [85]. Using *in vivo* animal models and *in vitro* studies with primary placental cells and proteomics approaches, she documented that these conditions could create a unique adverse intrauterine environment, which may predispose infants to different BPD phenotypes.

Finally, Bernard Thébaud (Ottawa, ON, Canada) addressed the pros and cons of cell-based therapy for BPD. Preclinical evidence shows that mesenchymal stromal cells (MSC)-based therapy may prevent alveolar defect and angiogenesis [86]. A recent phase II trial in premature infants did not find an effect of MSC-based therapy on the primary outcome (death or severe/moderate BPD) in the entire study population, but did find a reduction of severe BPD in the subgroup of infants born at 23–24 gestational weeks [87]. However, clinical translation of cell-based therapy often fails due to multifactorial reasons including lack of rigorous methodology, logistical and regulatory obstacles, and failure to address concerns of ethics institutions or other stakeholders [88]. The INCuBAToR concept (Innovative Neonatal Cellular

Therapy for Bronchopulmonary Dysplasia: Accelerating Translation of Research) has been designed to enhance the likelihood of clinical success of MSC therapy and will hopefully contribute to novel BPD treatment strategies in the future.

Take-home messages

- Oxygen injury to the developing lung drives proliferation of venous endothelial cells.
- Evidence was presented to suggest that IL-6 might be targeted therapeutically in disordered lung development.
- MSC-based therapies may reduce the severity of BPD in defined subgroups of affected infants, although measures are needed to improve trial design.

Concluding remarks

The 2022 ERS Congress celebrated the return to face-to-face meetings, while maintaining a diverse and extended programme for online attendees, enabled by the highly successful hybrid format. The paediatrics sessions at the congress presented key and recent advances in respiratory diseases research in children, some of which are summarised in this article. We hope the findings and proposals for future research may inspire both senior and young researchers to continue improving the quality of life of children with respiratory problems. We welcome everyone to attend and contribute to the 2023 ERS Congress in Milan.

Provenance: Commissioned article, peer reviewed.

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