



Key paediatric messages from the 2017 European Respiratory Society International Congress

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ABSTRACT In this article, the group chairs of the Paediatric Assembly of the European Respiratory Society (ERS) highlight some of the most interesting findings presented at the 2017 ERS International Congress, which was held in Milan, Italy.



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A review of highlights from selected presentations from #ERSCongress 2017 by the @ERStalk Paediatric Assembly <http://ow.ly/ixZj30jzIVy>

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Introduction

The Paediatric Assembly's contribution to the 2017 European Respiratory Society (ERS) International Congress in Milan included three symposia and one of each of the following sessions: state of the art, hot topic, grand round, year in review, meet the expert, challenging clinical case, and postgraduate course. It was also the first Congress for our new group "Lung and Airway Developmental Biology". In this review, the Assembly's group officers and our early career representative highlight some of the key messages from the Congress, referring also to recent publications.

Paediatric sleep medicine

Sleep-disordered breathing has major adverse effects on children, including reduced neurocognitive functioning, and appropriate treatment is associated with improvements in behaviour, socialisation and academic achievements [1]. While innovative approaches to the management of clinical referrals to paediatric sleep clinics have demonstrated marked improvements in clinical outcomes [2], we still need further validated approaches to increasing the capacity of sleep laboratories to diagnose obstructive sleep apnoea (OSA). For challenging children, such as those with intellectual and/or physical disabilities, sleep studies conducted in the reassuring home environment may be the best option. IKIZOGLU *et al.* [3] assessed the feasibility and accuracy of an unattended home sleep study in school-aged children with Down's syndrome. 19 children were recruited and paired laboratory and unattended home sleep studies were performed. Home studies were successful in 17 (89%) with the initial study and in the remaining two children with a repeated home sleep study. The accuracy of the unattended sleep study for mild OSA was poor, with significant overestimation of mild OSA. In contrast, the detection of severe OSA was similar between home and laboratory studies, with a negative predictive value of 100% in the home studies. Overall, these data support the recent published study on the feasibility of home sleep studies in children with Down's syndrome [4] and suggest that, in cases of suspected severe OSA, an initial home sleep study may facilitate diagnosis and minimise burden on the family.

New insights from studies of lung function

Measurement of ventilation distribution in cystic fibrosis

Cystic fibrosis (CF) lung disease is characterised by uneven ventilation distribution, which can be measured by the multiple-breath washout (MBW) technique. Lung clearance index (LCI) measured by MBW has already been shown to be a sensitive marker of CF lung disease, and is now being used as a surrogate outcome measure in clinical trials [5], as a surveillance tool to monitor structural lung disease [6], and as a prediction tool of pulmonary exacerbations in children with CF [7]. At this ERS Congress, OUDE ENGBERINK *et al.* [8] from Toronto, Canada, presented their data on the inter-test reproducibility of the LCI. Traditionally the inter-test reproducibility of the LCI has been described in terms of absolute change (*e.g.* 1 unit); however, if LCI is more variable at higher values, interpretation of absolute changes in LCI may be biased. The study group assessed whether inter-test reproducibility depends on the LCI value and whether relative changes are better suited to define reproducibility. In total, 619 MBW measurements were recorded for 148 children aged 3–6 years with CF and age-matched healthy controls, over a period of 12 months. Using relative changes, a physiologically or clinically relevant change in healthy preschool children was calculated to be $\pm 15\%$, whereas it was $\pm 30\%$ in CF children. The average relative change in both healthy and CF children was independent of the time interval between measurements. Thus, the authors concluded that LCI variability is proportional to its mean, but the interpretation of absolute changes will be biased. A percentage change in LCI greater than $\pm 15\%$ in preschool children can be considered physiologically relevant and greater than the biological variability of the test in healthy children, and may help to identify patients with clinically relevant changes in lung function.

Currently, MBW is performed either using 100% oxygen to wash out resident nitrogen (N_2) from the lung or using a gas mixture containing sulfur hexafluoride (SF_6). Recently, data have been published on higher LCI values measured with N_2 -MBW than concurrent SF_6 -MBW. STAHL *et al.* [9] investigated 16 preschool children with CF aged 2.5 ± 0.7 years with N_2 - and SF_6 -MBW using Exhalyzer D (Eco Medics, Dürnten, Switzerland). They confirmed a higher mean N_2 -LCI (mean 9.1 ± 2.6), which was about 2.2 ± 2.3 units higher than the SF_6 -LCI (mean 6.9 ± 0.8 ; $p < 0.01$). However, despite confirmation of higher N_2 -LCI compared to SF_6 -LCI in children with CF, the reason and clinical meaning of these findings remains unclear.

Another method for measuring the uneven ventilation distribution in CF is the vital capacity single-breath washout (VC SBW) test, which is less time-consuming than a MBW test. KJELLBERG *et al.* [10] compared this technique with spirometry in 31 teenagers and adults with CF aged 13–45 years (median 23 years) using the Exhalyzer D washout device. Washout results were related to 400 healthy control subjects for N_2 -MBW and 224 for N_2 -VC SBW. For the 31 CF subjects, forced expiratory volume in 1 s (FEV₁) was abnormal in only seven (23%) subjects, but VC SBW phase III slope (S_{III}) was abnormal in 20 (65%), LCI

in 29 (94%), S_{cond} (ventilation heterogeneity in the conductive lung zone) in 30 (97%), S_{acin} (ventilation heterogeneity in the acinar lung zone) in 24 (77%) and fast-to-slow regions specific ventilation ratio in 30 (97%). Among the 11 subjects with normal VC SBW S_{III} , 10 (91%) showed abnormal MBW results. Abnormal N_2 -VC SBW S_{III} was seen in the majority of teenagers and adult CF subjects with normal FEV₁, suggesting an additional value of this method, but normal S_{III} did not exclude pathological MBW outcomes.

Neonatology

In neonates, pulmonary dead space volume (V_D) is an index of ventilation inhomogeneity and one of the determinants of the magnitude of tidal volume to maintain optimal blood gases. DASSIOS *et al.* [11] identified different determinants influencing V_D in 61 mechanically ventilated infants (15 term, 46 preterm). V_D per kg body weight was related to gestational age, birth weight, weight and postmenstrual age at measurement, days of ventilation and the ratio of time to peak tidal expiratory flow/expiratory time. The median (interquartile range (IQR)) V_D per kg body weight was higher in prematurely born infants (2.3 (1.7–3.0) mL·kg⁻¹) compared to term infants (1.5 (1.3–2.1) mL·kg⁻¹; $p=0.003$) and in premature infants that developed bronchopulmonary dysplasia (BPD) (2.6 (1.8–3.4) mL·kg⁻¹) compared to those who did not (1.7 (1.1–1.9) mL·kg⁻¹; $p<0.001$). An optimum tidal volume will differ according to the underlying demographics and respiratory status.

Noninvasive ventilation

Early noninvasive respiratory support such as nasal continuous positive airway pressure (nCPAP) is the current way of preventing lung injury in preterm infants [12]. Although nasal high-flow therapy (nHFT) is in general better tolerated than nCPAP, a recent trial suggested that nHFT might be inferior to nCPAP in preventing intubation. In a late-breaking abstract, ZIVANOVIC *et al.* [13] demonstrated the effectiveness of nHFT as a primary respiratory support for preterm infants with respiratory distress syndrome. In this retrospective observational multicentre study, 381 preterm infants were included and the use of nHFT, without use of nCPAP, resulted in intubation rates comparable or lower than published data.

The use of long-term noninvasive ventilation has increased worldwide in children of all ages. There are different indications, different types of noninvasive ventilation and technical aspects, and different pathophysiological features of the respiratory failure [14]. Telemonitoring (TM) patients on noninvasive ventilation has been extensively studied in adult patients with neuromuscular disease (NMD) but, to date, not in children. In a 2-year longitudinal observational multicentre TM trial by TRUCCO *et al.* [15], 48 patients with NMD were enrolled. The median age was 16.4 years and the median ventilation per day was 10.5 h. Patient satisfaction was assessed using questionnaires. The total number of exacerbations was similar in TM patients and controls (59 *versus* 53), but the total hospitalisation rate and length of admission was reduced in TM patients. All patients reported improvement in the items involving communication.

Spirometry in management of asthma

As persistent bronchial obstruction may occur in asymptomatic children and is a risk factor for severe asthma episodes, at least annual measurement of FEV₁ using office-based spirometry was considered useful by the report of a recent ERS Task Force [16, 17]. Data from the Childhood Asthma Management in Primary Care (CHAMPIONS) study by LO *et al.* [18] are therefore of interest. This study investigated the prevalence of abnormal spirometry in children managed in primary care for asthma, the relationship between reported asthma control and lung function, and the subjective impact of spirometry on clinical decision-making. Data from a total of 586 children aged 5–16 years were obtained at clinical review, including the asthma control test (ACT), the childhood asthma control test (C-ACT; validated for age 4–11 years), baseline lung function and degree of FEV₁ reversibility post inhaled salbutamol, by practice nurses at 10 UK general practices (primary care). From the 549 children with usable lung function tests, 30% had abnormal lung function. Airway obstruction was associated with poor asthma control (and ACT score of <20), and median ACT and C-ACT scores for children with obstructed lung function were lower than in those with normal spirometry. However, symptom-based assessment alone missed almost a quarter of children with abnormal lung function and in a quarter of cases the clinical management plan was changed by the practice nurse after review of lung function. These results underline the importance of routine spirometry in the management of asthmatic children.

Improving outcomes in infants and children with wheeze

A primary care programme presented by CARROLL *et al.* [19] assessed the effect of a multimodal, sustained educational intervention aimed at healthcare professionals in 51 general practices in Staffordshire (UK) including a total of 2804 and 2816 children in 2014 and 2015, respectively. Following the intervention

there was a significant improvement ($p < 0.0001$) in asthma control in children within participating practices (the percentage of children with controlled asthma changed from 5.9% to 26.7%). There were no significant differences in the reported prevalence of asthma or overall treatment that children received.

The current consensus on use of noninvasive biomarkers for monitoring inflammation (specifically exhaled nitric oxide fraction (F_{eNO})) is that use should be reserved for selected cases [16, 17]. Data presented by FIELDING *et al.* [20] are therefore of interest, since these investigators addressed the question of how much F_{eNO} can vary without a change in clinical status. Data from seven clinical trials were pooled, resulting in data from 1115 children (58% male, mean age 12.6 years). Each trial was broken down into 3-month intervals, including 228, 209, 294 and 296 asthmatic children in the first, second, third and fourth 3-month interval, respectively. Individuals whose asthma was controlled and who had stable inhaled corticosteroid (ICS) treatment over a specific 3-month interval were identified. The median (IQR) change in F_{eNO} during the first 3 months was +2 (−6 to 15) ppb and values for the successive periods were +1 (−13 to 10) ppb, 0 (−8 to 10) ppb and +1 (−6 to 10) ppb. The median (IQR) percentage change in F_{eNO} for the first 3 months was +10% (−28% to 79%) and for the next three periods was +2% (−35% to 70%), +1% (−24% to 50%) and +5% (−21% to 46%). The authors concluded that F_{eNO} values vary considerably over time. The 75th centile values suggest that absolute F_{eNO} may rise by ≤ 15 ppb and % F_{eNO} by $\leq 80\%$, whereas the 25th centile values suggest that F_{eNO} may fall by ≤ 15 ppb or $\leq 40\%$ without a change in clinical status.

Gastro-oesophageal reflux (GOR) has been suggested as a cause of poor asthma control but treatment studies resulted in inconclusive results. The consensus view is that routine assessment of GOR or swallowing abnormalities is not necessary in children with asthma [16]. However, GOR might play a role in severe therapy-resistant asthma (STRA). TANNER *et al.* [21] determined the prevalence of GOR in children with STRA by the means of a 24-h pH study and assessed the relationship of the presence and severity of GOR to airway inflammation and symptoms. Of 82 children with STRA (mean age 11.6 years), 23% had GOR. No differences between children with and without GOR were found for asthma control, lung function, F_{eNO} , eosinophils or neutrophils in sputum and bronchoalveolar lavage. These data suggest that there is no relationship between GOR and airway inflammation in children with STRA.

In children with problematic asthma, adherence issues contribute to poor asthma control, and adherence to maintenance treatment is a matter that warrants attention at each contact with a healthcare provider [16, 22]. HOCH *et al.* [23] presented a pilot study to assess usability and feasibility of adherence monitoring devices to assess medication adherence over 3 months in 25 high-risk asthmatic children (aged 6–19 years) with at least one hospital admission or two emergency visits in the previous year. Sensors were placed on controller and rescue medications. 20 participants completed the study. Of the asthmatic children, 80% were very satisfied with the devices and 80% of the caregivers stated that their children were more likely to adhere to treatment. However, regardless of the satisfaction with these devices, average weekly adherence to controller medication ranged from 76% at study entry to only 36% at 3 months, with a mean adherence rate of 56%. These data suggest, disappointingly, that in this high-risk group, an intervention giving immediate feedback on adherence is not sufficient to improve adherence.

The recent update of the ERS Task Force Report on the classification and treatment of preschool wheezing concluded that ICSs remain the first-line therapy in children with multiple-trigger wheeze and in children with episodic viral wheeze and frequent or severe episodes [24]. GRIGG *et al.* [25] assessed the comparative effectiveness of current guideline-recommended therapies for preschool children (mean \pm SD age 3.2 \pm 1.3 years) with recurrent wheezing by the means of electronic medical records from the Optimum Patient Care Research Database in a UK population aged ≤ 5 years with asthma/wheeze. Two two-way matched comparisons were made: ICS ($n=990$) versus short-acting β -agonists (SABA) ($n=3960$) and leukotriene-receptor antagonists (LTRA) ($n=259$) versus SABA ($n=1036$). Year rates of severe exacerbations, defined as asthma-related emergency attendance, hospital admittance or systemic corticosteroid use, were compared using conditional regression analyses. No significant differences were found between matched cohorts, showing no evidence that either ICS or LTRA therapy is associated with fewer exacerbations during the one outcome year. These results suggest that we need better methods of targeting therapy to children with preschool wheeze. A potential solution is provided by the study of BEIGELMAN and BACHARIER [26], which reported efficacy of daily low-dose ICS in the subgroup of preschool children with a history of episodic wheezing, who are at high risk for asthma (based on having at least four exacerbations of wheezing during the previous 12 months lasting >24 h and the following major or minor criteria: one of the major criteria (parent-reported physician-diagnosed asthma, physician-diagnosed atopic dermatitis, or sensitisation to aeroallergen) or two minor criteria (wheezing unrelated to colds, peripheral blood eosinophilia, or sensitisation to milk, egg or peanut)).

Airway infections

Relationship with asthma

There is an ongoing debate on the causal relationship between early severe lower airway infections and later asthma. TURNER and THOMAS [27] obtained details of all paediatric admissions to Scottish hospitals in 2000–2013 and identified admissions with “any” bronchiolitis, respiratory syncytial virus (RSV) bronchiolitis and asthma. Survival analysis was used to explore the interval between admissions with bronchiolitis and asthma. There were a total of 25 808 admissions for bronchiolitis including 13 856 RSV bronchiolitis admissions. After 2 and 5 years of age there were 14 734 and 9080 asthma admissions, respectively. The odds ratio (OR) for an asthma admission by age 2 or 5 years being preceded by a bronchiolitis admission was 0.70 (95% CI 0.64–0.76) or 0.48 (95% CI 0.41–0.56), respectively. Survival analysis demonstrated that asthma admissions after 2 years of age that followed a bronchiolitis admission occurred at an average of 2.4 (95% CI 2.2–2.7) years earlier than asthma admissions that were not associated with a prior bronchiolitis admission.

By contrast, HOMAIRA *et al.* [28] found an increased risk of first asthma hospitalisation, which persisted up to age 7 years in children who had severe RSV disease in the first 2 years of life in a retrospective cohort analysis using population-based linked data from all children born in New South Wales, Australia, between 2000 and 2010. They used a time-dependent Cox model to determine the hazard ratio (HR) for the first asthma hospitalisation in children who had RSV hospitalisation in the first 2 years of life compared to those who did not. The cohort included a total of 847 516 children and 22 379 (3%) children had 36 560 episodes of asthma hospitalisations between ages 2 and 11 years. The adjusted HR (95% CI) for first asthma hospitalisation in children who had RSV hospitalisation, compared to those who did not, was 4.5 (4.2–4.8) at age 24–30 months, 3.4 (3.2–3.7) at 31–36 months, 3.0 (3.2–2.8) at 37–49 months and 2.6 (2.4–2.7) beyond 4 years, and the increased risk persisted up to 7 years of age.

It has been previously argued that RSV bronchiolitis plays an important role in the causation of asthma. More recently the spotlight has fallen on the possible role of the human rhinovirus. AMPAH *et al.* [29] explored the potential differential impact of these two pathogens in a retrospective study that sought to determine the likelihood of re-attending hospital in the year following an admission to hospital with RSV or rhinovirus lower respiratory tract infection in the first 6 months of life. Overall, 75% of the included children had experienced a RSV lower respiratory tract infection, but the authors found that those who presented initially with a rhinovirus infection were slightly more likely to re-attend hospital (60% *versus* 53%), and to present to hospital more frequently (2.88 *versus* 2.07 times). The significance of these differences is unclear and certainly cannot be extrapolated to any argument regarding the “causation” of asthma. Data from a number of studies indicate that asymptomatic infections with RSV are very uncommon while those with rhinovirus are common [30], suggesting that RSV is an important driver of symptoms, whereas pre-existing host factors may play a much greater role in symptomatic patients in whom rhinovirus is identified. In a related study by FRASSANITO *et al.* [31], it was reported that the stimulation of whole blood taken from infants with rhinovirus bronchiolitis was more likely to produce a T-helper cell type 2 (Th2) response based on interleukin (IL)-4/interferon- γ responses when stimulated with staphylococcal enterotoxin B than whole blood from those with RSV bronchiolitis. Whether this is due to differences in the host’s innate response or to pathogen differences remains unclear.

The question of whether respiratory infections in early childhood affect subsequent morbidity was addressed by VAN MEEL *et al.* [32] in a meta-analysis of 154 492 children from 37 birth cohorts assessing early-life respiratory tract infections and the risk of subsequent lower lung function and asthma. Associations of upper and lower respiratory tract infections (URTI and LRTI, respectively) by the age of 6 months, 1, 2, 3, 4 and 5 years with FEV₁, forced vital capacity (FVC), FEV₁/FVC, forced expiratory flow at 75% of FVC and asthma at a mean \pm SD age of 7 \pm 2 years were assessed using multilevel mixed effect models. Whereas both URTI and LRTI were associated with an increased risk for asthma (OR (95% CI) for URTI ranging from 1.25 (1.15–1.34) to 1.56 (1.47–1.66) and for LRTI ranging from 2.00 (1.85–2.10) to 3.72 (3.19–3.85)), only LRTI were associated with a lower lung function (Z-score (95% CI) ranging from –0.07 (–0.14––0.00) to –0.24 (–0.38––0.10)). These findings support a link between early-life respiratory tract infections and long-term respiratory morbidity.

The “protective” effect of traditional farming on the development of asthma is intriguing. PEKKANEN *et al.* [33] reported that exposure to cattle and determinants indicating microbial carriage from outdoors were found to be the strongest determinants of the protective microbial exposure. These data suggest that, in addition to diversity, farm-like taxonomic composition of the indoor bacterial/archaeal microbiota should be considered when assessing the “protective” effect of the farming environment on asthma development.

Relationship with bronchiectasis and primary ciliary dyskinesia

The importance of persistent bacterial bronchitis (PBB) of the lower airways in individuals without CF, a significant immunodeficiency or primary ciliary dyskinesia (PCD) is increasingly recognised [34, 35]. At a

session focusing on paediatric bronchiectasis, the key messages from the recently published ERS Task Force document that focused on this condition were presented [35], which highlighted the lack of information in many key areas including: 1) how to provide clear guidance to those in primary care to treat the condition early, before it becomes difficult to eradicate, while avoiding excessive use of antibiotics; 2) the optimal type and duration of therapy once the condition is suspected; and 3) how to develop more objective diagnostic tests that do not rely on response to treatment to make the diagnosis. Importantly, we do not have any prevalence data for any country or region in the world and do not fully understand the natural history of the disease if untreated. Although this disease has probably been a major source of morbidity for millennia, only now are we beginning to understand the nature of the bacterial–host interactions and the relationship with long-term structural pulmonary damage in the form of bronchiectasis [34–36].

Nontypeable *Haemophilus influenzae* (NTHi) is the most commonly isolated respiratory pathogen in studies addressing PBB with or without bronchiectasis. PCD is a well-established risk factor for the development of PBB and NTHi is again a common pathogen. LUCAS *et al.* [37] observed in studies utilising cultured nasal epithelial cells obtained from PCD and control subjects that the NTHi preferentially formed biofilms on and around cilia and that there were significant discrepancies in the response of epithelial cells from the PCD subjects and healthy controls when exposed to the pathogen, and speculated that these may contribute to the success of the pathogen in colonising the lower airways of such subjects. However, it is difficult to determine with such studies whether these are innate differences or are secondary to the disease process, possibly mediated through epigenetic changes. In a related study, SHOEMARK *et al.* [38] noted that patients with PCD demonstrated higher levels of inflammatory markers such as IL-1 β , IL-6, IL-10 and tumour necrosis factor (TNF)- α in their nasal cavities than both healthy “controls” and patients with CF. Not surprisingly, inflammatory cytokine levels correlated with the presence or absence of a respiratory pathogen.

In 2009, a consensus statement from the ERS Task Force on PCD recommended the use of nasal nitric oxide (nNO), electron microscopy (EM) and video microscopy as cornerstones of PCD diagnosis [39]. Data from 12 international cohorts on PCD, presented by HALBEISEN *et al.* [40], reported poor adherence to the 2009 consensus recommendations, due to the decrease in use of EM and the low use of test combinations, and suggest the need to implement the more recent evidence-based guidelines published by the ERS PCD Task Force [41]. Potential technologies to support diagnosis include a new portable nNO analyser (NIOX VERO nasal application; Circassia Pharmaceuticals Inc., Oxford, UK), which LUCAS *et al.* [42] reported can be used to differentiate patients with PCD from healthy individuals, and electron tomography (an extension of EM that produces high-resolution three-dimensional ultrastructural reconstructions), which SHOEMARK *et al.* [43] reported is effective in identifying defects that are difficult to identify using conventional EM. Indeed, the accuracy of currently available tests in PCD diagnosis remains sometimes questionable [41]. DELL *et al.* [44] reported that immunofluorescence microscopy together with 3DSIM super-resolution microscopy on airway epithelial cells was helpful to confirm or refute PCD diagnosis in seven cases where other testing methods were non-diagnostic. These results are compatible with the study of SHOEMARK *et al.* [45], which found immunofluorescence to be a highly specific, but not sensitive, diagnostic test for PCD. A practical clinical diagnostic questionnaire to identify patients requiring testing for PCD was presented by SNIJDERS *et al.* [46]. When PCD patients were confronted with “no PCD”, the presence of the disease was satisfactorily predicted (sensitivity 0.74, specificity 0.75).

Outcomes of PCD were addressed by LUCAS *et al.* [47], who reported that health-related quality of life decreases with age in patients with PCD. For all age groups, PCD was found to adversely affect physical, emotional and social functioning, and treatment burden.

Post-infectious bronchiolitis obliterans

SISMAN *et al.* [48] followed up longitudinally (median follow-up period 7.5 years, range 2–15 years) 15 children diagnosed with post-infectious bronchiolitis obliterans and treated appropriately. Measurements revealed that LCI was abnormal in 79%, spirometry in 47% and β_2 -bronchodilation (>12%) testing in 36%; diffusing capacity or transfer factor of the lung for carbon monoxide was within normal range in 90% and abnormal peak oxygen uptake was seen in only two children. It appears that the abnormal lung function tests do not reflect the degree of final functional loss.

Impact of host and pathogen genetics

Two studies reported apparent associations between infections and host genetic polymorphisms. AWASTHI *et al.* [49] from Lucknow, India, reported their findings from a study that included 350 infants and children aged 2–59 months admitted to hospital with severe radiologically confirmed pneumonia. They noted that those carrying the “A2” polymorphism in the IL-1 receptor antagonist (RA) gene had both

higher serum IL-1RA levels and adverse outcomes with empyema. TÖRMÄNEN *et al.* [50], exploring the long-term outcomes following acute bronchiolitis in an early infancy group, found that polymorphisms in the Toll-like receptor (TLR)1 and TLR10 genes were predictive of inhaled corticosteroid use at age 11–13 years, although no formal tests for asthma were included in the study.

Potential differences in two genotypes of *Mycoplasma pneumoniae* were explored in a study by RODMAN *et al.* [51] from Slovenia, which was able to identify 420 children in whom *M. pneumoniae* had been identified during an acute respiratory illness. The minority (n=110) infected with the type 2 genotype appeared to have slightly higher baseline C-reactive protein levels (33.7 versus 26.3 mg·L⁻¹) and hospitalisation rates (43.6% versus 32.9%) compared to those infected with the type 1 genotype, although the authors did note that the results were in contrast to their previous smaller study.

The suggestion that RSV subtypes could have an impact on disease severity has been the subject of a number of publications over a number of years. The latest contribution to this debate were data from NENNA *et al.* [52], who noted that in their samples, those with the RSV-A NA1 strain had more severe disease than those with other RSV-A strains, while RSV-B appeared to be more commonly identified in older infants, particularly those with a family history of asthma.

Prematurity and the lung

Preterm children remain at high risk for mortality and respiratory morbidities such as BPD and late respiratory disease (recurrent respiratory exacerbations, early wheeze, abnormalities of lung function and exercise tolerance). MORROW *et al.* [53] described antenatal determinants of these sequelae in a longitudinal prospective follow-up study. In a cohort of 587 preterm infants with a gestational age of <34 weeks and birth weights between 500 and 1250 g, perinatal information, assessments during the neonatal intensive care period and follow-up questionnaires until age 2 years were analysed. The researchers showed that both maternal smoking prior to the preterm birth and pre-existing hypertension increased the risk of having an infant with BPD two-fold.

The treatment of BPD includes home oxygen therapy (HOT) after discharge from hospital, a treatment modality addressed by data reported by PRAYLE *et al.* [54]. Maternal smoking history was associated with an additional 20 days of HOT and this effect was most marked in the group receiving HOT the longest; however, effects of postnatal exposure to cigarette smoke were not assessed.

The roles of passive and active smoke exposure ante- and postnatally on the development of early wheeze were described by VARDAS *et al.* [55]. Individual data of 27 993 mother–child pairs from 15 European birth cohorts were combined in pooled analyses taking into consideration potential confounders. Results showed that children with maternal exposure to passive smoking during pregnancy and no other smoking exposure were more likely to develop wheeze up to the age of 2 years (OR 1.11, 95% CI 1.03–1.20) compared with unexposed children. The risk of wheeze was further increased by children's postnatal passive smoke exposure in addition to their mothers' passive exposure during pregnancy (OR 1.29, 95% CI 1.19–1.40) and highest in children with both sources of passive exposure and mothers who smoked actively during pregnancy (OR 1.73, 95% CI 1.59–1.88). Numerous potentially effective tobacco control interventions have been studied [56, 57]. Smoke-free legislation is one of these interventions that has proven its effectiveness in different studies and there is a need to globally increase the uptake of these policies [57].

Mechanical ventilation in acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is one of the most problematic conditions to manage among all the mechanically ventilated patients on a (paediatric) intensive care unit. In a recent review article by GATTINONI *et al.* [58], the current problems associated with mechanical ventilation of adult patients with ARDS were discussed and a stepwise approach towards improvement of mechanical ventilation in preventing ventilator-induced lung injury was proposed. An important step would be to better define safety thresholds for the mechanical power normalised to functional lung volume and tissue heterogeneity. The potential of mechanical power is that it may be a single variable that unifies ventilator-related causes of lung injury. Although the role of mechanical power has been analysed in adults, studies in children are lacking. GUANZIROLI and co-workers [59, 60] investigated the role of mechanical power and its components in 50 adults and 11 children with ARDS and compared these findings to controls (30 adults and nine children). Higher mechanical power was found in children compared to adults and in children with ARDS compared to controls [59, 60].

Mechanisms of paediatric lung disease

LAUBE *et al.* [61] presented a study focused on factors involved in the interaction between the epithelium and the underlying mesenchyme during rat lung development. They showed a potential role for

neuregulin-1 β and leptin, two known factors produced and secreted by lung fibroblasts, in the regulation of the epithelial ion transporters cystic fibrosis transmembrane conductance regulator and epithelial Na⁺ channel (Na⁺ transport is essential for the liquid clearance at birth).

SHAHZAD *et al.* [62] showed that the complete inactivation of TNF-related apoptosis-inducing ligand (TRAIL) in mice, responsible for activating the apoptosis cell death mechanism, resulted in a decreased survival rate. Lung pathology was characterised by fewer but larger alveoli, and a large infiltration of inflammatory cells. The relevance of these data is that an inflammatory response to mechanical ventilation and oxygen exposure in the immature lung of newborn infants is linked to the development of chronic lung damage.

A potential therapeutic approach to BPD was presented by CHEN *et al.* [63], who examined the effect of interfering with the transforming growth factor (TGF)- β superfamily in mice. Administration of the ligand bone morphogenetic protein 9 in a neonatal rat model of oxygen-induced lung damage increased alveoli and reduced lung inflammation and fibrosis.

Two other animal studies focused on epigenetic regulation by miRNAs. CHAO *et al.* [64] examined the role of miR-154 in the control of branching morphogenesis and alveologenesis during lung development. They developed transgenic mice with an inducible miR-154 expression in lung epithelial cells, which resulted in increased alveolar airspaces but decreased septal thickness. They showed a significantly decreased expression of the mesenchymal growth factor fibroblast growth factor (FGF)10, again indicating the important cross-talk between epithelium and mesenchymal cells. Another miRNA, miR-135b, was identified as being dysregulated in the hyperoxia-induced mouse model for BPD by NARDIELLO *et al.* [65]. Treating the BPD mice with an antagonist to inhibit the function of miR-135b resulted in a moderate improvement of the pathology. At the molecular level, expression of one of the direct targets of miR-135b, Smad5, was completely restored by the treatment, indicating the importance of the TGF- β signalling pathway in this process.

MIZIKOVA *et al.* [66] presented analysis of the potential gene regulatory role of lysyl oxidases in mouse fibroblasts. These enzymes remodel the extracellular matrix (ECM), which is mandatory for cells to survive, and the ECM is recognised as an active component in the origin of lung diseases. Several target genes were found that are relevant to lung development and BPD. The role of the ECM was also investigated by CREMONA *et al.* [67], who reported on the effects of the ablation of the gene encoding the ECM protein tenascin C. Although there were significant effects on the development of the bronchial tree and the alveolarisation process, the knockout mice recovered from this developmental defect. However, ventilation of newborn knockout mice resulted in increased compliance.

Several other mouse studies were presented, aimed at analysing the fate and potential of specific cell populations during lung development. For example, EL AGHA and BELLUSCI [68] presented data on mice with an inducible CreERT2 inserted in the *Fgf10* gene, leading to expression of CreERT in the FGF10⁺ population. They showed that the cells that initially express *Fgf10* in the early stages of lung development later become either smooth muscle cells or lipofibroblasts [68, 69].

Omics in paediatric asthma

The symposium on “Omics in paediatric asthma and beyond” presented an update on current knowledge in terms of “omics” in childhood asthma by Victor Ortega (Winston-Salem, NC, USA), Silvia Carraro (Padua, Italy), Erika von Mutius (Munich, Germany) and Jean Bousquet (Montpellier, France). The overall conclusion of the talk “New insights on the genetics and epigenetics of paediatric asthma” was that genome-wide association studies for novel risk alleles and loci account for little of asthma prevalence. Linking associated variation to genes and pathways is the critical next step, and the goal of such studies is the translation of genetic study results to clinical care [70]. The talk “Metabolomics in paediatric asthma” defined “metabolomics” as the “analysis and interpretation of global metabolic data carried out *via* modern spectroscopic techniques and appropriate statistical interpretation”. The complexity of metabolic profiling was highlighted. For example, these “big datasets” may differ between a child with asthma and healthy controls, and vary with disease severity.

Another field of research that is developing rapidly is the analysis of the microbiota–host interactions in respiratory disease. Again, these analyses are complex, as illustrated by BIESBROEK *et al.* [71], who characterised upper respiratory microbiota profiles of a cohort of 60 healthy children at the ages of 1.5, 6, 12 and 24 months, and showed that early microbiota profiles change over time. The issue of data complexity was also discussed in the talk “The microbiome: a marker or driver of paediatric asthma?”, which concluded that, to date, most human studies show a rather small contribution of the microbiome to asthma development. Clearly much work remains to be done on the effect of normal development in order to confidently identify disease-specific “omics” profiles.

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