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SCIENTIFIC ASSEMBLY UPDATE

Paediatrics in Amsterdam

Ernst Eber*, Paul Aurora#, Karin C. Lødrup Carlsen¶, Anders Lindblad+, Jeannette E. Dankert-Roelse§, Robert I. Ross-Russell^f, Steve W. Turner, Fabio Midulla## and Gunilla Hedlin¶¶**

ABSTRACT: The aim of this update is to describe the paediatric highlights from the 2011 European Respiratory Society (ERS) Annual Congress in Amsterdam, the Netherlands. Abstracts from all seven groups of the ERS Paediatric Assembly (Paediatric Respiratory Physiology, Paediatric Asthma and Allergy, Cystic Fibrosis, Paediatric Respiratory Infection and Immunology, Neonatology and Paediatric Intensive Care, Paediatric Respiratory Epidemiology, and Paediatric Bronchology) are presented in the context of current literature.

KEYWORDS: Asthma, bronchoscopy, cystic fibrosis, epidemiology, lung function, respiratory infection

The 2011 European Respiratory Society (ERS) Annual Congress in Amsterdam, the Netherlands, included a large paediatric programme with numerous high-quality scientific presentations. For those colleagues who could not attend particular sessions, or even the whole Congress, this update will review the highlights of the abstracts presented by the Paediatric Assembly. These abstracts were selected by the Chairs from each of the paediatric scientific groups and are discussed in context of the current literature. Due to the large number of contributions to the Congress this summary cannot be comprehensive, but rather aims to address schemes of new research in major areas of paediatric respiratory medicine.

PAEDIATRIC RESPIRATORY PHYSIOLOGY

Forced oscillation

Several previous studies have reported changes in forced oscillation measures in asthmatic children following bronchodilatation [1], but there are limited data regarding such responses in health, and regarding relationships with asthma symptoms. SIMPSON *et al.* [2] presented data from 760 healthy children undergoing lung function testing using a commercial forced oscillation device. They described changes in the area under the reactance curve following bronchodilator, and calculated reference ranges that were related to baseline lung function, height and sex. ALBLOUSHI *et al.* [3] related forced oscillation changes with bronchodilator (resistance and reactance at 8 Hz) to baseline respiratory symptoms in children with mild asthma. Reactance changes after bronchodilator were significantly larger in those children reporting recent wheeze, whilst no difference was seen in resistance changes.

Plethysmography

In 1997, KLUG and BISGAARD [4] reported a method for measuring specific airway resistance (s*R*aw) plethysmographically in preschool children, utilising the one step calculation of DAB and ALEXANDER [5]. In this seminal paper, the authors investigated the effects of seating an adult in the plethysmograph with the child, breathing frequency and electronic compensation for phase shift in non-BTPS (body temperature (37°C) and pressure (generally same as ambient), saturated (47 mmHg)) conditions. COUTIER *et al.* [6] re-addressed the last of these questions in finding that s*R*aw measured during tidal breathing in young healthy children is significantly higher than when measured during panting manoeuvres. The authors hypothesised that software algorithms are unable to correct for thermal changes during tidal breathing as effectively as they can during panting.

There has been much progress in recent years in developing more detailed and sophisticated reference values for lung function measures from preschool years to adulthood [7], much of which is linked to the Global Lungs Initiative, which was founded with the support of the ERS (www.lungfunction.org). However, reference equations for infant lung function measurements remain limited due to paucity of data. NGUYEN *et al.* [8] reported plethysmographic data from 140 infants. They examined the relationships between tidal volume and respiratory compliance over a range

AFFILIATIONS
*Dept of Paediatrics, University Children's Hospital, Medical University of Graz, Graz, Austria.
¶Dept of Paediatric Respiratory Medicine, Great Ormond Street Hospital for Children, London,
**Dept of Child Health, University of Aberdeen, Aberdeen, and
^fDept of Paediatrics, Addenbrooke's Hospital, Cambridge, UK.
¶Dept of Paediatrics, Oslo University Hospital and the Faculty of Medicine, University of Oslo, Norway.
+Gothenburg CF centre, Queen Silvia Children's Hospital, Gothenburg, and
**Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden.
§Dept of Paediatrics, Atrium Medisch Centrum Parkstad, Heerlen, The Netherlands.
##Dept of Paediatrics, Sapienza University of Rome, Rome, Italy.

CORRESPONDENCE
E. Eber
Klinische Abteilung für Pulmonologie und Allergologie, Univ.-Klinik für Kinder- und Jugendheilkunde
Medizinische Universität Graz
Auenbruggerplatz 34/2
8036 Graz
Austria
E-mail: ernst.eber@medunigraz.at

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of age and body weight and concluded that simple correction for body weight is inadequate as it would result in an overestimation of predicted range for both parameters in the youngest infants and an underestimation in older infants. They suggested collecting a larger multicentre dataset to produce equipment-specific regression equations.

Multiple breath washout

A good volume of novel research from multiple breath washout (MBW) measurements has been published over the past decade [9]. A number of groups reported studies aimed at bringing this technique to the clinic, through the testing of two recently released commercial instruments. FUCHS *et al.* [10] described validation of an ultrasonic flow-sensor based commercial MBW system. They assessed accuracy of calculation of functional residual capacity (FRC) from nitrogen MBW using a novel lung model at a variety of FRC target volumes, using different respiratory rates and tidal volumes. Within-test repeatability of measurements was $<0.76\%$; mean difference between target FRC and measured FRC was 3.28%. The same authors, with further collaborators, reported feasibility and variability data using the same commercial equipment to collect lung clearance index (LCI) measurements in healthy children and adolescents at eight cystic fibrosis (CF) centres across Germany and Austria [11]. Intercentre variability was low at 2.9%, but overall success rates were disappointing at 75.5%. SINGER *et al.* [12] described bench validation of an alternative commercial nitrogen MBW instrument, also based on an ultrasonic flow-meter, but with a mainstream CO_2 sensor and a sidestream O_2 sensor. Again they used a lung model to measure a range of FRCs at varying tidal volumes and respiratory rates. The mean difference between measured and predicted FRCs in their study was 0.04%. VIKLUND *et al.* [13] reported MBW results from 10 adolescent and adult subjects with CF comparing the gold standard SF-6 mass spectrometer-based MBW system to an ultrasonic flow-meter nitrogen washout system. They used very similar software algorithms to calculate FRC and LCI from both instruments. While FRC values from the two instruments were similar, the N_2 LCI was significantly higher than the SF-6 LCI. On a related topic, LUM *et al.* [14] reported normal LCI data from 359 healthy subjects aged from birth to 19 yrs. Subjects were tested in London, UK, and Gothenburg, Sweden, using identical mass spectrometer hardware and software. The authors reported that LCI was constant from preschool years into adolescence, but significantly higher during infancy.

Cough and expiration reflexes

Forceful expiration in response to a stimulus can be subdivided into the cough reflex (CR), which is preceded by deep inspiration, or the expiration reflex (ER), a single expiratory effort [15]. The two reflexes are postulated to involve differing neural pathways, and to have different functions. VARECHOVA *et al.* [16] studied CR and ER in rabbits during different epochs of inspiration and expiration. In order to perform the study the researchers first had to demonstrate that ER could be elicited by a short, punctuate stimulus of the tracheal mucosa. They observed that CR incidence increased from 43% in early inspiration to 56% in late inspiration, but was almost absent in early expiration. Conversely, the incidence of ER increased throughout inspiration and further into early expiration, but then decreased into late expiration. The authors concluded that these different patterns during phases of breathing imply distinct control mechanisms.

Post-natal lung development

SCHULZ *et al.* [17] described an intrapulmonary deposition study in anaesthetised, intubated, spontaneously breathing rats. Aerosol concentration as a function of respiratory volume was determined by aerosol photometry. The highest deposition per breath was noted at the 35th post-natal day, being lower in both younger and older rats. This indicated that total deposition and deposition per unit time and surface area was higher in the developing rather than adult rat lung. The authors calculated that the equivalent developmental stage in human lungs would correspond to an age of 8 yrs and concluded that children at this age may, therefore, be more susceptible to airborne environmental health hazards.

Immune activation

Leukocyte-associated immunoglobulin-like receptor (LAIR)-1 is a collagen receptor that increases the threshold for activating signals on immune cells, thereby inhibiting immune activation [18]. HOUBEN *et al.* [19] measured airway compliance and resistance at age 1 month in 152 newborn infants and related this to LAIR-1 collected from amniotic fluid during labour and from cord blood. Amniotic fluid LAIR-1 was lower in children who wheezed at age of 6 and 9 months, and airway compliance and amniotic fluid LAIR-1 were positively correlated. This correlation did not change by adjustment for sex or maternal smoking. Airway resistance was not correlated. This study underscores the clinical impact of intrauterine immune activation.

PAEDIATRIC ASTHMA AND ALLERGY

Severe asthma

Severe asthma has received increased attention in past years, with a series of three review papers in the *European Respiratory Journal* describing clinical presentation [20], assessment [21] and pharmacological treatment [22] of severe asthma in childhood. MOSS *et al.* [23] reported omalizumab to reduce the required steroid dose in children $\leqslant 3$ yrs of age, with a corresponding improved quality of life. Whereas PITTS *et al.* [24], in a retrospective chart review, found severe side-effects in two out of 13 children (aged 9–17 yrs), with anaphylaxis and cardiomyopathy, respectively. FROST *et al.* [25] demonstrated that the use of a multi-disciplinary approach to assess severe asthma reduced the number of children eligible for omalizumab from 17 to seven out of 19 as modifiable factors were identified in the remaining children. The need for common approaches and definitions, collaboration to identify phenotypes and underlying mechanisms, as well as clinical trials of treatment options in this group of children was highlighted in the Paediatric Year in Review session at the ERS Congress. The higher burden of severe disease was recently confirmed in 6–12-yr-old children and a decrease in economic costs with improved control of disease was demonstrated [26].

Roles of allergy and infections

The individual contributions of allergy and viral infections in the initiation of asthma, as well as in asthma exacerbations, are still being debated. A randomised, controlled trial of 60 weeks of anti-immunoglobulin E treatment added to guideline asthma

medication improved asthma control and nearly eliminated the seasonal peaks of exacerbations in US inner-city adolescents and young adults with moderate or severe asthma [27]. This underpins the interaction between infections and allergen exposure in asthma development [28–30]. It is likely that deficiencies in anti-viral activity and epithelial barrier increase the susceptibility to severe respiratory infections in children with asthma [31]. After identification of impaired interferon production in mild-to-moderate asthma this has now also been demonstrated by EDWARDS *et al.* [32] in cultured bronchial epithelial cells from children with severe asthma. Allergy probably plays an important role in virus-triggered wheeze [29] and asthma development. The underlying mechanisms are unclear, but the eosinophil has been suggested as a common cell in allergy, asthma and viral infections [30]. In a mouse model of rhinovirus-induced asthma exacerbation, BARTLETT *et al.* [33] observed three different modes of allergen-virus interaction: allergen-induced, augmented by virus; virus-induced, augmented by allergen; and allergen and virus additive.

Asthma phenotypes

At present, there is still no agreement on how many phenotypes of asthma there may be in childhood, and how to identify them. The term ''wheeze'' in early life is a fuzzy phenotype [29], and does not necessarily represent asthma. Nevertheless, using advanced statistical methods, such as latent class analysis, temporal childhood phenotypes were identified in the first 8 yrs of life in two different cohorts (the British ALSPAC and the Dutch PIAMA birth cohorts) [34]. Despite remarkable similarities between the six and five classes identified, respectively, as well as their correlates with traits such as allergic sensitisation, lung function and asthma [34], this approach indicates classification based upon one criterion only. VAN DE KANT *et al.* [35] measured inflammatory markers in exhaled breath condensate and used a similar temporal approach to wheeze phenotypes (never, early-transient, intermittent and persistent); they found that children with intermittent and persistent wheeze at age 5 yrs had already had elevated inflammatory markers at preschool age, indicating augmented airway inflammation in these children. As yet, we have very limited knowledge of the onset and extent of remodelling in preschool children. In a biopsy study, O'REILLY *et al.* [36] demonstrated increased reticular basement membrane (RBM) thickness in preschool wheezers compared to controls. Follow-up at school age showed that children with and without asthma had similar RBM thickness in their preschool biopsies. However, children with increased airway smooth muscle in preschool age had a 10-fold increased risk of asthma at school age.

Very recently, various approaches were suggested to predict immunological correlates to varying phenotypes of asthma. In a publication from the US Severe Asthma Research Program it was suggested that intermediate asthma phenotypes could be predicted using bronchoalveolar lavage (BAL)-derived cytokines [37]. This proof of principle study used intermediate quantitative asthma phenotypes (determined by extreme values of BAL eosinophils and neutrophils, bronchodilator response to albuterol and methacholine sensitivity), testing five different statistical prediction models in order to identify multidimensional BAL cytokine profiles. Furthermore, JAMES *et al.* [38] found increased levels of the chitinase-like protein YKL-40 in children with severe asthma compared to healthy children, and suggested that serum YKL-40 might be a potential new biomarker of airway inflammation in children. In a study of children aged 6 yrs, SCHOOS *et al.* [39] suggested that exhaled nitric oxide fraction (F_{eNO}) and bronchial responsiveness are associated and continuous traits regardless of asthma, and that these surrogate markers should therefore be interpreted with caution in diagnosing asthma. Another study suggested that three clusters of patients had a complex interaction with three clusters of cytokines [40]. This work was performed in adults, but the approach is also highly relevant in paediatrics. The large EU-funded (FP7) MeDALL study was initiated in 2011 to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention and targets for therapy. The approaches rely on the applications of ''omics'' techniques (proteomics and metabolomics) with high-throughput measurement platforms integrated with biological and clinical data, largely from birth cohort studies throughout Europe [41].

Genetics and epigenetics

Genetic and epigenetic studies have provided some new insight into asthma susceptibility. Variation at the 17q21 asthma locus, encoding the ORMDL3 and GSDML genes, appears to specifically increase the risk for childhood-onset asthma [42]. Single nucleotide polymorphisms within several genes showed associations to asthma and obesity, but none of these associations were significant after correction for multiple testing [43]. Gene–environment interactions were demonstrated in different populations, with an interaction between tobacco smoke exposure and the alpha subunits of the nicotinic acetylcholine receptor for bronchial hyperresponsiveness in children [44]. Furthermore, the effect of day care on sensitisation and atopic wheezing was reported to differ in children with different variants of the Toll-like receptor 2 gene [45]. BUKVIC *et al.* [46] reported endotoxin exposure to be associated with a decreased risk of asthma in the whole population of investigated Croatian children but the effect of endotoxin exposure on asthma was found to differ among children with different variants of the *MD-2* gene. Recent epigenetic studies have found DNA methylation in ARG1 and ARG2 to be associated with F_{eNO} in children with asthma, thereby suggesting a possible role for epigenetic regulation of nitric oxide production [47]. Increased CD14 methylation from 2–10 yrs of age in children from a Norwegian birth cohort was found to be inversely correlated with soluble CD14 levels at 10 yrs of age [48]. The role of epigenetic mechanisms in early life exposures, particularly during *in utero* life, was recently reviewed [49] and is likely to gain further attention in the next few years.

Asthma management

Managing asthma involves control of the disease by pharmacological, as well as other, measures. Ciclesonide has recently been approved for children $\geqslant$12 yrs of age in many countries, and being a pro-drug has a proposed beneficial effect to side-effect ratio, with demonstrated effects on asthma control in adults [50]. In line with the latter study, in a large multicentre study in preschool children, BRAND *et al.* [51] found a modest reduction of exacerbation rates and improved lung function with ciclesonide.

Several studies have recently reported improved asthma control and reduced severity of disease in programmes of patient education [52–54]. This was also highlighted by SHEIKH *et al.* [55] with a study showing the need to train the trainers and by BIRD *et al.* [56] with a systematic review of the underlying reasons for barriers to asthma management. Programmes have been tested in low-income, inner-city environments with effects in children [57], and education appears to be effective in improving asthma control and preventing acute exacerbations in adolescents [53], although written action plans did not appear to significantly improve asthma control [58]. Furthermore, children with allergic diseases are at a disadvantage in day-care and schools. There is a general lack of knowledge and systematic approach to ensure medical facilities as well as relevant adjustments to secure the environment for children with allergic diseases. This has recently been investigated by a Task Force report on how to manage the allergic child at school [59].

CYSTIC FIBROSIS

New treatments

During the past years huge efforts have been made in developing new types of drugs to treat the basic defect in cystic fibrosis (CF), called CFTR potentiators and correctors. In a late-breaking abstract, PLANT *et al.* [60] reported that VX-770 (a CFTR potentiator) in a phase III trial including patients with the G551D mutation where CFTR is expressed on the apical surface but does not function properly, increased forced expiratory volume in 1 s (FEV_1) by 10.4% at week 24 and 10.1% at week 48 in the treatment arm while the placebo group was unchanged. The risk of pulmonary exacerbations decreased by 55%, and sweat chloride decreased by 48 $mmol \cdot L^{-1}$ through week 48 [61]. These are very exciting and promising results for all patients with this type of mutation. At present, no more information has been published regarding the ongoing phase III clinical trial with PTC124 in patients with premature stop codons [62]. Denufosol, a P2Y2 receptor agonist that activates alternative chloride channels, had previously shown promising results in phase II studies [63]. Unfortunately, this drug failed in a phase III trial and the project has now been halted. Studies of other drugs aiming to overcome the degradation of CFTR in class 2 mutations, such as deltaF508, are ongoing.

Mannitol, a sugar alcohol, functions as a hyperosmolar agent and is presently used for bronchial provocation testing. By creating an osmotic gradient it is thought to facilitate water movement into the lumen of the airways, increasing the water content in the airway surface liquid and thereby improving mucus clearance. A phase III study has shown a significant improvement in FEV_1 and pulmonary exacerbation rate during a period of 26 weeks, independent of rhDNase usage [64]. Mannitol (Bronchitol®) was approved by European Medicines Agency for use in patients aged $\geqslant$18 yrs as an add-on therapy to best standards of care as of October 2011.

As free elastase is thought to be a major cause of the development of bronchiectasis in CF [65], neutrophil elastase inhibitors could be a potential way to influence the progression of CF lung disease. There are now such substances available.

Lung function and imaging

It is difficult to monitor early CF lung disease. FEV_1 is not sensitive enough to mirror the progression of early lung disease and the correlation between FEV_1 and structural lung damage is poor. Another problem is the difficulty to measure lung function in children aged <5–6 yrs. In younger children, MBW to measure the LCI and the raised volume rapid thoracic compression technique measuring $FEV_{0.5}$ can also be used [66]. LCI reflects the degree of ventilation inhomogeneity in the peripheral airways where pathology starts in CF. High-resolution computed tomography (HRCT) may detect early structural lung damage in children with CF [67]. The place for these methods and parameters in routine care and as end-points in studies is presently discussed. THIA *et al.* [68] performed MBW and raised volume techniques in CF babies diagnosed by newborn screening (NBS) and healthy controls at age 3 months and 1 yr. They found an improvement at 1 yr in both LCI and $FEV_{0.5}$ and also in nutritional status, showing a satisfying effect of standard therapy. SIMPSON *et al.* [69] assessed the impact of pulmonary infection and the presence of free neutrophil elastase as a marker of airway inflammation on ventilation distribution in infants and young children with CF. They could not find an association between LCI and infection or inflammation but reported moment ratios to be more sensitive to lung disease associated with infection than LCI. LINDBLAD *et al.* [70] compared mean LCI at age 1–4 yrs with LCI, FEV_1 and chest radiograph abnormalities (Northern score) at 7 yrs of age. Increased LCI in the preschool years only correlated with Northern score, *i.e.* with the degree of structural lung changes at 7 yrs of age.

In children with CF aged 1–5 yrs, MOTT *et al.* [71] showed that the presence and extent of bronchiectasis is underestimated with expiratory scans alone compared with inspiratory scans. Therefore, it appears one can neither lower the radiation dose nor avoid the anaesthesia needed for an inspiratory scan in small children. Magnetic resonance imaging (MRI) does not involve radiation but its sensitivity to detect early CF lung disease has been questioned previously [72]. EICHINGER *et al.* [73] reported that MRI of the lung is sensitive to detect abnormal morphology, function and response to therapy in early CF lung disease, and suggested that MRI may be suitable for non-invasive diagnostic monitoring of disease severity and may serve as a novel end-point for clinical trials in early CF lung disease.

Airway infection

Aspergillus fumigatus is a common microorganism in CF sputum and BAL fluid. Apart from causing allergic bronchopulmonary aspergillosis there is growing evidence that *A. fumigatus* can also have a direct negative effect on lung function. In a retrospective study from the same group, THURSFIELD *et al.* [74] and ADAMS *et al.* [75] found that *A. fumigatus* in the airways of CF children, whether identified on direct smear or culture, is associated with worse lung function, despite the use of significantly more intravenous antibiotics in the group with *A. fumigatus* as compared to the one without. VANDERHELST *et al.* [76] underlined the increasing prevalence of chronic infection with Methicillin-resistant *Staphylococcus aureus* in CF patients and showed an association with a particular genotype and a larger decline in lung function.

Several abstracts also reported an increasing prevalence of *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* in CF patients indicating that it is a growing clinical problem [77–79]. ASHEROVA *et al.* [80] showed a high prevalence of *Achromobacter* in the toilets and sinks of an infectious ward, stressing that hygienic measures are to be improved. The authors suggested, but did not prove, a possible transmission route from the hospital environment and personnel hands to the patients.

Rhinovirus, like other viruses, has been shown to trigger pulmonary exacerbations and has been associated with impaired virus clearance from CF airway epithelium [81]. KIENINGER and co-workers [82, 83] reported evidence for an impaired early innate anti-viral response in cultured CF airway epithelial cells and also compared prevalence and the load of rhinovirus in BAL fluid from children with CF, non-CF bronchiectasis, asthma and healthy controls. They found a higher prevalence in CF compared to the other groups and also the highest load of rhinovirus, especially in children with an active exacerbation at the time of the BAL, and suggested a possible role for rhinovirus in CF lung disease progression.

To improve quality of life in patients with CF it is important to decrease the number of exacerbations or start treatment early. By home monitoring FEV_1 three times per week, ROBROEKS *et al.* [84] were able to detect an exacerbation 10 to 4 days before it became clinically evident.

To evaluate the effect of NBS on the clinical status of the patients later in life, a follow-up of the patients born in the 3 yrs prior to when NBS started in 1981 in New South Wales (Australia) and the 3 yrs after was performed by DIJK *et al.* [85]. The children showed significantly lower *Pseudomonas* colonisation, better lung function and nutritional state at the time of transfer to the adult clinic at 18 yrs of age for the patients diagnosed by NBS.

Diagnosis and care

Nasal potential difference has been used in diagnostic algorithms for diagnosing CF where routine tests have not been conclusive. COHEN-CYMBERKNOH *et al.* [86] evaluated the use of rectal biopsies for intestinal current measurement as a method to discriminate between CF and non-CF patients. The group found intestinal current measurement discriminative and recommended more studies to confirm their results.

Finally, as a very important reminder of the unequal CF care across Europe, DRACEA *et al.* [87] reported the outcome from a centre in Romania and the impact of lack of funding. To help to overcome these outcome differences is a huge task but of extreme importance for the ERS.

PAEDIATRIC RESPIRATORY INFECTION AND IMMUNOLOGY

Bronchiolitis and pneumonia

Endogenous, as well as exogenous, factors in common respiratory infections such as bronchiolitis and childhood pneumonia were discussed at the 2011 ERS Congress.

Wheezing is a common symptom in young children and young children are prone to bacterial infection. Combining these two facts has led to the hypothesis that positive bacterial cultures might be associated with wheezing episodes in young children independent of viral infections [88]. How bacteria may contribute to the development of preschool wheeze is largely unknown. VAN DE KANT *et al.* [89] investigated whether a cohort of preschool children with recurrent wheeze differed from healthy controls in bacterial colonisation in the upper respiratory tract and in pro-inflammatory markers in exhaled breath condensate. They found no evidence for an association between bacterial colonisation or infection and preschool recurrent wheeze [89].

There has been a long-standing hypothesis that vitamin D deficiency might be associated with an increased susceptibility for respiratory tract infections (RTIs), because vitamin D plays an important role in modulating the innate immune response against infections [90]. PILLAI *et al.* [91] showed in their systematic literature review that low vitamin D levels are strongly associated with an increased risk of acquiring acute RTIs, both viral and bacterial, and with increased RTI-related morbidity. Two intervention studies have suggested a protective effect by vitamin D supplementation in both toddlers and school age children [92, 93].

Respiratory syncytial virus (RSV) bronchiolitis is a major cause of infant morbidity and mortality. In earlier studies a beneficial effect of nebulised hypertonic saline in infants with moderate acute bronchiolitis has been reported [94]. At the ERS Congress, TEUNISSEN *et al.* [95] and NENNA *et al.* [96] presented rather disappointing results. The two studies, both appropriately powered, showed no effect of 7% or 3% hypertonic saline given by inhalation to infants hospitalised for moderate acute bronchiolitis on duration of hospital stay or clinical scores. Therefore, it remains questionable as to whether nebulisation of hypertonic saline should be introduced as a standard treatment option for infants hospitalised for moderate acute bronchiolitis.

The increased risk for a severe course of RSV bronchiolitis in prematurely born infants is well known [97]. In a large cohort, BUESCH *et al.* [98] assessed the independent risk of respiratory distress syndrome (RDS) on hospitalisation for a lower RTI and found that late preterm infants with RDS at birth are five times more likely to be hospitalised during the first year of life compared to late preterm infants without RDS. The costs of such hospitalisations are considerable. SHEFALI-PATEL *et al.* [99] showed that the adjusted mean difference in costs of care in late preterm babies with RSV lower RTI was £11,116 compared to infants without respiratory problem. As no effective treatment options are currently available for acute viral bronchiolitis, prevention will be the most effective cost-reducing factor.

Primary ciliary dyskinesia

Electron microscopy is often considered as the gold standard for diagnosing primary ciliary dyskinesia (PCD) [100]. In a cohort of paediatric PCD patients, NAUTA *et al.* [101] showed that in 29% of patients with PCD (proven by other diagnostic methods, including light microscopy and epithelial cell cultures) electron microscopy findings were completely normal. The authors concluded that a diagnosis of PCD cannot rely on a single technique, and thus recommended to combine at least two diagnostic techniques and that epithelial cell

cultures should be an integral part of the diagnostic work-up. It is believed that in the future genetic studies may further improve diagnostic accuracy.

NEONATOLOGY AND PAEDIATRIC INTENSIVE CARE

Neonatology

Neonatal resuscitation remains an area of increasing interest. The use of bag valve mask devices in the delivery room and neonatal intensive care unit has been under scrutiny. HARTUNG *et al.* [102] showed that different devices will provide different levels of pressure and flow to infants, depending on factors such as the leak. At a practical level this emphasises the care with which mask ventilation should be administered as different models can deliver quite different pressures and flows.

In a case–control study, GOROVENKO *et al.* [103] reviewed the angiotensin-converting enzyme (ACE) genotype in infants with severe perinatal asphyxia. Their data suggested that a DD genotype for ACE was much more common in severe birth asphyxia. Whether this reflects that such patients are at greater risk of hypoxic injury is unclear.

Historical use of pressure-controlled ventilation, used in part due to the difficulties of accurate volume control at low volumes, may give rise to excessive tidal volumes. CHOWDHURY *et al.* [104] reported that pressure-limited ventilation in infants born at or near term frequently results in volumes outside the normal tidal range, and that even within that range work of breathing may be increased at lower volumes. Modern ventilators can control volume in even very preterm infants and may reduce the risk of volutrauma and barotrauma. An important aspect of barotrauma relates to the infants' spontaneous respiratory pattern during mechanical ventilation. CHOWDHURY *et al.* [105] evaluated spontaneous respiratory effort in a group of ventilated infants receiving either synchronised intermittent mandatory ventilation (SIMV) or intermittent positive pressure ventilation (IPPV). In those on SIMV, most (75%) showed active expiration, with a further 20% showing synchrony. For non-synchronous ventilation (IPPV) the pattern was different with 50% of the patients showing a prolonged expiratory phase. Understanding the different patterns of breathing associated with different ventilator settings should help clinicians better understand the risks of complications such as pneumothorax or other barotrauma.

The organisation of neonatal services in rural areas can be complex. BHANDARI *et al.* [106] presented a model adopted in Nepal that acted as a very useful guide to the benefits of geographically defined resource allocation. Clear pathways and a focus on local training are essential. For those that require air transport, WITHERS *et al.* [107] investigated 141 infants to assess the predictors of in-flight hypoxia. Depressingly, post-menstrual age, weight and sex were all non-predictive of hypoxia which appeared to be rather idiosyncratic. Staff should be prepared to administer oxygen for most infants, despite the logistical problems that this creates.

Further evidence of the long-term complications of neonatal lung disease continues to be evident. It has been shown that the respiratory burden of prematurity is probably bigger than previously thought [108]. Infants born only moderately premature (32–36 weeks gestation) were shown to have an increased incidence of respiratory morbidity, and this increased with increasing prematurity. CHOUKROUN *et al.* [109] have similarly found a high percentage (60%) of school age children who were born at <32 weeks gestation with respiratory symptoms, and 54% of them had impaired lung function. In contrast, LIDBERG *et al.* [110], who investigated forced expiratory flows in 150 preterm and 100 term infants, found decreased flows in infants <32 weeks gestation (with increased risk of hospitalisation for RSV positive bronchiolitis) but similar expiratory flows in moderately preterm as compared to term infants.

Paediatric intensive care

At the other end of the spectrum, end of life issues in children and young adults with chronic respiratory conditions is an area that is often overlooked. In late stage CF, there is some evidence that CT scanning may provide prognostic information although the variability between patients remains high [111]. Different patterns of injury may be seen from infection/inflammation dominated to air trapping and hyperperfusion. There is considerable overlap between these in individual patients with different areas of the lungs showing different patterns, and the implication of these changes remains uncertain. Oxygen therapy in late stage disease has never been effectively shown to help, but a recent study concluded that overnight hypoxia is associated with more daytime symptoms [112]. This would suggest that administration of oxygen may have benefits in these patients beyond the maintenance of good saturations. Symptom assessment overall is probably inadequate in end-stage lung disease. Data from CF patients shows a substantial underestimation [113]. Major areas of undiagnosed problems include pain (especially chest pain in the late stages of disease) and bowel problems (both diarrhoea and constipation). Asking questions about these symptoms as part of a ''symptom control'' approach should be an important part of care.

BRUIJN *et al.* [114] presented data on children with acute lung injury. In a group of 98 ventilated patients, increased C-reactive protein (CRP) levels were associated with increased mortality. Even after correction for cardiovascular organ failure, a 10 $mg \cdot L^{-1}$ increase in CRP was associated with an increase in risk of mortality of 5%.

Outcomes following lung transplantation in children continue to steadily improve [115]. There remains a mismatch between the number of children requiring transplants and the number of available donors, meaning that alternative approaches, such as donation after cardiac death, are being investigated [116].

PAEDIATRIC RESPIRATORY EPIDEMIOLOGY

Prematurity and reduced lung function

The ALSPAC group has recently described the relationship between post-natal weight gain and respiratory outcomes among infants born with gestation appropriate weight [117]. KOTECHA *et al.* [118] applied their large dataset to address the issue of ''late preterm birth'' and reported that children born at 33–34 weeks gestation (but not 35–36 weeks) have significantly lower lung function values at 8–9 yrs of age similar to the decrements observed in the 25–32-week group; most of these differences were reduced by 14–17 yrs of age. An association

between extremely premature delivery and reduced spirometry in childhood is well-established. VOLLSAETER *et al.* [119] reported that this association persists into early adulthood. VOGT *et al.* [120] used a whole population dataset to relate gestation to prescription of inhaled corticosteroids and reported that there was a 10% increase of inhaled corticosteroid usage in 6–19 yr olds born at 37–38 weeks compared to those born at 39–41 weeks, and an odds ratio of >2 for those born at 24–28 weeks. In summary, gestation may be a more important determinant than birth weight for respiratory outcomes and the risk of life-long respiratory morbidity associated with ''short'' gestation may first emerge at 38 weeks.

Age at onset of reduced lung function

Some studies found childhood asthma to be associated with very early abnormalities in physiological measurements [121] but others did not [122]. DUIJTS *et al.* [123] related physiological measurements to phenotypes, and this extended their previous work relating wheezing pattern to six phenotypes by latent class analysis [124]. In adolescence, the most profound abnormalities were present in those with onset of wheeze after the age of 18 months and persistent wheezing [123]. These findings are consistent with those from MULLANE *et al.* [125] who were able to demonstrate that the persistent wheeze group already had reduced lung function at 1 month of age. VAN DER GUGTEN *et al.* [126] related infant lung function to later wheeze and found increased total respiratory resistance preceded early wheeze and reduced compliance preceded persistent wheeze at 5 yrs of age. TURNER *et al.* [127] and SONNENSCHEIN-VAN DER VOORT *et al.* [128], both relating fetal ultrasound measurements to respiratory outcomes, provided further evidence to support the concept that lung function is determined at an early stage of development. In the study by TURNER *et al.* [127], persistent low growth in the first and second trimesters was associated with reduced lung function and increased risk for asthma. SONNENSCHEIN-VAN DER VOORT *et al.* [128] reported that fetal growth restriction from the second trimester to birth was associated with increased wheeze, particularly in association with post-natal ''catch up'' growth. In summary, the evidence presented indicated that reduced lung function and associated symptoms appear to be determined in early life.

Post-natal exposures and reduced lung function

Although lung function may be determined by antenatal factors, early post-natal exposures are also important but can be more challenging to assess, factors include: infection [29], and inhaled [129] and dietary exposures [130]. STRIPPOLI *et al.* [131] modelled ambient air quality throughout childhood and performed spirometry in children aged 9–13 yrs. They found that early exposure to inhaled particles with a 50% cut-off aerodynamic diameter of 10 μm was associated with reduced forced vital capacity but no other spirometric indices. DOGARU *et al.* [132] related breast feeding to alveolar size using MRI technology. Although the study was underpowered there was evidence of an interaction where breastfeeding offset the reduction in lung volumes associated with maternal asthma. In a cross-sectional study, WONG *et al.* [133] found indoor endotoxin exposure to be positively correlated with wheeze. In summary, these studies demonstrate how new methods might be used to understand the relative importance of post-natal factors in the development of asthma. To further complicate the analysis, it is likely that the effects of these exposures may be modified by other exposures (*e.g.* second-hand tobacco smoke) and atopy [134].

Respiratory symptoms in infancy

The epidemiology of infant respiratory symptoms has been relatively neglected and the multinational EISL group (''Estudio Internacional de Sibilancias en Lactantes'') presented two papers on this subject. GARCIA-MARCOS *et al.* [135] considered latitude to modify risk or protective factors for respiratory symptoms. For example, they reported how the apparent protective effect of breastfeeding was greater for infants native to countries of higher latitude (North or South) compared to their equatorial peers. In a second paper, GARCIA-MARCOS *et al.* [136] reported early respiratory infection to be the risk factor most strongly linked with early wheeze across all centres. In Latin American centres, breastfeeding was protective against early wheeze and, in Europe, reduced socioeconomic status and eczema increased the risk for wheeze. STRIPPOLI *et al.* [137] reported cough prevalence in infancy and its outcome. Cough prevalence was 17% in infancy, persisted in many individuals and remained at 12% for children aged 9 yrs. Infancy may include a critical window where exposures influence the developing respiratory system, and exposures may differ between populations.

PAEDIATRIC BRONCHOLOGY

Technique and indications

Flexible airway endoscopy is a standardised and important diagnostic tool for evaluating respiratory disorders in children [138]. The most frequent indication for bronchoscopy in children is the presence of chronic respiratory signs or symptoms, such as stridor and wheezing [138]. Recurrent or persistent pneumonia represents another indication for airway endoscopy. GOKDEMIR *et al.* [139] performed a retrospective study in children who underwent flexible airway endoscopy for recurrent or persistent pneumonia. They reported that an underlying aetiology could be identified in 32% of the patients, the most frequent being foreign body aspiration (12%) and congenital airway anomalies (9%). Even though recurrent pneumonia is a well-established indication for bronchoscopy, this study is one of the first to provide evidence in a large cohort of patients that this technique is diagnostically useful in this indication.

Chronic cough is another indication for bronchoscopy in children. Again in a retrospective study, DOUROS *et al.* [140] evaluated children with chronic wet cough and compared the effectiveness of flexible bronchoscopy and HRCT in detecting airway abnormalities. They reported that HRCT can detect airway wall thickening and bronchiectasis, and that the severity of the findings correlated positively with the duration of the clinical symptoms and the intensity of neutrophilic inflammation in the airways. As HRCT scanning was less sensitive than flexible bronchoscopy in detecting airway abnormalities, it was suggested that the two modalities should be considered complementary for evaluating prolonged wet cough. This study confirms previous studies showing that

bronchoscopy is an important diagnostic technique for evaluating children with chronic wet cough [141].

The availability of smaller bronchoscopes has expanded the range and indications for this technique in neonates and premature babies. In symptomatic preterm infants who were intubated at birth MONDEJAR-LOPEZ *et al.* [142] diagnosed abnormal endoscopic findings in all infants. The most common were airway malacia (59%), followed by laryngotracheal cyst or granuloma (45%), left vocal cord paralysis (33%), subglottic stenosis (30%), supraglottic oedema (21%), and tracheal stenosis (7%). This study confirms a previous report demonstrating the importance of this technique in preterm infants with respiratory symptoms who were intubated after birth [143].

Special procedures

Several special procedures can be performed through the working channel of the flexible bronchoscope [138]. BAL is a useful technique to increase the diagnostic yield of flexible bronchoscopy for clinical and research purposes [144]. MONDEJAR-LOPEZ *et al.* [145] described the incidence of positive bacterial cultures in BAL fluid from children with chronic respiratory symptoms and assessed the differences between children with and without bronchiectasis. The most common bacteria were *Haemophilus influenzae* and *Streptococcus pneumoniae*, followed by *S. aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. While a positive bacterial culture in BAL fluid was found to be more common in children with bronchiectasis, the role of bacteria in other non-suppurative lung diseases should also be taken into account. This study underlines the importance of obtaining BAL cultures during flexible bronchoscopy, especially in children with chronic respiratory symptoms.

In a study designed to investigate whether BAL eosinophilia could identify specific clinical phenotypes of asthmatic and/or atopic children, SNIJDERS *et al.* [146] analysed BAL fluid and bronchial biopsies from 107 children. Children with high eosinophil counts in BAL fluid also had high eosinophil counts in the tissue. BAL eosinophilia was observed in 16% of the children and severe eosinophilia in 7.5%. Atopic asthmatics were more frequent in the so-called intermediate and severe eosinophilic groups, non-atopic asthmatics were equally distributed, and atopic children without asthma were observed in both the non-eosinophilic and severe eosinophilic groups. This study is important because it adds new information on lower respiratory inflammation not only in children with various asthmatic phenotypes, but also in atopic children without asthma.

Biopsy specimens can be taken from the mucosa, endobronchial lesions or lung parenchyma [138]. Unfortunately, due to the small sizes of the working channels of the paediatric bronchoscopes the material obtained with transbronchial biopsies is often insufficient. In a retrospective study, DE MIR *et al.* [147] reviewed 137 transbronchial biopsy samples, of which 25 were disregarded due to lack of information. In 22 procedures, a 3.6-mm flexible bronchoscope was used and in the rest a 4.9-mm instrument. 100 (90%) biopsies were considered adequate (91% of the biopsies taken with the 1.8-mm forceps and 63% taken with the 1.1-mm forceps). In the non-transplant population, the biopsies were diagnostic in 75% of the patients. The most frequent complications were bleeding (17%), pneumothorax (4.5%) and bronchospasm (3%). The investigators concluded that transbronchial biopsy through the flexible bronchoscope is a relatively safe and effective method for diagnosing and monitoring lung diseases in selected children. The 3.6-mm bronchoscope and 1.1-mm forceps performed poorly; thus, it was suggested to use the 1.8-mm forceps whenever possible. This study confirms previous reports that recommended use of an adult or rigid bronchoscope whenever feasible in order to achieve a higher diagnostic yield [148].

Suspected foreign body aspiration is a major indication for flexible airway endoscopy in children, especially because physical examination and radiology are often poorly sensitive. MODARESI *et al.* [149] retrospectively reviewed 188 paediatric patients with a history suggestive of foreign body aspiration and reported confirmation of foreign body aspiration in 112 (60%) children. They concluded that bronchoscopy should be performed in all children with a positive history of choking, even in the presence of a normal physical examination. This study confirms previous reports demonstrating that neither physical examination nor chest radiograph findings are sufficiently sensitive or specific [150].

In conclusion, many interesting and promising results were reported, emanating from studies performed in children. These studies will be even more important as the awareness of the relationship between lung growth, childhood airway and lung diseases and respiratory diseases in adulthood increases [151].

STATEMENT OF INTEREST

A statement of interest for K.C. Lødrup Carlsen can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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