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SCIENTIFIC ASSEMBLY UPDATE

Paediatrics in Vienna

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ABSTRACT: The aim of this article is to describe the paediatric highlights from the 2009 European Respiratory Society Annual Congress in Vienna, Austria. The best abstracts from the seven groups of the Paediatric Assembly (asthma and allergy, respiratory epidemiology, cystic fibrosis, respiratory physiology, respiratory infections and immunology, neonatology and paediatric intensive care, and bronchology) are presented alongside findings from the current literature.

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

The 2009 European Respiratory Society (ERS) Congress in Vienna, Austria, included a large paediatric programme, with many high-quality scientific presentations taking place. Herein we will present an overview of the highlights of the abstracts presented by the Paediatric Assembly. The abstracts were selected by the ERS Officers from each of the paediatric scientific groups and are set in the context of contemporary paediatric respiratory literature.

PAEDIATRIC ASTHMA AND ALLERGY

Preschool wheeze

In 2008, the ERS Task Force Report on the ''Definition, assessment and treatment of preschool wheeze'' was released, highlighting the importance of distinguishing episodic viral wheeze (EVW) from multiple trigger wheeze (MTW) [1]. A study from the UK showed that lung clearance index, conductive airways inhomogeneity and specific airways resistance showed more abnormalities in children with MTW than in children with EVW and healthy controls [2]. These differences in lung function support the notion that different phenotypes, such as EVW and MTW, can be distinguished within the whole group of preschool children with wheezing. However, it has been demonstrated that wheezing phenotypes in young children are unstable over time, and that individual patients may change from EVW to MTW and *vice versa* [3]. Whether such changes are accompanied by changes in lung function remains to be seen.

Another study from the UK showed that eosinophils in bronchoalveolar lavage (BAL) fluid were present in young children before they developed symptoms of persistent wheeze [4]. In a large population-based survey, the exhaled fraction of nitric oxide (F_{ENO}) at age 4 yrs was associated with asthma symptoms that persist up to the age of 8 yrs [5]. These results suggest that airways inflammation is important in the development and persistence of chronic wheeze, even in young children. However, this may only be true at group level. In a follow-up of their study showing inflammatory changes in mucosal biopsies of children with MTW [6], TURATO *et al.* [7] showed that the type and degree of inflammation in airway mucosal biopsies in preschool children could not predict remittance or persistence of wheeze over time. Therefore, in individual patients it is impossible to predict which young children with wheeze will continue to wheeze, and in whom wheeze will disappear over time. Although some variables are related to the persistence of wheeze over time, different prospective cohort studies have now shown that the prognostic value of these predictors is insufficient to allow for a reliable prediction of wheeze outcome in individual children [8–10].

Although it is well-established that approximately two thirds of wheezy preschool children have ceased to wheeze by the age of 6 yrs [11], the extent to which wheeze disappears over time has not been well studied in school-aged children and adolescents. Data from the Isle of Wight birth cohort now show that 30% of 4-yr-old wheezy children no longer wheeze at the age of 10 yrs [12]. At a population level, the presence and the pattern of wheeze is variable from birth throughout the first 10 yrs of life.

Asthma in school-aged children and adolescents

Over the past year, two large studies have shown that F_{ENO} monitoring in childhood asthma does

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not improve clinically relevant asthma outcomes in children [13, 14]. A large birth cohort study showed that at population level, F_{ENO} is more a marker of atopy than of asthma [15]. In this study, mean F_{ENO} levels were highest in atopic asthmatics and atopic nonasthmatics, but comparable in nonatopic asthmatics and healthy nonatopic controls [15]. These findings, which are in accordance with a recent study from the USA [16], may partly explain the disappointing results of F_{ENO} monitoring studies.

Because it would be intuitively appealing to monitor airway inflammation as the key pathophysiological mechanism in asthma, the search for other noninvasive markers of airway inflammation in children continues. Researchers from the Netherlands assessed profiles of volatile organic compounds (VOC) in exhaled air in a 1-yr follow-up study of 40 children with asthma, and showed significant changes in VOC patterns in children whose asthma exacerbated during this study period [17]. A collaborative study from the UK and the Ukraine using high-resolution ultrasonography of the brachial artery in children with asthma showed a dose-dependent relationship of endothelial dysfunction to forced expiratory volume in 1 s (FEV_1) values [18].

Viruses remain of interest as triggers of asthma flare-ups in children. In a Spanish study of 446 children hospitalised for acute wheezing, a causative virus was identified in 67.7%, in particular respiratory syncytial virus, rhinovirus, adenovirus, human bocavirus and human metapneumovirus [19]. In a collaborative study from Australia and Wisconsin (USA), rhinovirus was responsible for as much as 85% of acute asthma exacerbations. The use of a new PCR technique allowed these workers to identify several new human rhinovirus strains in these patients [20].

The importance of allergic rhinitis as an important comorbid condition in childhood asthma was not only addressed in a specific symposium during the ERS Annual Congress, but also in a number of original contributions. Dutch workers showed that 74% of children with asthma also had allergic rhinitis, which had not been recognised or treated in 37%, and which had a significant impact on asthma control questionnaire scores [21]. The concurrence of asthma and allergic rhinitis was also found in the Isle of Wight study [22], where allergic rhinitis doubled in prevalence during adolescence, and had a major impact on quality of life [23]. Treating allergic rhinitis in children with asthma may not only improve their rhinitis symptoms and quality of life, but also their degree of asthma control.

Throughout the symposia focusing on childhood asthma management, emphasis was put on ''getting the basics right'' in the treatment of asthma (table 1). A study from Brazil showed that in most children, asthma can be well controlled by monotherapy with low-dose inhaled corticosteroids, provided that patients are being regularly followed up [24]. Conversely, a large survey of >1,000 children with asthma in six countries showed that poor asthma control was common, despite maintenance treatment with inhaled corticosteroids [25]. Education alone appears to be unable to change this, as a large Canadian study failed to show any benefit from a multi-faceted education intervention in the emergency department for children with asthma [26]. The conflicting results of asthma education programmes, both in individual studies and in meta-analyses, have been discussed in depth elsewhere [27]. A key issue appears to be parental concerns regarding medication, and their beliefs on asthma as a chronic illness. In a focus group study from the Netherlands, such parental concerns and beliefs were of key importance in determining adherence to maintenance treatment with inhaled corticosteroids [28]. Parents have their own beliefs about illness and medication, which usually do not conform to the medical model of asthma. Repeated education and ongoing structured follow-up were the key success factors in modifying these beliefs, and improving treatment adherence [28]. This is in line with studies showing improved asthma control and adherence to treatment after home visits or telephone follow-up visits by asthma nurses [29, 30].

Doctors themselves may also be nonadherent to treatment. In a UK study, it was found that 11 out of 37 admissions for childhood asthma may have been prevented if the asthma clinical pathway had been followed as prescribed [31].

PAEDIATRIC RESPIRATORY EPIDEMIOLOGY

A number of old and new cohort studies have provided new insight into the aetiology, phenotypes and long-term outcome of childhood wheeze. In the Swedish Twin register, a 1,000 g decrease in birth weight was associated with an adjusted odds ratio for asthma of 1.57. Co-twin control analyses found an OR of 1.25 (95% CI 0.74–2.10) for dizygotic same-sexed, and 2.42 (95% CI 1.00–5.88) for monozygotic twins, with similar results for term and pre-term infants [32, 33]. This study provides further evidence for an association between fetal growth and childhood asthma, independent of gestational age and of shared environment and genes.

Although the evidence supporting the hygiene hypothesis remains inconclusive [34], to date the strongest data have been shown for a potential protective effect of farm life [35]. The mechanisms by which environmental exposures on a farm could confer protection from respiratory allergies are, however, not well understood. Data presented from the GABRIEL study supported a protective effect of raw unskimmed farm

TABLE 1 ''Getting the basics right'' in childhood asthma management

Important issues to consider in children in whom inhaled corticosteroid therapy is unsuccessful before adding other medications:
Adherence to treatment
Poor inhalation technique
Comorbid conditions, such as allergic rhinitis
Exposure to environmental allergic and nonallergic stimuli (cigarette smoke)
Addressing parental concerns and beliefs regarding medication

milk against asthma, hay fever and atopic sensitisation [36]. Further analysis of the biological components of shop and farm milk showed higher concentrations of fat, lactoferrin and somatic cells in farm milk but, surprisingly, lower bacterial loads [36]. Furthermore, the GABRIEL study provided novel evidence that farm life protects not only from respiratory symptoms, but also improves lung function [37] and decreases levels of exhaled nitric oxide [38].

There was quite some debate about the possible role of paracetamol in the pathogenesis of asthma [39, 40]. A pilot study from the ALSPAC cohort explored whether DNA methylation could explain the association. Results remained inconclusive due to low numbers [41]. In the Leicester cohort, a strong positive correlation was found between paracetamol intake and subsequent asthma. However, this effect largely disappeared after controlling for upper respiratory morbidity and reverse causation, suggesting that the association between paracetamol and asthma might be spurious rather than causal [42]. This limitation does not apply to studies on paracetamol use during pregnancy. Only randomised trials can give the ultimate answer to this clinically relevant question.

A growing number of studies have begun to define different phenotypes of wheeze using multidimensional approaches to classification [43–45]. Authors from the Paris birth cohort, analysing recurrent respiratory symptoms in infants, presented evidence for the existence of two different respiratory phenotypes in this age group [46]. However, these multivariate methods will always find clusters, whether these really exist or not. To find a way out of these circular research paths, Swiss workers took an objective statistical approach to decide whether the variability within childhood wheeze is better explained by distinct asthma phenotypes (*e.g.* different diseases) or by severity gradients. The first results, based on cross-sectional symptom data from the Leicester cohorts, support a gradient rather than a class model [47], but the analysis must be extended to include physiological measurements and longitudinal data.

Although the age-related changes in the sex ratio for asthma have been known for decades, the mechanisms explaining these remain poorly understood [48, 49]. An inverse relationship between testosterone levels and bronchial responsiveness was found in 321 young males [50], suggesting that sex hormones may help to explain the natural history of asthma through childhood.

CYSTIC FIBROSIS

Protocols for cystic fibrosis (CF) newborn screening usually utilise a stepwise approach with serum immunoreactive trypsin (IRT) as the initial test and genetic analysis for the most common mutations on samples with positive IRTs. Extended genetic testing platforms and different assays to assess pancreatic function, such as serum pancreatic associated protein (PAP), could potentially improve the diagnostic accuracy of newborn screening for CF. A study from the Netherlands showed similar positive and negative predictive values for the combination of IRT and PAP compared with a standard IRT/DNA programme [51]. Extended genetic testing yielded additional screen positive subjects, but raises a clinical dilemma, since the clinical significance of most of the detected mutations is currently unclear. As genetic testing will also detect a significant proportion of unaffected carriers of gene mutations, protocols not requiring genetic testing would ultimately be preferable.

While newborn screening enables early initiation of treatment, two presentations from Australia documented early disease progression in infants despite diagnosis by newborn screening. The Arrest CF trial combines imaging techniques (computed tomography; CT) with assessments of lung function and bronchoscopy derived specimens to quantify infection and inflammation. This combined approach will shed more light on the complex relationship between these different aspects of CF lung disease in a longitudinal trial. In a preliminary cross-sectional analysis, the investigators assessed the link between ventilation distribution assessed by multiple breath washout and structural lung disease, and did not find a close link between the two methods [52]. However, bronchial dilatation was found to be correlated with neutrophil elastase activity in BAL fluid raising the interesting question as to whether elastase activity may be a predictor of bronchiectasis [53]. Longitudinal rather than cross-sectional data will help to better understand the relevance of these CT findings as there is limited information on the appropriate techniques to detect early bronchiectasis in this age group. Interestingly, the quality of magnetic resonance imaging (MRI) based imaging of CF lung disease is improving rapidly and could potentially replace CT as a radiation neutral technique in the future [54].

Early aggressive intervention is thought to be a major factor prolonging life expectancy in CF, but it is less clear whether treatment has been equally successful in improving the outcome of patients with advanced disease. A cohort study from London documented significant improvements in survival of patients with an FEV_1 <30% over the last 20 yrs [55]. This highlights the need to continuously re-evaluate the criteria for lung transplantation which are largely based on a study performed almost 20 yrs ago that demonstrated FEV_1 <30 % to be associated with a 50% 2-yr mortality in CF patients [56].

Hypertonic saline (HS) has been shown to reduce pulmonary exacerbations and improve lung function in CF patients, and is currently being studied as an early intervention strategy in infants and young children. HS facilitates sputum expectoration, but also increases airway surface liquid fluid which is depleted in CF [57]. An alternative approach is to use a sugar rather than a salt as an osmotic agent, and early studies have demonstrated that mannitol administered as a dry powder may have similar efficacy [58]. A phase III trial of inhaled dry powder mannitol treatment demonstrated significant benefits in lung function [59]. Effects on pulmonary exacerbations were less clear cut. Further studies should help to better understand the efficacy of this treatment [60].

PAEDIATRIC RESPIRATORY PHYSIOLOGY

Exciting new technology has recently been developed to assess lung growth in infants and young children [61]. The apparent diffusion coefficient (ADC) of hyperpolarised helium 3 (^3He) by MRI is a noninvasive, apparently robust method for assessing alveolar size [62]. 49 term-born healthy children (25 male) aged 7–16 yrs (median 12.3yrs) underwent measurement of functional residual capacity (FRC) by plethysmography and ADC by

MRI. ADC was approximately normally distributed, and was unrelated to age and FRC [61]. These observations can only be explained by ongoing formation of new alveoli throughout childhood, which contradicts the current paradigm that alveoli only multiply for the first 3 yrs of life, and that subsequent lung growth is by alveolar enlargement. This is important because it signifies the potential of the lung to recover from early life insults. Conversely, it is possible that drugs, diseases and environmental exposures in later childhood may affect final structure and function of the alveoli.

There has been increasing attention over the last decade upon refining reference equations for lung function measurements in children. The greatest focus has understandably been on spirometry, but a presentation from Indianapolis (USA) described normative data for diffusion capacity of the lung for carbon monoxide ($D_{L,CO}$), with simultaneous measurement of haemoglobin (Hb) in 387 healthy individuals aged 6–18 yrs [63]. Equations for $D_{L,CO}$, alveolar volume (V_A), $D_{L,CO}/V_A$ and $D_{L,CO}$/Hb corrected for sex and Caucasian *versus* African–American race were presented. Two key points were that adjusting for Hb did not affect the result (as long as Hb is in normal range), and normalising $D_{L,CO}$ for V_A did not provide a benefit [63]. A six-centre study from Europe and South America analysed 1,117 measurements of interupter resistance (R_{int}) in children aged 2–13 yrs, which were used to develop sex-specific reference equations [64]. A close relationship was observed between the data obtained in different centres suggesting that these reference values are consistent between populations.

Two studies described the effect of pre-term birth on lung function measured during preschool years. From a group in northern Italy, 74 children born at a mean gestational age of 29 weeks underwent R_{int} and impedance measurement from forced oscillation technique (FOT) [65]. Results were comparable to those obtained in healthy children born at term. From Perth, Australia, a cohort of 150 children (74 bronchopulmonary dysplasia (BPD), 44 non-BPD and 32 controls) underwent spirometry and FOT between 4–8 yrs of age [66]. There were significant differences ($p<0.02$) between pre-term children (BPD and non-BPD) and healthy subjects in FEV_1, forced expiratory flow at 25–75% of forced vital capacity and FOT reactance but not forced vital capacity or FOT resistance. On a related topic, investigators from the EPICure study [67] reported a wide range of lung function tests in 49 children born extremely pre-term and 52 controls recruited from across the UK and measured at a mean age of 11 yrs [68]. Spirometry was better at discriminating between groups than $D_{L,CO}$, lung clearance index, or resistance or lung volumes measured in the plethysmograph. However, the authors cautioned that different investigations gave complementary information [68].

PAEDIATRIC RESPIRATORY INFECTIONS AND IMMUNOLOGY

A new diagnostic method, vibration response imaging (VRI), allows atelectasis and lung infiltrates to be visualised. In VRI, acoustic contact sensors detect vibration energy in the airways, which is processed into images by dedicated software. In a small proof-of-concept study in 12 patients, VRI could differentiate normal lungs from pneumonia and foreign body aspiration [69].

The use of galactomannan in BAL fluid as a marker for invasive pulmonary aspergillosis may reduce the need for open lung biopsy. In a retrospective study of 41 immunocompromised children, elevated galactomannan levels in BAL fluid showed a sensitivity and specificity of 82.4% and 87.5%, respectively. However, a negative test did not reduce the use of anti-fungal treatment [70].

In the treatment of bacterial lower respiratory infections, the frequent use of oxyminocephalosporins, a group of third generation cephalosporins, induces extended spectrum β-lactamase producing bacteria leading to a new pattern of bacterial resistance [71]. In most children with severe community acquired pneumonia, symptoms resolve within 24 h of starting intravenous penicillin therapy [72]. Given the risk of inducing new bacterial resistance when using new classes of broad spectrum antibiotics, this study highlights that treatment of pneumonia in children can, and probably should, be started with narrow spectrum antibiotics [72].

Several studies have shown that treatment according to current pleural empyema guidelines may not always lead to optimal results [73–76]. In the cases presented, early surgical drainage was associated with risk of developing bronchopleural fistula, and conservative management often appeared successful [73–76]. However, early surgical decortication of pleural empyema resulted in shorter hospitalisations and reduced morbidity. It remains unclear how these different interventions impact on the long-term outcome of pleural empyema.

Morbidity and mortality due to acute lower respiratory tract infections during the first 2 yrs of life are highest for children in Papua New Guinea. LAING and co-workers [77, 78] found that polymorphisms of genes associated with innate and adaptive immunity were associated with earlier and more severe respiratory infections in these patients. This finding may expand our knowledge as to which defects in the adaptive immune system can increase susceptibility for lower respiratory infections.

NEONATALOLOGY AND PAEDIATRIC INTENSIVE CARE

Clinical and demographic data on patients receiving non-invasive ventilation (NIV) are important for the planning of services and audit of performance. A recently established national register of children receiving NIV in eight accredited centres across France has now collected data about rare lung diseases in 82 patients, and recruitment will continue for the forthcoming years [79].

Increasing interest is being focused on the long-term respiratory outcome of premature birth [80]. Increased levels of carbon monoxide in exhaled breath of neonates in the neonatal intensive care unit on the third and 14th day of life significantly improved the ability to predict subsequent BPD [81]. However, the addition of carbon monoxide measurements only minimally increased the predictive levels (increasing the area under the curve from 94% to 97%), and the clinical relevance of such measurements remains uncertain. In a large study recording upper respiratory infections, hospital admissions and medication use annually during the first 3 yrs of life in 2,700 ex-premature babies (<32 weeks of gestation), children with BPD developed more symptoms than controls [82]. However, despite the large numbers there were no clear predictors of respiratory

morbidity, except the duration of oxygen requirement in the neonatal period [82]. A Swiss group has studied a very early cohort of 13 infants (now adults with a mean age of 38 yrs) with ''old'' BPD, following up their lung function from infancy to adulthood. As this group have become older, abnormalities of small airways appear to have stabilised; although, they remained well below the normal range [83]. Interestingly, between 30–40 yrs of age, residual volume/total lung capacity ratios increased from 26% to 39%. It remains difficult to know what effect there may be from a ''survival bias'' in this group as a number of the original cohort have died.

Fatal and near fatal asthma remains a rare but worrying problem in children. In an interesting study from Germany, a dramatic fall in both fatal and near fatal asthma between 1997 and 2008 was reported [84]. This may be as a result of increased use of inhaled corticosteroids.

In a study of cardiovascular response to acute hypoxia, 13 children aged 8–12 yrs with BPD were subjected to oxygen levels of 12%. In children with BPD, oxygen saturation decreased from 99% to 91%, compared with 92% in term-born controls [85]. Apparently, former BPD patients tolerate hypoxia well.

A study from Sweden showed high levels of the plasticiser di(2-ethylexyl)phtalate (DEHP) in the urine of children with tracheostomies [86]. DEHP is a well-recognised toxin and endocrine modifier, especially in children. As yet the implications of this finding remain uncertain.

PAEDIATRIC BRONCHOLOGY

Although the stridor associated with laryngomalacia usually disappears during the first year of life, laryngomalacia is associated with other bronchial anomalies in 15% of cases and associated clinical symptoms related to gastro-oesophageal reflux and microaspiration may occur [87, 88].

Almost 70% of infants with persistent and therapy-resistant wheezing have tracheo- or bronchomalacia (either primary or secondary to vascular compression), tracheal or bronchial stenosis, or tracheo-oesophageal fistula (TEF) [89]. The differential diagnosis of persistent wheezing in infants should also include airway narrowing due to lymph node compression in tuberculosis [90].

Fibreoptic bronchoscopy is an important diagnostic tool in the assessment of congenital airway and lung malformations. In patients with congenital lobar emphysema, for example, fibreoptic bronchoscopy may disclose bronchial valve mechanisms such as bronchial mucosal folds or bronchomalacia. In patients with bronchogenic cysts and cystic adenomatoid malformations, the most frequent endoscopic diagnosis is tracheomalacia or bronchomalacia [91]. During endoscopic examination of the airways in children with TEF, a catheter can be introduced into the fistula before surgical repair. This procedure lets the surgeon know exactly where the fistula is located. In addition, fibreoptic bronchoscopy to deliver methacrylate glue to a TEF may be a reasonable alternative to operative closure [92].

In children, BAL may both have diagnostic and therapeutic purposes [93]. Even in the absence of atopy, BAL fluid from children with asthma contains activated eosinophils even in the absence of atopy [94]. Although controlled studies are lacking, it has been shown that whole lung lavage is an effective treatment for alveolar proteinosis [95]. Unfortunately, this treatment may fail when adequate ventilation cannot be maintained during the lavage procedure. A new technique in young children was presented to overcome this problem. In this procedure, sequential whole lung lavage was performed with the use of an Arndt bronchial blocker device (Cook Medical, Limerick, Ireland) inserted through a 4.5-mm endotracheal tube, using a 2.2-mm bronchoscope for guidance, with the balloon inflated in a main bronchus, allowing the isolated lung to be lavaged while maintaining adequate ventilation of the other lung through the endotracheal tube [96].

Treatment of severe lower airway obstruction in children continues to evolve. Slide tracheoplasty was presented as an appropriate technique for correcting congenital long-segment tracheal stenosis with complete tracheal rings [97]. Airway stenting has been used successfully in severe lower airway obstruction in adults, and may be an attractive alternative in children [98]. Metal stents usually achieve airway patency and, in most cases, clinical improvement, whereas silicone stents seem less successful [98]. However, severe and sometimes fatal complications occur in a considerable proportion of children. These include the formation of granulation tissue and airway migration [99, 100]. More data from larger series of patients are needed to identify patients who may benefit from airways stenting.

STATEMENT OF INTEREST

None declared.

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