

SCIENTIFIC ASSEMBLY UPDATE

Paediatrics in Barcelona

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ABSTRACT

The aim of this update is to describe the paediatric highlights from the 2010 European Respiratory Society Annual Congress in Barcelona, Spain. Abstracts from the seven groups of the Paediatric Assembly (Respiratory Physiology; Asthma and Allergy; Cystic Fibrosis; Respiratory Infection and Immunology; Neonatology and Paediatric Intensive Care; Respiratory Epidemiology; Bronchology) are presented in the context of the current literature.

KEYWORDS

Asthma, atopy, bronchoscopy, cystic fibrosis, epidemiology, immunology, intensive care, lung function, respiratory infection

INTRODUCTION

The 2010 European Respiratory Society (ERS) Congress in Barcelona, Spain, included a large paediatric programme, containing numerous high-quality scientific presentations. As a service to those who could not attend a session 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, the summary cannot be comprehensive, but rather aims to address schemes of new research in major areas of paediatric respiratory medicine.

PAEDIATRIC ASTHMA AND ALLERGY

Inflammatory markers

Breathomics [1], metabolomics [2], biological profiling and exhaled breath analyses [3, 4] are used to identify, characterise or classify asthmatic and/or allergic children as well as to understand underlying mechanisms and optimise management. The increasing interest in research in these areas was reflected at the congress. Biological profiling of exhaled breath condensate (EBC) was used to characterise virus induced wheeze [5] and wheezing infants [6] respectively. In the EUROPA study van der Schee *et al.* [5] found that biomarkers could differentiate infants and young children with confirmed vs. non-confirmed wheeze, as well as those with respiratory syncytial virus positive vs. negative patients. Carraro *et al.* [6] demonstrated that different metabolic profiles could differentiate those with poorly controlled and severe asthma from those with mild asthma. As another way to profile

exhaled products, an electronic nose (the “e-nose”), was demonstrated as a novel way to profile exhaled products and found to be feasible to analyse profiles of volatile organic compounds (VOCs) in both infants and school children [7]. VOCs can also be potentially used to identify asthma [8] with eight of 945 different identified components discriminating between asthmatic and healthy children. Common to these “-omics” studies is still that they are exciting in view of better understanding mechanisms in asthma development and presentation, but that the clinical potential and value has yet to be determined. With ever more sensitive techniques, new biological inflammatory substances are found to be associated with asthma, such as the newly discovered eoxins [9]. Although many of these substances may suggest potential treatment targets for asthma, it is essential to assess whether they are related to asthma specifically (which was found in the case of eoxins) or may also be involved in inflammatory processes of other types of lung diseases.

After more than a decade in use, many of these questions are well on the way to be answered for exhaled nitric oxide (FENO). One important issue is whether or not this marker enables us to predict future disease or severity of disease. Franklin *et al.* [10] investigated FENO in 105 infants by the single breath method and reassessed the children at seven years of age for wheezing with subsequent categorisation into transient wheezers or persistent wheezers. They found no significant difference in infant FENO in children with or without current wheeze, nor was FENO (in contrast to spirometric values) significantly different according to wheezing categories by seven years. Likewise, in a six-year follow-up study of infants, Chawes *et al.* [11] found no association between FENO and lung function in infancy or at six years in the same children, whereas increased FENO in healthy babies of asthmatic mothers was predictive of transient, but not persistent wheeze.

Lung function testing

Lung function testing in paediatric asthma has made important progress in the last few years. With revised reference ranges of lung function parameters [12] the need for population-specific reference values as well as developmental aspects have been highlighted, and several of the old but also new reference values have been demonstrated to be inappropriate for specific populations [12-14]. Given the vast use of spirometry in every day clinical practice, the relative lack of published longitudinal lung function data in children is a paradox. The usefulness of lung function measurements has been discussed in relation to characterisation and severity of asthma [15-17]. A recent study from London, UK on the lung clearance index (LCI) showed that children with severe asthma had a higher LCI when compared with age-matched controls [18]. Forced expiratory volume in 1 second (FEV₁) on the other hand was not related to severity of asthma. The authors concluded that LCI appears to be a better discriminative test in assessing airway function in asthmatic children, and may be a particularly useful tool in assessing asthmatics with normal FEV₁. Thus, as has been reported many times, it appears that commonly used spirometric values are less useful in children than in adults and that other parameters of airways function may yield more relevant information.

Asthma prevention and management

The crucial question in asthma remains how to prevent its development. Thus, unravelling and assessing the potential impact of risk factors is mandatory, with subsequent intervention trials to see if avoidance of specific factors or targeted interventions can prevent disease. The Danish COPSAC study linked maternal plasma vitamin D during pregnancy to wheeze during the first six years and

described a non-significant inverse relationship [19]. A significant inverse association between plasma vitamin D in four year olds and asthma risk at that age was reported in the Dutch PIAMA study but this association was transient and plasma vitamin D levels at four years were not linked to asthma symptoms at age eight years [20]. A case-control study based on observations from the Dutch KOALA study reported that vitamin D supplementation during infancy was associated with a 50% reduction in asthma risk at 6-7 years of age [21]. The authors concluded that the use of vitamin D supplements in infancy may decrease asthma risk in later childhood, in line with several studies showing beneficial effects of increased vitamin D levels in reducing wheeze and atopic eczema [22]. Similarly, reduced vitamin D levels were associated with increased requirement for corticosteroid treatment [23] as well as with an increased risk of severe asthma exacerbations in the CAMP study [24]. Whether or not vitamin D supplementation can be a significant preventive strategy for asthma and/or other allergic diseases remains to be tested in randomised clinical trials; however, it is interesting that a randomised trial demonstrated a reduced risk of Influenza A in children taking vitamin D supplements [25].

Management of severe asthma remains difficult since we lack good criteria for understanding and classifying children in different ages with severe disease. Since they are relatively few (approximately 4.5% of asthmatic children [26]), few centres on their own will have large populations to test management. Thus, a common international approach is mandatory. This is discussed in the series of papers on problematic severe asthma from the GA²LEN group of paediatricians throughout Europe [15, 16, 27]. At the congress, a study from Texas, USA in collaboration with Novartis, was presented suggesting that the number needed to treat to prevent one exacerbation per year with omalizumab was 1.7-1.8 in 576 6-12-year-old children

with inadequately controlled asthma [28]. Improvements in asthma symptoms, quality of life and asthma exacerbations were also found in children with severe asthma after a 16-week open label, non-randomised trial in London, UK [29]. Thus, anti-IgE treatment has gained support for children with severe asthma associated with allergic inflammation [30, 31], but its definitive role in severe childhood asthma needs further evaluation. Other aspects that were debated and will receive more attention in the years to come are home-monitoring and patients' self-management. With the ever-increasing costs to society by allergic diseases in general, and asthma in particular, there is an urgent need to evaluate optimal patient management strategies including new virtual monitoring schemes.

CYSTIC FIBROSIS

Therapeutic strategies

New therapeutic strategies addressing the cystic fibrosis transmembrane conductance regulator (CFTR) or other chloride channels are emerging. The CFTR potentiator VX-770 has shown to be efficacious in patients with the G551D mutation where CFTR is present at the cell surface, but does not open properly. A phase II study demonstrated reduced sweat chloride concentrations, improved chloride secretion in nasal epithelium and also improvements in lung function [32, 33]. New evidence was presented that denufosal, an activator of an alternative chloride channel, also inhibits sodium absorption, an important component of CF pathophysiology [34]. A subgroup analysis for the first phase III study demonstrated larger lung function improvements for patients on limited concurrent therapy as well as in adolescent patients [35]. More information from large clinical trials will become available for both compounds in 2011.

Imaging and lung function

Imaging techniques have become an area of active research and longitudinal computed tomography (CT) data from Australia now show evidence for progression of bronchiectasis in early childhood [36]. Positron emission tomography (PET) scanning is currently being explored as a novel modality to capture airway inflammation [37]. Radiation exposure for both techniques limits their widespread use, but magnetic resonance imaging (MRI) technology is constantly improving and could potentially become an alternative imaging technique to capture lung disease [38].

More data support the use of LCI as a sensitive measure of lung disease. LCI was reported to be abnormal in 3-month-old CF infants diagnosed by newborn screening [39]. These results contrast with those previously reported by the Melbourne group [40], and have implications for the understanding and treatment of early CF lung disease. In addition, poor nutritional status in infancy was associated with an increased LCI [41]. Improvement of the LCI was demonstrated in children with normal FEV₁ after dornase alfa administration, further supporting its use in interventional studies [42, 43]. While uncertainty exists on defining the threshold for a significant change in the LCI, short term variability of the technique in both CF patients and controls was shown to be relatively low [44]. Multiple devices to measure LCI have entered the market and comparative studies with the current “gold standard”, mass spectrometry, are crucial to understand their validity [45].

Airway infection

Airway infection is usually dominated by bacteria and molecular techniques are demonstrating a rather complex bacterial microbiome in CF airways [46]. The contribution and significance of viral infections remains poorly defined. Malfroot *et al.* reported isolation of viruses in one third of exacerbations, which may be an underestimation as rhinovirus was not included in the analysis [47]. Using bronchial epithelial cells from young CF children, Stick *et al.* demonstrated a combination of decreased apoptosis, increased interleukin 8 response and decreased interferon gamma (IF γ) concentrations after in vitro rhinoviral infection, suggesting a dysregulated inflammatory response in CF epithelium [48, 49]. Interestingly, while an independent study confirmed a decreased IF γ response, the pro-inflammatory cytokine response was similar in CF and non CF human bronchial epithelial cells [50, 51]. Overall, these data highlight the difficulties of modelling the in vivo response in vitro; a problem that has plagued CF researchers over the last decades.

Increasingly, evidence suggests that aspergillus may play a role in CF patients beyond ABPA [52, 53]. Aspergillus was described as the most prominent organism in bronchoalveolar lavage (BAL) fluids from CF patients in one series and BAL positivity for aspergillus was linked to increased airway inflammation in another study [54, 55]. In addition, sensitisation to aspergillus, independent of ABPA, was found to be linked to poorer lung function [56]. While its pharmacokinetics are now better defined in CF patients, the benefit of antifungal therapy still remains controversial [57].

PAEDIATRIC RESPIRATORY EPIDEMIOLOGY

Paediatric Respiratory Epidemiology Award

The three paediatric respiratory epidemiology abstracts scored most highly by the reviewers were awarded prizes. The first, a study from Southampton, UK, described associations between maternal plasma fatty acid concentrations at 34 weeks gestation and asthma and allergy outcomes at age six years; plasma phosphatidylcholine arachidonic acid was positively associated with skin prick reactivity and increased risk for atopic wheeze while α -linolenic and eicosapentanoic acid were inversely associated with diagnosed asthma [58]. A second award went to the longitudinal ALSPAC cohort based in Bristol where the relationship between swimming pool attendance and asthma was explored; previous cross-sectional studies have reported a positive association but the ALSPAC group reported swimming pool attendance was associated with a 50% reduction in asthma prevalence and higher lung function [59]. A third award went to the Bern/Leicester collaboration who validated the Tucson Asthma Predictive Index (API) in their population as a tool to predict the outcome of early wheeze; the sensitivity for asthma at age ten years, based on information at three years of age, was 26% for the loose API and 37% for the stringent API and these relatively low numbers are consistent with those reported for the Tucson population [60].

International Study of Asthma and Allergies in Childhood

The International Study of Asthma and Allergies in Childhood (ISAAC) methodology continues to be applied to populations around the world and results highlight geographical variations. For example, in Romanian children the prevalence of asthma is lower in urban areas (2.1%) compared to the prevalence across the whole of Romania (3.2%) [61]. In Chile, by contrast, the prevalence of asthma was 40% lower in rural compared with urban areas [62]. In Cypriot children, the prevalence of asthma symptoms increased between 2000 and 2008 and this rise was 40% greater

in rural compared to urban areas [63]. The consistency of methodologies between centres gives assurance that these apparently conflicting results may be genuine but the underlying mechanisms are yet to be described.

Development of asthma

Mechanisms for the development of asthma are known to be active during early life and vitamin D has been the focus of much research (see above). While none of the studies on vitamin D and asthma development prove causation, they add to the burden of evidence supportive of a “dietary hypothesis” for asthma causation. Other early exposures which might influence childhood respiratory outcomes include maternal paracetamol and alcohol ingestion and antibiotic use during infancy. The effect of maternal paracetamol may be modified by maternal antioxidant genes [64]. Even low quantities of maternal alcohol during pregnancy were linked with reduced fetal size and childhood lung function but not increased asthma symptoms [65]. A systematic review reported the association between antibiotic use during infancy and subsequent asthma was of borderline significance once reverse causation was considered [66].

Other topics

While asthma again was the dominant theme among abstracts, there were many other important paediatric conditions covered. A rapid increase in empyema prevalence is described in the UK and a group in Newcastle observed that some of this rise may be attributable to increasing pneumonia prevalence but other factors may also be at play [67]. The H1N1 pandemic touched us all in 2009/10 and the management of suspected H1N1 infection in the UK was found to be mostly not consistent with guidelines but not to the detriment of children’s health [68].

PAEDIATRIC RESPIRATORY INFECTION AND IMMUNOLOGY

Community-acquired pneumonia, recurrent pneumonia

Despite widespread vaccination *Streptococcus pneumoniae* is still a frequent cause of community-acquired pneumonia in childhood. Even new vaccines do not cover all serotypes [69]. Thus, it is important to identify the *S. pneumoniae* serotypes causing pneumonia to differentiate failure of vaccination from pneumonia caused by serotypes not covered by the vaccines. Blood cultures yield positive results in only 10% of cases. Malfroot *et al.* showed that serotype specific serology may be helpful in identifying the aetiology of pneumococcal pneumonia in patients with negative blood cultures [70]. According to a retrospective study from Israel, penicillin still appears to be the first choice of treatment of uncomplicated community-acquired pneumonia in childhood [71]. The increasing prevalence of pneumonias complicated by parapneumonic effusions does not lead to long term sequelae in the majority of children: two years after a complicated pneumonia 75% of the tested schoolchildren showed normal lung function and exercise capacity; of those with decreased exercise capacity all but one had concurrent asthma [72].

Recurrent pneumonia is a frequent finding in children, but studies elucidating the underlying causes are rare. Two studies showed divergent results. In a study from the Netherlands, the main causes of recurrent pneumonia in 62 children were reflux or aspiration, primary or acquired immunodeficiency, congenital heart disease, or pre-existing lung disease. Asthma was not diagnosed as an underlying cause in any of these children; in one third no underlying cause could be identified [73]. In contrast, in a study from Brazil including 46 children with recurrent pneumonia

asthma was diagnosed in 78% and thus considered the most frequent underlying cause [74].

Other topics

Little is known about how to best follow up pulmonary involvement in children with immunodeficiency. Van de Ven *et al.* showed that, compared to lung function tests and chest X-rays, high resolution (HR) CT scanning is the most sensitive tool to detect pulmonary disease and can be used to differentiate between structural and interstitial lung disease in children with common variable immunodeficiency [75].

In 2009 a new virus, influenza A/H1N1, caused an influenza pandemic, with children being at risk to develop complications. A few studies showed that neurodevelopmental disorders, underlying diseases such as diabetes or CF, and young age were main risk factors for a severe course of H1N1 influenza with secondary bacterial pneumonia, admission to intensive care units and a few deaths [76, 77]. In a case series from Serbia, all asthmatic children admitted to hospital with H1N1 developed pneumonia compared with only 40% of children without asthma [78].

Variation in the management of acute viral bronchiolitis and lack of clear evidence for any single approach led to a systematic review of 48 randomised controlled trials in children <24 months with a first episode of bronchiolitis, comparing bronchodilators or corticosteroids (alone or combined) with placebo or other interventions. The authors reported that the use of epinephrine in outpatients led to reduced admissions, but no evidence was found for the use of other bronchodilators or corticosteroids [79].

In 2007, Bisgaard *et al.* published the observation that bacterial colonisation of the neonatal airways with pathogenic strains of *Haemophilus influenzae*, *S. pneumoniae* and *Moraxella catarrhalis* is associated with recurrent wheeze and asthma in early childhood [80]. In a prospective study to further elucidate the mechanisms underlying this observation it was found that neonates colonised with these bacteria had up-regulated nasal epithelial lining fluid (ELF) levels of interleukin (IL)-2, IL-10, IL-13, and CXCL8[IL-8] compared to the neonates without such a colonization, suggesting that colonisation is associated with a subclinical nasal inflammatory response preceding the development of atopic disease [81].

NEONATOLOGY AND PAEDIATRIC INTENSIVE CARE

Neonatology

Neonatal resuscitation is an area attracting considerable attention at present. New techniques have permitted imaging the very first breaths of life [82] and an international study has shown the importance of early sustained lung inflation on subsequent morbidity [83]. Concerns centre both on the amount of oxygen that is needed during resuscitation, as well as the pressures used to ventilate during the first minutes of life [84]. Data from Kelm *et al.* suggests that even if experienced operators are asked to manually ventilate a manikin (set to simulate a 1000g baby), the pressures and volumes delivered can vary considerably, depending on the equipment used [85]. This is important as other work has demonstrated that V_{ALV}/V_T ratios increase with increasing gestational age [86]. Consequently, ventilator settings need to take account of maturity as well as weight to avoid potential volutrauma.

Rescue steroids, administered antenatally to women in preterm labour, have been shown to improve neonatal outcome and increase lung compliance. However, there

have been clinical concerns that they may also have an adverse effect on long term lung growth. In a study of 109 babies whose mothers received rescue steroids, lung function at 12-24 months has been shown to be no different from a placebo group [87].

Paediatric intensive care

In PICU, non-invasive techniques for respiratory support are evolving. Recent data has shown that non-invasive ventilation (NIV) can be used successfully in children presenting with acute respiratory failure [88]. In a study from Australia, Foster and colleagues have shown that administration of high flow oxygen (up to 2ml/kg/min) can avoid the need for intubation [89]. In their study of almost 200 patients, the rate of intubation in the bronchiolitis group (110 patients) was down to 2%. Some concerns over the control of airway pressure with this technique do remain, but the reduction in invasive ventilation is encouraging.

As well as non-invasive treatment, non-invasive assessment of lung function is becoming a reality. Iles *et al.* have shown excellent early results of a non-invasive light based technique (structured light plethysmography) for evaluating lung function, which allows reconstruction of thoracic and abdominal volumes in real time from 3D reconstruction of video [90]. A chequered pattern of light is shone on to the chest wall and filmed from two angles, with an entirely non-touch technique. Seddon's group have also recently evaluated a new technique, using a volumetric vest in infants [91]. In a group of 20 infants with and without bronchopulmonary dysplasia (BPD), the vest differentiated patterns of breathing (such as T_i/T_e ratios) between groups. Electrical impedance tomography (EIT) has been available for longer. Humphreys *et al.* have shown acute changes in lung volume during elective intubation [92]. In a group of 38 children undergoing induction of anaesthesia prior to cardiac surgery, functional

residual capacity (FRC) dropped during the period of intubation, and mechanical ventilation redistributed ventilation towards the anterior parts of the lung.

PAEDIATRIC BRONCHOLOGY

Technique and indications

Flexible endoscopy of the airway has become an increasingly important tool for evaluating respiratory disorders in children and can also be useful in therapy. The technique has continuously improved and numerous publications have described indications, methods, diagnostic utility, and safety [93]. In a series of 316 diagnostic flexible bronchoscopies in 305 Greek children, Kyrvassilis *et al.* again showed that flexible bronchoscopy is a safe procedure, without major important side effects and with a diagnostic yield of 75% [94]. In their experience, stridor was the indication with the highest diagnostic yield and chronic cough the indication with the lowest. The availability of smaller bronchoscopes has expanded the range and indications for this technique also in neonates and premature babies. In a group of 123 neonates, Flores-Hernández *et al.* showed that flexible bronchoscopy is also safe in this age group; the main indications included persistent/recurrent atelectasis, stridor, and assessment of congenital abnormalities of the tracheobronchial tree [95]. Antón-Pacheco *et al.* reported flexible bronchoscopy to be an important diagnostic tool also in the management of children with craniofacial syndromes. They frequently encountered airway anomalies in patients with severe craniofacial syndromes, especially in those with respiratory symptoms [96]. Another important diagnostic application of flexible bronchoscopy is the evaluation of swallowing dysfunction in infants with suspected aspiration. In a study evaluating 94 patients, Peña *et al.* showed that fiberoptic endoscopic evaluation of swallowing provides important

diagnostic information to guide treatment in children with dysphagia and aspiration [97].

Special procedures

Several special procedures can be performed through the working channel of the flexible bronchoscope [93]. Bronchoalveolar lavage is particularly useful to increase the diagnostic yield of flexible bronchoscopy, and is routinely done during flexible bronchoscopy for clinical and research purposes [98]. Mammas *et al.* evaluated the presence of *S. pneumoniae* in bronchial lavage samples from 65 non-CF immunocompetent children with protracted purulent bronchitis [99]. They found that the most prevalent serotypes were 1, 18C, 19A and 19F, all sensitive to amoxicillin-clavulanic acid, and concluded that further data on serotype distribution would help to guide appropriate pneumococcal conjugate vaccine formulation. A useful research application of BAL is to obtain samples from children with severe asthma to evaluate the underlying inflammatory processes. In a study from London, UK including 72 children with severe asthma, Ullmann *et al.* found a poor relationship between blood markers of inflammation and local pulmonary markers as obtained by measurement of FENO, sputum induction, BAL, and endobronchial biopsy [100]. They thus concluded that in order to characterise children with severe asthma accurately, BAL samples and endobronchial biopsy specimens are required.

Therapeutic BAL can be indicated for removing airways material. In a case report, Caro-Aguillera *et al.* demonstrated the critical role of flexible bronchoscopy in the diagnosis and treatment of a patient with plastic bronchitis, an unusual condition characterised by the development of thick casts in the tracheobronchial tree [101]. Congenital tracheo-oesophageal fistula may be difficult to diagnose and manage and the recurrence rate reaches 10% after surgical treatment. A reasonable alternative to

operative closure is to close the fistula from the oesophagus via a flexible bronchoscope with a two component human fibrin glue (Tissucol®) [102].

Foreign body removal from the tracheobronchial tree is an important clinical application of rigid bronchoscopy in children. However, the most suitable technique for foreign body extraction remains controversial. Most physicians recommend that in the presence of a radiopaque foreign body or asphyxia removal of the foreign body should only be attempted with a rigid bronchoscope [103]. In a small series of seven children, Pavlov *et al.* reported the successful extraction of foreign bodies with a flexible bronchoscope, showing that in selected cases foreign bodies can be safely extracted also with this technique [104].

PAEDIATRIC RESPIRATORY PHYSIOLOGY

There is increasing interest in the early life origins of adult lung disease, but there are limited functional data available. Tran *et al.* presented the long term follow-up of the 1957 Melbourne childhood asthma cohort. At 50 years, the 198 subjects were classified as: Normals, Asthma, COPD and Overlap, based on spirometry, diffusing capacity for carbon monoxide, and multiple-breath washout (MBW) measurements. Of the 149 with childhood asthma, 15% had COPD and 8% had overlapping symptoms of both asthma and COPD. Of the 35 who had severe childhood asthma or persistent asthma, 43% and 15% respectively had COPD. These results demonstrate tracking of lung function from childhood to 50 years and that COPD in middle age is a common consequence of severe asthma in childhood [105].

The use of the MBW technique to quantify ventilation inhomogeneity in paediatric lung disease and development is now well established [106]. At this year's congress

a number of research groups reported data from alternative techniques to quantify inhomogeneity. Pham *et al.* reported electrical impedance tomography (EIT) recordings in spontaneously breathing term infants measured soon after birth and again at 3 and 6 months of age [107]. At all these ages the authors demonstrated that the dependent lung showed earlier filling and better ventilation than the non-dependent lung.

Singer *et al.* reported a modified tidal single breath washout (SBW) test, using a double tracer gas and a molar mass analyser [108]. The test was demonstrated to be feasible and to show differences between children with CF and healthy controls. More detailed comparative studies with MBW and traditional SBW measurements are now required.

Mauro *et al.* employed opto-electronic plethysmography (OEP) to quantify the inspiration, and the compressive and expiratory phases of cough in 74 children and adolescents with Duchenne muscular dystrophy (DMD) and age-matched controls. Adolescents with DMD demonstrated reduced chest wall volume expansion and reduced peak expiratory flow compared to control adolescents, while younger children with DMD showed normal results [109].

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