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# Scientific Assembly Update. Paediatrics in Vienna

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**Abstract:**

The aim of this report is to describe the highlights of the paediatric track at the European Respiratory Society annual congress in Vienna, Austria. The best abstracts in 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 and set in the context of the current literature.

The European Respiratory Society (ERS) Congress in Vienna, Austria, had a large paediatric track programme, with many high-quality scientific presentations. Because of the many, sometimes unavoidably conflicting, sessions, and as a service to those who could not attend, we present an overview of highlights of abstracts from the paediatric assembly, selected by the officers from each scientific group, and set in the context of contemporary paediatric respiratory literature.

## Paediatric asthma and allergy

### *Preschool wheeze*

In 2008, the ERS Task Force Report on 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 United Kingdom (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 distinction of early wheezing disorders into EVW and MTW. 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 established.

Another UK study showed that eosinophils in bronchoalveolar lavage 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 (FeNO) at the age of 4 years was associated with asthma symptoms persisting up to the age of 8 years.[5] These results suggest that airways inflammation is important in the development and persistence of chronic wheeze, even in young children. This may only be true at group level, however. In a follow-up of their study showing inflammatory changes in mucosal biopsies of children with

MTW,[6] colleagues from Italy 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.[7] In individual patients, therefore, 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,[11] the extent to which wheeze remits 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 decade of life.

*Asthma in school-aged children and adolescents*

Over the past year, two large studies have shown that FeNO monitoring in childhood asthma does not improve clinically relevant asthma outcomes in children.[13,14] A large birth cohort study showed that at population level FeNO is more a marker of atopy than of asthma.[15] In this study, mean FeNO levels were highest in atopic asthmatics and atopic nonasthmatics, but comparable in nonatopic asthmatics and healthy nonatopic controls. These findings, which are in accordance with a recent USA study,[16] may partly explain the disappointing results of FeNO 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 Ukraine using high-resolution ultrasonography of the brachial artery in children with asthma showed a dose-dependent relationship of endothelial dysfunction to $FEV_1$ values.[18]

Viruses remain of interest as triggers of asthma flare-ups in children. In a Spanish study of 446 children hospitalized 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, 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, 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 recognized 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 on monotherapy with low-dose inhaled corticosteroids, provided that patients are being regularly followed up.[24] Conversely, a large survey of > 1000 children with asthma in 6 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 provided new insight into the aetiology, phenotypes and long-term outcome of childhood wheeze. In the Swedish Twin register, a 1000 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 preterm infants.[32,33] This study provides further evidence for an association between foetal growth and childhood asthma, independent of gestational age and of shared environment and genes.

Although the evidence supporting the hygiene hypothesis remains inconclusive,[34] the strongest data up to now 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 milk against asthma, hay fever and atopic sensitization. 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 related to the possible role of paracetamol in the pathogenesis of asthma.[39,40] A pilot study from the ALSPAC cohort explored if 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. 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 gender 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 men,[50] suggesting that sex hormones may help to explain the natural history of asthma through childhood.

**Cystic fibrosis (CF)**

Protocols for CF newborn screening usually utilize a stepwise approach with serum immuno reactive 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 to a standard IRT/DNA program.[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 (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] On the other hand, bronchial dilatation was found to be correlated with neutrophil elastase activity in BAL fluid raising the interesting question 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 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 two decades.[55] This highlights the need to continuously re-evaluate criteria for lung transplantation which are largely based on a study performed almost two decades ago that demonstrated $FEV_1$ <30 % to be associated with a 50% two year 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 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 hyperpolarized helium 3 (3He) by magnetic resonance imaging (MRI) is a non-invasive, apparently robust method for assessing alveolar size.[62] 49 term-born healthy children (25 male) aged 7-16 (median 12.3) years 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 three years 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 described normative data for pulmonary diffusion capacity ($DL_{CO}$), with simultaneous measurement of haemoglobin (Hb) in 387 healthy individuals aged 6-18 years.[63] Equations for $DL_{CO}$, $V_A$ (alveolar volume), $DL_{CO}/V_A$ and $DL_{CO}$/Hb corrected for sex and Caucasian *vs* 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 normalizing $DL_{CO}$ for $V_A$ did not provide a benefit.[63] A six-centre study from Europe and South America analysed 1117 measurements of interupter resistance (Rint) in

children aged 2-13 years, 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 preterm birth on lung function measured during preschool years. From a group in northern Italy, 74 children born at a mean gestational age (GA) of 29 weeks underwent Rint and impedance measurement from forced oscillation (FOT).[65] Results were comparable to those obtained in healthy children born at term. From Perth, Australia, a cohort of 150 children (74 BPD, 44 nonBPD, 32 controls) underwent spirometry and FOT between 4-8 years.[66] There were significant differences ($p<0.02$) between preterm children (BPD and nonBPD) and healthy subjects in $FEV_1$, $FEF_{25-75}$ and FOT reactance but not FVC 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 preterm (EP) and 52 controls (C), recruited from across the United Kingdom, measured at mean age of 11y.[68] Spirometry was better at discriminating between groups than $DL_{CO}$, lung clearance index, or resistance or lung volumes measured in the plethysmograph. However the authors cautioned that different investigations gave complementary information.

**Paediatric respiratory infections and immunology**

A new diagnostic method, vibration response imaging (VRI), allows atelectasis and lung infiltrates to be visualized. 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 bronchoalveolar lavage (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 3rd generation cephalosporins, induces extended spectrum β lactamase producing bacteria (ESPL) leading to a new pattern of bacterial resistance.[71] In most children with severe community acquired pneumonia, symptoms resolve within 24 hrs 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.

Several studies showed 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 succesful. On the other hand, early surgical decortication of pleural empyema resulted in shorter hospitalizations and reduced morbidity. It remains unclear how these different interventions impact on the long-term outcome of pleural empyema.

The morbidity and mortality due to acute lower respiratory tract infections during the first two years of life are highest in the world for children in Papua New Guinea. Laing and coworkers found that polymorphisms of genes associated with innate and adaptive immunity were associated with earlier and more severe respiratory infections in these patients.[77,78] This finding may expand our knowledge 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 8 accredited centres across France has now collected data about rare lung diseases in 82 patients, and recruitment will continue for the upcoming years.[79]

Increasing interest is being focused on the long term respiratory outcome of premature birth.[80] Increased levels of carbon monoxide (CO) in exhaled breath of neonates in the NICU on the 3rd and 14$^{th}$ day of life significantly improved the ability to predict subsequent BPD.[81] However, the addition of CO measurements only increased the predictive levels minimally (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 years of life in 2700 ex-premature babies (<32 weeks of gestation), children with BPD developed more symptoms than controls.[82] Despite the large numbers, however, 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 years) 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 and 40 years of age, RV/TLC 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, thirteen 8-12 year old children with BPD were subjected to oxygen levels of 12%. In children with BPD, oxygen saturation decreased from 99% to 91%, as compared to 92% in term born controls.[85] Apparently, former BPD patients tolerate hypoxia well.

A study from Sweden showed high levels of of the plasticizer 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 gastroesophageal 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] Unofrtunately, 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 inserted through a 4.5 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] Severe and sometimes fatal complications occur in a considerable proportion of children, however. 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.

## References


1. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008; 32:1096-1110
2. Sonnappa S, Bastardo C, McKenzie S, Bush A, Aurora P. Physiological validation of temporal preschool wheeze phenotypes. Eur Respir J 2009;34(Suppl 53):P1234.
3. Schultz A, Devadason S, Savenije O, Sly P, LeSouëf PN, Brand PLP. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. Acta Paediatr 2009 Sep 17 (Epub ahead of print).
4. Thavagnanam S, Williamson G, Ennis M, Heaney L, Shields M. Eosinophils are elevated in bronchial alveolar lavage before children develop clinical symptoms. Eur Respir J 2009;34(Suppl 53):P1242.
5. Caudri D, Wijga A, Smit HA, Brunekreef B, Koppelman G, Kerkhof M, de Jongste JC. Predicting asthma in symptomatic preschool children: contribution of exhaled nitric oxide, rint and specific IgE. Eur Respir J 2009;34(Suppl 53):P1235.
6. Turato G, Barbato A, Baraldo S, Zanin ME, Bazzan E, Lokar-Oliani K et al. Nonatopic children with multitrigger wheezing have airway pathology comparable to atopic asthma. Am J Respir Crit Care Med 2008; 178:476-82.
7. Turato G, Baraldo S, Panizzolo C, Agostini S, Bazzan E, Oliani KL, Snijders D, Balestro E, Fantoni U, Barbato A, Saetta M. Airway pathology and symptom evolution in wheezing children. Eur Respir J 2009;34(Suppl 53):P1236.
8. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000; 162:1403-6.

**9.** Frank PI, Morris JA, Hazell ML, Linehan MF, Frank TL. Long term prognosis in preschool children with wheeze: longitudinal postal questionnaire study 1993-2004. BMJ 2008; 336:1423-6.

**10.** Caudri D, Wijga A, Schipper MA, Hoekstra M, Postma DS, Koppelman GH, Brunekreef B, Smit HA, de Jongste JC. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. J Allergy Clin Immunol 2009;124:903-10.

**11.** Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ et al. Asthma and wheezing in the first six years of life. N Engl J Med 1995; 332:133-138.

**12.** Karmaus W, Arshad HS, Roberts GC, Kurukularaatchy R, Ogbuanu IU, Ewart S, Huebner M, Matthews S. Little evidence for an allergic march. Eur Respir J 2009;34(Suppl 53):E1464.

**13.** de Jongste JC, Carraro S, Hop WC, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. Am J Respir Crit Care Med 2009; 179:93-7.

**14.** Szefler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. Lancet 2008; 372:1065-72.

**15.** Scott M, Roberts G, Raza A, Clayton B, Kurukularaatchy R, Karmaus W, Huebner M, Arshad H. Exhaled nitric oxide is more a biomarker of atopy than asthma. Eur Respir J 2009;34(Suppl 53):P2113.

**16.** Jackson DJ, Virnig CM, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Burton RM, Salazar LP, DaSilva DF, Shanovich KM, Tisler CJ, Gern JE, Lemanske Jr RF. Fractional exhaled nitric oxide measurements are most closely associated with allergic sensitization in school-aged children. J Allergy Clin Immunol 2009;124:949-53.

**17.** van Berkel J, Robroeks C, Dallinga J, Jöbsis Q, Moonen E, Wouters E, van Schooten FJ, Dompeling E. Volatile organic compounds in exhaled breath are associated with exacerbations in children with asthma. Eur Respir J 2009;34(Suppl 53):P1194.

**18.** Antipkin Y, Lapshyn V, Umanets T, Nakonechna A. Relationship between induced sputum eosinophilia and endothelial dysfunction in children with bronchial asthma. Eur Respir J 2009;34(Suppl 53):3280.

**19.** Garcia-Garcia ML, Calvo C, De Cea JM, Falcon A, Casas I, Perez-Brena P. Role of emerging respiratory viruses in severe acute wheezing episodes in children. Eur Respir J 2009;34(Suppl 53):4214.

**20.** Bizzintino J, Lee WM, Laing I, Zhang G, Vang F, Pappas T, Goldblatt J, Gern J, LeSouëf P. New rhinovirus strains predominate in children with acute asthma and are associated with more severe exacaerbations. Eur Respir J 2009;34(Suppl 53):4213.

**21.** de Groot E, Nijkamp A, Brand P, Duiverman E. Allergic rhinitis in children with asthma: a cros-sectional questionnaire-based survey. Eur Respir J 2009;34(Suppl 53):4215.

**22.** Kurukularaatchy R, Matthews S, Grundy J, Raza A, Williams P, Mitchell F, Huebner M, Arshad SH. Associations of adolescent rhinitis and asthma. Eur Respir J 2009;34(Suppl 53):4216.

**23.** Kurukularaatchy R, Roberts G, Karmaus W, Ewart S, Clayton B, Raza A, Arshad SH. The nature of adolescent rhinitis. Eur Respir J 2009;34(Suppl 53):4442.

**24.** Champs N, Lasmar L, Freitas S, Camargos P. Inhaled steroids doses to obtain asthma control in children: a randomized controlled trial. Eur Respir J 2009;34(Suppl 53):E1662.

**25.** Brand P, Carroll W, Wildhaber J. Parent and child perceptions on the impact of asthma: global results from the "Room to Breathe" survey. Eur Respir J 2009;34(Suppl 53):4438.

**26.** Ducharme F, Noya FJD, Rich H, Davis M, Ernst P, Resendes S, Khomenko L. Randomized controlled trial of a multi-faceted intervention initiated in the emergency department (ED) to improve asthma control. Eur Respir J 2009;34(Suppl 53):4444.

**27.** Brouwer AFJ, Brand PLP. Asthma education and monitoring: what has been shown to work. Paediatr Respir Rev 2008; 9:193-200.

**28.** Klok T, Roordink H, Brand P, Duiverman E, Kaptein A. 'Parents are self managers': a qualitative study in parents about their children's asthma. Eur Respir J 2009;34(Suppl 53):4439.

**29.** Bracken M, Fleming L, Hall P, van Stiphout N, Bossley C, Biggart E, Wilson NM, Bush A. The importance of nurse-led home visits in the assessment of children with problematic asthma. Arch Dis Child 2009;94:780-4.

**30.** McDonald M, Roddy M, Carrig C, Devitt M, Elnazir B. Evaluation of a paediatric asthma nurse led telephone clinic in the follow up of children with asthma. Eur Respir J 2009;34(Suppl 53):4443.

**31.** Dewlett S, Shah A, Pillai P, Cally T. A paediatric asthma clinical pathway in the emergency department – a tool to prevent hospital admission? A retrospective non randomised controlled study. Eur Respir J 2009;34(Suppl 53):4442.

**32.** Örtqvist AK, Lundholm C, Carlström E, Lichtenstein P, Cnattingius S, Almqvist C. Genetic and shared environmental factors do not confound the association between birth weight and childhood asthma: a Swedish twin study. Eur Respir J 2009;34(Suppl 53):1351

**33.** Ortqvist AK, Lundholm C, Carlström E, Lichtenstein P, Cnattingius S, Almqvist C. Familial factors do not confound the association between birth weight and childhood asthma. Pediatrics 2009; 124:e737-43.

**34.** Platts-Mills TA, Erwin E, Heymann P, Woodfolk J. Is the hygiene hypothesis still a viable explanation for the increased prevalence of asthma? Allergy 2005; 60 (Suppl 79): 25-31.

**35.** von Mutius E, Radon K. Living on a farm: impact on asthma induction and clinical course. Immunol Allergy Clin North Am 2008; 28: 631-47.

**36.** Loss G, Waser M, Kneifel W, Apprich S, Genuneit J, von Mutius E, Horak E, Cookson W, Braun-Fahrländer C. Can farm milk consumption prevent allergic diseases? First results from the GABRIEL advanced studies. Eur Respir J 2009;34(Suppl 53):1358.

**37.** Fuchs O, Genuneit J, Latzin P, Frey U, Braun-Fahrlaender C, Horak E, Cookson WOCM, von Mutius E. The influence of farming on lung function in school-age children – the GABRIEL advanced surveys. Eur Respir J 2009;34(Suppl 53):E2465.

**38.** Genuneit J, Latzin P, Fuchs O, Frey U, Braun-Fahrländer C, Horak E, Cookson WOCM, von Mutius E. Measurement of exhaled nitric oxide in school-age children in rural areas – the GABRIEL advanced surveys. Eur Respir J 2009;34(Suppl 53) :E4264.

**39.** Allmers H, Skudlik C, John AM, Acetaminophen use: a risk for asthma? Curr Allergy Asthma Rep 2009;9: 164-7.

**40.** Kanabar D, Dale S, Rawat M. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms. Clin Ther 2007; 29:2716-23.

**41.** Shaheen S, Newson R, Relton C, Henderson J, Ring S, Davey-Smith G, Holloway J.Relation of cord blood DNA methylation to prenatal paracetamol exposure and childhood asthma. Eur Respir J 2009;34(Suppl 53):1355.

**42.** Strippoli MPF, Spycher BD, Beardsmore CS, Silverman M,Kuehni CE. Paracetamol use and the risk of wheeze: causation or bias? Eur Respir J 2009;34(Suppl 53):1356.

**43.** Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. Eur Respir J 2008 ;31:974-81.

**44.** Spycher BD, Minder CE, Kuehni CE, Multivariate modelling of responses to conditional items: New possibilities for latent class analysis. Stat Med 2009;28:1927-39.

**45.** Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, Shaheen SO, Sterne JA. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax 2008;63:974-80.

**46.** Clarisse B, Dematteï C, Daures JP, Just J, Momas I. Respiratory phenotypes among Paris birth cohort infants and their related factors. Eur Respir J 2009;34(Suppl 53):E4253.

**47.** Spycher BD, Silverman M, Strippoli MPF, Kuehni CE. Childhood wheeze: one or several diseases? Eur Respir J 2009;34(Suppl 53): E4254

**48.** Postma DS. Gender differences in asthma development and progression. Gend Med 2007; 4 ( Suppl B): S133-46.

**49.** Almqvist C, Worm M, Leynaert B. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. Allergy 2008;63:47-57.

**50.** Osman M, Srivastava P, Russell G, To T, Helms P. Advantage males: inverse association of serum testosterone and bronchial hyper-responsiveness. Eur Respir J 2009;34(Suppl 53):E4269.

**51.** Vernooij-van Langen A, Loeber G, Elvers B, Triepels R, Gille H, van der Ploeg C, Reijntjens S, Dompeling E. Cystic fibrosis heelprick among a newborn population in the Netherlands: the CHOPIN study. Eur Respir J 2009;34(Suppl 53):1620.

**52.** Hall G, Nolan G, Logic K, Schulzke S, Murray C, Stick S, Ranganathan S, Robinson P, Sly P. Ventilation distribution is not influenced by structional lung disease in infants

with cystic fibrosis (CF) diagnosed following newborn screening (NBS). Eur Respir J 2009;34(Suppl 53):1621.

**53.** Sly P, Gangell C, De Klerk N, Ranganathan S. Neutrophillic inflammation predisposes to structural lung disease in cystic fibrosis (CF) via neutrophil elastase activity Eur Respir J 2009;34(Suppl 53):1622.

**54.** Eichinger M, Haeselbarth J, Niemann A, Hans Ulrich K, Mall M, Puderbach M. Magnetic-resonance-imaging (MRI) for assessment of regional threapy response in patients with cystic fibrosis (CF). Eur Respir J 2009;34(Suppl 53):E466.

**55.** George P, Pareek N, Bilton D, Banya W, Hodson M. Improved survival at low lung functions in cystic fibrosis (CF). Eur Respir J 2009;34(Suppl 53):1623.

**56.** Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992;326:1187-91.

**57.** Ratjen F. Restoring airway surface liquid in cystic fibrosis. N Engl J Med 2006;354:291-3.

**58.** Jaques A, Daviskas E, Turton JA, McKay K, Cooper P, Stirling RG, Robertson CF, Bye PT, Lesouëf PN, Shadbolt B, Anderson SD, Charlton B. Inhaled mannitol improves lung function in cystic fibrosis. Chest 2008;133:1388-96.

**59.** Bilton D, Robinson P, Cooper P, Charlton B. Randomised, double blind, placebo-controlled phase III study of inhaled dry powder mannitol in cystic fibrosis (CF). Eur Respir J 2009;34(Suppl 53):1619.

**60.** Minasian CC, Wallis C, Metcalfe C, Bush A. Comparison of inhaled mannitol, daily rhDNase, and a combination of both in children with cystic fibrosis : a randomised trial. Thorax 2009 Dec 8. [Epub ahead of print]

**61.** Narayanan M, Owers-Bradley J, Ball I, Mada M, Kuehni C, Spycher B, Garipov R, Silverman M, Beardsmore C. Evidence for continuous alveolisation during childhood, using 3He magnetic resonance. Eur Respir J 2009;34(Suppl 53):1618.

**62.** Peces-Barba G, Ruiz-Cabello J, Cremillieux Y, Rodriguez I, Dupuich D, Callot V, Ortega M, Rubio Arbo ML, Cortijo M, Gonzalez-Mangado N. Helium-3 MRI diffusion coefficient: correlation to morphometry in a model of mild emphysema. Eur Respir J 2003;22:14–19.

**63.** Kim YJ, Christoph K, Eigen H. Pulmonary diffusion capacity in healthy children – normative data based on gender and race. Eur Respir J 2009;34(Suppl 53):1612.

**64.** Lombardi E, Stocks J, Merkus P, Beydon N, Jones M, McKenzie S, Kivastik J, Stanojevic S. Reference ranges for interrupter resistance technique: the asthma UK initiative. Eur Respir J 2009;34(Suppl 53):E4310.

**65.** Calogero C, Lombardi E, Franchi S, Mele L, Aversa L, Bertini G, Gatti MG, Pignotti MS, Sigali E, Rusconi F. Pulmonary function at preschool age in an area-based cohort of very preterm infants. Eur Respir J 2009;34(Suppl 53):E4318.

**66.** Verheggen M, Wilson A, Pillow J, Stick S, Hall G. Relationship between lung function and respiratory symptoms in young children born preterm. Eur Respir J 2009;34(Suppl 53):E4322.

**67.** Hennessy EM, Bracewell MA, Wood N, Wolke D, Costeloe K, Gibson A, Marlow N; EPICure Study Group. Respiratory health in pre-school and school age children following extremely preterm birth. Arch Dis Child. 2008;93:1037-43.

**68.** Lum S, Kirkby J, Welsh L, Hennessy E, Marlow N, Stocks J. Respiratory follow-up for children born extremely preterm: which test is best? Eur Respir J 2009;34(Suppl 53):1617.

**69.** Saretta F, Guerra M, Stefani A, Canciani M. New tool for lung imaging: vibration response imaging (VRI). Experience in a paediatric population. Eur Respir J 2009;34(Suppl 53):3244.

**70.** de Mol M, de Jongste JC, Merkus PJFM, Janssens H. Diagnostic value of galactomannan in bronchoalveolar lavage for invasive pulmonary aspergillosis in immunocompromised children. Eur Respir J 2009;34(Suppl 53):3249**.**

**71.** Popova I, Iliesvka T, Zafirovski O. Characterization and prevalence of macrolide resistance *Streptococcus pneumoniae* infecting pediatric patients. Eur Respir J 2009;34(Suppl 53):E4525**.**

**72.** Richter D, Galic S, Cuk M, Novak M. Hospital treatment of community acquired pneumonia in children with penicillin. Eur Respir J 2009;34(Suppl 53):E4524

**73.** Valeri R, Gidaris D,Bandouraki MM, Doulianaki E, Nedelkopoulou N, Ioannidou S, Tsikopoulos G. Current indications for decortication in the treatment of empyema in children**.** Eur Respir J 2009;34(Suppl 53):E4530.

**74.** Kirvassilis F, Kontouli K, Hatziagorou E, Andrianaki D, Roilides E, Tsanakas J. **I**ncidence, aetiology and long-term evaluation of parapneumonic effusions complicated community acquired pneumonia during the period 1994-2008 in northern Greece. Eur Respir J 2009;34(Suppl 53):E4531.

**75.** Mojzíšová M, Kokešová A, Rygl M, Vyhnánek M, Svobodová T, Blazek D, Kyncl M, Šnajdauf J. Where is the right place for paediatric thoracic surgeon in the management of complicated pleuropneumonia? Eur Respir J 2009;34(Suppl 53):E4532.

**76.** Chingale A, O'Donnelln R, Iles R, Set P, Ross Russell R .Management of empyema complicating necrotising pneumonia. Eur Respir J 2009;34(Suppl 53):E4533.

**77.** Laing I, Lai M, Jacoby P, van den Biggelaar A, Pomat W, Orami T, Phuanukoonnon S, Opa C, Holt P, Upham J, Richmond P, Blackwell J, Siba P, Lehmann D**.** Innate immune gene polymorphisms had a lack of heterozygosity in 38% of polymorphisms studied and *TLR*2 A-16934t and A-15607g and *CD14* C-550T were related to the

incidence of acute lower respiratory infections (ALRIs) in early life in children from the highlands of Papua New Guinea (PNG). Eur Respir J 2009;34(Suppl 53):P4034.

**78.** Laing I, Lai M, Jacoby P, van den Biggelaar A, Pomat W, Orami T, Phuanukoonnon S, Opa C, Holt P, Upham J, Richmond P, Blackwell J, Siba P, Lehmann D. Adaptive immune gene polymorphisms are associated with earlier and increased incidence of acute lower respiratory infections (ALRIs) in children from papua new guinea (PNG). Eur Respir J 2009;34(Suppl 53):P4035.

**79.** Aubertin G, Malloul M, Vibert JF, Annick C, Fauroux B. National web-based register for noninvasive positive pressure ventilation in children. Eur Respir J 2009;34(Suppl 53):E1400.

**80.** Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. J Pediatr 2007;150:256-61.

**81.** May C, Patel S, Kennedy C, Pollina E, Rafferty G, Peacock J, Greenough A. Prediction of bronchopulmonary dysplasia. Eur Respir J 2009;34(Suppl 53):3056.

**82.** Wilson A, Pascoe E, Salven A, French N, Hagan R, Hall G. Respiratory symptoms in the first 3 years of life in ex-premature infants and children. Eur Respir J 2009;34(Suppl 53):3058.

**83.** Trachsel D, Amacher A, Muller D, Hammer J. Long-term pulmonary outcome of "old" BPD. Eur Respir J 2009;34(Suppl 53):3059.

**84.** Wisbauer M, Luise W, Schuster A. Fatal and near-fatal asthma in children: a two-year nationwide survey in Germany. Eur Respir J 2009;34(Suppl 53):3276.

**85.** Joshi S, Edwards JM, Wilson DG, Drayton M, Fraser AG, Kotecha S. Cardiovascular response to acute hypoxia in 8-12 year old children with chronic lung disease of prematurity. Eur Respir J 2009;34(Suppl 53):P4050.

**86.** Bjorling G, Laub M, Frostell C, Aune RE, Karlsson S, Jonsson BAG. Urine levels of plasticizers in children on long-term mechanical ventilation via PVC tracheostomy tubes. Eur Respir J 2009;34(Suppl 53):P4057.

**87.** Cakmak F, Uyan ZS, Ersu R, Karadag B, Karakoc F, Dagli E. Flexible bronchoscopy findings of the patients with stridor. Eur Respir J 2009; 34 (Suppl 53): 4102.

**88.** Midulla F, Guidi R, Tancredi GC, Quattrucci S, Ratjen F, Bottero S, Vestiti K, Francalacci P, Cutrera R. Microaspiration in infants with laryngomalacia. Laryngoscope 2004; 14:1592-6.

**89.** Uyan ZS, Pamukcu O, Carik E, Oktem S, Karakoc F, Karadag B, Ersu R, Dagli E. Bronchoscopy findings in children with asthma symptoms. Eur Respir J 2009; 34 (Suppl 53): 1819.

**90.** Kot'àtko P, Pohl J, Svobodova T, Jirousova K, Krepela K, Pohunek P. Tubercolosis in a young child presenting as an obstructive disease. Eur Respir J 2009; 34 (Suppl 53): 4099.

**91.** Thalhammer G, Zach M, Eber E. Diagnostic value of flexible bronchoscopy in children and adolescents with congenital thoracic malformations. Eur Respir J 2009; 34 (Suppl 53): 1817.

**92.** Caro P, Perez-Riuz E, Perez-Frias J, Moreno L, Argos MD, Calvo M, Sanchez F. Endoscopic diagnosis and management of congenital tracheo-esophageal fistula. Eur Respir J 2009; 34 (Suppl 53):1820.

**93.** de Blic J, Midulla F, Barbato A, Clement A, Dab I, Eber E, Green C, Grigg J, Kotecha S, Kurland G, Pohunek P, Ratjen F, Rossi G. Bronchoalveolar lavage in children. Eur Respir J 2000;15:217-31.

**94.** Snijders D, Bertuola F, Panizzolo C, Turato G, Agostini S, Baraldo S, Mastrotto C, Saetta M, Barbato A. Eosinophilic and neutrophilic mediators in BAL fluid of atopic and non athopic asthmatic children. Eur Respir J 2009; 34 (Suppl 53):4109.

**95.** Mahut B, Delacourt C, Mamou-Mani T. Pulmonary alveolar proteinosis. Pediatrics 1996; 97:117-22.

**96.** Primhak R, John R. Whole lavage in pulmonary alveolar proteinosis in a young child- a new technique. Eur Respir J 2009; 34 (Suppl 53):4095.

**97.** Zimmerman T, Cesnjevar R, Carbon R, Zenk J, Dittrich S, Gloeckler M, Schoenecker V. ALTE: long-segment tracheal stenosis, slide tracheoplasty and multidisciplinary approach in a 7 week old female. Eur Respir J 2009; 34 (Suppl 53):4097.

**98.** Nicolai T. Airway stents in children. Pediatr Pulmonol 2008;43:330-40.

**99.** Anton-Pacheco JIL, Luna C, Martinez A, Gomez-Acebo F, Garcia-Hernandez G. Outcome of airway stenting in the setting of pediatric tracheobronchial obstruction. Eur Respir J 2009; 34 (Suppl 53):18921.

**100.** Kadar L, Ujszàszi E, Gyorfy A, Simon N, Subicz A, Marialigeti T. Preliminary Hungarian experience with airway stenting in infants and children. Eur Respir J 2009; 34 (Suppl 53):1822.

**Table 1: "getting the basics right" in childhood asthma management**

Important issues to consider in children in whom inhaled corticosteroid therapy is unsuccesful, 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