The CFTR gene was cloned in 1989 using a positional cloning approach which included chromosome walking and jumping, linkage disequilibrium analysis and correlation of tissue expression pattern between CF and non-CF tissues. The gene comprises 27 coding exons, spanning over 250 kb on chromosome 7q31.2, and the transcript is 6.5 kb. The most common CF mutation is a 3bp deletion, causing a loss of phenylalanine at position 508 of the protein, ΔF508. The protein encoded by the CFTR gene is a chloride channel in the apical membrane of exocrine epithelial cells. It comprises 1480 amino acids with a molecular weight of ~170kDa. The protein comprises five domains: two membrane-spanning domains, each composed of six transmembrane segments that form the channel, two nucleotide-binding domains, capable of ATP hydrolysis, and a regulatory domain, which contains numerous phosphorylation sites. Phosphorylation of sites in the R domain by protein kinase A, regulated by cAMP, and the hydrolysis of ATP by the NBDs, are essential for activating the chloride channel.

Over 200 sequence variations (mutations, which are involved in disease expression and polymorphisms, which have no effect on the phenotype) have been identified so far along the entire CFTR gene. delF508 is found in ~70% of the CF chromosomes worldwide; however its frequency varies greatly among different ethnic groups, between 100% in the isolated Faroe Islands of Denmark to 18% in Tunisia. In Europe there is a clear decreasing gradient in the frequency of delF508 from northeast to southwest. The cloning of the CFTR gene and the identification of its mutations has enabled extensive research into the association between genotype and phenotype, which has contributed to our understanding the mechanisms responsible for the remarkable clinical heterogeneity of CF. The increased knowledge on the molecular mechanisms by which the mutations cause CF led to classify the different CFTR mutations into five major classes according to their effect on CFTR function. This led to the development of mutation-specific therapies using high-throughput screening for small molecules that lead to pharmacotherapy targeting the basic CFTR defect. The only mutation-specific drug available is ivacaftor, registered to treat patients with CF carrying a class III (gating) mutation. Although many of these mutations are rare, the disease-causing G551D mutation is fairly common and is identified in about 4% of patients with cystic fibrosis worldwide. G551D is expressed on the surface of epithelial cells but, compared with normal CFTR channels, has reduced function due to low channel open probability compared with normal CFTR (i.e., defective gating). This leads to a severe reduction in CFTR chloride transport activity and CF disease. Ivacaftor is a novel CFTR potentiator that increases chloride transport by potentiating the channel open probability of the CFTR protein. In-vitro studies of ivacaftor have shown significant improvements in CFTR chloride channel opening time, with improved chloride transport approaching 50% of normal CFTR. Phase 3 studies examined the effects of ivacaftor in patients with CF who had at least one copy of G551D. Ivacaftor improved lung function, weight, and patient-reported respiratory symptoms, reduced the frequency of pulmonary exacerbations, and reduced sweat chloride levels to below the diagnostic threshold. The results of these studies led to the approval of ivacaftor in North America, Australia, New Zealand, and Europe.

Class I nonsense mutation in the CFTR gene represents ~10% of the CF population. Ataluren (PTC124) is an orally bioavailable, investigational new drug that promotes ribosomal readthrough of premature stop codons. It is being developed as a disease-modifying treatment for nnCF, leading to production of full-length, functional CFTR. In a phase III trial, ataluren showed positive trends favoring ataluren vs. placebo at Week 48 for FEV1 and pulmonary exacerbation rate. Concomitant administration of inhaled tobramycin appeared to interfere with ataluren’s ability to enable readthrough of nonsense mutations. In nnCF patients not administered chronic inhaled tobramycin, ataluren produced a notable treatment effect compared with placebo. Another phase III study with patients not treated with inhaled aminoglycosides is ongoing.

Identifying all the mutations in the CFTR gene which are involved in typical CF and CF-related diseases and developing simple and inexpensive methods for screening a large number of mutations, will enable early genetic diagnosis of all the patients before the development of symptoms, preferably as neonates. A better understanding of the effect of different mutations along the CFTR gene on CFTR function will broaden our understanding of the different functions of the CFTR protein as well as the function of each CFTR domain and in developing therapies that will fix the molecular or structural defect caused by the mutation.

**OPPORTUNITIES OF NON-INVASIVE VENTILATION**

Pr Brigitte Fauroux, MD, PhD
Necker University Hospital, Paris, France

Noninvasive ventilation (NIV) and noninvasive continuous positive airway pressure (CPAP) are increasingly used in children for the treatment of acute and chronic respiratory failure. NIV is indicated when the patient presents a disequilibrium of the ventilatory balance, the aim of NIV will be to correct this disequilibrium by either unloading the respiratory muscles in case of an increase in respiratory load (as observed in cystic fibrosis), or by replacing them in case of respiratory muscle weakness (as observed in neuromuscular diseases). In cases of a failure of central drive (as in Ondine’s course), the aim of NIV will be to replace central drive. On the other hand, CPAP is indicated in patients who present a structural or anatomical upper airway obstruction, which exposes them to recurrent episodes of upper airway closure, responsible of apneas or hypopneas, especially during sleep. These children do not present overt respiratory failure as the bypass of the obstruction restores a normal breathing. In these patients, CPAP delivered by a noninvasive interface represents the technique of choice, with a tracheotomy being reserved for CPAP failure. NIV/CPAP is increasingly used in the intensive care unit (ICU). Indeed, acute respiratory failure (ARF) is one of the most common causes of ICU admission in children. In children with lower airway obstruction, such as asthma or viral bronchiolitis, NIV and CPAP have been shown to improve gas exchange, decrease the work of breathing and reduce the rate of intubation. In children with advanced cystic fibrosis lung disease, NIV has been shown to reduce the work of breathing which translates into an improvement in alveolar hypventilation. As such, NIV is recommended as a first line treatment for an acute hypercapnic respiratory exacerbation. In patients with upper airway obstruction, such as tracheo-laryngomalacia or stenosis or craniofacial malformation, CPAP may facilitate extubation or avoid recanululation after extubation. NIV may also be useful in moderate...
hypercapnic respiratory failure due to acute chest syndrome in sickle cell disease, pneumonia and also during acute ARF after liver-transplantation. Finally, NIV has also been shown to be useful in children with ARF due to heart disease by facilitating extubation after cardiac surgery. However, NIV has little or no proven benefit in patients with acute respiratory distress syndrome due to parenchymal or interstitial lung diseases, or when ARF is due to septic shock. In the chronic setting, the most common diseases that may require NIV are neuromuscular disorders, hypercapnic lung diseases, such as advanced cystic fibrosis lung disease, and central hypoventilation. Equipment used for NIV or CPAP is slightly different in the acute and chronic setting. In the ICU, ICU ventilators are used. At home, less sophisticated devices are used but their performance may be close to that of ICU ventilators. Different interfaces may be used for NIV or CPAP such as nasal masks, nasal pillows, oro-nasal masks, oral masks, mouthpieces or helmets. Ideally, the best interface should be small (with a minimal dead space), light-weight, easy to affix and to remove, and with a headgear that confers stability preventing movements or dislocation in order to minimize leaks. Facial or oro-nasal masks are generally preferred in the acute situation because of frequent mouth breathing during ARF. The helmet is a very useful interface in the acute setting because it has no direct contact with the patient’s face, thus avoiding any skin injury. In any case, the interface associated with the best tolerance and comfort, defined by the absence of any skin injury, pain, discomfort, and leaks, should be used. The criteria to initiate NIV or CPAP are not validated in children but most experts recommend NIV or CPAP in case of persistent hypercapnia despite optimal medical treatment. Indeed, the aim of NIV or CPAP is to maintain the maximal carbon dioxide level (CO2) below 50 mmHg by providing a sufficient tidal volume and minute ventilation. Settings should be individually adapted with careful monitoring, including CO2 monitoring.

In conclusion, even if NIV and CPAP are increasingly used in children, some issues still remain controversial. Since NIV success depends on the careful selection of the appropriate patient at the right time, we need more carefully conducted prospective studies in children with various disorders in order to better identify which patient would benefit most from NIV or CPAP. Furthermore, even if substantial improvements have been made by industries, the vast majority of ventilators were originally designed for adults. Uncertainties remain as to the performance of such ventilators when dealing with pediatric patients, especially regarding trigger sensitivity and minimal volume and flow delivered. Finally, manufacturers should continue to improve NIV interfaces, especially for younger children.

References
transmitted to a new host. Children usually have transmitted resistance and consequently the proportion of TB in children that is multidrug-resistant (MDR), is similar to the proportion that is MDR in new adult cases.\textsuperscript{7,10} Estimates have suggested that about 30,000 children develop MDR-TB each year,\textsuperscript{7} but these cases are likely to be found in hotspots where both the number of paediatric cases is high as well as the proportion that are MDR. By estimating the number of childhood TB cases and the number of MDR-TB cases, and then comparing to the number reported by National TB Programmes, a ‘gap’ can be determined.\textsuperscript{9} This allows a mechanism for the evaluation of services and also their progression over time. Setting targets for the number of child contacts that should be identified, the number that should receive preventive therapy and the number that should be treated for both TB and MDR-TB disease, has been suggested as a means of improving services.\textsuperscript{11}

References


NEW INSIGHTS INTO BRONCHOPULMONARY DYSPLASIA

Hugh O’Brodovich MD, FRCP(C)
For correspondence and reprint requests please contact: Hugh O’Brodovich MD
Pediatric Pulmonologist
Adalyn Jay Physician-in-Chief
Lucie Packard Children’s Hospital
Arline & Pete Harman Professor & Chair
Director, Stanford Child Health Research Institute
Department of Pediatrics
Stanford School of Medicine
300 Pasteur Drive, Room H310
Stanford, CA 94305-5208
Ph: (650) 725-3214
Fax: (650) 725-4719
email: hugh.obrodovich@stanford.edu

Keywords: genome-wide association study (GWAS), chronic lung disease, genetic predisposition to disease, premature, very low birth weight infant (VLBW)

Bronchopulmonary dysplasia (BPD) was first described by Northway in 1967\textsuperscript{1}. During that era this severe chronic lung disease usually occurred in moderately premature infants of 28-36 weeks gestational age (GA) and was associated with the patient’s exposure to high oxygen concentrations and ventilator pressures to maintain normal arterial blood gas tensions. The pathology of Northway’s (“Old BPD”) was characterized by extensive airway damage, impairment of mucociliary transport, hyper-responsiveness of the airways with obstructive and obliterator findings in the small airways. The distal lung units were filled with proteinaceous fluid, the interstitium had significant fibrosis, the lungs were hyperinflated, and usually associated with pulmonary hypertension. Research from the 1970s the 1990s provided a better understanding of the regulation of fetal lung maturation, the composition and properties of surfactant, the deleterious effects of high ventilator pressures on the lung and the physiologic effects of pH and PaCO\textsubscript{2}. This knowledge led to the appropriate use of antenatal corticosteroids, exogenous surfactant therapy, less volu-trauma and an improvement in physicians’ tolerance of “abnormal” blood gas tensions. This led to a dramatic reduction in the rate of BPD and also an increased rate of survival of prematurely born infants who were born between 24 and 28 weeks GA and who weighed less than 1500g at birth. Although the improvements in therapeutic approach, described above, significantly altered the clinical course of the lung disease in these very low birth weight (VLBW) infants, many still developed a chronic form of lung disease requiring ongoing supplemental oxygen and/or positive pressure support. However this new form of chronic lung disease had different clinical and pathologic characteristics. Most notably, this “new BPD” was characterized by an arrest of alveolar development, little or no airway damage or interstitial fibrosis, and lung volumes that were normal or mildly decreased.\textsuperscript{2,3} This new BPD occurs very frequently; indeed infants between 24 and 28 weeks GA have, on average, an approximate 50% chance of requiring supplemental oxygen at 36 weeks post menstrual age (PMA). It is important to note, however, that an individual institution’s incidence of BPD will depend on whether it uses a “physiologic” assessment of the need for supplemental oxygen at 36 weeks PMA.\textsuperscript{4} Unfortunately further research and clinical trials have not been able to substantially alter the rate of new BPD or what is more aptly referred to as chronic lung disease of infancy (CLDI).

Much work has been done by many different investigators in non-primate models of BPD, primate models of BPD and patients with BPD to investigate potential mechanisms and biomarkers and there are data supporting different hypotheses for the mechanisms leading to BPD. It is possible that different mechanisms play a role at different GA given that the fetal lung will be in different stages of lung development.

For some time it has been suspected that there may be a gene-environment interaction leading to the susceptibility to develop BPD in VLBW infants. Two twin studies\textsuperscript{5,6} came to comparable conclusions that heritable (genetic) factors play a significant role in the predisposition to develop new BPD. Indeed these publications estimated that genetic factors were responsible for 50-80% of the risk to develop BPD; this is significantly greater than the heritability shown for systemic hypertension, cancer or psychiatric disorders and adults.

To pursue potential genetic factors that might increase the risk for BPD, our research group performed a population-based study in California.\textsuperscript{7} This study was feasible because more than 90% of all NICU admissions in the state participate in the California perinatal quality care collaborative (www, cpqc.org). Accordingly, we were able to identify from calendar years 2005 -2008 a total of 2,154 singleton births of 25-29\textsubscript{6/7} weeks GA with BW < 1500g who had received a minimum of three days of intermittent positive pressure ventilation. Of these 2154 qualified singletons, who were in hospital and whose oxygen status was known at 36 weeks PMA, there were 1,063 who were breathing room air with the remaining 1,091 having a diagnosis of BPD. We were able to anonymously link these infants to their Guthrie newborn screening blood spots and our group developed a new

\textit{Pediatric Pulmonology}
Pediatric Pulmonology

S4 Abstract
technique8 for the isolation of non-amplified genomic DNA that was suitable for direct assessment on an Illumina 2.5 M single nucleotide polymorphism (SNP) platform. This enabled a genome wide association study (GWAS) which is a strategy to identify specific regions of the genome that might be associated with a predisposition to BPD. However, we were unable to identify any regions which met the strict criteria for genome wide significance2, an association with copy number or association with previously identified SNPs suggested to have an association with BPD10. There are several potential explanations for this negative GWAS. Although it is feasible that there are no heritable factors predisposing to BPD, the strong data from previous twin studies5,6 argues against this hypothesis. A second possibility is that the strict genome wide significance test, based on a Bonferroni correction, is too stringent. Another third possibility, which we favor, is that until the last two decades, infants who were born so prematurely would never have survived making it unlikely that a single area could have been favored. This, combined with the possibility that it may be multiple genes in multiple pathways that might represent the heritable factor, led us to perform another genetic study. We utilized a similar approach to identify premature born infants with and without new BPD and sequenced their exomes. In contrast to our GWAS, we identified specific pathways that were associated with the development of BPD.

References List

GLOBAL ADVANCES IN CHILDHOOD PNEUMONIA
Heather J Zar
Department of Paediatrics and Child Health, Red Cross War Memorial Children’s Hospital, University of Cape Town and MRC unit on Child & Adolescent Health, South Africa
Correspondence:
Prof Heather J. Zar
Dept of Paediatrics and Child Health
Pediatric Pulmonology

5th Floor, ICH Building
Red Cross War Memorial Children’s Hospital
Cape Town, South Africa
Tel: 2721-658-5324
Fax: 2721-689-1287
heather.zar@uct.ac.za

The incidence of severe childhood pneumonia has declined substantially in the last decade, with advances in immunization, improvements in socio-economic status and effective HIV preventative and treatment strategies. However, pneumonia remains a major cause of morbidity and mortality in children globally, responsible for approximately 15% (or just under 1 million deaths) of an estimated 6.3 million deaths annually in children. (1) In 2010, there were approximately 120 million episodes of childhood pneumonia with more than 14 million severe cases and 12 million hospitalizations. (2) Pneumonia incidence and severity is highest in the first 6 months of life. (3,4) Africa and southeast Asia have the highest caseload globally and the greatest proportion of severe cases. (5) Further, HIV-infected children have a 6-fold higher risk of developing severe pneumonia compared to uninfected children. (5) Other risk factors for pneumonia and for severe disease include young age, smoke exposure, chronic underlying disease, prematurity or low birth weight, low socio-economic status or malnutrition. (6,5) HIV-exposed but uninfected children, who have an HIV-infected mother, are emerging as another vulnerable group who may have a higher risk of pneumonia than HIV-unexposed infants (5).

The conjugate vaccines, H influenzae type b (Hib) and pneumococcal conjugate vaccines (PCV) have reduced the burden of childhood pneumonia. (6,5) PCV has led to a large decline in all-cause pneumonia hospitalization especially in children under 2 years of age with a more modest reduction in children aged 2 to 4 years. While PCV reduces severe invasive pneumococcal disease and bacteremia, prevention of non-bacteremic pneumococcal pneumonia is almost 20-fold greater compared to that of bacteremic pneumonia; the overall burden of disease prevented in HIV-infected children is much greater because of their susceptibility to disease. (7,5) PCV has also led to a decline in hospitalization for adult pneumonia due to indirect protection through reduction in circulating pneumonia causing pneumococci serotypes. (6,5) However, even in areas with high coverage for the 13-valent PCV, the incidence of pneumonia remains high especially in the first 6 months of life. (5)

Diagnosis of pneumonia has relied on clinical and radiological features. In community-based settings, World Health Organization (WHO) case management guidelines have recently changed, to classify children with lower chest indrawing as having pneumonia rather than severe pneumonia and recommending treatment with oral antibiotics as ambulatory cases. (9) Identifying the etiology of pneumonia is challenging as bacteremia is rare, distinguishing colonizing from pathogenic organisms may not be possible on respiratory specimens and co-infections are common. Recent diagnostic advances include improvements in specimen collection and improved molecular techniques for detection of organisms. Replacement disease, with non-vaccine serotypes due to an increase in non-vaccine serotype disease in communities with wide vaccine coverage may be a concern as widespread coverage with PCV13 is attained. Further, with high coverage for conjugate vaccines including PCV, the importance of vaccine-targeted pathogens can be anticipated to diminish while viral pathogens especially RSV and other bacteria, such as S aureus or pertussis, are emerging as prominent causes of childhood pneumonia. In areas of high TB prevalence, M tuberculosis has been reported to be associated with acute pneumonia in children, with culture confirmed disease occurring in approximately 7-8% of cases. Immunization of pregnant women to protect against pneumonia in the first 3 months of life is gaining prominence as a potential effective strategy for pathogens such as pertussis, influenza and RSV. A recent randomized controlled trial of influenza immunization of pregnant women reported a vaccine efficacy of approximately 50% amongst immunized women and similar reductions in infants under 6 months of age for influenza proven infection. (10) Immunization of pregnant women may offer a promising strategy to reduce the severity and burden of childhood pneumonia.
LATE CONSEQUENCES OF CHILDHOOD ASTHMA

Andrew Bush MB BS (Hons) MA MD FRCP FRCPCH FERS

Professor of Paediatrics and Head of Section (Paediatrics), Imperial College Professor of Paediatric Respiratory, National Heart and Lung Institute Consultant Paediatric Chest Physician, Royal Brompton Harefield NHS Foundation Trust.

Correspondence: Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK.

AB was supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London

Tel: -207-351-8222
Fax: -207-351-8763
e mail:- a.bush@imperial.ac.uk

References

Abstract S5

Introduction
The final outcomes in adult life of children who have had asthma are comprised of (a) the causes of the underlying asthma; (b) the consequences of asthma itself; and (c) the consequences of treatment. Treatment consequences also include treatment for associated conditions such as eczema and allergic rhinitis, which may also increase the burden of steroid therapy. These cannot readily be unpacked, and, since treatment has changed over the decades, the long-term outcomes of today’s asthma may be different. Finally, the really long-term cohorts (Melbourne, Aberdeen) did not have the modern ability to phenotype early asthma. The considerations of airway disease discussed in my bronchopulmonary dysplasia talk could not be applied, and sterile umbrella terms have to be accepted.

Early airflow obstruction, long term issues
The Global Lung Initiative (www.lungfunction.org/) has produced spirometry equations covering the entire life span; briefly, the threshold for respiratory symptoms and disability as the lung ages depends on being born with normal lung function; growing the lungs at a normal rate to a plateau age 20-25 years; and then the rate of decline in the ensuing decades is normal. Irrespective of the presence of asthma or wheeze, airflow obstruction shortly after birth tracks into the third decade, and will likely track thereafter as well. Early airflow obstruction is also a risk factor for the development of asthma.

Early wheeze, impaired lung growth
The CAMP study which compared asthma treatment with 400 mcg budesonide, 16 mg nedocromil or placebo daily for 4-6 years in children with asthma aged 5–13 years first identified that around one third of mild-moderate asthmatics had impaired development of airway function, irrespective of treatment. This was taken forward by the Manchester group, who used unsupervised techniques to study four wheeze phenotypes (none, transient, late onset and persistent) and five atopy phenotypes (none, dust mite, non-dust mite, multiple early and multiple late) and showed that impaired airway development was associated only with persistent wheeze and multiple early atopy combined. Acute asthma attacks also predicted a bad trajectory.

Early wheeze, later rate of decline of spirometry
The data are controversial. The Aberdeen cohort showed that those with asthma did not attain a normal first second forced expired volume (FEV1) plateau, and had an accelerated rate of FEV1 decline. Interestingly, those with ‘wheezy bronchitis’, which we would now describe as having episodic viral wheeze, had a normal FEV1 plateau but an accelerated decline in FEV1. An accelerated rate of decline predisposes to ‘COPD’ in adult life, but the TORCH and ECLIPSE studies have both shown that many COPD patients have a normal rate of change of FEV1, so accelerated decline is not a pre-requisite for the diagnosis.

By contrast, the Melbourne cohort, who recruited normal and mild and moderate asthmatics age 7, and enriched the cohort with severe asthmatics at age 10, and followed them to the sixth decade, showed that rate of change of FEV1 was the same and ran on parallel tracks for normal and all degrees of severity of asthma; thus the long-term differences were all determined in the very early years, before the children were recruited. There was no evidence of a difference in the rate of decline in FEV1 (mL/y, 95% CI) between the severe asthma group (15 mL/y [95% CI, 9.2-22 mL/y]) and all the other recruitment groups: control (16 mL/y [95% CI, 12-20 mL/y]), mild wheezy bronchitis (14 mL/y [95% CI, 8-19 mL/y]), wheezey bronchitis (16 mL/y [95% CI, 11-20 mL/y]) and persistent asthma (19 mL/y [95% CI, 13-24 mL/y]). The question of asthma and COPD is discussed below. This group has the best outcome data relating severity of asthma to likelihood of remission. Asthma remission at the age of 50 years was 64% in those with wheezy bronchitis, 47% for those with persistent asthma, and 15% for those with severe asthma in childhood. Multivariable analysis identified severe asthma in childhood (odds ratio [OR] 11.9 [95% CI, 3.4-41.8]), female sex (OR 2.0 [95% CI, 1.1-3.6]), and childhood hay fever (OR 2.0 [95% CI, 1.0-4.0]) as risk factors for “current asthma” at age 50 years.
Does asthma ever truly remit?

Asthmatics clearly become asymptomatic off all treatment, and a proportion of these remain symptom free. A challenging study from the Netherlands showed that adolescents and young adults with asthma in remission still had eosinophilic airway inflammation and remodelling to the same degree as those with ongoing symptomatic asthma. It is still unclear what this means for treatment and prognosis.

COPD and asthma

The current definition of COPD, requiring an FEV1/FVC ratio of 0.70, irrespective of age, is clearly flawed. So for women aged 30, FEV1/FVC ratio of 75% is wildly abnormal; above age 50, increasing numbers of normal people will have FEV1/FVC ratio <70%; and above age 70, >30% of normal people will have FEV1/FVC ratio <70%. Furthermore, the umbrella term COPD assumes (with no evidence) that the pathway to airflow obstruction is the same in a long term smoker as an asthmatic as a woman lifelong exposed to biomass fuel in the developing world. Having said that, nearly 50% of their severe asthmatics at age 10 had an FEV1/FVC ratio <70% in their fifties, and this was a stronger signal than smoking in this group. The odds ratio for adult COPD with severe asthma age 10 years was a staggering 32(3.4–269), much more than for smoking. Those with COPD in their fifties had the worst lung function at age 10, from which time spirometry ran parallel with the other groups.

What about treatment

The chief concern is adult height. The best data are from the CAMP study. In the budesonide but not the nedocromil group, there was a deficit in adjusted mean adult height compared with placebo of 1.2 cm; the deficit was greater for women (+1.8 cm, p <0.001) than for men (+0.8 cm, p=0.10). The deficit developed in the first 2 years of treatment, and growth velocity thereafter was similar in all three groups. There was a dose effect, with a decrement of 0.1 cm for each mg/kg daily dose of ICS, but no effect of cumulative prednisolone dosage. Longer duration of asthma at trial entry and atopy (any positive skin test) were also risk factors for reduced adult height, implying that asthma itself and possibly the treatment for other atopic conditions (above) was important.

Summary and conclusions

Early asthma has profound lifelong implications. Focus on the key antenatal and pre-school time period is essential if long term lung health is to be improved.

Further reading

7. van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prais JB. Airway inflammation is present during clinical remission of atopic asthma. Am J Respir Crit Care Med. 2001;164:2107–13
Viral infections and asthma exacerbations

Exacerbations of asthma, in children as well as in adults, are mostly associated with respiratory virus infections. The type and severity of the virus-induced LRTI damage to the host airways can be a direct consequence of the virulence of the virus, i.e. to its growth kinetic and cytopathic effects, but also the effect of the local host inflammatory response, that involves both the innate and the adaptive immunity, plays a fundamental role in the development of the signs and symptoms of the disease [4]. Desquamation of the damaged epithelial cells, release of pro-inflammatory mediators, recruitment and activation of inflammatory and immunocompetent cells, edema from enhanced vascular permeability, increased mucus secretion and bronchial smooth muscle contractions are all components of the bronchoconstriction that may follow infection by a variety of viruses. The inflammatory and immune responses facilitate clearance of the virus but also amplify pre-existing inflammation and contribute to disease exacerbation. Outside of the winter RSV season, the principal cause of LRTI precipitating wheezing symptoms and leading to hospitalization in infants and young children are HRVs [4,9]. Indeed HRV, besides stimulating bronchial epithelial cells to produce a variety of pro-inflammatory chemokines and cytokines, may activate the cholinergic or noncholinergic nerves, increase epithelial-derived nitric oxide synthesis, upregulate local ICAM-1 expression and lead to nonspecific T-cell responses and/or virus-specific T-cell proliferation [4]. Clinical and experimental studies have clearly shown that HRV infections in patients with asthma induce lower airway symptoms, variable airways obstruction and bronchial hyperresponsiveness, associated with eosinophil recruitment and activation.

Viral infections and allergic sensitization

Is it allergic sensitization that favors viral infection or is it viral infection that favors wheezing/asthma inception and exacerbation? Murine parainfluenza LRTI models suggest that the viral respiratory infection can induce allergic predisposition upregulating the high-affinity IgE receptor on lung antigen presenting cells, producing Th2 inflammatory cell and inflammatory mediators and increased immune response to inhalant allergens [2,9]. The importance of the viral infection as the initial event (“the first hit”) to favor airway allergic inflammation may therefore involve: a) the disruption of the airway epithelial barrier with enhanced allergen exposure, related to the viral-induced injury, and b) the role of the innate immune response to the virus in modulating the interaction between viral infection and inhalant allergen exposure [2]. On the opposite, viral infections may be favored by allergic sensitization since the Th2 bias, which is the characteristic of the immune responses against allergens in atopic individuals, may modify the host antimicrobial defenses and thus attenuate the ability to fight viral infections via immune deviation. Viral LRTI may be a marker for atopic predisposition and not the cause of future wheezing and asthma. In the Childhood Origins of Asthma (COAST) study, allergic sensitization to Aeroallergens was identified as a significant risk factor for viral induced wheeze but, having viral wheeze did not increase the risk of developing allergic sensitization [10]. It is probable that these 2 scenarios, either bronchiolitis as a cause or a marker for asthma theories, are not mutually exclusive.

Conclusion

Despite recent advances in the understanding of the complex mechanisms that regulate the virus-host interaction, what factors govern the selection of some individuals and not others to develop allergic sensitization and/or obstructive respiratory symptoms in later childhood after severe viral respiratory infections in infancy remain unclear.

References


II. TOPIC SESSIONS

IMPACT OF RHINITIS ON ASTHMA IN CHILDREN

Eelco Draaisma, Eric P. de Groot, and Paul L.P. Brand
Princess Amalia Children’s Centre, Isala Hospital, Zwolle, the Netherlands

Allergic rhinitis is one of the most common chronic diseases in children, with prevalences ranging from 6% in 3-yr olds to 25-24% in adolescents. Despite its high prevalence, surprisingly few studies have addressed the long-term treatment of the disease, or its impact on and relationship with asthma in children. It has long been recognized that asthma and allergic rhinitis frequently coexist, due to their similarities in anatomy, physiology and immunopathology. Conflicting results have been published on the relationship between allergic rhinitis on the one hand and morbidity of asthma in children on the other. Very few studies have assessed the impact of allergic rhinitis on asthma control. In an Italian study comparing 200 children with allergic rhinitis to 150 normal control subjects, the rhinitis children had a mean FEV1% predicted of 89%, compared to 100% in normal controls. Conversely, in a series of 203 children with asthma from our centre, 157 (76%) had symptoms of allergic rhinitis, but only half of these children had been recognized and treated as such by a physician. Asthma control was considerably poorer in asthmatic children with coexisting allergic rhinitis than in those without allergic rhinitis: the odds ratio of having an asthma control questionnaire score in the uncontrolled range was 2.74 (95% Cl 1.28-5.91, p=0.0081). The recommended long-term treatment for persistent allergic rhinitis is nasal corticosteroids, because these drugs effectively control nasal and systemic allergic rhinitis symptoms in the large majority of affected children. One year treatment with nasal corticosteroids is associated with a significant, but small (0.27-0.45 cm) reduction in height growth in children, similar to treatment with inhaled corticosteroids in children with asthma.

Pediatric Pulmonology

DOI 10.1002/ppul.23208
S8 Abstract

The scientific evidence on whether treatment of allergic rhinitis with nasal corticosteroids not only reduces rhinitis symptoms but also asthma morbidity and control is inconclusive. An old meta-analysis of four short-term pediatric studies suggested no effect on asthma symptoms and lung function. In our own observational study, children with allergic rhinitis treated with nasal steroids had better asthma control than children whose rhinitis symptoms were not treated with nasal steroids. A recent systematic review including 16 studies involving more than 3000 studies concluded that nasal corticosteroid treatment of allergic rhinitis improved risk outcomes associated with asthma. In a randomized controlled trial of 25 children teenagers with asthma and allergic rhinitis, treatment with fluticasone furoate nasal spray significantly improved exercise-induced bronchoconstriction (mean improvement in drop in FEV1%pred after exercise 9.4%). In another randomized controlled trial of 30 teenagers with asthma and allergic rhinitis, treatment of both conditions with 300 μg/day of fluticasone inhaled through the nose was equally effective as the combination of inhaled (500 μg) and intranasal (200 μg) fluticasone in controlling rhinitis and asthma symptoms.

Allergic rhinitis is a common chronic comorbidity of childhood and adolescent asthma, with considerable impact not only on nasal symptoms and quality of life, but also on asthma morbidity and control. Accumulating evidence indicates that effective treatment of allergic rhinitis with nasal corticosteroids not only controls allergic rhinitis, but also improves asthma control. However, further well-designed long-term randomized controlled trials are needed to corroborate the study findings available to date.

References

ROLE OF FOOD ALLERGY IN CHILDHOOD RESPIRATORY SYMPTOMS AND DISEASES
Gary WK Wong
Department of Paediatrics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, NT, Hong Kong. Email: wingkinwong@cuhk.edu.hk

Food allergy, asthma and allergic rhinitis are common atopic conditions. Many children have more than one of these common conditions. As food allergy is frequently the first manifestation of the allergic march, there has been a lot of research interest in investigating the role of food allergy in the development or exacerbation of respiratory symptoms such as an asthma attack. Birth cohort studies have identified that early and persistent sensitization to food allergens predicts subsequent development of asthma (1). However, it has been difficult to determine the exact role of food allergy in asthma exacerbations or level of control. Many patients believe that they have food allergy but subsequent objective testing could not confirm the disease as shown by many research studies (2). Many epidemiology studies used simple questionnaires to ascertain symptoms of food allergies and respiratory conditions without objective assessment and proper validation resulting in overestimation of food allergies and inaccurate interpretation of the relationship between food allergy and asthma. The most common food allergens include milk, eggs, wheat, soy, peanuts, tree nuts, and shellfish.

Despite the difficulties in establishing the diagnosis of food allergy, hospital-based study has confirmed that food allergy is a significant factor associated with life-threatening asthma exacerbations in children. A case-controlled study in London revealed that children with confirmed food allergy have a six-fold increase in the risk of life-threatening asthma exacerbation when compared to children with milder exacerbations (3). A more recent study of the participants from the US National Health and Nutrition Examination Survey revealed that the prevalence of clinical food allergy was 2.5% (4). Among those with likely food allergy defined by having symptoms of food allergy along with high levels of serum-specific IgE, they are more likely to have asthma (OR 3.8) and emergency visit for asthma in the past year (OR 6.9). In another retrospective chart review of 201 asthmatic children, those with peanut and milk allergies were found to have increased hospitalization and steroid use suggesting such food allergy to be markers of more severe asthma (5). Among the different manifestations of food allergies, anaphylaxis is the most severe form and is potentially fatal. The clinical manifestations range from skin reactions such as urticarial or morbilliform rash, gastrointestinal manifestations such as itchy oral mucosa or the tongue, cardiovascular changes such as syncope and shock, although respiratory manifestations including rhinorhoea, nasal congestion, wheeze and cough are common in those with more severe reactions. Most anaphylactic reactions occur within one hour of ingestion of the offending food. Among the asthmatics with food allergy, poorly controlled asthmatics are at higher risk to develop food-induced anaphylaxis. It is important to differentiate severe asthmatic exacerbation from anaphylactic reaction in order to offer appropriate treatment and prevent future anaphylactic episodes (6).

Although there is firm evidence of a link between food allergy and asthma, food allergy is an important factor affecting asthma control only in a minority of children with asthma. Therefore, dietary restrictions are not necessary unless food allergy is confirmed by objective testing. For those children with food allergy as a precipitating cause of their co-existing asthma, asthma exacerbations tend to be of sudden onset. In highly sensitive individuals, symptoms may be precipitated by exposure to aerosolized food proteins (7-8). The exact mechanisms of how food allergens may precipitate asthma are not clear. It is possible that small amount of allergens may reach the airways during mastication and swallowing. The allergic proteins can also elicit an effect in the lower airways via a systemic inflammatory response similar to the response to pollens in allergic rhinitis and asthma (9). In conclusion, for children presenting with poorly controlled asthma, evaluation of possible co-existing food allergy is needed. A detailed relevant history and objective testing such as skin-prick test or measurement of serum-specific IgE are necessary to determine if dietary restrictions are needed. For patients presenting with abrupt onset of severe bronchospasm along with other systemic symptoms, proper evaluation and treatment for possible anaphylaxis are warranted.

References

Pediatric Pulumonology
Introduction

For more than a decade, clinical care has been shaped by a focus on evidence based medicine (EBM). The success of the Cochrane collaborative has been driven by knowledge that adherence to evidence based practice will generally improve clinical outcomes. Evidence based practice is only effective if consistently applied. Too often, care is driven by traditional beliefs with no basis in facts, such as myths or dogmatic adherence to practices that have clearly been shown to be ineffective or dangerous. This is based on a misguided belief in the virtue of clinical wisdom. In this manuscript, I discuss common myths related to asthma diagnosis and care that may affect our patient’s perceptions or the care that we give.

Myth #1: Asthma is an allergic disease
Although half of children with asthma also have allergies, there are many children who are diagnosed as having asthma that have no increase in allergic mediators or increase in circulating eosinophils. Although allergens are known to trigger acute asthma in children, most patients with adult onset asthma, including many adolescents, do not have detectable allergies.

Myth #2: Asthma is bronchospasm
Smooth muscle hypertrophy and bronchospasm are characteristic of asthma. While bronchodilator medications are effective at improving symptoms of acute asthma, and confirming a diagnosis of asthma can hinge on evaluating hyperresponsiveness to bronchoprovocation challenge or to the reversal of airflow obstruction, it is possible to have airway hyperresponsiveness to provocation testing without having asthma symptoms. As has been well stated by others, asthma should never be defined as bronchospasm or “reactive airways disease”.

Abstract
S10 Abstract

Pediatric Pulmonology

protective effect. All dogs, regardless of size or breed, shed skin and dander as foreign protein and thus no breed of dog is “hypoallergenic.”

Myth #11: There is a myth, particularly in Latin America, that you have a child with asthma and acquire a Chihuahua dog the child will be cured because the asthma symptoms will be transferred to the dog

While there are fur dogs that do not shed (as opposed to hair dogs that shed their hair coat), no breed of dog is less allergic than others.

Myth #12: Intermittent low-dose inhaled corticosteroids (ICS) can prevent asthma in young children. The long term use of ICS is “disease modifying” in infants

Intermittent low-dose ICS do not increase the number of symptom free days in wheezy children when compared to placebo. While the regular use of ICS by infants with recurrent wheeze can reduce the number of wheezing episodes, this beneficial effect does not persist when the ICS are discontinued.

Myth #13: Levalbuterol/Levosolbutamol is safer and more effective than racemic salbutamol

Racemic salbutamol contains both the effective R-salbutamol and the ineffective enantiomer S-salbutamol. Although there was initially speculation that S-salbutamol was harmful – increasing side effects and inflammation – human studies have clearly shown that the addition of S-salbutamol does not decrease the effectiveness of R-salbutamol, nor does this increase side effects like heart rate or tremor; even in children with heart disease. Levosolbutamol is more expensive so its use should be discouraged.

Myth #14: The most effective way to give a therapeutic aerosol to an agitated child is to use blow by delivery

When a child is agitated, is tempting to use a tube or a mask to blow medication toward the child’s face with the hope that they will inhale at least some of this medication effectively. However, many studies have shown that even holding the mask just a centimeter from the face will dramatically decrease the amount of medication that reaches the child’s airways. The blow by technique is thus both inefficient and ineffective.

Conclusion

Understanding commonly held myths and dogma gives us the opportunity to re-examine and change practice when evidence contradicts our “clinical knowledge”. It is recognized that the evidence that we hold dear today may be refuted with better studies in the future and better knowledge of underlying disease pathophysiology.

References


ASTHMA PHENOTYPING IN CHILDREN: CLINICAL APPLICATIONS AND IMPLICATIONS

John Henderson
School of Social and Community Medicine, University of Bristol
A.J.Henderson@bristol.ac.uk

Summary

Asthma is a heterogeneous condition characterized by differences in clinical presentation, such as age of onset, natural history and severity of symptoms, and by its association with intermediate traits, including atopic sensitization and airway physiology. Using these observable characteristics, asthma can be disaggregated into a number of different phenotypes. This leaves a question about whether these descriptive phenotypes are true manifestations of distinct biological processes (endotypes) or whether they arise from stochastic variations in asthma presentation in person, place and time. If the former, they have the potential to contribute to understanding of pathways of asthma inception and asthma natural history, including responses to treatment. These open the possibilities of primary prevention and tailored approaches to treatment or personalised medicine for asthma in children. A substantial proportion of asthma has its onset during childhood. Therefore, longitudinal studies beginning at birth or during early childhood have made a major contribution to investigating factors in early life that influence asthma onset and natural history. It is generally acknowledged that asthma develops as a consequence of interactions between genetic susceptibility and environmental exposures and there is some evidence in support of this for specific pathways, e.g. endotoxin exposure and CD14 gene polymorphisms. However, despite considerable research firepower being directed towards identifying the causes of asthma, they remain largely unknown. It seems unlikely that any important risk factors have evaded detection, so definition of the end-point may be part of the explanation for the difficulties in detecting the drivers of the increase in asthma prevalence seen in most developed countries. If there are several asthma endotypes manifesting as phenotypic variation, it is likely that these will have individually specific gene-environment interactions underpinning them. Disaggregating asthma phenotypes may help to identify these previously hidden associations when asthma is considered as a unification of all of its component phenotypes and endotypes. Novel statistical approaches to longitudinal and multivariate analysis of asthma-related outcomes have identified sub-types of asthma but, to date, there is little convincing evidence that any of these is differentially associated with putative novel risk factors for asthma. Therefore, although different clusters of symptom progression over time or of symptoms with other measurable outcomes can be delineated, this exercise has been rather limited in identifying new asthma endotypes.

One of the inherent difficulties in translating phenotypes derived from longitudinal epidemiological data into clinical practice is that, although these are modelled on prospectively collected data, they are by their nature post hoc analyses and cannot be constructed without knowledge of future outcomes. This difficulty is encapsulated in the concept of predicting which infants and young children who wheeze will have persistence or resolution of their symptoms by school-age; when asthma is usually clinically apparent. Approaches to this problem have included the construction of risk-prediction tools based largely on clinically observable characteristics but their clinical utility in predicting the outcome for the individual is questionable. As a high proportion of childhood asthma is associated with wheeze that begins in the pre-school years, the European Respiratory Society convened a task force that reported in 2008 on the definition and treatment of pre-school wheeze; classifying wheezing as episodic (viral) wheeze and multi-trigger wheeze; the latter more likely to acquire a diagnosis of asthma and possibly more likely to respond to anti-inflammatory treatment. However, it has become clear that these rather artificial divisions based on triggers do not map to distinct biological disease processes and they are not stable over time; patients moving in both directions between groups as acknowledged in a review of the original task force report in 2014. Phenotype-directed treatment in this age group is still limited by considerable uncertainty about phenotypic classifications. Recently, an attempt has been made to reconcile epidemiological and clinical approaches to asthma phenotyping in early childhood. In the multicentre Protection against Allergy Study in Rural Environments (PASTURE), latent class modelling of longitudinal wheeze reports identified a similar pattern of phenotypes to those described earlier in ALSPAC and PIAMA. The authors of this study also classified phenotypes using clinically-relevant descriptors. The LCA approach had high sensitivity and specificity for clinical outcomes and the combined approach identified a clinically-relevant subgroup with high symptom load and decreased lung function but who had not been diagnosed or treated for asthma. This suggests the LCA phenotypes had reasonable external validity but it is interesting to note that the wheezing histories of the clinical phenotypes were indistinguishable from each other during the first two years of life. Therefore, the predictive value of early wheezing
history alone does not seem likely to be a useful indicator of future clinical disease phenotype. There is clearly a need for early indicators of specific disease phenotype if the goal of tailoring treatment to individual pathophysiological processes (personalised medicine) is to be realised in this field. Atopic status may be one of these but the concept of the ‘atopic march’ has recently been called into question, and atopy, in the same way as asthma, needs to be considered as more than a binary variable. However, using advanced statistical modelling, different patterns of atopic sensitisation show associations with different clinical asthma outcomes. The emerging possibility however is to use biomarkers of disease endotypes. There is good evidence that asthma has a high heritable component and a number of genetic variants (SNPs) have been identified in association with asthma, notably at the 17q21 locus near the ORMDL3/GSDMB gene. SNPs in this region are associated with wheeze that begins early and persists through childhood with a strong association with atopy and clinically diagnosed asthma.

Knowledge of the influences of genetic variants on asthma inception is starting to challenge established observational epidemiological findings; for example, the relationship between early life antibiotic prescription and asthma can be explained through increased susceptibility to viral infection associated with impaired antiviral immunity and variants at the 17q21 locus. The ability to analyse complex interplay between genetic susceptibility and environmental exposures using advanced statistical and data mining techniques and incorporating other biomarkers, including epigenomic modifications due to environmental exposures, promises to usher in a new era of discovery that can reveal information about the endotypes underpinning asthma’s phenotypic heterogeneity. This is required to develop tractable interventions that can be tailored to individual groups of patients and which may alter the natural history of progression of early wheeze to asthma.

References

PRESCHOOL WHEEZE AND WHEEZY INFANT: THE BEST PRACTICE

Paul L. P. Brand
Princess Amalia Children’s Centre, Isala Hospital, Zwolle, the Netherlands p.l.p.brand@isala.nl

Approximately one in three children has at least one episode of wheeze before their third birthday. At the population level, almost two thirds of wheezy preschoolers cease to wheeze by age 4-6 years, whilst the remaining children develop chronic persistent asthma. These different longitudinal patterns of wheeze over time are known as the transient and persistent wheeze phenotypes, respectively, and population studies have shown significant differences in the risk factors associated with these phenotypes. Although these findings have improved our understanding of the natural history and the multifaceted pathophysiology of preschool wheezing disorders, the lack of evidence based guidelines on the diagnosis and management of preschool wheezing disorders was a major limitation in providing these patients with effective care. In 2008, a European Respiratory Society (ERS) Task Force published a report on the classification, diagnosis and management of preschool wheezing. This report proposed to classify preschool wheezers into two phenotypes, based on the temporal pattern of symptoms: episodic viral wheeze (EVW, characterized by discrete episodes of wheezing associated with upper respiratory tract infections [URTIs], with symptom-free intervals between episodes) and multiple trigger wheeze (MTW, characterized by wheeze associated with URTIs and with other triggers) because it was felt at that time that this distinction was important in determining the choice of daily controller therapy. One of the main findings of this task force report, however, was that the evidence on which recommendations could be based was limited; the task force predicted that these recommendations would be likely to change as new evidence became available. In 2014, the ERS published an update of the Task Force report on preschool wheezing disorders, based on a review of the evidence published between 2008 and 2014. In the revised guidelines, it has now been recognized that the distinction between EVW and MTW is unclear in many cases. Children commonly cross over between phenotypes over time. In addition, it is the frequency and severity of episodes that usually determines the need for daily controller therapy, not the pattern over time. In contrast to popular belief, EVW of sufficient severity to warrant referral to and treatment by a hospital-based...
AEROSOL DELIVERY IN INFANTS – BEHAVIORAL CHALLENGES AND NOVEL CLINICAL SOLUTIONS

Israel Amirav M.D
Associate Professor of Pediatrics, University of Edmonton, Canada
amirav@ualberta.ca

Infancy is a time of marked and rapid changes in respiratory tract development (1). Infants (0–1 year of age) and young children (1–3 years of age) are a unique subgroup with regard to therapeutic aerosols. Anatomical, physiological and behavioral factors, peculiar to these age groups, present significant challenges for aerosol delivery to the respiratory tract. This presentation will review these challenges and will focus on a relatively neglected area – the face to mask interface which has proven to be an important determinant of successful aerosol delivery to infants.

There are both anatomical and behavioral challenges

From an anatomical perspective, the infant larynx is situated much higher in the upper respiratory tract close to the base of the tongue. The epiglottis is relatively narrow and floppy and located closer to the palate (2). The infant pharynx and supraglottic tissues are less rigid than those of adults and thus more susceptible to collapse with obstruction of the upper airways during inspiration. These anatomical differences could partially explain the infant preference for nose breathing and the relative difficulty of delivering therapeutic aerosols to the lower respiratory tract. The smaller caliber of infant airways is more susceptible to obstruction resulting from edema, hypersecretion and smooth muscle spasm that are present in all inflammatory airway diseases. These factors constitute an additional barrier to aerosol penetration into more peripheral airways. Deposition is greatly facilitated by breath-holding which prolongs particle residence and sedimentation in the airways. Since infants breathe tidally and with low tidal volumes, a greater proportion of the inhaled medication is likely to be exhaled due to the dead space of the mask and delivery/reservoir system/device distal to the inspiratory valve.

From a clinical perspective, the most important element is the fact that most infants resist the application of a face mask by squirming and crying and by vigorously pushing it away (3). It has been suggested that infants’ rejection of masks is caused by fear of being smothered and application of the excessive pressure on the mask required to achieve a mask-to-face seal which accounts for their rejection of masks. It has been shown that crying during aerosol administration virtually prevents effective aerosol therapy in children (4–6). The notion that crying facilitates aerosol delivery is a myth and all possible efforts should be made to avoid it.

Masks for delivering aerosols to infants and children appear in various shapes, dimensions and materials, and are arguably the single, most important, link in the chain between the aerosol generator and the lungs (7). However, there is little scientific evidence to support the design of existing, generally available, pediatric masks. Current facemasks for pediatric aerosol therapy have been merely smaller versions of those used for adults with little consideration given to infants’/toddlers’ special needs and facial dimensions.

We can divide optimal mask elements into ‘technical’ elements and those that are patient related (8). For aerosol therapy, most important, by far, is that the child accepts the treatment. Having the most sophisticated aerosol generator and valved holding chamber (VHC) and appropriate aerosol medications will provide little benefit if the child refuses the mask, as occurs in up to 50% of small children.

From a design perspective, the major elements that affect the efficiency of aerosol delivery using face masks are: 1. Vertical and horizontal alignment of the mask to the face, 2. Anatomically contoured, gentle and comfortable fit. 3. An effective seal between the mask and the infant’s face. 4. Minimal dead space. These design issues are especially problematic in infants and very young children whose face, in the first few years of life, undergoes rapid and marked developmental change while at the same time, due to their small tidal volume, the dead-space/tidal volume ratio is relatively high, at least to age about 18 months. The evidence-based re-design of masks designed specifically for infants and small children will be discussed and the resulting clinical development of a unique and child-friendly mask that
enables administration of aerosol therapy to sleeping infants will be detailed.

References

AEROSOL THERAPY: NOVEL DEVICES AND DRUGS
Bruce K Rubin, MD, MEng, MBA, FRCP
Department of Pediatrics, Virginia Commonwealth University School of Medicine, Children’s Hospital of Richmond, Virginia
To whom correspondence should be addressed: Bruce K. Rubin, MD, MEng, MBA, FAARC
Jessie Ball DuPont Distinguished Professor and Chair, Dept. of Pediatrics Professor of Biomedical Engineering
Children’s Hospital of Richmond at Virginia Commonwealth University
1001 East Marshall St. PO Box 980646
Telephone: 804 828-9602
E-mail address: brubin@vcu.edu

Introduction
The use of inhaled agents as therapy goes back hundreds of years but the modern history of aerosol therapy begins with the Sales-Girons pulverisateur jet nebulizer in 1858 and the Riker Medihaler pressurized metered dose inhaler (pMDI) introduced in 1956. Although there have been incremental advances in aerosol therapy over the last sixty years, in the last decade there have been dramatic advances in novel delivery systems and the types of medications that can be administered by aerosol. In this manuscript we will review some of these advances.

New Delivery Systems
Delivery systems that have been introduced in the last few years include closed and open mesh vibrating mesh nebulizer (VMN) devices that use piezo elements to vibrate horns or meshes to create an aerosol. VMN are small, portable, quiet, battery or AC powered, and can use higher medication load volumes, however they are more expensive to manufacture and maintain and are difficult to use with some drugs. A particular concern is that the pores of the mesh can clog with suspensions or with hyperosmolar medications that can crystallize on the pores. Examples of VMN include the PARi eFlow and the AeroNeb Go.

Small volume liquid inhalers have also been introduced, the most prominent among these being the Respimat soft mist inhaler. This device is disposable, with the energy of aerosolization produced by spring compression. Because it takes more than one second to deliver the aerosol at a velocity of approximately 10 m/s, this soft mist is less likely to produce a startling effect, can improve coordination, and gives a higher efficiency of drug delivery than other liquid inhalers. The dose chamber is small with a volume of 1.5 µL, limiting the amount of medication that can be given with each inhalation.

This device is used for both beta agonists and anticholinergics in Europe and has been introduced in the US with tiotropium bromide.

“Smart inhalers” include the AERx, the HaloLite Prodose, and breath controlled nebulizers including the iNeb and the Akita. These are more expensive devices but can track adherence, train the user in proper technique, and deliver medication at the optimal time of inhalation for deposition to targeted portions of the lung. In particular, the Akita has been used to deliver peptides to the distal airway, including GM-CSF as a therapy for pulmonary alveolar proteinosis.

Dry powder inhalers (DPI) have also evolved. There are now DPIs, including the Tudorza Pressair, that give the user feedback on inhalation technique and delivery of medication. There are also active DPIs that have a low plume velocity. These include the Teva Microdose which is piezo driven, the Inspironmatic (OPKO), and the Occoris (Team Consulting). These active DPIs disperse powder very much the same way as a pMDI and without the disadvantage of requiring an inspiratory disaggregating flow.

Commercially-available engineered particles are also now in use such as the Pulmospheres used to deliver trumycycin DPI. This is a simple inhalation device but the particles themselves are spherical and thus have low surface energy making them easier to disaggregate; and are hollow and porous allowing more sustained delivery of medication. Other novel formulations under development include aerosols with enhanced excipient growth that enables very fine particles to bypass the upper airway but then deposit in specific areas of the lung as they grow in size.

User interfaces have evolved to improve adherence. Novel interfaces include the SootherMask which incorporates a pacifier for use in small infants. This comes with a soother that is already in place or can allow the child to use their own. Because infants are preferential nose breathers, this can increase the amount of medication delivered to the lung, and because they are sucking on the soother, potentially this is better able to form a seal about the face and decrease distress.

Novel Therapy beyond Asthma
Aerosol antibiotics have a long history with publications documenting aerosolization of penicillin as early as 1944. In recent years, a number of aerosolized antibiotics have become commercially available primarily for the treatment of cystic fibrosis (CF). These include tobramycin, colistin/ polymyxin B, and aztreonam lysine (Cayston). Aerosol antibiotics are effective, not only in treating CF, but also in decreasing the risk of ventilator associated pneumonia. Nevertheless, these medications are not without potential toxicity and long term use can induce bacterial resistance to the antibiotic. There are a large variety of antibiotics that are being developed by aerosol including aminoglycosides, glycopeptides, beta lactams, fluoroquinolones, and liposomal amphotericin as an antifungal agent.

Macrolytics have also been developed, the most successful being dornase alfa, used to treat CF lung disease. Despite clear evidence that dornase improves pulmonary function in CF and decreases the frequency of exacerbations, it has no role to play in the treatment of non-CF bronchiectasis, COPD, or asthma. Hypertonic saline has also been introduced as a mucokinetic agent. It is generally well tolerated and inexpensive, but is not as effective as dornase in improving pulmonary function. Three percent hypertonic saline has been advocated for the treatment of bronchiolitis, but recent studies demonstrate that 3% saline is ineffective in bronchiolitis and does not reduce length of stay, duration of supplemental oxygen, or admissions to hospital from the emergency department.

A number of anti-inflammatory agents have been studied, including anti-proteases, anti-oxidants, and cytokine modifiers but none of these have been approved for clinical use. There are ongoing clinical trials of aerosol alpha 1-antiprotease (A1AT) as an aerosol, both for A1AT deficiency and for CF. There are also aerosol medications being evaluated for CF that inhibit serine proteases.

Pulmonary hypertension is well treated by aerosol agents, most notably iloprost which is a prostacyclin analog. Other agents with longer duration of action are also under study.

Pediatric Pulmonology
ASSURING ADHERENCE AND COMPLIANCE WITH AEROSOL THERAPY

A.C. Bos, MD, M. Engelkes, MD, H.M. Janssens, PhD
Department of Pediatric Pulmonology and Allergology, Erasmus Medical Center-Sophia Children’s Hospital, Rotterdam, the Netherlands
Department of Radiology, Erasmus MC, Rotterdam, the Netherlands
Department of Medical Informatics, Erasmus MC, Rotterdam, the Netherlands

Corresponding author: H.M. Janssens, MD, PhD, Erasmus MC-Sophia Children’s Hospital, dept. of Pediatric Pulmonology., Postbus 2060, room SP-3456, 3000 CB Rotterdam, The Netherlands, Phone +31 10 7036263, Fax +31 10 7036811, Email: h.janssens@erasmusmc.nl

Keywords: adherence; inhalation medication; aerosol therapy; cystic fibrosis; asthma

Aerosol therapy is the mainstay of the management of asthma and cystic fibrosis (CF) in children. For both respiratory disorders, good adherence is associated with improved lung function and fewer respiratory exacerbations.1 In fact, the risk of an asthma exacerbation in children with good adherence is 21-68% lower compared to children who are less adherent.2 Unfortunately, adherence to inhalation medication in children with asthma or CF is sub-optimal and often less than 50%.3,4 There is a wide variation in adherence, both between and within individual patients as well as in time, from day-to-day and week-to-week.3 Also, a variety of adherence patterns and behaviors are seen.3 Some patients use their device more than prescribed, others don’t take any, some start well and subsequently show decreased adherence, others start poorly and then adherence improves.3

Barriers for adherence

Understanding factors that influence adherence can help to optimize guidelines to manage asthma and CF. A long list of intentional and non-intentional barriers to adherence has been described, including time-pressure and inconvenience. Additionally, adherence to treatment decreases with the duration and complexity of treatment1, which explains why non-adherence is a major problem in CF patients as these patients have a complex and time consuming treatment regime.1 Only 32% of patients with CF are fully adherent to a twice or twice daily regimen of nebulized antibiotics.1 However, even with novel nebulizers designed to reduce treatment time, adherence is still poor.

Second, overall adherence tends to be poorer in teenagers than in children less than 12 years of age, partly due to decreased parental supervision in adolescence and shift of responsibilities from parents to adolescent child.1 Results on the influence of gender within adolescence are inconclusive, some studies did not find any effect of gender on adherence, while others suggested that adolescent girls are less adherent than adolescent boys.1

Third, in both asthma and CF, evening adherence is consistently better than morning adherence as many families experience difficulties encompassing the time-consuming nature of nebulized treatment in the hectic morning schedules described by many families.3 Another important factor is the need to believe the necessity of therapy.1 In CF, many parents (up to 32%) have an incomplete understanding of their children’s therapies.3

Fourth, relationships (family and treatment team) are important for adherence. Children from unhappy families with conflicted relationships are at greater risk of poor adherence.3 The relationship with the CF team can be a motivator for adherence.

Finally, psychological factors might be associated with adherence. In asthma, psychiatric co-morbidity is associated with worse medication adherence.5 However, in CF, current data are inconclusive. Optimistic acceptance and helpfulness, as well as worrying about the condition and anxiety disorders have been associated with greater adherence to CF treatment.1

Methods to assess adherence

Several methods can be used to assess adherence to inhalation medication. Subjective measures of adherence comprise patients’ self-reports, questionnaires, daily diaries and physician’s judgment.2 These methods all underestimate adherence due to social desirability bias and inaccurate recall.6

A problem for objective measures, such as pill counting, canister weighing and the use of prescription/dispensing/refill data, is “dumping”. This is the action by which patients try to conceal non-adherence by intentional emptying of the inhaler before study visits and, again, leads to overestimation of adherence. Electronic monitoring devices (EMDs) are the most objective method of adherence monitoring6 and are seen as the gold standard measure.2 EMDs are user-friendly, well accepted by patients, can be used to increase treatment adherence as it gives the opportunity to physicians to identify problems and to discuss this with the patient.8 EMDs have become available for both metered dose inhalers (MDI) (e.g. DOSER, MDI Chronolog, MDILOG and Smartinhaler), as well as for nebulizers (e.g. Nebulizer Chronolog, Akita and I-neb). The I-neb not only provides objective measurement of adherence, but also coaches the patient to improve inhaler technique by providing positive feedback signals. Positive feedback is given on each inhalation and at the completion of aerosol delivery. The Akita delivery system works in a similar way as the I-neb. Both nebulizers allow monitoring patient adherence to treatment, compliance with correct use and cleaning of the device. Health care providers can use this information to tailor their advice to overcome the patient’s specific barriers to non-adherence and to suit the needs of the individual patient.

Inhalation competence and contrivance

However, even if patients take medication daily, the delivery of drug into the lungs may fail due to an incorrect inhalation technique (competence) or knowing how to use the device effectively but choosing to use it in an inappropriate way (contrivance).7 A poor inhalation technique reduces the amount of deposited drug at the site of action and thus reduces the effects of medication. For this reason, patients need to be carefully instructed into how to use a device effectively and this needs to be repeated several times to ensure the inhalation is performed correctly. In addition, competence needs to be checked at every visit as it is shown that errors often recur within 4-6 weeks after initial training.8 For asthmatic children, it is known that competence related to inhalation therapy is poor. An incorrect inhalation technique is seen in up to 80% of the patients and lack of competence is described in all age groups.7 The level of
incorrect inhalation technique and type of mistakes differ per device, depending on the handling that need to be done. Repeated instructions are strongly effective for improvement of inhalation technique. However, even when repeated instructions were given, 10-20% of asthmatic patients still made mistakes. To the best of our knowledge, no studies have been published to date evaluating competence of inhalation medication in patients with CF.

Contrainviation is very common, particularly among patients who are prescribed a holding chamber. Even though patients and parents know the reasons for using the holding chamber, the perceived inconvenience of using the spacer and being too busy or in a rush are reasons for not using it. Other examples of contrivance are rapid inhalation with pMDIs in routine use and stopping inhaling as soon as a “breath-actuated” pMDI is triggered. For β₂-agonists poor adherence, competence and contrivance are less of an issue as the drug is used as required and poor technique is partly compensated by the high doses. Also, patients will immediately notice the incomplete response due to poor technique and will take further doses. For inhaled steroids, however, there is no immediate feedback that full benefit has not been achieved. Therefore, for these medications, poor adherence, poor competence and contrivance lead to poor control. This results in unnecessary dose increases and escalation of treatment regimens, as clinicians might think a dose of steroid is ineffective, while in fact the patients’ adherence or competence is poor or patients contrive not to use their spacer. Appropriate information and training seem to work to both increase levels of competence as well as reduce contrivance.

How to improve adherence?

Many strategies to improve adherence are described. Successful interventions to promote adherence are complex and multi-faceted and include combinations of counseling, education, more convenient care, self-monitoring, reinforcement, reminders, and other forms of additional attention or supervision. The effect of interventions on treatment adherence is known to be greater for children with CF than for children with asthma. Unfortunately, except for interventions immediately following an exacerbation, health care professionals seem to have little influence on adherence. However, clinicians should still focus on improving adherence and ensuring effective use of inhaler devices. First of all, clinicians need to educate patients; to convince that the therapy is effective and that the benefits compensate the invested time and effort and barriers to therapy and the patient’s or parent’s beliefs about the necessity and effectiveness of the treatments need to be reviewed regularly. Second, any medication regimen should be agreed upon by both physician and patient and the treatment plan needs to be simplified as much as possible. The patient needs to be encouraged to participate in the choices. Finally, time management needs to be discussed with patients and their families as many patients have trouble incorporating medication into daily routine. With this program patients are educated in the importance of treatment adherence, are stimulated to take more responsibilities and to incorporate their treatments in daily routine. The program consists of 3 stages, defining barriers to therapy, brainstorming about solutions to improve adherence and creating a personalized treatment plan.

Summary

For an optimal therapeutic effect of inhaled medication, patients need to use their inhalers effectively. This consists of adhering to the treatment regimen, and effective device use. Therefore inhalation instructions need to be repeated and patients and parents need to be educated, to assure good competence and reduce contrivance. Electronic monitoring devices can be used to monitor and increase adherence and competence in children with asthma or CF. Clinicians need to assure adherence with inhaled therapy by discussing illness perceptions, medication beliefs and practical adherence barriers.

References


EXERCISE IN ASTHMA - PHYSIOLOGY, TESTING, MYTH AND CONTROVERSY

Kai-Håkon Carlsen
University of Oslo, Institute of Clinical Medicine, Oslo University Hospital, Department of Paediatrics and Norwegian School of Sport Sciences, Oslo, Norway, k.h.carlsen@medisin.uio.no

Physical exercise is important for health and development in children and adolescents. Physical activity stimulates growth. Exercise induced asthma (EIA) occurs in most children with asthma without anti-inflammatory treatment, and fitness (measured by maximum workload by cycle ergometry) has been demonstrated to be related to psychological factors in children with asthma. As children with EIA may become passive and not participate in physical activity, all major international guidelines on treating childhood asthma have as one of their main objectives to treat and master EIA. Therefore it becomes important to diagnose and treat EIA correctly.

EIA is defined by the symptoms and signs of asthma seen after physical exercise and is traditionally diagnosed by exercise testing. The first standardised exercise tests to assess asthma were performed in the early 1960s. Running is the preferred exercise, and running on a treadmill is easy to standardise. Environmental conditions should be standardised (temperature, humidity as well as exercise load). A heavy exercise load increases the sensitivity of the test (1). The test is measured by the reduction in FEV₁ from before to after a high-intensity exercise of for 6-8 minutes, and exercise-induced bronchoconstriction (EIB) is defined by a reduction in FEV₁ of ≥10%.

It is agreed that symptoms and signs of EIA should be confirmed by an objective test, as there are several differential diagnoses to EIA. The degree of reduction in FEV₁ may also be looked upon as one of several measures of bronchial responsiveness, but other measures of bronchial responsiveness have been suggested for the diagnosis of EIA (2).

Myth: EIA should be diagnosed by a standardised exercise test

Controversy: Other objective measures may have greater sensitivity

In population-based studies of school children, the sensitivity of exercise tests to identify physician-diagnosed asthma has been low, but the specificity very high, whereas metacholine bronchial challenge had higher sensitivity, but lower specificity (3). Anderson et al. compared the mannitol test and metacholine challenge to diagnose exercise-induced asthma in a population from 6-50 years of age and found them rather equivalent (2). Sanchez-Garcia et al. recently reported the effectiveness of bronchodilator test, exercise test, mannitol test and metacholine bronchial challenge to diagnose EIB in 46 children less than 16 years complaining of asthma-like
symptoms triggered by exercise. The exercise test was positive in 23.9% of the children, the bronchodilator test in 21.7%, the mannitol test in 80% and the metacholine challenge in 91.11%. By combining metacholine with mannitol challenge, all were diagnosed (4).

Myth: Exercise related dyspnoea is commonly caused by EIA

Controversy: There are several other causes to exercise-related dyspnoea apart from EIA

Correct diagnosis is crucial to correct treatment. There are several differential diagnoses to EIA in physically active children and adolescents (5). Careful anamnesis and objective examination and tests may be necessary for a correct diagnosis. EIA may be identified by an exercise test or by other measures of bronchial hyperresponsiveness in combination with a history of dyspnoea usually coming shortly after a heavy exercise. Inspiratory dyspnoea during maximum exercise indicates exercise-induced laryngeal obstruction (EILO), also called vocal cord dysfunction. Other differential diagnoses in children may include poor physical fitness, other chronic disorders such as congenital heart disease or other chronic lung disease and dysfunctional breathing.

Myth: Physical activity protects against asthma development

Controversy: Physical activity causes asthma development in athletes

It has been maintained that physical activity may protect against asthma development. However, this is difficult to document, as it requires long term follow-up studies. Rasmussen followed 757 asymptomatic children, aged 9.5 - 11 years, for 10.5 years and examined their fitness by measuring maximum workload by cycle ergometer. He found that fitness at the first examination was inversely related to later development of physician-diagnosed asthma and that the risk for development of asthma during adolescence was reduced by 7% by an increase in the maximal workload of 1 W/kg. On further follow-up to 29 years, it was found that the tracking of physical fitness was high from 9 to 29 years, and that the risk of asthma development was reduced by 3% by an increase in maximal workload of 1 watt/kg at 9 years of age (6). On the other hand, Berntsen reported that 13 year-old children with asthma were as fit as healthy children (7). A systematic review and meta-analysis including 5 longitudinal and 34 cross-sectional studies showed that the longitudinal studies demonstrated physical activity to be a possible protective factor against asthma development (OR 0.87 (95% CI: 0.77-0.99)) (8). On the other hand, it has been shown beyond doubt that physical training and competition causes asthma development in elite athletes of endurance sports, most pronounced in swimmers and cross-country skiers (5). This is thought to be due to a combination of epithelial damage, increased airways inflammation, increased environmental exposure and increased parasympathetic activity due to endurance training, all together leading to increased bronchial responsiveness and asthma symptoms (9).

Myth: Physical activity improves asthma mastering, quality of life (QoL) and BHR

Controversy: Physical activity causes exercise-induced asthma

It has long been discussed as to whether physical activity and training improves bronchial asthma, lung function, QoL and BHR, whereas it has generally been acknowledged that physical training improves fitness in asthmatic children. Several systematic reviews and meta-analyses have been performed (10), and their conclusions mostly agree. The effect of physical training in children and adolescents with asthma usually found an improvement in fitness (V' O2max), maximum heart rate and QoL. Lung function was usually not affected, whereas recent reports tend to suggest an improvement in BHR (10). On the other hand, asthma symptoms induced by heavy physical activity is frequently reported in asthmatic children, and the treatment of EIA is a major objective in most international asthma guidelines. These facts taken together underscore the importance of optimal asthma management in children with asthma to enable them to master EIA and participate actively in physical training activities.

References


WHY THE USE OF THE ASTHMA PREDICTIVE INDEX REMAINS A USEFUL TOOL FOR DIAGNOSING ASTHMA IN CHILDHOOD

Jose A. Castro-Rodriguez,1 Renato T. Stein.2
1Divisions of Pediatrics & Public Health, School of Medicine, Pontificia Universidad Católica de Chile. Santiago, Chile, jacastro17@hotmail.com
2Institute Center, Biomedical Research Institute, Department of Pediatrics, School of Medicine, Pontificia Universidad Católica do Rio Grande do Sul, Porto Alegre, Brazil. Stein rsrteio@pucrs.br

Understanding which subset of infants and preschoolers with recurrent wheezing will have asthma once they reach school age may be quite important in the treatment decision-making process. Most asthma starts before a child completes 5 years of age and its impact long-term is quite significant. The greatest decline in lung function among children who will become persistent asthmatics occurs during this period and once this irreversible feature is underway, there is little room for recovery. Luckily, this is not a common feature for most children who wheeze early in life, since several milder wheeze phenotypes coexist at preschool age. Therefore, identifying which children with recurrent wheeze in the beginning of life will experience asthma at school age will help in providing a rationale for specific treatments and prevention strategies.

Despite the importance of the above, diagnosis of asthma at an early age remains a challenge for physicians. Since no accurate screening test using genetic or single biochemical markers have been developed to determine which preschooler with recurrent wheezing will have asthma at school age, the diagnosis of asthma needs to be based on clinical prediction scores. Four consecutive steps are necessary to develop prognostic or diagnostic prediction rules: development, validation/assessment, impact, and implementation.1

At the moment, at least five predictive rules for asthma have been developed. The likelihood ratio (LR) best reflects the diagnostic accuracy of a test. The positive LRs of different prediction rules reported for assessing the development of asthma at school age include the following: mAPI (LR=21 for asthma at age 6 years), Isle of Wight (LR=7.9 for asthma at age 10-11 years), ucAPI (LR=7.5 for asthma at age 7 years), original stringent API2

Pediatric Pulmonology
for predictive asthma at age of 4.9 Recently, when comparing with the API
7. Chang TS, Lemanske RF Jr, Guilbert TW, Gern JE, Coen MH, Evans MD,
6. Caudri D, Wijga A, Schipper CM, Hoekstra M, Postma DS, Koppelman
index to define risk of asthma in young children with recurrent wheezing. The PIAMA index was validated in different populations.3
However, the original stringent API is the only asthma prediction rule in which the third (impact) and fourth (implementation) steps of clinical prediction rules are presently being studied. When the original stringent API was compared and correlated with surrogate markers of airway inflammation, such as FeNO used as a minor criteria replacing eosinophil determination in the original API, it showed lower positive LR (1.99) for predictive asthma at age of 4.4 Recently, when comparing with the API (but replacing eosinophilia by specific IgE), the addition of volatile organic compounds and gene expression improved asthma diagnosis from 60 to 89%. It is well known that eosinophilia is a better predictor of remission of asthma than specific IgE or skin prick test. Finally, an implementation or application value of the original API for therapeutic strategies was recently published.10 For clinical use, the original stringent API is simple, inexpensive, noninvasive, and has been well validated. Therefore, clinicians worldwide can use a positive original stringent API to identify at-risk children and educate parents on the importance of asthma maintenance therapy and treatment of flares. Its major strength is its good positive LR (the effect on post-test probability of disease improved significantly), but since its sensitivity is modest it cannot be used to rule out the development of asthma. More studies are needed to explore the effect of asthma controller medications based on an infant/preschooler’s API status.

**References**


**ASTHMA PREDICTIVE INDICES ARE NOT USEFUL IN CLINICAL MANAGEMENT OF PRESCHOOL WITH WHEEZING**

Sotirios Foutzas and Paul L.P. Brand

 paediatric Respiratory Unit, Department of Paediatrics, University Hospital of Patras, Patras, Greece (SF) and Princess Amalia Children’s Centre, Iastra Hospital, Zvolle, the Netherlands (PB)

p.l.p.brand@isala.nl/p.l.p.brand@isala.nl

Approximately one in three children has at least one episode of wheeze before their third birthday. At the population level, almost two thirds of wheezy preschoolers cease to wheeze by age 4-6 years, whilst the remaining children develop chronic persistent asthma. These different longitudinal patterns of wheeze over time are known as the transient and persistent wheeze phenotypes, respectively, and population studies have shown significant differences in the risk factors associated with these phenotypes.1, 2 These observations from multiple population-based birth cohort studies have prompted research efforts to identify factors associated with the outcome of preschool wheezing after the age of six years, hoping that this could help not only in counseling parents of preschool children on the prognosis of their child’s condition, but also in selecting patients for treatment with long-term daily controller therapy such as inhaled corticosteroids.

Based on data from the Tucson Respiratory Study, Castro-Rodriguez et al. developed the Asthma Predictive Index (API). 3 Children with frequent wheeze (> 3 episodes) before the third birthday and one or more major criteria (parental doctor’s diagnosis of asthma, or doctor’s diagnosis of eczema in the child) or two or more minor criteria (doctor’s diagnosis of allergic rhinitis, wheezing apart from colds, or >4% eosinophils in the differential white blood cell count) had a positive stringent API, and this significantly increased their risk of having asthma by age 6. In the Tucson study, the sensitivity of the API was 28%, and its specificity 96%, figures that led the developers to propose it as a valuable tool to rule out subsequent asthma.3,4 However, 7 out of 10 children with asthma by the age of 6 years would have been misclassified by the API as not being at risk. Thus, a negative API does not reduce the probability of asthma in a clinically meaningful way and, therefore, it should not be used to rule out the disease in preschoolers with recurrent wheeze.5 Although the ability of a positive API to correctly identify asthma was reasonable (positive LR 7.4, post-test probability 42%), the proportion of children with a positive stringent API in the Tucson study was as low as 6.3%, meaning that any advantage of the index due to its (moderate) positive predictive power would be reserved only for a small proportion of children with troublesome symptoms. Subsequently, the results of several validation studies confirmed these flaws.6-7

Other simple symptom-based asthma prediction scores have shown similarly disappointing predictive values and likelihood ratios.6-9 Recently, data from a longitudinal study of carefully selected high-risk children in the Netherlands (N=198; asthma prevalence 38.4%), showed that a composite score, involving not only clinical and demographic characteristics, but also inflammatory profile of volatile organic compounds in exhaled breath condensate and genetic inflammatory profiles in blood mononuclear cells, considerably improved the ability to predict the outcome of preschool wheezing.10 The cutoff value of composite score with the highest area under the curve of the receiver operating characteristic curve had a sensitivity of 88% and a specificity of 90% to predict asthma at the age of 6. This corresponds to a positive LR of 8.8 which would increase the post-test probability of asthma to nearly 80%, and a negative LR of 1.3 which should
be considered excellent. However, the complicated nature of this composite score, involving the collection of exhaled breath condensate and RNA extraction from peripheral blood mononuclear cells, precludes its use in clinical practice.

In conclusion, the API and other simple clinical scoring systems have insufficient predictive value to be sufficiently useful and reliable to use as a counseling tool for parents, or to base clinical decisions on, such as the prescription of daily controller therapy. On the other hand, more complex prediction tools may be reliable but are based on extremely specific biomarkers which are very difficult to be introduced in clinical practice. At present, the only way to find out whether preschool children will outgrow their wheeze symptoms or develop chronic persistent asthma is to wait and see what happens when they grow older. Meanwhile, preschool children with recurrent troublesome symptoms of wheeze and shortness of breath should be treated with daily controller therapy, preferably inhaled corticosteroids, as this is associated with satisfactory asthma control in the majority of patients.11

References


NOVEL INSIGHTS INTO AIRWAY SMOOTH MUSCLE CONTRIBUTIONS TO ASTHMA: ROLES FOR IgE, IL-8 AND CFTR

Thomas Murphy
Duke University, Durham NC, USA, thomas.murphy@duke.edu

Asthma is a complex disorder of a relatively specific type of airway inflammation and hyperresponsiveness to a wide variety of stimuli. In the chronic state, plastic adaptation of the constituent cells and tissues occurs, both in asthma and CF(1). Research and drug-development have focused on the inflammatory processes, both because this is a major driver of the disease and because progress in the therapy of the chronic condition has come from related interventions. Despite improvements in controlling symptoms and exacerbations from therapies such as inhaled corticosteroids (CS), this approach has not led to the normalization of measures of airway hyperresponsiveness, which in turn reflects ongoing risk.

The role of airway smooth muscle (ASM) has historically centered on bronchospasm that occurs during exacerbations. In this model, ASM has a number of G protein-coupled receptors (GPCR) on the cell surface that transduce signals from mediators and cytokines from a variety of inflammatory cells that causes ASM contraction and airway narrowing. Over the past twenty years, research has demonstrated that ASM is itself an inflammatory tissue capable of synthesizing and secreting a variety of cytokines and factors, some of which are sensitive to treatment with CS and others are not.

More recently, attention has come to focus on the roles of ASM low affinity (FcεRII) and high affinity (FcεRI) receptors for IgE (2) and the ASM receptor for IL-8 (3). This has shed light not only on classical asthma but on hybrid syndromes such as the “asthma” that occurs commonly in cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD).

The consequences of ASM secretion of a variety of asthma-related mediators and cytokines are concerning because of the possibility that this can exacerbate the activities of neighboring inflammatory cells. Because of uncertainties regarding concentration-gradients and distances, many of these details have not been elucidated. The better established story about stimulation by IgE and IL-8 is that these can augment the phosphorylation of myosin light chain and/or increase the expression of myosin light chain kinase (MLCK) directly, causing augmented ASM shortening (3,4). Human ASM and airway epithelial cells each have CFTR channels that secrete chloride ion, which relaxes the ASM. In patients with CF, this chloride secretion is sharply reduced, causing increased tone. Stimulation of CF ASM with a beta agonist causes greater relaxation in human tissues and in genetically CF swine, thus serving to suggest an asthma phenotype, when it might not otherwise exist.

IgE stimulation of ASM augments the expression of IL-8, thus providing a potential mechanism for a synergistic increase in ASM contractility between these two factors. This augments the problem of airway exacerbations of CF, which is occasioned by large increases in IL-8 content of airway secretions from epithelial and inflammatory cells. Higher doses of CS help to reduce serum IgE levels in syndromes such as allergic bronchopulmonary aspergillosis, but there is no evidence that low dose ICS does the same (5,6). IL-8 production is not sensitive to CS treatment. Targeted interference with IL-8 signaling offers the possibility of a novel approach to reduced ASM hyperresponsiveness. The issues for the “asthma” of CF are more complex. CF ASM appears to be more responsive to treatment with beta agonists, giving false assurance that the underlying problem is asthma. A published Cochrane analysis provides evidence of no clinical benefit from the use of ICS in treating CF (5), despite registry data suggesting that in many centers the majority of patients receive this therapy. In light of increased reports of ICS-related impairment of growth (5), there appears to be a need for a change in clinical practice away from the routine use of ICS. These targets add to the list of non-CS-treatable targets that may be in the next generation of asthma therapies.

References

DOES ASTHMA EXIST IN INFANCY?

Petr Pohunek
Pediatric Pulmonology, Pediatric Department, Charles University Prague, 2nd Faculty of Medicine and University Hospital Motol, Prague, Czech Republic, petrpohunek@LFMoto1.cuni.cz

Introduction
Wheezing and obstructive breathing are very frequent symptoms in infancy. In various studies, the prevalence of such symptoms was found to be as high as 45%, with 15 to 20% of children having these symptoms recurrently(1). Wheezing in young children has been found to be associated with various risk factors and triggers, such as maternal smoking in pregnancy or viral infections. Fortunately, only a minority of children presenting with obstructive symptoms in the first or second year of life continue to have obstructive symptoms later in life. Among the triggers consistently associated with wheezing early in life, mainly viruses were found to be responsible both for acute episodes and increased bronchial responsiveness with following recurrent or persistent symptoms. Despite some inconsistencies in definitions and terminology of obstructive diseases that may be found throughout the world, the RSV-virus mostly acts as a causative agent for classical infantile bronchiolitis while rhinoviruses appear to be more responsible for other types of obstructive episodes and subsequent persistence of bronchial hyper-responsiveness presenting as recurrent wheezing(2). Many of these children keep wheezing even after non-specific triggers for many months and often are labeled with “asthma” and even treated with anti-asthma therapy. Their symptoms usually gradually disappear and, in many of them, full remission can be seen during late pre-school age. There are still no available reliable markers that can predict the long-term prognosis of such children as to the persistence of symptoms and development of “real” asthma later in life. This is the reason why many physicians refuse to use the label “asthma” before the age of 24-36 months despite often treating such children not only with a symptomatic reliever treatment but also with regular preventative drugs.

Bronchial obstruction in infancy and its relation to diagnosis of asthma
Several analyses have been published regarding the patterns of obstructive symptoms in young children, trying to determine the phenotypes and their predictive value for assessing future prognosis of early wheezers. Based on cohorts followed long-term, it is quite clear that most of the asthma persisting later in life originates at the age of about three. At this age, the prognosis can also be more reliably determined using some of the validated tools (e.g. Asthma Predictive Index)(3). Interestingly, aside from this most frequent phenotype, several authors found a distinct phenotype of persistent wheezing characterized by wheezing episodes starting in the first months of life and persisting for the rest of childhood or even into adulthood(4). Persistence of such symptoms with no apparent discontinuity suggests that this type of bronchial obstruction may have the same underlying pathology throughout life. This phenotype is often associated with validated risk factors for later development of asthma, such as positive family history of asthma and atopic dermatitis.

Several groups have analyzed biopsies of bronchial mucosa in young children searching for patterns of inflammation and morphological changes within the bronchial wall. This only partially helped to better understand the pathogenesis and prognosis of early bronchial obstruction. These studies usually suffer from using only small study groups as it is extremely difficult to obtain bronchial biopsies in very young children. Nevertheless, some features of remodeling, mainly reticular basement membrane (RBM) thickening, could be detected in early life, thus signaling early structural changes similar to those found in older children (5). Moreover, a recently published study confirmed such changes even in young children with positive risk factors for later development of asthma(6). A follow-up of a unique cohort of infants which were thoroughly invasively investigated due to respiratory symptoms did not find a significant association between the early markers in infancy, such as reduced lung function or thickened reticular basement membrane and typical ongoing eosinophilic asthma at the age of three or eight years. However, reduced lung function in symptomatic infants, increased RBM thickness and the presence of bronchial mast cells in infancy were associated with continuing obstructive symptoms at the age of three (7). Very early symptoms were found to be risk factors for reduced lung function at the age of eight. Active asthma at the age of eight was associated with reduced infant lung function and parental asthma. Moreover, reduced lung function in infancy was clearly associated with confirmed use of inhaled corticosteroids up to the age of 8 years(7,8). This suggests some continuum of early obstructive symptoms, reduction of lung function, airway remodeling and persistent asthma at later age. In addition, in the 2011 article, this group reported a case of a 10-month old boy who had a markedly thickened RBM of 9.2 μm who also had the highest number of mast cells, as well as eosinophils. At the age of 3 years he reportedly continued to wheeze, had frequent emergency visits and the highest purchased amount of anti-asthma drugs of all children included in the study.

Conclusion
Wheezing in infancy is a non-specific symptom that may be associated with many triggers, especially viral respiratory infections. Despite all the research conducted and published in this field, it remains very difficult, if not impossible, to reliably predict who of the infants that are wheezing during the first year of life will eventually develop asthma requiring long-term therapy. Nevertheless, some of the early wheezing phenotype studies signal persistence of early bronchial obstruction into later childhood or even adolescence, suggesting a continuous pathological pathway. Individual cases of older children whose current persistent asthma can be reliably retrospectively traced back into infancy confirm that persistent asthma can start in very early age, even in the first year of life.

References

THE POWER OF UNITY: BRINGING TOGETHER BIRTH COHORT DATA

John Henderson
School of Social and Community Medicine, University of Bristol, A.J.Henderson@bristol.ac.uk

Pediatric Pulmonology
小儿肺脏学

摘要

在过去的几十年中，已经越来越认识到在早期儿童期发展，可以导致自身无法治愈的疾病^{9}。一种可以追溯到对早期哮喘起因的研究，与某些常见呼吸道疾病的起源有关，这些可以追溯到家族史，或者对儿童期哮喘的研究。目前，哮喘的起源和相关的基因位点，可以通过基因组关联研究（GWAS）来确定，这些研究已经得到了广泛的应用。这些研究通常利用商业化的平台，需要控制和分析数据，以提高研究的统计学力量。这些研究的局限性在于需要大量的参与者，以提高发现的小效应和交互作用的统计学力量。因此，需要开发新的方法来提高研究的效率，以发现更小的效应和交互作用。这些方法包括机器学习，以及在复杂数据中识别潜在结构的统计学方法。}

在英国，有几个长期进行的研究，将儿童期哮喘作为核心结果，这些研究具有各自的特定特征，但都有共同的目标，即发现早期起因的哮喘。这些研究包括：

- 由艾文长期研究的父母和儿童（ALSPAC）
- 阿什福德的哮喘研究
- 伊斯沃尔特岛的出生队列研究
- 皮特福德的哮喘研究
- 伦敦纵向研究

这些研究通过合作研究，利用共同的数据资源和先进的计算工具，如

- 呼吸性气道的研究
- 哮喘和过敏的研究

参考文献

6. Torgerson DG, Ampleford EJ, Chiu GY, et al. Meta-analysis of genomewide association studies (GWAS) that utilised an agnostic approach to identifying SNPs across the genome that were associated with disease outcomes. For complex, polygenic diseases, such as asthma, that were recognised to have a large heritable component but for which candidate approaches had yielded only a few genes that were replicable across different populations, this presented a singular opportunity to advance understanding of asthma genetics. However, with no prior hypothesis that any one locus was associated with disease and many hundreds of thousands of SNPs typed on typical commercially available platforms, there was a need to control for a high proportion of false discoveries that were associated with the disease trait by chance. This called for large populations with the relevant outcome data and the availability of DNA for testing to yield sufficient statistical power to detect associations that were robust to adjustment for multiple testing (conventionally p < 5 x 10^-8). By combining several cohorts and meta-analysing effect estimated of associations with genomewide SNP data, international consortia have now published several GWAS of asthma^10, asthma sub-types and asthma-related traits, such as exhaled NO, revealing a number of novel loci for further evaluation. Of course, there are potential pitfalls associated with amalgamating data across large geographical boundaries; these include population stratification and lack of consistent definition of cases and controls, leading to misclassification of disease. It is perhaps rather remarkable that consistency of GWAS hits can arise from studies based on such widely disparate outcomes as self-reported symptoms and directly observed clinical test results, as was seen in two recent GWAS of allergic sensitization^13. However, there are likely to be efficiency gains in analysing commonly agreed phenotypes with greater specificity of disease traits. It has also been argued that the effect of environmental interactions with risk alleles is likely to vary geographically as a function of gradient of exposure, potentially obscuring signals where interactions might operate in opposing directions. Therefore, as we move towards studies of gene-gene and gene-environment interactions, where even the largest individual cohorts will struggle for statistical power, these issues become more pertinent. Pediatric Pulmonology

In the United Kingdom, there are several long-established, population-based, birth cohort studies that are either multidimensional and include respiratory outcomes, or which have asthma, allergy and respiratory disease as their core outcomes. Each of these cohort studies has particular aspects that makes it unique but all have common goals to discover the causes of asthma and related phenotypes. In 2005, Asthma UK recognised the potential of amalgamating data from these birth cohorts and funded the initial Study Team for Early Life Asthma Research (STELAR) Consortium, comprising the Asthma in Ashford Study, the Avon Longitudinal Study of Parents and Children (ALSPAC), the Isle of Wight Birth Cohort Study, the Manchester Asthma and Allergy Study (MAAS), and the Study of Eczema and Asthma To Observe the influence of Nutrition (SEATON). As these studies were at different stages of gestation, this network enabled the establishment of common objectives and operating protocols to ensure harmonisation of outcome measures at future clinic sweeps. Subsequently, the principal investigators of each cohort have agreed to share data and resources to create the Asthma eLab, a data repository for the unified dataset linked to computational facilities and a scientific social network to support collaborative research in a secure web-based environment. In this way eLab facilitates iterative interdisciplinary dialogue between clinicians, biostatisticians, geneticists and computer scientists to develop and process ideas. The development of a ‘Team Science’ approach backed by a large, harmonised data resource and advanced computational tools, such as machine learning approaches to identifying latent structures in complex data sets, promises to advance discovery and understanding of the early origins of asthma more rapidly and efficiently than any one cohort could manage alone.
Respiratory disease is the predominant cause of illness, death and chronic disease in children globally. Childhood pneumonia is the predominant cause of death in children under 5 years of age outside the neonatal period. Asthma is the commonest non-communicable disease in children occurring in approximately 15% of adolescents worldwide. Although the Africa childhood population constitutes only around 18% of the global childhood population, the incidence of childhood pneumonia and death is disproportionately high, accounting for almost 40% of deaths worldwide. Further, the prevalence of asthma in African adolescents is higher than the reported global average. The impact of early respiratory illness on child health has not been well studied in African children despite the high prevalence of risk factors for severe disease and the high incidence of disease.

We are undertaking a unique, multidisciplinary, South African birth cohort, the Drakenstein Child Health Study, to investigate the incidence, risk factors, etiology and long term impact of early lower respiratory tract infection (LRTI) on child health. The study aims to investigate the role and interaction of potential risk factors covering 7 areas (environmental, infectious, nutritional, genetic, psychosocial, maternal and immunological risk factors) that may impact on child health.

Pregnant women from a poor, peri-urban community with high exposure to infectious diseases and environmental risk factors are enrolled during the second trimester of pregnancy. Mothers are enrolled from primary health care facilities serving 2 different populations, a mixed race and a black African population. More than 90% of the population access health in the primary health care system which is well established including a strong HIV prevention and treatment program and national immunization program that includes 13-valent pneumococcal conjugate vaccine.

Mothers are followed through pregnancy and childbirth: 1000 mother-child pairs are then followed until children are at least 5 years of age. Biomedical, environmental, psychosocial, and demographic risk factors are longitudinally measured. Environmental exposures (carbon monoxide, particulate matter, dust microbione, SO2/NO2 and volatile organic compounds) are measured using monitors placed at home visits during the antenatal period and 4-6 months after birth. Maternal and child urine samples are longitudinally collected for urinary cotinine as a biomarker of tobacco smoke exposure. Lung function [tidal breathing measures, multiple breath washout testing, tidal exhaled nitric oxide and respiratory function using the forced oscillator technique (FOT)] is measured in children at 6 weeks, annually and during LRTI episodes.

Analysis of the infant follow-up indicates a high incidence of LRTI despite high immunization coverage and a high prevalence of risk factors associated with severe pneumonia. Microbiologic investigations including multiplex PCR measures are done longitudinally and at LRTI episodes to evaluate etiological pathogens. An intensive cohort is followed weekly for the first year of life during which clinical information, nasopharyngeal (NP) swabs and monthly stool samples are collected; data from NP samples preceding a LRTI should assist with attributing etiological diagnosis. The NP microbiome is also longitudinally studied to describe its composition in healthy children and to identify associations between patterns of nasopharyngeal colonization and the development of pneumonia or wheezing illness in children. The stool microbiome is longitudinally investigated to describe the composition and factors influencing this, as well as the association with respiratory illness. Other aspects include detailed evaluation of maternal mental and physical health and the impact on child health and infant brain imaging with evaluation of neurodevelopmental outcomes. A large biorepository has been created comprising several categories of biological specimens including blood, urine, respiratory specimens, stool and household dust microbiome specimens. This approach provides an innovative, longitudinal assessment of a range of clinical, molecular, environmental and socioeconomic variables impacting on child health and the evolution of chronic disease in a low and middle-income country setting. The DCHS is a unique African birth cohort study that uses sophisticated measures to comprehensively investigate the early life determinants of child health in an impoverished area of the world.

References

S22 Abstract
also no estimates of the burden of multi drug resistance or extremely drug resistance cases among children though these are likely to be significant.1,2 
the absence of a reliable estimate stems from a lack of an accurate sensitive
diagnostic test for TB in young children. The diagnosis of TB in children is
often based on indirect clues such as presence of evidence of infection and
suggestive radiological picture. This approach has potential for both under-
and over-diagnosis. Furthermore, children with TB do not get clearly
represented under a national TB control programme for several reasons.
Difficulty in obtaining sputum and the paucibacillary nature of primary
disease makes it difficult for any programme manager to get an easy
diagnosis of TB among children, particularly at resource-challenged
peripheral health facilities. The focus of TB control has been to break the
chain of transmission by quickly diagnosing and treating infectious adults.
As paediatric TB contributes little to the maintenance of TB epidemic, it has
largely kept childhood TB on the fringe of TB control strategies in most
countries. TB is also not adequately recognised as an important cause of
mortality within the overall child survival framework which focuses on
pneumonia, diarrhoea, malnutrition and neonatal diseases. The care of
children with TB is, thus, lost between the adult-oriented TB control
strategies and non TB-oriented child survival strategies disease. The
challenge remains to better understand its contribution to the common
causes of morbidity and mortality in young children, such as pneumonia,
malnutrition, meningitis and HIV. Increasing evidence suggests that TB may
be an important primary cause of illness or comorbidity in these contexts.
It is only in recent times that focus of the global effort has shifted to zero
deaths from TB and is now aiming to increase efforts for managing
childhood TB as well. WHO and a few countries like India have developed
separate guidelines specifically for childhood tuberculosis. Despite these
encouraging steps, expectedly enough, most programme managers prefer to
have paediatric TB case definitions and treatment guidelines as close to the
standard TB care protocols (adult guidelines) as possible, so that there is no
confusion while effecting delivery at peripheral health units. The marked
deterioration in prevalence of disease, availability of funds and health
infrastructure for TB control also make these guidelines quite varied in
approach and detail.3–5

Diagnosis of Childhood TB
Paediatric TB cases can be pulmonary or extrapulmonary. Bacillary
detection by culture is the gold standard for TB diagnosis but in resource
constrained countries, good quality smear positivity is considered a close
enough standard. However, this does not work as well for childhood TB due
to limited access to appropriate body specimen and also because primary
pulmonary as well as extra-pulmonary disease is not amenable to a smear-
based diagnosis due to low number of bacilli in the specimens. Under best
circumstances, acid fast bacilli (AFB) sputum smear microscopy is positive
in only about 10–15% of children with tuberculosis while culture gives a
better, yet modest yield of 30–40%. Cartridge based nucleic acid
amplification test (CB NAAT) like Xpert RifTM is the new rapid modality
now made available for bacteriological diagnosis but the test is far more
expensive than smear examination. Various studies have shown that the
sensitivity of CBNAAT is about 2–3 times that of the smear and almost as
much or a little less as Mtb culture. The challenge is to find the most suited
place for including this test in the diagnostic algorithm so that it is cost
effective. While AFB smear examination has all the features of a very
affordable point of care test except its lack of sensitivity, the CBNAAT with
significant gains over smear still remains very modest in its performance and
is far from being the much desired useful “rule out” test. The challenge for
resource limited countries is to find the most cost effective use. The rapidity
of this test (results available in less than 2 hours) certainly makes it useful as
it has the potential for decreasing the time to diagnosis in smear negative but
infectious culture positive cases, particularly in identifying presence of
rifampin-resistant strains. However, given the cost of CBNAAT, it cannot
replace the smear examination as the first test in all suspects and it may need
to be restricted to specimens received from those with a discernible lesion on
chest radiograph. In other words, CBNAAT perhaps will be best used to
confirm diagnosis amongst hitherto probable cases and not as the initial test.
This will, therefore, limit the ability and capacity to diagnose childhood TB
to centres where radiology is also possible and not to the community-based
microscopy centres under the RNTCP in India.3,6
The struggle to get the standardisation of other conventional tools like the
tuberculin skin test (TST) and radiology used as an adjunct in diagnosing TB
in symptomatic children continues. Lack of availability of a reliable
standardised preparation of tuberculin as the existing bulk lot of RT23 PPD
has come to an end on one hand and the availability and use of many
different strengths of tuberculin using the same cut-off on the other hand
confounds the picture. Interferon Gamma Release Assays [IGRAs], despite
their better specificity than TST, cannot accurately predict the risk of
infected individuals developing active TB disease. Given their increased
cost, replacing TST by IGRAs as a public health intervention in resource-
constrained settings is not recommended.4

Treatment of childhood TB
Amongst the major challenges around treatment of TB in children are
establishing the most appropriate dose of each drug; finding combined
formulations which could ensure adherence and decrease risks of missing
some of the drugs or doses; and, making treatment child-friendly. With the
change in the recommendations of dosages for anti-TB drugs for paediatric
use, there are not many formulations available which provide the three drugs
(RHZ) in the correct proportion as a combination. The tedious and
expensive process of regulatory clearances and the small market for these
drugs damps any efforts by the pharmaceutical companies from
evaluating and providing data for licensing of these formulations.
The drug combination for treating TB will need to be different for different
nations depending upon the rates of resistance to individual drugs in those
settings. In many countries like India, high levels of resistance to INH has
led to a situation where there is a need for a third companion drug (like
Ethambutol) to rifampin and INH in the continuation phase to prevent
likelihood of amplification of resistance to rifampin.
While the national programmes and guidelines are useful, an equally important
area to be covered for quality treatment is involvement of private sector doctors
who are often the first point of contact for a significant proportion of the patients.
Targeted and innovative educative interventions are needed to update them and
to effect a change to rational prescription behaviour. Countries like India and
Bangladesh have worked in these directions. The issues and challenges related to childhood TB are immense and
evolving. The paediatricians must persist with public health specialists for
sustained effort to improve and innovate.

References
children from developing countries. Semin Paediatr Infect Dis 2004;
2. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Beyers N. The burden of
childhood tuberculosis and the accuracy of routine surveillance data in high
3. Guidance for national tuberculosis programmes on the management of
5. Berti E, Galli L, Venturini E, de Martini M, Chiappini E. Tuberculosis in
children from developing countries. Semin Paediatr Infect Dis 2004;
Trials – TB treatment in Children Evid.-Based Child Health 2010, 5: 1566–
1577.

PERINATALLY ACQUIRED TUBERCULOSIS - DIAGNOSTIC AND THERAPEUTIC APPROACH
P Gousnard, Ae Bekker, RP Gie
Tygerberg Children’s Hospital, Stellenbosch University, Cape Town, South Africa, pgouss@sun.ac.za
The HIV epidemic has seen a resurgence of tuberculosis (TB) in young
women of childbearing age. In 2013, the World Health Organization (WHO)
reported 3.3 million new cases of TB in women, resulting in 510,000 deaths,
of which 180,000 (35%) were in HIV co-infected women (1). Infants born to mothers with TB (TB-exposed newborns), with or without HIV, are at high risk of TB infection and disease. Congenital TB transmission occurs with hematogenous spread via the placenta or with aspiration or ingestion of infected amniotic fluid before or at birth. Postnatal TB develops shortly after birth, due to respiratory droplet spread from an infectious TB source case, most commonly the mother. As the exact time of TB infection is difficult to determine, and the clinical presentation and management of congenital TB (rare) and postnatal TB (more common) are similar, these two entities are now combined into perinatal TB.

The true incidence of congenital TB is unknown with less than 300 cases reported in the literature prior to 1994 (7). The revised Cantwell’s criteria from 1994 are used to define true congenital TB in any infant with a TB lesion and one or more of the following: i) the lesion being present in the first week of life, ii) a primary hepatic complex or caseating hepatic granuloma, iii) TB infection of the placenta or endometrial TB in the mother, or iv) exclusion of the possibility of postnatal transmission by excluding TB in other contacts (7). Symptoms and signs of congenital TB may be present at birth, but often occur in the first weeks of life, and mainly involve the lung and liver. Perinatal TB includes symptoms and signs of respiratory distress, hepatomegaly, splenomegaly, fever, prematurity or low birth weight, cough, poor feeding, failure to thrive, abdominal distention, ascites, irritability, peripheral lymphadenopathy and sepsis syndrome. The diagnosis may be difficult due to non-specific symptoms that overlap with other conditions. It is also not a diagnosis that is often considered in a young infant. In one study, chest radiography was available for 53 of 75 infants, with miliary TB (30%), bronchopneumonia (32%) and lobar opacification (34%) the most common radiological presentations. Cavities were seen in 8%, lymph nodes visible in 8% and pleural effusions in 2%. The chest radiography was normal in 8% of cases. Diagnosis may be difficult in TB cases of the very young as skin test and interferon-gamma release assays are mostly negative (28). TB in children is paucibacillary in nature, however limited infant studies have reported more than 70% to be confirmed culture positive. (8,9). A possible explanation for this may be the high bacillary load found within recently infected infants. TB-exposed newborns are also at high risk of TB disease progression following TB infection. In the absence of chemoprophylaxis, up to 50% of infants will develop TB disease following exposure, with up to 30% of infants developing progressive pulmonary or disseminated disease.(2).

Standard three-/ four-drug treatment with isoniazid, rifampin and pyrazinamide, with or without ethambutol, remains the drugs of choice as first-line TB drug regimens in infants. There is very limited information on the side effects of these drugs in neonates and infants. There are also very limited PK and safety data available in neonates and infants for first-line TB drugs, with none available for long-term use in second-line TB drugs settings. [10] A mother with recently diagnosed or undiagnosed TB may pose an infectious risk not only to her own newborn but also to other newborns in the nursery. Heyns et al. reported on Kangaroo mother care (KMC) and the risk for transmission of TB. KMC has become the standard of care for low-risk prematurity infants born in developing countries. He reported on an infant (sentinel case) who was admitted to the pediatric intensive care unit (PICU) with extensive pulmonary tuberculosis and tracked back the contact as the mother in KMC. [5] It has previously been shown that there is a 60-80% TB transmission risk for infants from a close smear-positive TB source case, and 30-40% from a smear-negative TB source case (6). HIV co-infection also contributes to a high infant mortality with a four-fold increase observed among infants born to TB/HIV-infected women in India (3). Schaaf et al. have shown a 24% mortality in those aged less than 3 months of age with culture-confirmed TB in a South African study (4).

Conclusion

A high index of suspicion is imperative to recognize perinatal TB, where the mother is often the source case. Active screening of the mother for TB is essential. Symptoms and signs of perinatal TB is atypical and can go unrecognized with dire consequences for the young infant. Infants are very vulnerable for TB disease progression following infection, and if untreated, high associated mortality can occur.
evaluates for the presence of resistance to isoniazid and rifampicin. If the child is clinically suspected of having MDR-TB, treatment should be started whilst awaiting confirmation. WHO has placed the drugs used in the treatment of MDR-TB in five groups. Group 1 drugs are considered first-line with the remainder second-line. When designing a regimen to treat children with MDR-TB, the target should be to use at least four, but preferably five drugs, which are likely to have activity against the infecting organism. Decisions on which drugs to include in an MDR-TB treatment regimen should be guided by the DST of the child’s isolate. If this is not available, it should be guided by the DST pattern of the presumed source case. As they are the most potent drugs, with the fewest adverse effects, any first-line drugs to which the organism is still susceptible should be used. The next step is to add an injectable drug and then a fluoroquinolone. Further drugs from group four should then be added, including ethionamide (or prothionamide), cycloserine (or terizidone) and para-aminosalicylic acid (PAS). Finally, agents from group five can be added if required. Both clofazimine and linezolid have, in recent studies, demonstrated promising efficacy and should be considered useful drug options. Two newly licenced drugs, bedaquiline and delamanid, appear to have good efficacy against \textit{M. tuberculosis} and may in the future have a more prominent role in the treatment of pauci-MDR-TB. Children should be monitored for three reasons: to determine response to therapy; to identify adverse events early; and to promote adherence. Response to therapy includes clinical, microbiological and radiological monitoring and these should be evaluated at follow-up. Children should also be assessed at follow-up for symptoms and signs of adverse effects. Both ethionamide and PAS can cause hypothyroidism and the injectable drugs can cause renal impairment and hearing loss. Prior to the start of treatment, children should have a baseline assessment of thyroid function, renal function and have audiological and vision examinations. They should then have their hearing assessed as well as their renal and thyroid function during treatment. Adverse events should be managed early and aggressively to avoid permanent side effects or adherence compromise. At each consultation, adherence advice should take place; treatment supporters and counselling are also of benefit. If children are diagnosed early and treatment taken conscientiously, favourable treatment outcomes are achieved in greater than 80% of cases.

Few studies have been conducted to evaluate the correct management of children who have been exposed to MDR-TB. Observational data suggest that six months of preventive therapy with a fluoroquinolone-based regimen is likely to be effective in preventing the development of TB disease. Guidelines are inconsistent. Three trials will soon be conducted to evaluate the management of MDR-TB child contacts.

References


COMMUNITY ACQUIRED PNEUMONIA IN THE DEVELOPING WORLD

Varinder Singh

Prof. of Paediatrics, Lady Hardinge Medical College and assoc Kalawati Saran Children’s Hospital, N Delhi, India, 4vsingh@gmail.com

Pneumonia is a common lung problem of infectious origin that affects a huge proportion of children throughout the world. It is particularly common in the populous developing world and often leads to mortality among younger age groups. The situation can perhaps be improved by appropriate antimicrobial treatment, routine vaccination, improved nutrition, and effective oxygen therapy. Ever since the launch of the global concerted efforts to control morbidity and mortality due to acute respiratory infections, substantial advances have been made in the understanding of the clinical syndrome of pneumonia, its aetiology, and appropriate treatment.

Magnitude of the problem and efforts to control it

Community acquired pneumonia continues to be the leading cause of child mortality globally, particularly in the developing world where most of these deaths occur. In 1993, the World Development Report showed that acute respiratory infection was the leading cause contributing to 30% of all childhood deaths. The concerted efforts by National and International agencies have resulted in a 40% reduction in Under 5 mortality in the last decade largely due to a decrease in diarrhoea and pneumonia deaths. The world has witnessed a reduction in pneumonia incidence from 0.29 to 0.19 episodes per child-year between 1990 and 2011.

Even now, an estimated 120 million episodes of pneumonia and 1.1 million child deaths occur globally each year due to pneumonia, of which 80% are in first two years of life. Pneumococcus is responsible for 18% of cases with severe pneumonia and 33% of childhood pneumonia deaths. Nearly 33% of the global mortality due to pneumonia is contributed by India, even though only 17% of the world’s under-five children reside in India. Pneumonia contributes to 23% of total under-five deaths in India (about 8% in infancy and 15% between 1 mo - 5 years of age) with about 35 million episodes of pneumonia each year of which 4 million are severe.

This has led to the development a Global Action Plan for Pneumonia (GAPP) which focuses to promote the expansion and improvement in community case management, to reduce risk factors for disease, and works for the massive roll-out of vaccination against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae by countries through support from the GAVI Alliance. Diarrhoeal disease, the dethroned killer king, continues to be the second important cause of disease and death among children (600,000 diarrhoea deaths in 2012; of these 72% in under 2 years of age).

The strategies to manage and decrease deaths due to these two major killers have much in common. Breast feeding, zinc supplementation, Immunisation, adequate and appropriate nutrition, better hand and personal hygiene are important preventive interventions to control both these diseases. Further, young children often have more than one morbidity and underlying malnutrition increases the risk of death from both pneumonia as well as diarrhoea. An early detection through expanded community case management and early referral continues to be advocated through Integrated management of neonatal and childhood illnesses in many high burden countries, including India. Internationally, WHO, UNICEF and other agencies have launched a Global Action Plan for Pneumonia and...
Diarrhoea (GAPPD). The subsequent discussion critically analyses the various components of this strategy.2

Challenges posed by prevalent strategies and course correction

Diagnosis and case management

At the core of pneumonia control is the community case management strategy. The current community management algorithm used in most developing countries is based on initial studies of bacterial pneumonia from the 1980s. The strength for the case-management strategy was that clinical diagnosis of children with pneumonia was possible by the use of simple clinical signs such as respiratory rate and chest indrawing even in a community setting by a trained health worker. As most pneumonia deaths in the developing world were considered to be caused by bacteria, usually Streptococcus pneumoniae or Haemophilus influenzae, early diagnosis and treatment with first line antibiotics could prevent the pneumonia-related deaths. Further, under this strategy, children with a cough but who did not have pneumonia were not given antibiotics thus reducing selection pressure for antimicrobial resistance. Several studies from various nations indicate that this strategy did work and helped achieve its goals.

Over the years, the understanding of this pneumonia syndrome has improved and also several other developments have happened which challenge the initial case management algorithm. With the spread of HIV infection in parts of sub-Saharan Africa and Asia, there have been disproportionately high numbers of pneumonia deaths. The causes of infection in these cases are more likely to be varied and include pathogens unique to immunocompromised hosts e.g. those with TB or PCP. The availability of antiretroviral therapy further continues to modify this interaction between HIV and pneumonia. Data from vaccine-probe studies indicate that the predominant aetiologic agents are Streptococcus pneumoniae (18% of severe cases, 33% of deaths), Haemophilus influenzae type b (4% of severe episodes, 16% of deaths) and influenza virus (7% of severe episodes and 11% of deaths). Respiratory viruses such as respiratory syncytial virus (RSV), rhinovirus, human metapneumovirus, human bocavirus, and parainfluenza viruses also contribute considerably to the burden of childhood pneumonia in both affluent and in low income world. RSV was estimated to cause approximately 34 million episodes of ALRI in children under 5 years or 22% of all ALRI; 10% of episodes resulted in severe illness and hospitalisation and 99% of deaths due to RSV occurred in low income countries. With improved immunisation against the main bacterial pathogens, respiratory viruses may become more prominent as aetiologic agents of pneumonia. Severe pneumonia can result from infection with multiple pathogens such as bacterial-viral, viral-viral or mycobacteri-al-bacterial infections. The newer bugs as well as newer strains (such as novel H1N1) further complicate the picture.3,4

For appropriate management of a disease, it is important to make the correct diagnosis. The assumption that every child with fever and cough with fast breathing has bacterial pneumonia and needs antibiotic treatment is far less valid under a changed situation and understanding today. This simple clinical definition can overlap with that of other diseases that not only do not require an antibiotic (e.g. bronchiolitis, wheeze associated with lower respiratory infection, etc.) but need specific interventions including appropriate management of entailing hypoxemia, without which the child has increased suffering and even risk of death.5

Studies of non-severe pneumonia from Asian countries have shown that presence of wheezing contributes to a large proportion of perceived antibiotic treatment failure.6,7 Therefore the current case management protocol needs to be changed and WHO now recommends a trial of rapid-acting bronchodilator in children with wheeze and fast breathing before making a diagnosis of pneumonia. However, it offers new challenges as most health workers do not have skills or tools to auscultate chest. A separate management algorithm shall be needed for children with wheeze and shall entail teaching health workers what constitutes an effective response to bronchodilators for rational management. It would not be easy because infants with wheeze usually have viral bronchiolitis which does not have a predictable response to bronchodilators.5

Around 20% of children presenting to health facilities with pneumonia have hypoxemia which is associated with a marked increased risk of mortality. The clinical deterioration due to pneumonia is often rapid, especially among young infants where septicaemia and hypoxaemia are likely to be the major mechanisms leading to deterioration and death. This is particularly important for small infants, severely malnourished and those living with HIV/AIDS. The first contact health facility where the sickest child usually presents has limited options for case management. In many countries, oxygen supplies are either not present or available irregularly. Accurate recognition of the child with severe pneumonia, supported by a mechanism that allows prompt referral to a facility for antibiotics and oxygen, though critical is however currently inadequate in resource-limited settings. It is important to understand that further decline in mortality related to pneumonia will not only need improvement and consolidation of the current case management strategy but also need health system strengthening in these countries.

WHO recently revised recommendations on the basis of evidence from studies comparing antibiotic treatment for pneumonia. The newer guidelines now advise domiciliary oral antibiotics for children with pneumonia who have fast breathing and/or lower chest indrawing. It is only the children with severe disease (SpO2 <90% or inability to feed, altered sensorium or severe respiratory distress) who are advised admission for antibiotic and oxygen. Pulse oximetry, the “standard of care” for detecting, treating and monitoring hypoxaemia in higher income countries is not routinely available in health facilities of resource-challenged countries as it is moderately expensive. Further, a shorter 3–day regime is advocated for non-severe cases. It is pertinent to point out that the evidence for the efficacy for shortened regime comes from studies using the clinical definition which has been criticised for its inability to distinguish bacterial from viral pneumonia or from children with wheezing. A recent study from Pakistan reported radiological evidence of pneumonia in only 14% of children with WHO-defined non-severe pneumonia.1,8 Pulmonary tuberculosis is increasingly recognised as a cause of acute pneumonia especially in children in tuberculosis-endemic countries.

The difficulty of diagnosis as well as rational therapy is not restricted to community case management algorithm alone. Clinical data are often imprecise, and microbiological data is not only less often available but is also challenging to interpret. Additionally, chest radiographs, often used in the larger health facilities or in the private sector, have several difficulties e.g. they lag behind clinical presentation, lack ability to completely differentiate bacterial from viral aetiology, even when simultaneously taking into account several clinical factors—including hypoxia, history of fever, focal decreased breath sounds, and the absence of wheezing. There is a tendency to treat all hospitalised children with newer 3rd generation antibiotics or co-amoxycylav or vancomycin without adherence to the principle of antibiotic therapy. In this direction, efforts to develop guidelines for first and higher level referral facilities in both public and private sectors is needed. Country-specific guidelines such as those prepared by the Indian Academy of Paediatrics for rational therapy of all respiratory illnesses is a welcome step in this direction.

Preventive strategies

Prevention of respiratory illnesses and their consequent mortality can be achieved by the increase in vaccination against pneumococcus, Hib, measles, pertussis, and influenza. While the vaccination against Hib is introduced in many counties (about 90% of countries are covered after GAVI support), pneumococcal vaccination being expensive is still not included in the national programmes of most of the resource-limited countries. General health promoting strategies like breastfeeding and improved nutrition are focussed through integration of pneumonia control activities into integrated management of childhood illnesses. Strategies to reduce exposure to indoor air pollution and cigarette smoke are important preventive interventions to reduce the severity and incidence of childhood pneumonia. Early use of ART and of cotrimoxazole prophylaxis for those who are HIV infected reduces the burden as well as severity of pneumonia.

Social determinants

Beyond the health systems, factors associated with recognising need for care are important in determining formal care, and strongly linked to social determinants. In addition to specific action by the health system with an
enhanced community health worker role, a systems approach can help ensure barriers are addressed among poorer and more remote homes. While the management strategies used for respiratory disease control have borne fruit by decreasing both overall mortality as well as pneumonia-specific mortality, it continues to be a major burden of morbidity and mortality among children particularly in resource-poor regions and societies. More widespread implementation, improvement of diagnostic skills and capacities, robust medical systems and scale-up of immunisation with improved vaccines against childhood pneumonia agents shall be needed to achieve sustained reduction in respiratory morbidity and mortality.


DEVELOPED WORLD: IMPACT OF PNEUMOCOCCAL CONJUGATED VACCINE ON CHILDHOOD PNEUMONIA

Andrew A. Colin, MD
Miller School of Medicine, University of Miami, Miami, Florida, USA, acolin@med.miami.edu

Pneumonia is a highly prevalent disease in childhood with a reported incidence of 3-4% of the pediatric population below age 5 in the developed world. It is a fundamentally and dramatically different disease in developing countries in which the prevalence, severity and mortality are much higher. The determination of etiology of pneumonia is complicated; while studies from recent years continue to suggest that Streptococcus pneumoniae remains the leading cause of bacterial pneumonias around the globe, recent analyses of trends of community acquired pneumonia (CAP) indicate that Staphylococcus aureus (SA) and in particular methicillin resistant SA (MRSA) has become an important cause of CAP in the US, this trend, however, is not experienced in all developed countries.

Viruses are the predominant etiology of lower respiratory infections (LRI) in infancy and early childhood. Mixed viral and bacterial infection may be as high as a quarter of the cases of pneumonia. Mycoplasma pneumoniae appears to present 50% of cases of community-acquired pneumonia in children 5 years of age and older, and may play a more significant role in LRI of younger children than hitherto appreciated.

Routine vaccinations against Haemophilus influenzae and Streptococcus pneumoniae have both reduced the incidence of pneumonia in infancy and childhood, but the latter vaccination, with the heptavalent conjugated vaccine (PCV-7) that was introduced in 2000, was associated with a rising incidence in complicated pneumonia. Predominant amongst these complications is empyema, with a marked increase of cases and an alarming prevalence of MRSA being observed in many centers in the US. Necrotizing Pneumonia (NP), also termed Cavitatory Pneumonia, another facet of complicated pneumonia, emerged as a parallel complication with pleural involvement in many parts of the world. The diagnosis of NP, which requires use of CT scan, is often masked by the frequent parallel presence of empyema, and uncoupling the relative contribution of the two processes is sometimes difficult.

An analysis from 2010 reviewing hospitalizations in the US (1997-2006), spanning the period around the introduction of PCV7, revealed that rates of CAP decreased for infants <1 year of age but increased for children >5 years; systemic complications (acute respiratory failure, sepsis, ECMO) decreased only for infants <1 year of age; however, local complications (empyema, lung abscess, necrotizing pneumonia) increased for all age groups.

There is evidence that since PCV7 covers only 7 of more than 92 pneumococcal serotypes, with the introduction of the vaccination; non-vaccine types (NVT) have increased among asymptomatic carriers in a process dubbed “serotype replacement”. This increase in NVT consequently resulted in little or no net change in the bacterial carriage prevalence and may have reduced the benefits of vaccination. There is indeed evidence that the observed increase in invasive pneumococcal disease (IPD) was associated with such replacement, and IPD was often caused by pneumococcal types that were infrequently observed in the population prior to PCV7. A review of these observations addresses the surveillance biases that may affect these findings. It also contends that the magnitude of serotype replacement in disease can be partially attributed to a combination of lower invasiveness of the replacing serotypes, biases in the pre-vaccine carriage data (unmasking), and biases in the disease surveillance systems that could underestimate the true amount of replacement. The authors conclude that absence of prospective longitudinal studies designed to analyze these trends and connections, renders the statements of causality difficult, and emphasize the key role for future surveillance studies.

PCV13, which increased the conjugated vaccine from 7 to 13 serotypes, was licensed in the US and largely replaced PCV7 as of 2010. Studies from around the globe appear to all support a marked effect of reduction of morbidity, including IPD, and mortality associated with this vaccination. A study from Massachussets reveals that PCV13 reduced the prevalence of colonization with PCV13 serotypes among children 6–23 months old, but its efficacy was not shown among older children. Impressive effects are reported on reduction of morbidity. Two summary reports from the CDC (2013-2014) conclude that substantial direct and indirect effects are evident after 3 years of use. PCV13 appears highly effective at preventing IPD among children who receive the vaccine. Specifically; 89% effectiveness of >1 dose PCV13 vs. PCV13-type IPD; 88% reduction in PCV5-type IPD among children, leading to an estimated >20,000 cases of IPD and >2,000 deaths prevented.

Data from Israel spanning 2004 to 2013 were reported from an ongoing nationwide, prospective, population-based, active surveillance study and included all IPD episodes (Streptococcus pneumoniae isolated from blood and/or cerebrospinal fluid). The study showed that following initiation of a PCV national vaccination plan, a rapid and substantial 2-step IPD reduction was observed in children <5 years. The serotype-specific rate reduction reflected the sequential introduction of PCV7/PCV13. From Norway a prompt effect of replacing PCV7 with PCV13 on the epidemiology of IPD disease was also reported. It appears that the transition from PCV7 to PCV13 is indeed amplifying the effect of reduction of infections related to pneumococcal disease. Long-term surveillance will reveal the possible impact of replacement in this vaccinated population, but studies to date are suggesting that the pernicious burden of pneumococcal disease is being substantially reduced in childhood by the current vaccination regimen.

References
with three defined subcategories or tiers: 1) ventilator associated condition (VAC), a sustained episode of respiratory deterioration, both non-infectious and infectious in origin, 2) infectious ventilator associated conditions (IVAC), which aims to capture events related to infection, and finally 3) ventilator associated pneumonias (VAP), which attempts to capture new both probable and possible infection related events with purulent respiratory secretions and/or positive respiratory culture with probable cases dependent upon rigorous standards of quantitative or semiquantitative thresholds for pathogen growth. Previous clinical criteria for the diagnosis of VAP included two or more abnormal chest radiographs with at least one of the following signs: new or progressive and persistent infiltrate, consolidation, cavitation, and/or pneumatoceles (in infants ≤1 year of age). A few studies have examined the sensitivity and specificity of lower airway sampling in PICU patients and found the sensitivity and specificity of BAL (10^4 CFU/ml) to be 50 to 72% and 80 to 88%, respectively. Diagnostic testing is ordered for two purposes: to define whether a patient has pneumonia as the explanation for a constellation of new signs and symptoms and to determine the etiologic pathogen when pneumonia is present. For patients diagnosed with ARDS, suspicion of pneumonia should be high and the presence of only one of the three clinical criteria described should lead to more diagnostic testing. A high index of suspicion should also be present in patients who have unexplained hemodynamic instability or deterioration of blood gases during mechanical ventilation. In the absence of any of these findings, no further investigations are required. The incidence of colonization in hospitalized patients in general and even more in patients requiring endotracheal intubation is high. Antibiotic treatment of simple colonization is strongly discouraged. Routine monitoring of tracheal aspirate cultures to anticipate the etiology of a subsequent pneumonia has also been found to be misleading in a significant percentage of cases.

**Etiology**

Early onset VAP arises less than 48 hours after intubation, and is mainly due to organisms typically associated with community-acquired pneumonia, e.g., *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*. Late-onset VAP, which does not become symptomatic until at least 48 hours after intubation, is mainly associated with *Pseudomonas aeruginosa* (10–44%), *Staphylococcus aureus* (10–30%), *Enterobacter cloacae* (10%) and *Klebsiella pneumoniae* (10%). Infections due to gram-positive cocci, such as *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA), have been rapidly emerging in the United States. Fungal and viral agents are rare causes of VAP in immunocompetent hosts. (3,6)

**Additional risk factors**

In neonates, multiple risk factors make them highly predisposed to acquire nosocomial infections, including, but not restricted to, immature immune systems, less effective barriers of skin and mucous membranes, decreased activity of complement, and hypogammaglobulinemia in premature newborns. Low birth weight has also been shown to be a risk factor for the development of nosocomial pneumonia. In older children, genetic syndromes and reintubations led the list in risk factors for VAP. Gastric aspiration, worsening acute respiratory distress, septic shock and medications including steroids are independent risk factors. Almost all patients receiving MV have a nasogastric tube inserted to evacuate gastric and enteral secretions, prevent gastric distention, and/or provide nutritional support. The nasogastric tube is not generally considered to be a potential risk factor for VAP, but it may increase oropharyngeal colonization, cause stagnation of oropharyngeal secretions, and increase reflux and the risk of aspiration. Respiratory equipment itself may be a source of bacteria responsible for VAP.

**Treatment and prevention**

Treatment of suspected VAP is centered on an approach of initial empirical therapy with broad-spectrum antibiotics followed by de-escalation to specific antimicrobial therapy once culture results are known or discontinuation of antibiotics if VAP is no longer suspected. Two factors appear to render the choice of antibiotics particularly difficult in critically ill patients. First, VAPs are likely to result from highly resistant organisms, especially in patients who were previously treated with antibiotics. Second, multiple organisms are frequently cultured from the pulmonary secretions of patients considered to have pneumonia. Because of the emergence of multi-resistant, extended
spectrum lactamase-producing GNB in many institutions and the role played by gram-positive bacteria, such as MRSA, even a protocol combining ceftazidime or imipenem and amikacin would not ensure adequate coverage of all cases of VAP in these ICUs. Therefore, no “magic bullet” exists to cover all the microorganisms potentially responsible for VAP. Protocols for initial empiric therapy have emerged as a potentially effective means of avoiding unnecessary antibiotic administration while increasing the likelihood of initially appropriate therapy.

Future directions

The application of the new VAE definitions to adult units is occurring currently and has generated considerable debate. Although most studies do show that there is an adverse outcome for patients with VAEs, the value of reporting rates of VAP as a measure of quality-based payment is being debated. In an editorial comment to a recent prospective study, Niederman and Nair noted that there are not enough data to endorse the measurement of VACs as a reflection of quality of care, particularly because most episodes of a VAC are not VAP, and we do not have a prevention strategy that is able to prevent IVACs. (7,8) How well the new definitions of VAC and VAP will apply to pediatric units is unclear and will undoubtedly produce significant research and QI efforts for pediatric units in the U.S. in the future. A viable definition and risk stratification system incorporating preventable and nonpreventable risk factors for pediatric VAP would assist intensivists in the refinement of pediatric-specific VAP prevention bundles. (9,10) Larger, multicenter, randomized controlled trials using the new standard reference definitions of VAE/VAP to test additional interventions in children may be useful.

References

8. Niederman, MS and Nair, GB Managing ventilator complications in a “VACaum” of data. Chest 2015;147:5-6

AIRWAY INFLAMMATION IN CF AND THERAPEUTIC TARGETS

Malena Cohen-Cyberkenh, MD
Pediatric Pulmonary Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, Malena@hadassah.org.il

Lung disease in cystic fibrosis (CF) occurs as a consequence of a cascade of events initiated by CF transmembrane conductance regulator (CFTR) dysfunction. It leads to failure of chloride secretion and sodium hyperabsorption at the apical airway surface causing dehydration of the fluid layer and impaired mucociliary clearance. The desiccated mucus obstructs the airways and prevents elimination of bacteria from the lung, allowing chronic infection to become established. The resultant neutrophilic inflammation causes progressive damage to the airways. The vicious cycle of intense neutrophilic inflammation, oxidative stress and continuous infection contributes to irreversible airway destruction and fibrosis. Lung disease begins very early in life and some changes to the airways may even occur prenatal.1. The presence of inflammation and bacterial infection was demonstrated soon after diagnosis, in infants diagnosed by newborn screening. Inflammatory markers were found in high concentrations in bronchoalveolar lavage (BAL) fluid, even in infants with normal lung function and without apparent bacterial colonization. Once established, airway inflammation may be associated with decreased lung function and significant structural damage, including bronchiectasis and poorer nutritional status.2. Data derived from primary murine tracheal cells suggest that following P. aeruginosa infection, inflammatory mediators are concentrated in the thin dehydrated periciliary fluid layer of CF airway epithelial cells resulting in high chemokine concentration gradients across the epithelium and an exaggerated inflammatory response.3. Greater hospitalization rates, growth impairment and reduction of lung function are seen in CF patients as a consequence of respiratory viral infections, predisposing the patient’s airway to bacterial infections and earlier acquisition of P. aeruginosa.4. Fungi infections, mainly Aspergillus, may lead to an inflammatory response in the airways, playing a role in the pathogenesis of CF lung disease. Assessing airway inflammation in CF is essential for initiating early treatment. Forced expiratory volume in 1 second (FEV1) is a non-invasive and reproducible test and is considered the gold standard for monitoring disease progression; however, it shows a poor correlation with inflammation. Other tests e.g., multiple breath washout, sputum cultures, exhaled breath condensate, and BAL can help in assessing airway inflammation. High resolution computed tomography (HRCT), a sensitive tool to detect early structural changes, cannot distinguish between old scars and active inflammation. Positron emission tomography- CT (PET-CT) can directly measure neutrophilic activity and detect inflammation, however, it involves high radiation levels.5. Anti-inflammatory agents in CF have been the subject of intense investigation. Corticosteroids and non-steroidal anti-inflammatory drugs have shown some benefit, but considerable side effects limit their use. High-dose ibuprofen was shown to significantly slow the rate of decline in FEV1 especially for patients <13 years of age6,7, however, the use is limited specially because it has potential gastrointestinal and renal side effects. Azithromycin, used as an immuno-modulating agent for both patients with and without P. aeruginosa colonization, was shown to significantly reduce the number of respiratory exacerbations and the rate in decline of lung function, and to improve quality of life in patients colonized with P. aeruginosa and S. aureus.8,9. Early diagnosis, aggressive therapy, and continuous monitoring of the inflammation in the airways are required in order to avoid deterioration of lung function and improve survival of patients with CF.10

References


Pediatric Pulmonology
Typical pneumonia, usually caused by *Streptococcus pneumoniae*

**Introduction**

Email: matti.korppi@uta.fi

M. pneumoniae population, between atypical pneumonia and serological responses to infiltrate on chest radiograph is less prominent without alveolar solid and milder constitutional symptoms is called atypical pneumonia. The infiltrate on chest radiograph. Pneumonia with less acute onset, less fever prominent response in inflammatory markers and alveolar, often lobar, characterized by acute onset of fever and constitutional symptoms, serological evidence of bacteria or typical bacteria like pneumococcus. In addition, two or even community-acquired pneumonia (CAP) cases confirmed or suspected to þ Tel. Finland Center for Child Health Research Tampere University and University Hospital 2010;303:1707-15


**ATYPICAL PNEUMONIA**

Matti Korppi, MD, PhD, professor

Tampere University and University Hospital Center for Child Health Research FM-3 building, 33014 Tampere University, Finland

Tel. +358 (0) 50 318 6316

Email. matti.korppi@uta.fi

**Introduction**

Typical pneumonia, usually caused by *Streptococcus pneumoniae*, is characterized by acute onset of fever and constitutional symptoms, prominent response in inflammatory markers and alveolar, often lobar, infiltrate on chest radiograph. Pneumonia with less acute onset, less fever and milder constitutional symptoms is called atypical pneumonia. The infiltrate on chest radiograph is less prominent without alveolar solid consolidations. In the 1960’s, an association was found, first in the military population, between atypical pneumonia and serological responses to *Mycoplasma pneumoniae* called at that time Eaton agent, and in the 1980’s, again first in the military population, between atypical pneumonia and *Chlamydia (Chlamydiska pneumoniae*) called at that time Chlamydia TWAR. Currently, the term atypical pneumonia is still used for community-acquired pneumonia (CAP) cases confirmed or suspected to be caused by atypical bacteria, although no clinical, radiological or laboratory-based criteria can separate CAP caused by viruses, atypical bacteria or typical bacteria like pneumococcus. In addition, two or even more microbes, including also atypical bacteria, seem to be concomitantly involved with pediatric CAP in half or even more of the cases. Earlier, serological evidence of *Mycoplasma* or *Chlamydiska* infection was mainly found in school-aged children or young adults, but the development of polymerase chain reaction (PCR) -based tests has widened the age distribution also to preschool-aged children.

**Epidemiology**

Population-based data including hospitalized and non-hospitalized children with CAP caused by *M. pneumoniae* and *C. pneumoniae* is thirty years old. In these studies, serological evidence of *M. pneumoniae* etiology was found in 9% of children with CAP at <5 years of age, in 40% of children at 5-9 years of age and in 67% of children at 10-14 years of age. The figures for *C. pneumoniae* were 6%, 13% and 35%, respectively. Serological evidence of *M. pneumoniae* or *C. pneumoniae* etiology was found in >50% of CAP cases in 5-9 year-old children and in >75% of CAP cases in 10-14 year-old children. On the other hand, the incidence of pediatric CAP in children decreased by age from 30/10000/ year at <5 years of age to half (<20/ 10000/ year) at 5-9 years of age and to a fourth (<10/ 10000/ year) at 10-14 years of age. Over 80% of *Mycoplasma* cases were treated at home, 52% were mixed infections with *C. pneumoniae* or other bacteria, and all improved well although not all were treated with antibiotics effective against atypical bacteria. The incidence of *Mycoplasma pneumoniae* was 6.7/10000/ year at 5-9 and 10.6/10000/ year at 10-14 years of age, the figures being about two-times higher than in two old American studies. Unfortunately, newer strictly population-based data including both hospitalized and non-hospitalized children are not available on pediatric CAP caused by *M. pneumoniae* or *C. pneumoniae*.

During the last 15 years, three CAP studies including more than 100 children with methods available for both viruses and typical and atypical bacteria have been published. In two studies including hospitalized children only, *Mycoplasma* etiology was documented in 7-14% and *Chlamydiska pneumoniae* etiology in 3-9% of cases. In the serological study including both hospitalized and ambulatory patients, *Mycoplasma* etiology was documented in 27% and *Chlamydiska pneumoniae* in 8%. In a study focusing on atypical bacteria only, *M. pneumoniae* was identified in 36% and *C. pneumoniae* in 11% by PCR and/or serology. The figure for *M. pneumoniae* was 21% at 2-4, 46% at 5-7 and 59% at >7 years of age.

**Diagnosis**

The microbiological diagnosis of *M. pneumoniae* and *C. pneumoniae* etiology of CAP is challenging. Paired sera are needed for documentation of rises in microbe-specific antibodies, and culture methods are technically difficult and clinically non-sensitive. PCR-based tests for direct detection of *M. pneumoniae* or *C. pneumoniae* in respiratory samples have not been, at least until present, sufficiently sensitive and specific for clinical practice. Carriage of *M. pneumoniae* may happen during epidemics, which are usually slow and long, and thus PCR may give a false-positive test result.

The conventional complement fixation (CF) serology for *M. pneumoniae* infection, although managing rather well in adults, does not measure immunoglobulin M (IgM) and IgG antibodies separately, and is no longer used in pediatric practice. The enzyme immunoassay (EIA) measures IgM and IgG antibodies separately, but there are certain difficulties in the interpretation of the results. For example, IgM antibodies to *M. pneumoniae* may remain positive for many months after acute infection, and do not necessarily mean acute *Mycoplasma* infection.

The conventional microcinemunofluorescence (MIF) test measures *Chlamydiska pneumoniae* IgM and IgG antibodies separately, and the test is rather specific but non-sensitive. Antibody responses are often slow, and the response is not necessarily to be seen in paired sera taken at two to three weeks intervals. *M. pneumoniae* seems to cause chronic latent infections leading to variable subclinical serological responses triggered e.g. by viral infections, and of course, to real activations of latent infection with clinical symptoms. These characteristics explain the high number of mixed infections in children with CAP caused by *M. pneumoniae* in serology-based studies.

In an American study in children hospitalized for CAP, *M. pneumoniae* was found by EIA or PCR in 14%, and *C. pneumoniae* by MIF or PCR in 9%, and half of the cases were mixed infections with other viruses or bacteria. Either *M. pneumoniae* or *C. pneumoniae* with no co-infection was identified in 22% of the cases. In children treated at home for CAP, PCR was positive for *M. pneumoniae* in 7% and for *C. pneumoniae* in 6%, as reported earlier by the same research group.

According to the American Clinical Practice guidelines, children with signs and symptoms suspicious for *M. pneumoniae* should be tested to help antibiotic selection, but diagnostic testing for *C. pneumoniae* is not recommended, mainly due to the lack of a reliable and readily available test. The updated British Thoracic Society guidelines on diagnosis and treatment of pediatric CAP do not recommend routine microbiological testing in ambulatory patients, but recommend acute and convalescent serology for *M. pneumoniae* and *C. pneumoniae* in children treated for severe or complicated CAP in hospital.

**Treatment**

Both American and British guidelines recommend that CAP in children can be diagnosed without chest radiography or any laboratory measurements. The treatment should always cover *S. pneumoniae*, since most severe complications after CAP are connected to pneumococcal pneumonia. In addition, the finding of a virus or an atypical bacterium in respiratory specimen does not rule out pneumococcal infection. Both guidelines recommend that macrolides should be prescribed, in addition to penicillin, amoxicillin or another beta-lactam, if *Mycoplasma* etiology of CAP is suspected. Despite this recommendation, current evidence is insufficient to...
support or refute the effectiveness of macrolides or other antibiotics in children with Mycoplasma CAP. Seventeen studies were included in a recent systematic review including five in a meta-analysis, and the pooled risk difference although favoring treatment was only 0.12 and statistically nonsignificant. According to the American guidelines, antibiotics are not routinely required to preschool-aged children with CAP, and amoxicillin is the first-line oral therapy for children with CAP suspected to be of bacterial origin. Macrolides should be prescribed for school-aged children with findings compatible with CAP caused by atypical bacteria. According to the British guidelines, all children with CAP except those less than two years of age presenting with mild symptoms, should be treated with antibiotics, and oral amoxicillin is the first choice. Macrolides should be added if either M. pneumoniae or C. pneumoniae is suspected, if the clinical presentation is very severe, or if there is no response to first-line antibiotics. The suspicion of Mycoplasma or Chlamydia etiology is usually based on the clinical picture of CAP. No doubt, M. pneumoniae and C. pneumoniae cause CAP in children, and although spontaneous resolution is more likely the rule rather than the exception, there also are severe cases which need treatment with antibiotics effective to atypical bacteria. However, there is no existing clinical or laboratory-based algorithm to discern the cause of pneumonia in children. This means that certain overtreatment with antibiotics, and with macrolides combined with beta-lactams in particular, is justified in pediatric CAP.

References

THE GLOBAL WORLD AND ITS IMPACT ON INFLUENZA IN CHILDREN
Gary WK Wong
Department of Paediatrics
Prince of Wales Hospital
Chinese University of Hong Kong
Shatin, NT
Hong Kong
Email: wingkinwong@cuhk.edu.hk

Influenza has always been a major cause of upper and lower respiratory tract infections in children and adults. Both antigenic drift and antigenic shift ensure constant evolution of the virus resulting in seasonal epidemic and major pandemic infection in humans. It has been estimated that the global burden of influenza may be in the scale of up to 1 billion cases a year with 3 to 5 million cases of severe diseases resulting in up to half a million deaths (1). In the last 100 years, there have been 4 pandemics and the most notable one during 1918-1919 claiming an estimated between 50 million to 100 million lives (2). In the pediatric population, the disease burden is highest among infants and young children (3). Influenza-associated bacterial pneumonia is common and is the major cause of morbidity and mortality during pandemics (4). As disease in children is the frequent source of infection spreading to adults and elderlylies in the same household, a comprehensive program of prevention and treatment is needed to reduce the total burden of influenza in both children and adults. The frequent reassortment between viruses and jumping of the species barrier has resulted in outbreaks of human cases of avian influenza in the past 2 decades (5). Careful monitoring of the outbreaks of avian influenza in wild birds and domestic poultry is needed to assess the possible spread of diseases from birds to humans. The first documented human outbreak of avian influenza happened in Hong Kong in 1997 (6). Since then, there have been human outbreaks of H7N7, H7N9, and H5N6 infections (7). Patients infected with H5 influenza have been reported to have a very high mortality rate while H7 infections tend to be milder. Almost all cases of human infections of these avian strains had close contact history with birds or poultry. However, limited transmission between humans with close contact cannot be ruled out. For seasonal influenza, the majority of children and adults infected with influenza recover without long term complications. However, elderly persons and young children are more likely to develop severe disease possibly resulting in mortality. The main state of prevention is the use of vaccination. There are many challenges in the production of the seasonal influenza virus vaccine. Every year, the World Health Organization, based on available date, makes recommendation for the type of strains to be included for vaccine production. The effectiveness of the vaccine will depend on the match between vaccine strains and circulating strains each season. The second challenge is to have an adequate vaccination rate in the high risk groups as well as the general population. US estimates suggested that almost 6 million cases of influenza and 42,000 hospitalizations might have been prevented if the vaccination rate could reach the target of 70% (8). In order to shorten the duration of vaccine production and to improve the efficacy of vaccination, new approaches in vaccine development such as the use of recombinant proteins, virus-like particles, and DNA-based vaccine are being explored (9). In case of possible mutation in avian strains resulting in efficient human to human transmission, rapid production of effective vaccine will be crucial to control the global spread of the infection.

References

NEWBORN SCREENING IN EUROPE: METHODS AND OUTCOMES

Milan Macek
Department of Biology and Medical Genetics, Charles University Prague and 2nd School of Medicine, Prague, Czech Republic (milan.macek.jr@lfmotol.cuni.cz)

Early diagnosis of cystic fibrosis (CF; MIM 219700), i.e. during first several months of life, is considered as a favourable prognostic factor, which decreases the treatment burden and mitigates parental anxiety [1,2]. CF newborn screening (CFNBS) generally leads to an earlier and equitable disease diagnosis [1,2]. The strongest evidence of the positive impact of CFNBS was demonstrated by an Australian study that demonstrated marked improvement in survival at 25 years of age within a patient cohort diagnosed by CFNBS compared to symptomatically diagnosed cases where their diagnosis was established just prior to the commencement of the CFNBS scheme [3].

The scarcity and ongoing nature of existing long-term clinical and epidemiological studies following CFNBS, insufficient government support and/or health care resources hinder broader implementation of CFNBS in Europe, and beyond. CFNBS programmes are generally implemented within the frame of multi-disorder national or regional screening programmes which are traditionally assessed according to the “Wilson-Junger criteria”. Recently, these criteria were expanded by inclusion of a “ranking approach” that assesses the broader impact of a screening programme on patients, their caregivers, health care systems and structuring of health care pathways following a positive screening outcome [4]. Both the original and updated criteria clearly support establishment of nationwide CFNBS programmes, including documented delays in clinical diagnosis of CF in some Central-Eastern European countries [5]. Nonetheless, as in any other screening programmes, false positivity, which in the case of CFNBS is mainly related to the detection of CFTR gene mutation carriers in infancy and generation of inconclusive diagnoses, represents an issue which needs to be transparently dealt with. In Europe, the specific historical, cultural and/or legal (e.g. the German Gendiagnostikgesetz) context plays an important role in terms of the “relative weight” which is assigned mainly to the detection of carriers in within CFNBS schemes which utilise genetic testing of population-specific panels of CFTR mutations. Here, carrier detection is somewhat viewed as positive (mainly in terms of preventive intra-generational and trans-generational impacts of this knowledge), while elsewhere it is linked to substantial concerns [1,2].

Generally, the choice of a protocol is a “balancing act”, whereby avoidance of negative outcomes (e.g. carrier detection, parental distress) and detection of inconclusive cases, is weighed against timeliness of diagnosis and CFNBS costs [1,2]. Thus when genetic testing is not utilised, there is a marked increase of false positive results with a negative psychological impact on the family and health care services reflected by the need to assure follow-up sweat testing [1,2]. On the other hand, DNA testing increasingly detects carriers, thereby requiring genetic counselling which strained genetic services have a difficulty to provide in a timely manner. It also “produces” infants with an inconclusive diagnosis where long-term clinical monitoring is necessary. In the United States, mainly due to legal and health care insurance-related reasons, infants with an unclear diagnosis following CFNBS are designated as having the “CFTR related metabolic syndrome” (CRMS) [1,2]. However, in Europe there is consensus in favour of avoiding definitive diagnosis thus the term “CF Screen Positive Inconclusive Diagnosis” (CF-SPID) is advocated [1,2]. Established CFNBS problems now currently increasingly deal with issues related to the communication between professionals and patients, mainly aimed at avoiding misconceptions and minimising parental distress. Therefore, in the Internet information era, there is a need to provide accurate and up to date CFNBS portals to counter often outdated or misleading online information [1,2]. Although all CFNBS schemes utilise two steps (or “tiers”) comprising: a) initial measurement of immunoreactive trypsinogen (IRT) on a dried blood spot sample (i.e. the “Guthrie card”) and b) sweat test for confirmation or exclusion of CF diagnosis, they differ with regards to the intermediate tiers aimed at improving the specificity of the IRT testing. Intermediate tiers are performed either a) on the original- or less frequently on the b) newly sampled blood spot which represents a logistics challenge. The latter “resampling option” is utilised at approximately 3 weeks of age when IRT levels non-specific for CF have markedly decreased. Since the initial IRT cut-off has a significant effect on NBS performance with regard to both sensitivity and specificity, optimisation of its cut-off levels is crucial (usually more than 99th percentile) and should be continually monitored. Decrease of IRT cut-offs does not influence screening sensitivity, but negatively affects specificity which cannot be efficiently mitigated by an intermediate tier. The IRT cut-off value is also closely related to the day of sampling, which is in most European countries set up to three days-, while in others even up to eight days after birth. Some CFNBS programmes utilise a floating cut off to account for analytical and/or seasonal variability. Analytical issues include retesting in atypical levels, assay calibration or eludication of blood spot contamination with stools. False negative cases should be investigated to clarify whether the issue is of biological or analytical origin. IRT could also be measured from the second blood spot for reasons specified above [1,2].

DNA testing is used to increase the specificity of IRT-positive cases as a second or third tier procedure. The majority of CFNBS programmes use population-specific, pathogenic (i.e. “CF-causing mutations”) [6], Presence of at least one CFTR mutation indicates sweat testing where levels over 60mM confirm the diagnosis of CF in a timely manner. It is very important that only clearly pathogenic mutations (www.cftr2.org) are screened for [6]. The majority of IRT/DNA protocols achieve good sensitivity and specificity. It should be noted that the second IRT is only variably successful in distinguishing cases with one CFTR mutation from homozygous patients. Nowadays when genetic testing technology increasingly allows for extended CFTR gene analysis (EGA), detection of individuals with CFSPID is on the rise. This unwanted consequence of IRT/DNA(EGA) schemes is mainly due the interpretation challenge related to the detection of variants of unknown significance in cases which usually also have borderline or even normal sweat chloride concentrations [1,2].

In order to limit the disadvantages of DNA testing in CFNBS, another biomarker, pancreatitis associated protein (PAP), could be measured in the

Pediatric Pulmonology
original blood spot [7]. There is increasing evidence that IRT/PAP schemes have unacceptable sensitivities [7] and generate less CFSPID cases. However, their positive aspects are offset by higher need for sweat testing to exclude/confirm diagnosis of CF in PAP-positive instances. As with IRT testing, alternative PAP schemes include additional tiers aimed at increasing their sensitivity (e.g. EGA), but limit their positive aspects [7].

Increasing ethnic heterogeneity in Europe is challenging not only for genetic testing in terms of need for optimisation of mutation panels but also in terms of assessing IRT values beyond the established testing range. Respective complex optimisation approaches are termed “safety net (or failsafe)” strategies [7]. Importantly safety nets should take into account changing demographics and technological advances in genetic testing thereby enabling screening centres to move beyond targeted mutation panels [6]. Importantly, more studies are needed to assess the performance of IRT-PAP protocols [8] compared to well established IRT-DNA schemes.

Implementation of the programme is also to a large degree dependent on the ability of first line paediatric services to reliably symptomatically diagnose CF during the first year of life. There are marked differences between various European countries in this regard [9]. CFNBS should optimally be introduced via a pilot programme which should assess not only analytical parameters, but also public perception of CFNBS which also could be evaluated by a “satisfaction index” [1,2]. Following the diagnosis of CF following CFNBS, families in their reproductive age consider prenatal-(PND) or preimplantation diagnosis (PGD) for their successive pregnancies. Interestingly, CF incidence had halved following the introduction of CFNBS in regions studied due to availability of PND/PGD programmes [9]. Another interesting development is related to the success of CFTR modulation therapies (CFMT) which use orphan medicinal products (e.g. ivacaftor, lumacaftor) that are generally disease retarding and may markedly improve the quality of life and overall survival in CF. CFMTs in combination with CFNBS-enabled diagnosis may alter public perception of CFNBS and may even lead to the decreased uptake of PGD [10]. Naturally, all of this is dependent not only on the physical, but also financial availability of CFMT.

## References


3. Dijk FN, McKay K, Barzi F, Gaskin KJ, Fitzgerald DA. Improved survival in cystic fibrosis patients diagnosed by newborn screening compared to a historical cohort from the same centre. Arch Dis Childhood 96(12):1118-112


**PSEUDOMONAS INFECTION IN CF: PREVENTION AND SUPPRESSION**

Matthias Griese
Hauner Childrens Hospital
University of Munich
Lindwurmstr. 4
80337 München
Tel. ++49 89 44005 7871
Fax. ++49 89 44005 7872
matthias.griese@med.uni-muenchen.de

The clinical course of the most frequent life-threatening autosomal recessive disorder in Caucasians, cystic fibrosis (CF), is strongly influenced by the presence of the respiratory pathogen *Pseudomonas aeruginosa* (*Pae*). *Pae* is cultured in specimens from as much as 21% of CF patients less than one year of age and, in the absence of a prevention policy, increasing to >80% at 26 years or older. A study by Burns et al., combining results of bronchoalveolar lavage and serologic results, showed even higher rates of colonization particular in children younger than three years of age, indicating that *P. aeruginosa* infection occurs very early and may be intermittent or undetectable by culture.

Thus several prevention strategies have been established. Primary prevention, i.e. to protect CF patients from acquisition of the bacterium, include education about likely sources and controlling potential hazards, preventive treatment during respiratory tract infections and in the future possibly immunization. Secondary prevention, i.e. interventions after diagnosis of an airway colonization, is done by early eradication therapy with various schemes. The goal is to eradicate the organism again from the airways and to allow reparation of any injury. It is possible to predict success or failure of eradication from measurement of serum anti-*Pae* antibodies. In case of failure of early eradication in as much as 40% of the cases, infection of the airways with *Pae* becomes chronic. Now tertiary prevention, i.e. helping CF patients to preventing further physical deterioration of the lung disease and maximizing quality of life, is necessary and it includes regular suppression therapy with antimicrobials active against this organism.

Early detection of *P. aeruginosa* therefore is a major goal in CF patient care to use the window of opportunity for possible eradication. The early treatment policy however is cumbersome for the patients, long-standing, and expensive. Here we will describe the components and details of our approaches to achieve these goals in clinical practice.

**PULMONARY ASPERGILLOSIS IN CHILDREN**

Malena Cohen-Cymberknoh, MD
Pediatric Pulmonar Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

A variety of pulmonary syndromes are developed in response to *Aspergillus*, a ubiquitous fungus in the environment, and it is mainly dependent on systemic and local host immunity, the presence of pre-existing parenchymal lung damage, and the load of spores inhaled. Immuno-compromised patients, particularly those with neutropenia, are susceptible to invasive pulmonary aspergillosis (IPA) in the absence of pre-existing lung pathology. In these patients, quantitative or qualitative deficiencies of phagocyte function can allow hyphal growth and invasion through the bronchiole walls, with subsequent invasion of blood vessels and systemic dissemination. The major risk factor for IPA is chemotherapy-induced neutropenia, with the risk being directly proportional to both the severity and the duration of the neutropenia 1. IPA can also occur in the non-neutropenic host, and in those with mild degrees of immunosuppression including lung transplant recipients, the critically ill patients and patients on steroids. Serum galactomannan assay has been used in patients at risk, for the diagnosis of IPA 2,3.
**Chronic pulmonary aspergillosis** affects patients without obvious immune compromise, but with an underlying lung condition. In patients with cavitory pulmonary lesions, saprophytic colonization by Aspergillus leads to *aspergillum*: a tangled growth of aspergillus hyphae admixed with mucous and cellular debris in a cavity, with a rich blood supply from the bronchial and other branches of the systemic circulation, and consequently, a propensity to bleed. Most cases of aspergilloma do not respond to antifungal agents, therefore, observation alone is recommended.

*Aspergillus bronchitis* is manifested by persistent respiratory symptoms in patients with chronic aspergillus detected in sputum without evidence of *allergic bronchopulmonary aspergillosis* (ABPA) or other parenchymal aspergillus disease, especially in patients with cystic fibrosis (CF). In atopic individuals with an allergic or hypersensitivity response, aspergillus may trigger immune phenomena including allergic rhinitis, asthma, hypersensitivity pneumonitis and ABPA.

*Aspergillus hypersensitivity pneumonitis* is an extrinsic allergic alveolitis, which occurs as a consequence of contaminated water sources, but also can be the main antigen in some cases of farmer’s lung and malt worker’s lung disease. The acute disease can present within hours of exposure to the antigens with dyspnea, cough, fever, chills and myalgia, or with progressive shortness of breath in the sub-acute and chronic phases. Repeated exposures to the insulting antigens lead to a chronic form of hypersensitivity pneumonitis that is associated with irreversible pulmonary fibrosis.

ABPA is a hypersensitivity reaction to aspergillus antigens, mostly *A. fumigatus*. Patients usually present with wheezing, expectation of brown mucus plugs, pleuritic chest pain, and fever, and the diagnosis is confirmed by radiologic and serologic testing. It is typically seen in patients with long-standing asthma, but also occurs in up to 15% of patients with CF. In CF, due to overlap of symptoms, the diagnosis of ABPA is sometimes delayed or even missed, and might result in irreversible pulmonary damage. Treatment of ABPA in CF consists of either oral steroids or IV pulses of methylprednisolone or omalizumab combined with oral antifungal therapy (itraconazole or voriconazole) for a long time period.

The latest advances in aspergillus pulmonary syndromes consist in a better understanding of the underlying pathophysiology in patients at risk, improvement in diagnosis and the availability of more effective and well- tolerated therapies. To improve outcomes and to avoid irreversible consequences, it is critical that physicians can recognize and early treat patients at risk.

**References**

2. Dinand V, Anjan M, Oberoi JK, Khanna S, Yadav SP, Watail C, Sachdeva A. Threshold of galactomannan antigenemia positivity for early diagnosis of invasive pulmonary aspergillosis is an extrinsic allergic alveolitis, which occurs as a consequence of contaminated water sources, but also can be the main antigen in some cases of farmer’s lung and malt worker’s lung disease. The acute disease can present within hours of exposure to the antigens with dyspnea, cough, fever, chills and myalgia, or with progressive shortness of breath in the sub-acute and chronic phases. Repeated exposures to the insulting antigens lead to a chronic form of hypersensitivity pneumonitis that is associated with irreversible pulmonary fibrosis.

**Abstract S33**

**LONG TERM MORBIDITIES OF CHILDHOOD OBSTRUCTIVE SLEEP APNEA**

Daniel K. Ng, MB BS, MD. M Med Sc, FRCPCH
Department of Paediatrics, Kwong Wah Hospital, Hong Kong, China, dkkng@ha.org.hk

**Introduction**

Removal of tonsils and adenoid is the treatment of choice for childhood OSA with significant improvement of AHI. However, only 50-60% of T&A children had post-op AHI <1 and 66% of children had post-op AHI <5 within 12 months of T&A. More importantly, longer term follow-up, i.e. 3 years after T&A (mean age = 12 years), showed a further rise of AHI from the nadir. AHI >1 at 3 years after T&A is important as AHI >5 in children was shown to be associated with significant higher BP and decrease in grey matter volume over the prefrontal and temporal regions. Higher blood pressure, decreased baroreflex sensitivity, increased BP variability and grey matter density deficit constitute the long term morbidities that were attributed to the unresolved OSA which, given time, may well become adult OSA.

**Child-Adult OSA**

In fact, epidemiology studies support the origin of adult OSA being childhood OSA. Habitual snoring, the commonest symptom of OSA, served as a surrogate marker in a community survey. Habitual snoring had a male preponderance across all age groups: preschoolers (1.3:1), children (1.5:1), adults (2.3:1) and seniors (2.2:1) and the prevalence of habitual snoring was similar, with 16% in children and 23% in adults. Furthermore, prevalence of childhood OSA was estimated to be 2-5% and was similar to the prevalence of symptomatic adult OSA, i.e. AHI >5 plus daytime sleepiness, 3-7% of adult males and 2-5% of adult females. Longitudinal study was required to follow the evolution of childhood to adult OSA.

In a retrospective analysis of 19 adults who had childhood OSA treated with T&A in this department, 8 (42%) had unresolved OSA as adults. They had a much higher pre-op AHI than those who had resolved OSA during adulthood, 12 vs. 6. For those who had not undergone T&A (n=37), 43% had AHI >1. For this AHI >1 group, 31% remained OSA with AHI >5 after the age of 18. For the group with AHI <1, 19% developed adult OSA after 18 years of age. The initial AHI was higher in those who had adult OSA, 3.1 vs 0.7 (p=0.14).

**Conclusion**

A significant proportion of childhood OSA remained unresolved after T&A leading to persistent cardiovascular abnormalities and adult OSA. It is important to follow children with AHI >5 after T&A with a sleep PSG study so as to allow timely treatment of the residual OSA to prevent progression to adult OSA.

**References**

S34 Abstract


DIAGNOSIS OF OBSTRUCTIVE SLEEP DISORDERED BREATHING IN CHILDREN

Jean-Paul Praud
Correspondence: Jean-Paul Praud MD PhD, Pediatric Respiratory Medicine Division, Department of Pediatrics, Université de Sherbrooke, J1H 5N4, QC Canada. Tel: +1 (819) 346 1110, ext. 14851; fax: +1 (819) 564 5215; E-mail: Jean-Paul.Praud@USherbrooke.ca

Introduction
Obstructive sleep disordered breathing (OSDB) is characterized by respiratory disturbances due to sleep-related upper airway obstruction; its cardinal sign is habitual snoring during sleep. OSDB encompasses a continuum extending from primary snoring (defined by the absence of apnea/hypopneas, blood gas abnormalities or arousals) to obstructive sleep apnea (OSA, defined by the presence of repeated apneas/hypopneas, arousals and desaturations). According to the 2012 American Academy of Pediatrics recommendations, children with habitual snoring should undergo an in-hospital overnight polysomnography (PSG), the gold standard test to diagnose and score the severity of OSA. With a prevalence of habitual snoring as high as 10-15%, our health care systems however do not have sufficient resources to perform PSG in all these children. The consequent observation that many children undergo adenotonsillectomy (AT) without any laboratory testing is alarming, given that recognition of severe OSA allows prioritization for AT and prediction of perioperative complications, among others.

In this context, several national guidelines have recommended an alternative approach to assess OSDB in children. The quest for the most appropriate alternate means to predict and score the severity of OSA has been underway for many years. The present short contribution will focus on a few of these which have recently attracted attention, including patient history and physical examination, in-home overnight oximetry and respiratory polygraphy. In addition, recent progress on the measurement of biomarkers will be presented.

Patient history and physical examination
Though patient history and physical evaluation alone are often said to be too imprecise to predict OSA, national otorhinolaryngology societies recommend including them in their diagnostic algorithm for children with habitual snoring. As an illustrative example, the 2011 Guidelines from the American Otolaryngology-Head and Neck Surgery state that PSG is not always necessary for “otherwise healthy children > 3 years with a history consistent with nighttime snoring; restlessness; daytime symptoms, including somnolence, behavioral changes, and poor cognitive performance; and a physical exam consistent with adenotonsillar hypertrophy” (1). Similarly, recommendations by the German Society of Otorhinolaryngology, Head and Neck Surgery published in 2014 propose a diagnostic algorithm where patient history and clinical evaluation, in an otherwise healthy child, is used to decide on anti-inflammatory treatment or AT; in this algorithm, PSG is used only in atypical cases, young children < 2 years or children with comorbidities (2).

Recent studies attempted to increase the accuracy of clinical evaluation to predict OSA in children. In a 12-year retrospective study conducted in 800 snoring children > 5 years, tonsillar hypertrophy and parental history of AT was shown to confer a high specificity and likelihood for predicting moderate severity OSA (3); further assessment of 525 children from the same population concluded that nocturnal enuresis was associated with moderate to severe OSA (4).

Oximetry
Overnight oximetry (SpO2), which is more readily available than in-hospital overnight PSG and can be performed at home, is receiving continuous high interest. Its ability to diagnose the presence and severity of OSA, as well as to predict early post-AT complications, continues to be assessed. Among the limitations of overnight SpO2, the fact that upper airway obstruction is not always associated with oxygen desaturation implies that SpO2 cannot detect all hypopneas/apneas. In addition, different pulse oximeters have different sensitivities for detecting oxygen desaturation, in relation to their SpO2 sampling frequency and averaging time. Careful validation of study results in other settings is thus especially important.

Tsai et al. performed a retrospective study on 148 Taiwanese children aged 3 to 12 years (30% obese). They reported that the oxygen desaturation index (≥4% decrease in SpO2 per hour of sleep) was highly correlated with the AHI (r = 0.89). Overall, an oxygen desaturation index cut-off of 2.05 had a positive predictive value of 98% for OSAS. Moreover, they were able to predict mild, moderate and severe OSA with a relatively high sensitivity (77.7 to 89.1%) and specificity (86 to 88.9%), suggesting that oxygen desaturation index is a good predictor of OSA severity (5). Validation in other settings is needed.

The McGill Oximetry Score has been used since 10 years to predict OSA severity. In a retrospective study of 362 children 2 to 17 years old, the use of the McGill score effectively allowed prioritization of the most severe patients for AT and prediction of the occurrence of perioperative adverse events. Only 10% of the 362 children referred for OSA evaluation underwent PSG, resulting in estimated cost-savings of about 800 K$ (6).

In an attempt to increase the prediction accuracy of SpO2 for OSA, Alvarez et al. assessed the value of automated signal processing combining several conventional oximetry indexes (average saturation, minimum saturation, oxygen desaturation index of 3% and cumulative % of time spent below 85%, 90% and 95%) with statistical measures (central tendency, dispersion, symmetry and peakedness of SpO2 distribution) and nonlinear measures (irregularity, variability and complexity of the SpO2 recording). They concluded that such processing improves the performance of at-home SpO2 to detect OSA in children, hence decreasing the number of inconclusive SpO2 (7).

Reasoning that upper airway obstruction can be associated with arousal without oxygen desaturation, Sahadan et al. assessed the added value of pulse rate surge calculation (an index of arousal) to predict OSA. They showed that 12% of children with a normal SpO2, including young children < 5 years, could be predicted to have OSA (specificity of 97%). However, due to its very low sensitivity, pulse rate indices cannot be used to refute OSA (8).

Polygraphy
While the American Academy of Pediatrics recommends PSG as the gold standard test to diagnose OSA in children, many sleep laboratories, especially in Europe, use respiratory polygraphy for that purpose. Tan et al. showed that respiratory polygraphy systematically underestimated the apnea-hypopnea index compared to PSG. The consequent impact on treatment decisions was especially marked for children with mild to moderate OSA. They concluded that respiratory polygraphy is not identical to PSG, a difference which needs to be incorporated in the therapeutic algorithm of OSDB children when using respiratory polygraphy (9).

Biomarkers
Combining several urinary proteins has yielded a highly specific and sensitive proteomic signature to diagnose and predict OSA severity in...
children. These promising results have nevertheless been weakened by the
great variability of the urinary proteome when attempts were made to
reproduce the results in a larger population. Becker et al. showed that this
variability was dramatically reduced when diurnal variation and gender
were incorporated into the process. These results again appear promising for
the use of biomarkers alone to recognize OSDB children in need of
treatment, maybe including children with PS only (10).

References
1. Randel A. AAO-HNS Guidelines for Tonsillectomy in Children and
2. Urcsht MS, Poets CF, Stuck BA, Wiater A; Mitglieder der
Steuerungsgruppe der AG Padiatrie der Deutschen Gesellschaft für
adenotonsillectomy is associated with obstructive sleep apnea severity in
Kaditis AG. Nocturnal enuresis is associated with moderate-to-severe
obstructive sleep apnea in children with snoring. Pediatr Res 2014;76:555-
559.
5. Tsai CM(1), Kang CH, Su MC, Lin HC, Huang EY, Chen CC, Hung JC,
Niu CK, Liao DL, Yu HR. Usefulness of desaturation index for the
Otorhinolaryngol 2013;77:1286-1290.
obstructive sleep apnea when health care resources are rationed. JAMA
7. Álvarez D, Gutierrez-Tobal GC, Alonso ML, Teran J, del Campo F,
Hormero R. Statistical and nonlinear analysis of oximetry from respiratory
polygraphy to assist in the diagnosis of Sleep Apnea in children. Conf Proc
8. Sahadan DZ, Davey MJ, Horne RS, Nixon GM. Improving detection of
obstructive sleep apnoea by overnight oximetry in children using pulse rate
9. Tan HL, Gozal D, Ramirez HM, Bandla HP, Kheirandish-
Gozal L. Overnight polysomnography versus respiratory polygraphy in the
Contextualised urinary biomarker analysis facilitates diagnosis of paediatric

MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA (OSA) IN
CHILDREN
Pr Brigitte Fauroux, MD, PhD
Pediatrie non-invasive ventilation and sleep unit
Necker university hospital, Paris, France, brigitte.fauroux@aphp.fr
Obstructive sleep apnea (OSA) is relatively common in childhood, affecting
approximately 1 to 2% of children between the ages of 3 to 6 years 1. OSA
remains an underdiagnosed condition because sleep is not systematically
evaluated in routine care and because of the discrepancy and poor correlation
between symptoms, clinical examination and the objective assessment of
sleep by means of a polysomnography. However, OSA needs to be treated in
order to prevent or correct the end-organ morbidity associated with this
condition; i.e. the neuropsychological and cognitive impairment and to a
lesser extent, the cardiovascular and metabolic effects 1. OSA management is
based on a combination of factors including the patient’s age, symptoms, the
cause or associated or underlying condition, the risk factors (such as obesity),
and the results of a sleep study when performed or available.
Adenotonsillar hypertrophy is the first cause of classical OSA with
adenotonsillectomy being the first line treatment leading to the cure of OSA in
most cases 2. Indeed, as compared with a strategy of watchful waiting,
surgical treatment of OSA in school-age children does not significantly
improve attention or executive function as measured by neuropsychological
testing but does reduce symptoms and improve secondary outcomes of behavior, quality of life and polysomnographic findings, thus providing evidence of beneficial effects of early adenotonsillectomy 3. However, adenotonsillectomy does not cure OSA in approximately 20% of patients, with overweight or obesity, asthma and allergy being associated with a greater risk of residual OSA after surgery 4. In this case, an anti-inflammatory with topical steroids or the combination of topical steroids with montelukast has shown to be effective in improving residual OSA 5. Rapid maxillary expansion or oral jaw positioning appliance may be effective in a selected group of children with maxillary constriction and dental malocclusion 6. Noninvasive continuous positive airway pressure (CPAP), by maintaining airway patency throughout the whole breathing cycle, is a very effective treatment of the most severe forms of OSA 6. Indeed, OSA is very common in some rare disorders but which the number is very important including cranio-facial or upper airway malformations such as Pierre Robin sequence, Franceschetti syndrome, craniocriatostenoses, achondroplasia, Down syndrome, Prader-Willi syndrome, and mucopolysaccharidoses. As opposed to “common” OSA, anatomical and functional abnormalities of the upper airways represent the main determinant of the upper airway obstruction, clinical symptoms are often subtle or absent, the OSA is usually more severe than “common” OSA and can be observed at any age, which justifies a systematic sleep study. Adenotonsillectomy is rarely able to cure the OSA. The management of the OSA in these patients requires a multidisciplinary approach including, according to the underlying disease, a pediatric ENT surgeon, a pediatric maxillo-facial surgeon, an orthodontist, a pediatric neurorsurgeon, a pediatric sleep specialist and an expert in pediatric CPAP because of the frequent need of nocturnal ventilatory support 7.

In conclusion, variable efficacious treatments are available for OSA in children but validated indications for these different treatments are lacking and depend mostly on the patient but also on local experience and habits. Randomized controlled trials evaluating these different managements in homogenous groups of children, with careful neuropsychological, cognitive, quality of sleep and life evaluation are thus warranted.

References
1. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of
my outcomes in treatment of OSA in children: A multicenter retrospective
2013;368:2366-76.
4. Kheirandish-L, Goldbart AD, Gozal D. Intranasal steroids and oral
leukotriene modifier therapy in residual sleep-disordered breathing after
respiratory events during sleep in children treated with home continuous
positive airway pressure: description and clinical consequences. Sleep Med

FOLLOW-UP AFTER PRETERM BIRTH/BPD
Andrew Bush MB BS (Hons) MA MD FRCP FRCPCH FERS
Professor of Paediatrics and Head of Section (Paediatrics), Imperial
College
Professor of Paediatric Respiratory, National Heart and Lung Institute
Consultant Paediatric Chest Physician, Royal Brompton Harefield NHS
Foundation Trust.
Correspondence: Department of Paediatric Respiratory Medicine, Royal
Brompton Hospital, Sydney Street, London SW3 6NP, UK.
AB was supported by the NHRI Respiratory Disease Biomedical Research
Unit at the Royal Brompton and Harefield NHS Foundation Trust and
Pediatrie Pulmonology

Abstract  S35
Introduction. This presentation will focus purely on the respiratory aspects of preterm birth, but the important neurological, retinal, renal and other comorbidities must not be forgotten. Airway disease can be split into components (Table), and the contributions of each may differ between generations of BPD survivors. This is really important when reviewing studies talking about ‘asthma risk’; essential to know what it is the authors meant by asthma. In terms of change in clinical practice, today’s adult survivors were largely ventilated at slow rates with high airway pressures, whereas survivors coming through will be more likely to have had antenatal corticosteroids, more likely to have been given surfactant, and more likely to be ventilated at fast rates with lower mean airway pressures. The nature of the disease may change further with the recent changes in neonatal resuscitation and even more conservative ventilation strategies. Furthermore, the possibilities of coincident disease, and complications of whatever caused prematurity in the first place, must not be forgotten.

The scope of the problem. Although successive generations of survivors of prematurity have better spirometry than previous, despite modern neonatal intensive care, spirometry is not normal. Furthermore, the even greater population of late preterm babies have impaired spirometry into the teenage years, and are more likely to be given a diagnosis of ‘asthma’, even if born as late as 37-38 weeks gestation. So the problem of survivors of preterm delivery will not go away.

What is the nature of lung disease? Large airway disease should not be forgotten, especially since it may be surgically correctable. Especially in ‘new’ BPD, alveolar simplification leads to a reduced area for gas exchange and loss of alveolar tethering points and hence airway obstruction. ‘Old’ BPD in particular is characterised by increased airway smooth muscle. However, there is no evidence of cosinophilic or other airway inflammation, and hence no justification for the prescription of inhaled corticosteroids, unless there is coincident true atopic asthma. The same caveat must be applied to the diagnosis of ‘asthma’ in the late preterm survivor, and emphasises the lack of utility of the umbrella diagnosis of ‘asthma’. HRCT scans show focal abnormalities and evidence of lung destruction. Pulmonary hypertension may be a feature, related to alveolar hypoxia, alveolar hypoplasia, and also acquired pulmonary vein stenosis. Other comorbidities which may impact on lung disease include gastro-oesophageal reflux (for which many are treated, but the evidence for benefit is scant); abnormal swallow and aspiration secondary to neurological abnormalities; and abnormal chest wall mechanics. The functional correlate of these physiological abnormalities is increased respiratory morbidity, including cough, wheezy, respiratory infection and hospitalisation, even in adult life. However, most survivors function well from a respiratory point of view.

Management. Currently there are no specific therapies to offer. All we can offer is standard best respiratory care: immunisation including influenza; avoidance of pollution, especially tobacco and e-cigarettes; exercise and airway clearance if there is mucus hyper-secretion; and aggressive treatment of any respiratory infection. Bronchodilators should only be given to those with documented acutely reversible airflow obstruction.

Long term consequences. The effects of these minor decrements in lung function in the long term have not been well studied. There is concerning evidence that spirometry may deteriorate in the first year of life. In the longer term, there is some evidence of catch up growth in terms of airflow obstruction and neo-alveolarisation. However, whether there will be an accelerated rate of decline in lung function, and premature airflow obstruction, remains to be seen. In general, young adults have relatively subtle abnormalities of lung function and exercise performance, but increased respiratory morbidity. The chief importance of these abnormalities is their effects when the lung ages, which has yet to be determined.

Will preterm survivors contribute to the burden of ‘COPD’? It is likely that they will develop premature airflow obstruction, and this will likely be classified as COPD, but is it the same disease as is seen in lifelong heavy smokers? Again, this shows the lack of utility of umbrella terms for airway disease.

Further reading

Table: Components of airway disease

<table>
<thead>
<tr>
<th>Component</th>
<th>Pathophysiology</th>
<th>Relevance to BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed airflow obstruction</strong></td>
<td>• Intraluminal – iatrogenic granuloma, vocal cord palsy, acquired subglottic cysts</td>
<td>• Potentially new and old</td>
</tr>
<tr>
<td></td>
<td>• Luminal – failure of normal development</td>
<td>• ?Both</td>
</tr>
<tr>
<td></td>
<td>• Extraluminal – loss of alveolar tethering</td>
<td>• Both, especially new BPD</td>
</tr>
<tr>
<td><strong>Variable airflow obstruction</strong></td>
<td>• Intraluminal – mucus</td>
<td>• Possible, especially old BPD</td>
</tr>
<tr>
<td></td>
<td>• Luminal – bronchospasm, airway oedema</td>
<td>• Bronchospasm especially old BPD</td>
</tr>
<tr>
<td></td>
<td>• Extraluminal – loss of alveolar tethering</td>
<td>• Both, especially new BPD</td>
</tr>
<tr>
<td><strong>Airway inflammation</strong></td>
<td>• Neutrophilic</td>
<td>• No evidence in either new or old BPD</td>
</tr>
<tr>
<td></td>
<td>• Eosinophilic</td>
<td>•</td>
</tr>
<tr>
<td></td>
<td>• Both</td>
<td>•</td>
</tr>
<tr>
<td></td>
<td>• None</td>
<td>•</td>
</tr>
<tr>
<td><strong>Airway infection</strong></td>
<td>• Bacterial</td>
<td>• Acute infection only as far as is known</td>
</tr>
<tr>
<td></td>
<td>• Viral</td>
<td>•</td>
</tr>
</tbody>
</table>

LONG-TERM CARDIOPULMONARY CONSEQUENCES OF CHILDHOOD MALIGNANCIES AND THEIR TREATMENT

Dennis C. Stokes MD, MPH, Daniel M. Green MD, Melissa M. Hudson MD, Saumini Srinivasan MD, MS, Hiroto Inaba MD, PhD, Kirsten Ness PT, PhD, Leslie L. Robison PhD, Gregory T. Armstrong MD, MSCE

Division of Pulmonary and Sleep Medicine, Department of Pediatrics, University of Tennessee Health Science Center, and Departments of Oncology, Epidemiology and Cancer Control, and Pediatric Medicine, St. Jude Children’s Research Hospital, Memphis, Tennessee
Introduction  Progress in the treatment of childhood cancers over the past 30 years has led to a remarkable growth in the numbers of survivors of childhood cancer such that 1 in every 570 20-34 year-olds is a survivor of childhood cancer. (1) With increased survival, there has also been a recognition that childhood cancer and the therapies necessary to achieve these excellent cure rates result in various severe, disabling, or life-threatening complications. (2) Although some childhood malignancies originate in or metastasize to respiratory system structures, most cardiopulmonary impairments after childhood malignancy are the result of cancer therapies, including chemotherapy and radiation. (3-6) The St. Jude Lifetime Cohort (SJLIFE) study is a longitudinal study designed to characterize health outcomes among childhood cancer survivors as they age. This review discusses findings from SJLIFE and other pediatric cancer follow-up studies, and describes the effects of childhood cancer and its treatment on cardiopulmonary function, including exercise.

Effects of primary malignancy.  Primary malignancy can involve the respiratory system in a variety of ways including direct invasion of the lung and chest wall, pulmonary metastases from solid tumors, and secondary obstruction of airways from primary lesions and metastatic lymphadenopathy.

Effects of opportunistic pulmonary infections.  During cancer therapy, patients are prone to a variety of secondary infections from both common and opportunistic pulmonary infections. (Pneumocystis jiroveci, fungal infections, CMV). Many severe infections lead to a mixed picture of acute lung injury (ARDS) and infection. Limited numbers of follow-up studies have been done in cancer patients who have had opportunistic infections such as varicella and Pneumocystis, but effects of lung infections during therapy are often captured in other long term studies of lung function after cancer therapy.

Effects of cancer surgery.  Cancer surgery of primary malignancies which involve the lung and/or chest wall may result in significant lung dysfunction and loss of lung capacity. Studies of patients who have undergone removal of osteosarcoma metastases show largely mild reductions in total lung capacity, with greater reductions among patients with more metastectomy surgeries as would be expected. (7) Secondary chest wall deformity such as scoliosis (increased after spine irradiation) can also adversely affect lung mechanics.

Acute lung injury from chemotherapy and radiation during cancer therapy.  Many chemotherapeutic agents used during cancer therapy can induce acute lung injury, including bleomycin, Carmustine (BCNU), Lomustine, (CCNU), busulfan, and cyclophosphamide. Newer biologic agents have also been associated with acute pulmonary injury, pulmonary hemorrhage, and acute pulmonary injury. These agents may be synergistic with other lung injury agents including infections, high oxygen concentrations, and radiation. Radiation to the lungs and chest wall can cause an acute pneumonitis.

Late effects of radiation on lung function.  Radiation to the lungs and chest wall has profound effects on long term lung function and numerous studies have documented adverse effects of lung and mediastinal radiation on long term lung function. Craniospinal radiation includes significantly less lung at risk for radiation damage but a recent multicenter study has shown deficits in lung function in a small number of patients after craniospinal irradiation.

Late effects of chemotherapy on cardiopulmonary function

Lung function.  Follow-up studies of lung function in long term survivors of childhood cancer show that a significant number have abnormalities in lung function. (3-5) These abnormalities often are primarily in lung volumes and diffusing capacity for carbon monoxide, but some patients develop obstructive or mixed restrictive-obstructive patterns. In the St. Jude Lifetime Cohort, among survivors exposed to potentially pulmonary toxic therapies, 65% had abnormal pulmonary function. The highest prevalence of any lung function abnormality occurred among those treated with radiation (74%), followed by those treated with bleomycin (73%), and among those with a history of thoracotomy (53%). (3)

Cardiac function.  Cardiac function is adversely affected by several chemotherapeutic agents but the primary drugs associated with cardiac injury are the anthracyclines which have been associated with impaired left ventricular systolic and diastolic function. A large cross sectional study of adult cancer survivors also identified a surprising number (25%) with increased tricuspid regurgitant jet velocity on Doppler echocardiography in patients who had chest-directed radiotherapy, raising the possibility of pulmonary hypertension in this population through one or more potential mechanisms. (8)

Exercise.  Long term survivors of cancer therapy evaluated with formal exercise studies and human performance measures show a remarkable reduction in exercise capacity and muscle weakness. The various risk factors for this significant exercise disability, which include heart, lung, and skeletal muscle effects of therapy, are only now starting to be understood. (9)

Effects of human stem cell (HSCT) transplantation.  The acute and late complications of bone marrow transplantation are the subject of a separate discussion on transplantation. HSCT is associated with well described acute pulmonary complications including infection, hemorrhage, and idiopathic pneumonias. Long term follow-up studies of HSCT survivors show a significant number with abnormal lung function studies. Pre-transplant lung function may also help predict risk for morbidity and mortality with HSCT as well.

Areas for current and future research.  Many post therapy survivors have relatively mild impairments in lung volume and diffusing capacity but longer term longitudinal studies are required to determine whether these individuals show similar or accelerated age-related declines in lung function compared to the normal population. Recently identified genetic markers have been associated with worse outcomes in asthma, COPD, cystic fibrosis and other lung diseases. Whether these or other genetic factors may also contribute to worsened (or improved) pulmonary outcomes in cancer survivors will be an interesting area of investigation. Smoking rates in post cancer survivors are surprisingly high and the impact of this and other environmental factors will also emerge from longitudinal studies. (10) More studies are needed on the role of exercise and other forms of rehabilitation in improving the functional outcomes of cancer survivors with moderate and severe pulmonary impairment.

References


of these drugs in neonates and infants. There are also very limited PK and safety data available in neonates and infants for first-line TB drugs, with none available for long-term use in second-line TB drugs settings. [10] A mother with recently diagnosed or undiagnosed TB may pose an infectious risk not only to her own newborn but also to other newborns in the nursery. Heyns et al. reported on Kangaroo mother care (KMC) and the risk for transmission of TB. KMC has become the standard of care for low-risk preterm babies born in developing countries. He reported on an infant (sentinel case) who was admitted to the pediatric intensive care unit (PICU) with extensive pulmonary tuberculosis and tracked back the contact as the mother in KMC. [5] It has previously been shown that there is a 60-80% TB transmission risk for infants from a close smear-positive TB source case, and 30-40% from a smear-negative TB source case (6). HIV co-infection also contributes to a high infant mortality with a four-fold increase observed among infants born to TB/HIV-infected women in India (3). Schaaf et al. have shown a 24% mortality in those aged less than 3 months of age with culture confirmed TB in a South African study (4).

Conclusion

A high index of suspicion is imperative to recognize perinatal TB, where the mother is often the source case. Active screening of the mother for TB is essential. Symptoms and signs of perinatal TB is atypical and can go unrecognized with dire consequences for the young infant. Infants are very vulnerable for TB disease progression following infection, and if untreated, high associated mortality can occur.

References


BACK TO BASICS: RADIOLOGY OF THE PEDIATRIC CHEST

Robert H. Cleveland, MD
Professor of Radiology, Harvard Medical School, Department of Radiology Department of Medicine, Division of Respiratory Medicine, Boston Children’s Hospital, USA Robert.Cleveland@childrens.harvard.edu

This presentation will discuss the diminishing use of CT in pediatric imaging and the consequent increased reliance on chest radiography (CXR) in the practice of pediatric pulmonology.
At Boston Children’s Hospital, between 2006 and 2013, there was a 46% decrease in the overall use of CT. The cause of this decline is speculative but presumably relates to the heightened concern for reducing radiation exposure (ALARA concept) and an attempt to respond to societal concerns about the rising costs of medical care.

The volume of imaging that related to pulmonary issues was roughly 25% of the total imaging in both 2010 and 2014. However, in 2010 the percentage of chest imaging that was CT was 22%. By 2014, it had dropped to 5%. This was accompanied by an increase in percentage of CXR from 81% to 94% of pulmonary related imaging. Chest MRI (excluding cardiac) more than doubled in this time period as new software programs significantly shortened image acquisition times and increased spatial resolution. However MRI still accounted for only 0.5% of the total volume. Likewise in this time period, chest ultrasound (excluding cardiac) volume doubled from 0.4% to 0.8% of the chest imaging. This correlates with its usefulness in imaging for pleural disease and the growing awareness of its usefulness in imaging ILD and pulmonary edema.

With chest CT at such a low volume, CXR is now used more than 20 times as often as CT in our institution. Thus we have found it necessary to have a heightened appreciation of the nuances of CXR.

There are several steps or “rules” that, if followed, will enhance an observer’s ability to appreciate abnormalities on CXR. 1) When possible, look at the image BEFORE learning the history. This will decrease pre-test bias and increase the likelihood of seeing things unrelated to the issue in question. 2) Be confident in your ability to read a CXR and the CXR’s ability to reveal the abnormalities. Studies have shown that the level of radiologists’ confidence in reading mammograms is directly correlated with the accuracy of their interpretations. 3) Be detail oriented. Just because something “does not belong there”, do not ignore it. 4) If you have a concern, act on it. This may be a repeat CXR. It does not always need to be a CT or MRI.

A high percentage of CXR are obtained for nonspecific signs and symptoms. This often relates to some combination of cough, fever, wheeze. Do not be lulled into assuming it is just another case of bronchiolitis. Always be alert for the unexpected vascular ring, lucent foreign body, ILD, occult trauma, etc. Keep in mind that persistent, stable peribronchial thickening is the first radiographic manifestation of cystic fibrosis and not just reactive airways disease/asthma.

A series of CXR will be shown to emphasize the similarity of the CXR to accompanying high tech images, showing that the CT often looks just like the CXR. Situations where low tech imaging can be variably applied to making a correct diagnosis will be presented and rationales for preferred approaches will be discussed.

References


PULMONARY EDEMA IN INFANTS AND CHILDREN

Hugh O'Brodovich MD, FRCPC

For correspondence and reprint requests please contact: Hugh O’Brodovich MD

Pediatric Pulmonologist

Adalyn Jay Physician-in-Chief

Lucile Packard Children’s Hospital

Airline & Pete Harman Professor & Chair

Director, Stanford Child Health Research Institute

Department of Pediatrics

Stanford School of Medicine

300 Pasteur Drive, Room H310

Stanford, CA 94305-3208

Ph: (650) 723-5104 Fax: (650) 725-7419

email: hugh.obrodovich@stanford.edu

Keywords: Pulmonary edema; epithelial active Na⁺; transport; high altitude pulmonary edema; respiratory distress syndrome; ARDS

INTRODUCTION

To optimally treat the infant or child with acute pulmonary edema, it is important to understand the underlying mechanisms producing the edema and those responsible for the clearance of fluid from the alveolar space so that therapeutic interventions can be implemented at the bedside. If the lungs cannot clear the airspace fluid, there would be an unacceptably low oxygen level in the blood, pulmonary vascular resistance would remain elevated and there would continue to be an increased work of breathing. Indeed, studies in adults with CHF or ARDS have demonstrated improved survival when they had active absorption of airspace fluid.

ANATOMIC CONSIDERATIONS

Lung fluid exchange occurs across the lungs’ pulmonary arterioles, capillaries and venules into the interstitial space where it is then cleared by the lymphatics. When lymphatic pumping is exceeded, there is interstitial edema but because the majority of the alveolar basement membrane has a fused capillary endothelium and alveolar epithelium, gas exchange is largely preserved even when there is interstitial pulmonary edema. Only when the alveoli themselves are filled with fluid is there a significant impairment of gas exchange.

The alveolar epithelial membrane has much tighter intercellular junctions than the capillary endothelial membrane; the effective molecular radii are respectively 4 and 40 A. Thus small ions are osmotically active across the epithelial, but not endothelial, membrane. Only the very much larger proteins are osmotically active across the endothelium. Ion-determined osmotic pressure is important when discussing transepithelial fluid movement but it is only the protein derived osmotic pressure, or oncotic pressure, which acts across the endothelium.

The adult human lung can hold a few hundred ml in its interstitial compartment whereas the alveolar space can accommodate several liters of fluid. This anatomic difference, in part, explains why interstitial edema may resolve quickly whereas alveolar edema takes significantly longer periods of time. Juxta-capillary (J) receptors are distributed throughout the lung’s interstitium and are stimulated by the presence of edema. They induce an increase in respiratory rate and their continued activation is responsible, in large part, for the continued tachypnea seen in pulmonary edema even though hypoxemia has been corrected through the use of supplemental oxygen and positive airway pressure.

MECHANISMS LEADING TO PULMONARY EDEMA

All diseases that cause pulmonary edema do so by only one of two processes. The most frequent process is increased transvascular pressure gradient that causes augmented fluid movement out of the microvasculature. Two examples...
The clinical correlate being the acute lung injury (ALI) - “adult” respiratory distress syndrome (ARDS). Often diseases have both processes present simultaneously. The table lists some of the pulmonary diseases that are associated with pulmonary edema with the relative contribution of these two processes shown semi-quantitatively by the number of + signs. The underlying mechanisms are discussed in greater detail elsewhere 1.

<table>
<thead>
<tr>
<th>Pulmonary Edema</th>
<th>Transvascular INCREASED PRESSURE</th>
<th>INCREASED PERMEABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>+++++</td>
<td>++</td>
</tr>
<tr>
<td>Re-Expansion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal Respiratory Distress Syndrome</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>High Altitude</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>ALI / ARDS</td>
<td>+++++</td>
<td></td>
</tr>
</tbody>
</table>

**MECHANISMS FOR AIRSPACE FLUID CLEARANCE**

Alveolar fluid clearance (AFC) arises from the lung’s distal lung epithelia (DLE) actively transporting Na⁺ with Cl⁻ and water following. Humans have AFC rates of ~25%/h 2. To transport Na⁺ with Cl⁻ and water following, cells must have Na⁺ permeant ion channels on the apical membrane, Na⁺/K⁺ ATPase in the basolateral membrane and intercellular tight junctions. Under normal conditions, the activity of Na⁺ permeant ion channels on the apical membrane represents the rate limiting step in lung epithelial Na⁺ transport. Inadequate or abnormal active Na⁺ transport by the respiratory epithelium has been shown to play a pathogenic role in the initiation of two lung disorders characterized by airspace edema.

The newborn lung is filled with a protein-poor fluid that was secreted by the fetal epithelium. Although this fluid is not, strictly speaking, pulmonary edema, this airspace fluid must be cleared by the epithelia’s active transepithelial Na⁺ transport. As reviewed elsewhere 3, prematurely born infants frequently have immature epithelial Na⁺ transport and the resultant impairment of the clearance of this fetal lung liquid, combined with immaturity of the surfactant system, are the two factors that initiate the neonatal respiratory distress syndrome.

High altitude pulmonary edema is initiated by an excessive increase in pulmonary microvasculature pressure with an initial non-inflammatory leakage of fluid across the alveolar-capillary membrane that is followed by a secondary inflammatory reaction promoting an increase in permeability. Since human respiratory epithelial Na⁺ transport decreases in response to the decreased PO₂ at high altitude 4 and salmeterol, that both alters vascular tone and increases Na⁺ transport, diminishes the frequency of high altitude pulmonary edema 4, it is currently believed that normal or defective lung epithelial Na⁺ transport may be involved in the pathogenesis of high altitude pulmonary edema.

The ability to clear pulmonary edema correlates with patient survival and clinical parameters, such as length of ventilation and O₂ requirements, regardless if the patients have CHF- or ARDS-induced pulmonary edema 5, 6. Further details are available in a recent review 6.

**THERAPY FOR PULMONARY EDEMA**

Regardless of the cause of the pulmonary edema there are four key approaches to treat this common disorder.

**Correction of Hypoxemia**

The patient’s arterial oxygen saturation should be returned to normal levels as soon as possible. For mild and predominantly interstitial pulmonary edema, an increase in the FIO₂ will be very effective as it compensates for the low ventilation to perfusion (V/Q) ratios (0 < V/Q < 1) arising from airway dysfunction secondary to excess fluid within the bronchovascular sheaths and reflex vagal stimulation. When there is significant airspace pulmonary edema with much of the hypoxemia being secondary to shunt, by definition is V/Q = 0, then a physician must increase transpulmonary pressures and mean airway pressures to hold the lung at a higher volume and recruit lung units thereby decreasing the amount of shunt. This can be achieved through a variety of approaches, most commonly and effectively by increasing the positive end expiratory pressure. Increasing peak inspiratory pressure and prolonging the inspiratory time and duration of the inspiratory plateau will further increase mean airway pressures.

**Reduction of the rate of fluid filtration**

The rate of fluid filtration into the lung should be decreased and treating the disorder that is responsible for the pulmonary edema is the first priority. For example in CHF one would: i) improve cardiac contractility; ii) reduce preload; iii) relieve anxiety and its associated increased sympathetic nervous system activity (e.g. morphine) thereby reducing both preload and afterload for the heart; iv) decrease blood volume and left atrial pressure while increasing plasma colloidal osmotic pressures (e.g., administration of diuretics); v) decrease systemic or pulmonary vascular pressures or both using vasodilators and vi) reduce excessive salt and water intake. These therapeutic maneuvers will reduce the microvascular pressures in the lung regardless if the edema arises from hemodynamic or increased vascular permeability to water and solutes.

Diuretics, such as furosemide, can improve the patient’s status within a few minutes and prior to the diuresis. Indeed, diuretics are even beneficial in pulmonary edema in anuric patients. This effect arises from furosemide’s beneficial effect on vascular tone with a concomitant increase in the systemic venous capacitance. Diuresis helps manage body salt and water volumes but is directly responsible for only trivial amounts of fluid removal from the lung. Since the lung represents only 1 per cent of the total body weight, even a 3 liter diuresis would only remove 30 ml from the lungs, with the remaining fluid coming from the remainder of the body. This 30ml is trivial compared to the liters of fluid present in the airspaces of adult patients with florid alveolar edema.

In high permeability pulmonary edema, our goal is to return the permeability of the alveolar-capillary membrane back to normal levels. Regrettably, although many studies have been performed, there is no reliable proven way to directly modulate alveolar-capillary membrane permeability. Of course, therapy of the underlying cause, such as sepsis, is beneficial.

**Minimization of Treated Related Lung Damage**

For decades it has been known that the inhalation of excessively high concentrations of oxygen or the sub-optimal use of mechanical ventilation and over distension of the lung can promote damage to the lung’s epithelium and endothelium. Attention to treatment of the underlying condition combined with excellent supportive care using ‘lung-protective’ ventilatory strategies to minimize treatment-related lung damage have contributed to successful clinical outcomes 7.

**Augment the Rate of Clearance of Airspace Fluid**

Intact fluid clearance from the lung’s airspaces has been associated with survival, shorter periods of assisted ventilation and lower FIO₂ regardless if the patients have CHF- or ARDS-induced pulmonary edema 5, 8. Although it has been known for decades that exogenous catecholamines significantly augment airspace fluid clearance (e.g. 5) in animal models of pulmonary edema, recent randomized controlled trials have demonstrated that neither inhaled 9 nor intravenous 10 beta agonists improve the clinical outcomes of patients with pulmonary edema. It is unknown if the alveolar epithelium in these patients has become unresponsive to beta agonists, whether alternative approaches are required or that the currently used lung-protective strategies

Pediatric Pulmonology
are sufficiently protective to mask any benefit from an increase in alveolar fluid clearance.

References

PCD GENETICS: A COMPLEX PUZZLE

M. Boon
Department of Pediatrics, University Hospital Gasthuisberg Leuven, Belgium, mieke.boon@uzleuven.be

Primary ciliary dyskinesia (PCD) is a rare, congenital disorder, caused by abnormalities in the structure and/or function of the motile cilia. Patients with PCD present with chronic and recurrent upper and lower respiratory tract infections, sinus inversus in almost half of the cases and an increased incidence of male infertility [1].

The diagnosis of PCD is very challenging: evaluation of ciliary motility by light microscopy is the gold standard for diagnosis, but requires expert skills [2]. Evaluation by electron microscopy (TEM) can identify absent or diminished outer dynein arms (ODA) and/or inner dynein arms (IDA). Abnormalities of the central pair of microtubules (absence or displacement) are most often only present in a subset of the cilia. Screening tests to detect PCD are nasal nitric oxide measurement and nuclear imaging of mucociliary clearance.

Genetic studies of PCD patients were initiated in 1994 and showed abnormalities in 40% of PCD patients. In 2000, mutations in more than 30 genes have been detected to cause PCD. Until now, mutations in more than 30 genes have been detected to cause PCD and with this information around 60% of the cases can be solved genetically.

Several approaches can be used to search for new genes in PCD or other genetically heterozygous disorders [3]: genetic screening of experimental models with an abnormal phenotype (e.g. Chlamydomonas, Xenopus...) is a solid approach because cilia are well-conserved organisms and was able to identify the first PCD-causing gene, DNAI1. Homozygosity mapping in large families with PCD could identify several other genes. Analysis of transcriptomes or cilia proteomes from healthy control and patient samples is a more recently introduced technique that provides extensive information on the structure and function of cilia. Of course, the advent of massive parallel sequencing has allowed rapid detection of new genes that are involved in ciliary structure and function.

There is a clear correlation between the ultrastructural abnormalities and the mutated genes. Mutations in genes encoding several ODA components are identified as PCD-causing if affected by detrimental mutations: DNAH5, DNAI1, DNAI2, DNAI1, TXNDC3. Mutations in these genes cause partial or complete absence of the ODA on electron microscopy. Most of the cilia are completely immotile.

DNAH11 is also a component of the ODA. Mutations in DNAH11 have been described, but without TEM abnormalities. The cilia typically have a hyperkinetic, stiff beat pattern. In our cohort, more than 30% of the patients have PCD with normal ultrastructure. Using a whole exome sequencing approach, we were able to detect biallelic mutations in DNAH11 in 17/25 screened families of patients with PCD and normal ultrastructure[4]. In this way, the diagnosis of PCD with normal ultrastructure could be confirmed.

Mutations in the radial spoke head genes RSPH1, RSPH4A and RSPH9 cause absence or displacement of the central pair in a subset of the cilia. These have conserved motility, but the beating is not effective. Patients with mutations in these genes do not have situs abnormalities, as the nodal cilia (important for lateralization during embryogenesis) lack a central pair.

Mutations in another component of the central pair, HYDIN, also cause PCD without situs inversus. However, ultrastructural evaluation of the cilia is normal in patients with HYDIN mutations, as it is too small to see on TEM. Recently, mutations in several genes that are responsible for the cytoplasmic or axonomal assembly of ciliary proteins have been described: DNAF1 (LLRC50), DNAFA2 (KTU), DNAFA3, DNAFA4 (DIXC1), CDCDC103, HEATR2, LRRC6, ZMYND10, SPAG1 and C21orf59. These genes encode cytoplasmic proteins that are responsible for binding or assembly of the ODA and/or IDA components before intraflagellar transport to the axoneme. Consequently, the motor proteins are absent in the ciliary shaft but mislocalized in the cytoplasm.

CCDC151, CCDC114 and ARMC4 are components of the ODA-docking complex. Patients with mutations in these genes have ODA deficiency, CCDC164 and CCDC65 are components of the dynein regulating complex (DRC) and cause absence of the nexin links if mutated. These defects cause very subtle abnormalities in structure and function of the cilia, and can easily be missed.

CCDC39 and CCDC40 are also assembly factors, but are responsible for the attachment of IDA to the dynein regulating complex. Mutations in these genes cause an absence of IDA and disorganization of the microtubules. Patients with sensory ciliopathies like retinitis pigmentosa (caused by biallelic mutations in RPRG) or orofaciogigodigital syndrome (caused by biallelic mutations in OFD1) rarely have motile cilia dysfunction with symptoms of PCD.

Very recently, 2 genes were described, involved in a PCD-related disorder of mucociliary clearance characterized by a reduced generation of multiple motile cilia (RGMC), previously reported as ciliary aplasia. The respiratory epithelium of these patients has only one or two (instead of >200) motile cilia per cell. Using cell culture techniques, the innate nature of this disorder has been shown. In collaboration with several other centers, we identified mutations in CCNO and MCIIDAS in patients with a RGMC disorder[5, 6]. Both proteins are responsible for inducing ciliogenesis: CCNO is a cytoplasmic protein that induces centriole amplification and docking to the cell membrane. MCIIDAS is a nuclear protein that acts upstream of CCNO and also induces FOXJ-1 induced expression of motile proteins. Therefore.

Pediatric Pulmonology
Abstract

the cilia in MCIDAS mutated individuals are non-motile, while they have preserved motility in CCNO mutated individuals.

Although there is a strict correlation between gene mutation and TEM abnormality, there seem to be only minor genotypic-phenotypic correlations: milder phenotype in patients with RSPH1 mutations (often with normal nasal NO), a more severe phenotype in those with CCNO and CCDC39/40 mutations and probably absence of male infertility in CCDC114 mutants.

At this moment, around 60%-65% of PCD cases can be solved genetically, with DNAH5, DNAI1 and DANNI1 being mutated most frequently[7]. It is expected that the rapid evolution of ciliary genetics will continue and that several new genes will be identified in the near future.

References

INTERSTITIAL LUNG DISEASES

Matthias Griese
Hauner Childrens Hospital
University of Munich
Lindwarsstr. 4
80337 München
Tel ++49 89 44005 7871
Fax ++49 89 44005 7872
matthias.griese@med.uni-muenchen.de

Childhood interstitial lung diseases (ILD) represent a large spectrum of individually rare diffuse parenchymal lung diseases (DPLD), prevalent in children of all ages. Due to recent emphasis on orphan diseases, much progress has been made on the etiology, pathomechanisms, diagnosis, treatment and overall management of such diseases. Since many children are treated by pediatricians, general practitioners, general and specialized children’s hospitals, it is important to differentiate conditions from the many other children with frequent upper and lower respiratory tract symptoms, driven by recurrent infections or allergies, as ILD may be readily overlooked or patients lost among the other patients. Of great importance, novel classification systems have been suggested which hold more novel entities. In the group of developmental disorders (A1), larger patient series have been detailed, including filamin A deficiency and FOXP1 deficiency. Progress has been made in the group of children with chronic tachypnoe of infancy (A3), allowing differentiation in usual and aberrant cases. Larger series of children with surfactant dysfunction disorders (A4) have shown genotype-phenotype correlations for ABCA3, but not for SFPTC mutations. New identities have been described for alveolar proteinosis including genetic diseases and together with elegant novel therapeutic options like macrophage transplantation in model systems. Among the novel genetic diseases which have an ILD as central part of their clinical spectrum are STING and integrin a3 mutations. Tools for the collection of prospective data on all these rare entities are available and will be demonstrated during and after the presentation.

Non-CF Bronchietasis
Eitan Kerem, Department of Pediatrics and CF Center, Hadassah University Hospital, Jerusalem, Israel

Bronchiectasis is a permanent and, usually, progressive bronchial dilation resulting from the infection and chronic inflammation of the airway, leading to destruction and remodeling of the bronchial wall. Bronchiectasis without cystic fibrosis (non-CF bronchiectasis) is believed to be the end result in genetically predisposed children of chronic or repeated episodes of environmental insults which lead to bronchial injury and dilatation. Bronchiectasis is associated with chronic and frequently purulent expectoration, multiple exacerbations and progressive, potentially disabling dyspnea. These events gradually worsen the health-related quality of life and lung function of affected patients.

The original definition of bronchiectasis is pathological showing normal airway histology destruction with inflammation; however, since bronchiectasis is a structural phenomenon, the best non invasive method to diagnose it is by chest CT that demonstrates dilated airways with thickened wall. However, there is a complex relationship between the severity of radiological disease and that of the clinical syndrome. Furthermore, it is difficult to assess the severity of the disease. Patients may have severe diffuse bronchiectasis with minimal changes in pulmonary function. Bronchiectasis might be localized with purulent secretions or multilobar. A common clinical finding among patients with bronchiectasis is the chronic productive cough. The causes of bronchiectasis in children are variable. Exclusion of pancreatic sufficient CF is important. These patients may have borderline or normal sweat chloride values, rare CFTR mutations and CFTR sequencing is often required to rule out CFTR-associated disease. Other causes are primary ciliary dyskinesia, immunodeficiency, foreign body aspiration and recurrent food or gastric aspiration, connective tissue disorders, allergic bronchopulmonary aspergillosis as well as other miscellaneous conditions. The diagnostic work-up should include, in addition to sweat test, CFTR function by nasal potential difference and, if not available, CFTR mutation analysis or CFTR sequencing including MLPA. PCD can be ruled out by nasal NO screening and electron microscopy. However, cases of PCD with normal EM appearance or normal nasal NO have been reported. Bronchoscopy should be performed to exclude foreign body aspiration or congenital anomaly that predisposes for bronchiectasis as well as pH monitoring and upper GI series to rule out GERD. The immune work-up in a child that only has bronchiectasis is expensive and, most of the time, is negative. Therefore at this stage a full coding regions sequencing can be performed and may reveal mutations in immune regulating genes.

The treatment is based on non evidence-based recommendations and include augmenting the mucociliary clearance and antibiotics. Some would give continuous rotating oral antibiotics while others will treat only exacerbations with antibiotics. Recent studies show that azithromycin reduces the rate of exacerbations. Few studies show the advantage of inhaled antibiotics in patients colonized with Pseudomonas aeruginosa. Follow-up in a specialty clinic is mandatory.

EVIDENCE IN NON-INVASIVE VENTILATION IN CHILDREN

Dr. Martí Pons Òdena
PICU Hospital Universitari Sant Joan de Déu. University of Barcelona, Mpons@hajdcbn.org

Introduction
This paper will review different issues related to non-invasive ventilation (NIV) along with their current level of evidence-based medicine (EBM).
Strictly speaking, neither high flow oxygenation nor continuous positive airway pressure (CPAP) can be considered NIV, so the paper will mainly focus on bilevel positive airway pressure (BLPAP). Although it is well known that there are several levels of evidence, when doctors talk about evidence-based medicine, knowledge based on lower levels of evidence is usually underestimated or simply rejected. For this reason, the 2011 update by the Oxford Center of Evidence-Based Medicine is used to review evidence in NIV. Their introductory document says: “no evidence ranking system or decision tool can be used without a healthy dose of judgment and thought.” The levels are not intended to provide you with a definitive judgment about the quality of evidence. There will inevitably be cases where ‘lower level’ evidence – say from an observational study with a dramatic effect – will provide stronger evidence than a ‘higher level’ study – say a systematic review of few studies leading to an inconclusive result”. Table I. Thus, I would like to stress that sometimes, having a lower level of evidence does not mean having weaker evidence. Additionally, the questions in Table II should be answered before applying a recommendation to our patients. The current evidence-based medicine level on NIV in the pediatric critical care setting will be analyzed from its highest level to the lowest one.

**Systematic reviews and meta-analyses**

In a PubMed search for non-invasive ventilation and acute respiratory failure, 42 studies were found. Unfortunately, there are no studies in pediatric patients using BLPAP, but there are some systematic reviews in pediatric patients treated with negative and positive continuous pressure and in premature babies treated with CPAP, all of which demonstrate positive results.

**Randomized controlled trials**

Two hundred and twenty-five randomized controlled trials (RCT) were found if COPD patients are excluded. Again, data in pediatrics are disappointing. Generally speaking, it can be said that the use of initial NIV (iNIV: patients without previous invasive respiratory support in the acute setting) is supported by a single RCT in pediatric intensive care unit (PICU) patients with acute respiratory failure. Twenty-five patients per group were included. Inclusion criteria for Yanez’s study were: failure criteria with fraction of inspired oxygen (FiO<sub>2</sub>) &gt; 50% to maintain hemoglobin saturation (SpO<sub>2</sub>) &gt; 94%; &gt; 6 (infants) or Downes score &gt; 6 (children). Exclusion criteria: FiO<sub>2</sub> &gt; 60% and SpO<sub>2</sub> &lt; 90%; neuromuscular and oncologic diseases; obstructed upper airway; and shock with dopamine &gt; 6 mcg/kg/min.

Recently, another RCT has been published in 63 pediatric patients with respiratory failure after cardiopulmonary bypass surgery, 32 of whom received rescue NIV (rNIV: patients extubated to room air or oxygen who develop respiratory failure) with positive results and a re-intubation rate lower than 20%.

Although it is not specifically pediatric, I would like to point out a RCT published by Weng in 2008 that confirms the value of using hydrocolloid dressings to prevent skin sores, one of the most common complications in NIV.

**Cohort studies, mechanistic reasoning and case studies**

This is the EBM level with the most data. First of all, based on a cohort study published in 2012, we should differentiate three different types of NIV as commonly done in adult literature: iNIV, and post-extubation NIV that can be divided into rNIV previously defined, and elective NIV (eNIV, when the patient is directly extubated to NIV).

Almost all of the largest pediatric studies published have studied a mixed population (iNIV, rNIV, eNIV), making it difficult to identify reliable predictive factors of failure.

Nevertheless, several cohort studies with large samples (n &gt; 100 patients) have identified predictive factors of failure that can be summarized as a triad: lack of decrease in work of breathing (WOB), a younger age, and hypoxemia, measured in different ways (SpO<sub>2</sub>/FiO<sub>2</sub> (SF) ratio, acute respiratory distress syndrome (ARDS) diagnosis, higher FiO<sub>2</sub>). There are also several studies evaluating NIV in specific diseases (bronchiolitis, pneumonia, M. pneumonia, etc.) and situations (transport, postoperative cardiac patients, postoperative scoliosis, postoperative hepatic transplant, etc.) favoring the use of NIV.

It has also been observed throughout these studies that NIV ventilators, those turbine-based, have been used successfully in young infants regardless of not having official approval. Generally, conventional ventilators with NIV option have also been used successfully for NIV, but mainly in older children, although some conventional ventilators have also shown good results in infants in Yanez’s RCT.

The interface has been recognized as a crucial issue when using NIV, but it has been poorly studied in the majority of the pediatric cohort studies. Although data from adult studies clearly favor selection of an oronasal mask for hypoxemic patients, interfaces such as the helmet and even the nasopharyngeal tube have shown reasonably good results in cohort, several case and cross-over studies.

Finally, we should not forget studies with a lower level of evidence but can generate interesting hypotheses and improvements in the near future. For example, modes with neural trigger (NAVA) have shown better synchrony and higher variability in breathing pattern, perhaps promising better results for difficult patients, but not for all our patients.

To summarize, when talking about EBM of NIV in Pediatrics, it has to be admitted that we are far from adults in the highest levels of evidence. However, there are sufficient prospective observational studies with a “dramatic effect” to suggest that the appropriate use of NIV in pediatric patients is not only safe in several diseases and situations, it is beneficial.

**References**

1. Shah PS, Ohlsson A, Shah JP. Continuous negative extrathoracic pressure or continuous positive airway pressure compared to conventional ventilation for acute hypoxaemic respiratory failure in children. Cochrane Database Syst Rev. 2013 Nov 4;4:CD006699


PATIENT-VENTILATOR INTERACTIONS DURING NASAL VENTILATION: A LARYNGEAL PERSPECTIVE

Jean-Paul Praud MD PhD
Respiratory Medicine Division, Department of Pediatrics, University of Sherbrooke, QC – Canada, Jean-Paul.Praud@USherbrooke.ca

Introduction
A key aim of assisted intermittent positive pressure ventilation is to deliver ventilatory support in synchrony with the patient’s own respiratory efforts. Patient-ventilator asynchrony has been identified as an important factor in mechanical ventilation failure, with the presence of such asynchrony during more than 10% of respiratory cycles being considered as potentially deleterious (1). Hence, the study of patient-ventilator interaction has become a hot topic in recent years (1,2).

Moreover, when deemed efficient, non-invasive ventilation (NIV) is increasingly used in infants and children (3-5). NIV use enables to avoid the severe complications potentially associated with endotracheal intubation, such as ventilator-associated pneumonia, tracheal bleeding or stenosis.

However, while endotracheal ventilation delivers the gas directly into the trachea, in NIV, gas is insufflated at positive pressure into the upper airways. This important difference underlies the crucial role of the laryngeal valve during NIV. Indeed, if present, any laryngeal closure during NIV will impede the transmission of the insufflated gas into the lower airways. Potential consequences are lung hypoventilation and/or deviation of the gas into the digestive tract with significant complications such as gastric dilatation, increased gastro-esophageal reflexes and/or cardiopulmonary reflexes induced by esophageal distension.

Using laryngoscopy, Rodenstein’s team showed for the first time in the 90’s that the larynx can be closed during NIV in adult humans (6). While highlighting the importance of hypocapnia and high inspiratory flow, their assessment of the mechanisms at play was limited by the clinical nature of their studies. Since about ten years, we have attempted to further study the importance of laryngeal closure during NIV in healthy, full-term newborn lambs.

Active inspiratory laryngeal closure during NIV in lambs

Inspiratory laryngeal closure frequently develops when inspiratory pressures are increased during nasal pressure support ventilation (nPSV). In our experimental conditions, inspiratory laryngeal closure is present during more than 20% of respiratory cycles at a pressure support ventilation of 15/4 cmH2O in most lambs.

Inspiratory laryngeal closure is active and involves the reflex contraction of the laryngeal constrictor muscle against ventilator insufflation (7,8). The increase in upper airway resistance and decrease in inspiratory tracheal flow are related to the amplitude of laryngeal constrictor muscle EMG activity (7). Frequently, this active inspiratory laryngeal closure is even responsible for stopping inspiration and thus the cycling of the ventilator from inspiration to expiration.

Mechanisms and factors altering active inspiratory laryngeal closure in lambs during nPSV

Contrary to observations during nPSV, active inspiratory laryngeal closure against ventilator insufflations is not present during nasal neurally-adjusted ventilatory assist (NAVA), despite the use of grossly equivalent inspiratory pressures (8). The reasons for this difference are unclear.

The reflex activation of inspiratory laryngeal closure during nPSV does not originate from the upper airways, but from below the larynx (9). While bronchopulmonary C fibers are not involved in this reflex, the potential role of the bronchopulmonary slowly-adapting and/or rapidly-adapting receptors is unknown (10).

Hypocapnia is not a prerequisite for the presence of inspiratory active laryngeal closure against ventilator insufflations in NIV. However, a mild to moderate hypercapnia (PaCO2 = 50 mmHg) induced by adding CO2 into the insufflated gas consistently prevents the development of active laryngeal closure (unpublished data). Moderate hypoxia (PaO2 = 45 mmHg) has no consistent effect.

Inspiratory active laryngeal closure in nPSV cannot be prevented by decreasing the inspiratory pressure rise time (unpublished data).
Abstract S45

Clinical importance of inspiratory active laryngeal closure observed in lambs during nPSV
The occurrence frequency of inspiratory active laryngeal closure during nPSV in lambs with respiratory diseases is still unknown. Given that all our experiments were performed in healthy, full-term lambs, the observed active laryngeal closure may be a protective reflex mechanism against forced, unnecessary lung inflation at positive pressure. Hence, although the results previously obtained by Rodenstein’s team show that active inspiratory laryngeal closure can be present in humans during NIV, its clinical importance remains to be clarified. In summary, active inspiratory laryngeal closure can be observed in certain NIV modes. Although the clinical importance of this patient-ventilator asynchrony remains to be clarified, it may be especially relevant in knowing that mild to moderate hypercapnia, as well as the use of nNAVA, can prevent such laryngeal interference with the ventilator in NIV.

ACKNOWLEDGMENTS
This work is supported by the Canadian Institutes of Health Research and the Canada Research Chair in Neonatal Respiratory Physiology.

References

UPDATE ON PULMONARY COMPLICATIONS OF ORGAN AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

Dennis C. Stokes MD, MPH, Saumini Srinivasan MD, MS, Ashok Srinivasan MD, Hiroto Inaba, MD, PhD
Division of Pulmonary and Sleep Medicine, Department of Pediatrics, University of Tennessee Health Science Center and Le Bonheur Children’s Hospital and Departments of Bone Marrow Transplantation and Cellular Therapy, Oncology, and Pediatric Medicine, St. Jude Children’s Research Hospital, Memphis, Tennessee
Correspondence: Dennis C. Stokes MD MPH, St. Jude Professor of Pediatrics, University of Tennessee Health Science Center, and Chief, Division of Pulmonary and Sleep Medicine, Department of Pediatrics, Le Bonheur Children’s Hospital and St. Jude Children’s Research Hospital, Memphis, TN 38105.
Email: dstokes4@uthsc.edu, Ph: 901-287-5222, FAX: 901-287-6337

Introduction. Transplantation, including solid organ transplantation and bone marrow or allogeneic hematopoietic stem cell transplantation (HSCT), is associated with a variety of pulmonary complications. These complications include both infectious and non-infectious complications as well as immunologic complications related primarily to chronic rejection.(1,2) This review will update the status of these complications and discuss recent studies on late complications and follow-up lung function following both solid organ (primarily lung) and HSCT transplantation. Bronchiolitis obliterans (BO) syndrome remains a major complication of both lung transplantation and HSCT and progress in therapy and prevention and treatment in BO and related syndromes have been very slow in the past 20 years.(3)

Pulmonary complications of solid organ transplantation

Lung. Lung transplantation has continued to grow slowly in numbers of both adult and pediatric patients, although the number of pediatric transplants remains relatively low, less than 150 per year in the U.S. (1) Survival after lung transplantation has increased, although most of the improvement in survival has been in short term survival rather than improved longer term survival. Lung transplantation numbers remain limited by the availability of donor lungs, particularly for pediatric lung transplant; the lung allocation process for pediatric patients in the U.S. was challenged in 2014 and there has been debate about the survival benefit of lung transplantation for pediatric cystic fibrosis (CF) patients. A survival benefit appears to occur for older CF patients undergoing lung transplant according to newer statistical analyses of current lung allocation protocols. (1) Strategies to harvest lungs after a period of circulatory arrest represent a promising new approach to increase the numbers of donor lungs. The most common indication for pediatric lung transplantation remains CF and pre-transplant microbiology in CF significantly affects post lung transplant outcomes. Whereas CF patients with Staphylococcus aureus and Pseudomonas aeruginosa appear to do relatively well post transplantation compared to non-CF patients, a history of Burkholderia cepacia infection remains a major contraindication to lung transplantation. The increasing surveillance for atypical Mycobacterial infections (due in part by the use of chronic macrolide therapy) in CF has resulted in more detection of these organisms pre-transplant and particularly Mycobacterium abscessus can significantly complicate the pre and post transplant course. Fungal infections, including common fungi like Candida sp, Aspergillus and Mucor, as well as more rare saphrophytic fungi and molds, have emerged as significant infectious complications in the post transplant population. Viral infections, including common respiratory viruses such as respiratory syncytial virus (RSV), adenovirus, and cytomegalovirus (CMV) remain significant causes of morbidity in the post transplant population, although effective prophylaxis strategies for CMV have helped reduce the impact of CMV. Post transplant lymphoproliferative disease can occur in many types of transplant maintained on significant T-lymphocyte depleting immunosuppressive therapy. This complication is due to Epstein-Barr virus-driven B cell proliferation, and presents most commonly with nodular infiltrates and/ or lymphadenopathy.

Liver and kidney. Outcomes for pediatric liver and kidney transplantation are generally much better than outcomes for lung transplant. Postoperatively, liver transplant patients are at risk for a variety of respiratory complications, including pleural effusions and acute respiratory distress syndrome (ARDS). Pleural effusions, primarily right sided, are common post liver transplant. Respiratory function can also be affected by the extensive abdominal surgery, and diaphragmatic dysfunction or paralysis which occurs in up to 15% of liver transplant patients. Postoperative immunosuppression with sirolimus has been associated with a low risk of development of interstitial pneumonia. The role of combined lung-liver transplantation in cystic fibrosis is unclear although for many CF patients with significant lung and liver disease, this remains the only option for potential longer term survival. Kidney transplantation and the immunosuppression, required long term, result in an increased risk of pulmonary infections.

Pediatric Pulmonology
Pulmonary complications of bone marrow and hematopoietic stem cell transplantation (HSCT). Pulmonary complications of HSCT include numerous infectious complications, which vary in etiology according to the time of transplant and engraftment. (2) Non-infectious complications include mucositis, pulmonary edema, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, and pulmonary-hypertensive veno-occlusive disease. Late non-infectious complications post HSCT include bronchiolitis obliterans (BO) syndrome, and cryptogenic organizing pneumonia (formerly bronchiolitis obliterans-organizing pneumonia (BOOP)). (4-6)

**Lung function changes post HSCT.** A number of studies have examined lung function changes post HSCT, and the important role of pre-transplant lung function has been convincingly demonstrated. (5-8) Lung function prior to transplant provides a basis for comparison to post transplant studies, but studies from our institution and others also suggest that lung function studies prior to transplant can help predict future risk of pulmonary complications as well as mortality post transplant. Lower pre transplant FEV1 which was associated with a greater risk of all pulmonary complications and lower FVC and FEV1 were associated with lower overall survival post HSCT. Lower Lung Function Scores (a summation of FEV1 and DLCO) also predicted a higher risk of post transplant respiratory failure.(5-7)

**Advances in chronic lung allograft dysfunction (CLAD) and bronchiolitis obliterans (BO) syndrome.** Chronic lung allograft dysfunction (CLAD) is a general term used to describe a sustained loss of lung allograft function, and includes the well-defined bronchiolitis obliterans (BO) syndrome as well as less well standardized phenotypes such as restrictive physiology, diffuse alveolar damage, and pleuroparenchymal fibroelastosis. (1,3) Serial monitoring of lung function helps detect early PFT changes that prompt additional evaluations; known risk factors for development of BO in the lung transplant population include primary graft dysfunction, acute cellular rejection, lymphocyctic bronchiolitis, humoral rejection, GEP, infections, and evidence of BAL neutrophilia. (3) In lung transplant patients, transbronchial lung biopsy (TBB) can be used to monitor for early evidence of rejection and lead to increased immunosuppression. Recently TBB has been shown to have value even in younger lung and heart-lung transplant patients, although there are significant technical issues with the small biopsy forceps available for pediatric bronchoscopes. This difficulty may be helped by a new generation of ultrathin bronchoscopes with a larger (2 mm) operating channel for large TBB samples. (9) TBB has a low yield for small airway tissue sufficient to diagnose BO, thus high resolution CT on inspiration and expiration has become the major diagnostic tool for pediatric patients with suspected BO. Chronic azithromycin has been used in a number of BO patients, with the best evidence for benefit being in a subset of patients with suspected BO. Chronic azithromycin has been used in a number of BO patients, with the best evidence for benefit being in a subset of patients with suspected BO. Chronic azithromycin has been used in a number of BO patients, with the best evidence for benefit being in a subset of patients with suspected BO. Chronic azithromycin has been used in a number of BO patients, with the best evidence for benefit being in a subset of patients with suspected BO.

For patients with advanced BO post transplantation, the only therapy available is lung transplantation. In lung transplant patients who develop BO, the outcome after a second lung transplant is not as good as with a first transplant, and the risk of redeveloping recurrent BO is higher compared to the group requiring a second lung transplant for other causes. (1,3) A small number of lung transplants have been performed in HSCT patients developing advanced BO, and the results of one small series suggest that survival is similar to matched controls with CF endstage lung disease. (10)

**References**


**HOW TO PUBLISH YOUR PAPER**

Andrew Bush MB BS (Hons) MA MD FRCP FRCPC FERS Professor of Paediatrics and Head of Section (Paediatrics), Imperial College Professor of Paediatric Respiratory, National Heart and Lung Institute Consultant Paediatric Chest Physician, Royal Brompton Harefield NHS Foundation Trust.

Correspondence: Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK.

AB was supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London. Tel.: -207-351-8232. Fax: -207-351-8763. e-mail:a.bush@imperial.ac.uk

**Introduction.** Publish or perish is likely to be true for the academic for the foreseeable future. However, before trying to publish, it is a good idea to have something worth writing. You need a question which interests and excites you – because if it does not, no-one else will be interested or excited. And you need to be able to answer the only two worthwhile questions about any research project - So what? and, What for? The purpose of this presentation is to try to guide the reader away from the common traps which so often wreck a paper before it is started.

A common trap is the failure to distinguish between changes that are statistically significant, and may give important hints about disease mechanisms, and changes that are useful in the clinical management of the patient – a much more stringent test, requiring minimal overlap between groups. Absence of use as a clinical test does not disqualify the paper – but is likely to make it much less interesting. Chose a journal that publishes your sort of work (e.g. the New England Journal of Medicine, which never publishes animal work, so do not send your mouse model data there); and style your manuscript so it fits the

Pediatri Pulmonology
Journal. Keep to the word count – you may think you write like Tolstoy, but the editor will not agree, and may return overlapping manuscripts unreferred. Finally, nothingpees an editor more than a manuscript obviously in the style of someone else’s Journal, and likely previously rejected from it.

The title and abstract – your shop window. Editors and reviewers are busy people, and make snap judgements – maybe they should not, but they do. Grab their attention but be accurate – JaLo bares all may make them read on, but if all they find is the mouse CD200 pathway, disappointment will be followed by anger will be followed by rejection. Do not stuff it with abbreviations – this makes it indigestible.

The Introduction = why you did it. This should be focussed and relevant, not a long essay, setting forth the importance of the problem; why it has not been solved before and why you might be the person to solve it; and it MUST end with a logical HYPOTHESIS and MUST generate enthusiasm. At the end of the Introduction, the editor needs to think that the paper is potentially important, and be keen to know more.

The Methods – what you did. The reader must be able to reproduce the study in this section, including the selection criteria. You should use the online supplement if one is permitted by the journal. Key issues include how you checked the accuracy of data entry. There must be a statistical section, including a power calculation (or a reason why you have not done one); a statement about how you dealt with multiple comparisons, and what and why you set as the level of significance. Finally, state what tools and software packages you used.

The Results – what you found. You should use CONSORT and STROBE diagrams as appropriate. You must describe the patients you studied. KISS (=Keep It Simple Stupid) for the Tables – long turgid tables belong in the on-line supplement. The analyses must be focussed; hopeful comparisons and trawling are easily detected, as are endless post hoc analyses, which are at best hypothesis generating. Do not fudge the findings – p<0.07 is not significant, and if you miss the primary endpoint, your trial is NEGATIVE – your girlfriend is slightly pregnant! The editor did not come down with yesterday’s rain and will spot this.

The Discussion – what it means. Do not repeat the introduction, and do not extrapolate wildly beyond your study population. The tyro may find it useful to structure this section using five headings (Table). Special issues: Case reports. When doctors meet, they always talk about interesting cases, but Editors hate to publish them, because they are not cited. There must be a take-home message: SO WHAT! is even more important. This is not answered by a report of the 17th example of a rarity in the literature, or the first report of a rarity in your country, or an association between two rare conditions which will likely never happen again. Go for cases with a learning point. Special issues: Genetic studies. There are special pitfalls to avoid; SNPs with no biological readout, mere association with no biological plausibility or validation elsewhere, for example in animal or cell line studies; no validation in a second population, or the so-called replication in fact pinpoints different SNPs in the same gene. So the editor has asked you to revise your manuscript! You are probably outraged that anyone could possibly want your perfect paper changed in any way. But they do! Swallow your pride and your bile, and say you are grateful, even if you are not; and thank the reviewers for the helpful comments (even if you think they were idiots; remember they are probably good friends of the editor.). Prepare a point by point response, saying what you have done; what you have inserted; and where you have inserted it. Make the reviewers life easy. Summary. Good luck, it’s worth keeping on trying. Finally, ten top traps (courtesy Vic Chernick) to avoid:

1. You did not read the instructions
2. You have a major conflict of interest
3. The manuscript was not checked for typos; if the writing is careless, the editors will think the rest of the work was too
4. This is the 19th case of X (whatever X may be)
5. You have made no changes after submission elsewhere; the same reviewer may see your paper again, and offence will be taken if the comments are ignored!
6. There is no hypothesis anywhere to be found
7. There has been plagiarism including self-plagiarism (easily detected with modern software), key references are omitted or misquoted (especially if the editor is an author!)
8. There is no power calculation; the statistics are poor – always involve a statistician early not late in your work
9. Rambling, unfocussed, and far too many abbreviations (making the paper unreadable)
10. BORING!

You may think some of these are trivial, but a last piece of advice – why look for trouble?!

Further reading

Table: headings to give structure to the Discussion

- Statement of Principle Findings – should be a crisp summary of the take-home message
- Strengths and weaknesses of the study; remember there are always some problems!
- Strengths and weaknesses with respect to other studies, especially any discrepant results?
- Meaning of the study
- Unanswered questions and future research; should be detailed and focussed

HOW TO GET YOUR PAPER REJECTED, PART 2

Thomas Murphy MD
Editor in Chief
Pediatric Pulmonology, murphyseditorppul@hotmail.com

In March 2008, Dr. Victor Chernick, the Editor in Chief of Pediatric Pulmonology, published an article (1) entitled, “How to Get Your Paper Rejected”. The article was written in a humorous fashion that was meant to mimic what the American comedian David Letterman does with his “Top 10” lists of sardonic reasons why famous people and organizations get into trouble. While Dr. Chernick’s top 10 list was humorous, the underlying message was quite serious. More troublesome still, each of these problems continues to play a major role in the decision to reject manuscripts at our journal. Some reasons for the persistence of these problems have to do with changes in the specialty and in the journal itself.

1. The manuscript is not written in grammatically correct scientific American English and if authored by non English-speaking authors, it has not been checked by an English-speaking author. A related problem is lack of clarity and a compelling story. I list this as the number one problem, because there is a belief by some that problems with basic writing will simply be taken care of by the journal. An inadequately revised and edited manuscript creates an enormously negative

Pediatric Pulmonology
Abstract

impression at the journal and increases the workload of the editors. Experience is accumulating that if this is the quality of the writing, then the quality of the science will be lacking as well. As with all interactions, first impressions are extremely important, and editors are increasingly unforgiving of this.

2. The Instructions for Authors (IFA) are not followed. There is evidence they were not read. These are constantly amended, so the authors cannot assume that if they were familiar with the IFA five years ago, they will be up to date. An important component of the art of the first impression is that it is very important not to irritate the Managing Editor (ME). What you do not want as a contributor is a history of many emails between the ME and the other editors that deal with fixing your manuscript. The IFAs differ among journals. The requirement for figures to be submitted in a TIFF or EPS format for our journal follows from the software that the publisher uses to generate e-print and print issues. It is not a choice of the editorial staff and cannot be changed.

3. Challenges to the boundaries of plagiarism. Most journals utilize software (such as IThenticate) to measure and quantify identical text segments that appear in journals or the internet. It is not appropriate to lift text (including methods and discussion) from one’s own prior publications and certainly not from the publications of others. This includes internet-published dissertations. Duplicate publications continue to plague academic publishing. Simultaneous submission of the same manuscript to two different publishers is expressly forbidden.

4. Lack of appropriate citations. This problem appears when major citations are omitted, because this affects the interpretation of the data. A larger problem occurs when an authorwithholds information about a closely related prior publication from the same group that may also have some overlapping data. This kind of behavior has a corrosive effect on the trust the editors have for the group.

5. Lack of disclosure of a major conflict of interest. This is particularly applicable to industry-sponsored research. It is absolutely essential that the editors know whether or not the author has a relationship to the sponsor, and especially if that relationship will likely result in financial gain to the author if the product is successful.

6. Your manuscript has been rejected elsewhere and you now submit it to the next journal without any revisions that multiple reviewers have made. The lesson to be learned is that specific areas of research usually are reviewed by a small number of reviewers who happen to be prominent in this field. All the journals use them if they are willing. Thus the likelihood of getting the same reviewer the second time around is much greater than expected. Imagine the response of this reviewer who might have stayed up late and spent extra time on it to get it right and make the comments helpful. This same reviewer may have recommended revision and ultimate acceptance. The outcome the second time is less certain.

7. The manuscript lacks a hypothesis. This happens much more frequently than one would imagine. It happens especially frequently with email or telephone practice surveys. There needs to be an a priori question and an a priori anticipation of what constitutes a meaningful deviation in the signal and why. It is not enough to say “Look at the large variation. The fact that it is large is a problem that calls for fixing.” This is not a scientific approach.

8. Study design and statistics. Clinical studies especially need the input of statisticians each of whom has very extensive experience with pediatric clinical trials. One of the most frequent mistakes is the failure to perform a power analysis to determine how many control and treatment subjects are needed to find a predetermined measurable and (justified) relevant clinical effect.

9. Case Reports. The bar for acceptance of these is very high. The cases need to be UNIQUE, point in a different direction from the expected syndrome or outcomes and have clear appeal to international experts. If there are a few case reports that are similar to what is being submitted, the manuscript will be rejected.

10. Letters to the Editor. Letters to the Editor are not meant to be a vehicle for debate. They are meant to highlight assertions or changes in perception that emerge from a published article that raise questions about the field or about future directions. They are particularly helpful if they indicate a need for change in direction in research. What is not helpful is a letter that asserts simply that the authors were just plain wrong and the journal should never have published the article. This may prove to be correct, based on future studies, but it is not interpreted as helpful, because it only serves to stop discussions about these emerging areas.

11. Novel Areas of Dishonesty. The newest is “fake reviewers”. Authors are encouraged to list potential reviewers who are knowledgeable and fair. This helps the Associate Editors to find reviewers. An audit a few years ago from Wiley demonstrated that if your manuscript is reviewed by a recommended reviewer, it has no more chance of being published than it would if reviewed by individuals not known to the authors. The new problem is that some authors have resorted to providing a fake name linked to an email address of a friend or the author herself/himself. This co-conspirator then provides a favorable review. Sometimes the new reviewer is listed as being from a prestigious university, but the email address suggests a membership from elsewhere.

What to do if your manuscript is rejected. It is important to understand that the rejection rates for all the most popular journals, including Pediatric Pulmonology, is in the 70-90% range. When the rejection rates are this high, good manuscripts will sometimes be rejected. It is important to understand that the group of individuals with a history of manuscript-rejection includes a majority of the members of the editorial board!

Possibilities

1. Appeal the decision, if this allowed, to the Editor in Chief. Explain the reason for the appeal.
2. Meet with your team and review carefully the manuscript and the critiques. In many cases the study was not large enough to be convincing and more studies/experiments are needed. Sometimes a very thorough re-writing might be needed. Seek your own review from someone who has experience and expertise. Ask that their review not be friendly. If the study/writing can be improved, think carefully about which journal would be most interested. If appropriate, contact the journal to determine the potential level of interest.

From the earliest time of project-conception through to the final writing and submission, try to get into the head of a potential reviewer. A highly cited reference regarding how many reviewers assess new research was written and published by Dr. Fred Hoppin of Brown University in 2002 (2). It is still very relevant.

References


III. FINALIST’S ORAL COMMUNICATIONS

#92 - TOLL-LIKE RECEPTORS AND LUNG FUNCTION BY IMPULSE OSCILLOMETRY IN A 5-7-YEAR POST-BRONCHIOLITIS COHORT.

Lauhkonen E.1, Koponen P.1, Vuononvirta J.2, Nuolivirta K.3, Toikka J.4, Helminen M.5, Korppi M6
1 Tampere Center for Child Health Research, Tampere University Hospital - Tampere, Finland
2 Department of Infectious Disease Surveillance and Control, National Institute of Health and Welfare - Turku, Finland
3 Pediatrics, Seinäjoki Central Hospital - Seinäjoki, Finland

Pediatric Pulmonology

DOI 10.1002/ppul.23209
Background: Toll-like receptors (TLRs) are sentinelsof airway epithelial cells and crucial in the onset of innate immune response protecting the lung from pathogens, such as viruses. Genetic variations in TLRs have been associated with viral bronchiolitis severity and later asthma in children. The role of TLRs in the loss of lung function after viral bronchiolitis in infancy is less studied.

Methods: One hundred and two children hospitalized for bronchiolitis at age less than 6 months underwent impulse oscillometry (IOS) at median age of 6.3 years. Main parameters obtained were airflow impedance (Zrs), resistance (Rxs) and reactance (Xrs) at 5Hz in baseline, post-exercise and post-bronchodilator measurements. Data on single-nucleotide polymorphisms (SNP) of TLR 1 rs5743618, TLR 2 rs5743708 and TLR 6 rs5743810 (TLR2 subfamily) and TLR 3 rs3775291, TLR 4 rs4986790, TLR 7 rs179008 and TLR 8 rs2407992 were available for analysis.

Results: The TLR 4 rs4986790 A-allele associated significantly with greater change in Rrs5Hz (0.09 vs. -0.42, p = 0.03) in response to exercise. In TLR 6 rs5743810, the T-allele associated significantly with greater change in Zrs5Hz (0.99 vs. -0.04, p = 0.03), Rxs5z (0.77 vs. -0.03, p = 0.03) and Xrs5Hz (-0.52 vs. 0.05, p = 0.04) in response to exercise. In baseline lung function measurements, no significant associations were seen with any of the TLR polymorphisms.

Conclusion: No significant associations were found with investigated TLR-encoding SNPs and lung function at median age of 6.3 years after viral bronchiolitis in early infancy. Polymorphisms of TLR 4 and TLR 6 may be associated with airway reactivity to exercise.

#110 - ALBUTEROL VIA METERED-DOSE INHALER FOR ACUTE ASTHMA IN CHILDREN: LOWER DOSES ARE SUFFICIENT AND HIGHER DOSES ARE SAFE

Muchojo FP, 1 Souza JM, 2 Torres HC, 2 Lalibera IB, 2 Schwartsman C, 3 Rodrigues JC, 2 Silva Filho LV. 2
1 Institute of Education and Research, Hospital Israelita Albert Einstein - Sao Paulo, Brazil
2 Pneumology Unit, Instituto da Criança do Hospital das Clínicas, Medical School, Universidade de Sao Paulo - Sao Paulo, Brazil
3 Emergence Department, Instituto da Criança do Hospital das Clínicas, Medical School, Universidade de Sao Paulo - Sao Paulo, Brazil

Introduction: The ideal dosing of albuterol delivered by metered-dose inhalers (MDIs) in the treatment of acute asthma in childhood is not well established.

Methods: This randomized double blind multicenter study compared two dosage regimens of albuterol (delivered by MDIs with spacers) for the treatment of moderate to severe asthma exacerbations in children older than 2 years.

Dosages administered, at least three times in the first hour, were 200 μg (up to 25 kg) or 400 μg (> 25 kg) in the control group and 300 μg (up to 15 kg), 400 μg (> 15 to 20 kg), 500μg (> 20 to 25 kg) and 600μg (> 25 kg) in the study group. All patients received systemic corticosteroids and inhaled ipratropium. The maximum length of stay in the study was 4 hours (time of discharge or admission).

The main outcome was admission rate in both groups. The secondary outcomes were: forced expiratory volume in one second changes after 1 hour; changes in PRAM (Pediatric Respiratory Assessment Measure) score, respiratory rate and pulse oximetry after 1 hour and at the end of the study (discharge or admission); need for additional treatments; length of stay in the emergency room for discharged patients; impact of viral etiology or beta adrenergic receptor genotype on outcomes.

Safety outcomes were: changes in serum potassium, glucose, bicarbonate and pH levels; electrocardiogram abnormalities; albuterol plasma levels, heart rate and detection of tremors (yes/no).

The chi-square test was used to compare hospital admission and tremor rates. For all other outcomes, T test of comparison of means (variables with normal distribution), Mann Whitney testing (nonparametric data) and ANOVA with repeated measures were used. Alpha adopted: 0.05.

Results: There were no significant differences between groups in admission rates, need for additional treatments, length of stay in the emergency room for discharged patients, changes in forced expiratory volume in one second after 1 hour and changes in the PRAM score and pulse oximetry after 1 hour and the end of the study. The fall in the respiratory rate at the end of the study (in comparison with the initial time) was significantly higher in the control group in comparison with the study group (p = 0.046). No electrocardiogram abnormalities were detected. The plasma levels of albuterol were significantly higher in the study group (2.57 vs. 1.08 ng/ml, p = 0.042). For all other safety outcomes, there were no significant differences between groups.

There was no impact of viral etiology on admission rates and length of stay in the emergency room. Patients with the Arg16Arg genotype had higher admission rates than carriers of the Gly16Gly and Arg16Gly genotypes. Conclusions: Both albuterol dosage regimens resulted in similar efficacy and can be safely prescribed to children with acute asthma. Viral etiology did not influence the outcomes. In the studied population, the genotype Arg16Arg can be a risk factor for poor response to treatment in acute asthma.

Abstract S49

#19 - THE ASSOCIATION OF SERUM VITAMIN D LEVELS AND DISEASE SEVERITY IN CHILDREN DIAGNOSED WITH TUBERCULOSIS AT THE PHILIPPINE GENERAL HOSPITAL

Espiritu A, Tuazon A. Pediatries, University of the Philippines - Philippine General Hospital - Manila, Philippines

Background: The response to tuberculosis exposure and the risk of progression to disease is largely determined by immune status. Vitamin D has been discovered to have immune-modulating roles in a number of medical conditions including TB.

Objective: To determine the association of serum vitamin D levels with disease severity in children diagnosed with tuberculosis at the Philippine General Hospital.

Study Design: Case-control study.

Methodology: Untreated TB cases 0-18 years old were recruited and classified into either Non-severe TB (latent TB infection, uncomplicated pulmonary TB and uncomplicated extrapulmonary TB) or Severe TB (pulmonary TB with extensive parenchymal involvement and complicated extrapulmonary TB). Healthy controls were recruited from contacts of TB patients. All subjects were screened for risk factors for hypovitaminosis D that may confound the analysis. Eligible subjects were subsequently tested for serum 25-hydroxyvitamin D levels. Hypovitaminosis D was defined as 25 hydroxyvitamin D levels <30 ng/mL. Subjects were categorized as vitamin D sufficient (≥30 ng/mL), insufficient (21-29 ng/mL) and deficient (<20 ng/mL).

Results: Seventy-four children were recruited, consisting of 53 TB cases and 21 controls. Among cases, 23 had Severe TB while 30 had Non-severe TB. Age, sex and BMI were similar among all groups. Hypovitaminosis D was highly prevalent in the entire cohort, 71.7% in the TB cases and 81% in the controls. Among the children with hypovitaminosis D, deficiency was found to be more prevalent in the cases (44.7%) than in the controls (11.8%) (p value 0.017). Vitamin D deficiency conferred 6.1 odds of TB occurrence (p value 0.028). Comparing subgroups within the TB cases, the proportion of hypovitaminosis D was equally high in the Severe TB (69.6%) and Non-severe TB (73.5%) groups. However, deficiency was more prevalent in the Severe TB group (68.8%) than in the Non-severe TB group (27.3%) (p value 0.020). Vitamin D deficiency conferred 5.87 odds of severe TB occurrence (p value 0.014). Fisher’s exact test showed a significant association between vitamin D status and TB severity (p value < 0.05).

Conclusion: Vitamin D deficiency is associated with an increased risk of TB infection and developing a more severe TB disease.

Recommendations: Our suspicions of a generally poor vitamin D status among Filipino children are congruent with the results of our study. The degree of hypovitaminosis D was more severe in TB patients and more so...
among patients with severe disease. Larger prospective studies are recommended to further establish the direction of this relationship of vitamin D towards TB. Given the high endemicity of TB in the Philippines and the risk for vitamin D deficiency among Filipino children, these data can contribute to future policies for vitamin D fortification in the general population and supplementation in target groups at-risk for TB disease.

#98 - NONTUBERCULOSIS MYCOBACTERIUM INFECTION IN CHILDREN

Jiao JW
Beijing Pediatric Research Institute, Beijing Children’s Hospital - Beijing, China

Background: The infections caused by Nontuberculosis mycobacterium (NTM) are increasingly recognized worldwide. However, it is difficult to differentiate NTM from Mycobacterium tuberculosis (MTB) due to their similar clinical manifestation.

Objective: To understand the NTM prevalence in children with suspected mycobacterium infection.

Materials and Methods: A total of 79 suspected Mycobacteria clinical isolates from children with respiratory tract infection were collected from 2011 to 2013 in Beijing Children’s Hospital. Acid-fast staining, culture (PNB/TCH), multi-locus polymerase chain reaction (Multi-locus PCR), and sequencing of hsp65 gene were used to detect and identify the species of these samples. A drug susceptibility test for six anti-tuberculosis drugs was also performed.

Results: All the isolates were positive after acid-fast staining. Detection with PNB/TCH medium and multi-locus PCR identified that 68 isolates (86.1%) were MTB, two isolates (2.5%) were Mycobacterium bovis BCG, and the remaining 9 isolates were other mycobacteria species. Further sequencing of hsp65 gene showed that 8 out of 9 other mycobacteria species were NTM (including four strains of Mycobacterium fortuitum, two strains of Mycobacterium novocastrense, one strain of Mycobacterium gilvum, and one strain of Mycobacterium senegalense), the remaining one strain belonged to Gordonia spati. The drug resistance rates of 68 MTB isolates were 8.8% to rifampicin, 11.8% to isoniazid, 26.5% to streptomycin, 5.9% to ethambutol, 1.5% to ofloxacin and 0% to kanamycin respectively, while the drug resistance rate was much higher for 8 NTM isolates, up to 75%, 100%, 87.5%, 87.5%, 12.5% and 37.5% to the above mentioned six anti-tuberculosis drugs respectively.

Conclusions: The main species of mycobacteria isolated from children with respiratory tract infection is MTB. However, there is also quite a high proportion of NTM infection. We should pay more attention to species identification among patients with suspected mycobacterium infection.

#126 - HYponatREMIA AND ITS PRACTICAL USE IN CHILDREN WITH PNEUMONIA

Wrotek A.1, Czekaj-Kucharsk K.2, Jackowska T.1
1 Department of Pediatrics, Medical Center of Postgraduate Education, Bielski Hospital - 99-103 Marymoncka St., 01-813 Warsaw, 80 Cegielska St. - Warsaw, Poland
2 Department of Pediatrics, Bielski Hospital - Warsaw, Poland

Background: Community-acquired pneumonia (CAP) is one of the major causes of death in early childhood (under five years of age). Therefore, fast, cheap and easy to perform diagnostic and prognostic methods are required. CAP is frequently accompanied by hyponatremia (HN) and lowered sodium levels have been suggested to be associated with severity of CAP.

Aim: The goal of this prospective study was to analyze the frequency of HN in hospitalized patients and its correlation with disease severity in a possibly huge study group. The research also aimed to analyze the correlation between sodium levels and the outcome of the disease.

Material and Methods: The study lasted 5 years (2009-2013) and 560 children (266 female and 294 male) aged 3-60 months hospitalized due to CAP were included in this study. Only children with radiologically confirmed pneumonia met inclusion criteria. Laboratory (inflammatory markers) and clinical (tachypnea, tachycardia, oxygen blood saturation, fever, time for defervescence were analyzed as pneumonia severity markers and length of hospital and antibiotic treatment were used to assess clinical outcome of disease.

Results: Hyponatremia was observed in 38% (211/560) of children and in a majority of cases it was mild (94%), while in the remaining patients there was moderate (according to Ellisson-Berl scale) HN. Hyponatremic patients had increased inflammatory markers (CRP 24.9 vs. 10.8 mg/mL, p<0.01 and procalcitonin 0.31 vs. 0.21 mg/mL, p<0.01), increased neutrophil percentage (59 vs. 52%, p<0.01) and higher fever at admission (38.6 vs. 38.1 degrees Celsius, p<0.01). On the other hand, we found no significant differences (as previously reported) in heart or breath rate, oxygen blood saturation, white blood cell count, length of hospitalization or duration of antibiotic treatment. The presence of hyponatremia, even of higher degree (mild), did not correspond with the severity of pneumonia and ROC analysis showed area under the curve values of approximately 0.5 for hyponatremic and non-hyponatremic patients in each analyzed parameter.

Conclusions: Hyponatremia is a very frequent finding in children hospitalized due to pneumonia and is correlated with increased serum inflammatory markers and body temperature. The current study did not confirm use of HN as a prognostic tool, as it had no correlation with the outcome of treatment (length of hospital stay or antibiotic treatment). Certainly, the possibility of HN should be taken into consideration in each patient with pneumonia, although the predictive value of mild to moderate cases of HN remains insignificant.

#129 - THE USEFULNESS OF IP-10 LEVEL MEASUREMENT IN URINE IN DIAGNOSING MYCOBACTERIUM TUBERCULOSIS INFECTION IN CHILDREN

Komorowska-Piotrowska A.1, Strzelak A.1, Borowa A.2, Ziołkowski J.1, Krasiańska M.2, Feleszko W.1, Kulus M.1
1 Department of Pediatric Pulmonology and Allergology Department, Medical University of Warsaw - Warsaw, Poland
2 Department of Lung Disease and Tuberculosis for Children and Adolescents, The Mazovian Center for Treatment of Lung Diseases and Tuberculosis in Otwock - Otwock, Poland

Background: Diagnosis of childhood tuberculosis (TB) can be very difficult. The performance of tuberculin skin test (TST) and interferon gamma release assay (IGRA) in children seems to be suboptimal. Assessing biomarkers in urine could serve as an attractive alternative to TST and IGRA in the diagnosis of childhood TB due to its easy and non-invasive collection. Interferon gamma induced protein (IP-10) is a potential new marker for Mycobacterium tuberculosis (MTB) infection.

Aim of this study: To measure IP-10 level in urine of children suspected of TB, and to assess its ability to distinguish children infected with MTB from non-infected children, as well as active tuberculosis (ATB) from latent MTB infection (LTBI).

Methods: In this prospective study, we enrolled children (0-17 years of age) suspected of MTB infection due to previous contact with TB or presence of symptoms suggestive of TB. All children from the study group underwent TST and urine samples collection, and the majority also had an IGRA performed. According to the diagnosis, children were then divided into 4 groups: healthy contacts, LTBI, ATB and respiratory tract infection other than TB (RTI). We also enrolled a group of healthy patients with a population risk of MTB infection (control group) in whom only urine samples were collected.

Results: We enrolled a total number of 116 children aged 4 months–17 years: 17 (14.5%) with ATB, 15 (13%) with LTBI, 29 (25%) healthy contacts, 3 (2.5%) with RTI, and 52 (45%) to the control group. Median IP-10 levels were: 35.11 pg/ml in ATB, 57.26 pg/ml in LTBI, 15.6 pg/ml in healthy contact, 14.7 pg/ml in RTI and 34.1 pg/ml in the control group.
IP-10 level in urine correlated weakly with body mass (r = 0.31, p < 0.05) and TST result (r = 0.27, p < 0.05). We found no correlation between IP-10 level and age, height, body mass index (BMI), presence of BCG scar and IGRA result. The difference in IP-10 level in children under and ≥ 5 years of age was not statistically significant (p = 0.78).

There was a significant difference in IP-10 levels between MTB-infected children (ATB + LTBI group) and healthy contacts (p = 0.046), ATB and LTBI groups (p = 0.047), LTBI and control group (p = 0.045). The difference in IP-10 levels between ATB and RTI groups also proved statistically significant (p = 0.044). However, IP-10 results did not differ in LTBI and the healthy contact group (p = 0.42).

Conclusions: IP-10 level measurement in urine might be helpful in distinguishing children with ATB from RTI, LTBI and from healthy contacts. However, measuring IP-10 level in urine could not aid the differential diagnosis between healthy contacts and LTBI.

IP-10 level in urine is not age-dependent and thus could prove useful in children <5 years of age.

Reifications and proposals for action: The results of our study need to be taken with caution due to the relatively small sample size and low availability of IGRA results. Future research should concentrate on comparison of IP-10 levels with IGRA results in a larger population.

#78 - TIDAL EXHALED NITRIC OXIDE IN INFANTS IN THEIR FIRST MONTH OF LIFE - A LONGITUDINAL STUDY DURING NEONATAL LUNG DEVELOPMENT

Reim PS.1, Schmidt BJ.2, Joergenssen IM.2
1 Department of Clinical Medicine, University of Copenhagen - Copenhagen, Denmark
2 Department of Pediatrics, Nordsjaellands Hospital - Hilleroed, Denmark

Objective: In this study, the primary aim was to investigate levels of fractional exhaled nitric oxide (FeNO), measured online by tidal breathing (TB), in respiratory healthy infants during their first month of life, and to elucidate how various factors may affect these levels. Secondly we aimed to evaluate the TB-FeNO measurement method examining repeatability and success rate.

Methods: A total of 85 infants, admitted to the neonatal department of Nordsjaellands Hospital, Hilleroed, were enrolled in this prospective cohort study. Birth weight, gestational age at birth and the length of n-CPAP-treatment were sampled from the medical records of included infants. Infants who had congenital lung disease or who were treated with n-CPAP for more than 24 hours in total were excluded from the study. During the first month of life, each infant attended six to seven age-specific study visits depending on gestational age at birth. Three acceptable measurements of FeNO were obtained during tidal breathing at each study visit, and information on growth and general health was gathered.

Results: The mean level of FeNO ranged from 4.94 ppb to 8.66 ppb. Factors such as birth weight, gestational age and n-CPAP-treatment in the first 24 hours of life were proved not to have any statistically significant effect on FeNO levels.

Mean FeNO significantly increased with 2.69 [0.53; 4.85] (Δ FeNO) from first to last study visit. Among the investigated, potentially influential factors, the only factor found to affect Δ FeNO was FeNO at baseline (p-value < 0.001). Birth weight or gestational age did not affect Δ FeNO, and no significant interaction was found between these two factors. The success rate of TB-FeNO measurements ranged from 86.2% to 100%, increasing with days of age. Measurements presented with a mean variability of 7.12%.

Conclusion: In this neonatal study population, baseline FeNO affected the change in FeNO over time. We propose that the change in FeNO over time might reflect the stages of lung development in infants. Furthermore, we suggest that elevated levels of FeNO in the first period of life may reveal the risk of developing lung infections or atopic diseases in early childhood. Further studies in larger neonatal populations are needed to thoroughly investigate these hypotheses.

The reported values of FeNO are in good agreement with previously published values.

The TB-FeNO method was found to be simple and completely safe to perform, even in infants. The method was easily applicable in this age group yielding results with acceptable variability and a notably good success rate, which underlines the eligibility of TB-FeNO measurements as a future clinical tool in a neonatal setting.

#80 - ASTHMA AND BRONCHODILATOR USE IN PATIENTS WITH CYSTIC FIBROSIS

Levine H.1, Cohen-Cymberknob M.2, Klein N.1, Hoshen M.2, Massaffi H.1, Breuer O.2, Kerem E.1, Blau H.1
1 Pulmonary Institute, Schneider Children’s Medical Center - Petach-Tikva, Israel
2 Pulmonary Unit and CF Center, Hadassah-Hebrew University Medical Center - Jerusalem, Israel

Background: Asthma-like symptoms and bronchial responsiveness to bronchodilators in cystic fibrosis (CF) are associated with decreased and more rapid decline in FEV1.

Aims: To assess the prevalence of asthma and associated characteristics, as well as frequency of bronchodilator usage and its relationship to asthma in CF.

Methods: Patients with CF followed at the Schneider CF Center (n = 100) and Hadassah University Hospital (n = 77) were studied retrospectively.

Results: Among the 177 patients, 50% had >10% increase in FEV1 and 41% had >30% increase in MEF25-75% after bronchodilators, demonstrating reversible airways obstruction. No difference was found between pancreatic sufficient vs. insufficient patients or in those with asthma in 1st degree family members, high serum IgE levels or eosinophilia. There was also no change in airways reversibility in those with aspergillus or chronic pseudomonas infection. Seventy-one percent of patients with ABPA showed airway reversibility (p = 0.08). At Schneider, younger age correlated with reversible obstruction (p = 0.001). Seventy-two percent of patients with airway reversibility were treated with bronchodilators; however, 44% of all patients using bronchodilators did not have airway reversibility.

Conclusions: Reversible airway narrowing is a common finding in CF, more frequent at a younger age and in patients with ABPA. Interestingly, there was no correlation with markers of asthma and atopy or disease severity as expressed by pancreatic function. Bronchodilators are commonly prescribed in CF, even in those without reversibility of airway obstruction.

#132 - SUBJECTIVE GLOBAL NUTRITIONAL ASSESSMENT TOOL VS. WHO Z-SCORE TO PREDICT POSTOPERATIVE PULMONARY COMPLICATIONS IN CHILDREN UNDERGOING CARDIAC SURGERY

Reiner A.1, Requiron-Sy D., De Leon N.
1 Pediatric Pulmonology and Critical Care, Philippine Heart Center - Manila, Philippines

Background: During a major surgical procedure, metabolic needs rise to as much as twice those of basal requirements and not being able to meet these caloric demands due to malnutrition can lead to serious postoperative complications. Presently, there is no pediatric nutritional assessment tool that is used for preoperative risk stratification. We propose that a detailed nutritional assessment such as the Subjective Global Nutritional Assessment (SGNA) tool should be performed in pediatric patients to accurately identify those at risk of postoperative pulmonary complications.

Methods: Children aged one month to 18 years with congenital heart disease who underwent repair or palliative surgical treatment on a non-emergency basis were assessed nutritionally using the SGNA tool and the WHOZ score. This was performed one day prior to the procedure. Patients who...
had intra-operative complications excluded from the study. Meanwhile, those who had uneventful surgery were followed for up to 10 days postoperatively and those who developed atelectasis, pleural effusion, pneumothorax, pulmonary congestion, wheezing or pneumonia were identified. Results: A total of 130 children with congenital heart disease were assessed nutritionally using the SGNA tool and the WHO Z score. One hundred two children completed their respective surgical intervention without intraoperative problems. Forty percent were noted to be malnourished using the SGNA and 40% were malnourished using the WHO Z score. Meanwhile 37% were considered malnourished using the SGNA tool.Twenty seven out of 40% or 67.5% of those who were classified as malnourished by WHO Z score had pulmonary complications postoperatively. On an other hand almost all patients (37 out of 38) who were categorized as malnourished using the SGNA tool had pulmonary complications. These values translated into a sensitivity of 78.7%, a specificity of 98.2%, a positive predictive value of 97.4%, a negative predictive value of 84.4% and over all accuracy of 88.6% (p=0.006). These results were superior to those obtained with the WHO Z score which had a sensitivity of 57.4%, a specificity of 76.3%, a positive predictive value of 67.5%, a negative predictive value of 67.4% and over all accuracy of 66.8% (p=0.006).

Conclusion: When compared to the WHO Z score, the SGNA tool is a more reliable screening tool to predict postoperative pulmonary complications in pediatric patients undergoing cardiac surgery.

Key Words: Malnutrition, cardiac surgery, pulmonary complications

#41 - SMALL AIRWAYS TARGETING OF INHALED STEROIDS FOR SEVERE THERAPY RESISTANT ASTHMA IN CHILDREN USING SMART NEBULIZER TECHNOLOGY: A RETROSPECTIVE STUDY

Kloosterman SF., Tiddens HA., Overweel JL., de Jongste JC., Janssens HM. Pediatric Pulmonology, Erasmus Medical Center, Sophia Children’s Hospital - Rotterdam, Netherlands

Background: About 5% of all children with asthma have severe therapy resistant asthma (STRA) with considerable impact on daily life and decreased quality of life despite high doses of inhaled corticosteroids (ICS) and add-on controller therapy.

Small airways inflammation and obstruction has been related to asthma severity and therefore is of great interest in children with STRA. However, with current devices for delivery of inhaled drugs, the small airways are not effectively targeted.

The controlled-inhalation smart nebulizer Akita® Jet has highly efficient deposition in the small airways.

Aim: Retrospective 6-month follow-up of children with STRA treated with high dose ICS using the Akita® Jet.

Methods: Fourteen children aged 4-17 years with STRA used the Akita® Jet for high dose ICS (start dose either fluticasone 2mg bid or budesonide 1mg bid) and bronchodilators. All patients were frequently seen at the outpatient clinic. ICS were tapered down based on symptoms.

Primary endpoints: FEV1 and FEF75. Data regarding lung function, asthma symptoms, exercise tolerance, exacerbations and hospital admissions were collected retrospectively from patient charts.

Results: Three patients discontinued the treatment: 1 because of non-compliance, 1 because of no subjective improvement and 1 because of side-effects (weight gain and gingival inflammation). Eleven of 14 patients used the Akita® Jet 6 months or longer. Mean FEV1 improved significantly with 16% and 19% after 2 and 4 months respectively (p<0.05) and with 15% (NS) after 6 months in these 11 patients. Mean FEF75 improved significantly with 15%, 18% and 16% after 2, 4 and 6 months respectively (p<0.05). The children reported less asthma symptoms and increased exercise tolerance.

The total number of oral corticosteroid courses decreased from 22 in 6 months before start of the Akita® Jet to 3 in 6 months after start in this group of 11 patients. However, 3 children (27.3%) showed a deflection in length of ≥0.25 standard deviation score. Whenever possible, ICS were tapered down more drastically in these patients. Conclusion: Asthma symptoms and lung function improved substantially with high dose ICS with the Akita® Jet in children with STRA, although with a risk of serious side effects. Unfortunately, we are unable to clarify from this retrospective study whether the improvement was due to the high dose ICS, improved targeting of ICS to the small airways, or both.

#125 - STUDY OF THE PATTERN OF RESPIRATORY MORBIDITIES IN HIV INFECTED CHILDREN IN INDIA

Gupta S. Pediatrics, Lady Hardinge Medical College and associated Kalawati Saran Children’s Hospital - New Delhi, India

Objective: To study the pattern of respiratory morbidities in children with HIV/AIDS in India.

Method: A prospective observational study of 121 HIV infected children was conducted over 17 months (November 2011-March 2013) at Delhi. At each clinic visit (routine or symptom driven), they were assessed for any morbidities with special emphasis on respiratory problems by history, examination and relevant investigations. Throat swab, blood and sputum cultures were collected where indicated. These were supplemented with additional investigations such as bronchoscopy and CECT lung in those with persistent problems. All episodes of sickness were categorized on the basis of symptoms, signs and investigations into various clinical diagnoses.

Results: The commonest symptoms causing patients to seek care were respiratory (70%), followed by fever without a focus (60%) and ear discharge (33%). The incidence of respiratory morbidities was the highest (23.6 per 100 patient months), followed by dermatological (14.7 per 100 patient months) and diarrheal (13.3 per 100 patient months). Pneumonia (19.2 incidences per 100 patient months) was found to be the commonest respiratory morbidity in the patients followed by otitis media (17.2 per 100 patient months). Nearly one third (30%) of all patients had at least 1 episode of pneumonia in the study, while 5.2% had recurrent pneumonia. Incidences of persistent pneumonia were 1.3 per 100 patient months. There was a strong correlation between incidence of pneumonia and fall in CD4 counts. The correlation was found to be weak for other respiratory morbidities. In about a sixth of episodes of pneumonia (11/62), a definite microbiological diagnosis was possible (Mycobacterium tuberculosis in 2, pyogenic bacteria in 7, Candida in 2 and Pneumocystis jiroveci in 1). Over 90% of children with pneumonia were considered to have bacterial etiology, presumed viral etiology (2.9%), confirmed fungal pathogen (1.5%) and PJP (3%). Pneumonia by atypical organisms such as fungal and Pneumocystis jiroveci was found only in patients in CD4 category 4 of immunosuppression. TB was diagnosed in 6 (5.2%) patients. Pulmonary TB, TB lymphadenitis and disseminated TB were present in 2 patients each. Bronchiectasis was present in 12.3% of patients. PAH was present in 3.5% of patients.

Conclusion: The current study provides important information regarding the pattern of respiratory illness in HIV infected children in India. Infections by common organisms were found to be more frequent than atypical organisms in these patients. Isolation of a specific organism is very difficult in these patients. The strength of this study is its prospective nature involving a large number of patients.

#81 - PATIENT-VENTILATOR ASYNCHRONY OF LARYNGEAL ORIGIN DURING NASAL PRESSURE SUPPORT VENTILATION

Cantin D., Samson N., Djeddi DD., Praud JP. Pediatrics, University of Sherbrooke - Sherbrooke, Canada

Introduction: Nasal intermittent positive pressure ventilation is increasingly used in infants and children; however, patient-ventilator synchronization remains a very significant challenge and has spurred the attention of many researchers and clinicians in recent years. Patient-ventilator asynchrony occurs when there is a mismatch between the timing of the patient’s inspiration (and/or expiration) and that of the ventilator; a percentage of asynchronous breaths of at least 10% is considered a threat to the success of non-invasive ventilation (Thistle A, Intensive Care Med 2006).

Pediatric Pulmonology
Our research team is interested in specific patterns of patient-ventilator asynchrony during non-invasive ventilation, which are due to the interposition of the laryngeal valve between the ventilator and the lungs. Our studies in newborn lambs have repeatedly showed that the larynx can actively close and oppose gas insufflations by the ventilator during nasal pressure support ventilation (nPSV). Surprisingly, despite its potential importance, such patient-ventilator asynchrony of laryngeal origin is only beginning to receive clinical attention (Oppersma E, Crit Care, 2013; Navales P, Curr Opin Crit Care 2015).

Objective: The present study aimed i) to test the hypothesis that patient-ventilator asynchrony of laryngeal origin can present under various forms in nPSV and ii) to assess its prevalence in newborn lambs.

Methods: Nine lambs were studied at 4-5 days of life during a six-hour polysomnographic recording (154 cmH2O) while supported by nPSV. Recorded variables included EEG and eye movements, ECG, nasal mask pressure, thoraco-abdominal respiratory inductance plethysmography and electrical activity of the thyroarytenoid muscle (TA EMG, a laryngeal constrictor muscle). Data analysis was performed on one-minute epochs at 20-min intervals.

Results: Overall, in 10% (± 21 SD) of ventilatory cycles, active laryngeal closure was responsible for slowing down inspiratory flow during a portion of ventilator insufflation; this insufflation resumed unimpeded after the reopening of the larynx until normal cycling to expiration. Furthermore, in 65% (± 37 SD) of breaths, the strength and suddenness of this active laryngeal closure forced the ventilator to cycle prematurely to expiration. Finally, bursts of auto-triggering were occasionally observed, when prolonged TA EMG was present for a few seconds.

Conclusion: Our results confirm an unexpectedly high prevalence of patient-ventilator asynchrony of laryngeal origin during nPSV in healthy lambs. In addition, by clarifying for the first time the various forms that can be taken by this asynchrony, our results allow to recognize and ultimately prevent its occurrence, hence promoting the success of non-invasive ventilation.

Supported by the Canadian Institutes of Health Research, the Canada Research Chair in Neonatal Respiratory Physiology and the Université de Sherbrooke.

IV. POSTERS

1. BRONCHIAL ASThma AND OTHER CHRONIC OBSTRUCTIVE PULMONARY DISEASES

#9 - CORRELATION OF SERUM CYTOKINES IL-17E, IL-17F, IL-22 AND IL-23 LEVELS WITH SEVERITY OF ASThma IN CHILDREN (3-18 YEARS) IN A PHILIPPINE GENERAL HOSPITAL

Escano-Dumbrique J, Tuazon A.
Pediciatrics, Philippine General Hospital - Manila, Philippines

Background: Asthma is a chronic inflammatory disorder of the airways. The recently discovered Th17 cells have been recognized for their role in the pathogenesis of asthma. These cells produce IL-17A, IL-17E, IL-17F and IL-22, which are pro-inflammatory in nature. Th17 activity is regulated by IL-23. These cytokines are recognized as possible markers of disease severity in asthma.

Objective: To determine the correlation of the level of serum cytokines IL-17E, IL-17F, IL-22 and IL-23 with the severity of asthma.

Study Design: cross-sectional study.

Methods: Forty children with asthma (mean age 11.5 ± 3.8 years) were recruited and grouped based on severity of the disease (non-severe group n = 20 for intermittent and mild persistent asthma, severe group n = 20 for moderate and severe persistent asthma). Thirty healthy non-asthmatic children (mean age 9.2 ± 3.6 years) were recruited as controls. Blood serum was obtained and levels of IL-17E, IL-17F, IL-22 and IL-23 were determined using ELISA assay. Mann-Whitney test and Spearman Correlation were used in data analysis.

Results: The study showed no significant differences in serum cytokines between the asthmatic and non-asthmatic groups. No significant differences were likewise noted in the serum cytokines between the non-severe and severe asthmatic groups. A significant inverse correlation was found between levels of IL-17F and asthma severity. This was an interesting finding in this study, since most of the previous studies showed a positive correlation of this cytokine with asthma. Lower IL-17F levels were also observed to be associated with medium-dose inhaled corticosteroid use among severe asthmatics. Only IL-22 levels were found to be positively correlated with asthma severity, although the said correlation was only marginally significant (p-value < 0.10). This study also demonstrated significant positive inter-correlations between IL-23, IL-17F and IL-22 levels.

Conclusion: Our findings suggest that IL-22 could possibly be used as a marker of severe asthma. Further studies are needed to investigate the role of IL-17F among asthmatic Filipino children.

Recommendations: For future studies, it is recommended to conduct investigations in a larger population in order to determine standard values of IL-17E, IL-17F, IL-22 and IL-23 among Filipino children. It seems that Filipino children have lower concentrations of IL-17 cytokines compared to other studies. Future research on the association of asthma genotypes with cytokine expression could further elucidate the pathogenesis of the disease.
S54 Abstract

vitamin D levels and asthma severity as well as no association found between the prevalence of vitamin D insufficiency and/or deficiency and asthma and its severity. The overall prevalence of hypovitaminosis D (61.4%) is higher than the prevalence in comparable East Asia and Pacific populations such as Mongolia and China. Serum IL-17A levels were undetectable in 96% of the study population.

Reflections: Long-term vitamin D status determination is suggested to sufficiently correlate with geographical latitude and ultraviolet B radiation exposure of the study population. A genetic study on vitamin D receptors and enzymes for vitamin D metabolism may be performed to explain differences in response. Other methods of cytokine analysis with higher sensitivities in detecting IL-17A levels in children may be used.

#30 - SEROLOGICAL MARKERS OF CHLAMYDOPHILA PNEUMONIAE CHRONIC INFECTION ARE ASSOCIATED WITH POOR ASTHMA CONTROL IN CHILDREN

Vityutneva A.1, Alekseeva O.2, Ilyenkova N.2, Tereshchenko S.1
1 Department of child’s physical health, Scientific Research Institute of Medical Problems of the North - Krasnoyarsk, Russia
2 Department of Pediatrics, Krasnoyarsk State Medical University - Krasnoyarsk, Russia

Chlamydia pneumoniae (CP) infection is a frequent cause of acute respiratory infections, particularly in older children and young adults. CP infection may promote the exacerbation of asthmatic symptoms but also may evolve into a chronic, asymptomatic phase, which some researchers have linked with asthma pathogenesis [1,2]. The potential role of CP in asthma has been divided into three different aspects: asthma initiation, asthma prolongation, and asthma exacerbation [3]. Data regarding the role of CP in childhood asthma control are limited.

Methods: Specific IgA, IgM, and IgG antibodies to Chlamydia pneumoniae were detected with Savyon Diagnostics ELISA (enzyme-linked immunosorbent assay; Savyon Diagnostics, Ltd., Ashdod, Israel) kits in 20 uncontrolled asthmatic, 20 controlled asthmatic and 22 healthy children. All children were aged 6-14 years and had no signs of respiratory infections. Asthma control was assessed according to GINA-2012 criteria. IgG and IgA levels were determined with a semiquantitative test and IgM with a qualitative test. The two-tailed Fisher’s exact test was used to determine differences in prevalences.

Results: Prevalence of serological markers of CP infection according to asthma control is shown in Table 1.

<table>
<thead>
<tr>
<th>Specific antibodies</th>
<th>Uncontrolled asthma n = 20, abs (prop) 1</th>
<th>Controlled asthma n = 20, abs (prop) 2</th>
<th>Controlled asthma n = 22, abs (prop) 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>13 (.65)</td>
<td>5 (.25)</td>
<td>0</td>
<td>p1-2 = 0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p1-3 = 0.001</td>
</tr>
<tr>
<td>IgA</td>
<td>5 (.25)</td>
<td>0</td>
<td>0</td>
<td>p1-2 = 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p1-3 = 0.05</td>
</tr>
<tr>
<td>IgC</td>
<td>8 (.40)</td>
<td>7 (.35)</td>
<td>0</td>
<td>p1-2 = 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p1-3 = 0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p2-3 = 0.5</td>
</tr>
</tbody>
</table>

Specific IgA, a good serological marker of chronic CP infection, was only found in children with poor asthma control (p = 0.05). Specific IgM was only detected in the asthmatic group and twice more often in uncontrolled asthmatic children (p = 0.02). There were no statistical differences in specific IgG between the assigned groups.

Conclusion: The higher prevalence of specific IgA and IgM antibodies to CP in uncontrolled asthmatic children may indicate a possible pathophysiological role of this asymptomatic chronic infection. The need for specific antimicrobial treatment in infected asthmatic children with high levels of anti-CP IgA and/or IgM antibodies should be assessed in further studies.

Reference:

#37 - QUALITATIVE AND QUANTITATIVE CHANGES IN AIRWAY WALL EPITHELIAL BASEMENT MEMBRANE IN YOUNG AND ADULT RATS AFTER INDUCTION OF BRONCHIAL ASTHMA

Simunkova P1, Uhlik J.2, Vajner L.2, Pohunek P.1
1 Department of Pediatrics, 2nd Faculty of Medicine Charles University in Prague - Prague, Czech Republic
2 Department of Histology and Embryology, 2nd Faculty of Medicine Charles University in Prague - Prague, Czech Republic

Bronchial asthma is a chronic disease, characterized by inflammation of intrapulmonary airways. The histological correlate for asthma is known as airway remodeling. Features of remodeling have been observed in both adult and pediatric patients. However, their rate of development seems to differ among various age groups. Some findings have even been described in very young children at risk of developing asthma. The remodeling usually consists of changes within the bronchial epithelium including hyperplasia of its goblet cells, thickening of the basement membrane, differentiation and activation of myofibroblasts, proliferation of smooth muscle in airway walls, growth of submucosal glands, deposition of extracellular proteins and changes in vascularization. In this study, we focused on changes of the basement membrane (BM). Brown Norway rats were used, which are especially responsive to sensitization by various allergens and tend to develop a state which highly resembles, both clinically and morphologically, that of human bronchial asthma when stimulated with an appropriate allergen challenge. We compared BM membranes of young and adult rats to confirm possible differences in remodeling related to age. Young (4 weeks) and adult rats were sensitized by repeated intraperitoneal injections of ovalbumin (OA). During the following 2 weeks, the rats regularly inhaled the aerosolized OA in low concentration. Two control groups of each age were included simultaneously, the first of which was injected and inhaled by saline (treated controls) while the second group was untreated. At the end of the experiment, the animals were sacrificed and their lungs were processed for light microscopy. Reticular fibers of the BM lamina reticularis were visualized by Golgi silver impregnation. Two structural proteins of the basal lamina – laminin and collagen type IV – were detected by immunohistochesmy. The adult group of animals revealed a positive reaction to stimulation with ovalbumin in all portions of the observed BM. The situation in young rats was different; there was no significant disparity in thickness of laminin ply, although the lamina reticularis and collagen IV-positive layer were thicker in the experimental group. Together with results from our previous study (1), we suggest that adult individuals tend to react more with the epithelial component, while young individuals have more pronounced changes in outer airway walls. The study was supported by the grant IGA MH CR NT 11444 and by the Ministry of Health, Czech Republic (conceptual development of research organization, University Hospital Motol, Prague, Czech Republic, grant number 6601).

References:
#40 - 10-YEAR FOLLOW-UP OF ASTHMA MEDICATION CONSUMPTION AFTER RSV BRONCHIOLITIS

Golan Tripto 1, Goldbart DA 1, Shafat T 2, Tal A 1
1 Pediatrics, Soroka medical center, Faculty of Health Sciences, Ben-Gurion University of The Negev - Beer Sheva, Israel
2 Clinical Research Center, Soroka medical center, Faculty of Health Sciences, Ben-Gurion University of The Negev - Beer Sheva, Israel

**Background:** Acute bronchiolitis is a major cause of morbidity and mortality in infancy and early childhood worldwide. Respiratory Syncytial Virus (RSV) is the leading pathogen causing acute bronchiolitis with significant global disease burden. Acute bronchiolitis due to RSV is known to be associated with recurrent wheezing and asthma during early childhood.

**Objective:** To assess asthma-related morbidity (asthma medication usage and increased health care utilization) in infants who experienced RSV bronchiolitis in the first year of life, during a 10-year follow-up.

**Methods:** A retrospective study conducted at the Soroka University Medical Center during the years 2000 to 2010 which included infants that were discharged from the pediatric wards with a diagnosis of RSV bronchiolitis (positive nasal wash on ELISA). The control group included infants randomly selected from the computerized database of “Clalit Health Services”, that had no previous admissions and matched for age, gender and primary care physician. The primary outcome was defined as the use of asthma medications (relievers, controllers and systemic corticosteroids) per year, up to 10 years of age. Furthermore, emergency room visits, hospitalization and total health care cost per year were recorded during follow-up.

**Results:** 448 subjects were included: 231 in the RSV group and 217 in the control group. The post-RSV group consumed significantly more asthma medications per year, until the 10th year of life. During a 10-year follow-up, there were significantly more hospitalizations in the post-RSV group (75.5% vs. 25.5%, P<0.001), due to asthma (12.6% vs. 1.4% p<0.001) and pneumonia (31.2% vs. 4.6% p<0.001) in comparison to the control group. The estimated cost of treatment in the post-RSV group was significantly higher each year, until the 7th year of follow-up. Multivariate analysis showed an odds ratio of 3 - 4.8 of consuming asthma medications among post-RSV group up to 8 years of age, adjusted to gender and gestational age (p<0.05).

**Conclusion:** Infants with RSV bronchiolitis have increased health care utilization (asthma medication use and respiratory-related hospitalizations) in a 10-year follow-up, when compared to a control group.

---

#54 - EFFICACY AND SAFETY ASSESSMENT OF ONCE-DAILY TIOTROPIUM RESPIMAT® ADD-ON TO INHALED CORTICO-STEROIDS IN ADOLESCENT PATIENTS WITH SYMPTOMATIC ASTHMA

Hamelmann E 1, Boner A 2, Bernstein J 3, Moroni-Zentgraf P 4, Engel M 5, Avis M 5, Unseld A 6, Vandewalker 7
1 Klinik für Kinder- und Jugendmedizin der Ruhr-Universität, Bochum, Germany
2 Pediatric Department, University of Verona, Verona, Italy
3 University of Cincinnati Medical Sciences Building, Cincinnati, Ohio, USA
4 TA Respiratory Diseases, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany
5 Boehringer Ingelheim bv, Alkmaar, Netherlands
6 Global Biometrics and Clinical Applications, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany
7 Clinical Research of the Ozarks, Columbia, Missouri, USA

**Background:** Tiotropium Respimat® (tioR) add-on to inhaled corticosteroids (ICS) improves lung function in adult patients (pts). We examine the efficacy and safety of tioR add-on to at least ICS in adolescent pts with moderate asthma.

**Methods:** Phase III, 48-week, randomised, double-blind, placebo-controlled, parallel-group trial (NCT01257230) in asthmatic adolescents (12-17 years). Inclusion criteria: ≥3-month asthma history; pre-bronchodilator FEV1 ≥60% and <90% of predicted; screening 7-question Asthma Control Questionnaire (ACQ-7) score of ≥1.5. Pts randomised to once-daily tioR 5 µg, tioR 2.5 µg or placebo Respimat® (pboR) add-on to ICS (12-14 years: 200-400 µg budesonide or equivalent; >14 years: 400-800 µg). Primary end point at Week 24: peak FEV1(0-3h). Further efficacy end points: trough FEV1 and PEFam/pm (Weeks 24, 48); ACQ-7 responder rate (Week 24). Responders defined by a reduction in ACQ-7 score of ≥0.5.

**Results:** 397 pts treated. Mean age: 14.3 years (range 11-17 years); 65% male; mean BMI: 21.3 kg/m2; mean age of asthma onset: 6.5 years (range 0-17); exposure to second-hand smoke: 11.1%; mean FEV1% predicted at baseline: 82.8. TioR 5 µg significantly improved key lung function end points vs. pboR at 24 and 48 weeks; tioR 2.5 µg significantly improved the following end points: peak FEV1(0-3h) at 24 and 48 weeks; trough FEV1 at 48 weeks (Table). More pts receiving tioR showed improvement in symptom control at Week 24 vs. pboR; incidence of pts experiencing worsening of symptom control (≥0.5 increase in ACQ-7 score) following treatment with tioR was low. AEs comparable across treatment groups; small number of drug-related AEs (tioR 5 µg = 4, tioR 2.5 µg = 1, pboR = 1); no fatal AEs reported.

**Conclusion:** TioR add-on to ICS significantly improves lung function, provides a numerical increase in asthma control, has a safety profile comparable with pboR and is well tolerated in adolescent pts with symptomatic asthma.

**Study impact:** Data support long-term efficacy and safety of tioR 5 µg add-on to ICS in adolescents with moderate symptomatic asthma.
Abstract

**#60 - NO CORRELATION BETWEEN CHILDHOOD ASTHMA AND LEPTIN AND LEPTIN RECEPTOR SERUM LEVELS**

**Naśytna B**, S. Sobkowiak P.2, Schoneich N.2, Bętchorowicz A.2, Szczepankiewicz A.2,1

1 Laboratory of Molecular and Cell Biology, Department of Pulmonology, Pediatric Allergy and Clinical Immunology, Poznan University of Medical Sciences - Poznan, Poland
2 Department of Pulmonology, Pediatric Allergy and Clinical Immunology, Poznan University of Medical Sciences - Poznan, Poland

**Introduction:** Epidemiological data show a higher prevalence of asthma in obese adults and children compared to those of normal weight. Leptin, a hormone produced mainly by adipocytes, regulates food intake and energy balance. Recent research shows that it may also induce inflammation of the airways in the course of asthma. Leptin belongs to the long-chain helical cytokine family and is encoded by a gene on chromosome 7 (7q31.3). Leptin receptors, produced by a gene located on chromosome 1 (1p31), are distributed almost universally throughout the body and are especially present in bronchial and alveolar epithelial cells. By binding to its receptor, leptin changes the balance between Th1 and Th2 cytokines, resulting in a pro-inflammatory reaction. The aim of this study was to investigate whether serum levels of leptin and its receptor are significantly increased in children with diagnosed asthma.

**Methods:** We recruited 26 children with asthma and 10 control subjects. Diagnosis was made at least six months prior to inclusion in the study, based on clinical asthma symptoms and spirometry. Protein serum concentrations were measured using Leptin Human ELISA and Leptin Receptor Human ELISA kits (BioVender), according to manufacturer instructions.

**Results:** We have found no correlation between leptin (p = 0.49) and leptin receptor (p = 0.80) serum concentrations and asthma.

**Conclusions:** Our results suggest that there is no correlation between leptin and leptin receptor serum levels and asthma. This may be due to the limited sample size of the analyzed population. As this is only preliminary research, we hope to obtain significant results on a larger study group.

The study was supported by the Polish National Science Centre, grant no. 2011/01/D/NZ5/02771.

**#68 - THE CONNECTION BETWEEN EXHALED NITROGEN MONOXIDE LEVEL AND SPIROMETRY FUNCTION PARAMETERS IN CHILDREN TREATED FOR BRONCHIAL ASTHMA**

**Papp G.**

Paediatrics Department, Szigetvar Hospital - Szigetvar, Hungary

**Purpose:** Measuring exhaled nitrogen monoxide in case of respiratory, mainly eosinophilic, inflammation is an accepted non-invasive method. Based on data available in the literature, it can be used effectively in diagnosing bronchial asthma and controlled conditions and for keeping track of the drug response. The aim of this study was to investigate the case of the group showing higher FeNo values, spirometry function parameters proved to be significantly lower. FEV1% / FVC 32.34 (No 194) vs. 92.990 std: 16.927 (No:102) p = 0.0017/ FEV1/FVC /94.366 std: 5.98 (No:194) vs. 90.304 std:8.52 (No: 102) p = 0.0001/ Mef 50% / 101.53 std:25.38 (No:194) vs. 89.00 std 24.01 (No:102) p:0.0002/. The FEV1/FVC, / (r) = -0.2271, r squared = 0.05156 p < 0.0001/ FEV1% /
(Tr) = -0.1164 r squared = 0.01356 p = 0.0453/ MEF50% (Tr) = -0.1643 r squared = 0.02269 p = 0.0047 /and in case of exhaled NO slight, but significant inverse commensuration could be seen.

**Conclusion:** According to our research, the uplifted exhaled NO comes with lower spirometry function parameters. Based on our findings, we conclude that the higher level of respiratory inflammation is in the background of the decrease in age-specific spirometric parameters. Further studies are needed to be carried out when measuring respiratory inflammation to ascertain what additional advantages can be obtained while treating asthma.

**#69 - DYSANAPISIS AND EXPIRATORY FLOW LIMITATION DURING EXERCISE IN CHILDREN & ADOLESCENTS**

**Pianosi PT.**

Pediatric & Adolescent Medicine, Mayo Clinic - Rochester, MN, USA

**Introduction:** There are at least 2 reports of expiratory flow limitation (EFL) during heavy exercise in pre-pubertal children, suggesting this may be a normal phenomenon. A recent analysis of adults who demonstrated EFL at peak exercise characterized dysanapsis as a determinant of EFL. We reviewed >200 exercise tests employing tidal flow-volume loop analysis in children & adolescents in order to determine the role of dysanapsis as a determinant of EFL in a pediatric population.

**Methods:** Adolescents & children with a wide variety of diagnoses investigated for exertional dyspnea performed spirometry before undergoing maximal cycle ergometry testing with tidal flow-volume loop analysis. We computed the dysanapsis ratio (DR) for each subject as described by Mead (Dysanapsis in normal lungs. Am Rev Resp Dis 121.2; 1980: 339-342); estimating static elastic lung recoil pressure at 50% FVC from published normative values (Zapletal et al. Pulmonary elasticity in children & adolescents. J Appl Physiol 40.6; 1976: 953-61). DR = PEF50/FVC Pst (L) 50%. EFL was defined when the tidal expiratory flow-volume loop overlapped/exceeded the maximal expiratory flow-volume envelope over >10% of their tidal volume for >4 breaths.

**Results:** Of 200 exercise tests, patients with proven (by simultaneous laryngoscopy) exercise-induced laryngeal obstruction, or congenital heart disease were excluded. Our final sample consisted of 156 patients: (97 girls), mean ± SD: Ht 164 ± 14 cm, Wt 59 ± 16 kg; age 14.4 ± 2.8 (range 7-19) yrs; 43 of whom had asthma based on positive bronchoprovocation challenge or repeated demonstration of reversible obstruction on spirometry. FEV1 (94 ± 17 vs. 99 ± 16%pred) was similar in asthmatics and non-asthmatic patients (p = .075). DR was lower in patients with asthma than in those without: 0.0547 ± 0.021 vs. 0.0635 ± 0.016 (p = .015). Girls (regardless of diagnosis) had a higher DR than boys: 0.064 ± 0.017 vs. 0.057 ± 0.019 (p = .016) and were less likely to demonstrate EFL: 48% of girls vs. 66% of boys (x2, p = .027). Girls had lower FVC (3.75 ± 0.87 vs. 4.16 ± 1.44 L, p = .025) but similar FEV1, PEF50, and static elastic lung recoil pressure at 50% FVC, compared to boys. DR was lower in subjects with vs. without EFL (0.054 ± 0.016 vs. 0.068 ± 0.019, p<.00001), and there was an inverse correlation between DR vs. percentage of exercise tidal volume over which the expiratory flow-volume loop overlapped/exceeded the maximal expiratory flow-volume envelope (r = -0.62, p = .0005). In other words, greater degrees of EFL were associated with lower DR. The only spirometric parameter that distinguished these 2 groups was lower PEF50 in the group with EFL (4.00 ± 1.13 vs. 3.33 ± 1.27 L/sec, p = .0006).

**Conclusions:** Many children & adolescents who report exertional dyspnea exhibit EFL, particularly those with asthma, despite “normal” spirometry. Girls may have some protection from this phenomenon by virtue of larger conducting airways relative to (smaller) parenchymal size reflected in FVC.
#71 - EXHALED BREATH CONDENSATE: CAN THE MARKERS BE INDICATORS OF EPITHELIAL BARRIER DYSFUNCTION AND REMODELING IN PEDIATRIC ASTHMA?

Yüksel H.
Pediatric Allergy and Pulmonology, Celal Bayar University Medical Faculty - Manisa, Turkey

Background: Airway epithelium plays an important role as a physical barrier and in an allergic response; however, in asthma, the permeability is significantly increased leading to increased susceptibility to allergens and irritants. In this study, in order to demonstrate tissue damage and epithelial barrier integrity in children with atopic and non-atopic asthma, soluble e-cadherin and MMP-9 levels in condensed breathing air will be studied.

Methods: A total of 74 patients with asthma (35 atopic and 39 non-atopic) children were enrolled in this case-control study. Sociodemographic characteristics and asthma severity parameters during the last three-month period were recorded and pulmonary function tests were performed. The atopic asthma group consisted of patients with a positive allergen skin prick test with at least one proteolytic aeroallergen (house dust mites, yeast mixture and olive). E-cadherin and MMP-9 levels in Exhaled Breath Condensate (EBC) were studied by the ELISA method.

Results: The mean age of the 35 atopic and 39 non-atopic asthmatic children was determined to be 9.5 ± 2.9 and 9.7 ± 3.1, respectively. Atopic asthma exhibited significantly higher MMP-9 levels in their EBC samples than the non-atopic asthmatics (3.39 ± 7.3 pg/mL and 0.59 ± 0.27 pg/mL, respectively, p = 0.02). However, E-cadherin levels did not differ between atopic and non-atopic asthmatics (p = 0.97).

Conclusion: The higher MMP-9 levels in patients with atopic asthma show that proteolytic allergens cause more tissue damage, inflammatory cytokine release and remodeling. The absence of difference between the groups in terms of sE-cadherin levels suggests that atopy is not the primary factor for development of epithelial barrier dysfunction and asthma.

#76 - AIRWAY EPITHELIAL CELL IL-6 AND LEUKEMIA INHIBITORY FACTOR GENE EXPRESSION IS ASSOCIATED WITH ASTHMA SEVERITY AND/OR STEROID SENSITIVITY IN CHILDREN

Evano M.1, Lacoste A.1, Helbling JC.2, Moisan MP.2, Barat P.2, Corcuff JB.2
1 Université de Bordeaux (U1045), CHU de Bordeaux, Centre d’Investigation Clinique (CIC 1401), Université de Bordeaux - Bordeaux, France
2 Nutrition and Integrative Neurobiology, Université de Bordeaux - Bordeaux, France

Background: Many asthmatic patients continue to exhibit uncontrolled asthma, despite the administration of high-dose inhaled steroids (IS). Airway epithelial cells (AEC) have distinct activation profiles, which can influence IS response (Woodruff, 2007 #1).

Objectives: To compare the expression of specific genes possibly related to epithelial dysfunction and/or steroid sensitivity in cultured AEC in severe or moderate asthmatic and control school-age children.

Material & Methods: AEC were obtained by nasal brushings and primary cultures (2 passages). Cells were incubated in control conditions or in the presence of 10 ng/mL TNFα, 10-8M dexamethasone, or both. The rR-PCR-based expressions of FKBP51 (a regulator of steroid hormone receptor signaling), NFKB, IL-6, LIF (an IL-6 family neurotrophic cytokine), SERPIN B2 (a protease which inhibits plasminogen activation and promotes fibrin formation and deposition), and porin (a marker of mitochondrial mass) were determined. Gene expression was expressed as mean ± SD DCT, with 18S as the reference housekeeping gene.

Results: The study population was comprised of 6 control patients without asthma or lung disease (median age 11 yrs, min-max: 7-13), 8 with moderate asthma (11 yrs, 7-13), daily inhaled steroid (IC) dose =140 ± 167 μg fluticasone, and 4 patients with severe asthma (12 yrs, 7-14), daily IC dose = 500 μg. Only baseline expression of IL-6 and LIF was increased in severe asthma vs. moderate asthma or controls (IL-6: DCT 0.016 ± 0.007, 0.022 ± 0.005 and 0.052 ± 0.02, respectively; LIF: DCT: 0.107 ± 0.04, 0.055 ± 0.02, 0.163 ± 0.04, respectively). In severe asthma, TNFα further increased DCT (IL-6: DCT 0.028 ± 0.01, 0.042 ± 0.007, 0.070 ± 0.03, respectively; LIF DCT: 0.103 ± 0.05, 0.09 ± 0.03, 0.21 ± 0.06, which was decreased in the presence of dexamethasone (IL-6: DCT 0.012 ± 0.005, 0.010 ± 0.003, 0.046 ± 0.04, respectively; LIF: DCT 0.08 ± 0.02, 0.06 ± 0.02, 0.12 ± 0.04). Baseline expression of FKBP51 or its increase in the presence of Dex was not correlated to disease severity and higher IS use.

Conclusion: IL-6 and IL-6 expression in epithelial cells may represent markers of cell dysfunction/response to corticosteroid treatment in severe asthma in children.


#103 - IMMUNOHISTOPATHOLOGIC FEATURES OF BRONCHIAL ASTHMA IN CHILDREN WITH CONCOMITANT RESPIRATORY INFECTIONS

Bulaekov V., Balabolkin I.
Scientific Center for Children’s Health, Institute of Pediatrics - Moscow, Russia

Objective: To study features of inflammation of the respiratory tract and immune status in children with bronchial asthma and respiratory infections.

Methods: A total of 400 patients with bronchial asthma aged 6 months to 18 years were included for virological, immunological and histological study.

Results: Persistence of high respiratory virus antigen load was revealed in the nasopharynx of children with bronchial asthma and frequent respiratory infections. A significant correlation was found between the severity of bronchial obstruction and the frequency of virus-induced asthma exacerbations (p<0.01). Analysis of induced sputum and bronchoalveolar fluid revealed increased eosinocyte and neutrophil content. Histological study of bronchial mucosa and morphological characteristics of bronchial allergic inflammation showed bronchial epithelial shedding, infiltration of the submucosa by eosinocytes and lymphocytes and bronchial basement membrane thickening, which were most expressed in children with severe bronchial asthma. A close significant correlation was revealed between the levels of exhaled nitric oxide (NOexh) and eosinocyte count in induced sputum and bronchoalveolar fluid, as well as between basement membrane thickness and degree of lymphocyte infiltration of the bronchial mucosa (p < 0.05). In addition, IL-10, IL-12, and IFN-gamma levels were decreased while those of IL-4, IL-5, IL-6, IL-8, IL-13 and TNF-alpha were increased. This was accompanied by a rise in serum eotaxin, E-selectin, ICAM-1 and RANTES (p<0.01). The above changes were most expressed in children with severe bronchial asthma and also during acute exacerbation periods of the illness.

Conclusion: The findings of the present study testify to the anomalies on immunoregulation in patients with bronchial asthma and persistent respiratory viral infection. These anomalies lead to an aggravation of bronchial inflammation, hence warranting the search of new approaches to treatment, including immunotherapy.

#105 - ATYPICAL INFECTION IN CHILDREN OF ATOPIC BRONCHIAL ASThma

Bulaekov V., Balabolkin I., Zubkova I., Korolkova E.
Scientific Center for Children’s Health, Institute of Pediatrics - Moscow, Russia

Background: Chlamydophila pneumoniae and Mycoplasma pneumoniae are common pathogens causing acute illness in both the upper and lower airways. There is increasing evidence that infection with atypical pathogens may play an important role in the induction of asthma symptoms in the context of chronic persistent asthma or asthma exacerbations.

Pediatric Pulmonology
S58 Abstract

Purpose: The aim of our study was to examine the prevalence and role of atypical infection in children with atopic bronchial asthma. Methods: 217 children from the age of 3 to 15 years were studied: 157 with atopic asthma and 60 children without any signs of respiratory problems (control group). IgG, IgA, IgM antibodies directed against Chlamydiaeae (Chl) and Mycoplasma pneumoniae (Mpn) were measured in blood samples by means of enzymoimmunoassay.

Results: Prevalence of antibodies to Chl and Mpn in children with atopic asthma was 27% and 33% respectively comparatively to 25% and 30% respectively in the control group. As a whole, about half of the children surveyed in both groups were positive, testifying to the wide prevalence of Chl-Mpn infections among children. However, in the control group, mainly IgG antibodies were found, while IgA antibodies were much rarer and there were no IgM antibodies either to Chl or to Mpn (p<0.001). Of 80 positive children with asthma (51% of all patients with BA), 29 children displayed antibodies to Chl, 38 to Mpn, and 13 children had antibodies against both pathogens. Results in 65 (81%) of the 80 positive children with asthma allowed to confirm a current infection: 36 children (56%) with acute infection including 12 children with Chl, 19 with Mpn and 5 with both Chl and Mpn; and 29 (44%) with chronic infection, including 10 children with Chl, 11 with Mpn and 7 with both Chl and Mpn. In 15 (19%) patients, the infection appeared to be transmitted earlier. In children with atopic asthma and positive results for Chlamydiaeae and Mycoplasma pneumoniae infection, azithromycin treatment led to a reduction in symptoms (p = 0.01) and a decrease in levels of specific antibodies (p < 0.05).

Conclusions: The results of the study indicate a high prevalence of infection with atypical pathogens among children. However, in bronchial asthma, antibodies to several pathogens were detected significantly more often, and the infection presented as a chronic persistent form along with a tendency for exacerbations. Macrolide antibiotics are the main drugs for treatment.

#106 - STUDY OF THE SMALL AIRWAYS TO ASSESS ASTHMA CONTROL IN ASTHMATIC CHILDREN WITH NORMAL SPIROMETRY

Sardon O.1, Azaledegui G.1, Korta J.1, Corcuera P.1, Aldasoro A.1, Mintegui FJ.1, Emparanza JJ.2, Pérez-Yarza EG.3
1 Division of Pediatric Respiratory Medicine. Department of Pediatrics, Donostia University Hospital. University of the Basque Country (UPV/EHU). - San Sebastián, Spain
2 Epidemiology Unit (CIBER-ESP), Donostia University Hospital. - San Sebastián, Spain
3 Division of Pediatric Respiratory Medicine. Department of Pediatrics. Biomedical Research Centre Network for Respiratory Diseases (CIBERES), Donostia University Hospital. University of the Basque Country (UPV/EHU). - San Sebastián, Spain

Objective: To study the degree of agreement between clinical symptoms and small airways which were measured using airways resistance assessed by impulse oscillometry (IOS) and alveolar nitric oxide (CANO), in asthmatic children.

Methods: A cross-sectional study with prospective data collection was performed in children aged between 6-15 years old diagnosed with persistent asthma (GINA 2014) with FEV1 >80% at the time of inclusion. A forced spirometry, a bronchodilator test and the determination of R5-R20 (difference in resistance of the respiratory system at 5 Hz and resistance at 20 Hz) (MasterLab V5.3; Viasys, Wuerzberg, Germany) by IOS were performed in all children. Exhaled NO at multiple flow rates (30, 150 and 250 ml/s) was carried out with a CLD88sp analyzer. CANO was calculated according to the two-compartment model and an Asthma Control Questionnaire Test (ACT) was completed. Qualitative variables were sex, personal atopy, diagnosis and treatment. Quantitative variables were age, weight, height, CANO, ACT, FEV1, FVC, FEV1/FVC, FEF25-75, R5-R20. The association among R5-R20, CANO and ACT was studied using Spearman’s rho. Cohen’s kappa coefficient (Kc) was used to assess the degree of agreement for asthma control, with categorization of the variables according to normal published values among CANO, ACT and R5-R20.

Results: 30 subjects, distributed into group 1 (poor control, n = 9) and group 2 (good control, n = 21) were studied. Mean age was (mean ± SD) 11.1 ± 2.6 and 10.5 ± 2.7 years respectively. R5-R20 (mean ± SD) (kPa/L/s) was 0.11 ± 0.04 in group 1 and 0.13 ± 0.02 in group 2. CANO (median and range) (ppb) was 1.7 (0.3-5.7) in group 1 and 0.9 (0.1-15) in group 2. There was no association between R5-R20, CANO and ACT. No agreement was found to establish the degree of asthma control among the studied variables.

Conclusion: There was no agreement among the three measurement instruments analyzed to assess the degree of asthma control (ACT, R5-R20 and CANO). In our sample, no additional information was provided to assess asthma control by R5-R20 and CANO.

#112 - BRONCHODILATOR RESPONSE TO SALBUTAMOL IN PRESCHOOL INTERRUPTENT AND MILD PERSISTENT ASTHMATICS IS SIMILAR BUT MODIFIED BY ALLERGIC SENSITIZATION

Durlak W., Cichocka-Jarosz E., Jedynak-Wąsowicz U., Lis G. Department of Pediatrics, Chair of Pediatrics, Jagiellonian University Medical College - Krakow, Poland

Introduction: Intermittent and mild persistent asthma are defined by patterns of symptoms. The aim of this study was to compare bronchodilator response to salbutamol in preschool children with mild persistent and intermittent asthma using respiratory resistance measurement with the interrupter technique (Rint).

Material and Methods: Expiratory Rint was measured in groups of preschool children with intermittent asthma (n = 16; age = 4.3 ± 0.9 years; 50% boys), mild persistent asthma (n = 21; age = 5 ± 1.0; 76% boys) and healthy controls (n = 22; age = 4.5 ± 0.8; 41% boys) before and after salbutamol (400 ug with pMDI and spacer) inhalation. Measurements were performed with the Lung Test System (MES, Poland). Bronchodilator response (BDR) was expressed by Rint change as percentage of predicted value. The predicted values were estimated by the equations according to Merkus et al.(1). Allergic sensitization was assessed with skin prick tests (SPT) using a standard set of extracts.

Results: There were no significant differences in BDR between children with mild persistent and intermittent asthma (27 ± 23% vs. 26 ± 40%; p = 0.87). BDR was higher in intermittent asthmatics (26 ± 40% vs. 6 ± 19% p = 0.05) and mild persistent asthmatics (27 ± 23% vs. 6 ± 19% p < 0.05) when compared with healthy controls. Asthmatic children sensitized against dust mites had higher BDR than children with no sensitization (37 ± 31% vs. 16 ± 28%; p <0.05). No difference in BDR between asthmatics with and without outdoor allergen sensitization was observed.

Conclusion: BDR assessed with respiratory resistance measurement was higher in asthmatics than in healthy children. However, BDR between preschool children with intermittent and mild persistent asthma did not differ but was modified by allergic sensitization against house dust mite allergens.

Reflection: These results need to be confirmed on a larger group of patients including longitudinal assessment.


#122 - ADD-ON USE OF MAGNESIUM SULFATE IN CHILDREN WITH BRONCHIOLITIS

Gupta S. Pediatrics, Lady Harding Medical College - New Delhi, India

Objectives: To study the efficacy of intravenous Magnesium Sulfate as add-on therapy in moderate to severe bronchiolitis.
Methods: Patients presenting with 1st or 2nd episode of moderate to severe acute bronchiolitis who did not improve with conventional treatment (oxygen, IV fluids, epinephrine nebulisation) were included in the study. Intravenous Magnesium Sulfate was provided as add-on therapy to children in the intervention arm compared to normal saline given as placebo in the control arm. Composite Scores (sum of RDAI and YALE Scores) of the 2 groups was compared at enrolment, 3, 6, 12, 24 and 48 hours. Proportions of children showing improvement were compared with Z-statistics. Kaplan Meier statistics for the time to improvement was performed. Failure was defined as individuals showing an upward shift in severity of disease within 24 hours of enrolment or who left the hospital without completing the study or patients who did not receive the desired intervention as per the decision of the treating paediatrician during the study.

Sample Size: Seventy-eight (39 in each arm), planned to detect a change by 30% points in proportion of children with improved respiratory status at 24 hours of therapy in the intervention arm compared to controls in patients with moderate to severe bronchiolitis for a 2-sided \( \alpha = 0.5 \) and Power (1-\( \beta \)) of 90.

Results: The difference in proportion of patients showing improved respiratory status at 12 and 24 hours did not differ statistically between cases and controls (p = 0.881 and 0.731 respectively). Median time duration of oxygen requirement, time taken to resume feeding, time taken to shift to a less severe category and duration of hospital stay also did not show significant difference between cases and controls. No significant difference was observed in the final outcome of patients in both groups (p = 0.138) in terms of success or failure of therapy.

Conclusions: This study concludes that addition of intravenous Magnesium sulfate to conventional therapy in moderate to severe bronchiolitis does not lead to significant overall clinical improvement.

#137 - ENDOTHELIAL DYSFUNCTION IN CHILDREN WITH BRONCHIAL ASThma

Polvakov V.1, Makieieva N.2
1 Pulmonology, Regional Children Clinical Hospital - Kharkiv, Ukraine
2 Department of Pediatrics #2, Kharkiv National Medical University - Kharkiv, Ukraine

Background and aim: Knowledge on the pathophysiology of exacerbations of bronchial asthma (BA) is still debated. Studying lung barrier function status in children with BA could help in our understanding of exacerbation mechanisms. The aim of this study was to evaluate the correlations between lung function indices and parameters defining the status of endothelial, alveolar epithelial and connective tissue lung barriers in children with bronchial asthma (BA) during exacerbation.

Methods: 130 children aged 1-17 years suffering from BA were examined, including patients with intermittent BA (1st group), mild persistent BA (2st group) and moderate-severe persistent BA (3rd group). All patients were in the exacerbation period of BA. Twenty-seven healthy children were included in a control group. Each patient underwent evaluation including spirometry, Doppler echocardiography with measurement of pulmonary artery pressure (PAP), impulse oscillometry, and status of endothelial (serum endothelin-1 (ET-1) level, serum nitrite (NO2-), serum nitrate (NO3-)) level, alveolar epithelial (transforming growth factor beta-1 (TGF-\( \beta 1 \)) and tumor necrosis factor alpha (TNF-\( \alpha \)) levels in exhaled breath condensate) and connective tissue (serum glycosaminoglycans (GaGs) level, serum GaG fractions, oxiproline and uronic acid levels in urine) lung barrier functions. Statistical analyses were performed with StatSoft Statistica Version 8 (Tulsa, OK). Multivariate regression modeling was performed to address the association between main lung function indices (forced expiratory volume in 1 second (FEV1), expiratory airway resistance (Rexp), PAP) and parameters of endothelial, alveolar epithelial and connective tissue lung barriers. The clinical studies from which materials were obtained for the current study were approved by the Medical Ethics Committee of the Kharkiv National Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants and their parents gave written informed consent.

Results: Using multivariate regression modeling, the significant correlates of FEV1 included age (p = 0.014), Rexp (p = 0.023), ET-1 (p = 0.008), NO2- (p = 0.019), TNF-\( \alpha \) (p = 0.038), GAGs (p = 0.006) and oxiproline (p = 0.022). The significant correlates of Rexp and PAP (p = 0.018), ET-1 (p = 0.031), TNF-\( \alpha \) (p = 0.044) and GAGs (p = 0.037) were determined. There were significant correlates between PAP and ET-1 (p = 0.007), NO3- (p = 0.011), GAGs (p = 0.038) and Rexp (p = 0.023).

Conclusions: Multivariate regression modeling data demonstrate the effect of lung barrier function disorders on the mechanisms of BA exacerbation development with special emphasis on endothelial dysfunction and connective tissue disorganization.

Pediatric Pulmonology
Purpose: Pentraxin 3 (PTX3), known as an acute-phase protein, increases in plasma during inflammation. We aimed to evaluate the usefulness of PTX3 as an inflammatory marker in lower respiratory infection and examine the correlation with previously known biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT).

Materials and methods: We selected the 117 patients admitted at Seoul Saint Mary’s Hospital with lower respiratory infection using the WHO criteria. We obtained history of fever duration and peak temperature before admission and maintained a record of hospital stay. Upon admission, WBC, erythrocyte sedimentation rate, CRP and multiplex respiratory virus polymerase chain reaction with nasal swab were performed.

Results: We found that there was no significant difference in the level of PTX-3 with any type of virus in comparison with those with no causative agent. PTX-3 showed significant correlation with peak temperature and duration of fever before admission and interleukin (IL)-6. PCT showed significant correlation with peak temperature and duration of fever before admission, and hospital stay. PCT also showed significant correlation with IL-6 and G-CSF. CRP showed significant correlation with duration of fever before admission, total WBC and neutrophils. PCT was significant in predicting hospital stay for 7 days or more.

Conclusion: PTX-3 reflected disease severity but failed to predict hospital stay. There was no difference in PTX-3 levels in the different types of viruses.

#16 - EVALUATION OF CLINICAL, LABORATORY AND RADIOLOGICAL FINDINGS IN HOSPITALIZED PATIENTS DIAGNOSED WITH LOWER RESPIRATORY TRACT INFECTIONS

Pekcan S.
Pediatric Pulmonology, Necmettin Erbakan University Meram Medical School - Konya, Turkey

Viral agents are the major cause of acute lower respiratory tract infections in children.

Purpose: The evaluation of clinical, laboratory and radiological findings of treated hospitalized patients diagnosed with lower respiratory tract infections, with identification of viral agents and investigation of seasonal distribution of agents.

Method: This study was a retrospective chart review of 785 patients who were diagnosed with acute lower respiratory tract infection between December 2010-June 2013 in the Department of Pediatrics, Necmettin Erbakan University, Meram Faculty of Medicine. Demographic, clinical, laboratory and radiological findings were recorded. Nasopharyngeal aspirates of patients were studied by the polymerase chain reaction (PCR) method.

Result: One or more viral agents were detected in 329 (41.9%) patients included in the study. Respiratory syncytial virus B (RSV B) (41%), rhinovirus (15.5%) and with RSV (12.8%) were most frequently isolated. In addition, multiple viral agents were detected in 28 patients (8.5%). Furthermore, the study showed differences in virus distribution according to seasons and age groups. Levels of leukocytes, neutrophils and hospitalization period were significantly lower in patients with a detected viral agent than patients with a non-detected viral agent (p < 0.05). However, no significant difference was found for CRP levels between the two groups (p = 0.906). Chest radiographs were normal in a large proportion of patients with identified viral agents (68%).

Conclusion: RSV, rhinovirus and influenza A are crucial for childhood pneumonias in the Turkish society. Mixed infections are not associated with disease severity. More studies are needed for assessing the reliability of CRP and radiological findings in diagnosing lower respiratory tract infections caused by viral agents.

Keywords: Children, respiratory tract, viral agents, bronchiolitis, pneumonia, respiratory syncytial virus
Clinical Microbiology and Infectious diseases, Hadassah Medical Center - Jerusalem, Israel

**Objective:** The aim was to determine the microbial pathogens in the lungs of Familial Dysautonomia (FD) patients, which can serve as a model for recurrent lung aspiration. The causes for aspirations are defective coordination of the nasopharynx and esophageal muscles as well as gastroesophageal reflux (GER), vomiting and increased salivation.

**Methods:** The data were obtained retrospectively from the charts of 250 FD patients between 1987 and 2012 at the Israeli Center for Familial Dysautonomia, Hadassah-Hebrew University Hospital. Ninety-seven FD patients were included in the study and their first respiratory tract culture at respiratory event was retrieved by one of three methods: 1. Deep bronchial lavage (DBL) with instillation saline by a long thin tube through a bronchial tube, followed by suction or by Bronchoalveolar Lavage (BAL) with a bronchoscope; 2. Deep coughed sputum; 3. Endotracheal Aspirate (ETA) through a tracheostomy or through an endotracheal tube in a mechanically-ventilated patient.

**Results:** A total of 266 cultures, 125 via DBL/BAL, 67 by spumt, and 74 via ETA were analyzed. Twenty-six species of bacteria and 10 species of fungi were identified. Out of the 97 patients, 55.7% (54 patients) had at least one culture with an infectious agent, while no evidence of bacterial infection was found in 44.3% (43 patients). Fifteen patients (15.5%) had at least one positive fungal culture, and 19 patients (19.6%) had at least one culture with a mixed infection. The most common bacterial pathogen obtained overall was *Haemophilus influenzae* (HI) (32.0%, Confidence Interval, CI = 22.85-42.20%), while the most common fungal pathogen was *Candida albicans* (11.3% CI = 5.80 - 19.39%). The most common bacterial pathogen via BAL/DBL was HI (23.2%, CI = 14.56 - 33.80%), the most common fungal pathogen was *Candida albicans* (8.5%, CI = 3.50-16.80%). The most common bacterial pathogen by sputum was HI (37.9% CI = 20.69-57.74%), while there was no most common fungal pathogen by sputum. *Candida al* and *Candida lusitaniae*, *Candida parapsilosis*, *Cladosporium* species, *Penicillium* species, *Rhodotorula glutinis*, and *Candida colliculosa* were each 3.4%. *C. al* = 0.09 - 17.76%. The most common pathogens by ETA were *Pseudomonas aeruginosa* (80%, CI = 44.39 - 97.48%) and *Candida albicans* (40%, CI = 12.16 - 73.76%). Other common pathogens found included *Streptococcus* and *Staphylococcus* species, and *Moraxella catarrhalis*.

**Conclusions:** This is the first study to show species of bacteria and fungi in the lungs of FD patients and serves as an evidence base for empiric therapy while microbial results are still pending. FD might serve as a model for other diseases associated with lung aspiration.

**Abstract S61**

Schmidt CM,1 Franco CL,1 Pinto LF,2 Vasconcellos CS,2 Santos TC,3 Sias SM.1

1 Department of Pediatrics, Fluminense Federal University - Niterói, Brazil
2 Medical student, Fluminense Federal University - Niterói, Brazil
3 Medical doctor, Fluminense Federal University - Niterói, Brazil

**AIM:** To present a case of Mycoplasma pneumoniae complicated with Swyer-James-McLeod Syndrome (SJS).

**METHODS:** The information was obtained from hospital records and a bibliographic review was done.

**BACKGROUND:** Community-acquired pneumonia (CAP) is one of the most important causes of childhood morbidity and mortality. Its severity depends on age, host immunity and etiology. Microbial etiology of pneumonia still remains a challenge in children. CAP can be caused by viruses, typical (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*) and atypical (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) bacteria, *Mycochristi bacterium tuberculosis* and fungi. *M. pneumoniae* has been found in both school-age children and younger age group. Children less than five years can have a more complicated clinical course. PIBO is a disease that usually occurs after infection of the lower airways mainly by virus and also by *M. pneumoniae*. The patients usually maintain cough and/or wheezing after the initial acute episode and can have failure to thrive. Suggestive chest X-ray and computed tomography have replaced the need for more invasive procedures. SJS is characterized by unilateral hyperlucent lung with reduced volume secondary to deficiency of blood supply. This syndrome can be secondary to PIBO. Adenovirus subtypes 3, 7, and 21, *M. pneumoniae*, measles virus, *Bordetella pertussis*, Influenza A and M. tuberculosis are microorganisms that have been associated with PIBO.

High resolution computed tomography (HRCT) is the imaging technique of choice in establishing diagnosis of SJS and PIBO.

**CASE REPORT:** We report the case of a 3-year-old boy that was admitted to the hospital with fever and cough for seven days. Crackles and wheezing were present on physical examination. Chest X-ray showed a consolidation in the left lung base with a small amount of pleural effusion. Initially, penicillin was prescribed. As the symptoms persisted, cefuroxime and penicillin was prescribed. After discharge, the patient had repeated episodes of respiratory infections and wheezing. HRCT showed reduced lung volume, bronchial wall thickening, bronchiectasis, ground-glass opacities and atelectasis in the left lung. There were small areas of air trapping in the right lung. Currently he is 5 years old, is using inhaled bronchodilators and corticosteroids, and undergoes chest physiotherapy. Although he still exhibits some recurrent pulmonary infections and bronchospasm, his growth is well.

Pediatric Pulmonology

#26 - THE CLINICAL IMPACT OF ADJUVANT THERAPY ON THE OUTCOME OF SEVERE ADENOVIRUS PNEUMONIA IN CHILDREN

Ker SY,1 Nathan AM,2 Sam IC,3 Thavagnanam S,2 Eg KP,2 de Bruyne JA.2

1 Pediatric Pulmonology, University Putra Malaysia - Kuala Lumpur, Malaysia
2 Pediatric Pulmonology, University Malaya - Kuala Lumpur, Malaysia
3 Microbiology, University Malaya - Kuala Lumpur, Malaysia

**Background:** Adenovirus causes childhood pneumonia with a mortality rate of up to 20%. There is currently no treatment to prevent bronchiectasis or bronchiolitis obliterans (BO) which develops in up to 60% of survivors.

**Aims:** To determine the clinical impact of adjuvant therapy on the outcome of severe adenovirus pneumonia in children.

**Methods:** This was a retrospective review of the clinical features and outcome of severe adenovirus pneumonia in a single center in Malaysia from June 2010 till July 2013. Severe pneumonia was defined as pneumonia needing any forms of ventilatory support or resulting in death. Adenovirus was detected in respiratory samples by immunofluorescent assay or cell culture. The diagnosis of pneumonia was supported by chest radiography. High Resolution Computed Tomography (HRCT) confirmed the diagnosis of BO.

**Results:** Seventeen patients fulfilled the inclusion criteria. Two data sets were missing. Mean age was 12 (SD 6.9) months. More than half (n = 8) had a previous history of lower respiratory tract infection and one-third had other comorbidities. Mean duration of fever at presentation was 6.4 (SD 5) days. Extra-pulmonary manifestations were present in 8 patients: shock (n = 5), seizures (n = 3), hepatitis (n = 2) and acute renal failure (n = 1). Three children had seizures before admission and all developed BO. The mean lengths of stay in hospital and in the intensive care unit (ICU) were 23(SD 17.5) and 10.3 (SD 11.5) days respectively. All patients received invasive (n = 6) or non-invasive ventilation (n = 8) except for one child, who was managed conservatively. All patients received oxygen and empirical antibiotic therapy. The mortality rate was 26.7% (n = 4). Eleven patients survived the acute infection but 8 (72.7%) developed BO, half of which required long-term home therapy. Most survivors (n = 9) received intravenous methylprednisolone and intravenous immunoglobulin (IVIG) during the acute illness with no adverse sequelae. Six survivors required re-admission for recurrent pneumonia.

**Conclusion:** Adenovirus pneumonia in young children is a disease with high mortality and morbidity. Methylprednisolone and intravenous immunoglobulin were safe but did not prevent the development of BO.
CONCLUSION: M. pneumoniae should be considered as a possible etiology of CAP in young children, especially if the treatment failed with antibiotics for typical bacteria. When these patients remain symptomatic, it is important to exclude complications such as PIBO and SIMS.

AIM: This study aimed to describe CA-MRSA pulmonary infection in previously healthy children.

METHODS: We conducted a case report on four cases of necrotizing pneumonia in previously healthy children and adolescents admitted to the hospital between October 2011 and November 2014.

BACKGROUND: The emergence of community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) has led to an increase in staphylococcal disease burden. Necrotizing fasciitis, necrotizing pneumonia and severe sepsis caused by S. aureus were rarely reported in healthy individuals prior to the emergence of CA-MRSA. In contrast to decreasing incidence among adults, both invasive and noninvasive CA-MRSA infections in children are becoming more frequent. CA-MRSA necrotizing pneumonia is a distinct syndrome of hemoptysis, high fever, hypotension and cavitary lung lesions confirmed by radiography. It is most common in children and young adult patients and often takes a rapidly progressive, fatal course. Many reported cases of MRSA community-acquired pneumonia (CAP) associated with high mortality and morbidity carry the Panton-Valentine leukocidin (PVL) gene. There is a need for heightened awareness regarding this disease.

CASE REPORT: All cases were males between the ages of one to 14 years. Clinical manifestations were fever, cough and pleuritic pain. Recent history of postural lesions was observed. One patient showed signs of sepsis. History of tuberculosis (TB) contact was present in one patient with negative tuberculin test. Chest X-ray or computed tomography revealed cavitary lesions in all patients, pleural effusion in three patients and bilateral lesions in one patient. Penicillin or amoxicillin-clavulanic acid was initiated as preliminary treatment. Chest tube placement occurred in one patient with empyema. For each patient, positive CA-MRSA cultures were isolated from different sites: blood and urine; bronchoalveolar lavage, pleural effusion and nasal swab. PVL-positive MRSA strains were found in two patients. Treatment was changed to vancomycin or linezolid if clinical condition worsened or once culture results were obtained. The antibiotic regimen lasted between two and four weeks. All patients showed significant improvement after treatment with the proper antibiotic.

CONCLUSION: These cases emphasize CA-MRSA should be considered as a possible etiology of CAP, especially if previous history of or concomitant skin lesion is present and cavitary lesions are observed on imaging tests. For suspected cases, treatment should cover this pathogen while awaiting culture and antibiotic susceptibility results. Obtaining blood and sputum cultures, when available, is important for patients who are hospitalized with CAP and have cavitary infiltrates. In high TB burden countries, TB should be considered as a differential diagnosis in patients with cavitary lesions, cough and/or fever for more than two weeks.
Pulmonary abscess is a rare complication of community – acquired pneumonia in immunocompetent children. The aim of the study was to describe the epidemiology and clinical characteristics of children hospitalized with pneumonia complicated by lung abscess.

**Methods:** A retrospective review of medical records of all patients treated in the Department of Pediatric Pulmonology, Allergy and Clinical Immunology of Karol Marcinkowski Medical University from January 2004 to December 2013 with the diagnosis of pneumonia. Analyzed data included anthropometric parameters, present comorbidities, clinical presentation, treatment, length of hospital stay as well as the presence and type of complications.

**Results:** In the given study period, 2080 children were admitted because of pneumonia, and 18 (0.86%) cases were complicated with lung abscess. Median age of the children was 5.25 (from 3 to 15) years, and there were 11 (61%) males. In 13 (72%) cases, the right lung was affected and in all cases abscess was unilateral. Ten (55%) patients were previously healthy, 2 (11%) had asthma, 3 (16.7%) were atopic, 2 (11%) suffered from epilepsy; nephrotic syndrome, cerebral palsy and heart defect were present in 1 child each. There were 5 (33%) inpatients and 12 transfers from other hospitals. Most frequent clinical signs on presentation consisted in fever in 17 (94%) patients, cough in 16 (89%), dyspnea in 14 (78%), chest pain in 5 (28%) and abdominal pain in 4 (22%). Median time from the onset of symptoms to the radiological diagnosis of abscess was 9.5 (from 1 to 60) days. In 8 (44%) cases, other complications such as empyema, necrotizing pneumonia or pneumothorax were also present. Single abscess was present in 10 (55%) cases. Etiological factor was isolated in 7 (39%) cases, the most common being Streptococcus pneumoniae and Staphylococcus aureus. Twelve (67%) patients were treated with antibiotic therapy only while surgical procedures, namely segmentectomy and lobectomy, were performed in 6 patients. In two of these patients, lung sequestration was finally diagnosed based on histological examination. Last surgical procedure was performed in 2008 and since then, all children have been treated in a conservative manner. Median duration of antibiotic treatment was 66 (from 30 to 98) days and most frequently-used antibiotics were 3rd generation cephalosporins, vancomycin, clindamycin, carbapenems, metronidazole and linezolid. Median hospital stay was 44 (from 15 to 86) days. In 7 (39%) children, complete radiological remission was observed, 4 (22%) patients were lost to follow up, although improvement was documented in all of them in at least one radiological examination. Median time for radiological abnormalities regression was 102.5 (from 56 to 195) days.

**Conclusions:** Lung abscess is rare but severe complication of community – acquired pneumonia can occur in otherwise healthy children. In many cases watchful, conservative treatment is effective.
Tuberculosis (TB) is caused by infection with Mycobacterium tuberculosis (MTB), and is a major cause of morbidity and mortality worldwide. Despite the widespread use of the Bacillus Calmette-Guérin (BCG) vaccine, its true effectiveness has been debated for decades. In seventy-five samples were collected and of these 85.7% were expectorated years. The majority of patients (79.5%) were HIV positive. One hundred and Children with bronchiectasis have an increased risk of burg, South Africa Faculty of Health Sciences, University of the Witwatersrand. - Johannes-

#116 - IN SILICO PREDICTION OF HUMAN PROMISCUOUS MHC CLASS I RESTRICTED CD4+ T CELL EPITOPE IN THE PPE PROTEIN FAMILY OF MYCOBACTERIUM TUBERCULOSIS

Xiao J.
TB Lab, Beijing Children’s Hospital - Beijing, China

Tuberculosis (TB) is caused by infection with Mycobacterium tuberculosis (MTB), and is a major cause of morbidity and mortality worldwide. Despite the widespread use of the Mycobacterium bovis bacille Calmette-Guérin (BCG) vaccine, its true effectiveness has been debated for decades. In addition, sensitivity of the tuberculin skin test and the IFN-γ-release assay is suboptimal, and none of these tests distinguish between latent infection and active disease. Therefore, there is a pressing need to detect new TB antigens to develop effective vaccines and set up sensitive immunological assays. In this study, through database access to protein sequences of the PPE protein family, and through the use of bioinformatics programs including SignalP4.1 server, SecretomeP 2.0 server, DAS server, and NetMHCII2.2 server, ten promiscuous epitope peptides were identified; six from PPE8 and others from PPE12, PPE21 and PPE62. All ten bind to more than three human leukocyte antigen (HLA) molecules. Prediction analysis showed that these promiscuous epitope peptides may be important targets in subunit vaccines or diagnostic antigens against MTB. In addition, they could be used in immunological assays to evaluate the level of protection, the effect on pathology reduction, and the profile of cytokines and antibodies induced by them.

4. NON-INFECTIONOUS RESPIRATORY DISORDERS

#6 - BACTERIA ISOLATED FROM THE AIRWAYS OF CHILDREN WITH BRONCHIECTASIS ACCORDING TO HIV STATUS

Verwey C., Velaphi S.
Department of Paediatrics, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand. - Johannesburg, South Africa

Background: Children with bronchiectasis have an increased risk of developing recurrent lower respiratory tract infections caused by the bacteria colonizing their airways. It is routine to take airway samples from patients with bronchiectasis to determine the bacteria that colonize their airways. This guides the choice of antimicrobials used during a chest infection. It is not known whether there is a difference between the number, type and density of bacteria found in the airways of HIV positive and HIV negative patients with bronchiectasis.

Objective: To determine the bacteria isolated from the airways of children with bronchiectasis according to their HIV status. Methods: Records of children under 16 years of age with the diagnosis of bronchiectasis who had been seen in pediatric pulmonology at the Chris Hani Baragwanath Academic Hospital between April 2011 and March 2013 were reviewed. Data were collected on patient demographics, HIV status and characteristics of the airway samples collected from all the patients. Data collected on the airway samples included number of samples collected per patient, type of samples collected, quality of the samples collected, number and type of organisms cultured and density of individual organisms cultured. Comparisons between HIV negative and HIV positive patients were made.

Results: A total of 78 patients were included with a mean age was 9.7 ± 3.3 years. The majority of patients (79.5%) were HIV positive. One hundred and seventy-five samples were collected and of these 85.7% were expectorated sputum. Gram negative organisms (71.6%) were more common than gram positive organisms (28.4%). H. influenzae was the most common organism identified (36.0%) followed by S. pneumoniae (13.1%), S. aureus (11.3%) and M. catarrhalis (10.8%). When comparing HIV positive and HIV negative patients with bronchiectasis, there was no difference in the number, type and density of bacteria isolated. Conclusion: Number, type and density of bacteria isolated in the airways of children with bronchiectasis is not associated with the HIV status of the patient.

#12 - CONGENITAL PULMONARY ANOMALIES IN CHILDHOOD: ETIOLOGIES, PROGNOSIS AND FOLLOW UP

Sismanlar T.
Pediatric Pulmonology, Gazi University Hospital - Ankara, Turkey

Patients with congenital pulmonary abnormalities and chest wall deformities and who were followed in the Gazi University Pediatric Pulmonology clinic over a six year-period were reviewed. Congenital abnormalities were detected in 5% patients (169 of 3246 patients). The most common abnormality was chest wall deformity 49% (84 patients) (pectus excavatum, carinatum, scoliosis, rib deformity). Twenty-one patients (12%) with pectus excavatum, 18 patients (10%) with malacia (bronchomalacia, tracheomalacia), 9 patients (5%) with diaphragmatic eventration, 6 patients (3%) with congenital cystic adenomatoid malformation, 5 patients (2%) with congenital lobar emphysema, 5 patients with diaphragmatic hernia and 4 patients with bronchogenic cyst were detected. All chest wall deformities and malacia patients were clinically followed. Two of the diaphragmatic eventration patients had surgery. Two of four bronchogenic cyst patients and one of six congenital cystic adenomatoid malformation patients had spontaneous regression. Reflux and recurrent lower respiratory tract infection in patients with tracheoesophageal fistula were the most common reasons for admission. Forty-six patients had surgery. Mean follow-up time was 18.5 months. Only two patients died in this group. One died after surgery for diaphragmatic hernia repair. The second had pectus excavatum as well as Dandy Walker syndrome and died with severe lower respiratory infection and respiratory distress. Chest wall deformities and congenital pulmonary abnormalities are not rare in childhood. These patients need to be followed in terms of regression, progression, complications and surgery.

#23 - THYROGLOSSAL DUCT CYST AT THE BASE OF THE TONGUE IN THE NEONATE/INFANT IN JAPAN

Masatsugu Isobe M.,1 Tomoharu Kato T.,2 Shuichi Tsuchiya S.3
1 Pediatrics, Nagaoka Medical co-op Children Clinic - Nagaoka, Japan
2 Pediatrics, Kasukabe Kojin Clinic - Kasukabe, Japan
3 Pediatrics, Joetsu General Hospital - Joetsu, Japan

Background: Thyroglossal duct cyst at the base of the tongue is a rare disease that may cause upper airway obstruction in children. Evaluating its severity is important because the thyroglossal duct may be fatal if not correctly treated.

Objective: The purpose of this study is to report our experience treating three patients with a thyroglossal duct cyst at the base of the tongue, and to evaluate the clinical course as well as the findings obtained by transnasal laryngofibroscopy. We also investigated the reports of 19 cases in Japan with a review of the Japanese literature: “Japana Centra Revuo Medicina” Methods: 1) Case reports of three children with thyroglossal duct cyst at the base of the tongue. 2) Review of the Japanese literature on thyroglossal duct cyst at the base of the tongue.

Results: 1-1) Patient #1 was a female infant of 3 months of age. Just after birth, she showed signs of upper airway obstruction including recurrent stridor, retraction and wheezing, and breathing difficulty after feeding. Laryngoscopy by a practicing otolaryngologist was performed three times and showed no abnormality. We performed a transnasal laryngofibroscopy in supine position and detected an 11mm diameter thyroglossal duct cyst at the base of the tongue. A cystectomy was performed. 1-2) Patient #2 was a 2-
year-old boy. He consulted a practicing otolaryngologist due to a fever and stridor. By identifying the subglottic stenosis using laryngoscopy, he was diagnosed with croup syndrome. He was then referred to our department for treatment. After treatment, we performed a transnasal laryngofibroscopy in supine position for proper diagnosis. A thyroglossal duct cyst at the base of the tongue was detected which was 14mm in diameter. 1-3) Patient #3 was a 1-month-old girl with inspiratory stridor after birth. Laryngoscopy in supine position revealed a cystic mass (8mm width) at the base of the tongue. However, the cyst spontaneously decreased in size within a month. Repeated laryngoscopy at the age of 5 months revealed no recurrence of the cyst. 2) Nineteen cases (male/female = 10/9) of thyroglossal duct cysts at the base of the tongue have been reported in Japan in detailed case reports (from 1997 to 2014). Laryngomalacia with the cyst was observed in 7 cases. Misdiagnoses during initial laryngoscopy were made in nine cases. Spontaneous regression or disappearance of the cyst was observed in 4 cases.

Conclusions: Laryngoscopy in supine position is useful in assessing airway stenosis with stridor, retraction, and dyspnea in neonates/infants, and is essential especially for diagnosing the thyroglossal duct cyst. We emphasize that thyroglossal duct cysts sometimes disappear smoothly in the cases of a few small-sized cysts and it is important to keep continued observation and laryngoscopy in mind.

#42 - CASE SERIES OF PULMONARY ALVEOLAR MICROLITHIASIS
Emiraloglu N., Kiper N., Yalcın E., Eroşö D., Ozelcil U.
Pediatric Pulmonology, Hacettepe University Faculty of Medicine - Ankara, Turkey

Case Series of Pulmonary Alveolar Microlithiasis
Background: Pulmonary alveolar microlithiasis (PAM) is a rare genetic disease characterized by microlith formation in the alveolar space. The disease is usually discovered from birth up to 40 yrs of age and is often diagnosed incidentally during radiography of the chest for other reasons. Many patients are asymptomatic and the majority of patients either have normal or restrictive pulmonary function. While it remains static in some patients, it progresses into pulmonary fibrosis, respiratory failure and cor pulmonale in others. As of yet, there is no consensus as to the management of the disease. Lung transplantation can be considered for the patients with end-stage lung disease. Disodium etidronate has been used because of its effect on the precipitation of hydroxyapatite microcrystals.

Cases: Here we present the clinical, radiological and pathological features of 9 children with pulmonary alveolar microlithiasis followed at the Hacettepe University Pediatric Pulmonology Department. The median age at diagnosis was 11 years (4-19 years). PAM was diagnosed incidentally in 7 patients; one patient presented with cyanosis and the other patient presented with failure to thrive. Chest radiograph showed sand-storm appearance with calcific densities throughout both lungs and thoracic computed tomography revealed ground-glass opacities throughout both lungs, interlobular septal thickening and millimetric nodular opacities in all patients. (Figure) Only one patient had small pleuritis and valvular heart disease. Abdominal ultrasound was normal in all patients. Restrictive pulmonary function tests were observed in 2 of the patients. Both patients had lung biopsies and revealed varying calcification sizes in the alveoli. Disodium etidronate treatment was started in all patients and they remained asymptomatic on clinical follow-up.

Conclusion: PAM is a rare parenchymal lung disease and patients are mostly asymptomatic in the childhood population. Chest radiograms reveal a sandstorm appearance; small opacities especially in the middle and lower zones of both lungs are typical for PAM. Extensive calcification results in ground glass opacification and interlobular septal thickening on CT scans. In some patients with PAM, calcification can also be seen in extra pulmonary organs such as kidneys, gallbladder, urethra, seminal vesicles, pleura and heart. With the exception of lung transplantation, there is no known effective treatment for the disease. Herein, we used etidronate in all the patients; however six of the patients discontinued the treatment having no symptoms on clinical follow-up. Etidronate was also shown to be effective in removing calcifications from the lungs of PAM patients and improvement in chest imagings; however there was no improvement on lung images of the patients.

#46 - PAEDIATRIC HYPERSENSITIVITY PNEUMONITIS PRESENTING WITH TUBERCULOSIS-LIKE SYMPTOMS
Lukoseviciute-Zike D., Miseviciene V., Zaveckiene J.
1 Pediatric clinic department of pulmonary diseases, Hospital of Lithuanian University of Health Sciences Kauno klinikos - Kaunas, Lithuania
2 Radiology, Hospital of Lithuanian University of Health Sciences Kauno klinikos - Kaunas, Lithuania

Objective: Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis is an immune-mediated hypersensitivity disease caused by a nonatopic immunologic response to inhaled agents. The frequency of the disease among Lithuanian children is extremely rare and exact epidemiology is unknown. A wide spectrum of antigens can trigger HP, including avian antigens, rodent antigens, fungi, bacteria and low molecular weight chemicals. Bird fancier’s lung is the most common HP in children. Clinical features are dependent upon the stage of the disease and can include fever, chills, cough, dyspnea, and weight loss. Importantly, sub-acute and chronic HP may mimic several other lung diseases.

Aim and methods: Retrospective analysis of two clinical cases of HP in adolescent patients is presented.

Result: The first case was a 13-year-old girl, who lived in an old house, kept two parrots and was exposed to frankincense overuse at home; another – a 16-year-old boy – kept 50 parrots in a one bedroom flat and recently bought a new species of them. At the beginning, both patients showed symptoms of prolonged and recurrent respiratory infection, pneumonia. Pulmonary tuberculosis (TB) was suspected according to epidemiological TB situation in Lithuania; clinical picture was diffuse micro nodular infiltration on chest X-rays and ineffective prescribed nonspecific treatment. At that time, data regarding possible risk factors was not collected. The diagnosis of HP in the first case was confirmed by detailed anamnesis, positive provocation test with frankincense, specific findings on lung biopsy and CT scan images. Lung biopsy revealed nonspecific interstitial granulomas, infiltration with mononuclear cell and several giant cells. CT scan demonstrated “ground–glass” picture, micronodules and fibrotic changes in the lower lung zones. The second HP diagnosis was confirmed by detailed anamnesis, positive provocation test to parrots and specific findings on lung CT scan images. Both patients were successfully treated with systemic corticosteroids for some time and risk factors were eliminated.

Conclusion: Clinical picture is not specific in paediatric HP and could mimic other lung diseases. Therefore, high suspicion of HP and disclosure of possible risk factors are very important. Lung biopsy is the most specific diagnostic method for HP, but careful history, positive provocation test to suspected antigen and lung CT scan test could be equivalent to the first method and even quicker with less traumatic criteria. Although avian antigens are the most common cause of paediatric HP, nowadays other new antigens, such as frankincense, are possible, especially if the child is exposed to the latter in large amounts.

#47 - WHEN DO YOU BECOME AN ADULT? A SURVEY ON UK PAEDIATRIC INTENSIVE CARE (PICU) EXPERIENCE ON PULMONARY EMBOLISM
Elliot FM
Department of Paediatrics, Whiston Hospital - Merseyside, United Kingdom

Introduction: Following a recent confirmed case of a 15-year-old boy with pulmonary embolism (PE) in our hospital, we decided to see if there is any national policy or protocol for diagnosing and managing PE in children.

Pediatric Pulmonology
ABSTRACT

Methods: A list of all paediatric intensive care units in the UK was obtained. Each unit was telephoned by our registrar who spoke to one of the consultants in the unit. Four simple questions were asked:

1. Have you diagnosed a case of PE in the last 4-5 years?
2. Do you have a departmental guideline for diagnosing PE?
3. Do you have a departmental guideline for the management of PE?
4. Would you be able to manage PE without the adult respiratory team (in conjunction with the adult respiratory team)?

Results: A total of nine Paediatric intensive care units were contacted. Out of nine units, only one unit had a case of PE in a neonate that needed ECHO. One unit had one case of possible PE that was not confirmed. None of the 9 units had a departmental guideline to diagnose and manage PE. With regard to management, three of the units would ask for help from the adult respiratory team. Three units would seek advice from the haematology team. Two would seek advice from the haematology team and adult team. One unit would seek advice from the cardiology team.

Conclusion: There is lack of experience amongst paediatricians in diagnosis and management of pulmonary embolism. A clear policy is needed to ensure prompt diagnosis and appropriate management of this rare but potentially serious diagnosis in the paediatric population.

#79 - TYPES OF LARYNGOMALACIA AND ITS CLINICAL COURSE IN CHILDREN ADMITTED TO THE TERTIARY LEVEL HOSPITAL IN KRAKOW

Kusak B., Cichocka-Jarosz E., Jedynak-Wasowicz U., Lis G.
Department of Pediatrics, Chair of Pediatrics Jagiellonian University Medical College - Krakow, Poland

The aim of the study was to: a) evaluate the types of laryngomalacia (LM) and their relation with signs and symptoms in children having undergone fiberobronchoscopy at the Institute of Pediatrics in Krakow between January 2006 and December 2012; b) estimate the prevalence of LM in the Malopolskie voivodship.

METHODS: The results of 756 fiberobronchoscopic examinations (FB) were reviewed. Charts with established LM diagnosis were reanalyzed (video recordings) by a single observer and classified into the following types (Ref.1 ): type 1 - prolapse of the mucosa overlying the arytenoid cartilages, type 2 - foreshortened aryepiglottic folds, type 3 - posterior displacement of the epiglottis or changes in its shape. The estimation of LM prevalence was performed taking into consideration the reported number of live births in the voivodship and with the assumption that almost all children with suspected clinically relevant LM are referred to our hospital.

Results: Out of 77 children (52% boys; mean age 5.8 with range: 0.1-50 months) with LM, the following malacia types were identified: type 1 in 87% (n = 61), type 2 in 24% (n = 17), type 3 in 16% (n = 11) of examined children. Coincidence of the different types was observed, for this reason sum of percents is above 100. Endoscopy of lower airways revealed their malacias as well. Prevalence of LM in small children is relatively high in the middle-south region of Poland.


#87 - RECURRENT PULMONARY INFECTIONS AS PRESENTATION OF ABSENT PULMONARY VEINS: A TWO CASE REPORT

Basora E., Ali-Dinar T., Colin A.
Pediatric Pulmonology, University of Miami / Miller School of Medicine - Miami, FL, USA

Background: Developmental anomalies of pulmonary veins occur in early fetal life due to disruption in embryonic venous system formation. This congenital agenesis is speculated to result from improper incorporation of pulmonary veins into the left atrium with presentation in early life. An acquired form, however, likely results from progressive neoproliferative processes stemming from uncontrolled growth of myofibroblast-like connective tissue.

Case Reports: We present two pediatric cases of absent pulmonary veins presenting with recurrent pulmonary infections. Case 1: An 8-year-old Hispanic male with history of recurrent pneumonias. Failure to visualize the right pulmonary vein on echocardiography raised the suspicion of the diagnosis which was, though delayed, later confirmed with a 3-D CT scan and ultimately cardiac catheterization. Case 2: A 2-year-old Kuwaiti male with history of multiple lung infections including unconfirmed pulmonary tuberculosis. A ventilation/perfusion scan revealed absent perfusion to the affected lung suggestive of a vascular anomaly. A 3-D CT scan, echocardiography and cardiac catheterization confirmed the diagnosis of absent right pulmonary vein. Both patients underwent right pneumonectomy; failing attempted corrective surgery in the younger. Both have a stable course over 5- and 9- year follow up respectively.

Conclusion: Absent pulmonary veins is an extremely rare entity that is often overlooked in the differential diagnosis of recurrent pulmonary infections and/or hemoptysis. The diagnosis should be suggested by echocardiography showing decreased blood flow in the pulmonary artery of the affected side. Because of its dire consequences with risk of bleeding and eventual pneumonectomy, it should be conclusively established by cardiac catheterization. Our cases emphasize the consideration of this unique diagnosis in cases of recurrent and unexplained pulmonary infections or hemorrhage.

#130 - PNEUMOTHORAX IN YOUNG POPULATION

Ashkenazi M.1, Ben Nun A.2, Bak A.1, Simanski D.2, Efrati O.1, Lavie M.1, Sarouk I.1, Dagan A.1, Bar Aluma B.1
1 Pediatric Pulmonology, Edmond and Lilly Safra children’s hospital - Ramat Gan, Israel
2 Thorax Surgery, Sheba medical center - Ramat Gan, Israel

Background: Pneumothorax is an accumulation of air in the pleural cavity, which can be classified into traumatic, iatrogenic or spontaneous (SP), that could be subdivided into primary spontaneous Pneumothorax (PSP) which is a condition without preexisting lung disease, or secondary spontaneous Pneumothorax (SP) which is a complication of a preexisting lung disease. The incidence of PSP is estimated at 7.4-18/100000 per year among men and 1.2-6/100000 among women. Our goal was to explore the epidemiology of SP and the efficacy of the different treatments for SSP.

Methods: A retrospective patient’s file study to investigate the epidemiology and treatment of SP in young population in hospitalized patients in a tertiary center was performed through a search in the digital archive (available from 01/01/1995) of the Sheba Medical Center for hospitalized patients and younger than 40y. The treatment was divided into operative and non-operative.

Results: A total of 750 patients were enrolled in the study, 624 males and 126 females. We could not demonstrate any significant change regarding
percentage of patients operated, recurrence rates after non operative treatment and non-operative treatment among PSP and SSP. Female gender showed an increased risk of SSP when having SP (OR 2.19), this ratio was higher in the younger the population (OR 6.43 among pediatric population). Asthma was the most prevalent disease causing SSP in young people. The most prevalent operation that was performed was a combination of pleura abrasion and segmentectomy. The recurrence risk after Abrasion & Segmentectomy was significantly higher than after Abrasion alone. The recurrence risk for SSP after non operative treatment was significantly higher. The average admission length for SSP was significantly higher.

Conclusions: We show in our large cohort that, among the pediatric population, when a female has a SP, we strongly recommend to look for a primary lung disease. We recommend positively considering surgery as a first treatment for SSP. The higher recurrence rate after Abrasion & Segmentectomy is attributed to the worse basic situation of the lungs than those who underwent Abrasion alone. More studies are needed to determine the risk factors and to produce clear guidelines regarding surgery as first treatment, resulting in shorter admission and reduced costs.

#133 - PEDIATRIC PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Cinel G.1, Kiper N.2, Orhan D.3, Emiraloglu N.2, Yalcin E.2, Dogru D.3, Ozcelik U.3, Oguz B.3, Haliloglu M.4
1 Pediatric Pulmonology Department, Ankara Child Health and Diseases, Hematology Oncology Education and Research Hospital - Ankara, Turkey
2 Pediatric Pulmonology Department, Hacettepe University, Ihsan Dogramaci Children’s Hospital - Ankara, Turkey
3 Pediatric Pathology Department, Hacettepe University, Ihsan Dogramaci Children’s Hospital - Ankara, Turkey
4 Radiology Department, Hacettepe University, Ihsan Dogramaci Children’s Hospital - Ankara, Turkey

Introduction: Langerhans Cell Histiocytosis (LCH) is a very rare disease in childhood (0.1-1/100000 in children younger than 18 year old); and is classified under diffuse parenchymal lung diseases (DPLD). Isolated pulmonary LCH represents less than 1% of patients; but lung involvement is observed in 25% of multisystemic disease, at the time of diagnosis.

Methods: We retrospectively assessed the files of 130 DPLD patients who had been followed-up at the Hacettepe University Pediatric Pulmonology Department. In this study, we present clinical, laboratory, radiological and histopathological findings and follow-up of 7 children in this group who had been diagnosed as LCH with lung involvement.

Results: We evaluated 7 patients with pulmonary LCH (4 males, 3 females); the median age was 11.6 (2.3-14.6) at the time of diagnosis. Six patients had pulmonary involvement as a part of the multisystemic disease; only 1 had isolated pulmonary LCH. The most common symptoms were bone aches, shortness of breath, reduction in exercise capacity and cough. Positive findings in their physical examination were bilaterally crackles and rhonchi, decrease in respiratory sounds, retractions and clubbing. On chest x-rays and thorax computerized tomography, multiple, small air cysts were seen on lung parenchyma; in addition, lytic bone lesions on ribs were determined in patients with bone involvement. All patients had the exact diagnosis with tissue biopsies (1 bone, 6 lung biopsies). The common findings of the lung biopsies were dilated airways, cystic cavities and millimetric nodular cell infiltrations consisting of Langerhans cells (CD1a and S100 positive), multinuclear giant cells and eosinophils surrounding these areas. All patients had chemotherapy (Vinblastin and prednisolon) at our Oncology department. On their follow-up, 2 had recurrent pneumothorax and thus pleurodesis was treatment, resulting in shorter admission and reduced costs.

Conclusion: LCH is very rare in childhood and clinical findings may vary. Multisystemic disease can be associated with versatile course; from spontaneous remission to rapid deterioration and death.
Materials and methods: Eighteen very preterm infants who were hospitalized in the neonatal intensive care unit of the University Hospital of Poitiers and suffering from BPD were included and respectively divided into two groups according to their initial parenteral caloric and protein intake. Early protein intake was defined as introduction of parenteral amino acid solutions from day 1 of life, late intake from day 2 or later. Respiratory function of these children was studied between 3 and 6 years by lung function tests, including measurements of airway resistance, functional residual capacity (FRC) by helium dilution and exhaled NO.

Results: Airway resistance was significantly lower in the group who received early protein intake [p = 0.002]. In addition, an inverse correlation was shown between total protein intake on the first 3 days of life and lung resistance [r = -0.68; p = 0.002]. However, we did not find any significant relationship between caloric intake and studied lung function parameters. FRC was significantly higher in children who had received a low protein intake during their first week of life. Exhaled NO was not significantly different between the two groups.

Conclusion: Early parenteral protein intake appears to reduce bronchial obstruction in children with BPD. This long term improvement in lung function underlines the importance of adapting both quantitatively and qualitatively parenteral nutrition of very premature infants.

Keywords: Bronchopulmonary dysplasia, Parenteral nutrition, Protein intake, Respiratory function tests, Prematurity

Conclusion: CLM are a heterogeneous group of disorders that can be diagnosed at early age with the new imaging modalities such as chest CT, prenatal ultrasound, CT angiography and magnetic resonance imaging. CLM may present later in childhood or even in adult life. The clinical manifestation of these malformations varies from respiratory distress to an incidental finding on routine chest radiography. Although antenatally-diagnosed lesions may spontaneously regress before birth, evidence-based information for advising parents regarding management options is lacking.

Keywords: Bronchogenic cyst, CCAM, CCAM type 2, CLE, enteric cyst, thymic adenomatoid malformation, pulmonary sequestration, bronchial atresia

Results: Antenatal diagnosis of CCAM was made in 16 patients. Forty-nine patients had postnatal diagnosis. In 4 patients, the diagnosis was not established until the fifth year of age. The most frequent common radiological findings were lung cysts and pneumonic consolidation. The mean age of the diagnosis was 25 months. Fifty-nine patients had no symptom in the neonatal period. The most common congenital malformations associated with CCAM and hyperinflation with mediastinal shift in CLE are bronchogenic cyst and congenital lobar emphysema (CLE).

Keywords: Bronchopulmonary dysplasia, Parenteral nutrition, Protein intake, Respiratory function tests, Prematurity

CDH still represents today one of the most dramatic presentations of all respiratory emergencies in neonates and, at the same time, a difficult balance in critical care requiring early perioperative and hemodynamic stabilization. This congenital malformation occurs in approximately 1 in 4,000 live births as a defect of the diaphragmatic anatomy causing herniation of the intestinal tract in the thoracic cavity during fetal life. Other malformations including heart, neural tube, intestinal tract, renal and skeletal defects in certain syndromes can also be associated in fifty percent of cases. Clinical symptoms generally are observed at birth as severe respiratory distress, cyanosis and scaphoid abdomen. Infants in less severe respiratory failure can manifest varying degrees of tachypnea with cyanosis. A subtle presentation, also including feeding problems and associated with mild respiratory distress, can occur in small hernias, also in relation with the timing and degree of visceral herniation. Consequently, diagnosis can occur later in life (approximately in 5% of all cases) although prenatal diagnosis today is generally the rule. Rarely does a neonate with CDH manifests no symptoms during the first few hours after birth or even days of life. We describe the case of a 27-day-old female out-born neonate admitted at our Division for an urgent consultation for bilious vomiting and then surgically treated for CDH. No previous diagnosis was performed, before or after the birth period and at the Birth-Center, until our first observation. In particular, parents remarked the onset of worsening vomiting with evident presence of bile during the previous few days. Moderate dehydration because of initial starvation was observed at admission. Ultrasonography demonstrated a herniated midgut in the left hemi-thorax with associated mild fluid layer; the stomach, liver and spleen were conversely orthotopically disposed. Surgical correction by closure of the diaphragmatic cleft after reduction of the herniated intestinal tract enabled resolution. The remission of all symptoms was observed within a few days. In CDH, the defect possibly varies from a few centimeters to a complete absence of hemi-diaphragm and rarely involving the entire diaphragm. The survival rate is related to the extension of the defect that can affect pulmonary development and the pulmonary vascular bed. Clinical spectrum includes a wide range of possibilities from post-natal death to no symptoms and diagnosis later in life. Our case demonstrates an exceptionally delayed and strictly clinical presentation consisting in only repeated bilious vomiting after a long wellbeing period after birth in an apparently healthy infant.

Conclusion: CLM are a heterogeneous group of disorders that can be diagnosed at early age with the new imaging modalities such as chest CT, prenatal ultrasound, CT angiography and magnetic resonance imaging. CLM may present later in childhood or even in adult life. The clinical manifestation of these malformations varies from respiratory distress to an incidental finding on routine chest radiography. Although antenatally-diagnosed lesions may spontaneously regress before birth, evidence-based information for advising parents regarding management options is lacking.

Keywords: Bronchogenic cyst, CCAM, CCAM type 2, CLE, enteric cyst, thymic adenomatoid malformation, pulmonary sequestration, bronchial atresia

Results: Antenatal diagnosis of CCAM was made in 16 patients. Forty-nine patients had postnatal diagnosis. In 4 patients, the diagnosis was not established until the fifth year of age. The most common common radiological findings were lung cysts and pneumonic consolidation. The mean age of the diagnosis was 25 months. Fifty-nine patients had no symptom in the neonatal period. The most common congenital malformations associated with CCAM and hyperinflation with mediastinal shift in CLE are bronchogenic cyst and congenital lobar emphysema (CLE).

Keywords: Bronchopulmonary dysplasia, Parenteral nutrition, Protein intake, Respiratory function tests, Prematurity

CDH still represents today one of the most dramatic presentations of all respiratory emergencies in neonates and, at the same time, a difficult balance in critical care requiring early perioperative and hemodynamic stabilization. This congenital malformation occurs in approximately 1 in 4,000 live births as a defect of the diaphragmatic anatomy causing herniation of the intestinal tract in the thoracic cavity during fetal life. Other malformations including heart, neural tube, intestinal tract, renal and skeletal defects in certain syndromes can also be associated in fifty percent of cases. Clinical symptoms generally are observed at birth as severe respiratory distress, cyanosis and scaphoid abdomen. Infants in less severe respiratory failure can manifest varying degrees of tachypnea with cyanosis. A subtle presentation, also including feeding problems and associated with mild respiratory distress, can occur in small hernias, also in relation with the timing and degree of visceral herniation. Consequently, diagnosis can occur later in life (approximately in 5% of all cases) although prenatal diagnosis today is generally the rule. Rarely does a neonate with CDH manifests no symptoms during the first few hours after birth or even days of life. We describe the case of a 27-day-old female out-born neonate admitted at our Division for an urgent consultation for bilious vomiting and then surgically treated for CDH. No previous diagnosis was performed, before or after the birth period and at the Birth-Center, until our first observation. In particular, parents remarked the onset of worsening vomiting with evident presence of bile during the previous few days. Moderate dehydration because of initial starvation was observed at admission. Ultrasonography demonstrated a herniated midgut in the left hemi-thorax with associated mild fluid layer; the stomach, liver and spleen were conversely orthotopically disposed. Surgical correction by closure of the diaphragmatic cleft after reduction of the herniated intestinal tract enabled resolution. The remission of all symptoms was observed within a few days. In CDH, the defect possibly varies from a few centimeters to a complete absence of hemi-diaphragm and rarely involving the entire diaphragm. The survival rate is related to the extension of the defect that can affect pulmonary development and the pulmonary vascular bed. Clinical spectrum includes a wide range of possibilities from post-natal death to no symptoms and diagnosis later in life. Our case demonstrates an exceptionally delayed and strictly clinical presentation consisting in only repeated bilious vomiting after a long wellbeing period after birth in an apparently healthy infant.

Conclusion: CLM are a heterogeneous group of disorders that can be diagnosed at early age with the new imaging modalities such as chest CT, prenatal ultrasound, CT angiography and magnetic resonance imaging. CLM may present later in childhood or even in adult life. The clinical manifestation of these malformations varies from respiratory distress to an incidental finding on routine chest radiography. Although antenatally-diagnosed lesions may spontaneously regress before birth, evidence-based information for advising parents regarding management options is lacking.
Objective: Prematurely born infants are more susceptible to various respiratory disorders such as Respiratory distress (RD), upper or lower airway infection and Bronchopulmonary Dysplasia (BPD). Expired Nitrogen Oxide in ventilated infants suffering from BPD has shown to be elevated on day 28 postnatally. Continuous Positive Airway Pressure (CPAP) is more frequently used than mechanical ventilation in treating infants with respiratory disorder. The purpose of this study was to develop a method for measuring Tidal Breath Fractional Exhaled Nitrogen Oxide (TB FeNO) in CPAP-treated infants. We hypothesized that FeNO measurements were eligible as a biomarker for inflammatory processes in the neonatal airway or as a marker of lung development in the premature infant.

Methods: Six infants with gestational age at birth ranging from 28 + 4 to 41 + 1 weeks were enrolled in this pilot study. The inclusion criteria were nasal CPAP treatment for more than 24 hours. Exclusion criteria were known congenital lung disease. After informed consent from their parents, the children had as many measurements as possible (1-7) during their hospital stay. We attempted to measure FeNO during CPAP treatment and immediately after disconnection of the CPAP (Benveniste valve high flow system). Depending on the respiratory stability of the child, they were measured again after 5 minutes or after a 1-hour pause or longer.

Results: Median postnatal age was 28 days (range 5-60 days). Median weight at time of measurement was 2.62 kg (range 1.39 kg-6.2 kg). The fifteen measurements during CPAP were unsuccessful. Thirteen measurements immediately after disconnection were successful. One infant was stable for five minutes and 3 infants were stable without CPAP for 1 to 5 hours. Mean FeNO was 3.5 ppb (range 0.6-10.1 ppb). Interestingly, the infant with the highest FeNO (10.1 ppb) required nasal CPAP for 33 days.

Conclusion: Our setup did not allow measuring TB FeNO in infants during CPAP treatment. With a sensitivity of 0.1 ppb per second, the Eco Medics CLD 88 sp worked well in infants without CPAP treatment. The inspired flow during CPAP by the Benveniste valve reaches up to 15 liters per minute and thus decreases the expiratory concentration of FeNO 1000-fold given the small infant tidal volumes. Results obtained immediately after disconnection of the CPAP treatment were in good concordance with measurements after 5 minutes as well as after hours of pause in CPAP treatment.

6. CYSTIC FIBROSIS

#86 - AQUAGENIC KERATODERMA (AK): A SKIN CLUE IN A YOUNG BOY WITH CYSTIC FIBROSIS (CF)

Basory E., Yousef S., Colin A.
Pedicatric Pulmonology, University of Miami / Miller School of Medicine - Miami, FL, USA

Background: AK has been recently recognized as a cutaneous manifestation of CF. It is estimated that more than half the patients with AK have documented CF with predominance of young females and carriers of the delta F508 mutation including heterozygous carriers. AK is clinically characterized by premature edema and hyperwrinkling of palms and/or soles with the presence of translucent/white papules after water immersion. The accentuation of skin lesions after water immersion is known as the “hand-in-the-bucket” sign and is considered diagnostic. Mutations in the CF transmembrane conductance regulator (CFTR) gene are speculated to support the assumption of delta F508 as a possible predisposing factor for AK. AK has been recently recognized as a cutaneous manifestation of CF, which further expands the spectrum of CFTR-related disorders. Most CF practitioners may not be familiar with such cutaneous phenotype; we therefore choose to report our case. Screening for CFTR gene mutations is recommended in cases of AK with a milder phenotype of AK.

Conclusion: AK is a recently recognized manifestation of CF, which further expands the spectrum of CFTR-related disorders. Most CF practitioners may not be familiar with such cutaneous phenotype; we therefore choose to report our case. Screening for CFTR gene mutations is recommended in cases of AK where it may be the sole presentation of asymptomatic carriers of CF. Our case supports the assumption of delta F508 as a possible predisposing factor for AK.

#89 - IMPAIRED NEUTROPHIL EXTRACELLULAR TRAPS FORMATION IN CHILDREN SUFFERING FROM CYSTIC FIBROSIS

Bokonjic D., Stojnic N.2, Colic M.3, Mihajlovic D.3, Vasilijic S.4, Minic P.2, Vucevic D.3

1 Department of Pediatrics, University clinical hospital - Foca, Bosnia-Herzegovina.  
2 Helen Schneider Hospital for Women, Rabin Medical Center - Petach-Tikva, Israel.  
3 Diagnostic Imaging, Pediatric Imaging Unit, The Edmond and Lily Safra Children’s Hospital, Sheba Medical Center - Ramat-Gan, Israel.
Cystic fibrosis (CF) is the most common monogenic autosomal recessive genetic disorder in whites that affects mostly the lungs. Stage of pulmonary disease in patients suffering from CF is the main predictive factor of survival, hence understanding the pathophysiological mechanisms of disease in lungs is important for treatment. Within the innate immune system, granulocytes play a crucial role in the defense against infections. In 2004, it was discovered that activated neutrophils release neutrophil extracellular traps (NETs) as a possible novel antimicrobial mechanism. NETs are formed through a unique process, termed “NETosis”, which is initiated through contact with different pathogens (TLR2 and TLR4), cytokines (IL-8, TNF), or chemical-like compounds (PMA – phorbol 12-myristate 13-acetate). Chromatin from stimulated granulocytes begins to decondensate through the process mediated by NADPH-dependent oxidase, MPO, neutrophil elastase and proteins from azurophil granules. DNA from neutrophils is released into the cytoplasm and merges with various antimicrobial factors such as histones and proteases. The complex is then released through the plasma membrane out of the cell and forms NETs on the surface and around the granulocytes. The function of NETs is to catch and destroy microbes using different antimicrobial mechanisms. The aim of the study is to investigate the process of NETosis in children suffering from CF. Neutrophils were isolated from peripheral blood of underage patients diagnosed with cystic fibrosis and healthy volunteers (control sample). Cells were stimulated with phorbol 12-myristate 13-acetate (PMA) to induce NETs release and reactive oxygen species (ROS) formation. NET release was detected by extracellular DNA level measurement and ROS formation by luminol-based chemiluminescence assay. Apoptosis was detected by Annexin V-fluorescein isothiocyanate/propidium iodide staining. Preliminary results showed that neutrophils from CF patients expressed a decreased release of NET (5.9 ± 1.24% of total DNA) compared to control samples (19.61 ± 4.69% of total DNA). At the same time, reduced production of ROS was identified in neutrophils of CF patients, which is in correlation with the known role of ROS in NET formation. The detected decrease in NET in CF patients was not a consequence of apoptosis since there was no difference in neutrophil apoptosis between CF patients and control samples. Results of this study contribute to the better understanding of granulocyte dysfunction in children suffering from CF and indicate the possibility that modulation of the NET process can influence treatment outcome.

#990 - NEW OPPORTUNITIES FOR EARLY DIAGNOSIS OF CARBOHYDRATE METABOLISM DISORDER IN ST. PETERSBURG CHILDREN WITH MUCOVISCIDOSIS

Matveeva T.
State Pediatric Medical University, St. Petersburg City Children’s Hospital N4 - St. Petersburg, Russia

Purpose: to optimize diagnostics of carbohydrate metabolism disorder in children with mucoviscidosis.

Materials and methods: A total of 42 pediatric patients with mixed form of mucoviscidosis was examined in 2012-2014. Mutation delF508 of the CFTR gene was found in most children (31%); it was homozygous in 12 of these patients, and in 19 patients it was found in compound with other mutations. No genetic defect was found in 5 children. Patients above 3 years of age had an oral glucose tolerance test (OGTT). In order to assess sensitivity of tissues to insulin, Homa and Caro indices were calculated during the study. Additionally, 14 patients (half of whom aged 3-11, and the other half adolescents) underwent a 24-hour glucose test with MiniMed Paradigm 722.

Results: The OGTT revealed carbohydrate metabolism disorder in 9 examined children (21%); diabetes mellitus was diagnosed in 6 patients (14%), and impaired glucose tolerance was found in 3 patients (7%). Diabetes and carbohydrate metabolism disorder were found reliably more frequently in children above 11 years of age. During the 24-hour continuous glucose test, intractable postprandial hyperglycemia was found in 3 children from the 3-11 age group (43%) and in all adolescents. In accordance with calculated results of insulin resistance indices (Homa and Caro), 71% of the patients with carbohydrate metabolism disorder had a reduced Caro index (<0.332) on the 120th minute of the OGTT, which indicates insulin resistance in these patients. The incidence of carbohydrate metabolism disorder in the subgroup of children with more frequent mutation of CFTR-delF508 was 35%; all the cases of mucoviscidosis and diabetes mellitus were linked to the delF508 mutation of the CFTR gene both in homozygous state and in compound. The incidence of carbohydrate metabolism disorder in patients with the delF508 CFTR mutation in homozygous state was 33%, compared to 37% in children with the delF508 CFTR mutation in compound.

Conclusion: The incidence of carbohydrate metabolism disorder, including diabetes mellitus, was reliably higher in children with the mixed form of mucoviscidosis (21%) than in the overall population. Carbohydrate metabolism disorder was predominantly found in children over 11 years of age, with the morbidity increasing age-proportionally. Taking into consideration the results of the 24-hour glucose monitoring test, this method of examination is advisable for patients with mucoviscidosis, because it allows diagnosing hidden hyperglycemia that is intractable by standard methods. With regard to the discovered changes in the Caro index, it is quite likely that insulin resistance may be the primary cause of carbohydrate metabolism disorder in children with mucoviscidosis. Carbohydrate metabolism disorders, including diabetes mellitus associated with mucoviscidosis, were more frequently found in patients with delF508 mutation of the CFTR gene.

#139 - A CASE OF CYSTIC FIBROSIS WITHOUT AN IDENTIFIED MUTATION

Ferreira I., Couto Guerra I., Barbosa T., Senra V., Rocha H.
Pediatrics, Centro Materno-Infantil do Norte, Centro Hospitalar do Porto - Porto, Portugal

Introduction: Cystic Fibrosis (CF) is the most common autosomal recessive genetic disorder in the Caucasian population. The estimated incidence of CF in Portugal is 1/6000 new cases of newborn infants per year. It results from the mutation of a gene located on chromosome 7, which encodes the transmembrane protein synthesis (CFTR), usually identified by molecular genetic studies. We report the case of a child with a history and sweat test compatible with CF, with no mutation identified.

Case-report: Ten-year-old girl, of gypsy ethnicity, daughter of consanguineous parents. She had a history of obstipation and a pneumonia of the middle lobe at the age of 3. Referred to our pediatric hospital at 7 years of age, with recurrent episodes of wheezing since 3 years old, always with normal weight gain. She was medicated daily with inhaled corticosteroids and bronchodilators on demand, maintaining poor clinical control. On examination, she was eupeptic, without signs of respiratory distress, hypoxemia, chest deformity, clubbing or changes to pulmonary auscultation. Chest radiography revealed hyperinflation and bilateral hyperlucent rounded images, predominantly in the right lung field, and respiratory function tests revealed no changes. Analytically, she had a normal immunological study and positive skin tests to mites. The sweat test was performed three times with chloride above 60 mmol/L and the pancreatic elastase in feces was 138 mg/g (moderate impairment). The extended molecular testing for cystic fibrosis identified no mutation. Currently she is 10 years old and is under inhaled (salbutamol and budesonide) and pancreatin therapy, maintaining good weight gain and mild sporadic pulmonary exacerbations. Pseudomonas was isolated from sputum, without
any isolations after eradication therapy with inhaled tobramycin and oral ciprofloxacin. Chest CT revealed normal airway caliber, with bronchial wall thickening, but without bronchiectasis; lung parenchyma with a slight diffuse ground glass pattern.

Discussion: In Portugal, the most frequent mutation is F508del (69%), followed by the R334W mutation (12.8%). However, worldwide, less than 20 CFTR mutations have a frequency greater than 0.1%, and these frequencies vary between different geographical regions and ethnic groups. The extensive molecular study used in this case identifies about 98% of the most frequent mutations in the Portuguese population, however it returned negative for this child. This case illustrates an atypical situation of cystic fibrosis, which may constitute 1-5% of the cases in which mutations are not identified.

7. RESPIRATORY MANIFESTATIONS OF EXTRA-PULMONARY DISEASES (INCLUDING AIDS)

#29 - RESPIRATORY OUTCOMES OF GASTROESOPHAGEAL REFLUX IN INFANCY - A POPULATION-BASED COHORT STUDY

Currie SM.1, Martin AJ.2, Baghurst P.3, Dowling K.3
1 Paediatrics and Child Health, Hawke’s Bay district Health Board - Hastings, New Zealand
2 Pulmonary Medicine, Children’s Youth and Women’s Health Service - Adelaide, Australia
3 Public Health Research Unit, Children Youth and Women’s Health Service - Adelaide, Australia

Objectives: To determine the relationship between infant spilling and respiratory symptoms in both infancy and middle childhood (9 years of age).

Methods: A prospective birth cohort was followed with daily symptom diaries for the first 2 years of life, and reviewed at 9 years of age (range: 8-11 years). The prevalence of spilling in the first 2 years of life, respiratory symptoms in the first two years and at 9 years, and symptoms of gastroesophageal reflux at 9 years were measured. Lung function testing was performed on children at 9 years of age.

Results: A total of 836 children had daily symptom diaries completed for the first 2 years of life. Of these 693 (83%) were followed up at 9 (8-11) years. In the first 24 months of life there was a correlation between frequency of spilling and episodes of wheeze (P<.0005), days of moist cough (P=.006), and days of nasal symptoms (P<.001). These relationships persisted in multivariate analysis with potential confounders. There was no relationship between frequency of spilling in infancy and symptoms of cough or wheeze at 9 years. Children who had more frequent spilling in infancy did not have abnormal lung function tests. Those children who had symptoms of gastroesophageal reflux at 9 years were more likely to report respiratory symptoms in the last year (P<.006). There was no significant relationship between reflux symptoms at 9 years and lung function.

Conclusions: Spilling in infancy is common, but outgrown by the majority of children. It is related to respiratory symptoms (wheeze, cough, nasal symptoms, and episodes of respiratory infection) in the first 2 years of life, but not to respiratory symptoms nor abnormal lung function in middle childhood.

#74 - ATYPICAL PRESENTATION OF PNEUMOCYSTIS JIROVECCI PNEUMONIA IN A 6-MONTH OLD PATIENT WITH CONGENITAL IMMUNODEFICIENCY

Taseen K.1, Bergeron C.2, Rola-Plesczynski M.1, Patenaude YG.3, Counil FP.4
1 Pediatrics, Centre hospitalier universitaire de Sherbrooke - Sherbrooke, Canada
2 Microbiology and Infectiology, Centre hospitalier universitaire de Sherbrooke - Sherbrooke, Canada
3 Diagnostic Radiology, Centre hospitalier universitaire de Sherbrooke - Sherbrooke, Canada

Background: Pneumocystis jirovecii pneumonia is a life threatening infection. Quick identification of the pathogen is critical due to the urgency of required management. Its rarity can lead to delayed diagnosis in early infancy. We describe a case of a 6-month old infant with common cold symptoms who was diagnosed with Pneumocystis jirovecii pneumonia.

Methods:

Case review:

Clinical Case: A 6-month-old female of Afghan non-consanguineous parents presented with a month long history of cough and low-grade fever. The patient was known for severe intrauterine growth restriction and was delivered by C-section at 34 weeks for a biophysical profile of 2 out of 8 and bradycardia. She was also known for a right polydactyly with duplication of thumb phalanges, anemia and leucopenia. A genetic work up showed nothing of significance. She was discharged from neonatology with a follow up from the hematologist. At 4 months, her CBC showed only persisting lymphopenia at 1.9×10^9/L. Parents had consulted at the emergency department twice before admission in the last 4 weeks, each time for cough and low-grade fever. She was diagnosed with viral upper respiratory tract infection with clear lungs on auscultation on both occasions. Suspicion by the radiologist for a subtle yet persisting granular pattern on her chest X-ray prompted a consultation with the pediatrics team. Upon admission, the patient was non- lethargic, afebrile and eupneic (RR 40/min, SpO2 100% at room air). Parents described a slight decrease in feeding and non-persisting tachypnea that accompanied cough. Auscultation demonstrated scattered crackles and rhonchi with subtle intercostal retractions. Her growth chart revealed curves consistent with failure to thrive. A thoracic CT scan mainly showed diffuse ground glass opacities with non-necrotic mediastinal lymph nodes. Immunofluorescence assay on broncho-alveolar lavage (BAL) was positive for Pneumocystis jirovecii. Laboratory investigation showed peripheral blood lymphocytes at 2×10^9/L. Immunological work-up revealed undetectable IgG and IgM and all lymphocyte subsets were below normal values. HIV status for mother and infant was negative. Following the BAL, the patient became lethargic with tachypnea. Her cerebrospinal fluid showed diffuse ground glass pattern.

Clinical Case: A 6-month-old female of Afghan non-consanguineous parents presented with a month long history of cough and low-grade fever. The patient was known for severe intrauterine growth restriction and was delivered by C-section at 34 weeks for a biophysical profile of 2 out of 8 and bradycardia. She was also known for a right polydactyly with duplication of thumb phalanges, anemia and leucopenia. A genetic work up showed nothing of significance. She was discharged from neonatology with a follow up from the hematologist. At 4 months, her CBC showed only persisting lymphopenia at 1.9×10^9/L. Parents had consulted at the emergency department twice before admission in the last 4 weeks, each time for cough and low-grade fever. She was diagnosed with viral upper respiratory tract infection with clear lungs on auscultation on both occasions. Suspicion by the radiologist for a subtle yet persisting granular pattern on her chest X-ray prompted a consultation with the pediatrics team. Upon admission, the patient was non- lethargic, afebrile and eupneic (RR 40/min, SpO2 100% at room air). Parents described a slight decrease in feeding and non-persisting tachypnea that accompanied cough. Auscultation demonstrated scattered crackles and rhonchi with subtle intercostal retractions. Her growth chart revealed curves consistent with failure to thrive. A thoracic CT scan mainly showed diffuse ground glass opacities with non-necrotic mediastinal lymph nodes. Immunofluorescence assay on broncho-alveolar lavage (BAL) was positive for Pneumocystis jirovecii. Laboratory investigation showed peripheral blood lymphocytes at 2×10^9/L. Immunological work-up revealed undetectable IgG and IgM and all lymphocyte subsets were below normal values. HIV status for mother and infant was negative. Following the BAL, the patient became lethargic with tachypnea. Her cerebrospinal fluid showed diffuse ground glass pattern.

Conclusion: Pneumocystis jirovecii pneumonia is a rare pneumopathy in infants, exclusively seen in immunocompromised patients. This case illustrates its possible atypical presentation, such as the lack of respiratory distress or hypoxemia. This case also demonstrates the importance of carefully assessing chest X-rays taken in an emergency department setting.

#93 - STRIDOR IN CROHN’S DISEASE - CASE REPORT

Göcs E.1, Benedek P.2, Uhreczyk G.1
1 Pulmonology, Heim Pál Children’s Hospital - Budapest, Hungary
2 ENT Department, Heim Pál Children’s Hospital - Budapest, Hungary

Extraintestinal manifestations of Crohn’s disease are well recognized. Upper airway involvement is extremely rare and can present with airway obstruction in any age group, including the pediatric patient. We describe the case of a 9-year-old boy who has been treated for Crohn’s disease for several years. His gastrointestinal symptoms responded to steroid and immunosuppressive therapy, thus the treatment was terminated. After some weeks he experienced recurrent diarrhea, but this time he also had difficulty in breathing. Examination of his larynx revealed chronic inflammatory changes of the epiglottis and aryepiglottic folds, the ENT specialist found that a biopsy would have been very dangerous. We supposed a chronic inflammation of laryngeal cartilage, and steroid treatment was induced. Intestinal symptoms responded, but the upper airway obstruction failed to respond to steroids and immunosuppressive treatment, hence infliximab was initiated. Although the progression of the airway obstruction was prevented, the endoscopic picture does not show complete recovery. At the moment, the
child goes to school, does sports, and has moderate stridor at nights. As this case is still open, further ideas during CIPP XIV are welcome!

138 - VASCULAR MALFORMATIONS AS RARE CAUSES OF RESPIRATORY DISORDERS

Kreslova M.1, Jehlicka P.1, Vondrakova R.2, Sykora J.1
1 Pediatric Department, Faculty Hospital Pilsen - Pilsen, Czech Republic
2 Department of Radiology, Faculty Hospital Pilsen - Pilsen, Czech Republic

The purpose of the study is to focus on less common extra-pulmonary causes of dyspnoea and of recurrent respiratory infections in childhood. The method leading to the main diagnosis is presented in two particular cases. The incidence of vascular malformations is about 3%. However, the severity of symptoms depends on the level of tracheal and oesophageal compression. In 2014 in the Faculty Hospital in Pilsen, vascular malformations were found as a cause of dyspnoea in two children aged 4 and 7 years. The first case shows a 4-year-old girl with recurrent bronchitis and double-sided bronchopneumonia, which started at the age of 3. Vascular ring (double-aortic arch) caused compression of the trachea and bronchi, leading to recurrent respiratory infections. The vascular malformation was confirmed with echocardiography, which was performed before the planned bronchoscopy. Chest computed tomography confirmed our diagnosis. The girl remains without any respiratory symptoms after surgical correction. The second case describes a 7-year-old overweight boy suffering from hypoacusis and respiratory symptoms – recurrent cough, dyspnoea, wheezing. Due to an asymmetric auscultation and the corresponding radiographic findings, rigid bronchoscopy was performed to exclude an inhaled foreign body. The patient was treated with antiasthmatic drugs (inhaled corticosteroid and long-actingbeta2-agonist). Right aortic arch and agenesis of the left pulmonary artery were demonstrated by echocardiography. Severe ciliary dyskinesia and acid gastro-oesophageal reflux were established. Left lung hypoplasia with compensatory enlargement and right lung herniation occurred due to the vascular deficit. This was verified by chest computed tomography. Tracheal deviation was seen on endoscopy. Perfusion of the left lung was not demonstrated. In 2014, two rare vascular abnormalities causing respiratory problems were diagnosed at our department. Recurrent respiratory infections in children are common. However, they may indicate serious extra-pulmonary disease. It is necessary to also consider congenital anomalies. Echocardiographic and bronchoscopic examination should be considered for all children with recurrent respiratory infections or shortness of breath to clarify the aetiology.

8. NEUROMUSCULAR AND CHEST WALL DISEASES (INCLUDING SIDS)

25 - EXPERIENCES OF PATIENTS ON LONG TERM VENTILATION TRANSFERRING TO ADULT SERVICES

Narayan O.1, Bajgoric S.2, Cecil-Oakes I.1, Thomas A.1, Samuels M.2
1 Department of Respiratory Medicine, Birmingham Children’s Hospital - Birmingham, United Kingdom
2 Academic Department of Paediatrics, University Hospital of North Midlands - Stoke On Trent, United Kingdom

This was a qualitative study to improve the transition from paediatrics to adult services.

Aims: Medical advances mean that more children with serious illnesses are surviving into adulthood. Recent legislation and guidelines stress the importance of delivering improved joined-up services for children undergoing transition to adult services [1,2]. A qualitative study was performed to explore the experiences of patients receiving long-term ventilation (LTV).

Methods: Questionnaire-based telephone interviews were conducted with 21 patients (14 males, median age 26 years, range 14–57) on LTV or their carers.

All had previously been within children’s services and were now under adult respiratory care at a UK teaching hospital. The underlying causes for LTV included: Duchenne muscular dystrophy (9), other muscular dystrophies (6), congenital central hypoventilation syndrome (4) and other (2).

Results: Thematic analysis of the data identified 3 main themes:

1. Variability: the age at which transition occurred varied (17-25), as did the option to attend combined clinics, which was only given to 3 of the 21 patients. There were discrepancies in the provision of community services, which was described as being “post-code dependent”

2. Unfamiliarity: patients expressed concerns about the unfamiliarity of adult doctors with their background and condition, which was often interpreted as insensitivity or lack of knowledge. They expressed frustration at having to repeat their story to numerous health care professionals.

3. Separation of services: care under children’s services was reported as being more holistic when compared with the single organ approach in adult services. However, the thoroughness of adult physicians in patient management was appreciated.

Conclusion: Our study highlights the gap that needs to be bridged between children and adult services for patients on LTV. Early transition planning should occur to alleviate the unfamiliarity commonly experienced. This should include information about adult care and the differences in service provision. The utilisation of health care passports can do much to avoid physician unfamiliarity with the patient’s situation. These changes need to be uniformly adopted in order to improve patient satisfaction, care and long term outcome.

References

Care Act 2014
Care Quality Commission. From the pond into the sea: Children’s transition to adult healthcare services. June 2014.

9. EPIDEMIOLOGY, ENVIRONMENTAL RISKS, PREVENTION, SOCIO-ECONOMIC COST, PUBLIC HEALTH RESOURCES

27 - INCREASED RESPIRATORY HOSPITALIZATIONS IN LATE PREMATURITY: CLINICAL COURSE AND OUTCOME

Breuer O.1, Nassar H.2, Cohen-Cymberknoh M.1, Kerem E.1
1 Pediatric Pulmonology and CF Center, Hadassah-Hebrew University Medical Center - Jerusalem, Israel
2 The Faculty of Medicine, The Hebrew University of Jerusalem - Jerusalem, Israel

Introduction: Up to 10% of births occur at late preterm (LPT), defined as births at 34-0/7 to 36-6/7 weeks gestational age. It is currently considered that LPT infants have increased respiratory morbidity beyond the neonatal period. Still, it has not yet been determined whether LPT infants have a worse clinical outcome in respiratory hospitalizations during the first two years of life.

Objective: To compare the clinical course and outcomes of children born LPT with full term infants (FT, ≥37 weeks) who were admitted to the pediatric ward with respiratory illness in the first two years of life.

Study design: Records of patients < age 2 years admitted during the year 2012 to the hospital due to a respiratory illness were reviewed.

Results: 486 patients met inclusion criteria; 51 (10.5%) were LPT, and 435 (89.5%) were FT. The two groups were similar with regard to age and sex at admission, days of fever prior to admission, chronic medical or supplemental oxygen treatment, chronic respiratory and non-respiratory morbidity and diagnosis at admission (p > 0.1). Bronchiolitis was the most common diagnosis (52.3%) for both groups. LPT had a significantly increased risk for recurrent hospitalization due to respiratory illnesses in the year following current admission (21% vs. 10.6%, p<0.05, odds ratio = 2.23, 95% CI = 1.06-4.72), adjusted for multiple covariates. A diagnosis of bronchiolitis or asthma was recorded in all readmissions of LPT infants vs. 86% of FT (p < 0.05, odds ratio = 27.08, 95% CI = 1.55-474.2).
Other major or minor outcomes indices such as hospital length of stay, admission to the pediatric intensive care unit, medical treatment during hospitalization, days of supplemental oxygen treatment, resource utilization, microbiological diagnosis and recommended treatment and follow-up on discharge, were similar between groups (p > 0.1).

**Conclusion:** Infants who were born at late prematurity and hospitalized for a respiratory illness are at increased risk for recurrent hospitalizations due to respiratory causes during the first two years of life. Defining the causes of the respiratory morbidity (e.g. asthma) and providing preventive therapy might reduce hospitalization and save costs.

#32 - INTENSIVE CARE SIGNIFICANTLY INCREASES THE HOSPITALISATION COSTS OF INFANT BRONCHIOLITIS

**Hvickilė P.1, Forma L.2, Korppi M.3**

1 Centre for Child Health Research, University of Tampere and Tampere University Hospital - Tampere, Finland
2 School of Health Sciences, University of Tampere - Tampere, Finland

**Aim:** Up to 3% of infants with bronchiolitis under 12-months-of-age are hospitalised and of whom up to 9% require intensive care. We evaluated the costs of bronchiolitis hospitalisation and the factors associated with high costs, with a special focus on whether infants needed intensive care. This study was conducted from the viewpoint of the care provider.

**Methods:** Baseline and cost data were retrospectively collected using electronic files of the Tampere University Hospital, Finland, for 80 infants under 12-months-of-age who were treated in the paediatric intensive care unit (PICU) for bronchiolitis during a 13-year period. We calculated the total daily hospitalisation costs for patients admitted to the PICU (including the costs in the PICU, at the ward and in the emergency department) and compared these costs with those of 104 treated at the ward and those of 56 outpatients treated in the emergency department. Statistical analyses were performed with SPSS 21 software. Spearman’s correlation, analysis of variance, chi-square test and Mann-Whitney U-test were used for total costs in univariate analyses, and linear regression analysis with logarithmic transformation for costs per patient per day in the PICU group in both univariate and multivariate analyses.

**Results:** The mean hospitalisation cost for the PICU patient was €8,061 (95% CI 6,193-9,929), compared to €1,834 (1,649-2,020) for the other inpatients and €359 (331-387) for the outpatients. The hospitalisation costs per patient correlated strongly with the total length of stay (r = 0.960; p < 0.001) and length of PICU stay (r = 0.681; p < 0.001), and modestly with gestational age (r = -0.346; p < 0.001) and age on hospital admission (r = -0.344, p < 0.001). The mean hospitalisation costs per patient for the infants treated in the PICU were €6,337 (95% CI €3,929-8,745) in those born at more than 37 weeks of gestation and €10,575 (€7,556-13,595) in those born at less than 32 weeks of gestation. In the multivariate linear regression analyses, only the treatment year and length of PICU stay retained a statistically significant association with the costs per patient per day in the PICU group.

**Conclusion:** The total hospitalisation costs of infants treated in the PICU for bronchiolitis at less than 12-months-of-age were approximately 4 times higher than in other inpatients and over 20 times higher than in outpatients. The costs were associated only with the length of hospital stay and the length of PICU stay. The patients who were treated in the PICU were younger and more often preterm than those treated at the ward or in the emergency department only. New strategies are required to reduce hospital stays and costs by decreasing the need for intensive care for bronchiolitis.

#61 - QUALITY OF LIFE OF CHILDREN WITH ASTHMA IN SCOTLAND AND LITHUANIA

**Tamulskienė V.1, Turner S.2, Vaikaičiūtė E.3, Valulis A.4**

1 Institute of Public Health, Faculty of Medicine, Vilnius university - Vilnius, Lithuania
2 Child Health, University of Aberdeen - Aberdeen, United Kingdom
3 Medical Academy, Lithuanian University of Health Science - Kaunas, Lithuania
4 Clinic of Children’s Diseases & Institute of Public Health, Vilnius University - Vilnius, Lithuania

**Background:** Asthma is a common chronic condition, especially among children. Asthma negatively affects health related quality of life (QoL) of patients and their family members. It was decided to compare QoL in children with asthma in populations of Scotland and Lithuania where cultural, economical and environmental contexts are different.

**Methods:** QoL was determined by completing The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) in 219 children from 7 to 18 years with asthma who live in Scotland and in 186 school age children from Kaunas city (Lithuania). All children were recruited from primary care centers. The PAQLQ is composed of 23 questions, describing 3 dimensions of quality of life: symptoms, activity, emotions. The responses were evaluated on a 7-point scale according to R. Likert, where 7 corresponded to the best QoL. An overall QoL score was also determined. The relationship of QoL with age, gender, asthma severity and concomitant disease were also assessed.

**Results:** The mean age of children was 11.4 ± 2.8 years in Lithuania vs. 11.8 (± 2.4) years in Scotland, with 66% and 56% being boys respectively. Overall QoL was higher in the Scottish population compared to Lithuanian. The median score (IQR) for overall QoL was 6.1 (5.3; 6.8) in Scotland and 4.7 (4.1; 5.2) in Lithuania (p < 0.005). The median scores (IQR) for symptoms, emotions and activity domains respectively were 6.1 (5.3; 6.8); 6.5 (5.9; 7.0); 3.8 (2.8; 4.8) in Scotland and 4.7 (3.8; 5.4); 4.1 (3.6; 4.7); 4.0 (3.6; 4.6) for children’s QoL in Lithuania. Overall QoL was not related to gender and age. In both populations, QoL was significantly associated with asthma severity, but the use of inhaled steroid was related to QoL only in the Scottish children population, as well as smoking exposure. The presence of allergic rhinitis was associated with the QoL of children with asthma in Scotland, but not in Lithuania.

**Conclusions:** Scottish children with asthma assessed all domains and overall QoL better than Lithuanians. In both studies, QoL was significantly associated with asthma severity, but the effect of other determinants was ambiguous. This may be explained by cultural differences and inequalities and can be an area for further research.

**Main messages:** QoL in both studies was associated with asthma severity which supposes the necessity of an individualized approach of asthma management in children. Due to identification of other determinants of QoL, further studies need to be performed.

#73 - CLINICAL FEATURES AND PROBLEMS OF LONG TERM HOME MECHANICAL VENTILATION FOR THE PEDIATRIC PATIENTS

**Obata T**

Department of Pediatrics, Kagoshima Seikyo Hospital - Kagoshima City, Japan

**Background:** Owing to both social and familial reasons, the number of patients dependent on home mechanical ventilation (HMV) has increased in Japan recently. On the other hand, although various problems in practice of HMV have come to be solved, only a few reports were found. We began HMV management for the patients at our hospital in 2005.

**Objectives:** The purpose of this study is to clarify the current situation and the problems surrounding patients and their families with long term home mechanical ventilation (LT-HMV).

**Subjects and methods:** The clinical charts of the patients in whom HMV was initiated and who had been followed at our hospital during the past nine years were reviewed to obtain data such as underlying diseases, the cause that induced HMV, current situation and major problems in maintaining HMV. In addition, we interviewed the families to learn about their recent impressions and problems they are facing related to the LT-HMV.
Results: Eleven patients from 6 months to 30 years of age, who were initiated on HMV, were followed between May 2005 and July 2014. The underlying diseases were cerebral palsy in five, neuromuscular disease in three, post-resuscitation coma from cardiopulmonary arrest at ER in two, and sequelae of acute encephalopathy in one case. All cases underwent tracheotomy, i.e. six cases after prolonged emergency tracheal intubation (age: 14 to 30 years), five cases because of difficulties during intubation (age: 6 months to 9 years). One patient was weaned from HMV. Another patient went back to school life and spends several hours every day without MV. Seven patients are dependent on HMV. The mean duration of HMV is 3.6 years, ranging from 3 months to 9 years. As a major complication, intratracheal granuloma formation was found in five cases. Eventually, one patient died of pneumonia at the age of 2 years. Another patient moved to another area in Japan with his family. Nine patients remained. Although the parents understand that tracheotomy is inevitable, because the structural deformities in the patient’s airway render tracheal reintubation difficult, they wanted to postpone the procedure as much as possible. The deformities such as scoliosis, thoracic deformity and joint contracture worsen year by year and cause difficulties in patient care. The families, especially the parents, also complain regarding anxiety that their own health problems and aging will make them unsuitable as caregivers.

Conclusion: A multidisciplinary approach as well as social services is essential to improve the care of LT-HMV patients and their families, and an individual care plan should be considered for each patient.

#108 - IMPORTANCE OF VIRAL DIAGNOSIS IN SEVERE LOWER RESPIRATORY TRACT INFECTIONS IN PRESCHOOL CHILDREN AND INFANTS: 4 YEAR STUDY

Ulmeanu A., Zapuciuoiu C.
Pulmonology, Children Emergency Hospital “Grigore Alexandrescu” - Bucharest, Romania

Introduction: Lower respiratory tract infection (LRTI) is a major cause of pediatric morbidity and mortality. A viral etiology is encountered in more than 60% of cases.

Purpose: In this study we aim to determine the impact of viral detections on hospitalization cost and use of antibiotics in children with severe LRTI.

Methods: We performed a retrospective 4 year study comprised of children from 0-5 years with severe LRTI. We compared three groups: children with specified viral infection determined by RT-PCR, children with unspecified but with clinical and laboratory signs of viral infection and children with uncomplicated bacterial infection. All three groups had important signs of respiratory distress. Not included were children with bacterial complicated viral infection, children with neuromuscular disease, congenital cardiac disease and immunodeficiency.

Results: We recorded 39969 admissions with 18.6% being diagnosed as LRTI. From this group, 48% had the diagnosis of viral infection and 52% had the diagnosis of bacterial infection. Only 2% (n = 67) of the viral group had a viral determination. The etiology was: VSR 70%, Influenza 11%, Para-influenzae 4.5% and HMPV, Rhinovirus, Bocavirus, Adenovirus all with 3%. We compared a group of 62 cases with specified viral infection with a group with unspecified viral infection. The mean hospitalization was 6 days for the first and 5 days for the second group. The hospitalization cost was 20% higher in the group with viral determination compared with the group without viral determination. For both groups, 90% of the children received an antibiotic and 8% of the cases received a combination of 2 or more antibiotics. The most used group of antimicrobials for both groups was: Cephalexin 47% followed by Aminopenicillins 44%. When comparing the whole viral group with the bacterial group, we discovered that the mean length of hospital stay for the bacterial group was 11 days compared with 5.5 days. The hospitalization cost was 2.5 higher in this group and antibiotic use was 100%. In 73% of the cases, we encountered an association of 2 or more antimicrobials and the most used antibiotics were: Cephalexin 79%, Aminoglycosides 50%, Carbapenems 39%, and Fluoroquinolones in 24% of the cases.

Conclusion: In our study, viral diagnosis did not shorten the length of stay or influence antibiotic treatment. In contrary, cost was higher in the viral specified group. The rate of antibiotic use was very high in both groups which can be explained by the fact that the LRTIs were complicated with severe respiratory distress. As in other studies in the literature, our study suggests that if the clinician’s attitude towards therapy does not change, the use of viral determination in clinical practice is limited.

Acknowledgement: This work is supported by SOP HRD, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390

10. INVESTIGATION AND DIAGNOSTIC TESTS

#56 - THE COMPARISON BETWEEN DUAL-ENERGY CT SCAN AND SCINTIGRAPHY OF THE LUNG IN PULMONARY VASCULAR DISORDERS

Li YJ., Dai ZK., Cheng HC., Chen IC., Hsu JS.
Pediatrics, Kaohsiung Medical University Hospital. - Kaohsiung, Taiwan

Introduction: Currently available DECT scanners, characterized by dual-source DECT systems, single-source scanners with fast kilovoltage switching, and CT systems with layered detector configurations, enable simultaneous acquisition of data at different tube voltages for dual-energy imaging, allowing analyses of the various materials and tissue components within voxels of a CT image. Applications of this paradigm in the thorax include characterization of the pulmonary blood pool in the setting of acute or chronic pulmonary embolism (PE) and characterization of diseases of the lung parenchyma.

Hypothesis: We hypothesize that DECT can individually provide both anatomic and functional information regarding the lungs in a variety of vascular pulmonary diseases based on a single contrast-enhanced CT examination.

Aims: In this study, we attempted to ascertain whether DECT can be used as an alternative to pulmonary scintigraphy which needs more patient cooperation and time, especially in pediatric patients.

Materials and Methods: From April 2012 to Dec 2012, we prospectively studied the characteristic finding in unique pulmonary vascular disorders, compared with pulmonary scintigraphy. Utilizing cardiac echo gram, selective pulmonary angiography, scintigraphy, pulmonary function tests and pulmonary scintigraphy, we enrolled five patients with idiopathic pulmonary hemosiderosis (1), idiopathic pulmonary arterial hypertension (1), hypoplastic left pulmonary artery associated with hypoplastic left lung and pulmonary hypertension (1), VSD with pulmonary hypertension (1), and Tetrology of Fallot with bicuspid pulmonary valve (1).

Conclusion: The quality of DECT was found to improve the diagnosis of various pulmonary vascular disorders, comparatively to pulmonary scintigraphy. Further developments in DECT techniques and CT scanner technology will further foster and enhance the utility of this application and open new avenues in lung imaging.

#66 - CONTINUOUS LARYNGOSCOPY EXERCISE (CLE) TEST IN CHILDREN SUSPECTED OF EXERCISE-INDUCED LARYNGEAL OBSTRUCTION (EILO)

Buchwald E., Christensen P. Nielsen KG.
Pediatric Pulmonary Service, Copenhagen University Hospital - Copenhagen, Denmark

Background and aims: Exercise-induced laryngeal obstruction (EILO) is an important differential diagnosis of exercise-induced asthma (EIA) in children. EILO is often erroneously interpreted as EIA due to some similarities in the medical history including its relation to exercise and negative impact on physical capacity. Correct diagnosis using CLE test in these children may prevent anxiety and useless long-term asthma treatment. Knowledge regarding the presence of this condition in childhood is limited and only few studies have been published. Our aim was to describe the feasibility and results of CLE in a referred cohort of children with suspicion of EILO.

Pediatric Pulmonology
Methods: We performed a CLE test which provided a direct video-laryngoscopic visualization of the larynx during a maximal exercise test using a flexible, fixed fiberoptic laryngoscope mounted on a "hat" while placed in one nostril securing a clear view of the supraglottic and glottis structures of the larynx during the entire exercise test.

Results: Thirty-six children (25 females/11 males) with a mean (range) age = 14 (9-18) years were referred due to suspected EILO during a period of 3 years. Four children (3 females / 1 male) did not show up. The CLE test was completed in the remaining group of 32 children with a feasibility of 100%. Most children were participating in high performance sports and 66% received asthma medication (Beta-2-agonists as needed and/or inhaled corticosteroids) despite negative tests for underlying asthma disease (beta-2 reversibility and ELIA). Baseline lung function was normal in most children with mean (range) FEV1 = 97% (66-130) of predicted; FVC = 106% (77-139); FEV1/FVC = 0.9 and PEF = 89% (65-123) and Body Mass Index (BMI) = 20.2 (15.2-28.5). Glottic (n = 1) or supraglottic obstruction (n = 10) or combined (n = 1) during maximal exercise was demonstrated in 12 children (37.5%), whereas no abnormalities were observed in 14 children (43.7%). In two children, the results were inconclusive due to no obvious obstruction, but subjective symptoms. In the remaining 4 children, other abnormalities were revealed after placement of the flexible fiberoptic laryngoscope before initiation of the exercise test: 2 children with recurrens paresis; 1 severe laryngeal malformation at rest and 1 with suspected subglottic stenosis. No significant difference could be demonstrated between positive and negative results according to gender, baseline lung function, asthma medication and BMI.

Conclusions: CLE test is a feasible method in school age children and may provide a significant diagnostic yield when EILO is suspected. Thus, in this cohort, 50% of the children exhibited either EILO (37.5%) or other laryngeal abnormalities (12.5%). Correct diagnosis may relieve patients from anxiety and prevent unnecessary long-term asthma treatment. Further studies regarding treatment are urgently needed.

#75 - COMPUTER BRONCHOPHONOGRAPHY - METHOD OF ASSESSMENT OF THE BREATHING PATTERN BY RECORDING THE ACOUSTIC PARAMETERS IN CHILDREN

Shatalina S.¹, Geppe N.¹, Malishev V.², Starostina L.¹, Kolosova N.¹
¹ Department of Children’s Diseases, The First Moscow State Medical University n.a. I.M. Sechenov - Moscow, Russia
² Department of Environmental Engineering and Safety, National Research University “Moscow Power Engineering Institute” - Moscow, Russia

Background: Respiratory sounds are important in the diagnosis of lung diseases. The development of assessment methods of respiratory function in younger children is necessary.

Aim: To evaluate respiratory sounds by computer bronchophonography (CBPhG) in healthy children to determine the benchmark in different frequency ranges, especially in children in the first years of life. To introduce the CBPhG method for assessment of respiratory function in children with bronchopulmonary diseases, especially with airway obstruction.

Materials and methods: Lung function was examined by CBPhG in 144 healthy children (age 1-15 years). Registration of respiratory sounds was recorded for a period of 10 seconds by a high sensitivity transducer in a wide range of frequencies (from 0.2 to 12.5kHz) during quiet breathing: low 0.2-1.2, middle 1.2-5.0 and high frequency >5.0 kHz. CBPhG has a high overall reliability (88.7%), sensitivity (86.4%) and specificity (90.9%).

Herein, we evaluated the acoustic component of the work of breathing (AC).

Results: Regardless of age, AC data were (mean +/- standard deviation) 0.24 +/- 0.08 mC in high, 3.04 +/- 0.13 mC in middle and 71.7 +/- 9.8 mC in low frequency ranges in healthy children.

Conclusions: CBPhG is a highly sensitive method which may be used for assessment of respiratory function in all ages, especially in childhood. This method allows to assess respiratory sounds and to use the results for the diagnosis of bronchopulmonary diseases.

#83 - ELECTRICAL ACTIVITY OF DIAPHRAGM MONITORING AS A USEFUL TOOL IN MAKING A PHYSIOLOGICAL DIAGNOSIS OF CONGENITAL CENTRAL HYPOVENTILATION SYNDROME

Division of Neonatal Intensive Care, Tokyo Women’s Medical University Medical Center East - Tokyo, Japan

Purpose: To evaluate the usefulness of Electrical activity of diaphragm (Edi) monitoring in making a respiratory physiological diagnosis of Congenital Central Hypoventilation Syndrome (CCHS).

Introduction: CCHS is mostly diagnosed by genetic testing. However, respiratory physiological diagnosis is also important for appropriate respiratory care in preventing hypoventilation. We have reported the Ventilatory Response to CO2 (VR CO2), which evaluates the physiological response of the respiratory center, as a diagnostic tool in CCHS. As a new approach, we focused on the Edi, which is used in Neu rally Adjusted Ventilatory Assist mode ventilation for detection of central respiratory drive. The Edi peak increases in response to inspiratory effort such as CO2 retention, and decreases or is absent in central hypoventilation. There are only a few case reports regarding Edi monitoring in CCHS, and these were performed under respiratory support. In this study, we monitored the Edi in multiple cases of CCHS without respiratory support for a precise evaluation of the respiratory center.

Method: The subjects were 3 infants diagnosed with CCHS by genetic testing. The Edi catheter was placed at the esophage-gastric junction to detect the Edi. It was analyzed and displayed on the Servo-i ventilator (Maquet, Sweden). We monitored the Edi from an awake state to natural sleep under room air, and when CO2 was rebreathed in a closed circuit.

Monitoring was performed without respiratory support and the EtCO2 was recorded simultaneously. We compared the Edi peak between an awake state and during sleep and studied the correlation between the Edi peak and EtCO2. The values of Edi peak in normal infants when awake and during sleep are reported to be 16 ± 6, and 10 ± 4 μV, respectively.

Result: The mean Edi peak of all cases when awake and during sleep was 15.6 ± 2.7 and 4.8 ± 1.9 μV, respectively. The Edi peak during sleep was significantly lower than normal (p < 0.001). Although the mean EtCO2 during sleep elevated from 4.0% to 6.3%, the Edi peak of case1 and case3 were almost unchanged and the Edi peak of case2 slightly increased but was sometimes absent. When CO2 was rebreathed in a closed circuit, the EtCO2 of all cases elevated up to approximately 10%, but the median Edi peak of case1, case2 and case3 was 5.5 (5.3-5.7), 8.6 (3.4-14.3) and 6.9 (3.6-8.7) μV, respectively. The Edi peak of all cases did not respond to remarkable CO2 retention.

Conclusion: The Edi peak during sleep was lower or occasionally absent and did not respond to CO2 retention in CCHS. These findings suggest that Edi monitoring represents a disorder of the respiratory center and is useful in making a respiratory physiological diagnosis of CCHS. As the Edi monitoring can be performed more rapidly and more easily than genetic testing, it can lead to early diagnosis and appropriate respiratory care. In the future, we hope to use Edi monitoring to establish diagnostic criteria and to assess the severity of CCHS.

#118 - T-CELL-BASED SCREENING ASSAY FOR LATENT TUBERCULOSIS INFECTION IN HEALTH CARE WORKERS IN A PEDIATRIC HOSPITAL: A CROSS-SECTIONAL STUDY

Lin Sun L.S.
Beijing Children’s Hospital, Beijing Pediatric Research Institute - Beijing, China

Background: Health care workers (HCWs) are at risk of occupational exposure to patients with undetected active tuberculosis in hospital settings. Although children carry 10% to 20% of the global burden of TB disease, there is no available study on the prevalence of latent tuberculosis infection (LTBI) in HCWs in children’s hospitals. The current study was designed to compare the performance of T-SPOT.TB and tuberculin skin test (TST) in LTBI screening and to assess the risk factors associated with positive test results.

Pediatric Pulmonology
Methods: The study enrolled 227 volunteer HCWs in a pediatric hospital in Beijing, China. All participants were subjected to T-SPOT.TB and TST.

Results: Doctors had a higher prevalence of T-SPOT.TB and TST than workers in other job categories (35.3% vs. 10.5% for T-SPOT.TB and 82.4% vs. 55.2% for TST using a ≥10 mm cutoff). Agreement between the two tests was poor (κ = 0.142). In multivariate analysis, TST was affected by previous bacillus Calmette–Guérin (BCG) vaccination (OR 3.08, 95% CI 1.46-6.49), T-SPOT.TB positivity was associated with increasing age (OR 1.07, 95% CI 1.00-1.13) and being a doctor (OR 7.52, 95% CI 1.41-39.93).

Conclusions: In this pediatric hospital setting, the prevalence of LTBI in doctors was found to be much higher than that in nondirected contract participants. T-SPOT.TB was found to be superior to TST for the screening of LTBI in BCG-vaccinated HCWs.

#134 - DIAGNOSIS OF PNEUMONIA IN CHILDREN: LUNG ULTRASOUND VERSUS CHEST X-RAY

Mon Sc.1 Fufezan O.2, Schnell C.3, Sas V.3
1 Mother and Child, University of Medicine and Pharmacy “Iuliu Hatieganu” - Cluj-Napoca, Romania
2 Radiology, Emergency Clinical Hospital for Children - Cluj-Napoca, Romania
3 Pediatrics III, Emergency Clinical Hospital for Children - Cluj-Napoca, Romania

Introduction: Lung ultrasound (LUS) is a relatively new diagnostic method of acute pneumonia in children. It is a noninvasive imaging technique, accessible, relatively inexpensive, without irradiation, which can reveal pulmonary consolidation or pleural effusion.

Objectives: The objectives of this study were to evaluate the accuracy of LUS in diagnosis of acute pneumonia versus chest X-ray (CXR).

Methods: We included children admitted in the Department of Pediatrics III (Clinical Emergency Hospital for Children, Cluj-Napoca, Romania), between 2009 and 2014, with positive CXR or LUS for pneumonia.

Results: We included 66 patients aged 5 months to 19 years (mean age of 6.5 years). The number of children with a positive CXR was 64/66 (97%). LUS showed specific signs of pneumonia in 59/66 (89%) patients. There were 2/66 (3%) patients with positive LUS and negative CXR, and 7/66 (11%) children with negative LUS but a positive CXR. LUS was more sensitive in detecting pleural effusion compared to CXR.

Conclusions: Despite lower sensitivity of LUS versus CXR for detecting pneumonia shown in this study, LUS can detect pneumonia in children with negative LUS but a positive CXR. LUS was more sensitive in detecting pleural effusion.

#141 - LUNG ULTRASOUND (LUS) IN THE DIAGNOSIS AND MONITORING OF COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN

Krenke K
Department of Pediatric Pneumonology and Allergy, Medical University of Warsaw - Warsaw, Poland

The aim of the study was to evaluate the usefulness and accuracy of LUS in the diagnosis and monitoring of childhood community acquired pneumonia (CAP).

Methods: This prospective study was carried out between January 2013 and May 2014. Consecutive children older than 1 month referred to the hospital with suspicion of CAP were enrolled. CAP was diagnosed in children meeting clinical and radiological criteria. All patients underwent LUS on the day of admission, followed by chest radiograph performed in less than 24 hours after LUS. Demonstration of hypoechogenic lung lesion was a major ultrasound criterion of pneumonia. Bronchogram signs, pleural line abnormalities and/or pleural fluid were assessed as concomitant pneumonia findings. Patients with CAP diagnosis underwent follow-up LUS between the 5th and 7th day and between the 10th and 14th day after hospital admission.

Results: One hundred and six children, median age 52.5 months (IQR 26-86 months), were enrolled. CAP was diagnosed in 76 children, while pneumonia was excluded in the remaining 30 subjects. Chest radiograph (CXR) showed unilateral and bilateral lung involvement in 63 and 13 patients, respectively. Thus, 89 pneumonia-affected lungs were revealed by CXR. LUS revealed signs consistent with pneumonia in 71 children (61 and 10 children with unilateral and bilateral lesions, respectively). Hence, 81 pneumatic lungs were visualized using LUS. In all LUS-positive patients, pneumonia was also confirmed by CXR. In 5 patients with false negative LUS findings, CXR showed parahilar lung consolidations. We observed almost perfect agreement (Cohen kappa coefficient of 0.89) between LUS and CXR with respect to diagnosing pneumonia, with consistent findings in 101 patients. The diagnostic sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of LUS in children with CAP was 93.4%, 100%, 100%, 85.7% and 95.3%, respectively. Follow-up CXR at day 5-7 was performed in 25 patients. Pneumonic infiltrates were still present in 15 of them. At the same time point, LUS was able to demonstrate pneumatic findings in 14 patients. At day 10-14 of follow-up, CXR was performed in 31 patients and recorded positive findings in 20 cases. In 18 of them, LUS also yielded positive results. We found almost perfect agreement between CXR and LUS at day 5-7 and at day 10-14 (Cohen kappa coefficient of 0.92 and 0.93, respectively). No adverse effect related to LUS was observed.

Conclusions: LUS is a highly accurate and safe diagnostic method in children with CAP.

Reflections and proposals for action: The results of our study highlight the rationale for a wider use of ultrasound in the diagnosis and follow-up of childhood CAP.

11. THERAPEUTIC PROCEDURES

#13 - MASSIVE HEMOPTYSIS IN CHILDHOOD AND BRONCHIAL ARTERIAL EMBOLIZATION

Aslan AT
Pediatric Pulmonology, Gazi University Hospital - Ankara, Turkey

Hemoptysis in children is a rare but potentially life-threatening symptom in childhood. Hemoptysis, when massive and untreated, has a mortality rate of more than 50%. With interventional radiological procedures and surgery, this rate has dropped to 25%. The experience with bronchial arterial embolization in childhood is very limited; only a few case reports with short-term follow-up have been reported. We report herein two patients with massive hemoptysis due to abnormal systemic arterial bleeding of the lung; neither patient had any lung or systemic disease. In both cases, the bleeding was controlled with endovascular embolization. The first case was an 8-year-old girl with recurrent massive hemoptysis due to bronchial artery bleeding, in whom repeat embolization was performed. The second case represents the longest follow-up without any complication after repeat embolization reported in the literature. Both of these children had rare vascular anomalies without parenchymal lung disease, and were treated successfully with bronchial arterial embolization. Massive hemoptysis due to abnormal systemic bleeding of the lung in the absence of parenchymal disease is an uncommon and severe symptom in childhood. Embolization can be the first treatment option in children and can be repeated safely when needed.

#36 - MODIFIED HIGH FLOW SYSTEM IN CHILDREN WITH PNEUMONIA

Chaisupamongkollarp T.1, Vareesunthorn I.2, Preuithipan A.2
1 Nursing Department, Faculty of Medicine, Ramathibodi Hospital.
2 Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital.
Mahidol University - Bangkok, Thailand
Background: High flow nasal cannula (HFNC) is a novel noninvasive treatment for neonates and children with respiratory distress symptoms. HFNC is well-tolerated in young children. It has been shown to be useful in various conditions. In our Ramathibodi Hospital, we devised our modified HFNC and have been using it to treat children with respiratory distress since May 2011.

Objective: To evaluate the efficacy of modified HFNC in children with pneumonia who developed respiratory distress and to identify possible complications associated with this respiratory support.

Study design: Cohort prospective study.

Methods: This study was conducted at the Ramathibodi Hospital between April 2013–March 2014. Children younger than 10 years old with a diagnosis of pneumonia who developed respiratory distress symptoms and/or hypoxemia after receiving conventional oxygen therapy were recruited and put on modified HFNC. Heart rate, respiratory rate, and respiratory clinical score were recorded before and at 1-2 hours, 4-6 hours, and 8-12 hours after treatment with modified HFNC. Complications associated with HFNC were also recorded.

Results: Forty children met the criteria for inclusion, aged 12 (2-49 months), body weight 8.7 ± 3.6 kg. Twenty five (62.5%) were male. Heart rate, respiratory rate, and respiratory clinical score were significantly improved over time especially 1-2 hours after being on HFNC. Possible complications related to HFNC included feeding intolerance (n = 7, 17.5%), epistaxis (n = 5, 12.5%) and nasal mucosa redness (n = 3, 7.5%). Only 2 cases had worsening respiratory distress 12 hours after applying HFNC due to progressive pneumonia and sepsisemia.

Conclusion: Modified HFNC is safe and effective in the treatment of children with pneumonia. Very few minor complications are reported.

#39 - HIGH FLOW NASAL CANNULA IN CHILDREN WITH POSTEXTUBATION STRIDOR: A PILOT STUDY

Preathipan A., Wilawan P., Lertburrian R.
Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital. Mahidol University - Bangkok, Thailand

Background: High flow nasal cannula (HFNC) provides positive airway (distending) pressure and delivers warm humidified stable oxygen. These effects of HFNC theoretically may be used to treat postextubation stridor.

Objectives: To assess the efficacy and report adverse effects of HFNC in postextubation stridor.

Design: Prospective study

Setting: Pediatric intensive care unit

Subjects and Methods: Twenty one patients (aged < 8 years) with postextubation stridor, who still had Down’s croup score of > 3 after receiving IV corticosteroids, nebulized corticosteroids and epinephrine. Croup score, comfort scores and vital signs were recorded before and at 1-2 hours, 4-6 hours, and 8-12 hours after administration of HFNC.

Results: The average age when chest CT was performed was 6 years of age, with that of 11 infants without airway diseases in whom chest CT was performed at 6 years of age. The antero-posterior of 10.6 ± 0.8mm and transverse diameter was 10.4 ± 0.8mm the group with external stenting, and 10.1 ± 1.2mm and 10.6 ± 1.1 mm in the group without airway diseases, respectively. No significant difference was observed.

Conclusions: This study shows that external stenting against tracheomalacia did not affect the development of the trachea up to 6 years of age. Because the trachea is still developing in these infants, further studies are needed to examine the long term effects of external stenting in the development of the trachea.

#102 - INVESTIGATION OF THE EFFICACY OF AN EXTERNAL VENTILATOR (RTX®) FOR CHILDREN HOSPITALIZED WITH RESPIRATORY DISORDERS

Minato TM1, Okada KO2, Kamoi YK1, Yamada HY1, Tokuda OT1, Fujibayashi HF1, Ueda MU1
1 Pediatrics, Toyooka Hospital - Toyooka, Japan
2 Pediatrics, OKADA Kodomonomori Clinic - Saitama, Japan

Introduction: The RTX® ventilator (United Hayek Medical, London, United Kingdom) is an external ventilator that uses a cuirass. The cuirass is a plastic shell over the thorax, by which physiological ventilatory assistance is obtained quickly by simply making internal pressure adjustments within the cuirass. The RTX® does not cause barotrauma, volutrauma, or the possible development of pneumothorax, as seen with positive pressure ventilation (PPV). Furthermore, the clearance mode also helps to clear sputum. Because the pathophysiological characteristics (peripheral airway resistance due to small airway size, hyperplasia of bronchial goblet cells, etc.) of children often cause sputum clearance difficult during respiratory disorders, use of the RTX® is thought to be effective in children who can rapidly progress to respiratory failure. We have seen that many children in a poor mood because of a respiratory disorder slept well after starting the RTX®, and their respiratory status stabilized. Therefore, we investigated the efficacy of RTX® treatment in children. Methods: An RTX® was used first in continuous negative mode for 1 to 2 hours, followed by secretion clearance mode to clear sputum. The above procedure was performed twice daily. The Modified Pulmonary Index Score (MPIS), which consists of the six categories [heart rate (HR), respiratory rate (RR), accessory muscle use, inhalation-exhalation ratio, wheezing, and SpO2] was observed on the day of starting the RTX® and the next day. The degree of improvement in each category was investigated for different levels of severity. A questionnaire was also given to the medical staff who applied the RTX® to investigate its efficacy. Results: There were 59 patients in the moderate group with MPIS ≤ 11 and 13 patients in the severe group with MPIS ≥ 12. Significant

Pediatric Pulmonology
improvements in MPIS were obtained in both the moderate and severe groups. By individual MPIS category, the level of improvement was the greatest in HR (actual data significantly decreased from 144 ± 20/min to 123 ± 19/min), followed by SpO2, wheezing, and RR. In comparison with the level of improvement in each category by level of severity, the level of improvement in accessory muscle use was found to be significantly better in the severe group. In the survey of medical staff, 13 (88%) replied that the RTX\textsuperscript{a} was effective. Two major reasons were the smoothness of sputum clearance and improved sleep after wearing the RTX\textsuperscript{a} compared to before use. Conclusion: The RTX\textsuperscript{a} for children with respiratory disorders is an effective method by which significant improvement in MPIS is obtained regardless of the level of severity. The mechanisms for this improvement are thought to be involved in stabilizing circulatory dynamics, facilitating secretion clearance, and decreasing effort with respiration due to support of respiratory muscle use. The RTX\textsuperscript{a} is a unique ventilator which aims at improving a child’s breathing problem using different mechanisms from PPV.

### 12. CELLULAR AND MOLECULAR BIOLOGY

#### #17 - EVALUATION OF SELECTED IMMUNOLOGICAL PARAMETERS IN FULL-TERM AND PRETERM INFANTS WITH RECURRENT RESPIRATORY SYMPTOMS

Dmowska H.\textsuperscript{1}, Piatosa B.\textsuperscript{2}

\textsuperscript{1}The Pulmonology Outpatients’ Clinic, The Children’s Memorial Health Institute - Warsaw, Poland
\textsuperscript{2}Histocompatibility Laboratory, The Children’s Memorial Health Institute, Warsaw, Poland

The major respiratory problems in infancy and early childhood are respiratory exacerbations with airway obstruction, particularly among very immature infants. The aim of the study was to determine the distribution of T and B lymphocytes, intracellular cytokine production, total IgE and allergen-specific IgE, and to compare the obtained values in relation to gestational age and birth weight of the infants under study.

**Material and methods**: The preterm neonates (n = 31) were divided into three groups: < 28 weeks (n = 11), 28–32 weeks (n = 12) and > 32 weeks (n = 8). The control group consisted of 14 term infants. For the purpose of the study, the following data were extracted from medical records: sex, type of birth, gestational age, birth weight, APGAR score, need for mechanical ventilation, prevalence of bronchopulmonary dysplasia (BPD) and parental history of atopy. All the children presented recurrent (more than three) respiratory exacerbations with wheezing. Lymphocyte subsets were studied in peripheral venous blood: T lymphocytes including CD4 and CD8 subpopulations, B lymphocytes and natural killer cells. Intracellular cytokine production, namely IL2, IL4, IL10, IL13, was analyzed using multicolor flow cytometry. Atopic predisposition was assessed using measurements of serum concentrations of total IgE and 7 types of allergen-specific (egg white, cow’s milk, soya bean, D. pteronyssinus, D. farinae, timothy grass, birth) IgE.

**Results**: We found a similar distribution of CD3, CD4, CD8, CD19 lymphocyte subsets. The Th1:Th2 balance presented type-1 immune response dominance. The differences in mean values of intracellular cytokine production were not significant. Total IgE and allergen-specific IgE did not differ significantly between the four groups.
Conclusions: The pattern of lymphocyte subpopulation and ability to produce intracellular cytokines did not differ significantly between very preterm and full term infants with recurrent respiratory symptoms. There were no differences in the mean concentration of total and allergen-specific IgE between the four groups of infants.

Sobkowiak P.1, Hoffmann A.2, Narozna B.2, Breborowicz A.1, Szczepankiewicz A.2
1 Pediatric Pulmonology, Allergy and Clinical Immunology, Poznan University of Medical Sciences - Poznan, Poland
2 Laboratory of Molecular and Cell Biology, Poznan University of Medical Sciences - Poznan, Poland

Background: Neuroimmune interactions are responsible for neuronal dysfunction and structural changes in asthmatic airways thus enhancing the process of neurogenic inflammation. The most important mediators are neurotrophins, neuropeptides, neuropeptides and histamine pathway components as they all play a role in the pathophysiology and the course of allergic asthma.

Methods: In the analysis, we included 22 asthmatic patients, aged between 6-16 years. Asthma diagnosis was made according to GINA 2006 guidelines at least 6 months before inclusion in the study. The RNA samples were collected twice: during asthma exacerbation and during asymptomatic period. The expression of 31 genes associated with neurogenic inflammation was altered during exacerbation in childhood allergic asthma.

Results: The significant increase in expression of three genes, HRH1, NTF3 and NTF4, their receptors (NTRK1, NTRK2, NTRK3, NGFR), tyrosine kinases (FYN, MAPK, PLCγ), neuropeptides: SP, NKA, CGRP, NEP/CD10, histamine metabolism pathway (HDC, HNMT, DAO, histamine receptors H1-H4), neuropeptides (IL1β, IL6) and ion channel receptors (TRPV1, TRPA1).

Conclusions: The expression of three genes (histamine receptor 1, neurotrophin 3, neurotrophin 4) was significantly increased during asthma exacerbation as compared to the asymptomatic period. The current study confirms our previous finding showing increased serum levels of two neurotrophins (NTF3 and NTF4) during asthma exacerbation. The results indicate that neurogenic inflammation genes may be important markers of asthma exacerbation in children.

Yu HR., Li SC., Li SC., Tseng WN., Tuin YL., Chen CC., Sheen JM., Tiao MM., Huang CC., Hsieh KS., Huang LT.
Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Center - Kaohsiung, Taiwan

Glucocorticoids have been administered to mothers at risk of premature delivery to induce maturation of preterm fetal lungs and prevent the development of respiratory distress syndrome for many years. MicroRNAs (miRNAs) play an important role in cell proliferation, differentiation and organ development; however only a few studies have reported an association between miRNAs and lung development. The aim of this study was to investigate changes in miRNA profiles after prenatal glucocorticoid therapy for fetal lung development. We compared differences in miRNA expression profiles between postnatal day 7 (D7) and postnatal day 120 (D120) of rat lung tissues, followed by validation using quantitative real-time reverse transcriptase-polymerase chain reactions. The miRNA profiles of rat lung tissues after prenatal dexamethasone therapy were also studied. MiRNAs with two fold-changes were selected. There were 6 upregulated miRNAs and 6 downregulated miRNAs at D120 compared with D7. Of these differentially expressed miRNAs, miR-101-3p and miR-99b-5p were responsible for the lowest and highest expressions of miRNA at D7, respectively. Prenatal dexamethasone treatment had a limited impact on the miRNA profiles of rat lung tissues. This finding may help to further clarify the mechanism of normal lung development. However, it cannot totally represent the effects of prenatal dexamethasone treatment on the lung development of premature babies. Further studies are needed to investigate the impact of prenatal corticosteroids on fetal lung miRNA profiles.

Grosse-Oenbrink J., Olbrich H., Loges NT., Omran H.
General Pediatrics, University Children’s Hospital Muenster - Muenster, Germany

Introduction: Mucociliary clearance in asthmatic airways is impaired by structural damage of the respiratory epithelium, mucus hypersecretion, abnormal mucus rheology and a decreased ciliary beat frequency (CBF). Whether the altered cytokine profile in asthma influences the CBF has not been sufficiently studied. We aimed to show whether the TH2 cytokines interleukin-13 (IL13) and interleukin-4 (IL4) and interferon (IF) gamma affect the CBF.

Methods: We obtained respiratory epithelial cells from nasal conchae or polyps in patients who underwent ear, nose and throat surgery after informed consent using protocols approved by the Institutional Ethics Review Board. The respiratory epithelial cells were used to prepare multicellular cell cultures (spheroids) as described previously. After addition of the TH2 cytokines (IL4, IL13; IL4+IL13) and IF gamma and IF gamma+IL13 (concentration levels 0.1, 1, 10 ng/ml) to the spheroids, the latter were processed for high-speed videomicroscopy.

Results: The addition of the TH2 cytokines resulted in a dose-dependent negative effect on the mean CBF. The maximum change in CBF was observed with the highest concentration level (10 ng/ml). Addition of IL4 and IL13 and IL4 + IL13 (10 ng/ml each) to the spheroids reduced the CBF by 12%, 12% and 19%, respectively. Addition of IF gamma (10 ng/ml) to the spheroids increased the CBF by 7% compared to untreated controls. Addition of increasing concentrations of IL13 (0.1 ng/ml, 1 ng/ml and 10 ng/ ml) plus IF gamma (10 ng/ml) to the spheroids resulted in a dose-dependent decrease in CBF. Addition of IF gamma + IL13 (10 ng/ml each) resulted in a CBF similar to the CBF of untreated controls: IF gamma reversed the negative effect of IL13 to the CBF.

Conclusions: The TH2 cytokines IL4 and IL13 negatively affect the ciliary function while IF gamma restores the ciliary function in our cell culture model. Our study encourages further research to investigate IF gamma as a treatment option in diseases with impaired mucociliary clearance such as asthma.

#62 - ALTERED EXPRESSION OF THREE NEUROGENIC PATHWAY GENES DURING ASTHMA EXACERBATION IN PEDIATRIC PATIENTS

#77 - THE CILIARY BEAT FREQUENCY OF THE RESPIRATORY EPITHELIUM IS DECREASED BY INTERLEUKIN-4 AND INTERLEUKIN-13 AND IS INCREASED BY INTERFERON GAMMA

Piazza SL.1, Upham JW.2, Yerkovich ST.3, Chang AB.1
1 Child Health Division, Menzies School of Health Research - Darwin, Australia
2 Department of Respiratory Medicine, Princess Alexandra Hospital - Brisbane, Australia
3 Queensland Lung Transplant Service, The Prince Charles Hospital - Brisbane, Australia

Abstract S79
Background: Non-typeable Haemophilus influenzae (NTHi) is commonly associated with chronic suppurative lung disease in children. We have previously shown that children with chronic suppurative lung disease have a reduced capacity to produce IFN-γ in response to NTHi compared with healthy control children.

Aim: The aim of this study was to determine if deficient systemic NTHi-specific IFN-γ production is associated with heightened systemic or airway inflammation.

Method: We measured a panel of cytokines (IFN-γ, IL-1β, IL-6, IL-8, IL-12 p70), antimicrobial proteins (LL-37, IP-10) as well as cellular and clinical factors associated with airway and systemic inflammation in 70 children with chronic suppurative lung disease. IFN-γ was measured in peripheral blood mononuclear cells challenged in vitro with live NTHi. Regression analysis was used to assess the association between the systemic and airway inflammation and the capacity to produce IFN-γ.

Results: On multivariate regression, NTHi-specific IFN-γ production was significantly negatively associated with BAL concentrations of the inflammatory cytokines IL-6 (β = -0.316; 95% CI -0.49, -0.14; p = 0.001) and IL-1β (β = -0.023; 95% CI -0.04, -0.01; p = 0.001). This association was independent of bacterial or viral infection, BAL cellularity and the severity of bronchiectasis (using modified Bhalla score on chest CT scans). We found limited evidence of systemic inflammation in children with chronic suppurative lung disease.

Conclusion: Airway inflammation involving elevated IL-6 and IL-1β may impair the capacity of children with CSLD to produce IFN-γ in response to NTHi. Future studies to identify the mechanisms driving this relationship between the adaptive IFN-γ response and airway inflammation are required to better inform effective, long-term prevention strategies for children at risk of CSLD.

13. PEDIATRIC PULMONOLOGY IN DEVELOPING COUNTRIES

#33 - CHILDREN HOSPITALIZED WITH TUBERCULOSIS AT AN INSTITUTION IN A HIGHLY ENDEMIC REGION

López Revilla JW, Mendoza Fox CA, Davila Edquen JE. 1 Pediatrics, Hospital Nacional Hipólito Unanue - Lima, Peru 2 Pediatrics, Hospital Edgardo Rebagliati Martins - Lima, Peru

Introduction: Tuberculosis (TB) is a serious health problem and there is a high prevalence of this condition in Peru. The clinical presentation in children is different from that of adults and more difficult to diagnose.

Aims: To identify the epidemiological and clinical characteristics, chest X-ray and role of auxiliary tests for TB (Tuberculin skin test and direct TB mycobacteria detection) in children hospitalized at an institution in a highly endemic region of Lima, Peru.

Methods: The clinical files of 113 patients hospitalized with TB in the Pediatric Department of Hospital Hipólito Unanue (Lima, Peru) from 2005 to 2012 were reviewed. Tuberculin skin test (PPD), chest X-ray and TB mycobacteria testing were performed on all patients.

Results: The participants were 65% male. The age of the patients ranged from less than one to 14 years of age and 70% of patients were between the ages of 10 and 14 years. Seventy-seven percent of patients were eutrophic. A TB intradomiciliary contact was present in 43% of cases. The most frequent symptoms were cough (78.7%), fever (73.7%), hypoxemia (46.9%) and diaphoresis (40.7%). The most frequent signs were diminished breath sounds (61.6%), egophony (33.7%), diminished vocal vibrations (20.3%) and cracklings (20.3%). TB mycobacteria were detected in 21% of the biological samples. The most frequent chest X-ray findings were pleural effusion (46%), consolidation (45%), interstitial infiltrate (31.8%) and hilar enlargement (26.5%); the left lung was most frequently involved. The PPD was positive in 83.2% of cases and was most frequently positive in older, eutrophic patients. Pleural-parenchymal TB represented 40.7% of cases, while parenchymal and systemic TB represented 34.5% and 9.7% of cases, respectively.

Conclusion: The most frequent clinical presentation of pediatric TB cases was pleural-parenchymal TB, which had specific signs and symptoms. The 10-14 year age group and eutrophic patients were the most affected. PPD positivity and intradomiciliary TB contacts contribute to the diagnosis.

#52 - COUNSELLING FOR PARENTS AND CHILDREN WITH SENSITIVE BRONCHI

Jankovic N, Pajovic R., Strainovic LV, Divanovic P. Pediatrics, Public Health Institution Primary Health Centre Podgorica - Podgorica, Montenegro

Introduction: Asthma, as a chronic lung disease, is increasingly growing in children. According to some data, around 6% of schoolchildren have asthma. Within our Primary Health Centre, on February 27, 2013, we opened the Counselling for the purposes of easier monitoring and education of children and parents. We provide them with instructions on how to avoid and how to treat the asthma attack. Four Pediatriests work in this Counselling, two nurses and 1 physiotherapist. In addition to drug therapy, children have to be educated on how to properly breathe when having an asthma attack.

Objective: to verify to what extent, in this relatively short period of time, we have managed to make primarily parents, and then the children themselves interested in cooperating with us.

Method: All of the visits to our Counselling in the period ranging from its opening and the next 20 months have been recorded electronically, and the data studied by retrospective analysis. The Counselling is open once a week.

Results: For the last 20 months, the Counselling has been visited by 277 children, or 3-4 children per day of work. There were 168 (60%) boys and 109 (40%) girls. The average age was 7, with boys being 6.8 and girls 7.1. A smaller number of children decided to have physical therapy- 15 (5.4%).

Conclusion: It is obvious that more boys than girls visited us, which coincides with the data that asthma is more frequent in the male population. In the male population, asthma starts earlier than with the girls. Through this Counselling, we can better perceive the problems of children having asthma and help resolve them through education. Within the Counselling, we perform spirometry and pulse oximetry. We introduce parents to choosing the flow meter for easier monitoring of children in home conditions. We provide layouts and testing of bronchodilators via baby models and volumetric chambers and present usage of assets for disease control.

Reflection: We have indicated the need for educating staff in pre-school institutions, as well as of teachers. We provide recommendations for practicing sports.

#53 - FREQUENCY OF RESPIRATORY INFECTIONS AND USE OF ANTIBIOTICS IN THEIR TREATMENT IN A PEDIATRIC DISPENSARY

Rasicvic FB, Pajovic R., Strainovic LV. Pediatrics, Public Health Institution Primary Health Centre Podgorica - Podgorica, Montenegro

Introduction: Respiratory diseases are the most frequent reason for children visiting the pediatric dispensary. Irrational prescription of antibiotics in acute respiratory infections is not only without effect but also leads to the development of bacterial resistance to antibiotics, which is one of the growing problems worldwide.

Objective: Identify the frequency of respiratory infections and estimate how much antibiotics are prescribed in everyday practice for their treatment.

Method and material: Retrospective review of the data from daily records in a pediatric dispensary in the Primary Health Centre in Podgorica, in October 2014.

Results: In the reviewed period, a total of 1201 children were examined. There were 608 first examinations (50.6%), 263 control examinations (21.9%), 162 short visits (13.5%), while there were 168 preventive
examinations (13.9%). Out of the total number of examined children, there were 468 (38.9%) children with respiratory disease, 235 (50.2%) boys and 233 (49.8%) girls. Out of the total number of first examinations, 292 (48.1%) children had respiratory disease and out of a total number of control examinations, there were 176 (66.9%) children with respiratory disease. Distribution of the respiratory diseases according to the diagnoses is as follows: JOO 57 (12.1%), J01 2 (0.4%), J02 31 (6.7%), J03 51 (10.8%), J04 9 (1.9%), J06 192 (41.1%), J20 75 (16.1%), J21 32 (6.8%), J30.4 2 (0.5%), J45 13 (2.8%) and 84.9 4 (0.8%). With regard to age, the majority of children were 0-3 years of age - 217 (46.3%), followed by 4-7 years of age -126 (26.9%), 8-11 years of age - 62 (13.3%), age 12-15 years - 37 (7.9%) and age 16-19 years - 26 (5.6%). Out of the total number, antibiotics were prescribed to 68 (14.5%) children, 32 (47.1%) boys and 36 (52.9%) girls. Distribution according to the age of children who were prescribed antibiotics was: age 0-3 - 21 children (30.9%), age 4-7 - 21 children (30.9%), age 8-11 - 9 children (13.2%), age 12-15 - 11 children (16.2%) and age 16-19 - 6 children (8.8%). According to the diagnoses: JOO (0%), J01 (1.5%), J02 (22.1%), J03 (44.2%), J04 (0%), J06 (17.5%), J30 (4.4%) and J21 (2.9%). With regard to type of antibiotics: amoxicillin to 37 children (54.5%), cephalaxin to 19 children (27.9%), phenoxymethyl penicillin to 4 children (5.9%), azithromycin to 3 children (4.4%) and cefixime to 5 children (7.4%).

Conclusion: Almost half of the children in the first examination were children with acute respiratory infection and more than half of them in control examinations. Antibiotics were prescribed to 14.5% of children, equally at age 0-3 and 4-7. Antibiotics were mainly prescribed for acute tonsillitis and the most frequently prescribed antibiotic was amoxicillin. It is recommended that antibiotics in respiratory infections are prescribed only in strictly indicated cases, in order to prevent the development of bacterial resistance to antibiotics and to reduce treatment costs.

#119-TB-ASSOCIATED PROMOTER SNP OF IFITM3 REGULATES MCP-1 SECRETION IN H37RV-STIMULATED BLOOD CELLS

Shen CS, Jiao WW, Shen AD.
Key Laboratory of Major Diseases in Children and National, Key Discipline of Pediatrics, (Capital Medical University), Ministry of Education, Beijing Pediatric Research Institute, Beijing Children’s Hospital, Capital Medical University, No. 56 Nan-li-shi Road, Beijing 100045, China

Background: In our previous study, the -204 G/T Single Nucleotide Polymorphism (SNP) within the IFITM3 promoter region was associated with Pediatric Tuberculosis (TB). The TB susceptible -204G allele, which increased the incidence of TB disease, was also associated with decreased promoter activity in Peripheral Blood Mononuclear Cells (PBMCs) in a recessive genetic model. The mechanism has not been fully understood. Since inappropriately regulated secretion of cytokines was an important factor in the development of TB disease, we thus attempted to determine whether the -204G/T SNP could be associated with cytokine generation in blood.

Material and Methods: 61 peripheral venous blood samples were collected from healthy children for physical examination. The -204G/T genotype of each sample was confirmed by PCR based sequencing. Samples were stimulated by 7.5×103 µL heat-inactivated M. tuberculosis H37Rv strain independently in RPMI-1640 medium. Culture supernatants were then collected 20 hours later for cytokine measurements. A Milliplex MAP Human Cytokine/Chemokine Panel (#CYTOMAG-60K, Millipore, USA) containing 20 major cytokines (EGF, IFNg, IL-10, IL-12p40, IL-12p70, IL-13, sCD40L, IL17A, IL1a, IL-1b, IL-2, IL-4, IL-6, IP-10, MCF-1, MIP1a, MIP1b, TNFa, TNFb, VEGF) was ordered and used for quantitative determination of these cytokines in each sample on a Luminex 200 device (Luminex, 175 USA). Data were subsequently analyzed by MilliplexTM Analyst Software (Version 3.5, Millipore, USA).

Results: By sequencing, 7 samples with TT genotype, 25 with TG, and 29 with GG were included in this study. Among these 20 detected cytokines, 5 cytokines were not within the scope of detection range: levels of IL-13, IL-4 and TNFβ were too low to be detected by this method, while levels of MIP1a and MIP1b were too high to be detected. By statistical analysis, among the remaining 15 cytokines, MCP-1 was secreted in a statistically different manner among three groups with the Kruskal-Wallis test P value for TT, TG and GG groups at 0.0028. The P value of the Mann Whitney test was 0.0356 between blood cells with ‘TT’+’TG’ genotypes and those with ‘GG’ genotype, with an apparent trend that blood cells with GG genotype released higher levels of MCP-1.

Conclusions: Our data demonstrate that the TB-susceptible -204GG genotype is associated with higher levels of MCP-1 in blood samples stimulated by M. tuberculosis. Previous research proved that MCP-1 influences the expression of cytokines related to T helper responses, and MCP-1(-/-) mice had the ability to clear M. tuberculosis with an intact Th1-like response. Since the GG genotype is associated with a reduced promoter activity of IFITM3, this study also leads to the hypothesis that expression levels of IFITM3 and MCP-1 may be negatively correlated, which deserves further confirmation.

#121 - FACTORS THAT PREDICT FOR POSITIVE GENEXPERT MTB/RIF ON BRONCHOALVEOLAR LAVAGE SAMPLES IN CHILDREN WITH SUSPECTED TUBERCULOSIS

Goussard P.
Pediatrics and Child Health, Stellenbosch University - Cape Town, South Africa

Background: Pilot studies have reported that GeneXpert MTB/RIF (Xpert) testing of bronchoalveolar lavage (BAL) samples improves diagnostic yield and the rapid detection of drug resistance in children undergoing bronchoscopy for complicated intrathoracic tuberculosis (TB).

Aim: To determine factors predictive of positive Xpert on BAL in children with suspected tuberculosis.

Methods: Children < 13 years undergoing fibre-optic bronchoscopy for suspected complicated intrathoracic TB, between October 2012 and January 2014, were studied. Clinical data, including duration of TB treatment prior to bronchoscopy and chest X-ray changes, were collected. During bronchoscopy under general anaesthesia, airways were evaluated for compression, severity of obstruction and lymph gland ulceration into the airways. BAL samples obtained were analysed by fluorescent smear microscopy, automated liquid culture and Xpert.

Results: Forty children (3 HIV positive, median age 18 months) were studied. The median duration of TB treatment prior to bronchoscopy was 8 days (range 0–85 days). TB was confirmed in 31 (78%) cases by either BAL, Xpert or culture. Xpert and culture were positive in 29 (73%) (8 were also ZN positive) and 23 (58%) cases respectively. In 21 (53%) cases, both Xpert and culture were positive. Incremental value of Xpert was 8 cases (35%); only 2 cases were culture positive but Xpert negative. The median time to culture positivity was 14 days (7-44 days). Positive Xpert was associated with lymph nodes ulcerating into the airway (p = 0.03) but not with airway obstruction (p = 0.5), chest x-ray changes (p =) or duration of treatment < 14 days (p =).

Conclusion: In children with complicated pulmonary TB, Xpert on BAL increases the diagnostic yield by >35% and is associated with lymph node ulceration into the airways.

#142 - PULMONARY HYDATIDOSIS IN CHILDREN

Quevedo K., Mendoza Fox CI.
Pediatrics, Hospital Nacional Hipolito Unanue - Lima, Peru

Introduction: Cystic echinococcosis (CE), caused by the larval stage of Echinococcus granulosus (EG), is recognized as a public health problem. CE is endemic in Latin America. In some parts of Peru, the incidence can be

Pediatric Pulmonology
as high as 64.4 per 100,000 persons, with more than 50% children. Pulmonary Hydatidosis is the most frequent clinical presentation in children, representing 50-70% of cases. Tuberculosis has similar clinical manifestations and Peru is one of the countries with the highest prevalence (100 cases per 100000); furthermore, in the area where our Hospital is located, the prevalence is 263.9-275/100000.

Aims: Find and establish the demographics, clinical characteristics and diagnostic yield of auxiliary tests of pathologically-confirmed pulmonary hydatidosis in children.

Methods: The clinical files of patients hospitalized between January 2002 and January 2013 in the Pediatric Department of Hospital Hipólitó Unanue (Lima, Peru), were reviewed. Patients without pathological confirmation of pulmonary hydatidosis were excluded.

Results: A total of 32 patients were included: 50% boys and 50% girls. The age range was from 3 to 14 years, with a mean of 9 years. Breeding animals (dogs, sheep) was detected in 56% of cases. The average time of disease evolution was 60 days. The most frequent clinical manifestations were cough (96.9%), fever (81.3%), thoracic pain and hemoptysis (both 50% each), dyspnea (43.8%), hypoxemia (31.3%) and expectoration of residual CE (21.9%). Breath sounds were decreased in 94% of cases, dullness in 31% and tubal murmur in 13% of patients. Eosinophilia and anemia was detected in 44% and 47% of cases, respectively. Patients had only pulmonary involvement in 62.5% of cases, in the remaining patients there was also hepatic or abdominal disease. The diagnostic yield of chest CT scan was 95.65%, chest X-ray 86.21%, chest ultrasound 73.68% and serological indirect immunofluorescence 71.43%.

Conclusion: Pulmonary hydatidosis is an endemic disease in Peru. It has similar clinical characteristics with Tuberculosis. Chest CT scan had the best diagnostic yield.

14. MISCELLANEOUS

#15 - COMPLICATED RECURRENT ACUTE RESPIRATORY FAIL- URE IN CHILDHOOD. A CASE-MANAGEMENT AND REPORT

Todisco N.
Maternal-Infantile, University Hospital “San Giovanni di Dio e Ruggi d’Aragona” - Salerno, Italy

Tracheomalacia is a failure of the normal cartilaginous support of the trachea. It recurs in almost 30% of children undergoing bronchoscopy for respiratory distress; it can be diagnosed incidentally in mild cases but nevertheless presents many symptoms such as prolonged expiration, cyanosis, brassy cough, apnea, feeding problems and recurrent pneumonia. It rarely necessitates any treatment. Chiari malformation is a congenital or acquired herniation of the cerebellum through the foramen magnum. Type I (CM1) is the isolated protrusion of the cerebellar tonsils of 5 mm or more. Although in many cases asymptomatic, it can incur headaches, ocular and lower cranial nerve signs, ataxia. Onset occurs usually in the third decade of life. Its prevalence is still unknown and inheritance recurs in 10-15% of cases. We describe the clinical case of a 20-month-old male subject born prematurely at 30 wks of gestation from twin births. Reanimation was necessary to treat early acute RDS with mechanical ventilation for several days and exogenous surfactant administration. The infant was finally discharged healthy after eight weeks from birth. Only a few months later, he began to present wheezing, recurrent vomiting, disturbed sleep and difficulties in breathing. Many hospitalizations where required until, at age of 11 months, during a severe RDS complicated by pneumonia and pneumothorax, the infant underwent bronchoscopy, of which the result was negative under curare. Another episode of acute severe RDS required critical care in a different UTIP after only a few months. In this occasion, bronchoscopy, repeated in spontaneous breathing, revealed severe tracheomalacia of the entire trachea. Tracheostomy restored respiratory function and spontaneous breathing. A brief healthy status followed until recurrence of vomiting, continuous perspiration, repeated central sleep apneas (27/hr at polysomnography). MNR revealed downward displacement below 16 mm of the cerebellar tonsils through the foramen magnum. This condition, in agreement with treatment of CM1, necessitated surgical enlargement of the foramen magnum as the only measure leading to the complete regression of all of the symptoms. Currently, at the age of 20 months, the patient is waiting for tracheostomy removal. The twin, until now healthy, has also presented a mild herniation of cerebellar tonsils at MNR of less than 3 mm and is asymptomatic. The clinical case highlights some original aspects which need to be considered: A rare association between rare diseases, tracheomalacia and CM1, in a preterm newborn both leading to respiratory problems; the very early onset of CM1 before the second year of life despite common reports and the familiar recurrence in both twins. Last, tracheomalacia as model of illness, maybe complication of prematurity, and cause of acute life-threatening condition in which diagnosis is as apparently simple as is treatment, when necessitated. Spontaneous maturation of cartilaginous rings only allows normal respiration in spite of any treatment.

#97 - A SERIES OF CHILDREN WITH CONGENITAL CENTRAL HYPOVENTILATION SYNDROME

Wong PC., Teoh OH., Goh AEN.
Respiratory Medicine Service, Department of Paediatric Medicine, KK Women’s and Children’s Hospital - Singapore, Singapore

Introduction: Congenital central hypoventilation syndrome (CCHS) is a rare disease where there is an inborn failure of autonomic control of breathing. In the majority of cases, there is a polyalanine repeat expansion mutation (PARM), with the number of repeats correlating with clinical severity. We present herein 3 children with CCHS, with confirmed mutations in the PHOX2B gene.

Case series: A 2-year old child presented at birth with recurrent apnoeas and severe alveolar hypoventilation. Genotyping confirmed a diagnosis of CCHS with 20/29 PARMs. Her phenotype was consistent with Haddad syndrome, with CCHS and Hirschsprung’s disease. Her clinical course was complicated by feeding difficulties and persistent intestinal dysmotility. She is currently on nocturnal bilevel ventilation via tracheostomy. The second case is a 6-year old child, also diagnosed in the neonatal period with Haddad syndrome. He is doing well on nocturnal bilevel ventilation via tracheostomy, and is planned for subsequent decannulation. Our third case is a 6-year old child who presented with neonatal onset CCHS, with the genotype of 20/26 PARMs. He was mechanically ventilated from birth via tracheostomy, and subsequently required only ventilatory support in sleep. Diaphragmatic pacing (DP) was initiated at the age of 5 years, with the hope for eventual decannulation. However, he demonstrated evidence of severe obstructive sleep apnoea with paradoxical movement of the vocal cords while on DP, possibly due to dysynchrony with the pacing and underlying impaired reflex mechanisms and autonomic control of breathing described in CCHS. Adjustments were made to the initial settings of DP, and adequate ventilation was achieved with the tracheostomy uncapped in sleep.

Discussion: CCHS remains an intriguing disease since its first description in 1970, with varied phenotypic features. Locally, all our patients were mechanically ventilated via tracheostomy from time of diagnosis. All were subsequently able to be taken off daytime ventilation, despite genotyping predictive of a more severe clinical course. As most affected patients would require lifelong ventilatory support in sleep, DP is a newer alternative that may permit tracheostomy decannulation. Challenges in the management of CCHS patients include not only the ventilatory aspects, but also management of the associated comorbidities from autonomic nervous system dysregulation and continued vigilance for tumours of neural crest origin.

Pediatric Pulmonology
**#114 - IN VITRO EVALUATION OF A SPACER IN A PEDIATRIC MODEL OF MECHANICAL VENTILATION**

Brokhettala NB,
Laboratoire Protec’Som, R&D - Valognes, France

**Rationale:** The objective of this study was to evaluate the mass of salbutamol delivered by a pMDI or a mesh nebulizer using a spacer in a pediatric model of mechanical ventilation.

**Methods:** For the use with pMDI (Ventoline, 100 µg/puff, GlaxoSmithKline, France), the spacer (Combihaler, Laboratoire Protec’Som, France) was compared with a T-piece. For the nebulization of salbutamol (2.5 mg/2.5 ml), a mesh nebulizer (Aeroneb Solo, Aerogen, Ireland) was used with a T-adapter or a spacer. In this study, a respirator (Volume controlled, Vc = 155 mL, f = 25/min, PEEP = 6, P max = 8, ratio between the inspiratory time and the expiratory time = 50/50) and a model of lung Dual TTL model 5600i (Michigan Instruments) were used. A filter was placed after the 5.0 mm endotracheal tube. The concentration of salbutamol was measured by spectrophotometry after the use of the pMDI and after nebulization Values, expressed as mean ± SD, were compared using one-way ANOVA.

**Results:** With pMDI, the mass of salbutamol deposited on the filter was twice higher with the spacer compared with the T-piece (19 ± 1.5 µg vs. 8.2 ± 1.7 µg). After nebulization, salbutamol aerosol delivery increased with the spacer in comparison with the T-adapter (32.7 ± 3.5% vs. 22.1 ± 2.0%). In addition, the use of a spacer reduced the mass of salbutamol deposited between the Y-piece and the endotracheal tube compared with the T-adapter.

**Conclusions:** In pediatric conditions, with the pMDI, the spacer increases the deposition of salbutamol by a factor of 2 compared with the T-piece. For the nebulization of salbutamol (2.5 mg/2.5 ml), the concentration of salbutamol was measured by spectrophotometry after the use of the pMDI and after nebulization Values, expressed as mean ± SD, were compared using one-way ANOVA.

**Results:** With pMDI, the mass of salbutamol deposited on the filter was twice higher with the spacer compared with the T-piece (19 ± 1.5 µg vs. 8.2 ± 1.7 µg). After nebulization, salbutamol aerosol delivery increased with the spacer in comparison with the T-adapter (32.7 ± 3.5% vs. 22.1 ± 2.0%). In addition, the use of a spacer reduced the mass of salbutamol deposited between the Y-piece and the endotracheal tube compared with the T-adapter.

**Conclusions:** In pediatric conditions, with the pMDI, the spacer increases the deposition of salbutamol by a factor of 2 compared with the T-piece. Concerning the nebulization, the deposition of salbutamol is increased by a factor of 1.5 with the spacer compared with T-adapter.

**#135 - RANDOMIZED, SINGLE-BLINDED STUDY TO EVALUATE THE EFFICACY OF GRINTUSS AND MUCOLIT PEDIATRIC SYRUPS FOR COUGH DUE TO UPPER RESPIRATORY TRACT INFECTION**

Cohen Herman Avner CH¹, Moshe Hoshen HM², Ran D Balicer BR³, Blau Hana BH¹, Gur Shmuel GS⁴
¹ Pediatric Community Ambulatory Clinic, Sherute Briut Clalit - Petah-Tikva, Israel
² Clalit Research Institute, Clalit, Chief Physicians Office, Sherute Briut Clalit - Tel-Aviv, Israel
³ Pulmonary Institute,, Schneider Children’s Medical Center of Israel - Petah-Tikva, Israel
⁴ Pediatric Ambulatory Center, Sherute Briut Clalit - Kefar Saba, Israel

**Objectives:** Cough is a common symptom in pediatric practice. It can be particularly troubling to children and their parents. It often results in discomfort to the child and loss of sleep for both the child and parents. As a result, children miss day care or school and parents miss a day of work. In an attempt to treat cough, caregivers frequently administer over-the-counter medications to their children with little evidence of proven efficacy, and the disapproval of professional organizations such as the American Academy of Pediatrics, and the US Food and Drug Administration (FDA). Grintuss syrup contains a combination of specific fractions of substances such as resins, polysaccharides, saponins, flavonoids and sugars derived from *Grindelia robusta*, *Plantago lanceolata*, *Helichrysum italicum*, and honey. It has been suggested that Grintuss pediatric syrup may have a protective effect on the mucus of the upper respiratory tract exerted by a local mechanical barrier. Cysteine derivates (carbocysteine, acetylcysteine) are mucolytic drugs that act by breaking disulfide bridges between macromolecules and lead to reduced mucus viscosity in the respiratory tract. These derivates are widely used for pediatric patients to treat acute cough in various European and African countries (14). The aim of this study was to compare the effects of Grintuss and Mucolit (carbocysteine) pediatric syrups for nocturnal and daytime cough associated with childhood upper respiratory tract infections (URIs).

**Methods:** A survey was conducted among parents on 4 consecutive days, first on the day of presentation, and then on the 4 following days, where treatment was Grintuss or Mucolit, with single-blinded randomization. Participants included 150 children aged 2 to 5 years with URIs, nocturnal and day-time cough, and illness duration of ≤7 days from 4 general pediatric community clinics. Eligible children received the study preparation at the first evening and then 3 times per day for 3 days. Main outcome measures were cough frequency, cough severity, bothersome nature of cough, and sleep quality for child and parent. The trend for improvement over the 4 days was steeper for Grintuss (p<0.05) for all cough parameters.

**Conclusion:** Grintuss and Mucolit syrups are both effective and safe treatments for children over 2 years of age. Grintuss appears to produce faster (first night) and more effective response (over four days of treatment) as to clinical cough symptoms. This is true for daytime and nocturnal cough effects and for improvement of sleep for child and parents.
Index

A
Aldasoro A., S58
Aleksseeva O., S54
Ali-Dinar T., S66
Alves FA., S62
Alves MF., S62
Amirav Israel, S12
Araujo V A., S62
Armstrong Gregory T., S36
Ashkenazi M., S66
Aslan AT., S78
Avis M., S55
Azaldegui G., S58

B
Baghurst P., S71
Bajgoric S., S72
Bak A., S66
Balabolkin I., S57
Bar Aluma B., S66
Barat P., S57
Barbosa T., S70
Bardin R., S68
Barros CA., S62
Basora E., S66, S69
Becker Ae., S22, S38
Ben Nun A., S66
Benedek P., S71
Bergeron C., S71
Bernstein J., S55
Bielecka T., S62
Blau Hana BH., S83
Blau H., S51, S68
Bloch C., S60
Bokonjic D., S69
Boner A., S55
Boon M., S41
Borowa A., S50
Box AC., S14
Bott-Lebreton L., S67
Boukhettala NB., S83
Bourgoin-Heck M., S67
Brand Paul L.P., S7, S11, S17
Breborowicz A., S56, S63, S79
Breuer O., S51, S72, S74
Bruno KE, S62
Buchvald F., S74
Bulgakova V., S57
Bulteau-Cowan A., S67
Bush A., S5, S35, S46

C
Cantin D., S52
Cardoso CA., S62
Carlson KH., S15
Castro-Rodriguez JA., S16
Cecil-Oakes I., S72
Chaisapanmongkollarp T., S76
Chang AB., S79
Chen CC., S79
Cheng HC., S74
Chen IC., S74
Christensen P., S74
Chun YH., S62
Cicullo A., S62, S68
Cichocka-Jarosz E., S58, S66
Cinel G., S67
Cleveland RH., S38
Cohen Herman Avner CH., S83
Cohen-Cymberknoh M., S28, S32, S51, S72
Colic M., S69
Colin A., S66, S69
Colin Andrew A., S26
Corbo M., S62, S68
Corcuera P., S58
Corcuff JB., S57
Coulin FP., S71
Couto Guerra I., S70
Criscuolo A., S62, S68
Currie SM., S71
Czekaj-Kucharz K., S50

D
Dagan A., S66
Dai ZK., S74
Davila Edquen JE., S80
de Bruyne JA., S61
de Groot Eric P., S7
de Jongste JC., S52
De Leon N., S51
Della Monica V., S62, S68
Diaz V., S67
Dishop M., S67
Divanovic P., S80
Djeddi DD., S52
Dmowska H., S78
Dogru D., S67
Dowing K., S71
Draaisma Eelco, S7
Drouot X., S67
Durlak W., S58

E
Efrati O., S66
Eg KP., S61
Elliott FM., S65
Emiralioglu N., S65, S67, S68
Emparanza JI, S58
Engelkes M., S14
Engel M., S55
Erosz D., S65, S68
Escano-Dumbrique J., S53
Espiritu A., S49

F
Fauroux B., S1, S35
Fayon M., S57
Feleszko W., S50, S62
Fernandes MA., S62
Fernandes RB., S62
Ferreira L., S70
Forma L., S73
Fouzas Sotiriou S., S17
Franco CL., S61
Frascogna A., S62, S68
Fufezan O., S76
Fujibayashi HF., S77

G
Gäcs E., S71
Geppe N., S75
Gie RP., S22, S38
Giroso D., S6
Goh AEN., S82
Goldbart DA., S55
Goussar P., S22, S38, S81
Green DM., S36
Gries M., S32, S42
Grosse-Onnebrink J., S79
Gupta S., S52, S58
Gur Shmuel G., S83

H
Halioglu M., S67
Hamelmans E., S55
Hasegawa H., S75, S79
Heikkilä P., S73
Helbling JC., S57
Helminen M., S48
Henderson J., S10, S19
Henni N., S75, S79
Hoffmann A., S79
Hoshen M., S51
Hoshina J., S77
Hothi Jaspal, S27
Hsieh KS., S79
Hsueh KS., S79
Huang CC, S79
Huang LT., S79
Hudson M., S36
Husseini K., S67

I
Ilyenkova N., S54
Inaba H., S36, S45
Isobe M., S64

J
Jackowska T., S50
Jankovic N., S22, S38

<table>
<thead>
<tr>
<th>Name</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssens H.M.</td>
<td>S14, S52</td>
</tr>
<tr>
<td>Jedynak-Wąsowicz U.</td>
<td>S58, S66</td>
</tr>
<tr>
<td>Jehlicka P.</td>
<td>S72</td>
</tr>
<tr>
<td>Jiao JW.</td>
<td>S50</td>
</tr>
<tr>
<td>Jiao WW.</td>
<td>S81</td>
</tr>
<tr>
<td>Joergensen IM.</td>
<td>S51</td>
</tr>
<tr>
<td>Joficzuk - Potoczny K.</td>
<td>S63</td>
</tr>
<tr>
<td>Kamoi YK.</td>
<td>S77</td>
</tr>
<tr>
<td>Kee SY.</td>
<td>S61</td>
</tr>
<tr>
<td>Kerem E.</td>
<td>S72</td>
</tr>
<tr>
<td>Khosla I.</td>
<td>S63</td>
</tr>
<tr>
<td>Kim HH.</td>
<td>S62</td>
</tr>
<tr>
<td>Kim HS.</td>
<td>S62</td>
</tr>
<tr>
<td>Kim JT.</td>
<td>S62</td>
</tr>
<tr>
<td>Kiper N.</td>
<td>S65, S67, S68</td>
</tr>
<tr>
<td>Klein N.</td>
<td>S51</td>
</tr>
<tr>
<td>Kloosterman SF.</td>
<td>S52</td>
</tr>
<tr>
<td>Kodera T.</td>
<td>S75, S79</td>
</tr>
<tr>
<td>Kolosova N.</td>
<td>S75</td>
</tr>
<tr>
<td>Komorowska-Piotrowska A.</td>
<td>S50, S62</td>
</tr>
<tr>
<td>Koponen P.</td>
<td>S48</td>
</tr>
<tr>
<td>Korolkova E.</td>
<td>S57</td>
</tr>
<tr>
<td>Korppi M.</td>
<td>S48, S73</td>
</tr>
<tr>
<td>Korppi Matti</td>
<td>S29</td>
</tr>
<tr>
<td>Korta J.</td>
<td>S58</td>
</tr>
<tr>
<td>Krasinska M.</td>
<td>S50, S62</td>
</tr>
<tr>
<td>Krenke K.</td>
<td>S62, S67, S68</td>
</tr>
<tr>
<td>Kipcza M.</td>
<td>S55</td>
</tr>
<tr>
<td>Kiper N.</td>
<td>S65, S67, S68</td>
</tr>
<tr>
<td>Klepin J.</td>
<td>S62</td>
</tr>
<tr>
<td>Klis M.</td>
<td>S50</td>
</tr>
<tr>
<td>Klus B.</td>
<td>S66</td>
</tr>
<tr>
<td>Lacoste A.</td>
<td>S57</td>
</tr>
<tr>
<td>Lalibera IB.</td>
<td>S49</td>
</tr>
<tr>
<td>Lange J.</td>
<td>S67</td>
</tr>
<tr>
<td>Lauhkonen E.</td>
<td>S48</td>
</tr>
<tr>
<td>Lavie M.</td>
<td>S66</td>
</tr>
<tr>
<td>Lee EK.</td>
<td>S62</td>
</tr>
<tr>
<td>Lertbunrian R.</td>
<td>S77</td>
</tr>
<tr>
<td>Levine H.</td>
<td>S51, S68</td>
</tr>
<tr>
<td>Lin Sun LS.</td>
<td>S75</td>
</tr>
<tr>
<td>Li SC.</td>
<td>S79</td>
</tr>
<tr>
<td>Lisc H.</td>
<td>S58, S66</td>
</tr>
<tr>
<td>Li YJ.</td>
<td>S74</td>
</tr>
<tr>
<td>Loges NT.</td>
<td>S79</td>
</tr>
<tr>
<td>Lopez Revilla JW.</td>
<td>S80</td>
</tr>
<tr>
<td>Lukosevicu- Zike D.</td>
<td>S65</td>
</tr>
<tr>
<td>Maayan C.</td>
<td>S60</td>
</tr>
<tr>
<td>Macek Milan</td>
<td>S31</td>
</tr>
<tr>
<td>Makieiewa N.</td>
<td>S59</td>
</tr>
<tr>
<td>Malishev V.</td>
<td>S75</td>
</tr>
<tr>
<td>Matkowsky P.</td>
<td>S63</td>
</tr>
<tr>
<td>Man SC.</td>
<td>S76</td>
</tr>
<tr>
<td>Martin AJ.</td>
<td>S71</td>
</tr>
<tr>
<td>Mashiach R.</td>
<td>S68</td>
</tr>
<tr>
<td>Matveeva T.</td>
<td>S70</td>
</tr>
<tr>
<td>Mei-Zahav M.</td>
<td>S68</td>
</tr>
<tr>
<td>Meizer I.</td>
<td>S68</td>
</tr>
<tr>
<td>Mendoza Fox CJ.</td>
<td>S80, S81</td>
</tr>
<tr>
<td>Mihajlovic D.</td>
<td>S69</td>
</tr>
<tr>
<td>Minato TM.</td>
<td>S77</td>
</tr>
<tr>
<td>Minic P.</td>
<td>S69</td>
</tr>
<tr>
<td>Minetegui FJ.</td>
<td>S58</td>
</tr>
<tr>
<td>Misevicie V.</td>
<td>S65</td>
</tr>
<tr>
<td>Mohotti K.</td>
<td>S60</td>
</tr>
<tr>
<td>Moisian MP.</td>
<td>S57</td>
</tr>
<tr>
<td>Moroni-Zentgraf P.</td>
<td>S55</td>
</tr>
<tr>
<td>Morycinski S.</td>
<td>S63</td>
</tr>
<tr>
<td>Moshe Hoshen HM.</td>
<td>S83</td>
</tr>
<tr>
<td>Muchao FP.</td>
<td>S49</td>
</tr>
<tr>
<td>Mulliez-Petipas J.</td>
<td>S67</td>
</tr>
<tr>
<td>Murphy T.</td>
<td>S18, S48</td>
</tr>
<tr>
<td>Muskin Wintner E.</td>
<td>S60</td>
</tr>
<tr>
<td>Mussaffi H.</td>
<td>S51, S68</td>
</tr>
<tr>
<td>Muto J.</td>
<td>S75, S79</td>
</tr>
<tr>
<td>Narayan O.</td>
<td>S72</td>
</tr>
<tr>
<td>Narozna B.</td>
<td>S56, S79</td>
</tr>
<tr>
<td>Nazzar H.</td>
<td>S72</td>
</tr>
<tr>
<td>Nathan AM.</td>
<td>S61</td>
</tr>
<tr>
<td>Navi NP.</td>
<td>S62</td>
</tr>
<tr>
<td>Ness K.</td>
<td>S36</td>
</tr>
<tr>
<td>Ng DK.</td>
<td>S33</td>
</tr>
<tr>
<td>Nielsen KG.</td>
<td>S74</td>
</tr>
<tr>
<td>Nuolivirta K.</td>
<td>S48</td>
</tr>
<tr>
<td>O BRODovich H.</td>
<td>S3, S39</td>
</tr>
<tr>
<td>Oguz B.</td>
<td>S67</td>
</tr>
<tr>
<td>Ohta T.</td>
<td>S73</td>
</tr>
<tr>
<td>Okada KO.</td>
<td>S77</td>
</tr>
<tr>
<td>Olbrich H.</td>
<td>S79</td>
</tr>
<tr>
<td>Olcese R.</td>
<td>S6</td>
</tr>
<tr>
<td>Omran H.</td>
<td>S79</td>
</tr>
<tr>
<td>Onikiienko O.</td>
<td>S59</td>
</tr>
<tr>
<td>Orhan D.</td>
<td>S67</td>
</tr>
<tr>
<td>Overweel JL.</td>
<td>S52</td>
</tr>
<tr>
<td>Ozcelik U.</td>
<td>S65, S67, S68</td>
</tr>
<tr>
<td>Pajovic R.</td>
<td>S80</td>
</tr>
<tr>
<td>Papp G.</td>
<td>S56</td>
</tr>
<tr>
<td>Patenaude YG.</td>
<td>S71</td>
</tr>
<tr>
<td>Pekcan S.</td>
<td>S60</td>
</tr>
<tr>
<td>Pérez-Yarza EG.</td>
<td>S58</td>
</tr>
<tr>
<td>Pianosi PT.</td>
<td>S56</td>
</tr>
<tr>
<td>Piatosa B.</td>
<td>S78</td>
</tr>
<tr>
<td>Piorri L.</td>
<td>S62, S68</td>
</tr>
<tr>
<td>Pinto LF.</td>
<td>S61</td>
</tr>
<tr>
<td>Pizzutto SJ.</td>
<td>S79</td>
</tr>
<tr>
<td>Pohunek P.</td>
<td>S54</td>
</tr>
<tr>
<td>Pohunek Petr</td>
<td>S19</td>
</tr>
<tr>
<td>Polyakov V.</td>
<td>S59</td>
</tr>
<tr>
<td>Pons Ódena M.</td>
<td>S42</td>
</tr>
<tr>
<td>Prais D.</td>
<td>S68</td>
</tr>
<tr>
<td>Praul JP.</td>
<td>S34, S44, S52</td>
</tr>
<tr>
<td>PreuTheipa A.</td>
<td>S76</td>
</tr>
<tr>
<td>PreuTheipa A.</td>
<td>S77</td>
</tr>
<tr>
<td>Quevedo K.</td>
<td>S81</td>
</tr>
<tr>
<td>Raising FB</td>
<td>S80</td>
</tr>
<tr>
<td>Ran D Balicer BR.</td>
<td>S83</td>
</tr>
<tr>
<td>Raviv-Zilka L.</td>
<td>S68</td>
</tr>
<tr>
<td>Reim FS.</td>
<td>S51</td>
</tr>
<tr>
<td>Requiron-Sy.F.</td>
<td>S51</td>
</tr>
<tr>
<td>Robison L.</td>
<td>S36</td>
</tr>
<tr>
<td>Rocha H.</td>
<td>S70</td>
</tr>
<tr>
<td>Rodrigues JC.</td>
<td>S49</td>
</tr>
<tr>
<td>Rola-Pleszczyński M.</td>
<td>S71</td>
</tr>
<tr>
<td>Rossi GA.</td>
<td>S6</td>
</tr>
<tr>
<td>Roxas A.</td>
<td>S51</td>
</tr>
<tr>
<td>Rubin BK.</td>
<td>S9, S13</td>
</tr>
<tr>
<td>Sacco O.</td>
<td>S6</td>
</tr>
<tr>
<td>Sam IC.</td>
<td>S61</td>
</tr>
<tr>
<td>Samson N.</td>
<td>S52</td>
</tr>
<tr>
<td>Samuels M.</td>
<td>S72</td>
</tr>
<tr>
<td>Santos TC.</td>
<td>S61</td>
</tr>
<tr>
<td>Sardon O.</td>
<td>S58</td>
</tr>
<tr>
<td>Sarouk I.</td>
<td>S66</td>
</tr>
<tr>
<td>Sasi V.</td>
<td>S76</td>
</tr>
<tr>
<td>Schmidt B.J.</td>
<td>S51, S69</td>
</tr>
<tr>
<td>Schmidt CM.</td>
<td>S61, S62</td>
</tr>
<tr>
<td>Schnell C.</td>
<td>S76</td>
</tr>
<tr>
<td>Schoneich N.</td>
<td>S55</td>
</tr>
<tr>
<td>Schvartsman C.</td>
<td>S49</td>
</tr>
<tr>
<td>Seddon JA.</td>
<td>S2, S23</td>
</tr>
<tr>
<td>Senatorova G.</td>
<td>S59</td>
</tr>
<tr>
<td>Senra V.</td>
<td>S70</td>
</tr>
<tr>
<td>Shafat T.</td>
<td>S55</td>
</tr>
<tr>
<td>Shatalina S.</td>
<td>S75</td>
</tr>
<tr>
<td>Shatin NT.</td>
<td>S30</td>
</tr>
<tr>
<td>Sheen JM.</td>
<td>S79</td>
</tr>
<tr>
<td>Shen AD.</td>
<td>S81</td>
</tr>
<tr>
<td>Shen CS.</td>
<td>S81</td>
</tr>
<tr>
<td>Shuich Tsuchiya S.</td>
<td>S64</td>
</tr>
<tr>
<td>Sias SM.</td>
<td>S61, S62</td>
</tr>
<tr>
<td>Silva Filho LV.</td>
<td>S49</td>
</tr>
<tr>
<td>Silvestri M.</td>
<td>S6</td>
</tr>
<tr>
<td>Simanovsky N.</td>
<td>S60</td>
</tr>
<tr>
<td>Simanski D.</td>
<td>S66</td>
</tr>
<tr>
<td>Simunkova P.</td>
<td>S54</td>
</tr>
<tr>
<td>Singh V.</td>
<td>S21, S24</td>
</tr>
<tr>
<td>Sirsimanlar T.</td>
<td>S64</td>
</tr>
<tr>
<td>Sobkowiak P.</td>
<td>S55, S79</td>
</tr>
<tr>
<td>Souza JM.</td>
<td>S48</td>
</tr>
<tr>
<td>Srinivasan A.</td>
<td>S45</td>
</tr>
<tr>
<td>Srinivasan S.</td>
<td>S36, S45</td>
</tr>
<tr>
<td>Stauffer P.</td>
<td>S68</td>
</tr>
<tr>
<td>Starostina L.</td>
<td>S75</td>
</tr>
<tr>
<td>Stein RT.</td>
<td>S16</td>
</tr>
<tr>
<td>Stojnic N.</td>
<td>S69</td>
</tr>
<tr>
<td>Stokes DC.</td>
<td>S27, S36, S45</td>
</tr>
<tr>
<td>Strainovic LV.</td>
<td>S80</td>
</tr>
<tr>
<td>Sirzelak A.</td>
<td>S50</td>
</tr>
<tr>
<td>Skylora J.</td>
<td>S72</td>
</tr>
<tr>
<td>Szczepanikiewicz A.</td>
<td>S56, S79</td>
</tr>
<tr>
<td>Tain YL.</td>
<td>S79</td>
</tr>
<tr>
<td>Tal A.</td>
<td>S55</td>
</tr>
<tr>
<td>Taminskiene V.</td>
<td>S73</td>
</tr>
<tr>
<td>Tanega-Alling K.</td>
<td>S53</td>
</tr>
<tr>
<td>Taseen K.</td>
<td>S71</td>
</tr>
<tr>
<td>Teoh OH.</td>
<td>S82</td>
</tr>
<tr>
<td>Tereshchenko S.</td>
<td>S54</td>
</tr>
</tbody>
</table>
S86  Abstract

Thavaganam S., S61  
Thomas A., S72  
Tiao MM., S79  
Tiddens HA., S52  
Todisco N., S62, S68, S82  
Toikka J., S48  
Tokuda OT, S77  
Tomii Y., S75, S79  
Tomoharu Kato T., S64  
Torres HC., S48  
Tosca M., S6  
Tripto Golan, S54  
Tseng WN., S79  
Tsuruta S., S75, S79  
Tuazon A., S49, S53  
Turner S., S73  

U  
Uchiyama T., S75, S79  
Ueda MU., S77  
Uhereczky G., S71  
Ulbin J., S54  
Ulmeanu A., S74  
Unseld A., S55  
Upham JW., S79  

V  
Vaitkaitiene E., S73  
Vajner L., S54  
Valiulis A., S73  
Vandewalker , S55  
Vareesunthorn L., S76  
Vasconcellos CS., S61  
Vasilijic S., S69  
Velaphi S., S64  
Verwey C., S64  
Visconti M., S62, S68  
Vityutneva A., S54  
Vondrakova R, S72  
Vucevic D., S69  
Vuononvirta J., S48  

W  
Wang TM., S78  
Wasa M., S75, S79  
Weerasinghe SM., S60  
Wielebska A., S63  
Wilawan P., S77  
Wojsyk - Banaszak I, S63  
Wong GWK, S8, S30  
Wong PC., S82  

Won S., S62  
Woo YY., S61  
Wrotek A., S50  

X  
Xiao J., S64  

Y  
Yalcin E., S65, S67, S68  
Yamada HY., S77  
Yamada Y., S75, S79  
Yerkovich ST., S79  
Yoon JS., S62  
Yousef S., S69  
Yu HR., S79  
Yuksel H., S57  

Z  
Zapucioiu C., S74  
Zar HJ., S4, S21  
Zaveckiene J, S65  
Ziolkowski J., S50  
Zubkova I., S57  

Pediatric Pulmonology